کتاب پزشکی

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Notice

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Applied Biopharmaceutics & Pharmacokinetics
Sixth Edition

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∗ The content of this book represents the personal views of the authors and not that of the FDA.
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## Contents

Preface xiii  
Glossary xv

1. **Introduction to Biopharmaceutics and Pharmacokinetics** 1  
   - Drug Product Performance 1  
   - Biopharmaceutics 1  
   - Pharmacokinetics 3  
   - Clinical Pharmacokinetics 4  
   - Practical Focus 4  
   - Pharmacodynamics 5  
   - Drug Exposure and Drug Response 5  
   - Toxicokinetics and Clinical Toxicology 5  
   - Measurement of Drug Concentrations 6  
   - Basic Pharmacokinetics and Pharmacokinetic Models 10  
   - Chapter Summary 15  
   - Learning Questions 17  
   - References 17  
   - Bibliography 18

2. **Mathematical Fundamentals in Pharmacokinetics** 19  
   - Math Self-Exam 19  
   - Estimation and the Use of Calculators and Computers 20  
   - Practice Problems 22  
   - Calculus 24  
   - Graphs 26  
   - Units in Pharmacokinetics 31  
   - Measurement and Use of Significant Figures 32  
   - Units for Expressing Blood Concentrations 33  
   - Statistics 33  
   - Practical Focus 34  
   - Rates and Orders of Reactions 35  
   - Chapter Summary 40  
   - Learning Questions 40  
   - References 42  
   - Bibliography 42

3. **One-Compartment Open Model: Intravenous Bolus Administration** 43  
   - Elimination Rate Constant 44  
   - Apparent Volume of Distribution 45  
   - Clearance 48  
   - Practical Focus 50  
   - Clinical Application 53  
   - Calculation of $k$ from Urinary Excretion Data 53  
   - Practice Problem 54  
   - Clinical Application 56  
   - Chapter Summary 57  
   - Learning Questions 57  
   - Reference 59  
   - Bibliography 59

4. **Multicompartment Models: Intravenous Bolus Administration** 61  
   - Two-Compartment Open Model 63  
   - Clinical Application 68  
   - Practice Problem 68  
   - Practical Focus 69  
   - Three-Compartment Open Model 77  
   - Determination of Compartment Models 79  
   - Practical Application 84  
   - Chapter Summary 86  
   - Learning Questions 87  
   - References 88  
   - Bibliography 89

5. **Intravenous Infusion** 91  
   - One-Compartment Model Drugs 91  
   - Infusion Method for Calculating Patient Elimination Half-Life 95

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## Contents

6. **Drug Elimination and Clearance** 107  
   - Drug Elimination 107  
   - The Kidney 108  
   - Renal Drug Excretion 111  
   - Clinical Application 114  
   - Practice Problems 114  
   - Drug Clearance 114  
   - Clearance Models 116  
   - Renal Clearance 118  
   - Determination of Renal Clearance 121  
   - Relationship of Clearance to Elimination Half-Life and Volume of Distribution 125  
   - Chapter Summary 127  
   - Learning Questions 127  
   - References 129  
   - Bibliography 129

7. **Pharmacokinetics of Oral Absorption** 131  
   - Pharmacokinetics of Drug Absorption 131  
   - Significance of Absorption Rate Constants 133  
   - Zero-Order Absorption Model 133  
   - Clinical Application—Transdermal Drug Delivery 134  
   - First-Order Absorption Model 134  
   - Practice Problem 142  
   - Chapter Summary 149  
   - Learning Questions 149  
   - References 150  
   - Bibliography 151

8. **Multiple-Dosage Regimens** 153  
   - Drug Accumulation 153  
   - Clinical Example 157  
   - Repetitive Intravenous Injections 158  
   - Intermittent Intravenous Infusion 163  
   - Estimation of $k$ and $V_o$ of Aminoglycosides in Clinical Situations 165  
   - Multiple-Oral-Dose Regimen 166  
   - Loading Dose 168  
   - Dosage Regimen Schedules 169  
   - Practice Problems 171  
   - Chapter Summary 173  
   - Learning Questions 174  
   - References 175  
   - Bibliography 175

9. **Nonlinear Pharmacokinetics** 177  
   - Saturable Enzymatic Elimination Processes 179  
   - Practice Problem 180  
   - Drug Elimination by Capacity-Limited Pharmacokinetics: One-Compartment Model, IV Bolus Injection 181  
   - Clinical Focus 191  
   - Drugs Distributed as One-Compartment Model and Eliminated by Nonlinear Pharmacokinetics 191  
   - Chronopharmacokinetics and Time-Dependent Pharmacokinetics 193  
   - Bioavailability of Drugs that Follow Nonlinear Pharmacokinetics 196  
   - Nonlinear Pharmacokinetics Due to Drug–Protein Binding 196  
   - Potential Reasons for Unsuspected Nonlinearity 200  
   - Chapter Summary 200  
   - Learning Questions 200  
   - References 202  
   - Bibliography 203

10. **Physiologic Drug Distribution and Protein Binding** 205  
    - Physiologic Factors of Distribution 205  
    - Clinical Focus 213  
    - Apparent Volume Distribution 213  
    - Practice Problem 216  
    - Protein Binding of Drugs 219  
    - Clinical Examples 221  
    - Effect of Protein Binding on the Apparent Volume of Distribution 222  
    - Relationship of Plasma Drug–Protein Binding to Distribution and Elimination 227  
    - Determinants of Protein Binding 231  
    - Kinetics of Protein Binding 232  
    - Practical Focus 233  
    - Determination of Binding Constants and Binding Sites by Graphic Methods 233  
    - Clinical Significance of Drug–Protein Binding 236  
    - Modeling Drug Distribution 247  
    - Chapter Summary 248  
    - Learning Questions 249  
    - References 250  
    - Bibliography 251
### 11. Drug Elimination and Hepatic Clearance 253

- Route of Drug Administration and Extrahepatic Drug Metabolism 253
- Practical Focus 255
- Hepatic Clearance 255
- Enzyme Kinetics 257
- Clinical Example 261
- Practice Problem 263
- Anatomy and Physiology of the Liver 265
- Hepatic Enzymes Involved in the Biotransformation of Drugs 267
- Drug Biotransformation Reactions 269
- Pathways of Drug Biotransformation 270
- First-Pass Effects 282
- Hepatic Clearance of a Protein-Bound Drug: Restrictive and Nonrestrictive Clearance from Binding 287
- Effect of Changing Intrinsic Clearance and/or Blood Flow on Hepatic Extraction and Elimination Half-Life after IV and Oral Dosing 288
- Biliary Excretion of Drugs 289
- Role of Transporters in Hepatic Clearance and Bioavailability 292
- Chapter Summary 293
- Learning Questions 294
- References 296
- Bibliography 298

### 12. Pharmacogenetics 301

- Polymorphism 303
- Pharmacogenomics 306
- Adverse Drug Reactions Attributed to Genetic Differences 308
- Genetic Polymorphism in Drug Metabolism: Cytochrome P-450 Isozymes 310
- Genetic Polymorphism in Drug Transport: MDR1 (P-Glycoprotein) and Multidrug Resistance 311
- Genetic Polymorphism in Drug Targets 312
- Relationship of Pharmacokinetics/Pharmacodynamics and Pharmacogenetics/Pharmacogenomics 313
- Clinical Example 315
- Summary 316
- Glossary 316
- Abbreviations 317
- References 317
- Bibliography 318

### 13. Physiologic Factors Related to Drug Absorption 321

- Drug Absorption and Design of a Drug Product 321
- Route of Drug Administration 321
- Nature of Cell Membranes 324
- Passage of Drugs Across Cell Membranes 326
- Oral Drug Absorption During Drug Product Development 333
- Drug Interactions in the Gastrointestinal Tract 334
- Oral Drug Absorption 336
- Methods for Studying Factors that Affect Drug Absorption 348
- Clinical Examples 351
- Effect of Disease States on Drug Absorption 351
- Miscellaneous Routes of Drug Administration 353
- Chapter Summary 355
- Learning Questions 356
- References 357
- Bibliography 359

### 14. Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance 361

- Biopharmaceutic Factors Affecting Drug Bioavailability 361
- Rate-Limiting Steps in Drug Absorption 363
- Physicochemical Nature of the Drug 366
- Formulation Factors Affecting Drug Product Performance 368
- Drug Product Performance, In Vitro: Dissolution and Drug Release Testing 370
- Compendial Methods of Dissolution 374
- Alternative Methods of Dissolution Testing 376
- Meeting Dissolution Requirements 378
- Problems of Variable Control in Dissolution Testing 379
- Performance of Drug Products: In Vitro–In Vivo Correlation 380
- Dissolution Profile Comparisons 386
- Drug Product Stability 386
- Considerations in the Design of a Drug Product 387
- Drug Product Considerations 389
- Clinical Example 394
- Chapter Summary 398
- Learning Questions 399
- References 399
- Bibliography 401
20. Application of Pharmacokinetics to Clinical Situations 565
   Medication Therapy Management 565
   Individualization of Drug Dosage Regimens 566
   Therapeutic Drug Monitoring 567
   Clinical Example 574
   Design of Dosage Regimens 576
   Conversion from Intravenous Infusion to Oral Dosing 578
   Determination of Dose 579
   Practice Problems 580
   Effect of Changing Dose and Dosing Interval on $C_{\text{max}}, C_{\text{min}},$ and $C_{\text{av}}$ 580
   Determination of Frequency of Drug Administration 581
   Determination of Both Dose and Dosage Interval 582
   Determination of Route of Administration 583
   Dosing of Drugs in Infants and Children 584
   Dosing of Drugs in the Elderly 585
   Dosing of Drugs in the Obese Patient 588
   Pharmacokinetics of Drug Interactions 590
   Inhibition of Drug Metabolism 594
   Inhibition of Monoamine Oxidase (MAO) 595
   Induction of Drug Metabolism 596
   Inhibition of Drug Absorption 596
   Inhibition of Biliary Excretion 596
   Altered Renal Reabsorption Due to Changing Urinary pH 596
   Practical Focus 597
   Effect of Food on Drug Disposition 597
   Adverse Viral Drug Interactions 597
   Population Pharmacokinetics 597
   Regional Pharmacokinetics 608
   Chapter Summary 609
   Learning Questions 610
   References 613
   Bibliography 614

21. Dose Adjustment in Renal and Hepatic Disease 617
   Renal Impairment 617
   Pharmacokinetic Considerations 617
   General Approaches for Dose Adjustment in Renal Disease 618
   Measurement of Glomerular Filtration Rate 621
   Serum Creatinine Concentration and Creatinine Clearance 622
   Practice Problems 624
   Dose Adjustment for Uremic Patients 627
   Extracorporeal Removal of Drugs 638
   Clinical Examples 642
   Effect of Hepatic Disease on Pharmacokinetics 645
   Chapter Summary 651
   Learning Questions 652
   References 653
   Bibliography 655

Appendix A Statistics 693
Appendix B Applications of Computers in Pharmacokinetics 707
Appendix C Solutions to Frequently Asked Questions (FAQs) and Learning Questions 717
Appendix D Guiding Principles for Human and Animal Research 761
Appendix E Popular Drugs and Pharmacokinetic Parameters 767
Index 773
The publication of this sixth edition of *Applied Biopharmaceutics and Pharmacokinetics* represents over 30 years in print. We are grateful to our readers for their loyalty and helpful suggestions throughout the years. As with the previous editions, we want to continue to maintain our original scope and objectives.

This text integrates basic scientific principles with drug product development and clinical pharmacy practice.

The major objective is to provide the reader with a basic and practical understanding of the principles of biopharmaceutics and pharmacokinetics that can be applied to drug product development and to drug therapy. This revised and updated edition of the text remains unique in teaching basic concepts that may be applied to understanding complex issues associated with *in vivo* drug delivery that are essential for safe and efficacious drug therapy.

The primary audience is pharmacy students enrolled in pharmaceutical science courses in pharmacokinetics and biopharmaceutics. This text fulfills course work offered in separate or combined courses in these subjects. Secondary audiences for this textbook are research and development scientists in pharmaceutics, biopharmaceutics, and pharmacokinetics.

**There are many improvements in this edition.**
- *Chapter Objectives* are added at the beginning of each chapter.
- *Chapter Summary* at the end of each chapter.
- *Frequently Asked Questions* are seeded within each chapter to help the student focus on key concepts.
- Most chapters are revised to reflect our current understanding of drug disposition, pharmacodynamics, and drug therapy.
- The growing importance of drug transporters, CYP enzymes, and influence of pharmacogenetics on long-term drug response and other relevant topics have been updated to reflect current knowledge and application of pharmacokinetic/pharmacodynamics to drug therapy.
- *Chapter 15 is expanded and re-titled, Drug Product Performance, In Vivo: Bioavailability and Bioequivalence*, to reflect the consideration of bioequivalence as an *in vivo* measure of drug product performance and that bioequivalence is important in both brand and generic drug product development.
- *Chapter 16 is now titled, Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy*. This chapter describes the types of safety and efficacy risks and various means for preventing them including the roles of drug product quality and drug product performance.
- In addition, the concept of quality-by-design (QbD) may be applied to improve critical quality attributes essential for drug product safety and efficacy.
- *Practical examples and questions are included* to encourage students to apply the principles in patient care and drug consultation situations.
- *Active learning and outcome-based objectives are highlighted.*

Leon Shargel
Susanna Wu-Pong
Andrew B.C. Yu
Glossary

A, B, C  Preexponential constants for three-compartment model equation

a, b, c  Exponents for three-compartment model equation

\( \alpha, \beta, \gamma \)  Exponents for three-compartment model equation (equivalent to \( a, b, c \) above)

\( \lambda_1, \lambda_2, \lambda_3 \)  Exponents for three-compartment-type exponential equation (equivalent to \( a, b, c \) above; more terms may be added and indexed numerically with \( \lambda \) subscripts for multiexponential models)

Ab  Amount of drug in the body of time \( t \); see also \( D_B \)

\( Ab^\infty \)  Total amount of drug in the body

ABC  ABC transport protein

AE  Adverse event

ANDA  Abbreviated New Drug Application; see also NDA

ANOVA  Analysis of variance

API  Active pharmaceutical ingredient

AUC  Area under the plasma level–time curve

\([\text{AUC}]_0^\infty \)  Area under the plasma level–time curve extrapolated to infinite time

\([\text{AUC}]_0 \)  Area under the plasma level–time curve from \( t = 0 \) to last measurable plasma drug concentration at time \( t \)

AUMC  Area under the (first) moment–time curve

BA  Bioavailability

BCS  Biopharmaceutics classification system

BDDCS  Drug disposition classification system

BE  Bioequivalence

BLA  Biologic license application

BM  Biomarker

BMI  Body mass index

BRCP  Breast cancer-resistance protein (an ABC transporter)

BUN  Blood urea nitrogen

\( C \)  Concentration (mass/volume)

\( C_a \)  Drug concentration in arterial plasma

\( C_{av}^{\infty} \)  Average steady-state plasma drug concentration; see also

\( C_c \) or \( C_p \)  Concentration of drug in the central compartment or in plasma

\( C_{Cr} \)  Serum creatinine concentration, usually expressed as mg%

CE  Clinical endpoint

\( C_{eff} \)  Minimum effective drug concentration

\( C_{GI} \)  Concentration of drug in gastrointestinal tract

CI  Confidence interval

\( C_m \)  Metabolite plasma concentration

\( C_{max} \)  Maximum concentration of drug
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>Maximum steady-state drug concentration; see also $C_{\text{ssmax}}$</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Minimum concentration of drug</td>
</tr>
<tr>
<td>$C_{\text{ss}}$</td>
<td>Concentration of drug at steady state</td>
</tr>
<tr>
<td>$C_{\text{ssav}}$</td>
<td>Average concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{ssmax}}$</td>
<td>Maximum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{ssmin}}$</td>
<td>Minimum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{p}}$</td>
<td>Concentration of drug in plasma</td>
</tr>
<tr>
<td>$C_{\text{v}}$</td>
<td>Drug concentration in venous plasma</td>
</tr>
<tr>
<td>$C_{p\text{,max}}$</td>
<td>Steady-state plasma drug concentration (equivalent to $C_{\text{ss}}$)</td>
</tr>
<tr>
<td>$C_{p\text{,o}}$</td>
<td>Last measured plasma drug concentration</td>
</tr>
<tr>
<td>$C_{\text{cp}}$</td>
<td>Concentration of drug in tissue</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{max}}$</td>
<td>Maximum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{min}}$</td>
<td>Minimum concentration at steady state</td>
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<tr>
<td>$C_{\text{cp}}(t)$</td>
<td>Concentration of drug in plasma at zero time ($t = 0$) (equivalent to $C_{0}$)</td>
</tr>
<tr>
<td>$C_{\text{cp}}(t)$</td>
<td>Concentration of drug in plasma at time $t$</td>
</tr>
<tr>
<td>$C_{\text{cp}}(\infty)$</td>
<td>Steady-state plasma drug concentration</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{last}}$</td>
<td>Last measured plasma drug concentration</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{SS}}$</td>
<td>Concentration of drug at steady state</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{av}}$</td>
<td>Average concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{max}}$</td>
<td>Maximum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{min}}$</td>
<td>Minimum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{t}}$</td>
<td>Concentration of drug in tissue</td>
</tr>
<tr>
<td>$C_{\text{cp}}$</td>
<td>Concentration of drug in plasma</td>
</tr>
<tr>
<td>$C_{\text{cp}}(t)$</td>
<td>Concentration of drug in plasma at time $t$</td>
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<tr>
<td>$C_{\text{cp}}(\infty)$</td>
<td>Steady-state plasma drug concentration</td>
</tr>
<tr>
<td>$C_{\text{cp},\text{last}}$</td>
<td>Last measured plasma drug concentration</td>
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<tr>
<td>$C_{\text{cp},\text{SS}}$</td>
<td>Concentration of drug at steady state</td>
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<td>$C_{\text{cp},\text{av}}$</td>
<td>Average concentration at steady state</td>
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<td>$C_{\text{cp},\text{max}}$</td>
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<tr>
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<td>Minimum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{v}}$</td>
<td>Drug concentration in venous plasma</td>
</tr>
<tr>
<td>$C_{\text{v},\text{max}}$</td>
<td>Maximum steady-state drug concentration; see also $C_{\text{ssmax}}$</td>
</tr>
<tr>
<td>$C_{\text{v},\text{min}}$</td>
<td>Minimum steady-state drug concentration; see also $C_{\text{ssmin}}$</td>
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<tr>
<td>$C_{\text{v}}(t)$</td>
<td>Concentration of drug in plasma at time $t$</td>
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<td>$C_{\text{v}}(\infty)$</td>
<td>Steady-state plasma drug concentration</td>
</tr>
<tr>
<td>$C_{\text{v},\text{last}}$</td>
<td>Last measured plasma drug concentration</td>
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<tr>
<td>$C_{\text{v},\text{SS}}$</td>
<td>Concentration of drug at steady state</td>
</tr>
<tr>
<td>$C_{\text{v},\text{av}}$</td>
<td>Average concentration at steady state</td>
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<td>$C_{\text{v},\text{max}}$</td>
<td>Maximum concentration at steady state</td>
</tr>
<tr>
<td>$C_{\text{v},\text{min}}$</td>
<td>Minimum concentration at steady state</td>
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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$D_{B}$</td>
<td>Amount of drug in body</td>
</tr>
<tr>
<td>$D_{E}$</td>
<td>Drug eliminated</td>
</tr>
<tr>
<td>$D_{\text{E}}$</td>
<td>Drug eliminated</td>
</tr>
<tr>
<td>$D_{G\text{I}}$</td>
<td>Amount of drug in gastrointestinal tract</td>
</tr>
<tr>
<td>$D_{L}$</td>
<td>Loading (initial) dose</td>
</tr>
<tr>
<td>$D_{\text{m}}$</td>
<td>Maintenance dose</td>
</tr>
<tr>
<td>$D_{N}$</td>
<td>Normal dose</td>
</tr>
<tr>
<td>$D_{P}$</td>
<td>Drug in central compartment</td>
</tr>
<tr>
<td>$D_{1}$</td>
<td>Amount of drug in tissue</td>
</tr>
<tr>
<td>$D_{a}$</td>
<td>Amount of drug in urine</td>
</tr>
<tr>
<td>$D_{s}$</td>
<td>Dose of drug</td>
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<tr>
<td>$D_{0}$</td>
<td>Dose of drug</td>
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<tr>
<td>$D_{0}$</td>
<td>Amount of drug at zero time ($t = 0$)</td>
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<tr>
<td>$D_{\text{E}}$</td>
<td>Pharmacologic effect</td>
</tr>
<tr>
<td>$E$</td>
<td>Pharmacologic effect</td>
</tr>
<tr>
<td>$e$</td>
<td>Intercept on y axis of graph relating pharmacologic response to log drug concentration</td>
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<tr>
<td>$e\text{GFR}$</td>
<td>Estimate of GFR based on an MDRD equation</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>Maximum pharmacologic effect</td>
</tr>
<tr>
<td>$E_{0}$</td>
<td>Pharmacologic effect at zero drug concentration</td>
</tr>
<tr>
<td>$E_{C_{\text{50}}}$</td>
<td>Drug concentration that produces 50% maximum pharmacologic effect</td>
</tr>
<tr>
<td>$F$</td>
<td>Fraction of dose absorbed (bioavailability factor)</td>
</tr>
<tr>
<td>$f$</td>
<td>Fraction of dose remaining in the body</td>
</tr>
<tr>
<td>$f_{e}$</td>
<td>Fraction of unchanged drug excreted unchanged in urine</td>
</tr>
<tr>
<td>$f_{u}$</td>
<td>Unbound fraction of drug</td>
</tr>
<tr>
<td>$f(t)$</td>
<td>Function representing drug elimination over time (time is the independent variable)</td>
</tr>
<tr>
<td>$f'(t)$</td>
<td>Derivative of $f(t)$</td>
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<tr>
<td>$%CV$</td>
<td>Percent coefficient of variation</td>
</tr>
<tr>
<td>$G\text{FR}$</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>$\text{GI}$</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>$\text{GMP}$</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>$I$</td>
<td>Inhibitor concentration</td>
</tr>
<tr>
<td>$[I]$</td>
<td>Inhibitor concentration</td>
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Glossary of pharmacokinetic and pharmacodynamic terms.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBW</td>
<td>Ideal body weight</td>
</tr>
<tr>
<td>IVIVC</td>
<td>In vitro–in vivo correlation</td>
</tr>
<tr>
<td>k</td>
<td>Overall drug elimination rate constant ( k = k_e + k_m ); first-order rate constant, similar to ( k_{el} )</td>
</tr>
<tr>
<td>( K_a )</td>
<td>Association binding constant</td>
</tr>
<tr>
<td>( k_a )</td>
<td>First-order absorption rate constant ( K_a/k_a )</td>
</tr>
<tr>
<td>( K_d )</td>
<td>Dissociation binding constant</td>
</tr>
<tr>
<td>( k_e )</td>
<td>Excretion rate constant (first order) ( k_e = k_{el} )</td>
</tr>
<tr>
<td>( k_{el} )</td>
<td>Excretion rate constant (first order) ( k_{el} = k_{e0} )</td>
</tr>
<tr>
<td>( k_{e0} )</td>
<td>Transfer rate constant out of the effect compartment ( k_{e0} = k_{e0} )</td>
</tr>
<tr>
<td>( k_i )</td>
<td>Inhibition constant: ( = k_i/k_{10} )</td>
</tr>
<tr>
<td>( K_M )</td>
<td>Michaelis–Menten constant</td>
</tr>
<tr>
<td>( k_m )</td>
<td>Metabolism rate constant (first order) ( k_m = k_{m1} )</td>
</tr>
<tr>
<td>( k_N )</td>
<td>Normal elimination rate constant (first order) ( k_N = k_{N1} )</td>
</tr>
<tr>
<td>( k_{NR} )</td>
<td>Nonrenal elimination constant of normal patient ( k_{NR} = k_{NR1} )</td>
</tr>
<tr>
<td>( k_{NR}^U )</td>
<td>Renal elimination constant of uremic patient ( k_{NR}^U = k_{NR1}^U )</td>
</tr>
<tr>
<td>( k_u )</td>
<td>Uremic elimination rate constant (first order) ( k_u = k_{u1} )</td>
</tr>
<tr>
<td>( k_{on} )</td>
<td>First-order association rate constant ( k_{on} = k_{on1} )</td>
</tr>
<tr>
<td>( k_{off} )</td>
<td>First-order dissociation constant ( k_{off} = k_{off1} )</td>
</tr>
<tr>
<td>( k_0 )</td>
<td>Zero-order absorption rate constant ( k_0 = k_01 )</td>
</tr>
<tr>
<td>( k_{le} )</td>
<td>Transfer rate constant from the central to the effect compartment ( k_{le} = k_{le1} )</td>
</tr>
<tr>
<td>( k_{21} )</td>
<td>Transfer rate constant (from the tissue to the central compartment); first-order transfer rate constant from compartment 2 to compartment 1 ( k_{21} = k_{211} )</td>
</tr>
<tr>
<td>LBW</td>
<td>Lean body weight</td>
</tr>
<tr>
<td>m</td>
<td>Slope (also slope of ( E ) versus ( \log C ))</td>
</tr>
<tr>
<td>( M_u )</td>
<td>Amount of metabolite excreted in urine ( M_u = M_u1 )</td>
</tr>
<tr>
<td>mAbs</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>MAT</td>
<td>Mean absorption time</td>
</tr>
<tr>
<td>MDR1</td>
<td>p-Glycoprotein, ABCB1</td>
</tr>
<tr>
<td>MDRD</td>
<td>MDRD equation used to estimate of GFR</td>
</tr>
<tr>
<td>MDT</td>
<td>Mean dissolution time</td>
</tr>
<tr>
<td>MEC</td>
<td>Minimum effective concentration</td>
</tr>
<tr>
<td>miRNA</td>
<td>MicroRNA</td>
</tr>
<tr>
<td>MLP</td>
<td>Maximum life-span potential</td>
</tr>
<tr>
<td>MRP</td>
<td>Multidrug resistance-associated proteins</td>
</tr>
<tr>
<td>MRT</td>
<td>Mean residence time</td>
</tr>
<tr>
<td>MRT(_c)</td>
<td>Mean residence time from the central compartment</td>
</tr>
<tr>
<td>MRT(_p)</td>
<td>Mean residence time from the peripheral compartment</td>
</tr>
<tr>
<td>MRT(_t)</td>
<td>Mean residence time from the tissue compartment (same as MRT(_p))</td>
</tr>
<tr>
<td>MTC</td>
<td>Minimum toxic concentration</td>
</tr>
<tr>
<td>( \mu_0 )</td>
<td>Area under the zero moment curve (same as AUC) ( \mu_0 = \mu_01 )</td>
</tr>
<tr>
<td>( \mu_1 )</td>
<td>Area under the first moment curve (same as AUC) ( \mu_1 = \mu_11 )</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>NONMEN</td>
<td>Nonlinear mixed-effect model</td>
</tr>
<tr>
<td>NTI</td>
<td>Narrow therapeutic index; see also critical dose drug</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter drugs</td>
</tr>
<tr>
<td>OATP</td>
<td>Organic anion transporting polypeptide</td>
</tr>
<tr>
<td>OAT</td>
<td>Organic anion transporter</td>
</tr>
<tr>
<td>P</td>
<td>Amount of protein</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>P-gp</td>
<td>p-Glycoprotein, MDR1, ABCB1</td>
</tr>
<tr>
<td>PGt</td>
<td>Pharmacogenetics</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PPI</td>
<td>Patient package insert</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QbD</td>
<td>Quality by design</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
</tbody>
</table>
GLOSSARY

\( R \) Infusion rate; ratio of \( C_{\text{max}} \) after \( n \) dose to \( C_{\text{max}} \) after one dose (see Chapter 8) (accumulation ratio); pharmacologic response (see Chapter 19)

\( r \) Ratio of mole of drug bound to total moles of protein

\( R_{\text{max}} \) Maximum pharmacologic response

RLD Reference-listed drug

RNA Ribonucleic acid

RNAi RNA interference

SD Standard deviation

siRNA Small inhibitory RNA

SNP Single-nucleotide polymorphism

\( t \) Time (hours or minutes); denotes tissue when used as a subscript

\( t_{\text{eff}} \) Duration of pharmacologic response to drug

\( t_{\text{inf}} \) Infusion period

\( t_{\text{lag}} \) Lag time

\( t_{\text{max}} \) Time of occurrence for maximum (peak) drug concentration

\( t_0 \) Initial or zero time

\( t_{1/2} \) Half-life

\( \tau \) Time interval between doses

USP United States Pharmacopeia

\( V \) Volume (L or mL)

\( v \) Velocity

\( V_{\text{app}} \) Apparent volume of distribution (binding)

\( V_C \) Volume of central compartment

\( V_D \) Volume of distribution

\( V_e \) Volume of the effect compartment

\( V_i \) \( V_i \) and \( V \) are the reaction velocity with and without inhibitor, respectively

\( V_{\text{max}} \) Maximum metabolic rate

\( V_p \) Volume of plasma (central compartment)

\( V_t \) Volume of tissue compartment

\( (V_D)_{\text{exp}} \) Extrapolated volume of distribution

\( (V_D)_{\text{SS}} \) or \( V_{\text{DSS}} \) Steady-state volume of distribution
Chapter Objectives

- Define drug product performance and biopharmaceutics.
- Describe how the principles of biopharmaceutics can affect drug product performance.
- Define pharmacokinetics and describe how pharmacokinetics is related to pharmacodynamics and drug toxicity.
- Define a pharmacokinetic model and list the assumptions that are used in developing a pharmacokinetic model.

DRUG PRODUCT PERFORMANCE

Drugs are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Drugs are given in a variety of dosage forms or drug products such as solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc., for systemic or local therapeutic activity. Drug products can be considered to be drug delivery systems that release and deliver drug to the site of action such that they produce the desired therapeutic effect and are also designed specifically to meet the patient’s needs including palatability, convenience, and safety.

*Drug product performance* is defined as the release of the drug substance from the drug product either for local drug action or for drug absorption into the plasma for systemic therapeutic activity. Advances in pharmaceutical technology and manufacturing have focused on developing quality drug products that are safer, more effective, and more convenient for the patient.

BIOPHARMACEUTICS

*Biopharmaceutics* examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. The importance of the drug substance and the drug formulation on absorption, and *in vivo* distribution of the drug to the site of action, is described as a sequence of events that precede elicitation of a drug’s therapeutic effect. A general scheme describing this dynamic relationship is illustrated in Fig. 1-1.

First, the drug in its dosage form is taken by the patient either by an oral, intravenous, subcutaneous, transdermal, etc., route of administration. Next, the drug is released from the dosage form in a predictable and characterizable manner. Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue, into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. A pharmacologic...
response results when the drug concentration at the site of action reaches or exceeds the minimum effective concentration (MEC). The suggested dosing regimen, including starting dose, maintenance dose, dosage form, and dosing interval, is determined in clinical trials to provide the drug concentrations that are therapeutically effective in most patients. This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form and the physicochemical properties of the drug.

Historically, pharmaceutical scientists have evaluated the relative drug availability to the body in vivo after giving a drug product by different routes to an animal or human, and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. In addition, the bioavailability (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products. In other words, the nature of the drug molecule, the route of delivery, and the formulation of the dosage form can determine whether an administered drug is therapeutically effective, toxic, or has no apparent effect at all.

The US Food and Drug Administration (FDA) approves all drug products to be marketed in the United States. The pharmaceutical manufacturers must perform extensive research and development prior to approval. The manufacturer of a new drug product must submit a New Drug Application (NDA) to the FDA, whereas a generic drug pharmaceutical manufacturer must submit an Abbreviated New Drug Application (ANDA). Both the new and generic drug product manufacturer must characterize their drug and drug product and demonstrate that the drug product performs appropriately before the products can become available to consumers in the United States.

Biopharmaceutics provides the scientific basis for drug product design and drug product development. Each step in the manufacturing process of a finished dosage form may potentially affect the release of the drug from the drug product and the availability of the drug at the site of action. The most important steps in the manufacturing process are termed critical manufacturing variables. Examples of biopharmaceutic considerations in drug product design are listed in Table 1-1. A detailed discussion of drug product design is found in Chapter 14. Knowledge of physiologic factors necessary for designing oral products are discussed in Chapter 13. Finally, drug product quality and drug product testing are discussed in later chapters.

Thus, biopharmaceutics involves factors that influence (1) the design of the drug product, (2) stability of the drug within the drug product, (3) the manufacture of the drug product, (4) the release of the drug from the drug product, (5) the rate of dissolution/release of the drug at the absorption site, and (6) delivery of drug to the site of action, which may involve targeting a localized area (eg, colon for Crohn disease) for action or systemic absorption of the drug.
Both the pharmacist and the pharmaceutical scientist must understand these complex relationships to objectively choose the most appropriate drug product for therapeutic success.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. Studies in biopharmaceutics use both in vitro and in vivo methods. In vitro methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. In vivo methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 14. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability, and large-scale production of the drug and drug product on the biologic performance of the drug. Moreover, biopharmaceutics considers the properties of the drug and dosage form in a physiologic environment, the drug’s intended therapeutic use, and the route of administration.

PHARMACOKINETICS

After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both. The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics. Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion). The description of drug distribution and elimination is often termed drug disposition. Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.

The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biologic sampling techniques, analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation ultimately for the purpose of designing and predicting optimal dosing regimens for individuals or groups of patients. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer

<table>
<thead>
<tr>
<th>TABLE 1-1 Biopharmaceutic Considerations in Drug Product Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Items</strong></td>
</tr>
<tr>
<td>Therapeutic objective</td>
</tr>
<tr>
<td>Drug (active pharmaceutical ingredient, API)</td>
</tr>
<tr>
<td>Route of administration</td>
</tr>
<tr>
<td>Drug dosage and dosage regimen</td>
</tr>
<tr>
<td>Type of drug product</td>
</tr>
<tr>
<td>Excipients</td>
</tr>
<tr>
<td>Method of manufacture</td>
</tr>
</tbody>
</table>
techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

**CLINICAL PHARMACOKINETICS**

During the drug development process, large numbers of patients are tested by the manufacturer to determine optimum dosing regimens, which are then recommended in the package insert to produce the desired pharmacologic response in the majority of the anticipated patient population. However, intrapatient and interindividual variations will frequently result in either a subtherapeutic (drug concentration below the MEC) or toxic response (drug concentrations above the minimum toxic concentration, MTC), which may then require adjustment to the dosing regimen. Clinical pharmacokinetics is the application of pharmacokinetic methods to drug therapy. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient’s disease state and patient-specific considerations.

The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 1-2 is a list of 10 age-adjusted rates of death from 10 leading causes of death in the United States, 2003. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy (see Chapter 12). The study of pharmacokinetic differences of drugs in various population groups is termed population pharmacokinetics (Sheiner and Ludden, 1992).

Clinical pharmacokinetics is also applied to therapeutic drug monitoring (TDM) for very potent drugs, such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity. For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (eg, theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (eg, warfarin). Pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the clinical pharmacokinetic service (CPKS). Some drugs frequently monitored are the aminoglycosides and anti-convulsants. Other drugs closely monitored are those used in cancer chemotherapy, in order to minimize adverse side effects (Rodman and Evans, 1991).

<table>
<thead>
<tr>
<th>TABLE 1-2</th>
<th>Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death* in the US, 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Rank</td>
</tr>
<tr>
<td>Disease of heart</td>
<td>1</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>3</td>
</tr>
<tr>
<td>Chronic lower respiration diseases</td>
<td>4</td>
</tr>
<tr>
<td>Accidents and others*</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia and influenza</td>
<td>7</td>
</tr>
<tr>
<td>Alzheimers</td>
<td>8</td>
</tr>
<tr>
<td>Nephrotis, nephrotic syndrome, and nephrosis</td>
<td>9</td>
</tr>
<tr>
<td>Septicemia</td>
<td>10</td>
</tr>
</tbody>
</table>


**PRACTICAL FOCUS**

Relationship of Drug Concentrations to Drug Response

The initiation of drug therapy starts with the manufacturer’s recommended dosage regimen that includes the drug dose and frequency of doses (eg, 100 mg every 8 hours). Due to individual differences in the patient’s genetic makeup (see Chapter 12 on pharmacogenetics) or pharmacokinetics, the recommended dosage regimen drug may not provide the desired therapeutic outcome. The measurement of plasma drug concentrations can confirm whether the drug dose was subtherapeutic due to the patient’s individual pharmacokinetic profile (observed by low plasma drug concentrations) or was not responsive to drug therapy due to genetic difference in receptor response. In this...
case, the drug concentrations are in the therapeutic range but the patient does not respond to drug treatment. Figure 1-2 shows that the concentration of drug in the body can range from subtherapeutic to toxic. In contrast, some patients respond to drug treatment at lower drug doses that results in lower drug concentrations. Other patients may need higher drug concentrations to obtain a therapeutic effect which requires higher drug doses. It is desirable that adverse drug responses occur at drug concentrations higher relative to the therapeutic drug concentrations, but for many potent drugs, adverse effects can also occur close to the same drug concentrations as needed for the therapeutic effect.

**Frequently Asked Questions**

- Which is more closely related to drug response, the total drug dose administered or the concentration of the drug in the body?
- Why do individualized dosing regimens need to be determined for some patients?

**PHARMACODYNAMICS**

*Pharmacodynamics* refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response. Pharmacokinetic–pharmacodynamic models are constructed to relate plasma drug level to drug concentration at the site of action and establish the intensity and time course of the drug. Pharmacodynamics and pharmacokinetic–pharmacodynamic models are discussed more fully in Chapter 19.

**DRUG EXPOSURE AND DRUG RESPONSE**

*Drug exposure* refers to the dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., $C_{\text{max}}$, $C_{\text{min}}$, $C_{ss}$, AUC) (FDA Guidance, 2003). *Drug response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (e.g., receptor occupancy) to a presumed mechanistic effect (e.g., ACE inhibition), to a potential or accepted surrogate (e.g., effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety.

Toxicologic and efficacy studies provide information on the safety and effectiveness of the drug during development and in special patient populations such as subjects with renal and hepatic insufficiencies. For many drugs, clinical use is based on weighing the risks of favorable and unfavorable outcomes at a particular dose. For some potent drugs, the doses and dosing rate may need to be titrated in order to obtain the desired effect and be tolerated.

**TOXICOKINETICS AND CLINICAL TOXICOLOGY**

*Toxicokinetics* is the application of pharmacokinetic principles to the design, conduct, and interpretation of drug safety evaluation studies (Leal et al, 1993) and in validating dose-related exposure in animals. Toxicokinetic data aid in the interpretation of
toxicologic findings in animals and extrapolation of the resulting data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.

Clinical toxicology is the study of adverse effects of drugs and toxic substances (poisons) in the body. The pharmacokinetics of a drug in an overmedicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in lower therapeutic doses. At very high doses, the drug concentration in the body may saturate enzymes involved in the absorption, biotransformation, or active renal secretion mechanisms, thereby changing the pharmacokinetics from linear to nonlinear pharmacokinetics. Nonlinear pharmacokinetics is discussed in Chapter 9. Drugs frequently involved in toxicity cases include acetaminophen, salicylates, morphine, and the tricylic antidepressants (TCAs). Many of these drugs can be assayed conveniently by fluorescence immunoassay (FIA) kits.

MEASUREMENT OF DRUG CONCENTRATIONS

Because drug concentrations are an important element in determining individual or population pharmacokinetics, drug concentrations are measured in biologic samples, such as milk, saliva, plasma, and urine. Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic matrices. Such measurements are generally validated so that accurate information is generated for pharmacokinetic and clinical monitoring. In general, chromatographic and mass spectrometric methods are most frequently employed for drug concentration measurement, because chromatography separates the drug from other related materials that may cause assay interference and mass spectrometry allows detection of molecules or molecule fragments based on their mass to charge ratio.

Sampling of Biologic Specimens

Only a few biologic specimens may be obtained safely from the patient to gain information as to the drug concentration in the body. Invasive methods include sampling blood, spinal fluid, synovial fluid, tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient. In contrast, noninvasive methods include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention.

The measurement of drug and metabolite concentration in each of these biologic materials yields important information, such as the amount of drug retained in, or transported into, that region of the tissue or fluid, the likely pharmacologic or toxicologic outcome of drug dosing, and drug metabolite formation or transport. Analytical methods should be able to distinguish between protein-bound and unbound parent drug and each metabolite, and the pharmacologically active species should be identified. Such distinctions between metabolites in each tissue and fluid are especially important for initial pharmacokinetic modeling of a drug.

Drug Concentrations in Blood, Plasma, or Serum

Measurement of drug and metabolite concentrations (levels) in the blood, serum, or plasma is the most direct approach to assessing the pharmacokinetics of the drug in the body. Whole blood contains cellular elements including red blood cells, white blood cells, platelets, and various other proteins, such as albumin and globulins (Table 1-3). In general, serum or plasma is most commonly used for drug measurement. To obtain serum, whole blood is allowed to clot and the serum is collected from the supernatant after centrifugation. Plasma is obtained from the supernatant of centrifuged whole blood to which an anticoagulant, such as heparin, has been added. Therefore, the protein content of serum and plasma is not the same. Plasma perfuses all the tissues of the body, including the cellular elements in the blood. Assuming that a drug in the plasma is in dynamic equilibrium with the tissues, then changes in the drug concentration in plasma will reflect changes in tissue drug concentrations. Drugs in the plasma are often bound to plasma proteins, and often plasma proteins are filtered from the plasma before drug concentrations are measured. This is the unbound drug concentration. Alternatively, drug concentration
may be measured from unfiltered plasma; this is the total plasma drug concentration. When interpreting plasma concentrations, it is important to understand what type of plasma concentration the data reflect.

PLASMA CONCENTRATION–TIME CURVE

The plasma drug concentration (level)–time curve is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered. The concentration of drug in each plasma sample is plotted on rectangular-coordinate graph paper against the corresponding time at which the plasma sample was removed. As the drug reaches the general (systemic) circulation, plasma drug concentrations will rise up to a maximum if the drug was given by an extravascular route. Usually, absorption of a drug is more rapid than elimination. As the drug is being absorbed into the systemic circulation, the drug is distributed to all the tissues in the body and is also simultaneously being eliminated. Elimination of a drug can proceed by excretion, biotransformation, or a combination of both. Other elimination mechanisms may also be involved, such as elimination in the feces, sweat or exhaled air.

The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in Fig. 1-3. MEC and MTC represent the minimum effective concentration and minimum toxic concentration of drug, respectively. For some drugs, such as those acting on the autonomic nervous system, it is useful to know the concentration of drug that will just barely produce a pharmacologic effect (ie, MEC). Assuming the drug concentration in the plasma is in equilibrium with the tissues, the MEC reflects the minimum concentration of drug needed
at the receptors to produce the desired pharmacologic effect. Similarly, the MTC represents the drug concentration needed to just barely produce a toxic effect. The onset time corresponds to the time required for the drug to reach the MEC. The intensity of the pharmacologic effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response, up to a maximum. The duration of drug action is the difference between the onset time and the time for the drug to decline back to the MEC.

The therapeutic window is the concentrations between the MEC and the MTC. Drugs with a wide therapeutic window are generally considered safer than drugs with a narrow therapeutic window. Sometimes the term therapeutic index is used. This term refers to the ratio between the toxic and therapeutic dose.

In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as peak plasma level, time for peak plasma level, and area under the curve, or AUC (Fig. 1-4). The time for peak plasma level is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption. The peak plasma level or maximum drug concentration is related to the dose, the rate constant for absorption, and the elimination constant of the drug. The AUC is related to the amount of drug absorbed systemically. These and other pharmacokinetic parameters are discussed in succeeding chapters.

### Frequently Asked Questions

- **At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?**
- **What happens if plasma concentrations fall outside of the therapeutic window?**

### Drug Concentrations in Tissues

Tissue biopsies are occasionally removed for diagnostic purposes, such as the verification of a malignancy. Usually, only a small sample of tissue is removed, making drug concentration measurement difficult. Drug concentrations in tissue biopsies may not reflect drug concentration in other tissues nor the drug concentration in all parts of the tissue from which the biopsy material was removed. For example, if the tissue biopsy was for the diagnosis of a tumor within the tissue, the blood flow to the tumor cells may not be the same as the blood flow to other cells in this tissue. In fact, for many tissues, blood flow to one part of the tissues need not be the same as the blood flow to another part of the same tissue. The measurement of the drug concentration in tissue biopsy material may be used to ascertain if the drug reached the tissues and reached the proper concentration within the tissue.

### Drug Concentrations in Urine and Feces

Measurement of drug in urine is an indirect method to ascertain the bioavailability of a drug. The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption. The use of urinary drug excretion measurements to establish various pharmacokinetic parameters is discussed in Chapter 15.
Measurement of drug in feces may reflect drug that has not been absorbed after an oral dose or may reflect drug that has been expelled by biliary secretion after systemic absorption. Fecal drug excretion is often performed in mass balance studies, in which the investigator attempts to account for the entire dose given to the patient. For a mass balance study, both urine and feces are collected and their drug content measured. For certain solid oral dosage forms that do not dissolve in the gastrointestinal tract but slowly leach out drug, fecal collection is performed to recover the dosage form. The undissolved dosage form is then assayed for residual drug.

**Drug Concentrations in Saliva**

Saliva drug concentrations have been reviewed for many drugs for therapeutic drug monitoring (Pippenger and Massoud, 1984). Because only free drug diffuses into the saliva, saliva drug levels tend to approximate free drug rather than total plasma drug concentration. The saliva/plasma drug concentration ratio is less than 1 for many drugs. The saliva/plasma drug concentration ratio is mostly influenced by the pKa of the drug and the pH of the saliva. Weak acid drugs and weak base drugs with pKa significantly different than pH 7.4 (plasma pH) generally have better correlation to plasma drug levels. The saliva drug concentrations taken after equilibrium with the plasma drug concentration generally provide more stable indication of drug levels in the body. The use of salivary drug concentrations as a therapeutic indicator should be used with caution and preferably as a secondary indicator.

**Forensic Drug Measurements**

Forensic science is the application of science to personal injury, murder, and other legal proceedings. Drug measurements in tissues obtained at autopsy or in other bodily fluids such as saliva, urine, and blood may be useful if a suspect or victim has taken an overdose of a legal medication, has been poisoned, or has been using drugs of abuse such as opiates (e.g., heroin), cocaine, or marijuana. The appearance of social drugs in blood, urine, and saliva drug analysis shows short-term drug abuse. These drugs may be eliminated rapidly, making it more difficult to prove that the subject has been using drugs of abuse. The analysis for drugs of abuse in hair samples by very sensitive assay methods, such as gas chromatography coupled with mass spectrometry, provides information regarding past drug exposure. A study by Cone et al (1993) showed that the hair samples from subjects who were known drug abusers contained cocaine and 6-acetylmorphine, a metabolite of heroin (diacetylmorphine).

**Significance of Measuring Plasma Drug Concentrations**

The intensity of the pharmacologic or toxic effect of a drug is often related to the concentration of the drug at the receptor site, usually located in the tissue cells. Because most of the tissue cells are richly perfused with tissue fluids or plasma, measuring the plasma drug level is a responsive method of monitoring the course of therapy.

Clinically, individual variations in the pharmacokinetics of drugs are quite common. Monitoring the concentration of drugs in the blood or plasma ascertains that the calculated dose actually delivers the plasma level required for therapeutic effect. With some drugs, receptor expression and/or sensitivity in individuals varies, so monitoring of plasma levels is needed to distinguish the patient who is receiving too much of a drug from the patient who is supersensitive to the drug. Moreover, the patient’s physiologic functions may be affected by disease, nutrition, environment, concurrent drug therapy, and other factors. Pharmacokinetic models allow more accurate interpretation of the relationship between plasma drug levels and pharmacologic response.

In the absence of pharmacokinetic information, plasma drug levels are relatively useless for dosage adjustment. For example, suppose a single blood sample from a patient was assayed and found to contain 10 mg/mL. According to the literature, the maximum safe concentration of this drug is 15 mg/mL. In order to apply this information properly, it is important to know when the blood sample was drawn, what dose of the drug was given, and the route of administration. If the proper information is available, the use of pharmacokinetic equations and models may describe the blood level–time curve...
accurately and be used to modify dosing for that specific patient.

Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order to individualize and optimize therapeutic drug regimens. When alterations in physiologic functions occur, monitoring plasma drug concentrations may provide a guide to the progress of the disease state and enable the investigator to modify the drug dosage accordingly. Clinically, sound medical judgment and observation are most important. Therapeutic decisions should not be based solely on plasma drug concentrations.

In many cases, the pharmacodynamic response to the drug may be more important to measure than just the plasma drug concentration. For example, the electrophysiology of the heart, including an electrocardiogram (ECG), is important to assess in patients medicated with cardiotonic drugs such as digoxin. For an anticoagulant drug, such as dicumarol, prothrombin clotting time may indicate whether proper dosage was achieved. Most diabetic patients taking insulin will monitor their own blood or urine glucose levels.

For drugs that act irreversibly at the receptor site, plasma drug concentrations may not accurately predict pharmacodynamic response. Drugs used in cancer chemotherapy often interfere with nucleic acid or protein biosynthesis to destroy tumor cells. For these drugs, the plasma drug concentration does not relate directly to the pharmacodynamic response. In this case, other pathophysiologic parameters and side effects are monitored in the patient to prevent adverse toxicity.

**BASIC PHARMACOKINETICS AND PHARMACOKINETIC MODELS**

Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously. Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events require the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

A model is a hypothesis using mathematical terms to describe quantitative relationships concisely. The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process. The key parameters in a process are commonly estimated by fitting the model to the experimental data, known as variables. A pharmacokinetic parameter is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as \( k \) depend on the method of tissue sampling, the timing of the sample, drug analysis, and the predictive model selected.

A pharmacokinetic function relates an independent variable to a dependent variable, often through the use of parameters. For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time. In this case, the drug concentration depends on the time after the administration of the dose, where the time:concentration relationship is defined by a pharmacokinetic parameter, \( k \), the elimination rate constant.

Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination to predict drug concentrations in the body as a function of time. Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug

7. Explain drug interactions

Simplifying assumptions are made in pharmacokinetic models to describe a complex biologic system concerning the movement of drugs within the body. For example, most pharmacokinetic models assume that the plasma drug concentration reflects drug concentrations globally within the body.

A model may be empirically, physiologically, or compartmentally based. The model that simply interpolates the data and allows an empirical formula to estimate drug level over time is justified when limited information is available. Empirical models are practical but not very useful in explaining the mechanism of the actual process by which the drug is absorbed, distributed, and eliminated in the body. Examples of empirical models used in pharmacokinetics are described in Chapter 22.

Physiologically based models also have limitations. Using the example above, and apart from the necessity to sample tissue and monitor blood flow to the liver in vivo, the investigator needs to understand the following questions. What is the clinical implication of the liver drug concentration value? Should the drug concentration in the blood within the tissue be determined and subtracted from the drug in the liver tissue? What type of cell is representative of the liver if a selective biopsy liver tissue sample can be collected without contamination from its surroundings? Indeed, depending on the spatial location of the liver tissue from the hepatic blood vessels, tissue drug concentrations can differ depending on distance to the blood vessel or even on the type of cell in the liver. Moreover, changes in the liver blood perfusion will alter the tissue drug concentration. If heterogeneous liver tissue is homogenized and assayed, the homogenized tissue represents only a hypothetical concentration that is an average of all the cells and blood in the liver at the time of collection. Since tissue homogenization is not practical for human subjects, the drug concentration in the liver may be estimated by knowing the liver extraction ratio for the drug based on knowledge of the physiologic and biochemical composition of the body organs.

A great number of models have been developed to estimate regional and global information about drug disposition in the body. Some physiologic pharmacokinetic models are also discussed in Chapter 22. Individual pharmacokinetic processes are discussed in separate chapters under the topics of drug absorption, drug distribution, drug elimination, and pharmacokinetic drug interactions involving one or all of the above processes. Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered. Practical considerations have limited the growth of new pharmacokinetic models.

A very simple and useful tool in pharmacokinetics is compartmentally based models. For example, assume a drug is given by intravenous injection and that the drug dissolves (distributes) rapidly in the body fluids. One pharmacokinetic model that can describe this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug. The concentration of the drug in the tank after a given dose is governed by two parameters: (1) the fluid volume of the tank that will dilute the drug, and (2) the elimination rate of drug per unit of time. Though this model is perhaps an overly simplistic view of drug disposition in the human body, a drug’s pharmacokinetic properties can frequently be described using a fluid-filled tank model called the one-compartment open model (see below). In both the tank and the one-compartment body model, a fraction of the drug would be continually eliminated as a function of time (Fig. 1-5). In pharmacokinetics, these parameters are assumed to be constant for a given drug. If drug concentrations in the tank are determined at various time intervals following administration of a known dose, then the volume of fluid in the tank or compartment (V_D, volume of distribution) and the rate of drug elimination can be estimated.

In practice, pharmacokinetic parameters such as k and V_D are determined experimentally from a set of drug concentrations collected over various times and known as data. The number of parameters needed to describe the model depends on the complexity of the process and on the route of drug administration.
In general, as the number of parameters required to model the data increases, accurate estimation of these parameters becomes increasingly more difficult. With complex pharmacokinetic models, computer programs are used to facilitate parameter estimation. However, for the parameters to be valid, the number of data points should always exceed the number of parameters in the model.

Because a model is based on a hypothesis and simplifying assumptions, a certain degree of caution is necessary when relying totally on the pharmacokinetic model to predict drug action. For some drugs, plasma drug concentrations are not useful in predicting drug activity. For other drugs, an individual’s genetic differences, disease state, and the compensatory response of the body may modify the response to the drug. If a simple model does not fit all the experimental observations accurately, a new, more elaborate model may be proposed and subsequently tested. Since limited data are generally available in most clinical situations, pharmacokinetic data should be interpreted along with clinical observations rather than replacing sound judgment by the clinician. Development of pharmacometric statistical models may help to improve prediction of drug levels among patients in the population (Sheiner and Beal, 1982; Mallet et al, 1988). However, it will be some time before these methods become generally accepted.

Compartment Models

If the tissue drug concentrations and binding are known, physiologic pharmacokinetic models, which are based on actual tissues and their respective blood flow, describe the data realistically. Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay. On the other hand, tissue samples are often not available for human subjects, so most physiological models assume an average set of blood flow for individual subjects.

In contrast, because of the vast complexity of the body, drug kinetics in the body are frequently simplified to be represented by one or more tanks, or compartments, that communicate reversibly with each other. A compartment is not a real physiologic or anatomic region but is considered a tissue or group of tissues that have similar blood flow and drug affinity. Within each compartment, the drug is considered to be uniformly distributed. Mixing of the drug within a compartment is rapid and homogeneous and is considered to be “well stirred,” so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment. Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment. The model is an open system because drug can be eliminated from the system. Compartment models are based on linear assumptions using linear differential equations.

Mammillary Model

A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment. The mammillary model is the most common compartment model used in pharmacokinetics. The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment. In the one-compartment model, drug is both added to and eliminated from a central compartment. The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with drug. When an intravenous dose of drug is given, the drug enters directly into the central compartment. Elimination of drug occurs from the central compartment because the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

In a two-compartment model, drug can move between the central or plasma compartment to and
from the tissue compartment. Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues. In this model, the total amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment. Knowing the parameters of either the one- or two-compartment model, one can estimate the amount of drug left in the body and the amount of drug eliminated from the body at any time. The compartmental models are particularly useful when little information is known about the tissues.

Several types of compartment models are described in Fig. 1-6. The pharmacokinetic rate constants are represented by the letter $k$. Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue compartment. The drawing of models has three functions. The model (1) enables the pharmacokineticist to write differential equations to describe drug concentration changes in each compartment, (2) gives a visual representation of the rate processes, and (3) shows how many pharmacokinetic constants are necessary to describe the process adequately.

### Example

Two parameters are needed to describe model 1 (Fig. 1-6): the volume of the compartment and the elimination rate constant, $k$. In the case of model 4, the pharmacokinetic parameters consist of the volumes of compartments 1 and 2 and the rate constants—$k_a$, $k$, $k_{12}$, and $k_{21}$—for a total of six parameters.

In studying these models, it is important to know whether drug concentration data may be sampled directly from each compartment. For models 3 and 4 (Fig. 1-6), data concerning compartment 2 cannot be obtained easily because tissues are not easily sampled and may not contain homogeneous concentrations of drug. If the amount of drug absorbed and eliminated per unit time is obtained by sampling compartment 1, then the amount of drug contained in the tissue compartment 2 can be estimated mathematically. The appropriate mathematical equations for describing these models and evaluating the various pharmacokinetic parameters are given in subsequent chapters.

### Catenary Model

In pharmacokinetics, the mammillary model must be distinguished from another type of compartmental model called the catenary model. The catenary model consists of compartments joined to one another like the compartments of a train (Fig. 1-7). In contrast, the mammillary model consists of one or more compartments around a central compartment like...
satellites. Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

**Physiologic Pharmacokinetic Model (Flow Model)**

Physiologic pharmacokinetic models, also known as blood flow or perfusion models, are pharmacokinetic models based on known anatomic and physiologic data. The models describe the data kinetically, with the consideration that blood flow is responsible for distributing drug to various parts of the body. Uptake of drug into organs is determined by the binding of drug in these tissues. In contrast to an estimated tissue volume of distribution, the actual tissue volume is used. Because there are many tissue organs in the body, each tissue volume must be obtained and its drug concentration described. The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do. Unfortunately, much of the information required for adequately describing a physiologic pharmacokinetic model is experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how physiologic factors may change drug distribution from one animal species to another. Other major differences are described below.

First, no data fitting is required in the perfusion model. Drug concentrations in the various tissues are predicted by organ tissue size, blood flow, and experimentally determined drug tissue–blood ratios (ie, partition of drug between tissue and blood).

Second, blood flow, tissue size, and the drug tissue–blood ratios may vary due to certain pathophysiologic conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models.

Third, and most important of all, physiologically based pharmacokinetic models can be applied to several species, and, for some drugs, human data may be extrapolated. Extrapolation from animal data is not possible with the compartment models, because the volume of distribution in such models is a mathematical concept that does not relate simply to blood volume and blood flow. To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models. Tissue levels of some of these drugs cannot be predicted successfully with compartment models, although they generally describe blood levels well. An example of a perfusion model is shown in Fig. 1-8.

The number of tissue compartments in a perfusion model varies with the drug. Typically, the tissues or organs that have no drug penetration are excluded from consideration. Thus, such organs as the brain, the bones, and other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs. To describe

![Pharmacokinetic model of drug perfusion](image-url)

FIGURE 1-8 Pharmacokinetic model of drug perfusion. The $k_s$ represent kinetic constants: $k_e$ is the first-order rate constant for urinary drug excretion and $k_m$ is the rate constant for hepatic elimination. Each "box" represents a tissue compartment. Organs of major importance in drug absorption are considered separately, while other tissues are grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue). The size or mass of each tissue compartment is determined physiologically rather than by mathematical estimation. The concentration of drug in the tissue is determined by the ability of the tissue to accumulate drug as well as by the rate of blood perfusion to the tissue, represented by $Q$. 
each organ separately with a differential equation would make the model very complex and mathematically difficult. A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single compartment.

A perfusion model has been used successfully to describe the distribution of lidocaine in blood and various organs. In this case, organs such as lung, liver, brain, and muscle were individually described by differential equations, whereas other tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue), as shown in Fig. 1-8. Figure 1-9 shows that the blood concentration of lidocaine declines biexponentially and was well predicted by the physiologic model based on blood flow. The tissue lidocaine levels in the lung, muscle, and adipose and other organs are shown in Fig. 1-10. The model shows that adipose tissue accumulates drugs slowly because of low blood supply. In contrast, vascular tissues, like the lung, equilibrate rapidly with the blood and start to decline as soon as drug level in the blood starts to fall. The physiologic pharmacokinetic model provides a realistic means of modeling tissue drug levels. Unfortunately, the simulated tissue levels in Fig. 1-10 cannot be verified in humans because drug levels in tissues are not available. A criticism of physiologic pharmacokinetic models in general has been that there are fewer data points than parameters that one tries to fit. Consequently, the projected data are not well constrained.

The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data (Sawada et al, 1985). The mass of various body organs or tissues, extent of protein binding, drug metabolism capacity, and blood flow in humans and other species are often known or can be determined. Thus, physiologic and anatomic parameters can be used to predict the effects of drugs on humans from the effects on animals in cases where human experimentation is difficult or restricted.

**CHAPTER SUMMARY**

Drug product performance is the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable. Biopharmaceutics provides the scientific basis for drug product design and drug product performance by examining the interrelationship of the physical/chemical properties of the drug, the drug product in which the drug is given, and the route of administration on the rate and extent of
Chapter 1

systemic drug absorption. Pharmacokinetics is the science of the dynamics (kinetics) of drug absorption, distribution, and elimination (ie, excretion and metabolism), whereas clinical pharmacokinetics considers the applications of pharmacokinetics to drug therapy.

The quantitative measurement of drug concentrations in the plasma after dose administration is important to obtain relevant data of systemic drug exposure. The plasma drug concentration versus time profile provides the basic data from which various pharmacokinetic models can be developed that predict the time course of drug action, relates the drug concentration to the pharmacodynamic effect or adverse response, and enables the development of individualized therapeutic dosage regimens and new and novel drug delivery systems.

FIGURE 1-10  Measured and best fit predictions of CyA concentration in arterial blood and various organs/tissues in rat. Each plot and vertical bar represent the mean and standard deviation, respectively. Solid and dotted lines are the physiological based pharmacokinetic (PBPK) best fit predictions based on the parameters associated with the Linear or Nonlinear model, respectively.

(Reproduced with permission from Kawai R, Mathew D, Tanaka C, Rowland M: Physiologically Based Pharmacokinetics of Cyclosporine A: Extension to Tissue Distribution Kinetics in Rats and Scale-up to Human, JPET 287:457–468, 1998.)
LEARNING QUESTIONS

1. What is the significance of the plasma level–time curve? How does the curve relate to the pharmacologic activity of a drug?

2. What is the purpose of pharmacokinetic models?

3. Draw a diagram describing a three-compartment model with first-order absorption and drug elimination from compartment 1.

4. The pharmacokinetic model presented in Fig. 1-11 represents a drug that is eliminated by renal excretion, biliary excretion, and drug metabolism. The metabolite distribution is described by a one-compartment open model. The following questions pertain to Fig. 1-11.
   a. How many parameters are needed to describe the model if the drug is injected intravenously (ie, the rate of drug absorption may be neglected)?
   b. Which compartment(s) can be sampled?
   c. What would be the overall elimination rate constant for elimination of drug from compartment 1?
   d. Write an expression describing the rate of change of drug concentration in compartment 1 (\(\frac{dC_1}{dt}\)).

5. Give two reasons for the measurement of the plasma drug concentration, \(C_p\), assuming (a) the \(C_p\) relates directly to the pharmacodynamic activity of the drug and (b) the \(C_p\) does not relate to the pharmacodynamic activity of the drug.

6. Consider two biologic compartments separated by a biologic membrane. Drug A is found in compartment 1 and in compartment 2 in a concentration of \(c_1\) and \(c_2\), respectively.
   a. What possible conditions or situations would result in concentration \(c_1 > c_2\) at equilibrium?
   b. How would you experimentally demonstrate these conditions given above?
   c. Under what conditions would \(c_1 = c_2\) at equilibrium?
   d. The total amount of Drug A in each biologic compartment is \(A_1\) and \(A_2\), respectively. Describe a condition in which \(A_1 > A_2\), but \(c_1 = c_2\) at equilibrium.

   Include in your discussion, how the physicochemical properties of Drug A or the biologic properties of each compartment might influence equilibrium conditions.

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Chapter 1


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Mathematical Fundamentals in Pharmacokinetics

Chapter Objectives

► Solve algebraic equations that contain exponents and logarithms and transform numbers accurately as needed.
► Transform numbers accurately between 10^x, e^x, log, and ln and common pharmacokinetic units.
► Give the proper units to common pharmacokinetic terms such as t_{1/2}, clearance, volume, concentration, rate constants, and mass.
► Use the rectangular coordinate system (Cartesian coordinates) and semilog graphs to plot data and obtain the line of best fit.
► Calculate the area under the curve, k, k, slope, y intercept, and half-life from a graph.
► Differentiate between and define rates and order of reactions for zero- and first-order processes.

Because pharmacokinetics and biopharmaceutics have a strong mathematical basis, a solid foundation in mathematical principles in algebra, calculus, exponentials, logarithms, and unit analysis are critical for students in these disciplines. A self-exam is included in this chapter to provide a self-assessment of possible weaknesses in one’s basic math skills. Difficulties with questions in the self-exam indicate that a review of mathematical essentials is necessary. Mathematical fundamentals are summarized here for review purposes only. For a more complete discussion of fundamental principles, a suitable textbook in mathematics should be consulted.

MATH SELF-EXAM

1. What are the units for concentration, mass, and volume?
2. A drug solution has a concentration of 50 mg/mL. What amount of drug is contained within 20.5 mL of the solution? In 0.4 L? What volume of the solution will contain 30 mg of drug?
3. Convert the units in the above solution from mg/mL to g/L and μg/μL. If the molecular weight of the drug is 325 Da, what are the units in M?
4. If 20 mg of drug are added to a container of water and result in a concentration of 0.55 mg/L, what volume of water was in the container?
5. For the following equation:
   \[ y = 0.5x + 2 \]
   a. Sketch a plot of the equation.
   b. Describe the relevance of each part of this equation.
   c. If x = 0.6, what is y?
   d. If y = 4.1, what is x?
6. Solve the following equations for x:
   a. log x = 0.95
   b. e^x = 0.44
   c. ln x = 1.22
Students often ask why they should learn to calculate pharmacokinetic problems manually if software is available. Computer software is a tool that allows one to solve more complex pharmacokinetic problems rapidly, but efficient use requires a thorough understanding of the subject. Many different pharmacokinetic software packages are available that use different algorithms and underlying assumptions. The use of these software packages requires an understanding of the basic principles of pharmacokinetics. Thus, the practitioner must first understand the fundamentals of pharmacokinetics to properly use the software and interpret the program output.

In addition, the necessary pharmacokinetic software programs may not always be available in every practice situation. Some free pharmacokinetic software programs are available on the Internet, but these programs may not be validated for use in a clinical or research setting.

Calculation accuracy is important! In pharmacy, accurate dosage regimen calculations have critical importance, and errors can be extremely costly, either in terms of patient adverse reaction, death, or financial cost. In pharmaceutical manufacturing, all calculations are double checked so that each ingredient in the drug product is accurate. Double checking is a good manufacturing practice (GMP). Good habits can and should be developed to limit calculation errors. Whenever a calculation affecting drug dose is made, one should mentally approximate whether the answer is correct given the set of information. For example, for a given problem, consider whether the number in the answer has the correct magnitude and units; eg, if the correct answer should be between 100 and 200 mg, then answers such as 12.5 mg or 1250 mg have to be wrong.

The units for the answer to a problem should also be checked carefully; eg, if the expected answer is a concentration unit, then mg/L or μg/mL are acceptable; and units such as L or mg/h are definitely wrong. In addition, if available doses are available in mg dosage forms, and the calculated answer is in mg, a calculation error may have been made. Incorrect units may result from an incorrect substitution or the selection of an incorrect formula. In a pharmacokinetic calculation, the answer is correct only if both the number and the units are correct.
A common example of dose checking and calculation error is heparin. Hospital prescription orders of “heparin 1000u” are often miswritten as “heparin 10000u” by physicians. Better labeling, awareness, and checking by pharmacists are a great help to minimize serious dosing errors.

**Approximation**

Approximation is a useful process for checking whether the answer to a given set of calculations is probably correct. Approximation can be performed with pencil and paper and sometimes with pencil, graph paper, and ruler. The procedure is especially useful in a busy environment when answers must be checked quickly.

To estimate a series of computations, round the numbers and write the numbers using scientific notation. Then perform the series of calculations, remembering the laws of exponents. For example, estimate the answer to the following problem:

\[
\frac{58 \times 489}{2114 \times 0.04} = \frac{6 \times 10^5 \times 10^2}{2 \times 10^3 \times 4 \times 10^{-1}} = \frac{30 \times 10^3}{8 \times 10} = 400
\]

The precise answer to the above calculation is 335.4. Notice, the approximated answer should be somewhat less than 400, since \(30 \div 8\) is between 3 and 4.

For some pharmacokinetic problems, data, such as time versus drug concentration, may be plotted on either regular or semilog graph paper. The approximated answer to the problem may be obtained by inspection of the line that is fitted to all the data points. Graphical methods for solving pharmacokinetic problems are given later in this chapter.

**Calculators**

A handheld scientific calculator is essential for calculations. Most scientific calculators include exponential and logarithmic functions, both of which are frequently used in pharmacokinetics. Additional functions such as mean, standard deviation, and linear regression analysis are used to determine the half-life of drugs. Statistical parameters, such as correlation coefficient, are used to determine how well the model agrees with the observed data.

**Exponents and Logarithms**

**Exponents**

In the expression

\[ N = b^x \quad (2.1) \]

\(x\) is the exponent, \(b\) is the base, and \(N\) represents the number when \(b\) is raised to the \(x\)th power, ie, \(b^x\). For example,

\[ 1000 = 10^3 \]

where 3 is the exponent, 10 is the base, and \(10^3\) is the third power of the base, 10. The numeric value, \(N\) in Equation 2.1, is 1000. In this example, the reverse can be stated: that the log of \(N\) to the base 10 is 3 (ie, \(\log 1000 = 3\)). Thus, taking the log of the number \(N\) has the effect of “compressing” the number; some numbers are easier to handle when “compressed” or transformed to base 10. Transformation simplifies many mathematical operations.

**Laws of Exponents**

<table>
<thead>
<tr>
<th>Exponent Law</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a^x \cdot a^y = a^{x+y})</td>
<td>(10^2 \cdot 10^3 = 10^5)</td>
</tr>
<tr>
<td>((a^x)^y = a^{xy})</td>
<td>((10^2)^3 = 10^6)</td>
</tr>
<tr>
<td>(\frac{a^x}{a^y} = a^{x-y})</td>
<td>(\frac{10^5}{10^2} = 10^3)</td>
</tr>
<tr>
<td>(\frac{1}{a^x} = a^{-x})</td>
<td>(\frac{1}{10^5} = 10^{-3})</td>
</tr>
<tr>
<td>(\sqrt[3]{a} = a^{\frac{1}{3}})</td>
<td>(\sqrt[3]{10^2} = 10^{\frac{2}{3}})</td>
</tr>
</tbody>
</table>

**Logarithms**

The logarithm of a positive number \(N\) to a given base \(b\) is the exponent (or the power) \(x\) to which the base must be raised to equal the number \(N\). Therefore, if

\[ N = b^x \quad (2.2) \]

then

\[ \log_b N = x \quad (2.3) \]
For example, with common logarithms (log), or logarithms using base 10,

\[ 100 = 10^2 \]

\[ \log 100 = 2 \]

The number 100 is considered the **antilogarithm** of 2.

Natural logarithms (ln) use the base \( e \), whose value is 2.718282. To relate natural logarithms to common logarithms, the following equation is used:

\[ 2.303 \log N = \ln N \quad (2.4) \]

### Exponential Expression | Common Logarithmic (log) (base 10) Statement | Natural Log (ln) (base e) Statement
---|---|---
\( 10^3 = 1000 \) | \( \log 1000 = 3 \) | \( \ln 1000 = 6.91 \)
\( 10^2 = 100 \) | \( \log 100 = 2 \) | \( \ln 100 = 4.61 \)
\( 10^1 = 10 \) | \( \log 10 = 1 \) | \( \ln 10 = 2.30 \)
\( 10^0 = 1 \) | \( \log 1 = 0 \) | \( \ln 1 = 0 \)
\( 10^{-1} = 0.1 \) | \( \log 0.1 = -1 \) | \( \ln 0.1 = -2.30 \)
\( 10^{-2} = 0.01 \) | \( \log 0.01 = -2 \) | \( \ln 0.01 = -4.61 \)
\( 10^{-3} = 0.001 \) | \( \log 0.001 = -3 \) | \( \ln 0.001 = -6.91 \)

### Laws of Logarithms

\[ \log ab = \log a + \log b \]
\[ \log \frac{a}{b} = \log a - \log b \]
\[ \log a^x = x \log a \]
\[ -\log \frac{a}{b} = \log \frac{b}{a} \]

Of special interest is the following relationship:

\[ \ln e^x = -x \quad (2.5) \]

Equation 2.5 can be compared with the following example:

\[ \log 10^{-2} = -2 \]

A logarithm does not have units. A logarithm is dimensionless and is considered a real number. The logarithm of 1 is 0; the logarithm of a number less than 1 is a negative number, and the logarithm of a number greater than 1 is a positive number.

### PRACTICE PROBLEMS

Many calculators and computers have logarithmic and exponential functions. The following problems review methods for calculations involving logarithmic or exponential functions using a calculator. Earlier editions of this text demonstrate the use of logarithmic and exponential tables to perform these problems. Before starting any new calculations, be sure to clear the calculator of any previous numbers.

1. Find the log of 35.

**Solution**

Enter the number 35 into your calculator.
Press the LOG function key.
Answer = 1.5441
(For some calculators, the LOG function key is pressed first, followed by the number; the answer is obtained by pressing the = key.)
Notice that the correct answer for log 35 is the same as calculating the exponent of 10, which will equal 35 as shown below.

\[ 35 = 10^{1.5441} \]

Estimation—Since the number 35 is between 10 and 100 (ie, \( 10^1 \) and \( 10^2 \)), then the log of 35 must be between 1.0 and 2.0.

2. Find the log of 0.028.

**Estimation**—Since the number 0.028 is between \( 10^{-1} \) and \( 10^{-2} \), then the log of 0.028 must be between –1.0 and –2.0.

**Solution**

Use the same procedure as above.
Enter the number 0.028 into your calculator.
Press the LOG function key.
Answer = –1.553

3. Find the antilog of 0.028.

The process for finding an antilog is the reverse of finding a log. The antilog is the number that
corresponds to the logarithm, such that the antilog for 3 (in base 10) is 1000 (or 10^3). This problem is the inverse of Practice Problem 2, above. In this case, the calculation determines what the number is when 10 is raised to 0.028 (ie, 10^{0.028}).

Solution
The following methods may be used, depending on the type of calculator being used.

Method 1
If your calculator has a function key marked 10^x, then do the following:
Enter 0.028.
Press 10^x.
Answer = 1.0666

Method 2
Some calculators assume that the user knows that 10^x is the inverse of \log x. For this calculation:
Enter 0.028.
Press the key marked INV.
Then press the key marked LOG.
Answer = 1.0666

4. Evaluate \( e^{-1.3} \).

Solution
The following methods may be used, depending on the type of calculator being used.

Method 1
If your calculator has a function key marked \( e^x \), then do the following:
Enter 1.3.
Change the sign to minus by pressing the key marked \( \pm \).
Press \( e^x \).
Answer = 0.2725

Method 2
Some calculators assume that the user knows that \( e^x \) is the inverse of \( \ln x \). For this calculation:
Enter 1.3.
Change the sign to minus by pressing the key marked \( \pm \).
Press the key marked INV.
Then press the key marked LN.
Answer = 0.2725

5. Find the value of \( k \) in the following expression:
\[ 25 = 50e^{-4k} \]

Solution
\[ e^{-4k} = \frac{25}{50} = 0.50 \]
Take the natural logarithm, \( \ln \), for both sides of the equation:
\[ \ln e^{-4k} = \ln 0.50 \]
From Equation 2.5, \( \ln e^x = -x \). Therefore, \( \ln e^{-4k} = -4k \) and \( \ln 0.50 = -0.693 \).
(Calculator: Enter 0.5, then press the LN function key.)
\[ 4k = 0.693 \]
\[ k = \frac{-0.693}{-4} = 0.173 \]

6. A very common problem in pharmacokinetics is to evaluate an expression such as
\[ C_p = C_0e^{-kt} \]
For example, find the value of \( C_p \) in the following equation when \( t = 2 \):
\[ C_p = 35e^{-0.15t} \]

Solution
Using a calculator:
Enter 0.15.
Press \( \pm \) key = 0.15
Multiply by 2 = -0.30
Press \( e^x \) function key = 0.7408
Multiply by 35 = 25.93
\[ C_p = 35e^{-0.15t} = 35(0.7408) = 25.93 \]
Because \( e^{-x} = \frac{1}{e^x} \), as the value for \( x \) becomes larger, the value for \( e^{-x} \) becomes smaller.
Spreadsheets for Performing Calculations

Spreadsheet software, such as LOTUS 123, QUATRO PRO, and EXCEL, is available on many personal computers, including both the MAC and IBM-compatible PCs. These spreadsheets are composed of a grid as shown in Fig. B-2 of Appendix B. Detailed spreadsheet operation examples are found in Appendix B.

CALCULUS

Since pharmacokinetic models consider drugs in the body to be in a dynamic state, calculus is an important mathematic tool for analyzing drug movement quantitatively. Differential equations are used to relate the concentrations of drugs in various body organs over time. Integrated equations are frequently used to model the cumulative therapeutic or toxic responses of drugs in the body.

Differential Calculus

Differential calculus is a branch of calculus that involves finding the rate at which a variable quantity is changing. For example, a specific amount of drug $X$ is placed in a beaker of water to dissolve. The rate at which the drug dissolves is determined by the rate of drug diffusing away from the surface of the solid drug and is expressed by the Noyes-Whitney equation:

\[
\text{Dissolution rate} = \frac{dX}{dt} = \frac{DA}{l}(C_1 - C_2)
\]

where $d = \text{a very small change}$; $X = \text{drug } X$; $t = \text{time}$; $D = \text{diffusion coefficient}$; $A = \text{effective surface area of drug}$; $l = \text{length of diffusion layer}$; $C_1 = \text{surface concentration of drug in the diffusion layer}$; and $C_2 = \text{concentration of drug in the bulk solution}$.

The derivative $dX/dt$ may be interpreted as a change in $X$ (or a derivative of $X$) with respect to a change in $t$.

In pharmacokinetics, the amount or concentration of drug in the body is a variable quantity (dependent variable), and time is considered to be an independent variable. Thus, we consider the amount or concentration of drug to vary with respect to time.

Integral Calculus

Integration is the reverse of differentiation and is considered the summation of $f(x) \cdot dx$; the integral sign $\int$ implies summation. For example, given the function $y = ax$, plotted in Fig. 2-1, the integration is $\int ax \cdot dx$. Compare Fig. 2-1 to a second graph (Fig. 2-2), where the function $y = Ae^{-t}$, is commonly observed after an intravenous bolus drug injection. The integration process is actually a summing up of the small individual pieces under the graph. When $x$ is specified and is given boundaries from $a$ to $b$, then the

EXAMPLE

The concentration $C$ of a drug changes as a function of time $t$:

\[
C = f(t)
\]

Consider the following data:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Plasma Concentration of Drug C ($\mu$g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

The concentration of drug $C$ in the plasma is declining by $2 \mu$g/mL for each hour of time. The rate of change in the concentration of the drug with respect to time (ie, the derivative of $C$) may be expressed as

\[
\frac{dC}{dt} = 2 \mu$g/mL/h
\]

Here, $f(t)$ is a mathematical equation that describes how $C$ changes, expressed as

\[
C = 12 - 2t
\]
expression becomes a definite integral, i.e., the summing up of the area from \( x = a \) to \( x = b \).

A definite integral of a mathematical function is the sum of individual areas under the graph of that function. There are several reasonably accurate numerical methods for approximating an area. These methods can be programmed into a computer for rapid calculation. The trapezoidal rule is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the area under the curve (AUC).

For example, Fig. 2-2 shows a curve depicting the elimination of a drug from the plasma after a single intravenous injection. The drug plasma levels and the corresponding time intervals plotted in Fig. 2-2 are as follows:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Plasma Drug Level (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>38.9</td>
</tr>
<tr>
<td>1.0</td>
<td>30.3</td>
</tr>
<tr>
<td>2.0</td>
<td>18.4</td>
</tr>
<tr>
<td>3.0</td>
<td>11.1</td>
</tr>
<tr>
<td>4.0</td>
<td>6.77</td>
</tr>
<tr>
<td>5.0</td>
<td>4.10</td>
</tr>
</tbody>
</table>

The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

\[
[AUC]_t = \frac{C_n + C_{n-1}}{2} (t_n - t_{n-1})
\]  \hspace{1cm} (2.8)

where \([AUC]_t = \text{area under the curve}, \ t_n = \text{time of observation of drug concentration } C_n, \text{ and } t_{n-1} = \text{time of prior observation of drug concentration corresponding to } C_{n-1}.\)

To obtain the AUC from 1 to 4 hours in Fig. 2-2, each portion of this area must be summed. The AUC between 1 and 2 hours is calculated by proper substitution into Equation 2.8:

\[
[AUC]_1^2 = \frac{30.3 + 18.4}{2} (2 - 1) = 24.35 \, \mu g \, h/mL
\]

Similarly, the AUC between 2 and 3 hours is calculated as 14.75 \( \mu g \, h/mL \), and the AUC between 3 and 4 hours is calculated as 8.94 \( \mu g \, h/mL \). The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together.

\[
[AUC]_1^4 = [AUC]_1^2 + [AUC]_2^3 + [AUC]_3^4
\]

\[
= 24.35 + 14.75 + 8.94
\]

\[
= 48.04 \, \mu g \, hr/mL
\]

The total area under the plasma drug level–time curve from time zero to infinity (Fig. 2-2) is obtained...
by summation of each individual area between each pair of consecutive data points using the trapezoidal rule. The value on the y axis when time equals 0 is estimated by back extrapolation of the data points using a log linear plot (ie, log y vs x). The last plasma level time curve is extrapolated to \( t = \infty \). In this case the residual area \([\text{AUC}]_{t_n}^\infty\) is calculated as follows:

\[
[\text{AUC}]_{t_n}^\infty = \frac{C_{pm}}{k} \tag{2.9}
\]

where \( C_{pm} \) = last observed plasma concentration at \( t_n \) and \( k \) = slope obtained from the terminal portion of the curve.

The trapezoidal rule written in its full form to calculate the AUC from \( t = 0 \) to \( t = \infty \) is as follows:

\[
[\text{AUC}]_{t_n}^\infty = \sum [\text{AUC}]_{t_n}^{t_n} + \frac{C_{pm}}{k}
\]

This numerical method of obtaining the AUC is fairly accurate if sufficient data points are available. As the number of data points increases, the trapezoidal method of approximating the area becomes more accurate.

The trapezoidal rule assumes a linear or straight-line function between data points. If the data points are spaced widely, then the normal curvature of the line will cause a greater error in the area estimate.

**Frequently Asked Questions**

- **What are the units for logarithms?**
- **What is the difference between a common log and a natural log (ln)?**

**GRAPHS**

The construction of a curve or straight line by plotting observed or experimental data on a graph is an important method of visualizing relationships between variables. By general custom, the values of the independent variable (x) are placed on the horizontal line in a plane, or on the abscissa (x axis), whereas the values of the dependent variable are placed on the vertical line in the plane, or on the ordinate (y axis), as demonstrated in Fig. 2-3. The values are usually arranged so that they increase linearly or logarithmically from left to right and from bottom to top.

In pharmacokinetics, time is the independent variable and is plotted on the abscissa (x axis), whereas drug concentration is the dependent variable and is plotted on the ordinate (y axis).

Two types of graphs or graph paper are usually used in pharmacokinetics. These are Cartesian or rectangular coordinate (Fig. 2-4) and semilog graph or graph paper (Fig. 2-5).

Semilog paper is available with one, two, three, or more cycles per sheet, each cycle representing a 10-fold increase in the numbers, or a single log unit. This paper allows placement of the data at logarithmic intervals so that the numbers need not be converted to their corresponding log values prior to plotting on the graph. Similarly, when plotted using a computer program, one to three logarithmic cycles are generally plotted on a graph.

**Curve Fitting**

Fitting a curve to the points on a graph implies that there is some sort of relationship between the variables.
x and y, such as dose of drug versus pharmacologic effect (e.g., lowering of blood pressure). Moreover, when using curve fitting, the relationship is not confined to isolated points but is a continuous function of x and y. In many cases, a hypothesis is made concerning the relationship between the variables x and y. Then, an empirical equation is formed that best describes the hypothesis. This empirical equation must satisfactorily fit the experimental or observed data. If the relationship between x and y is linearly related, then the relationship between the two can be expressed as a straight line.

Physiologic variables are not always linearly related. However, the data may be arranged or transformed to express the relationship between the variables as a straight line. Straight lines are very useful for accurately predicting values for which there are no experimental observations. The general equation of a straight line is

\[ y = mx + b \tag{2.10} \]

where \( m = \) slope and \( b = y \) intercept. Equation 2.10 could yield any one of the graphs shown in Fig. 2-6, depending on the value of \( m \). The absolute magnitude of \( m \) gives some idea of the steepness of the curve. For example, as the value of \( m \) approaches 0, the line becomes more horizontal. As the absolute value of \( m \) becomes larger, the line slopes farther upward or downward, depending on whether \( m \) is positive or negative, respectively. For example, the equation

\[ y = -15x + 7 \]

indicates a slope of –15 and a y intercept at +7. The negative sign indicates that the curve is sloping downward from left to right, and the positive nature of the y intercept says that the line intercepts the y axis at +7, above the x axis.

**Determination of the Slope**

**Slope of a Straight Line on a Rectangular Coordinate Graph**

The value of the slope may be determined from any two points on the curve (Fig. 2-7). The slope of the curve is equal to \( \Delta y/\Delta x \), as shown in the following equation:

\[ \text{Slope} = \frac{y_2 - y_1}{x_2 - x_1} \tag{2.11} \]

The slope of the line plotted in Fig. 2-7 is

\[ m = \frac{2 - 3}{3 - 1} = -\frac{1}{2} \]

![Figure 2-6](image_url)
Chapter 2

Because the y intercept is equal to 3.5, the equation for the curve by substitution into Equation 2.10 is

\[ y = \frac{1}{2}x + 3.5 \]

Slope of a Straight Line on a Semilog Graph

When using semilog paper, the y values are plotted on a logarithmic scale without performing actual logarithmic conversions, whereas the corresponding x values are plotted on a linear scale. However, to determine the slope of a straight line on semilog paper graph, the y values must be converted to logarithms, as shown in the following equation:

\[ \text{Slope} = 2.3 \left( \frac{\log y_2 - \log y_1}{x_2 - x_1} \right) = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} \] (2.12)

The slope value is often used to calculate k, a constant that determines the rate of drug decline:

\[ k = 2.3 \text{ slope} \]

Least-Squares Method

Very often an empirical equation is calculated to show the relationship between two variables. Experimentally, data may be obtained that suggest a linear relationship between an independent variable x and a dependent variable y. The straight line that characterizes the relationship between the two variables is called a regression line. In many cases, the experimental data may have some error and therefore show a certain amount of scatter or deviations from linearity. The least-squares method is a useful procedure for obtaining the line of best fit through a set of data points by minimizing the deviation between the experimental and the theoretical line. In using this method, it is often assumed, for simplicity, that there is a linear relationship between the variables. If a linear line deviates substantially from the data, it may suggest the need for a nonlinear regression model, although several variables (multiple linear regression) may be involved. Nonlinear regression models are complex mathematical procedures that are best performed with a computer program (see Appendix B).

When the equation of a linear model is examined, the dependent variables can be expressed as the sum of products of the independent variables and parameters. In nonlinear models, at least one of the parameters appears as other than a coefficient. For example,

- Linear model: \( y = ax, y = ax + bx + cx^2 \),
- Nonlinear model: \( y = ax/(b + cx), y = 10e^{-3x} \)

The second nonlinear example as written is nonlinear, but may be transformed to a linear equation by taking the natural log on both sides:

\[ \ln y = -3x + \ln 10 \]

Problems of Fitting Points to a Graph

When x and y data points are plotted on a graph, a relationship between the x and y variables is sought. Linear relationships are useful for predicting values for the dependent variable y, given values for the independent variable x.

The linear regression calculation using the least-squares method is used for calculation of a straight line through a given set of points. However, it is important to realize that, when using this method, one has already assumed that the data points are related linearly. Indeed, for three points, this linear relationship may not always be true. As shown in Fig. 2-8, Riggs (1963) calculated three different curves that fit the data accurately. Generally, one should consider the law of parsimony, which broadly means “keep it simple”;
that is, if a choice between two hypotheses is available, choose the more simple relationship.

If a linear relationship exists between the $x$ and $y$ variables, one must be careful as to the estimated value for the dependent variable $y$, assuming a value for the independent variable $x$. Interpolation, which means filling the gap between the observed data on a graph, is usually safe and assumes that the trend between the observed data points is consistent and predictable. In contrast, the process of extrapolation means predicting new data beyond the observed data, and assumes that the same trend obtained between two data points will extend in either direction beyond the last observed data points. The use of extrapolation may be erroneous if the regression line no longer follows the same trend beyond the measured points.

**Determination of Order**

Graphical representation of experimental data provides a visual relationship between the $x$ values (generally time) and the $y$ axis (generally drug concentrations). Much can be learned by inspecting the line that connects the data points on a graph. The relationship between the $x$ and $y$ data will determine the order of the process, data quality, basic kinetics, number of outliers, and provide the basis for an underlying pharmacokinetic model. To determine the order of reaction, first plot the data on a rectangular graph. If the data appear to be a curve rather than a straight line, the reaction rate for the data is non-zero order. In this case, plot the data on a semilog graph. If the data now appear to form a straight line with good correlation using linear regression, then the data likely follow first-order kinetics. This simple graph interpretation is true for one-compartment, IV bolus (Chapter 3). Curves that deviate from this format are discussed in other chapters in terms of route of administration and pharmacokinetic model.

**PRACTICE PROBLEMS**

1. Plot the following data and obtain the equation for the line that best fits the data by (a) using a ruler and (b) using the method of least squares.

<table>
<thead>
<tr>
<th>$x$ (mg)</th>
<th>$y$ (hour)</th>
<th>$x$ (mg)</th>
<th>$y$ (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1</td>
<td>5</td>
<td>15.3</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>6</td>
<td>17.9</td>
</tr>
<tr>
<td>3</td>
<td>8.7</td>
<td>7</td>
<td>22.0</td>
</tr>
<tr>
<td>4</td>
<td>12.9</td>
<td>8</td>
<td>23.0</td>
</tr>
</tbody>
</table>

**Solution**

**Ruler**

Place a ruler or a straight edge over the data points and draw the best line that can be observed. Take any two points and determine the slope by the slope formula given in Equation 2.11 and the $y$ intercept. This method can give a reasonably quick approximation if there is very little scatter in the data.
b. Least-Squares Method

In the least-squares method the slope \( m \) and the \( y \) intercept \( b \) (Equation 2.13) are calculated so that the average sum of the deviations squared is minimized. The deviation, \( d \), is defined by

\[ b + mx - y = d \]  

(2.13)

If there are no deviations from linearity, then \( d = 0 \) and the exact form of Equation 2.13 is as follows:

\[ b + mx - y = 0 \]

To find the slope, \( m \), and the intercept, \( b \), the following equations are used:

\[ m = \frac{\sum(x)\sum(y) - n\sum(xy)}{[\sum(x)]^2 - n\sum(x^2)} \]  

(2.14)

\[ b = \frac{\sum(x)\sum(xy) - \sum(x^2)\sum y}{[\sum(x)]^2 - n\sum(x^2)} \]  

(2.15)

where \( n \) is the number of data points.

Using the data above, tabulate values for \( x \), \( y \), \( x^2 \), and \( xy \) as shown below:

<table>
<thead>
<tr>
<th>( x )</th>
<th>( y )</th>
<th>( x^2 )</th>
<th>( xy )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>4</td>
<td>12.0</td>
</tr>
<tr>
<td>3</td>
<td>8.7</td>
<td>9</td>
<td>26.1</td>
</tr>
<tr>
<td>4</td>
<td>12.9</td>
<td>16</td>
<td>51.6</td>
</tr>
<tr>
<td>5</td>
<td>15.3</td>
<td>25</td>
<td>76.5</td>
</tr>
<tr>
<td>6</td>
<td>17.9</td>
<td>36</td>
<td>107.4</td>
</tr>
<tr>
<td>7</td>
<td>22.0</td>
<td>49</td>
<td>154.0</td>
</tr>
<tr>
<td>8</td>
<td>23.0</td>
<td>64</td>
<td>184.0</td>
</tr>
<tr>
<td>( \Sigma x = 36 )</td>
<td>( \Sigma y = 108.9 )</td>
<td>( \Sigma x^2 = 204 )</td>
<td>( \Sigma xy = 614.7 )</td>
</tr>
</tbody>
</table>

Now substitute the values into Equations 2.14 and 2.15.

\[
\begin{align*}
 b &= \frac{(36)(614.7) - (204)(108.9)}{(36)^2 - (8)(204)} = 0.257 \text{ mg} \\
m &= \frac{(36)(108.9) - (8)(614.7)}{(36)^2 - (8)(204)} = 2.97 \text{ mg/h}
\end{align*}
\]

Therefore, the linear equation that best fits the data is

\[ y = 2.97x + 0.257 \]

Although an equation for a straight line is obtained by the least-squares procedure, the reliability of the values should be ascertained. A correlation coefficient, \( r \), is a useful statistical term that indicates the relationship of the \( x \), \( y \) data to a straight line. For a perfect linear relationship between \( x \) and \( y \), \( r = +1 \) if the slope is ascending and \( -1 \) if the slope is descending. If \( r = 0 \), then no linear relationship exists between \( x \) and \( y \). Usually, \( r \geq 0.95 \) demonstrates good evidence or a strong correlation that there is a linear relationship between \( x \) and \( y \).

2. Determination of slope can be carried out using a calculator. Many calculators have a statistical linear regression program to determine the slope of the regression line and the coefficient of correlation. The calculator must be cleared and the statistical routine initiated. For regular linear regression, the data may be entered directly in pairs as follows:

a. Linear Regression

<table>
<thead>
<tr>
<th>Enter Time</th>
<th>Enter Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
</tbody>
</table>

In this case, the slope should be 10 if linear regression is performed correctly, and the process is zero order. This slope value should be close to the slope determined by graphic method on regular graph paper.
b. Log Linear Regression

In this case, the data below are not a linear relationship but can be transformed (take the log of concentration) to make the data linear. Use the same linear regression program above, except, each time after concentration is entered, press LOG as shown below:

<table>
<thead>
<tr>
<th>Enter Time</th>
<th>Enter Concentration</th>
<th>Key Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>LOG</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>LOG</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>LOG</td>
</tr>
</tbody>
</table>

The slope obtained should approximate the value determined by graphic method on the semilog paper. The slope value is –0.151.

If the LN key is pressed each time instead of LOG in all the steps above, the slope will be –0.346, or equal to –\(k\), the elimination constant. This is a shortcut method sometimes used to determine \(k\) of a first-order process. The regression involves regressing \(\ln C\) versus time directly, ie, \(\ln C = -kt + \text{intercept}\), the slope \(m\) is –\(k\) (see later section of this chapter).

**UNITS IN PHARMACOKINETICS**

For an equation to be valid, the units or dimensions must be constant on both sides of the equation. Many different units are used in pharmacokinetics, as listed in Table 2-1. For an accurate equation, both the integers and the units must balance. For example, a common expression for total body clearance is

\[Cl_T = kV_d\] (2.16)

After insertion of the proper units for each term in the above equation from Table 2-1,

\[\text{mL/h} = \frac{1}{h} \text{mL} \]

Thus, the above equation is valid, as shown by the equality mL/h = mL/h.

An important rule in using equations with different units is that the units may be added or subtracted as long as they are alike, but divided or multiplied if they are different. When in doubt, check the equation by inserting the proper units. For example,

\[\text{AUC} = \frac{FD_c}{kV_d} = \text{concentration \times time}\]

\[\frac{\mu g}{mL \cdot h} = \frac{1}{h \cdot \text{L}} \Rightarrow \frac{\mu g}{h \cdot \text{mL}}\] (2.17)

Certain terms have no units. These terms include logarithms and ratios. Percent may have no units and is expressed mathematically as a decimal between 0 and 1 or as 0% to 100%, respectively. On occasion, percent may indicate mass/volume, volume/volume, or mass/mass. Table 2-1 lists common pharmacokinetic parameters with their symbols and units.

A constant is often inserted in an equation to quantify the relationship of the dependent variable to the independent variable. For example, Fick’s law of diffusion relates the rate of drug diffusion, \(dQ/dt\), to the change in drug concentration, \(C\), the surface area of the membrane, \(A\), and the thickness of the membrane, \(h\). In order to make this relationship an equation, a diffusion constant \(D\) is inserted:

\[\frac{dQ}{dt} = \frac{DA}{h} \times \Delta C\] (2.18)

To obtain the proper units for \(D\), the units for each of the other terms must be inserted:

\[\frac{\mu g}{h} = \frac{D(\text{cm}^2)}{\text{cm}} \times \frac{\text{mg}}{\text{cm}^2}\]

\[D = \text{cm}^2/h\]

The diffusion constant \(D\) must have the units of area/time or cm\(^2\)/h if the rate of diffusion is in mg/h.

Graphs should always have the axes (abscissa and ordinate) properly labeled with units. For example, in Fig. 2-7 the amount of drug on the ordinate (y axis)
Chapter 2

is given in milligrams and the time on the abscissa (x axis) is given in hours. The equation that best fits the points on this curve is the equation for a straight line, or \( y = mx + b \). Because the slope \( m = \Delta y/\Delta x \), the units for the slope should be milligrams per hour (mg/h). Similarly, the units for the y intercept \( b \) should be the same units as those for \( y \), namely, milligrams (mg).

### MEASUREMENT AND USE OF SIGNIFICANT FIGURES

Every measurement is performed within a certain degree of accuracy, which is limited by the instrument used for the measurement. For example, the weight of freight on a truck may be measured accurately to the nearest 0.5 kg, whereas the mass of drug in a tablet may be measured to 0.001 g (1 mg). Measuring the weight of freight on a truck to the nearest milligram is not necessary and would require a very costly balance or scale to detect a change in a milligram quantity.

**Significant figures** are the number of accurate digits in a measurement. If a balance measures the mass of a drug to the nearest milligram, measurements containing digits representing less than 1 mg are inaccurate. For example, in reading the weight or mass of a drug of 123.8 mg from this balance, the 0.8 mg is only approximate; the number is therefore rounded to 124 mg and reported as the observed mass.

### TABLE 2-1 Common Units Used in Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>( \frac{dD}{dt} )</td>
<td>Mass/Time</td>
<td>mg/h</td>
</tr>
<tr>
<td>Zero-order rate constant</td>
<td>( k_0 )</td>
<td>Concentration/Time</td>
<td>( \mu g/mL \ h )</td>
</tr>
<tr>
<td>First-order rate constant</td>
<td>( k )</td>
<td>( \frac{1}{\text{Time}} )</td>
<td>1/h or h(^{-1})</td>
</tr>
<tr>
<td>Drug dose</td>
<td>( D_0 )</td>
<td>Mass</td>
<td>mg</td>
</tr>
<tr>
<td>Concentration</td>
<td>( C )</td>
<td>Mass/Volume</td>
<td>( \mu g/mL )</td>
</tr>
<tr>
<td>Plasma drug concentration</td>
<td>( C_p )</td>
<td>Drug/Volume</td>
<td>( \mu g/mL )</td>
</tr>
<tr>
<td>Volume</td>
<td>( V )</td>
<td>Volume</td>
<td>mL or L</td>
</tr>
<tr>
<td>Area under the curve</td>
<td>AUC</td>
<td>Concentration \times time</td>
<td>( \mu g \ h/mL )</td>
</tr>
<tr>
<td>Fraction of drug absorbed</td>
<td>( F )</td>
<td>No units</td>
<td>0 to 1</td>
</tr>
<tr>
<td>Clearance</td>
<td>( Cl )</td>
<td>Volume/Time</td>
<td>mL/h</td>
</tr>
<tr>
<td>Half-life</td>
<td>( t_{1/2} )</td>
<td>Time</td>
<td>h</td>
</tr>
</tbody>
</table>
For practical calculation purposes, all figures may be used until the final number (answer) is obtained. However, the answer should retain only the number of significant figures in the least accurate initial measurement.

**UNITS FOR EXPRESSING BLOOD CONCENTRATIONS**

Various units have been used in pharmacology, toxicology, and the clinical laboratory to express drug concentrations in blood, plasma, or serum. Drug concentrations or drug levels should be expressed as mass/volume. The expressions mcg/mL, μg/mL, and mg/L are equivalent and are commonly reported in the literature. Drug concentrations may also be reported as mg% or mg/dL, both of which indicate milligrams of drug per 100 mL (deciliter). Two older expressions for drug concentration occasionally used in veterinary medicine are the terms ppm and ppb, which indicate the number of parts of drug per million parts of blood (ppm) or per billion parts of blood (ppb), respectively. One ppm is equivalent to 1.0 μg/mL. The accurate interconversion of units is often necessary to prevent confusion and misinterpretation.

**STATISTICS**

All measurements have some degree of error. An error is the difference between the true or absolute value and the observed value. Errors in measurement may be determinate (constant) or indeterminate (random, accidental). Determinate errors may be minimized in analytical procedures by using properly calibrated instrumentation, standardized chemicals, and appropriate blanks and control samples. Indeterminate errors are random and occur due to chance. For practical purposes, several measurements of a given sample are usually performed, and the result averaged. The mean ± SD is often reported. SD or standard deviation (see Appendix A) is a statistical way of expressing the spread between the individual measurements from the mean. A small SD relative to the mean value is indicative of good consistency and reproducibility of the measurements. A large SD indicates poor consistency and data fluctuations. Frequently, the variability of the measurements may be expressed as RSD or relative standard deviation, which is calculated as the SD divided as the mean of the data. RSD allows variability to be expressed on a percent basis and is useful in comparing the variability of two sets of measurements when the means are different.

In measurements involving a single subject or sample, only measuring error is involved. On the other hand, when two or more samples or subjects in a group are measured, there is usually variation due to individual differences. For example, the weight of each student in a class is likely different from that of the others because of individual physical differences such as height and sex. Therefore, in determining the weight of a group of students, we deal with variations due to biologic differences as well as weighing errors. A major error in group measurement is sampling error, an error due to nonuniform sampling. Sampling is essential because the measurement of all members in the group is not practical.

We use statistics to obtain a valid interpretation of the experimental data. Statistics is the logical use of mathematics, which includes (1) experimental design, (2) collection of data, (3) analysis of data, (4) interpretation of data, and (5) hypothesis testing. A more complete discussion of statistics is found in Appendix A.

**Probability Concept and Reaction Order**

Consider two molecules D and E bouncing around in an empty bottle. There is a fixed chance molecule D may collide with molecule E depending on how big the bottle (volume) is. If we now add nine more D molecules into the bottle, there will be 10 “D molecules.” The chance of a D molecule colliding with an E molecule is greatly increased.

If D is a drug substrate molecule and E is the enzyme molecule, we now realize a biotransformation reaction may occur during the collision. The example illustrates that the metabolic reaction occurring is related to the “concentration” of E molecules.

If there are no E molecules in the above bottle, and if we now postulate that the bottle has a hole, the rate of a given molecule bounces around and exits
the bottle via the hole is “concentration” dependent. For example, if drug molecule $D$ is injected into the body, how long will it reside there before it exits? Probability or probability density function (Chapter 22) will be introduced to describe the rate of drug entering and exiting the body.

**PRACTICAL FOCUS**

In pharmacokinetics and therapeutics, plasma or tissue samples are often monitored to determine if a prescribed dose needs to be adjusted. Comparisons of literature data from several medical centers are often made. The pharmacist should be familiar with all units involving dosing and be able to convert easily between units. Some physicians prescribe a drug dose based on body weight, whereas others prefer the body surface area method. Significant differences in plasma drug concentrations may result if the dose is calculated based on a different method. Drug concentrations may also be different if the dose is injected rapidly versus infused over a period of time. Table 2-2 lists some of the common methods of dosing.

Most potent drugs are dosed precisely for the individual patient, and the body weight of the patient should be known. For example, theophylline is dosed at 5 mg/kg. Since the body weight (BW) of individuals may vary with age, sex, disease, and nutritional state, an individualized dose based on body weight will more accurately reflect the appropriate therapy needed for the patient. For drugs with a narrow therapeutic index and potential for side effects, dosing based on body surface is common. During chemotherapy with antitumor drugs, many drugs are dosed according to the body surface area (BSA) of the patient. The body surface area may be determined from the weight of the patient using the empirical equation

$$BSA = \left(\frac{BW}{70 \text{ kg}}\right)^{0.73} \times 1.73 \text{ m}^2$$

where BSA = body surface area in m$^2$, and BW = body weight in kg. Some common units and conversions used in pharmacokinetics and toxicology are listed in Table 2-3.

<table>
<thead>
<tr>
<th>Table 2-2</th>
<th>Dosing Unit Based on Body Weight or Body Surface Area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method</strong></td>
<td><strong>Oral Drug Unit</strong></td>
</tr>
<tr>
<td>General</td>
<td>mg</td>
</tr>
<tr>
<td>BW</td>
<td>mg/kg</td>
</tr>
<tr>
<td>BSA</td>
<td>mg/1.73 m$^2$</td>
</tr>
</tbody>
</table>

*BW, body weight; BSA, body surface area.

<table>
<thead>
<tr>
<th>Table 2-3</th>
<th>Pharmacokinetic Units and Conversions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Units in Volume</strong></td>
<td><strong>Volume (Based on Body Weight)</strong></td>
</tr>
<tr>
<td>mL</td>
<td>mL/kg</td>
</tr>
<tr>
<td>dL</td>
<td>dL/kg</td>
</tr>
<tr>
<td>L</td>
<td>L/kg</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td><strong>Weight Conversion</strong></td>
</tr>
<tr>
<td>g/L</td>
<td>1 kg = 1000 g</td>
</tr>
<tr>
<td>mg/L</td>
<td>1 g = 1000 mg</td>
</tr>
<tr>
<td>mg/dL</td>
<td>1 mg = 1000 μg</td>
</tr>
<tr>
<td>mg/mL</td>
<td>1 μg = 1000 ng</td>
</tr>
<tr>
<td>ng/mL</td>
<td>1 ng = 1000 pg</td>
</tr>
<tr>
<td>pg/mL</td>
<td></td>
</tr>
</tbody>
</table>

**Examples of Concentration Conversion Used in Toxicology and Therapeutics**

- $1 \text{ mg/}% = 1 \text{ mg/dL}$
- $1 \text{ mg/L} = 1 \text{ μg/mL}$
- $1 \text{ μg/L} = 1 \text{ ng/mL}$
- $1 \text{ ng/L} = 1 \text{ pg/mL}$
**EXAMPLE**

The rate of ethanol elimination in four alcoholics undergoing detoxification was reported to be 17 to 33 mg/dL/h (Jones, 1993). (1) What is the rate of elimination in μg/mL/h? (2) The peak blood concentration in one subject (SP) is 90 μg/dL. What is his peak blood concentration in μg/mL? (3) To which category would SP belong according to the following classification for blood alcohol (where values are in mg%)?

- a. >0.55 mg%—fatal
- b. 0.50–0.55 mg%—dead drunk
- c. 0.10–0.50 mg%—illegal
- d. 0.05–0.10 mg%—questionable
- e. <0.05 mg%—safe

**Solution**

1. 17 μg/dL/h = 17,000 μg/100 mL/h = 170 μg/mL/h
   33 μg/dL/h = 33,000 μg/100 mL/h = 330 μg/mL/h
2. 90 μg/dL = 90 μg/100 mL = 0.9 μg/mL
3. 90 mg/dL = 0.090 mg/100 dL = 0.090 mg%
   Subject SP is questionable.

**PRACTICE PROBLEM**

The volume of distribution of theophylline is 0.7 L/kg. In most patients, the optimal benefits of theophylline therapy are seen at serum concentration of >10 mg/L; setting a plasma drug concentration of 5 mg/L lower therapeutic limit may result in reduced clinical efficacy (Eder and Bryan, 1996). (1) What is the volume of distribution in a 20-year-old male patient weighing 70 kg? (2) What is the total dose for the patient if he is dosed at 5 mg/kg?

**Solution**

1. (5 mg/L is an alternative way to express 5 μg/mL)
   - Volume of distribution of patient = 0.7 L/kg × 70 kg = 49 L
2. Dose for patient = 5 mg/kg × 70 kg = 350 mg

**RATES AND ORDERS OF REACTIONS**

**Rate**

The rate of a chemical reaction of process is the velocity with which the reaction occurs. Consider the following chemical reaction:

\[ \text{drug } A \rightarrow \text{drug } B \]

If the amount of drug \( A \) is decreasing with respect to time (ie, the reaction is going in a forward direction), then the rate of this reaction can be expressed as

\[ \frac{-dA}{dt} \]

Since the amount of drug \( B \) is increasing with respect to time, the rate of the reaction can also be expressed as

\[ \frac{+dB}{dt} \]

Usually only the parent (or pharmacologically active) drug is measured experimentally. The metabolites of the drug or the products of the decomposition of the drug may not be known or may be very difficult to quantitate. The rate of a reaction is determined experimentally by measuring the disappearance of drug \( A \) at given time intervals.

**Rate Constant**

The order of a reaction refers to the way in which the concentration of drug or reactants influences the rate of a chemical reaction or process.

**Zero-Order Reactions**

If the amount of drug \( A \) is decreasing at a constant time interval \( t \), then the rate of disappearance of drug \( A \) is expressed as

\[ \frac{dA}{dt} = -k_0 \quad (2.19) \]

The term \( k_0 \) is the zero-order rate constant and is expressed in units of mass/time (eg, mg/min).
Integration of Equation 2.19 yields the following expression:

\[ A = -k_0 t + A_0 \]  \hspace{1cm} (2.20)

where \( A_0 \) is the amount of drug at \( t = 0 \). Based on this expression (Equation 2.20), a graph of \( A \) versus \( t \) yields a straight line (Fig. 2-9). The \( y \) intercept is equal to \( A_0 \), and the slope of the line is equal to \( k_0 \).

Equation 2.20 may be expressed in terms of drug concentration, which can be measured directly.

\[ C = -k_0 t + C_0 \]  \hspace{1cm} (2.21)

\( C_0 \) is the drug concentration at time 0, \( C \) is the drug concentration at time \( t \), and \( k_0 \) is the zero-order decomposition constant.

**EXAMPLE**

A pharmacist weighs exactly 10 g of a drug and dissolves it in 100 mL of water. The solution is kept at room temperature, and samples are removed periodically and assayed for the drug. The pharmacist obtains the following data:

<table>
<thead>
<tr>
<th>Drug Concentration (mg/mL)</th>
<th>Time (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>70</td>
<td>12</td>
</tr>
</tbody>
</table>

From these data, a graph constructed by plotting the concentration of drug versus time will yield a straight line. Therefore, the rate of decline in drug concentration is of zero order.

The zero-order rate constant \( k_0 \) may be obtained from the slope of the line or by proper substitution into Equation 2.21.

If

\[ C_0 = \text{concentration of 100 mg/mL at } t = 0 \]

and

\[ C = \text{concentration of 90 mg/mL at } t = 4 \text{ hour} \]

then

\[ 90 = -k_0(4) + 100 \]

and

\[ k_0 = 2.5 \text{ mg/mL h} \]

Careful examination of the data will also show that the concentration of drug declines 5 mg/mL for each 2-hour interval. Therefore, the zero-order rate constant may be obtained by dividing 5 mg/mL by 2 hours:

\[ k_0 = \frac{5 \text{ mg/mL}}{2 \text{ h}} = 2.5 \text{ mg/mL h} \]
In addition to drug degradation, zero-order rate processes are important for saturable processes in the body including drug binding to macromolecules, formation of drug-enzyme complexes, and carrier-mediated transport. In fact, zero-order kinetics also has the potential to occur any time a drug is interacting with a protein molecule for transport or metabolism. For example, amino acid transporters in the gut, such as p-glycoprotein (P-gp) (see Chapter 13) are involved in transport of drugs such as methyldopa into the plasma. When these transporters become saturated, drug absorption becomes zero order. Similarly, metabolism of drugs can become nonlinear when metabolic enzymes become saturated and rates of metabolism become zero order.

First-Order Reactions

If the amount of drug $A$ is decreasing at a rate that is proportional to the amount of drug $A$ remaining, then the rate of disappearance of drug $A$ is expressed as

$$\frac{dA}{dt} = -kA$$  \hspace{1cm} (2.22)

where $k$ is the first-order rate constant and is expressed in units of time$^{-1}$ (eg, h$^{-1}$). Integration of Equation 2.22 yields the following expression:

$$\ln A = -kt + \ln A_0$$  \hspace{1cm} (2.23)

Equation 2.23 may also be expressed as

$$A = A_0 e^{-kt}$$  \hspace{1cm} (2.24)

Because $\ln = 2.3 \log$, Equation 2.23 becomes

$$\log A = \frac{-kt}{2.3} + \log A_0$$  \hspace{1cm} (2.25)

When drug decomposition involves a solution, starting with initial concentration $C_0$, it is often convenient to express the rate of change in drug decomposition, $dC/dt$, in terms of drug concentration, $C$, rather than the amount because drug concentration is assayed. Hence,

$$\frac{dC}{dt} = -kC$$  \hspace{1cm} (2.26)

$$\ln C = -kt + \ln C_0$$  \hspace{1cm} (2.27)

Equation 2.27 may be expressed as

$$C = C_0 e^{-kt}$$  \hspace{1cm} (2.28)

Because $\ln = 2.3 \log$, Equation 2.27 becomes

$$\log C = \frac{-kt}{2.3} + \log C_0$$  \hspace{1cm} (2.29)

According to Equation 2.25, a graph of $\log A$ versus $t$ will yield a straight line (Fig. 2-10), the $y$ intercept will be $\log A_0$, and the slope of the line will be $-k/2.3$ (Fig. 2-10). Similarly, a graph of $\log C$ versus $t$ will yield a straight line according to Equation 2.29. The $y$ intercept will be $\log C_0$, and the slope of the line will be $-k/2.3$. For convenience, $C$ versus $t$ may be plotted on semilog paper without the need to convert $C$ to $\log C$. An example is shown in Fig. 2-11.

Zero versus First-Order Processes

For zero-order kinetics, the rate and rate constant are the same and have the same units, concentration/time or mass/time. For first-order kinetics, rate and
rate constant are different and have different units. The rate constant is $k$ and has units of reciprocal time ($1/t$) or time$^{-1}$. A first-order rate is $-kC$ and has units of concentration/time or mass/time. Note in the case of first-order processes, the rate is concentration or mass dependent; whereas, in zero-order processes, rate is independent of concentration or mass. If the time course of the first-order rate process is considered, then the rate is changing since the concentration is changing, but not the rate constant. In contrast, the rate for a zero-order rate process is constant for the entire time (Table 2-4). Drug decomposition can be zero order, first order, and on occasion demonstrate a higher-order kinetic process. Most kinetic processes in the body are first order in nature, including drug transport, clearance, and metabolism. In the case of saturable rate processes, the reaction order can change from a first-order rate to a zero order if kinetic process becomes saturated.

**Half-Life**

Half-life ($t_{1/2}$) expresses the period of time required for the amount or concentration of a drug to decrease by one-half.

**First-Order Half-Life**

The $t_{1/2}$ for a first-order reaction may be found by means of the following equation:

$$ t_{1/2} = \frac{0.693}{k} \quad (2.30) $$

<table>
<thead>
<tr>
<th>Equation</th>
<th>Zero-Order Reaction</th>
<th>First-Order Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate constant—units</td>
<td>$(mg/L)/h$</td>
<td>$1/h$</td>
</tr>
<tr>
<td>Half-life, $t_{1/2}$ (units = time)</td>
<td>$t_{1/2} = 0.5C/k_0$ (not constant)</td>
<td>$t_{1/2} = 0.693/k$ (constant)</td>
</tr>
<tr>
<td>Effect of time on rate</td>
<td>Zero-order rate is constant with respect to time</td>
<td>First-order rate will change with respect to time as concentration changes</td>
</tr>
<tr>
<td>Effect of time on rate constant</td>
<td>Rate constant with respect to time changes as the concentration changes</td>
<td>Rate constant remains constant with respect to time</td>
</tr>
<tr>
<td>Drug concentrations versus time—plotted on rectangular coordinates</td>
<td>Drug concentrations decline linearly for a zero-order rate process</td>
<td>Drug concentrations decline nonlinearly for a first-order rate process</td>
</tr>
<tr>
<td>Drug concentrations versus time—plotted on a semilogarithmic graph</td>
<td>Drug concentrations decline nonlinearly for a zero-order rate process</td>
<td>Drug concentrations decline linearly for a single first-order rate process</td>
</tr>
</tbody>
</table>

![Figure 2-11](image-url) This graph demonstrates the constancy of the $t_{1/2}$ in a first-order reaction.
It is apparent from this equation that, for a first-order reaction, $t_{1/2}$ is a constant. No matter what the initial amount or concentration of drug is, the time required for the amount to decrease by one-half is a constant (Fig. 2-11).

**Zero-Order Half-Life**

In contrast to the first-order $t_{1/2}$, the $t_{1/2}$ for a zero-order process is not constant. The zero-order $t_{1/2}$ is proportional to the initial amount or concentration of the drug and is inversely proportional to the zero-order rate constant $k_0$:

$$t_{1/2} = \frac{0.5A_0}{k_0} \quad (2.31)$$

Because the $t_{1/2}$ changes as drug concentrations decline, the zero-order $t_{1/2}$ has little practical value.

**EXAMPLE**

A pharmacist dissolves exactly 10 g of a drug into 100 mL of water. The solution is kept at room temperature, and samples are removed periodically and assayed for the drug. The pharmacist obtains the following data:

<table>
<thead>
<tr>
<th>Drug Concentration (mg/mL)</th>
<th>Time (hour)</th>
<th>Log Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.00</td>
<td>0</td>
<td>2.00</td>
</tr>
<tr>
<td>50.00</td>
<td>4</td>
<td>1.70</td>
</tr>
<tr>
<td>25.00</td>
<td>8</td>
<td>1.40</td>
</tr>
<tr>
<td>12.50</td>
<td>12</td>
<td>1.10</td>
</tr>
<tr>
<td>6.25</td>
<td>16</td>
<td>0.80</td>
</tr>
<tr>
<td>3.13</td>
<td>20</td>
<td>0.50</td>
</tr>
<tr>
<td>1.56</td>
<td>24</td>
<td>0.20</td>
</tr>
</tbody>
</table>

With these data, a graph constructed by plotting the logarithm of the drug concentrations versus time will yield a straight line on rectangular coordinates. More conveniently, the drug concentration values can be plotted directly at a logarithmic axis on semilog paper against time, and a straight line will be obtained (Fig. 2-11). The relationship of time versus drug concentration in Fig. 2-11 indicates a first-order reaction.

The $t_{1/2}$ for a first-order process is constant and may be obtained from any two points on the graph that shows a 50% decline in drug concentration. In this example, the $t_{1/2}$ is 4 hours. The first-order rate constant may be found by (1) obtaining the product of 2.3 times the slope or (2) by dividing 0.693 by the $t_{1/2}$ as follows:

$$\text{Slope} = \frac{k}{2.3} = \frac{\log y_2 - \log y_1}{x_2 - x_1}$$

$$k = \frac{2.3 (\log 50 - \log 100)}{4 - 0} = 0.173 \text{ h}^{-1}$$

$$k = \frac{0.693}{t_{1/2}} = 0.693 \times 4 = 0.173 \text{ h}^{-1}$$

**Frequently Asked Questions**

- **How is the rate and order of reaction determined graphically?**
- **How do I know my graph is first order when plotted on semilog paper?**
- **I plotted the plasma drug concentration versus time on semilog paper, and got a slope with an incorrect $k$. Why?**
- **I performed linear regression on $t$ versus $\ln C_p$. How do I determine the $C_p^0$ from the intercept?**
- **What is the difference between a rate and a rate constant?**
CHAPTER SUMMARY

Pharmacokinetics uses models to predict drug movement in the body for dosing optimization. Pharmacokinetics involves relationships between an independent variable \(x\), usually “time” and dependent variable \(y\), usually drug concentration. Pharmacokinetic processes are usually zero-order, first-order, or a combination of both zero-order and first-order processes. A graph of these variables is usually linear or log-linear. Several methods may be used to determine how predictive is the \(x-y\) relationship, including curve fitting, least squares, and linear regression. The slope of the \(\log_{10}\) drug concentration versus time plot equals \(-k/2.3\). The slope of the natural log or \(\ln\) drug concentration versus time plot equals \(-k\). A declining slope is observed by the minus “–” sign. For a first-order reaction, the half-life is the time required for the amount or concentration of drug to decrease by half. For a zero-order rate process, the rate of change in drug amount or concentration is constant with respect to time. The zero-order rate constant, \(k_0\), has the units of \((\text{mg/L})/\text{h}\). For a first-order process, the rate of change in drug amount or concentration is dependent upon the drug amount or concentration remaining in the system. The first-order rate constant has the units of reciprocal time, \(k^{-1}\). The elimination half-life, \(t_{1/2}\), for a first-order rate process is constant. The area under the curve (AUC) can be calculated using the trapezoidal rule. The AUC represents the total amount of drug in the system for measurable time period. The major units in pharmacokinetics are based on mass, volume, concentration, and time.

LEARNING QUESTIONS

1. Plot the following data on both semilog graph paper and standard rectangular coordinates.

<table>
<thead>
<tr>
<th>Time (minute)</th>
<th>Drug A (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>96.0</td>
</tr>
<tr>
<td>20</td>
<td>89.0</td>
</tr>
<tr>
<td>40</td>
<td>73.0</td>
</tr>
<tr>
<td>60</td>
<td>57.0</td>
</tr>
<tr>
<td>90</td>
<td>34.0</td>
</tr>
<tr>
<td>120</td>
<td>10.0</td>
</tr>
<tr>
<td>130</td>
<td>2.5</td>
</tr>
</tbody>
</table>

a. Does the decrease in the amount of drug \(A\) appear to be a zero-order or a first-order process?
b. What is the rate constant \(k\)?
c. What is the half-life \(t_{1/2}\)?
d. Does the amount of drug \(A\) extrapolate to zero on the \(x\) axis?
e. What is the equation for the line produced on the graph?

2. Plot the following data on both semilog graph paper and standard rectangular coordinates.

<table>
<thead>
<tr>
<th>Time (minute)</th>
<th>Drug A (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>70.0</td>
</tr>
<tr>
<td>10</td>
<td>58.0</td>
</tr>
<tr>
<td>20</td>
<td>42.0</td>
</tr>
<tr>
<td>30</td>
<td>31.0</td>
</tr>
<tr>
<td>60</td>
<td>12.0</td>
</tr>
<tr>
<td>90</td>
<td>4.5</td>
</tr>
<tr>
<td>120</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Answer questions a, b, c, d, and e as stated in Question 1.
3. A pharmacist dissolved a few milligrams of a new antibiotic drug into exactly 100 mL of distilled water and placed the solution in a refrigerator (5°C). At various time intervals, the pharmacist removed a 10-mL aliquot from the solution and measured the amount of drug contained in each aliquot. The following data were obtained.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Antibiotic (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>84.5</td>
</tr>
<tr>
<td>1.0</td>
<td>81.2</td>
</tr>
<tr>
<td>2.0</td>
<td>74.5</td>
</tr>
<tr>
<td>4.0</td>
<td>61.0</td>
</tr>
<tr>
<td>6.0</td>
<td>48.0</td>
</tr>
<tr>
<td>8.0</td>
<td>35.0</td>
</tr>
<tr>
<td>12.0</td>
<td>8.7</td>
</tr>
</tbody>
</table>

a. Is the decomposition of this antibiotic a first-order or a zero-order process?
b. What is the rate of decomposition of this antibiotic?
c. How many milligrams of antibiotics were in the original solution prepared by the pharmacist?
d. Give the equation for the line that best fits the experimental data.

4. A solution of a drug was freshly prepared at a concentration of 300 mg/mL. After 30 days at 25°C, the drug concentration in the solution was 75 mg/mL.

a. Assuming first-order kinetics, when will the drug decline to one-half of the original concentration?
b. Assuming zero-order kinetics, when will the drug decline to one-half of the original concentration?

5. How many half-lives \( t_{1/2} \) would it take for 99.9% of any initial concentration of a drug to decompose? Assume first-order kinetics.

6. If the half-life for decomposition of a drug is 12 hours, how long will it take for 125 mg of the drug to decompose by 30%? Assume first-order kinetics and constant temperature.

7. Exactly 300 mg of a drug are dissolved into an unknown volume of distilled water. After complete dissolution of the drug, 1.0-mL samples were removed and assayed for the drug. The following results were obtained:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.45</td>
</tr>
<tr>
<td>2.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Assuming zero-order decomposition of the drug, what was the original volume of water in which the drug was dissolved?

8. For most drugs, the overall rate of drug elimination is proportional to the amount of drug remaining in the body. What does this imply about the kinetic order of drug elimination?

9. A single cell is placed into a culture tube containing nutrient agar. If the number of cells doubles every 2 minutes and the culture tube is completely filled in 8 hours, how long does it take for the culture tube to be only half full of cells?

10. The volume of distribution of warfarin is 9.8 ± 4.2 L. Assuming normal distribution, this would mean that 95% of the subjects would have a volume of distribution ranging from ——— L to ——— L.

11. Which of the following functions has the steepest declining slope? \( t \) is the independent variable and \( y \) is the dependent variable.

a. \( y = 2e^{-3t} \)
b. \( y = 3e^{-2t} \)
c. \( y = 2e^t \)

12. Which of the following equations predicts \( y \) increasing as \( t \) increases? \( t \) is a positive number.

a. \( y = 2e^{-3t} \)
b. \( y = 3e^{-2t} \)
c. \( y = 2e^t \)
13. Which of the following would result in an error message if you took the log of $x$ using a calculator?
   a. $x = 2.5$
   b. $x = 0.024$
   c. $x = 10^{-2}$
   d. $x = -0.2$

14. Which of the following equation(s) would have the greatest value at $t$ equal to 0 assuming that $t$ is not negative?
   a. $e^{-3t}$
   b. $3e^{-2t}$
   c. $2te^t$

REFERENCES


BIBLIOGRAPHY


Chapter Objectives

- Describe a one-compartment model, IV bolus injection.
- Provide the pharmacokinetic terms that describe a one-compartment model, IV bolus injection, and the underlying assumptions.
- Explain how drugs follow one-compartment kinetics using drug examples that follow one-compartment kinetics.
- Calculate pharmacokinetic parameters from drug concentration–time data using a one-compartment model.
- Simulate one-compartment plasma drug level graphically using the one-compartment model equation.
- Calculate the IV bolus dose of a drug using the one-compartment model equation.
- Relate the relevance of the magnitude of the volume of distribution and clearance of various drugs to underlying processes in the body.
- Derive model parameters from slope and intercept of the appropriate graphs.

The most common and the most desirable route of drug administration is the oral route in which dosage forms (drug products) such as tablets, capsules, or oral solutions are generally used. In order to develop pharmacokinetic models to describe and predict drug disposition kinetically, the model must account for both the route of administration and the pharmacokinetic behavior of the drug in the body. Once drug disposition can be predicted by a pharmacokinetic model, then dosing regimens for individuals or groups of patients can be calculated.

The one-compartment open model is the simplest way to describe the process of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (ie, the model is “open”), and the entire body acts like a single, uniform compartment. The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus). The simplest pharmacokinetic model that describes drug disposition in the body is the IV bolus model where the drug is injected all at once into a box (the human body) or compartment, and the drug distributes/equilibrates instantaneously and rapidly throughout the compartment. Drug elimination from the compartment also begins to occur immediately after the IV bolus injection.

Of course, this model is a simplistic view of drug disposition in the body, which in reality is infinitely more complex than a single compartment. In the body, when a drug is given in the form of an IV bolus, the entire dose of drug enters the bloodstream immediately, and the drug “absorption process” into the plasma is considered to be instantaneous. In most cases, the drug quickly distributes via the circulatory system to potentially all the tissues in the body. Uptake of drugs by various tissue organs will occur at varying rates and extents, depending on the blood flow to the tissue, the lipophilicity of the drug, the molecular weight of the drug, and the binding affinity of the drug for the tissue mass. Most drugs are eliminated from the body either through the kidney and/or by being metabolized in the liver. Because of rapid drug equilibration between the blood and tissues, drug distribution and elimination occur as if the dose is all dissolved in a tank...
of uniform fluid (a single compartment) from which the drug is eliminated. The volume in which the drug seems to be distributed is termed the apparent volume of distribution, \(V_D\). The apparent volume of distribution assumes that the drug is theoretically rapidly and uniformly distributed in the body throughout the apparent volume. The \(V_D\) is determined from the injected amount or the dose and the plasma drug concentration \(C_p\) immediately after injection. For simplicity, it is assumed that the injected dose disperses and distributes instantly. This model is also termed a well-stirred one-compartment model. If the plasma drug concentration–time curve is not linear on a semilog plot after an IV bolus dose, then the drug may be unevenly distributed in different regions in which some tissues are slowly penetrated (see two-compartment model, Chapter 4).

The apparent volume of distribution is a pharmacokinetic parameter of the one-compartment model and governs the plasma concentration of the drug after a given dose. Another pharmacokinetic parameter is the elimination rate constant, \(k\), which is proportional to the rate at which the drug concentration in the body declines over time. The one-compartment model that describes the distribution and elimination after an IV bolus dose is given in Fig. 3-1.

The one-compartment open model predicts plasma concentrations as a function of time, but does not predict actual drug levels in the tissues. However, the model assumes that changes in the plasma levels of a drug will result in proportional changes in tissue drug levels, since their pharmacokinetic profile is consistent with inclusion of drug within the vascular compartment and the various drug concentrations within the compartment are in equilibrium. The drug in the body, \(D_B\), cannot be measured directly; however, accessible body fluids (such as blood) can be sampled to determine drug concentrations at various time intervals.

**FIGURE 3-1** Pharmacokinetic model for a drug administered by rapid intravenous injection. \(D_B\) = drug in body; \(V_D\) = apparent volume of distribution; \(k\) = elimination rate constant.

**ELIMINATION RATE CONSTANT**

The rate of elimination for most drugs from a tissue or from the body is a first-order process, in which the rate of elimination at any point in time is dependent on the amount or concentration of drug present at that instant. The elimination rate constant, \(k\), is a first-order elimination rate constant with units of \(\text{time}^{-1}\) (eg, \(\text{h}^{-1}\) or \(1/\text{h}\)). Generally, the parent or active drug is measured in the vascular compartment. Total removal or elimination of the parent drug from this compartment is affected by metabolism (biotransformation) and excretion. The elimination rate constant represents the sum of each of these processes:

\[
k = k_m + k_e \tag{3.1}
\]

where \(k_m\) = first-order rate process of metabolism and \(k_e\) = first-order rate process of excretion. There may be several routes of elimination of drug by metabolism or excretion. In such a case, each of these processes has its own first-order rate constant.

A rate expression for Fig. 3-1 is

\[
\frac{dD_B}{dt} = -kD_B \tag{3.2}
\]

This expression shows that the rate of elimination of drug in the body is a first-order process, depending on the overall elimination rate constant, \(k\), and the amount of drug in the body, \(D_B\), remaining at any given time, \(t\). Integration of Equation 3.2 gives the following expression:

\[
\log D_B = \frac{-kt}{2.3} + \log D_B^0 \tag{3.3}
\]

where \(D_B\) = the drug in the body at time \(t\) and \(D_B^0\) is the amount of drug in the body at \(t = 0\). When \(\log D_B\) is plotted against \(t\) for this equation, a straight line is obtained (Fig. 3-2). In practice, instead of transforming values of \(D_B\) to their corresponding logarithms, each value of \(D_B\) is placed at logarithmic intervals on semilog paper.

Equation 3.3 can also be expressed as

\[
D_B = D_B^0 e^{-kt} \tag{3.4}
\]
**APPARENT VOLUME OF DISTRIBUTION**

In general, drug equilibrates rapidly in the body. When plasma or any other biologic compartment is sampled and analyzed for drug content, the results are usually reported in units of concentration instead of amount. Each individual tissue in the body may contain a different concentration of drug due to differences in blood flow and drug affinity for that tissue. The amount of drug in a given location can be related to its concentration by a proportionality constant that reflects the apparent volume of fluid in which the drug is dissolved. The *volume of distribution* represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment. The volume of distribution is the apparent volume ($V_D$) in which the drug is dissolved (Equation 3.5). Because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space, the term *apparent* volume of distribution is used.

The amount of drug in the body is not determined directly. Instead, blood samples are collected at periodic intervals and analyzed for their drug concentrations. The $V_D$ relates the concentration of drug in plasma ($C_p$) and the amount of drug in the body ($D_B$), as in the following equation:

$$D_B = V_D C_p$$  \hspace{1cm} (3.5)

Substituting Equation 3.5 into Equation 3.3, a similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

$$\log C_p = -\frac{kt}{2.3} + \log C_p^0$$ \hspace{1cm} (3.6)

where $C_p = \text{concentration of drug in plasma at time } t$ and $C_p^0 = \text{concentration of drug in plasma at } t = 0$. Equation 3.6 can also be expressed as

$$C_p = C_p^0 e^{-kt}$$ \hspace{1cm} (3.7)

The relationship between apparent volume, drug concentration, and total amount of drug may be better understood by the following example.

**EXAMPLE**

Exactly 1 g of a drug is dissolved in an unknown volume of water. Upon assay, the concentration of this solution is 1 mg/mL. What is the original volume of this solution?

The original volume of the solution may be obtained by the following proportion, remembering that 1 g = 1000 mg:

$$\frac{1000 \text{ mg}}{x \text{ mL}} = \frac{1 \text{ mg}}{1 \text{ mL}} \hspace{1cm} x = 1000 \text{ mL}$$

Therefore, the original volume was 1000 mL or 1 L. If, in the above example, the volume of the solution is known to be 1 L and the concentration of the solution is 1 mg/mL, then, to calculate the total amount of drug present,
$x \text{ mg} \over 1000 \text{ mL} = \frac{1 \text{ mg} \text{ mL}^{-1}}{} x=1000 \text{ mg}$

Therefore, the total amount of drug in the solution is 1000 mg or 1 g.

From the preceding example, if the volume of solution in which the drug is dissolved and the drug concentration of the solution are known, then the total amount of drug present in the solution may be calculated. This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

$$V_D = \frac{\text{Dose}}{C_p} = \frac{D_B^0}{C_p}$$ (3.8)

where $D = \text{total amount of drug}$, $V = \text{total volume}$, and $C = \text{drug concentration}$. From Equation 3.8, which is similar to Equation 3.5, if any two parameters are known, then the third term may be calculated.

Calculation of Volume of Distribution

In a one-compartment model (IV administration), the $V_D$ is calculated with the following equation:

$$V_D = \frac{\text{Dose}}{C_p} = \frac{D_B^0}{C_p}$$ (3.9)

When $C_p^0$ is determined by extrapolation, $C_p^0$ represents the instantaneous drug concentration after drug equilibration in the body at $t = 0$ (Fig. 3-3). The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, $D_B^0$, at $t = 0$. Because both $D_B^0$ and $C_p^0$ are known at $t = 0$, then the apparent volume of distribution, $V_D$, may be calculated from Equation 3.9.

From Equation 3.2 (repeated here), the rate of drug elimination is

$$\frac{dD_B}{dt} = -kD_B$$

Substituting Equation 3.5, $D_B = V_D C_p$, into Equation 3.2, the following expression is obtained:

$$\frac{dD_B}{dt} = -kV_D C_p$$ (3.10)

Rearrangement of Equation 3.10 gives

$$dD_B = -kV_D C_p dt$$ (3.11)

As both $k$ and $V_D$ are constants, Equation 3.10 may be integrated as follows:

$$\int_0^{D_B} dD_B = -kV_D \int_0^{C_p} dt$$ (3.12)

Equation 3.12 shows that a small change in time ($dt$) results in a small change in the amount of drug in the body, $D_B$. The integral $\int_0^{\infty} C_p dt$ represents the AUC, which is the summation of the area under the curve from $t = 0$ to $t = \infty$. Thus, the apparent $V_D$ may also be calculated from knowledge of the dose, elimination rate constant, and the area under the curve.
One-Compartment Open Model: Intravenous Bolus Administration

47

If \( V_D \) is a very large number—ie, >100% of body weight—then it may be assumed that the drug is concentrated in certain tissue compartments. Thus, the apparent \( V_D \) is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

Pharmacologists often attempt to conceptualize the apparent \( V_D \) as a true physiologic or anatomic fluid compartment. By expressing the \( V_D \) in terms of percent of body weight, values for the \( V_D \) may be found that appear to correspond to true anatomic volumes (Table 3-1). However, it may be only fortuitous that the value for the apparent \( V_D \) of a drug has the same value as a real anatomic volume. If a drug is to be considered to be distributed in a true physiologic volume, then an investigation is needed to test this hypothesis.

Given the apparent \( V_D \) for a particular drug, the total amount of drug in the body at any time after administration of the drug may be determined by the measurement of the drug concentration in the plasma (Equation 3.5). Because the magnitude of the apparent \( V_D \) is a useful indicator for the amount of drug outside the sampling compartment (usually the blood), the larger the apparent \( V_D \) the greater the amount of drug in the extravascular tissues.

For each drug, the apparent \( V_D \) is a constant. In certain pathologic cases, the apparent \( V_D \) for the drug may be altered if the distribution of the drug is changed. For example, in edematous conditions, the total body water and total extracellular water increases; this is reflected in a larger apparent \( V_D \) value for a drug that is highly water soluble. Similarly, changes in total body weight and lean body mass (which normally occur with age) may also affect the apparent \( V_D \).

(AUC) from \( t = 0 \) to \( t = \infty \). The \( \text{AUC}_0^\infty \) is usually estimated by the trapezoidal rule (see Chapter 2). After integration, Equation 3.12 becomes

\[
D_0 = k V_D \text{[AUC]}_0^\infty
\]

which upon rearrangement yields the following equation:

\[
V_D = \frac{D_0}{k[AUC]}_0^\infty
\]

(3.13)

The calculation of the apparent \( V_D \) by means of Equation 3.13 is a model-independent method, because no pharmacokinetic model is considered and the AUC is determined directly by the trapezoidal rule.

**Significance of the Apparent Volume of Distribution**

The apparent volume of distribution is not a true physiologic volume, but rather reflects the space the drug seems to occupy in the body. Equation 3.9 shows that the apparent \( V_D \) is dependent on \( C_p^0 \), and thus is the proportionality constant between \( C_p^0 \) and dose. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. If a drug is highly bound to plasma proteins or concentrates in the vascular region, then \( C_p^0 \) will be higher, resulting in a smaller apparent \( V_D \). Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect \( V_D \).

For some drugs, the volume of distribution may be several times the body mass. In this case, a very small \( C_p^0 \) may occur in the body due to concentration of the drug in peripheral tissues and organs, resulting in a large \( V_D \). Drugs with a large apparent \( V_D \) are more concentrated in extravascular tissues and less concentrated intravascularly.

The apparent \( V_D \) is a volume term that can be expressed as a simple volume or in terms of percent of body weight. In expressing the apparent \( V_D \) in terms of percent body weight, a 1-L volume is assumed to be equal to the weight of 1 kg. For example, if the \( V_D \) is 3500 mL for a subject weighing 70 kg, the \( V_D \) expressed as percent of body weight is

\[
\frac{3.5 \text{ kg}}{70 \text{ kg}} \times 100 = 5\% \text{ of body weight}
\]

Table 3-1 **Fluid in the Body**

<table>
<thead>
<tr>
<th>Water Compartiment</th>
<th>Percent of Body Weight</th>
<th>Percent of Total Body Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Total extracellular water</td>
<td>27.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Total intracellular water</td>
<td>33.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Total body water</td>
<td>60.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Chapter 3

Drug Elimination Expressed as Volume per Unit Time

The concept of expressing a rate in terms of volume per unit time (eg, L/h or mL/min) is convenient because it is a constant.

Drug Elimination Expressed as Amount per Unit Time

The expression of drug elimination from the body in terms of mass per unit time (eg, mg/min, or mg/h) is simple, absolute, and unambiguous. For a zero-order elimination process, expressing the rate of drug elimination as mass per unit time is convenient because the elimination rate is constant (Fig. 3-4A). However, drug clearance is not constant for a drug that has zero-order elimination (see Chapter 6). For most drugs, the rate of drug elimination is a first-order elimination process, ie, the elimination rate is not constant and changes with respect to the drug concentration in the body. For first-order elimination, drug clearance expressed as volume per unit time (eg, L/h or mL/min) is convenient because it is a constant.
the plasma drug concentration at all times. This observation is based on a first-order process governing drug elimination. For many drugs, the rate of drug elimination is dependent on the plasma drug concentration, multiplied by a constant factor \((dC/dt = kC)\). When the plasma drug concentration is high, the rate of drug removal is high, and vice versa.

Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time. Mathematically, the rate of drug elimination is similar to Equation 3.10:

\[
\frac{dD_B}{dt} = -kC_p V_D
\]  

Equation 3.2a

Dividing this expression on both sides by \(C_p\) yields Equation 3.14:

\[
\frac{dD_B}{C_p} = -k \frac{V_D}{C_p}
\]  

Equation 3.14

\[
\frac{dD_B}{C_p} = -k V_D / C_l
\]  

Equation 3.15

where \(dD_B/dt\) is the rate of drug elimination from the body (mg/L), \(C_p\) is the plasma drug concentration (mg/L), \(k\) is a first-order rate constant (h\(^{-1}\) or 1/h), and \(V_D\) is the apparent volume of distribution (L). \(C_l\) is clearance and has the units L/h in this example. In the example in Fig. 3-4B, \(C_l\) is in mL/min.

Clearance, \(C_l\), is expressed as volume/time. Equation 3.15 shows that clearance is a constant because \(V_D\) and \(k\) are both constants. \(D_B\) is the amount of drug in the body, and \(dD_B/dt\) is the rate of change (of amount) of drug in the body with respect to time. The negative sign refers to the drug exiting from the body.

**Drug Elimination Expressed as Fraction Eliminated per Unit Time**

Consider a compartment volume, containing \(V_D\) liters. If \(C_l\) is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to \(C_l/V_D\).

Expressing drug elimination as the fraction of total drug eliminated is applicable regardless of whether one is dealing with an amount or a volume (Fig. 3-4C). This approach is most flexible and convenient because of its dimensionless nature. Thus, it is valid to express drug elimination as a fraction (eg, one-tenth of the amount of drug in the body is eliminated or one-tenth of the drug volume is eliminated). Pharmacokineticists have incorporated this concept into the first-order equation (ie, \(k\)) that describes drug elimination from the one-compartment model. Indeed, the universal nature of many processes forms the basis of the first-order equation of drug elimination (eg, a fraction of the total drug molecules in the body will perfuse the glomeruli, a fraction of the filtered drug molecules will be reabsorbed at the renal tubules, and a fraction of the filtered drug molecules will be excreted from the body giving an overall first-order drug elimination rate constant, \(k\)). The rate of drug elimination is the product of \(k\) and the drug concentration (Equation 3.2a). The first-order equation of drug elimination can also be based on probability and a consideration of the statistical moment theory (see Chapter 20).

**Clearance and Volume of Distribution Ratio, \(C_l/V_D\)**

Consider that 100 mg of drug is dissolved in 10 mL of fluid and 10 mg of drug is removed in the first minute. The drug elimination process could be described as:

a. Number of mg of drug eliminated per minute (mg/min)

b. Number of mL of fluid cleared of drug per minute

c. Fraction of drug eliminated per minute

The relationship of the three drug elimination processes is illustrated in Fig. 3-4A–C. Note that in Figure 3-4C, the fraction \(C_l/V_D\) is dependent on both the volume of distribution and the rate of drug clearance from the body. This clearance concept forms the basis of classical pharmacokinetics and is later extended to flow models in pharmacokinetic modeling. If the drug concentration is
population values (derived from a large population of subjects or patients) reported in the literature. The values of $Cl$ and $V_D$ for the patient are adjusted using a computer program. Ultimately, a new pair of $Cl$ and $V_D$ values that better fit the observed plasma drug concentration is found. The process is repeated through iterations until the “best” parameters are obtained. Since many mathematical techniques (algorithms) are available for iteration, different results may be obtained using different iterative programs. An objective test to determine the accuracy of the estimated clearance and $V_D$ values is to monitor how accurately those parameters will predict the plasma level of the drug after a new dose is given to the patient. In subsequent chapters, mean predictive error will be discussed and calculated in order to determine the performance of various drug monitoring methods in practice.

The ratio of $Cl/V_D$ may be calculated regardless of compartment model type using minimal plasma samples. Clinical pharmacists have applied many variations of this approach to therapeutic drug monitoring and drug dosage adjustments in patients.

**PRACTICAL FOCUS**

The most accurate kinetic method to determine the volume of distribution and the distribution kinetic of a drug in a patient is to give the drug by a single IV bolus dose. An IV bolus dose avoids many variables such as delayed, irregular, and/or incomplete absorption compared to other routes of administration.

The IV single dose Equation 3.22 may be modified to calculate the elimination rate constant or half-life of a drug in a patient when two plasma samples and their time of collection are known:

$$\ln C_p = \ln C_p^0 - k t$$ (3.22)

If the first plasma sample is taken at $t_1$ instead of at 0 and corresponds to plasma drug concentration, then $C_2$ is the concentration at time $t_2$ and $t$ is set to $(t_2 - t_1)$.

$$C_2 = C_1 e^{-k(t_2-t_1)}$$

$$\ln C_2 = \ln C_1 - k(t_2-t_1)$$ (3.23)
and drug clearance is then calculated as the fixed volume of plasma fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (e.g., mL/min, L/h).

Alternatively, $Cl_T$ may be defined as the rate of drug elimination divided by the plasma drug concentration. Thus, clearance is expressed in terms of the volume of plasma containing drug that is eliminated per unit time. This clearance definition is equivalent to the previous definition and provides a practical way to calculate clearance based on plasma drug concentration data.

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration (C}_p\text{)}} \quad (3.28)$$

$$Cl_T = \frac{(dD_e/dt)}{C_p} = (\mu g/min)/(\mu g/mL) = mL/min \quad (3.29)$$

where $D_e$ is the amount of drug eliminated and $dD_e/dt$ is the rate of drug elimination.

Rearrangement of Equation 3.29 gives Equation 3.30:

$$\text{Drug elimination } \frac{dD_e}{dt} = C_p Cl_T \quad (3.30)$$

Therefore $Cl_T$ is a constant for a specific drug and represents the slope of the line obtained by plotting $dD_e/dt$ versus $C_p$, as shown in Equation 3.30.

For drugs that follow first-order elimination, the rate of drug elimination is dependent on the amount of drug remaining in the body.

$$\frac{dD_e}{dt} = kD_e = kC_pV_D \quad (3.31)$$

Substituting the elimination rate in Equation 3.30 for $kC_pV_D$ in Equation 3.31 and solving for $Cl_T$ gives Equation 3.32:

$$Cl_T \frac{kC_pV_D}{C_p} = kV_D \quad (3.32)$$

Equation 3.32 shows that clearance, $Cl_T$, is the product of $V_D$ and $k$, both of which are constant. This Equation 3.32 is similar to Equation 3.19 shown earlier. As the plasma drug concentration decreases
during elimination, the rate of drug elimination, \( \frac{dD}{dt} \), will decrease accordingly, but clearance will remain constant. Clearance will be constant as long as the rate of drug elimination is a first-order process.

For some drugs, the elimination rate processes are not well known and few or no model assumptions are desirable; in this situation, a noncompartmental method may be used to calculate certain pharmacokinetic parameters such as clearance, which can be determined directly from the plasma drug concentration–time curve by

\[
Cl_t = \frac{D_0}{[\text{AUC}]_0^\infty} \tag{3.33}
\]

where \( D_0 \) is the dose and \([\text{AUC}]_0^\infty = \int_0^\infty C_p \, dt\).

Because \([\text{AUC}]_0^\infty\) is calculated from the plasma drug concentration–time curve from 0 to infinity (\(\infty\)) using the trapezoidal rule, no compartmental model is assumed. However, to extrapolate the data to infinity, no compartmental model is assumed. The preference to replace the compartment model, the \( Cl_t \) is numerically similar to the product of \( V_D \) and \( k \).

The approach (Equation 3.33) of using \([\text{AUC}]_0^\infty\) to calculate body clearance is preferred by some statisticians/pharmacokineticists who desire an alternative way to calculate drug clearance without a compartmental model. The alternative approach is often referred to as a noncompartmental method of analyzing the data. The noncompartmental approach may be modified in different ways in order to avoid subjective interpolation or extrapolation (see Chapters 6 and 22 for more discussion).

In the noncompartmental approach, the two model parameters, (1) clearance and (2) volume of distribution govern drug elimination from the physiologic (plasma) fluid directly and no compartment model is assumed. The preference to replace \( k \) with \( Cl/V_D \) was prompted by Equation 3.19 as rearranged in the above section:

\[
k = \frac{Cl}{V_D} \tag{3.19}
\]

For a drug to be eliminated from the body fluid, the volume cleared of drug over the size of the pool indicates that \( k \) is really computed from \( Cl \) and \( V_D \).

In contrast, the classical one-compartment model is described by two model parameters: (1) elimination constant, \( k \) and (2) volume of distribution, \( V_D \). Clearance is derived from \( Cl = kV_D \). The classical approach considers \( V_D \) the volume in which the drug appears to dissolve, and \( k \) reflects how the drug declines due to excretion or metabolism over time. In chemical kinetics, the rate constant, \( k \), is related to “encounters” or “collisions” when a chemical reaction takes place. An ordinary hydrolysis or oxidation reaction occurring in the test tube can also occur in the body. Classical pharmacokineticists similarly realized that regardless of whether the reaction occurs in a beaker or in the body fluid, the drug molecules must encounter the enzyme molecule for biotransformation or the exit site (glomeruli) to be eliminated. The probability of getting to the glomeruli or metabolic site during systemic circulation must be first order because both events are probability or chance related (ie, a fraction of drug concentration will be eliminated). Therefore, the rate of elimination (\( dCl/dt \)) is related to drug concentration and is aptly described by

\[
k \times C_p \tag{3.34}
\]

The compartment model provides a useful way to track mass balance of the drug in the body. It is virtually impossible to account for all the drug in the body with a detailed quantitative model. However, keeping track of systemic concentrations and the mass balance of the dose in the body is still important to understand a drug’s pharmacokinetic properties. For example, the kinetic parameters for drugs such as aspirin and acetaminophen were determined using mass balance which indicates that both drugs are over 90% metabolized (see percent urinary excretion in Appendix E). It is important for a pharmacist to apply such scientific principles during drug modeling in order to optimize dosing. Drug metabolism may be equally well described by applying clearance and first-order/saturation kinetics concepts to kinetic models.
CLINICAL APPLICATION

IV bolus injection provides a simple way to study the pharmacokinetics of a drug. The pharmacokinetic parameters of the drug are determined from the slope and the intercept of the plasma drug concentration–time curve obtained after IV bolus injection. This approach is particularly useful for a new or investigational drug when little pharmacokinetic information is known. In practice, rapid bolus injection is often not desirable for many drugs and a slow IV drip or IV drug infusion is preferred. Rapid injection of a large drug dose may trigger adverse drug reactions (ADR) that would have been avoided if the body had sufficient time to slowly equilibrate with the drug. This is particularly true for certain classes of antiarrhythmics, anticonvulsants, antitumor, anticoagulants oligonucleotide drugs, and some systemic anesthetics. Immediately after an intravenous injection, the concentrated drug solution/vehicle is directly exposed to the heart, lung, and other vital organs before full dilution in the entire body. During the drug’s first pass through the body, some tissues may react adversely to a transient high drug concentration because of the high plasma/tissue drug concentration difference (gradients) that exists prior to full dilution and equilibration. Most intravenous drugs are formulated as aqueous solutions, lightly buffered with a suitable pH for this reason. A poorly soluble drug may precipitate from solution if injected too fast. Suspensions or drugs designed for IM injection only could cause serious injury or fatality if injected intravenously. For example, the antibiotic Bicillin intended for IM injection has a precaution accompanying the packaging to ensure that the drug will not be injected accidently into a vein. Pharmacists should be especially alert to verify extravascular injection when drugs are designed for IM injection.

With many drugs, the initial phase or transient plasma concentrations are not considered as important as the steady-state “trough” level during long-term drug dosing. However, drugs with the therapeutic endpoint (eg, target plasma drug concentration) that lie within the steep initial distributive phase, are much harder to dose accurately and not overshoot the target endpoint. This scenario is particularly true for some drugs used in critical care where rapid responses are needed and IV bolus routes are used more often. Many new biotechnological drugs are administered intravenously because of instability or poor systemic absorption by the oral route. The choice of a proper drug dose and rate of infusion relative to the elimination half-life of the drug is an important consideration for safe drug administration. Individual patients may behave very differently with regard to drug metabolism, drug transport, and drug efflux in target cell sites. Drug receptors and enzymes may have genetic variability making some people more prone to allergic reactions, drug interactions, and side effects. Simple kinetic half-life determination coupled with a careful review of the patient’s chart by a pharmacist can greatly improve drug safety and efficacy.

Frequently Asked Question

CALCULATION OF $k$ FROM URINARY EXCRETION DATA

The elimination rate constant $k$ may be calculated from urinary excretion data. In this calculation the excretion rate of the drug is assumed to be first order. The term $k_e$ is the renal excretion rate constant, and $D_u$ is the amount of drug excreted in the urine.

$$\frac{dD_u}{dt} = k_e D_u$$

(3.35)

From Equation 3.4, $D_B$ can be substituted for $D_u^0 e^{-kt}$:

$$\frac{dD_u}{dt} = k_e D_u^0 e^{-kt}$$

(3.36)

Taking the natural logarithm of both sides and then transforming to common logarithms, the following expression is obtained:

$$\log \frac{dD_u}{dt} = \frac{-kt}{2.3} + \log k_e D_u^0$$

(3.37)
for most drugs are renal excretion and metabolism (biotransformation), $k_w$ is approximately equal to $k_{nr}$.

$$k_{nr} = k_m$$

(3.39)

The drug urinary excretion rate ($dD_u/dt$) cannot be determined experimentally for any given instant. Therefore, the average rate of urinary drug excretion, $D_u/t$, is plotted against the time corresponding to the midpoint of the collection interval, $t^*$, for the collection of the urine sample. In practice, urine is collected over a specified time interval, and the urine specimen is analyzed for drug. An average urinary excretion rate is then calculated for that collection period. The average value of $dD_u/dt$ is plotted on a semilogarithmic scale against the time that corresponds to the midpoint (average time) of the collection period.

**PRACTICE PROBLEM**

A single IV dose of an antibiotic was given to a 50-kg woman at a dose level of 20 mg/kg. Urine and blood samples were removed periodically and assayed for parent drug. The following data were obtained:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>$C_p$ (μg/mL)</th>
<th>$D_u$ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>4.2</td>
<td>160</td>
</tr>
<tr>
<td>0.50</td>
<td>3.5</td>
<td>140</td>
</tr>
<tr>
<td>1.0</td>
<td>2.5</td>
<td>200</td>
</tr>
<tr>
<td>2.0</td>
<td>1.25</td>
<td>250</td>
</tr>
<tr>
<td>4.0</td>
<td>0.31</td>
<td>188</td>
</tr>
<tr>
<td>6.0</td>
<td>0.08</td>
<td>46</td>
</tr>
</tbody>
</table>

**Solution**

Set up the following table:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>$D_u$ (mg)</th>
<th>$D_u/t$ (mg/h)</th>
<th>$t^*$ (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>160</td>
<td>160/0.25</td>
<td>0.125</td>
</tr>
<tr>
<td>0.50</td>
<td>140</td>
<td>140/0.25</td>
<td>0.375</td>
</tr>
<tr>
<td>1.0</td>
<td>200</td>
<td>200/0.5</td>
<td>0.750</td>
</tr>
<tr>
<td>2.0</td>
<td>250</td>
<td>250/1</td>
<td>1.50</td>
</tr>
<tr>
<td>4.0</td>
<td>188</td>
<td>188/2</td>
<td>3.0</td>
</tr>
<tr>
<td>6.0</td>
<td>46</td>
<td>46/2</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Here $t^*$ = midpoint of collection period and $t$ = time interval for collection of urine sample.
Construct a graph on a semilogarithmic scale of $D_u/t$ versus $t$. The slope of this line should equal $-k/2.3$. It is usually easier to determine the elimination $t_{1/2}$ directly from the curve and then calculate $k$ from

$$k = \frac{0.693}{t_{1/2}}$$

In this problem, $t_{1/2} = 1.0$ h and $k = 0.693$ h$^{-1}$. A similar graph of the $C_p$ values versus $t$ should yield a curve with a slope having the same value as that derived from the previous curve. Note that the slope of the log excretion rate constant is a function of elimination rate constant $k$ and not of the urinary excretion rate constant $k_e$ (Fig. 3-6).

An alternative method for the calculation of the elimination rate constant $k$ from urinary excretion data is the sigma-minus method, or the amount of drug remaining to be excreted method. The sigma-minus method is sometimes preferred over the previous method because fluctuations in the rate of elimination are minimized.

The amount of unchanged drug in the urine can be expressed as a function of time through the following equation:

$$D_u = k \frac{D_0}{k} (1 - e^{-kt})$$

Equation 3.43 describes the relationship for the amount of drug remaining to be excreted ($D_u - D_0$) versus time.

A linear curve is obtained by graphing the logarithm scale of the amount of unchanged drug yet to be eliminated, log ($D_u - D_0$) versus time. On semilog paper, the slope of this curve is $-k/2.3$ and the $y$ intercept is ($D_0$) (Fig. 3-7).

**PRACTICE PROBLEM**

Using the data in the preceding problem, determine the elimination rate constant.

**Solution**

Construct the following table:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>$D_u$ (mg)</th>
<th>Cumulative $D_u$</th>
<th>$D_u - D_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>160</td>
<td>160</td>
<td>824</td>
</tr>
<tr>
<td>0.50</td>
<td>140</td>
<td>300</td>
<td>684</td>
</tr>
<tr>
<td>1.0</td>
<td>200</td>
<td>500</td>
<td>484</td>
</tr>
<tr>
<td>2.0</td>
<td>250</td>
<td>750</td>
<td>234</td>
</tr>
<tr>
<td>4.0</td>
<td>188</td>
<td>938</td>
<td>46</td>
</tr>
<tr>
<td>6.0</td>
<td>46</td>
<td>984</td>
<td>0</td>
</tr>
</tbody>
</table>

Plot log ($D_u - D_0$) versus time. Use a semilogarithmic scale for ($D_u - D_0$). Evaluate $k$ and $t_{1/2}$ from the curve.
Comparison of the Rate and the Sigma-Minus Methods

The rate method does not require knowledge of $D_u^\infty$ and the loss of one urine specimen does not invalidate the entire urinary drug excretion study. The sigma-minus method requires an accurate determination of $D_u^\infty$, which requires the collection of urine until urinary drug excretion is complete. A small error in the assessment of $D_u^\infty$ introduces an error in terms of curvature of the plot, because each point is based on log $(D_u^\infty - D_u)$ versus time. Fluctuations in the rate of drug elimination and experimental errors including incomplete bladder emptying for a collection period cause appreciable departure from linearity using the rate method, whereas the accuracy of the sigma-minus method is less affected. The rate method is applicable to zero-order drug elimination process, while the sigma-minus method is not. Lastly, the renal drug excretion rate constant may be obtained from the rate method but not from the sigma-minus method.

**Clinical Application**

The sigma-minus method and the excretion rate method were applied to the urinary drug excretion in subjects following the smoking of a single marijuana cigarette (Huestis et al, 1996). The urinary excretion curves of 11-nor-carboxy 9-tetrahydrocannabinol (THCCOOH), a metabolite of marijuana, in one subject from 24 to 144 hours after smoking one marijuana cigarette are shown in Figs. 3-8 and 3-9.

A total of 199.7 mg of THCCOOH was excreted in the urine over 7 days, which represents 0.54% of the total 9-tetrahydrocannabinol available in the cigarette. Using either urinary drug excretion method, the elimination half-life was determined to be about 30 hours. However, the urinary drug excretion rate method data were more scattered (variable) and the correlation coefficient $r$ was equal to 0.744 (Fig. 3-9), compared to the correlation coefficient $r$ of 0.992 using the sigma-minus method (Fig. 3-8).

**Problems in Obtaining Valid Urinary Excretion Data**

Certain factors can make it difficult to obtain valid urinary excretion data. Some of these factors are as follows:

1. A significant fraction of the unchanged drug must be excreted in the urine.

---

**FIGURE 3-8** Amount remaining to be excreted method. The half-life of THCCOOH was calculated to be 29.9 hours from the slope of this curve; the correlation coefficient $r$ was equal to 0.992. (Data from Huestis et al, 1996.)

**FIGURE 3-9** Excretion rate method. The half-life of THCCOOH was calculated to be 30.7 hour from the slope of this curve; the correlation coefficient $r$ was equal to 0.744. (Data from Huestis et al, 1996.)

**FIGURE 3-10** Graph showing the cumulative urinary excretion of drug as a function of time.
2. The assay technique must be specific for the unchanged drug and must not include interference due to drug metabolites that have similar chemical structures.

3. Frequent sampling is necessary for a good curve description.

4. Urine samples should be collected periodically until almost all of the drug is excreted. A graph of the cumulative drug excreted versus time will yield a curve that approaches an asymptote at “infinite” time (Fig. 3-10). In practice, approximately seven elimination half-lives are needed for 99% of the drug to be eliminated.

5. Variations in urinary pH and volume may cause significant variation in urinary excretion rates.

6. Subjects should be carefully instructed as to the necessity of giving a complete urine specimen (i.e., completely emptying the bladder).

CHAPTER SUMMARY

The one-compartment model assumes that the drug is uniformly distributed within a single hypothetical compartment volume from which the drug concentration can be sampled and assayed easily. The one-compartment model, IV bolus drug injection, provides the simplest approach for estimating the apparent volume of distribution, \( V_D \), and the elimination rate constant, \( k \). If \( V_D \), \( k \), and the drug dose are known, the model equation allows drug concentration in the compartment (body) at any time to be calculated. The volume plasma fluid and extracellular fluid may be relatively constant under normal conditions. However, these volumes added together do not usually numerically equal to the (apparent) volume of distribution of the drug, which may be larger or smaller depending on how widely the drug distributes into tissues.

The one-compartment model may be described with the two model parameters, clearance and volume of distribution. Alternatively, the one-compartment model can also be described by two model parameters, the elimination constant, \( k \), and volume of distribution. The latter model explains that drugs are fractionally removed at any time, whatever the initial drug concentration is, and \( k \) as a ratio of \( Cl/V_D \). Clearance may be computed by \( Cl = kV_D \). Drug clearance is constant for a first-order process regardless of the drug concentration. Clearance is expressed as the apparent volume of fluid of the dissolved drug that is removed per unit time. Expressing drug elimination as the fraction of total drug eliminated per time is applicable regardless of whether one is dealing with an amount or a volume. This approach is most flexible and convenient because of its dimensionless nature (\( k \) is expressed as \( h^{-1} \) or \( \text{min}^{-1} \)). The one-compartment model may assume either a first-order or zero-order elimination rate depending on whether the drug follows linear kinetics or not. An alternative way to model the plasma drug concentration without a compartment model and calculate clearance is sometimes useful. This alternative non-compartmental approach avoids some basic assumptions inherent in the one-compartment model.

LEARNING QUESTIONS

1. A 70-kg volunteer is given an intravenous dose of an antibiotic, and serum drug concentrations were determined at 2 hours and 5 hours after administration. The drug concentrations were 1.2 and 0.3 \( \mu g/mL \), respectively. What is the biologic half-life for this drug, assuming first-order elimination kinetics?

2. A 50-kg woman was given a single IV dose of an antibacterial drug at a dose level of 6 mg/kg. Blood samples were taken at various time
3. The concentration of the drug \( C_p \) was determined in the plasma fraction of each blood sample and the following data were obtained:

<table>
<thead>
<tr>
<th>t (hour)</th>
<th>( C_p ) (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>8.21</td>
</tr>
<tr>
<td>0.50</td>
<td>7.87</td>
</tr>
<tr>
<td>1.00</td>
<td>7.23</td>
</tr>
<tr>
<td>3.00</td>
<td>5.15</td>
</tr>
<tr>
<td>6.00</td>
<td>3.09</td>
</tr>
<tr>
<td>12.0</td>
<td>1.11</td>
</tr>
<tr>
<td>18.0</td>
<td>0.40</td>
</tr>
</tbody>
</table>

a. What are the values for \( V_D \), \( k \), and \( t_{1/2} \) for this drug?
b. This antibacterial agent is not effective at a plasma concentration of less than 2 μg/mL. What is the duration of activity for this drug?
c. How long would it take for 99.9% of this drug to be eliminated?
d. If the dose of the antibiotic was doubled exactly, what would be the increase in duration of activity?

4. A new drug was given in a single intravenous dose of 200 mg to an 80-kg adult male patient. After 6 hours, the plasma drug concentration of drug was 1.5 mg/100 mL of plasma. Assuming that the apparent \( V_D \) is 10% of body weight, compute the total amount of drug in the body fluids after 6 hours. What is the half-life of this drug?

5. A new antibiotic drug was given in a single intravenous bolus of 4 mg/kg to five healthy male adults ranging in age from 23 to 38 years (average weight 75 kg). The pharmacokinetics of the plasma drug concentration–time curve for this drug fits a one-compartment model. The equation of the curve that best fits the data is

\[
C_p = 78e^{-0.46t}
\]

Determine the following (assume units of μg/mL for \( C_p \) and hour for \( t \)):
a. What is the \( t_{1/2} \)?
b. What is the \( V_D \)?
c. What is the plasma level of the drug after 4 hours?
d. How much drug is left in the body after 4 hours?
e. Predict what body water compartment this drug might occupy and explain why you made this prediction.
f. Assuming the drug is no longer effective when levels decline to less than 2 μg/mL, when should you administer the next dose?

6. Define the term *apparent volume of distribution*. What criteria are necessary for the measurement of the apparent volume of distribution to be useful in pharmacokinetic calculations?

7. A rather intoxicated young man (75 kg, age 21) was admitted to a rehabilitation center. His blood alcohol content was found to be 210 mg%. Assuming the average elimination rate of alcohol is 10 mL of ethanol per hour, how long would it take for his blood alcohol concentration to decline to less than the legal blood alcohol concentration of 100 mg%? (Hint: Alcohol is eliminated by zero-order kinetics.) The specific gravity of alcohol is 0.8. The apparent volume of distribution for alcohol is 60% of body weight.

8. A single IV bolus injection containing 500 mg of cefamandole nafate (Mandol, Lilly) is given to an adult female patient (63 years, 55 kg) for a septicemic infection. The apparent volume of distribution is 0.1 L/kg and the elimination half-life is 0.75 hour. Assuming the drug is eliminated by first-order kinetics and may be described by a one-compartment model, calculate the following:
a. The \( C_p^0 \)
b. The amount of drug in the body 4 hours after the dose is given
c. The time for the drug to decline to 0.5 μg/mL, the minimum inhibitory concentration for streptococci
9. If the amount of drug in the body declines from 100% of the dose (IV bolus injection) to 25% of the dose in 8 hours, what is the elimination half-life for this drug? (Assume first-order kinetics.)

10. A drug has an elimination half-life of 8 hours and follows first-order elimination kinetics. If a single 600-mg dose is given to an adult female patient (62 kg) by rapid IV injection, what percent of the dose is eliminated (lost) in 24 hours assuming the apparent Vₚ is 400 mL/kg? What is the expected plasma drug concentration (Cₚ) at 24 hours postdose?

11. For drugs that follow the kinetics of a one-compartment open model, must the tissues and plasma have the same drug concentration? Why?

12. An adult male patient (age 35 years, weight 72 kg) with a urinary tract infection was given a single intravenous bolus of an antibiotic (dose = 300 mg). The patient was instructed to empty his bladder prior to being medicated. After dose administration, the patient saved his urine specimens for drug analysis. The urine specimens were analyzed for both drug content and sterility (lack of bacteriuria). The drug assays gave the following results:

<table>
<thead>
<tr>
<th>t (hour)</th>
<th>Amount of Drug in Urine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
</tr>
</tbody>
</table>

a. Assuming first-order elimination, calculate the elimination half-life for the antibiotic in this patient.

b. What are the practical problems in obtaining valid urinary drug excretion data for the determination of the drug elimination half-life?

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**REFERENCE**


**BIBLIOGRAPHY**


Chapter Objectives

- Define the pharmacokinetic terms used in a two- and three-compartment model.
- Explain using examples why drugs follow one-compartment, two-compartment, or three-compartment kinetics.
- Use equations and graph to simulate plasma drug concentration at various time periods after an IV bolus injection of a drug that follows the pharmacokinetics of a two- and three-compartment model drug.
- Relate the relevance of the magnitude of the volume of distribution and clearance of various drugs to underlying processes in the body.
- Estimate two-compartment model parameters by using the method of residuals.
- Calculate clearance and alpha and beta half-lives of a two-compartment model drug.
- Explain how drug metabolic enzymes, transportors, and binding proteins in the body may modify the distribution and/or elimination phase of a drug after IV bolus.

Pharmacokinetic models are used to simplify all the complex processes that occur during drug administration that include drug distribution and elimination in the body. The model simplification is necessary because of the inability to measure quantitatively all the rate processes in the body, including the lack of access to biological samples from the interior of the body. As described in Chapter 3, pharmacokinetic models are used to simulate drug disposition so dosing regimens for individuals or groups of patients can be calculated.

Compartmental models are classical pharmacokinetic models that simulate the kinetic processes of drug absorption, distribution, and elimination with little physiologic detail. In contrast, the more sophisticated physiologic model is discussed in Chapter 22. In compartmental models, drug tissue concentration, $C_t$, is assumed to be uniform within a given hypothetical compartment. Hence, all muscle mass and connective tissues may be lumped into one hypothetical tissue compartment that equilibrates with drug from the central (or plasma) compartment. Since no data are collected on the tissue mass, the theoretical tissue concentration cannot be confirmed and used to forecast actual tissue drug levels. Only a theoretical, $C_t$, concentration of drug in the tissue compartment can be calculated. Moreover, drug concentrations in a particular tissue mass may not be homogeneously distributed. However, plasma concentrations, $C_p$, are kinetically simulated by considering the presence of a tissue compartment. Indeed, most drugs given by IV bolus dose decline in a biphasic fashion, that is, plasma drug concentrations rapidly decline soon after IV bolus injection, and then decline moderately as some of the drug that initially distributes (equilibrates) into the tissue moves back into the plasma. Although $C_t$ is not useful, $D_t$, or amount of drug in the tissue compartment is useful because it shows how much drug accumulates extravascularly in the body at any time. The two-compartment model provides a simple way to keep track of the mass balance of the drug in the body.

Multicompartment models provide answers to such questions as: (1) How much of a dose is eliminated? (2) How much drug remains in the plasma compartment? and (3) How much drug accumulates in
the tissue compartment? The latter information is particularly useful for drug safety since the amount of drug in a deep tissue compartment may be harder to eliminate by renal excretion or by dialysis after drug overdose.

Multicompartment models explain the observation that, after a rapid IV bolus drug injection, the plasma level–time curve does not decline linearly, implying that the drug does not equilibrate rapidly in the body, as observed for a single first-order rate process in a one-compartment model. Instead, a biphasic or triphasic drug concentration decline is often observed. The initial decline phase represents the drug leaving the plasma compartment (composed of blood and highly perfused tissues) and entering one or more tissue compartments as well as being eliminated. Later, the plasma drug concentrations decline more gradually after drug distribution to the tissues is completed, or plasma drug equilibrium with peripheral tissues occurs. Drug kinetics after distribution is characterized by the composite rate constant, \( b \) (or \( b' \)), which can be obtained from the terminal slope (Equation 4.10 or 4.11).

Nonlinear plasma drug level–time decline occurs because some drugs distribute at various rates into different tissue groups. Multicompartment models were developed to explain and predict plasma and tissue concentrations for those types of drugs. In contrast, a one-compartment model is used when the drug appears to distribute into tissues instantaneously and uniformly. For both one- and multicompartment models, the drug in the tissues that have the highest blood perfusion equilibrates rapidly with the drug in the plasma. These highly perfused tissues and blood make up the central compartment (often considered as the plasma compartment). While this initial drug distribution is taking place, multicompartment drugs are delivered concurrently to one or more peripheral compartments (often considered as the tissue compartment) composed of groups of tissues with lower blood perfusion and different affinity for the drug. A drug will concentrate in a tissue in accordance with the affinity of the drug for that particular tissue. For example, lipid-soluble drugs tend to accumulate in fat tissues. Drugs that bind plasma proteins may be more concentrated in the plasma, because protein-bound drugs do not diffuse easily into the tissues. Drugs may also bind with tissue proteins and other macromolecules, such as DNA and melanin.

Tissue sampling is invasive, and the drug concentration in the tissue sample may not represent the drug concentration in the entire organ. Occasionally, tissue samples may be collected after a drug overdose episode. For example, the two-compartment model has been used to describe the distribution of colchicine, even though the drug’s toxic tissue levels after fatal overdoses has only been recently described (Rochdi et al., 1992). Colchicine distribution is now known to be affected by P-gp (also known as ABCB1 or MDR1, a common transport protein of the ABC cassette transporter subfamily found in the body). A drug transporter is now known to influence the curvature in the log plasma drug concentration–time graph. The drug isotretinoin has a long half-life because of substantial distribution into lipid tissues.

Kinetic analysis of a multicompartment model assumes that all transfer rate processes for the passage of drug into or out of individual compartments are first-order processes. On the basis of this assumption, the plasma level–time curve for a drug that follows a multicompartment model is best described by the summation of a series of exponential terms, each corresponding to first-order rate processes associated with a given compartment. Most multicompartment models used in pharmacokinetics are mamillary models. Mamillary models are well connected and dynamically exchange drug concentration between compartments making them very suitable for modeling drug distribution.

Because of these distribution factors, drugs will generally concentrate unevenly in the tissues, and different groups of tissues will accumulate the drug at different rates. A summary of the approximate blood flow to major human tissues is presented in Table 4-1. Many different tissues and rate processes are involved in the distribution of any drug. However, limited physiologic significance has been assigned to a few groups of tissues (Table 4-2).

The nonlinear profile of plasma drug concentration–time is the result of many factors interacting together, including blood flow to the tissues, the permeability of the drug into the tissues, the capacity of the tissues to accumulate drug, and the effect of disease factors on these processes (see Chapter 10). Impaired cardiac function may produce a change in blood flow
Multicompartment Models: Intravenous Bolus Administration

and these affect the drug distributive phase, whereas impairment of the kidney or the liver may decrease drug elimination as shown by a prolonged elimination half-life and corresponding reduction in the slope of the terminal elimination phase of the curve. Frequently, multiple factors can complicate the distribution profile in such a way that the profile can only be described clearly with the assistance of a simulation model.

**TWO-COMPARTMENT OPEN MODEL**

Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process. The plasma level–time curve for a drug that follows a two-compartment model (Fig. 4-1) shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes—distribution and elimination. A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model. In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment. The **central compartment** represents the blood, extracellular fluid, and highly perfused tissues. The drug distributes rapidly and uniformly in the central compartment. A second compartment, known as the

---

**TABLE 4-1 Blood Flow to Human Tissues**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Percent Body Weight</th>
<th>Percent Cardiac Output</th>
<th>Blood Flow (mL/100 g tissue per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.02</td>
<td>1</td>
<td>550</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.4</td>
<td>24</td>
<td>450</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.04</td>
<td>2</td>
<td>400</td>
</tr>
<tr>
<td>Liver</td>
<td>2.0</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Hepatic Portal</td>
<td></td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Portal-drained viscera</td>
<td>2.0</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Heart (basal)</td>
<td>0.4</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>Brain</td>
<td>2.0</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Skin</td>
<td>7.0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Muscle (basal)</td>
<td>40.0</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>7.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fat</td>
<td>15.0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>


Tissue uptake will also depend on such factors as fat solubility, degree of ionization, partitioning, and protein binding of the drug.

Adapted with permission from Eger (1963).

**TABLE 4-2 General Grouping of Tissues According to Blood Supply**

<table>
<thead>
<tr>
<th>Blood Supply</th>
<th>Tissue Group</th>
<th>Percent Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly perfused</td>
<td>Heart, brain, hepatic-portal system, kidney, and endocrine glands</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Skin and muscle</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Adipose (fat) tissue and marrow</td>
<td>19</td>
</tr>
<tr>
<td>Slowly perfused</td>
<td>Bone, ligaments, tendons, cartilage, teeth, and hair</td>
<td>22</td>
</tr>
</tbody>
</table>

*Tissue uptake will also depend on such factors as fat solubility, degree of ionization, partitioning, and protein binding of the drug.

Adapted with permission from Eger (1963).
tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly. Drug transfer between the two compartments is assumed to take place by first-order processes.

There are several possible two-compartment models (Fig. 4-2). Model A is used most often and describes the plasma level–time curve observed in Fig. 4-1. By convention, compartment 1 is the central compartment and compartment 2 is the tissue compartment. The rate constants \( k_{12} \) and \( k_{21} \) represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (\( k_{12} \)) and from compartment 2 to compartment 1 (\( k_{21} \)). The transfer constants are sometimes termed micro-constants, and their values cannot be estimated directly.

Most two-compartment models assume that elimination occurs from the central compartment model, as shown in Fig. 4-2 (model A), unless other information about the drug is known. Drug elimination is presumed to occur from the central compartment, because the major sites of drug elimination (renal excretion and hepatic drug metabolism) occur in organs such as the kidney and liver, which are highly perfused with blood.

The plasma level–time curve for a drug that follows a two-compartment model may be divided into two parts, (a) a distribution phase and (b) an elimination phase. The two-compartment model assumes that, at \( t = 0 \), no drug is in the tissue compartment. After an IV bolus injection, drug equilibrates rapidly in the central compartment. The distribution phase of the curve represents the initial, more rapid decline of drug from the central compartment into the tissue compartment (Fig. 4-1, line \( a \)). Although drug elimination and distribution occur concurrently during the distribution phase, there is a net transfer of drug from the central compartment to the tissue compartment. The fraction of drug in the tissue compartment during the distribution phase increases up to a maximum in a given tissue, whose value may be greater or less than the plasma drug concentration. At maximum tissue concentrations, the rate of drug entry into the tissue equals the rate of drug exit from the tissue. The fraction of drug in the tissue compartment is now in equilibrium (distribution equilibrium) with the fraction of drug in the central compartment (Fig. 4-3), and the drug concentrations in both the central and tissue compartments decline in parallel and more slowly compared to the distribution phase. This decline is a first-order process and is called the elimination phase or the beta (\( \beta \)) phase (Fig. 4-1, line \( b \)). Since plasma and tissue concentrations decline in parallel, plasma drug concentrations provide some indication of the concentration of drug in the tissue. At this point, drug kinetics appears to follow a one-compartment model in which drug elimination is a first-order process described by \( b \) (also known as beta). A typical tissue drug level curve after a single intravenous dose is shown in Fig. 4-3.
Tissue drug concentrations in the pharmacokinetic model are theoretical only. The drug level in the theoretical tissue compartment can be calculated once the parameters for the model are determined. However, the drug concentration in the tissue compartment represents the average drug concentration in a group of tissues rather than any real anatomic tissue drug concentration. In reality, drug concentrations may vary among different tissues and possibly within an individual tissue. These varying tissue drug concentrations are due to differences in the partitioning of drug into the tissues, as discussed in Chapter 10.

In terms of the pharmacokinetic model, the differences in tissue drug concentration is reflected in the $k_{12}/k_{21}$ ratio. Thus, tissue drug concentration may be higher or lower than the plasma drug concentrations, depending on the properties of the individual tissue. Moreover, the elimination rates of drug from the tissue compartment may not be the same as the elimination rates from the central compartment. For example, if $k_{12}C_p$ is greater than $k_{21}C_t$ (rate into tissue > rate out of tissue), tissue drug concentrations will increase and plasma drug concentrations will decrease. Real tissue drug concentration can sometimes be calculated by the addition of compartments to the model until a compartment that mimics the experimental tissue concentrations is found.

In spite of the hypothetical nature of the tissue compartment, the theoretical tissue level is still valuable information for clinicians. The theoretical tissue concentration, together with the blood concentration, gives an accurate method of calculating the total amount of drug remaining in the body at any time (see digoxin example in Table 4-5). This information would not be available without pharmacokinetic models.

In practice, a blood sample is removed periodically from the central compartment and the plasma is analyzed for the presence of drug. The drug plasma level–time curve represents a phase of initial rapid equilibration with the central compartment (the distribution phase), followed by an elimination phase after the tissue compartment has also equilibrated with drug. The distribution phase may take minutes or hours and may be missed entirely if the blood is sampled too late or at wide intervals after drug administration.

In the model depicted above, $k_{12}$ and $k_{21}$ are first-order rate constants that govern the rate of drug distribution into and out of the tissues:

$$\frac{dC_c}{dt} = k_{12}C_p - k_{21}C_t$$  \hspace{1cm} (4.1)

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by Equations 4.2 and 4.3:

$$C_p = \frac{D_p}{V_p}$$  \hspace{1cm} (4.2)

$$C_t = \frac{D_t}{V_t}$$  \hspace{1cm} (4.3)

where $D_p = \text{amount of drug in the central compartment}$, $D_t = \text{amount of drug in the tissue compartment}$, $V_p = \text{volume of drug in the central compartment}$, and $V_t = \text{volume of drug in the tissue compartment}$.

$$\frac{dC_p}{dt} = k_{21} \frac{D_t}{V_t} - k_{12} \frac{D_p}{V_p} - k \frac{D_p}{V_d}$$  \hspace{1cm} (4.4)

$$\frac{dC_t}{dt} = k_{12} \frac{D_p}{V_p} - k_{21} \frac{D_t}{V_t}$$  \hspace{1cm} (4.5)

Solving Equations 4.4 and 4.5 will give Equations 4.6 and 4.7, which describe the change in drug concentration in the blood and in the tissue with respect to time:
Chapter 4

Equations 4.13 and 4.14, and do not have actual physiologic significance.

\[
C_p = \frac{D_0}{V_p} \left( \frac{k_{21} - a}{b - a} e^{-at} + \frac{k_{21} - b}{a - b} e^{-bt} \right) 
\]  
(4.6)

\[
C_t = \frac{D_0}{V_t} \left( \frac{k_{12} - a}{b - a} e^{-at} + \frac{k_{12} - b}{a - b} e^{-bt} \right) 
\]  
(4.7)

\[
D_b = \frac{D_0}{V_b} \left( \frac{k_{21} - a}{b - a} e^{-at} + \frac{k_{21} - b}{a - b} e^{-bt} \right) 
\]  
(4.8)

\[
D_t = \frac{D_0}{V_t} \left( \frac{k_{12} - a}{b - a} e^{-at} + \frac{k_{12} - b}{a - b} e^{-bt} \right) 
\]  
(4.9)

where \( D_0 = \) dose given intravenously, \( t = \) time after administration of dose, and \( a \) and \( b \) are constants that depend solely on \( k_{12}, k_{21} \), and \( k \). The amount of drug remaining in the plasma and tissue compartment at any time may be described realistically by Equations 4.8 and 4.9.

The rate constants for the transfer of drug between compartments are referred to as microconstants or transfer constants. They relate the amount of drug being transferred per unit time from one compartment to the other. The values for these microconstants cannot be determined by direct measurement, but they can be estimated by a graphic method.

\[
a + b = k_{12} + k_{21} + k 
\]  
(4.10)

\[
ab = k_{21}k 
\]  
(4.11)

The constants \( a \) and \( b \) are hybrid first-order rate constants for the distribution phase and elimination phase, respectively. The mathematical relationship of \( a \) and \( b \) to the rate constants are given by Equations 4.10 and 4.11, which are derived after integration of Equations 4.4 and 4.5. Equation 4.6 can be transformed into the following expression:

\[
C_p = Ae^{-at} + Be^{-bt} 
\]  
(4.12)

\( A \) and \( B \) are intercepts on the y axis for each exponential segment of the curve in Equation 4.12. These values may be obtained graphically by the method of residuals or by computer. Intercepts \( A \) and \( B \) are actually hybrid constants, as shown in

Method of Residuals

The method of residuals (also known as feathering or peeling) is a useful procedure for fitting a curve to the experimental data of a drug when the drug does not clearly follow a one-compartment model. For example, 100 mg of a drug was administered by rapid IV injection to a healthy 70-kg adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed for drug. The following data were obtained:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Plasma Concentration (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43.00</td>
</tr>
<tr>
<td>0.5</td>
<td>32.00</td>
</tr>
<tr>
<td>1.0</td>
<td>20.00</td>
</tr>
<tr>
<td>1.5</td>
<td>14.00</td>
</tr>
<tr>
<td>2.0</td>
<td>11.00</td>
</tr>
<tr>
<td>4.0</td>
<td>6.50</td>
</tr>
<tr>
<td>8.0</td>
<td>2.80</td>
</tr>
<tr>
<td>12.0</td>
<td>1.20</td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
</tr>
</tbody>
</table>

When these data are plotted on semilogarithmic graph paper, a curved line is observed (Fig. 4-4). The curved-line relationship between the logarithm of the plasma concentration and time indicates that the drug is distributed in more than one compartment. From these data a biexponential equation, Equation 4.12, may be derived, either by computer or by the method of residuals.

As shown in the biexponential curve in Fig. 4-4, the decline in the initial distribution phase is more
which, in common logarithms, is:

$$\log C_p = -\frac{b t}{2.3} + \log B$$  \hspace{1cm} (4.16)

From Equation 4.16, the rate constant can be obtained from the slope ($-b/2.3$) of a straight line representing the terminal exponential phase (Fig. 4-4). The $t_{1/2}$ for the elimination phase (beta half-life) can be derived from the following relationship:

$$t_{1/2} = \frac{0.693}{b}$$  \hspace{1cm} (4.17)

In the sample case considered here, $b$ was found to be 0.21 h$^{-1}$. From this information the regression line for the terminal exponential or $b$ phase is extrapolated to the $y$ axis; the $y$ intercept is equal to $B$, or 15 μg/mL. Values from the extrapolated line are then subtracted from the original experimental data points (Table 4-3) and a straight line is obtained. This line represents the rapidly distributed $a$ phase (Fig. 4-4).

The new line obtained by graphing the logarithm of the residual plasma concentration ($C_p - C'_p$) against time represents the $a$ phase. The value for $a$ is 1.8 h$^{-1}$, and the $y$ intercept is 45 μg/mL. The elimination $t_{1/2b}$ is computed from $b$ by use of Equation 4.17 and has the value of 3.3 hours.

![Plasma level–time curve for a two-compartment open model.](image)

**TABLE 4-3 Application of the Method of Residuals**

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>$C_p$ Observed Plasma Level</th>
<th>$C'_p$ Extrapolated Plasma Concentration</th>
<th>$C_p - C'_p$ Residual Plasma Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>43.0</td>
<td>14.5</td>
<td>28.5</td>
</tr>
<tr>
<td>0.5</td>
<td>32.0</td>
<td>13.5</td>
<td>18.5</td>
</tr>
<tr>
<td>1.0</td>
<td>20.0</td>
<td>12.3</td>
<td>7.7</td>
</tr>
<tr>
<td>1.5</td>
<td>14.0</td>
<td>11.0</td>
<td>3.0</td>
</tr>
<tr>
<td>2.0</td>
<td>11.0</td>
<td>10.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4.0</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.0</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A number of pharmacokinetic parameters may be derived by proper substitution of rate constants $a$ and $b$ and $y$ intercepts $A$ and $B$ into the following equations:

$$k = \frac{ab(A + B)}{Ab + Ba} \quad (4.18)$$

$$k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)} \quad (4.19)$$

$$k_{21} = \frac{Ab + Ba}{A + B} \quad (4.20)$$

### CLINICAL APPLICATION

**Digoxin in a Normal Patient and in a Renal-Failure Patient—Simulation of Plasma and Tissue Level of a Two-Compartment Model Drug**

Once the pharmacokinetic parameters are determined for an individual, the amount of drug remaining in the plasma and tissue compartment may be calculated using Equations 4.8 and 4.9. The pharmacokinetic data for digoxin were calculated in a normal and in a renal-impaired, 70-kg subject using the parameters in Table 4-4 as reported in the literature. The amount of digoxin remaining in the plasma and tissue compartment is tabulated in Table 4-5 and plotted in Fig. 4-5. It can be seen that digoxin stored in the plasma declines rapidly during the initial distributive phase, while drug amount in the tissue compartment takes 3–4 hours to accumulate for a normal subject. It is interesting that clinicians have recommended that digoxin plasma samples be taken at least several hours after IV bolus dosing (3–4+ hours, Winters, 1994, and 4–8 hours, Schumacher, 1995) for a normal subject, since the equilibrated level is more representative of myocardium digoxin level. In the simulation below, the amount of the drug in the plasma compartment at any time divided by $V_p$ (54.6 L for the normal subject) will yield the plasma digoxin level. At 4 hours after an IV dose of 0.25 mg, $C_p = D_p/V_p = 24.43 \mu g/54.6 \text{ L} = 0.45 \text{ ng/mL}$, corresponding to $3 \times 0.45 \text{ ng/mL} = 1.35 \text{ ng/mL}$ if a full loading dose of 0.75 mg is given in a single dose. Although the initial plasma drug levels were much higher than after equilibration, the digoxin plasma concentrations are generally regarded as not toxic, since drug distribution is occurring rapidly.

The tissue drug levels were not calculated. The tissue drug concentration represents the hypothetical tissue pool, which may not represent actual drug concentrations in the myocardium. In contrast, the amount of drug remaining in the tissue pool is real, since the amount of drug is calculated using mass balance. The rate of drug entry into the tissue in micrograms per hour at any time is $k_{12}D_p$, while the rate of drug leaving the tissue is $k_{21}D$, in the same units. Both of these rates may be calculated from Table 4-5 using $k_{12}$ and $k_{21}$ values listed in Table 4-4.

Although some clinicians assume that tissue and plasma concentrations are equal when at full equilibration, tissue and plasma drug ratios are determined by the partition coefficient (a drug-specific physical ratio that measures the lipid/water affinity of a drug) and the extent of protein binding of the drug. Figure 4-5 shows that the time for the RF (renal-failure or renal-impaired) patient to reach stable tissue drug levels is longer than the time for the normal subject due to changes in the elimination and transfer rate constants. As expected, a significantly higher amount of digoxin remains in both the plasma and tissue compartment in the renally impaired subject compared to the normal subject.

### TABLE 4-4 Two-Compartment Model Pharmacokinetic Parameters of Digoxin

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unit</th>
<th>Normal</th>
<th>Renal Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{12}$</td>
<td>h$^{-1}$</td>
<td>1.02</td>
<td>0.45</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>h$^{-1}$</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>$k$</td>
<td>h$^{-1}$</td>
<td>0.18</td>
<td>0.04</td>
</tr>
<tr>
<td>$V_p$</td>
<td>L/kg</td>
<td>0.78</td>
<td>0.73</td>
</tr>
<tr>
<td>$D$</td>
<td>μg/kg</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>$a$</td>
<td>1/h</td>
<td>1.331</td>
<td>0.593</td>
</tr>
<tr>
<td>$b$</td>
<td>1/h</td>
<td>0.019</td>
<td>0.007</td>
</tr>
</tbody>
</table>

### PRACTICE PROBLEM

From Figure 4-5 or Table 4-4, how many hours does it take for maximum tissue concentration to be reached in the normal and the renal-impaired patient?
The distribution half-life of digoxin is about 35 minutes based on Table 4-4. Both clinical experience and simulated tissue amount in Table 4-4 recommend “several hours” for equilibration, longer than $5 \times 35$ minutes. (1) Is digoxin elimination in tissue adequately modeled in this example? (2) Digoxin was not known to be a P-gp substrate when the data were analyzed, can the presence of a transporter at the target site change tissue drug concentration, necessitating a longer equilibration time?

Generally, the ability to obtain a blood sample and get accurate data in the alpha (distribution) phase...

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Normal Renal Function</th>
<th>Renal Failure (RF)</th>
<th>Digoxin Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$D_p$ ($\mu$g)</td>
<td>$D_t$ ($\mu$g)</td>
<td>$D_p$ ($\mu$g)</td>
</tr>
<tr>
<td>0.00</td>
<td>252.00</td>
<td>0.00</td>
<td>252.00</td>
</tr>
<tr>
<td>0.10</td>
<td>223.68</td>
<td>24.04</td>
<td>240.01</td>
</tr>
<tr>
<td>0.60</td>
<td>126.94</td>
<td>105.54</td>
<td>189.63</td>
</tr>
<tr>
<td>1.00</td>
<td>84.62</td>
<td>140.46</td>
<td>158.78</td>
</tr>
<tr>
<td>2.00</td>
<td>40.06</td>
<td>174.93</td>
<td>107.12</td>
</tr>
<tr>
<td>3.00</td>
<td>27.95</td>
<td>181.45</td>
<td>78.44</td>
</tr>
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<td>4.00</td>
<td>24.43</td>
<td>180.62</td>
<td>62.45</td>
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<tr>
<td>5.00</td>
<td>23.17</td>
<td>177.91</td>
<td>53.48</td>
</tr>
<tr>
<td>6.00</td>
<td>22.53</td>
<td>174.74</td>
<td>48.39</td>
</tr>
<tr>
<td>7.00</td>
<td>22.05</td>
<td>171.50</td>
<td>45.45</td>
</tr>
<tr>
<td>8.00</td>
<td>21.62</td>
<td>168.28</td>
<td>43.69</td>
</tr>
<tr>
<td>9.00</td>
<td>21.21</td>
<td>165.12</td>
<td>41.85</td>
</tr>
<tr>
<td>10.00</td>
<td>20.81</td>
<td>162.01</td>
<td>40.89</td>
</tr>
<tr>
<td>11.00</td>
<td>20.42</td>
<td>158.96</td>
<td>40.32</td>
</tr>
<tr>
<td>12.00</td>
<td>20.03</td>
<td>155.97</td>
<td>39.62</td>
</tr>
<tr>
<td>13.00</td>
<td>19.65</td>
<td>153.04</td>
<td>39.32</td>
</tr>
<tr>
<td>16.00</td>
<td>18.57</td>
<td>144.56</td>
<td>38.62</td>
</tr>
<tr>
<td>24.00</td>
<td>15.95</td>
<td>124.17</td>
<td>37.44</td>
</tr>
</tbody>
</table>

* $D_p$, drug in plasma compartment; $D_t$, drug in tissue compartment.
Source: Data generated from parameters published by Harron (1989).

**PRACTICAL FOCUS**

The distribution half-life of digoxin is about 35 minutes based on Table 4-4. Both clinical experience and simulated tissue amount in Table 4-4 recommend “several hours” for equilibration, longer than $5t \frac{1}{2}_a \times 0.694/a$ or $5 \times 35$ minutes. (1) Is digoxin elimination in tissue adequately modeled in this example? (2) Digoxin was not known to be a P-gp substrate when the data were analyzed, can the presence of a transporter at the target site change tissue drug concentration, necessitating a longer equilibration time?

Generally, the ability to obtain a blood sample and get accurate data in the alpha (distribution) phase...
Since clearance is the term most often used in clinical
pharmacy, why is it necessary to know the other
pharmacokinetic parameters?

Apparent Volumes of Distribution
As discussed in Chapter 3, the apparent \( V_d \) is a useful parameter that relates plasma concentration to the amount of drug in the body. For drugs with large extravascular distribution, the apparent volume of distribution is generally large. Conversely, for polar drugs with low lipid solubility, the apparent \( V_d \) is generally small. Drugs with high peripheral tissue binding also contribute to a large apparent \( V_d \). In multiple-compartment kinetics, such as the two-compartment model, several types of volumes of distribution, each based on different assumptions, can be calculated. Volumes of distribution generally reflect the extent of drug distribution in the body on a relative basis, and the calculations depend on the availability of data. In general, it is important to refer to the same volume parameter when comparing kinetic changes in disease states. Unfortunately, values of apparent volumes of distribution of drugs from tables in the clinical literature are often listed without specifying the underlying kinetic processes, model parameters, or methods of calculation.

Volume of the Central Compartment
The volume of the central compartment is useful for determining the drug concentration directly after an IV injection into the body. In clinical pharmacy, this volume is also referred to as \( V_i \) or the initial volume of distribution as the drug distributes within the plasma and other accessible body fluids. This volume is generally smaller than the terminal volume of distribution after drug distribution to tissue is completed. The volume of the central compartment is generally greater than 3 L, which is the volume of the plasma fluid for an average adult. For many polar drugs, an initial volume of 7–10 L may be interpreted as rapid drug distribution within the plasma and some extracellular fluids. For example, the \( V_p \) of moxalactam ranges from 0.12 to 0.15 L/kg, corresponding to about 8.4 to 10.5 L for a typical
At time $t = 0$, $e^0 = 1$. Therefore,

$$C_p^0 = A + B \quad (4.23)$$

$V_p$ is determined from Equation 4.24 by measuring $A$ and $B$ after feathering the curve, as discussed previously:

$$V_p = \frac{D_0}{A + B} \quad (4.24)$$

Alternatively, the volume of the central compartment may be calculated from the $[AUC]_0^{-\infty}$ in a manner similar to the calculation for the apparent $VD$ in the one-compartment model. For a one-compartment model

$$[AUC]_0^{-\infty} = \frac{D_0}{kV_p} \quad (4.25)$$

In contrast, $[AUC]_0^{-\infty}$ for the two-compartment model is:

$$[AUC]_0^{-\infty} = \frac{D_0}{kV_p} \quad (4.26)$$

Rearrangement of this equation yields:

$$V_p = \frac{D_0}{k[AUC]_0^{-\infty}} \quad (4.27)$$

### Table 4-6 Pharmacokinetic Parameters (mean ± SD) of Moxalactam in Three Groups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>$A$ $\mu g/mL$</th>
<th>$B$ $\mu g/mL$</th>
<th>$a$ $h^{-1}$</th>
<th>$b$ $h^{-1}$</th>
<th>$k$ $h^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138.9 ± 114.9</td>
<td>157.8 ± 87.1</td>
<td>6.8 ± 4.5</td>
<td>0.20 ± 0.12</td>
<td>0.38 ± 0.26</td>
</tr>
<tr>
<td>2</td>
<td>115.4 ± 65.9</td>
<td>115.0 ± 40.8</td>
<td>5.3 ± 3.5</td>
<td>0.27 ± 0.08</td>
<td>0.50 ± 0.17</td>
</tr>
<tr>
<td>3</td>
<td>102.9 ± 39.4</td>
<td>89.0 ± 36.7</td>
<td>5.6 ± 3.8</td>
<td>0.37 ± 0.09</td>
<td>0.71 ± 0.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>$V_p$ L/kg</th>
<th>$V_t$ L/kg</th>
<th>$(V_{p\alpha})$ L/kg</th>
<th>$(V_{p\beta})$ L/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.12 ± 0.05</td>
<td>0.08 ± 0.04</td>
<td>0.20 ± 0.09</td>
<td>0.21 ± 0.09</td>
</tr>
<tr>
<td>2</td>
<td>0.14 ± 0.06</td>
<td>0.09 ± 0.04</td>
<td>0.23 ± 0.10</td>
<td>0.24 ± 0.12</td>
</tr>
<tr>
<td>3</td>
<td>0.15 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>0.25 ± 0.08</td>
<td>0.29 ± 0.09</td>
</tr>
</tbody>
</table>

70-kg patient (Table 4-6). In contrast, $V_p$ of hydro- morphine is about 24 L, possibly because of its rapid exit from the plasma into tissues even during the initial phase.

As in the case of the one-compartment model, $V_p$ may be determined from the dose and the instantaneous plasma–drug concentration, $C_p^0$. $V_p$ is also useful in the determination of drug clearance if $k$ is known, as in Chapter 3.

In the two-compartment model, $V_p$ may also be considered a mass balance factor governed by the mass balance between dose and concentration, i.e., drug concentration multiplied by the volume of the fluid must equal the dose at time $= 0$. At time $= 0$, no drug is eliminated, $D_0 = V_pC_p^0$. The basic model assumption is that plasma–drug concentration is representative of drug concentration within the distribution fluid. If this statement is true, then the volume of distribution will be 3 L; if it is not, then distribution of drug may also occur outside the vascular pool.

$$V_p = \frac{D_0}{C_p^0} \quad (4.21)$$

At zero time ($t = 0$), all of the drug in the body is in the central compartment. $C_p^0$ can be shown to be equal to $A + B$ by the following equation.

$$C_p^0 = A e^{-at} + B e^{-bt} \quad (4.22)$$
**Apparent Volume of Distribution at Steady State**

At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment. These rates of drug transfer are described by the following expressions:

\[ D_{p,21} = D_p k_{12} \quad (4.28) \]

\[ D_s = \frac{k_{12} D_p}{k_{21}} \quad (4.29) \]

Because the amount of drug in the central compartment, \( D_p \), is equal to \( V_p C_p \), by substitution in the above equation,

\[ D_s = \frac{k_{12} C_p V_p}{k_{21}} \quad (4.30) \]

The total amount of drug in the body at steady state is equal to the sum of the amount of drug in the tissue compartment, \( D_t \), and the amount of drug in the central compartment, \( D_p \). Therefore, the apparent volume of drug at steady state \( (V_D)_{ss} \) may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state:

\[ (V_D)_{ss} = \frac{D_p + D_t}{C_p} \quad (4.31) \]

Substituting Equation 4.30 into Equation 4.31, and expressing \( D_p \) as \( V_p C_p \), a more useful equation for the calculation of \( (V_D)_{ss} \) is obtained:

\[ (V_D)_{ss} = \frac{C_p V_p + k_{12} V_p C_p/k_{21}}{C_p} \quad (4.32) \]

which reduces to

\[ (V_D)_{ss} = V_p + \frac{k_{12}}{k_{21}} V_p \quad (4.33) \]

In practice, Equation 4.33 is used to calculate \( (V_D)_{ss} \). The \( (V_D)_{ss} \) is a function of the transfer constants, \( k_{12} \) and \( k_{21} \), which represent the rate constants of drug going into and out of the tissue compartment, respectively. The magnitude of \( (V_D)_{ss} \) is dependent on the hemodynamic factors responsible for drug distribution and on the physical properties of the drug, properties which, in turn, determine the relative amount of intra- and extravascular drug remaining in the body.

**Extrapolated Volume of Distribution**

The extrapolated volume of distribution \( (V_D)_{exp} \) is calculated by the following equation:

\[ (V_D)_{exp} = \frac{D_0}{B} \quad (4.34) \]

where \( B \) is the \( y \) intercept obtained by extrapolation of the \( b \) phase of the plasma level curve to the \( y \) axis (Fig. 4-4). Because the \( y \) intercept is a hybrid constant, as shown by Equation 4.14, \( (V_D)_{exp} \) may also be calculated by the following expression:

\[ (V_D)_{exp} = V_p \left( a - \frac{b}{k_{21} - b} \right) \quad (4.35) \]

This equation shows that a change in the distribution of a drug, which is observed by a change in the value for \( V_p \), will be reflected in a change in \( (V_D)_{exp} \).

**Volume of Distribution by Area**

The volume of distribution by area \( (V_D)_{area} \), also known as \( (V_D)_β \), is obtained through calculations similar to those used to find \( V_p \), except that the rate constant \( b \) is used instead of the overall elimination rate constant \( k \). \( (V_D)_β \) is often calculated from total body clearance divided by \( b \) and is influenced by drug elimination in the beta, or \( b \), phase. Reduced drug clearance from the body may increase AUC, such that \( (V_D)_β \) is either reduced or unchanged depending on the value of \( b \), as shown by Equation 4.35.

\[ (V_D)_β = (V_D)_{area} = \frac{D_0}{b[AUC]_0} \quad (4.36) \]

Generally, reduced drug clearance is accompanied by a decrease in the constant \( b \) (ie, an increase in the \( b \) elimination half-life). For example, in patients with renal dysfunction, the elimination
half-life of the antibiotic amoxacillin is longer because renal clearance is reduced.

Because total body clearance is equal to \( D_0/ [\text{AUC}]_\infty \), \((V_D)_b\) may be expressed in terms of clearance and the rate constant \( b\):

\[
(V_D)_b = \frac{Cl}{b} \quad (4.37)
\]

Substituting \(kV_p\) for clearance in Equation 4.37, one obtains:

\[
(V_D)_b = \frac{kV_p}{b} \quad (4.38)
\]

Theoretically, the value for \( b\) may remain unchanged in patients showing various degrees of moderate renal impairment. In this case, a reduction in \((V_D)_b\) may account for all the decrease in \(Cl\), while \( b\) is unchanged in Equation 4.38. Within the body, a redistribution of drug between the plasma and the tissue will mask the expected decline in \( b\). The following example in two patients shows that the \( b\) elimination rate constant remains the same, while the distributional rate constants change. Interestingly, \( V_p\) is unchanged, while \((V_D)_b\) would be greatly changed in the simulated example. An example of a drug showing a constant \( b\) slope while the renal function as measured by \( Cl_{cr}\) decreases from 107 to 56, 34, and 6 mL/min (see Chapter 6) has been observed with the aminoglycoside drug gentamicin in various patients after IV bolus dose (Schentag et al. 1977). Gentamicin follows polyexponential decline with a significant distributive phase. The following simulation problem may help clarify the situation by changing \( k\) and clearance while keeping \( b\) constant.

**PRACTICE PROBLEM**

Simulated plasma drug concentrations after an IV bolus dose (100 mg) of an antibiotic in two patients, Patient 1 with a normal \( k\), and Patient 2 with a reduced \( k\), are shown in Fig. 4-6. The data in the two patients were simulated with parameters using the two-compartment model equation. The parameters used are as follows:

<table>
<thead>
<tr>
<th>Patient</th>
<th>( k)</th>
<th>( V_p)</th>
<th>( Cl)</th>
<th>( k_{12})</th>
<th>( k_{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.3 h(^{-1})</td>
<td>10 L</td>
<td>3 L/h</td>
<td>5 h(^{-1})</td>
<td>0.2 h(^{-1})</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.1 h(^{-1})</td>
<td>10 L</td>
<td>1 L/h</td>
<td>2 h(^{-1})</td>
<td>0.25 h(^{-1})</td>
</tr>
</tbody>
</table>

**Questions**

1. Is a reduction in drug clearance generally accompanied by an increase in plasma drug concentration, regardless of which compartment model the drug follows?
2. Is a reduction in drug clearance generally accompanied by an increase in the \( b\) elimination half-life of a drug? [Find \((V_D)_b\) using Equation 4.37, then \( b\) using Equation 4.38.]
3. Many antibiotics follow multiexponential plasma drug concentration profiles indicating drug distribution into tissue compartments. In clinical pharmacokinetics, the terminal half-life is often determined with limited early data. Which patient has a greater terminal half-life based on the simulated data?

**Solution**

1. A reduction in drug clearance results in less drug being removed from the body per unit time. Drug clearance is model independent. Therefore, the plasma drug concentration should be higher in subjects with decreased drug clearance compared to subjects with...
normal drug clearance, regardless of which compartment model is used (see Fig. 4-6).

2. Clearance in the two-compartment model is affected by the elimination rate constant, \( b \), and the volume of distribution in the \( b \) phase, which reflects the data. A decrease in the \( (V_D)_b \) with \( b \) unchanged is possible, although this is not the common case. When this happens, the terminal data (see Fig. 4-6) conclude that the beta elimination half-lives of patients 1 and 2 are the same due to a similar \( b \). Actually, the real elimination half-life of the drug derived from \( k \) is a much better parameter, since \( k \) reflects the changes in renal function, but not \( b \), which remains unchanged since it is masked by the changes in \( (V_D)_b \).

3. Both patients have the same \( b \) value (\( b = 0.011 \) h\(^{-1}\)); the terminal slopes are identical. Ignoring early points by only taking terminal data would lead to an erroneous conclusion that the renal elimination process is unchanged, while the volume of distribution of the renally impaired patient is smaller. In this case, the renally impaired patient has a clearance of 1 L/h compared with 3 L/h for the normal subject, and yet the terminal slopes are the same. The rapid distribution of drug into the tissue in the normal subject causes a longer and steeper distribution phase. Later, redistribution of drug out of tissues masks the effect of rapid drug elimination through the kidney. In the renally impaired patient, distribution to tissue is reduced; as a result, little drug is redistributed out from the tissue in the \( b \) phase. Hence, it appears that the beta phases are identical in the two patients.

### Significance of the Volumes of Distribution

From Equations 4.31 and 4.32 we can observe that \( (V_D)_b \) is affected by changes in the overall elimination rate (ie, change in \( k \)) and by change in total body clearance of the drug. After the drug is distributed, the total amount of drug in the body during the elimination of \( b \) phase is calculated by using \( (V_D)_b \).

\( V_p \) is sometimes called the initial volume of distribution and is useful in the calculation of drug clearance. The magnitudes of the various apparent volumes of distribution have the following relationships to each other:

\[
(V_D)_\exp > (V_D)_\beta > V_p
\]

Calculation of another \( (V_D)_\alpha \), is possible in multiple dosing or infusion (see Chapters 5 and 8). \( (V_D)_\alpha \) is much larger than \( V_p \); it approximates \( (V_D)_\beta \) but differs somewhat in value, depending on the transfer constants.

In a study involving a cardiotonic drug given intravenously to a group of normal and congestive heart failure (CHF) patients, the average AUC for CHF was 40% higher than in the normal subjects. The \( b \) elimination constant was 40% less in CHF patients, whereas the average \( (V_D)_\beta \) remained essentially the same. In spite of the edematous conditions of these patients, the volume of distribution apparently remained constant. No change was found in the \( V_p \) or \( (V_D)_\beta \). In this study, a 40% increase in AUC in the CHF subjects was offset by a 40% smaller \( b \) elimination constant estimated by using computer methods. Because the dose was the same, the \( (V_D)_\beta \) would not change unless the increase in AUC is not accompanied by a change in \( b \) elimination constant.

From Equation 4.31, the clearance of the drug in CHF patients was reduced by 40% and accompanied by a corresponding decrease in the \( b \) elimination constant, possibly due to a reduction in renal blood flow as a result of reduced cardiac output in CHF patients. In physiologic pharmacokinetics, clearance (\( Cl \)) and volume of distribution \( (V_D)_\beta \) are assumed to be independent parameters that explain the impact of disease factors on drug disposition. Thus, an increase in AUC of a cardiotonic in a CHF patient was assumed to be due to a reduction in drug clearance, since the volume of distribution was unchanged. The elimination half-life was reduced due to reduction in drug clearance. In reality, pharmacokinetic changes in a complex system are dependent on many factors that interact within the system. Clearance is affected by drug uptake, metabolism, binding, and more; all of these factors can also influence the drug distribution volume. Many parameters are assumed to be constant and independent for simplification of the model. Blood flow is an independent parameter that will affect both clearance and distribution. However, blood flow...
Multicompartment Models: Intravenous Bolus Administration

is, in turn, affected and regulated by many physiologic compensatory factors.

For drugs that follow two-compartment model kinetics, changes in disease states may not result in different pharmacokinetic parameters. Conversely, changes in pharmacokinetic parameters should not be attributed to physiologic changes without careful consideration of method of curve fitting and intersubject differences. Equation 4.38 shows that, unlike a simple one-compartment open model, \((V_t)_B\) may be estimated from \(k\), \(b\), and \(V_p\). Errors in fitting are easily carried over to the other parameter estimates even if the calculations are performed by computer. The terms \(k_{12}\) and \(k_{21}\) often fluctuate due to minor fitting and experimental difference and may affect calculation of other parameters.

**Frequently Asked Questions**

- **What is the significance of the apparent volume of distribution?**
- **Why are there different volumes of distribution in the multiple compartment models?**

**Drug in the Tissue Compartment**

The apparent volume of the tissue compartment \((V_t)\) is a conceptual volume only and does not represent true anatomic volumes. The \(V_t\) may be calculated from knowledge of the transfer rate constants and \(V_p\):

\[
V_t = \frac{V_p k_{12}}{k_{21}} \quad (4.39)
\]

The calculation of the amount of drug in the tissue compartment does not entail the use of \(V_t\). Calculation of the amount of drug in the tissue compartment provides an estimate for drug accumulation in the tissues of the body. This information is vital in estimating chronic toxicity and relating the duration of pharmacologic activity to dose. Tissue compartment drug concentration is an average estimate of the tissue pool and does not mean that all tissues have this concentration. The drug concentration in a tissue biopsy will provide an estimate for drug in that tissue sample. Due to differences in blood flow and drug partitioning into the tissue, and heterogeneity, even a biopsy from the same tissue may have different drug concentrations. Together with \(V_p\) and \(C_p\), used to calculate the amount of drug in the plasma, the compartment model provides mass balance information. Moreover, the pharmacodynamic activity may correlate better with the tissue drug concentration–time curve. To calculate the amount of drug in the tissue compartment \(D_t\), the following expression is used:

\[
D_t = \frac{k_{12}D_p^0}{a - b} (e^{-bt} - e^{-at}) \quad (4.40)
\]

**PRACTICAL FOCUS**

The therapeutic plasma concentration of digoxin is between 1 and 2 ng/mL; because digoxin has a long elimination half-life, it takes a long time to reach a stable, constant (steady-state) level in the body. A loading dose is usually given with the initiation of digoxin therapy. Consider the implications of the loading dose of 1 mg suggested for a 70-kg subject.

The clinical source cited an apparent volume of distribution of 7.3 L/kg for digoxin in determining the loading dose. Use the pharmacokinetic parameters for digoxin in Table 4-4.

**Solution**

The loading dose was calculated by considering the body as a one-compartment during steady state, at which time the drug well penetrates the tissue compartment. The volume of distribution \((V_p)_B\) of digoxin is much larger than \(V_p\), or the volume of the plasma compartment.

Using Equation (4.38),

\[
(V_t)_B = \frac{kV_p^0}{b} = \frac{0.18/h \times 0.78L/kg}{0.19/h} = 7.39 L/kg
\]

\[
D_t = 7390 \frac{mL}{kg} \times 70 \text{ kg} \times 1.5 \frac{ng}{mL}
\]

where \(D_t = (Vd)_B\).
Chapter 4

The desired steady plasma concentration, \((C_{P,ss})\), was selected by choosing a value in the middle of the therapeutic range. The loading dose is generally divided into two or three doses or is administered as 50% in the first dose with the remaining drug given in two divided doses 6–8 hours apart to minimize potential side effects from overdigitization. If the entire loading dose were administered intravenously, the plasma level would be about 4–5 ng/mL after 1 hour, while the level would drop to about 1.5 ng/mL at about 4 hours. The exact level after a given IV dose may be calculated using Equation 4.6 at any time desired. The pharmacokinetic parameters for digoxin are available in Table 4-4.

In addition to metabolism, digoxin distribution is affected by a number of processes besides blood flow. It and many other drugs are P-gp (P-glycoprotein) substrates, a transporter that is often located in cell membranes that efflux drug in and out of cells, and can theoretically affect \(k_{12}\) (cell uptake) and \(k_{21}\) (cell efflux). Some transporters such as P-gp or ABC (ATP-binding cassette) transporters exhibit genetic variability and therefore can contribute to pharmacokinetic variability between patients. For example, if drug transporters avidly carry drug to metabolic sites, then metabolism \(k\) would increase, and plasma levels AUC would decrease. The converse is also true; examples of drugs that are known to increase digoxin level include amidiodarone, quinidine, and verapamil. Verapamil is a common agent used to test if an unknown substrate can be blocked by a P-gp inhibitor.

Many anti-cancer drugs such as taxol, vincristine, vinblastine are P-gp substrates. P-gp can be located in GI, kidney, liver, and entry to BBB (see Chapter 10 for distribution and Chapter 12 for genetically expressed transporters). There are other organic anion and cation transporters in the body which contribute to efflux of drug into and out of cells. Efflux and translocation of a drug can cause a drug to lose efficacy (MDR resistance) in many anti-cancer drugs. It may not always be possible to distinguish a specific drug transporter in a specific organ or tissue in vivo due to ongoing perfusion and the potential for multiple transporter/carriers involved. These factors and drug binding to proteins in blood, cell, and cell membranes, and diffusion limiting processes contribute to “multiexponential” drug distribution kinetically for many drugs. Much of in vivo kinetics information can be learned by examining the kinetics of the IV bolus time-concentration profile when a suitable substrate probe is administered.

Drug Clearance

The definition of clearance of a drug that follows a two-compartment model is similar to that of the one-compartment model. **Clearance** is the volume of plasma that is cleared of drug per unit time. Clearance may be calculated without consideration of the compartment model. Thus, clearance may be viewed as a physiologic concept for drug removal, even though the development of clearance is rooted in classical pharmacokinetics.

Clearance is often calculated by a noncompartmental approach, as in Equation 4.35, in which the bolus IV dose is divided by the area under the plasma–time concentration curve from zero to infinity, \([\text{AUC}]_0^\infty\). In evaluating the \([\text{AUC}]_0^\infty\) early time points must be collected frequently to observe the rapid decline in drug concentrations (distribution phase) for drugs with multicompartment pharmacokinetics. In the calculation of clearance using the noncompartmental approach, underestimating the area can inflate the calculated value of clearance.

\[
Cl = \frac{D_0}{[\text{AUC}]_0^\infty} \tag{4.41}
\]

Equation 4.41 may be rearranged to Equation 4.42 to show that \(Cl\) in the two-compartment model is the product of \((V_D)_p\) and \(b\).

\[
Cl = (V_D)_p b \tag{4.42}
\]

If both parameters are known, then calculation of clearance is simple and more accurate than using the trapezoidal rule to obtain area. Clearance calculations that use the two-compartment model are viewed as model dependent because more assumptions are required, and such calculations cannot be regarded as noncompartmental. However, the assumptions provide additional information and, in some sense, specifically describe the drug concentration–time profile as biphasic.

Clearance is a term that is useful in calculating average drug concentrations. With many drugs, a
biphasic profile suggests a rapid tissue distribution phase followed by a slower elimination phase. Multicompartment pharmacokinetics is an important consideration in understanding drug permeation and toxicity. For example, the plasma–time profiles of aminoglycosides, such as gentamicin, are more useful in explaining toxicity than average plasma or drug concentration taken at peak or trough time.

Elimination Rate Constant
In the two-compartment model (IV administration), the elimination rate constant, $k$, represents the elimination of drug from the central compartment, whereas $b$ represents drug elimination during the beta or elimination phase, when distribution is mostly complete. Because of redistribution of drug out of the tissue compartment, the plasma–drug level curve declines more slowly in the $b$ phase. Hence $b$ is smaller than $k$; thus $k$ is a true elimination constant, whereas $b$ is a hybrid elimination rate constant that is influenced by the rate of transfer of drug into and out of the tissue compartment. When it is impractical to determine $k$, $b$ is calculated from the $b$ slope. The $t_{1/2B}$ is often used to calculate the drug dose.

THREE-COMPARTMENT OPEN MODEL

The three-compartment model is an extension of the two-compartment model, with an additional deep tissue compartment. A drug that demonstrates the necessity of a three-compartment open model is distributed most rapidly to a highly perfused central compartment, less rapidly to the second or tissue compartment, and very slowly to the third or deep tissue compartment, containing such poorly perfused tissue as bone and fat. The deep tissue compartment may also represent tightly bound drug in the tissues. The three-compartment open model is shown in Fig. 4-7.

A solution of the differential equation describing the rates of flow of drug into and out of the central compartment gives the following equation:

$$C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct} \quad (4.43)$$

where $A$, $B$, and $C$ are the $y$ intercepts of extrapolated lines for the central, tissue, and deep tissue compartments, respectively, and $a$, $b$, and $c$ are first-order rate constants for the central, tissue, and deep tissue compartments, respectively.

A three-compartment equation may be written by statisticians in the literature as

$$C_p = A e^{−λ_1t} + B e^{−λ_2t} + C e^{−λ_3t} \quad (4.43a)$$

Instead of $a$, $b$, $c$, etc., $λ_1$, $λ_2$, $λ_3$ are substituted to express the triexponential feature of the equation. Similarly, the $n$-compartment model may be expressed with $λ_1$, $λ_2$, ..., $λ_n$. In classical pharmacokinetics, the symbols $a$, $b$, $c$ that we have adopted are actually Greek symbols, $α$, $β$, $χ$. The preexponential terms are sometimes expressed as $C_1$, $C_2$, and $C_3$.

The parameters in Equation 4.43 may be solved graphically by the method of residuals (Fig. 4-8) or by computer. The calculations for the elimination rate constant $k$, volume of the central compartment, and area are shown in the following equations:

$$k = \frac{(A + B + C) abc}{Abc + Bac + Cab} \quad (4.44)$$

$$V_p = \frac{D_p}{A + B + C} \quad (4.45)$$

$$[\text{AUC}] = \frac{A}{a} + \frac{B}{b} + \frac{C}{c} \quad (4.46)$$

FIGURE 4-7  Three-compartment open model. This model, as with the previous two-compartment models, assumes that all drug elimination occurs via the central compartment.
pharmacokinetics of a one-compartment model (Vallner et al, 1981), a two-compartment model (Parab et al, 1988) or a three-compartment model (Hill et al, 1991), respectively. A comparison of these studies is listed in Table 4-7.

Comments

The adequacy of the pharmacokinetic model will depend on the sampling intervals and the drug assay. The first two studies showed a similar elimination half-life. However, both Vallner et al (1981) and Parab et al (1988) did not observe a three-compartment pharmacokinetic model due to lack of appropriate description of the early distribution phases for hydromorphone. After an IV bolus injection, hydromorphone is very rapidly distributed into the tissues. Hill et al (1991) obtained a triexponential function by closely sampling early time periods after the dose. Average distribution half-lives were 1.27 and 14.7 minutes, and the average terminal elimination was 184 minutes ($t_{1/2b}$). The average values for systemic clearance ($Cl$) was 1.66 L/min; the initial dilution volume was 24.4 L. If distribution is rapid, the drug becomes distributed during the absorption phase. Thus, hydromorphone pharmacokinetics follows a one-compartment model after a single oral dose.

Hydromorphone is administered to relieve acute pain in cancer or postoperative patients. Rapid pain

**CLINICAL APPLICATION**

**Hydromorphone (Dilaudid)**

Three independent studies on the pharmacokinetics of hydromorphone after a bolus intravenous injection reported that hydromorphone followed the

**TABLE 4-7  Comparison of Hydromorphone Pharmacokinetics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Timing of Blood Samples</th>
<th>Pharmacokinetic Parameters</th>
</tr>
</thead>
</table>
| 6 Males, 25–29 years; mean weight, 76.8 kg  
Dose, 2-mg IV bolus  
Vallner et al, 1981 | 0, 15, 30, 45 minutes  
1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours | One-compartment model  
Terminal $t_{1/2}$ = 2.64 (± 0.88) hours |
| 8 Males, 20–30 years; weight, 50–86 kg  
Dose, 2-mg IV bolus  
Parab et al, 1988 | 0, 3, 7, 15, 30, 45 minutes  
1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours | Two-compartment model  
Terminal $t_{1/2}$ = 2.36 (± 0.58) hours |
| 10 Males, 21–38 years; mean weight, 72.7 kg  
Dose, 10, 20, and 40 µg/kg, IV bolus  
Hill et al, 1991 | 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 45 minutes  
1, 1.5, 2, 2.5, 3, 4, 5 hours | Three-compartment model  
Terminal $t_{1/2}$ = 3.07 (± 0.25) hours |
relief is obtained by IV injection. Although the drug is effective orally, about 50%–60% of the drug is cleared by the liver through first-pass effects. The pharmacokinetics of hydromorphone after IV injection suggests a multicompartment model. The site of action is probably within the central nervous system, as part of the tissue compartment. The initial volume or initial dilution volume, \( V_p \), is the volume into which IV injections are injected and diluted. Hydromorphone follows linear kinetics, ie, drug concentration is proportional to dose. Hydromorphone systemic clearance is much larger than the glomerular filtration rate (GFR) of 120 mL/min (see Chapter 6), hence the drug is probably metabolized significantly by the hepatic route. A clearance of 1.66 L/min is faster than the blood flow of 1.2–1.5 L/min to the liver. The drug must be rapidly extracted or, in addition, must have extrahepatic elimination. When the distribution phase is short, the distribution phase may be disregarded provided that the targeted plasma concentration is sufficiently low and the terminal elimination phase is relatively long. If the drug has a sufficiently high target plasma drug concentration and the elimination half-life is short, the distributive phase must not be ignored. For example, lidocaine’s effective target concentration often lies close to the distributive phase, since its beta elimination half-life is very short, and ignoring the alpha phase will result in a large error in dosing projection.

**DETERMINATION OF COMPARTMENT MODELS**

Models based on compartmental analysis should always use the fewest number of compartments necessary to describe the experimental data adequately. Once an empirical equation is derived from the experimental observations, it becomes necessary to examine how well the theoretical values that are calculated from the derived equation fit the experimental data.

The observed number of compartments or exponential phases will depend on (1) the route of drug administration, (2) the rate of drug absorption, (3) the total time for blood sampling, (4) the number of samples taken within the collection period, and (5) the assay sensitivity. If drug distribution is rapid, then, after oral administration, the drug will become distributed during the absorption phase and the distribution phase will not be observed. For example, theophylline follows the kinetics of a one-compartment model after oral absorption, but after intravenous bolus (given as aminophylline), theophylline follows the kinetics of a two-compartment model. Furthermore, if theophylline is given by a slow intravenous infusion rather than by intravenous bolus, the distribution phase will not be observed. Hydromorphone (Dilaudid), which follows a three-compartment model, also follows a one-compartment model after oral administration, since the first two distribution phases are rapid.

**CLINICAL APPLICATION**

Loperamide (Imodium®) is an opioid anti-diarrhea agent that is useful for illustrating the importance of understanding drug distribution. Loperamide has little central opiate effect. Loperamide is a P-gp (an efflux transporter) substrate. The presence of P-gp transporter at the blood–brain barrier allows the drug to be pumped out of the cell at the cell membrane surface without the substrate (loperamide) entering into the interior of the cell. Mice that have had the gene for P-gp removed experimentally show profound central opioid effects when administered loperamide. Hypothesizing the presence of a tissue compartment coupled with a suitable molecular probe can provide a powerful approach toward elucidating the mechanism of drug distribution and improving drug safety.
Chapter 4

of the tissue to store drug is also a factor. Distribution half-life is generally short for many drugs because of the ample blood supply to and rapid drug equilibration in the tissue compartment. However, there is some supporting evidence that a drug with a long elimination half-life is often associated with a longer distribution phase. It is conceivable that a tissue with little blood supply and affinity for the drug may not attain a sufficiently high drug concentration to exert its impact on the overall plasma drug concentration profile during rapid elimination. In contrast, drugs such as digoxin have a long elimination half-life, and drug is eliminated slowly to allow more time for distribution to tissues. Human follicle-stimulating hormone (hFSH) injected intravenously has a very long elimination half-life, and its distribution half-life is also quite long. Drugs such as lidocaine, theophylline, and milrinone have short elimination half-lives and generally relatively short distributional half-lives.

In order to examine the effect of changing $k$ (from 0.6–0.2 h$^{-1}$) on the distributional (alpha phase) and elimination (beta phase) half-lives of various drugs, four simulations based on a two-compartment model were generated (Table 4-8). The simulations show that a drug with a smaller $k$ has a longer beta elimination half-life, and drug is eliminated slowly to allow more time for distribution to tissues. Human follicle-stimulating hormone (hFSH) injected intravenously has a very long elimination half-life, and its distribution half-life is also quite long. Drugs such as lidocaine, theophylline, and milrinone have short elimination half-lives and generally relatively short distributional half-lives.

In order to examine the effect of changing $k$ (from 0.6–0.2 h$^{-1}$) on the distributional (alpha phase) and elimination (beta phase) half-lives of various drugs, four simulations based on a two-compartment model were generated (Table 4-8). The simulations show that a drug with a smaller $k$ has a longer beta elimination half-life. Keeping all other parameters ($k_{12}, k_{21}, V_p$) constant, a smaller $k$ will result in a smaller $a$, or a slower distributional phase. Examples of drugs with various distribution and elimination half-lives are shown in Table 4-8.

**CLINICAL APPLICATION**

**Moxalactam Disodium—Effect of Changing Renal Function in Patients with Sepsis**

The pharmacokinetics of moxalactam disodium, a recently discontinued antibiotic (see Table 4-6), was examined in 40 patients with abdominal sepsis (Swanson et al, 1983). The patients were grouped according to creatinine clearances into three groups:

Group 1: Average creatinine clearance = 35.5 mL/min/1.73 m$^2$
Group 2: Average creatinine clearance = 67.1 ± 6.7 mL/min/1.73 m$^2$
TABLE 4-8 Comparison of Beta Half-Life and Distributional Half-Life of Selected Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Beta Half-Life</th>
<th>Distributional Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>1.8 hours</td>
<td>8 minutes</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1 hours</td>
<td>18 minutes</td>
</tr>
<tr>
<td>Theophylline</td>
<td>4.33 hours</td>
<td>7.2 minutes</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>2 hours</td>
<td>11 minutes</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 hours</td>
<td>14.7 minutes</td>
</tr>
<tr>
<td>Milrinone</td>
<td>3.6 hours</td>
<td>4.6 minutes</td>
</tr>
<tr>
<td>Procainamide</td>
<td>2.5–4.7 hours</td>
<td>6 minutes</td>
</tr>
<tr>
<td>Quinidine</td>
<td>6–8 hours</td>
<td>7 minutes</td>
</tr>
<tr>
<td>Lithium</td>
<td>21.39 hours</td>
<td>5 hours</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1.6 days</td>
<td>35 minutes</td>
</tr>
<tr>
<td>Human FSH</td>
<td>1 day</td>
<td>60 minutes</td>
</tr>
<tr>
<td>IgG1 kappa MAB</td>
<td>9.6 days</td>
<td>6.7 hours</td>
</tr>
<tr>
<td>Simulation 1</td>
<td>13.26 hours</td>
<td>36.24 minutes</td>
</tr>
<tr>
<td>Simulation 2</td>
<td>16.60 hours</td>
<td>43.38 minutes</td>
</tr>
<tr>
<td>Simulation 3</td>
<td>26.83 hours</td>
<td>53.70 minutes</td>
</tr>
<tr>
<td>Simulation 4</td>
<td>213.7 hours</td>
<td>1.12 hours</td>
</tr>
</tbody>
</table>

Simulation was performed using $V_p$ of 10 L; dose = 100 mg; $k_{12} = 0.5$ h$^{-1}$; $k_{21} = 0.1$ h$^{-1}$; $k = 0.6, 0.4, 0.2,$ and 0.02 hour for simulations 1–4, respectively (using Equations 4.10 and 4.11).

Source: Data from manufacturer and Schumacher (1995).

Group 3: Average creatinine clearance = 117.2 ± 29.9 mL/min/1.73 m$^2$

After intravenous bolus administration, the serum drug concentrations followed a biexponential decline (Fig. 4-10). The pharmacokinetics at steady state (2 g every 8 hours) was also examined in these patients. Mean steady-state serum concentrations ranged from 27.0 to 211.0 μg/mL and correlated inversely with creatinine clearance ($r = 0.91, p < 0.0001$). The terminal half-life ranged from 1.27 to 8.27 hours and reflected the varying renal function of the patients. Moxalactam total body clearance ($Cl$) had excellent correlation with creatinine clearance ($r^2 = 0.92$). $Cl$ determined by noncompartmental data analysis was in agreement with $Cl$ determined by nonlinear least-squares regression ($r = 0.99, p < 0.0001$). Moxalactam total body clearance was best predicted from creatinine clearance corrected for body surface area.

Questions (Refer to Table 4-6)

1. Calculate the beta half-life of moxalactam in the most renally impaired group.
2. What indicator is used to predict moxalactam clearance in the body?
3. What is the beta volume of distribution of patients in group 3 with normal renal function?
4. What is the initial volume ($V_i$) of moxalactam?

Solutions

1. Mean beta half-life is $0.693/0.20 = 3.47$ hours in the most renally impaired group.
2. Creatinine is mainly filtered through the kidney, and creatinine clearance is used as an indicator of renal glomerular filtration rate. Group 3 has normal renal function (average creatinine clearance = 117.2 mL/min/1.73 m²) (see Chapter 6).

3. Beta volume of distribution: Moxalactam clearance in group 3 subjects is 125.9 mL/min. From Equation 4.31,

\[
(V_b)_p = \frac{Cl}{b} = \frac{125.9 \text{ mL/min} \times 60 \text{ min/h}}{0.37 \text{ h}^{-1}} = 20.416 \text{ mL or 20.4 L}
\]

4. The volume of the plasma compartment, \(V_p\), is sometimes referred to as the initial volume. \(V_p\) ranges from 0.12 to 0.15 L/kg among the three groups and is considerably smaller than the steady-state volume of distribution.

Clinical Example—Azithromycin Pharmacokinetics

Following oral administration, azithromycin (Zithromax®) is an antibiotic that is rapidly absorbed and widely distributed throughout the body. Azithromycin is rapidly distributed into tissues, with high drug concentrations within cells, resulting in significantly higher azithromycin concentrations in tissue than in plasma. The high values for plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues.

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. With this regimen, \(C_{min}\) and \(C_{max}\) remained essentially unchanged from day 2 through day 5 of therapy. However, without a loading dose, azithromycin \(C_{min}\) levels required 5–7 days to reach desirable plasma levels.

The pharmacokinetic parameters of azithromycin in healthy elderly male subjects (65–85 years) were similar to those in young adults. Although higher peak drug concentrations (increased by 30%–50%) were observed in elderly women, no significant accumulation occurred.

Questions

1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At peak \(C_t\), the drug is well equilibrated between the plasma and the tissue compartment, \(C_p = C_t\), and the rates of drug diffusion into and from the plasma compartment are equal.

2. What happens after peak \(C_t\)?

3. Why is a loading dose used?

4. What is \(V_p\)? How is this volume related to \(V_p^*\)?

5. What population factors could affect the concentration of azithromycin?

Solutions

1. For a drug that follows a multicompartment model, the rates of drug diffusion into the tissues from the plasma and from the tissues into the plasma are equal at peak tissue concentrations. However, the tissue drug concentration is generally not equal to the plasma drug concentration.

2. After peak \(C_t\), the rate out of the tissue exceeds the rate into the tissue, and \(C_t\) falls. The decline of \(C_t\) parallels that of \(C_p\), and occurs because distribution equilibrium has occurred.

3. When drugs are given in a multiple-dose regimen, a loading dose may be given to achieve desired therapeutic drug concentrations more rapidly (see Chapter 8).

4. The volume of the plasma compartment, \(V_p\), is sometimes referred to as the initial volume.

5. Age and gender may affect the \(C_{max}\) level of the drug.

PRACTICAL PROBLEM

Clinical Example—Etoposide Pharmacokinetics

Etoposide is a drug used for the treatment of lung cancer. Understanding the distribution of etoposide in normal and metastatic tissues is important to avoid
drug toxicity. Etoposide follows a two-compartment model. The \((V_D)_β\) is 0.28 L/kg, and the beta elimination half-life is 12.9 hours. Total body clearance is 0.25 mL/min/kg.

**Questions**

1. What is the \((V_D)_β\) in a 70-kg subject?
2. How is the \((V_D)_β\) different than the volume of the plasma fluid, \(V_p\)?
3. Why is the \((V_D)_β\) useful if it does not represent a real tissue volume?
4. How is \((V_D)_β\) calculated from plasma time-concentration profile data for etoposide? Is \((V_D)_β\) related to total body clearance?
5. Etoposide was recently shown to be a P-gp substrate. How may this affect drug tolerance in different patients?

**Solutions**

1. \((V_D)_β\) of etoposide in a 70-kg subject is 0.28 L/kg \times 70 kg = 19.6 L.
2. The plasma fluid volume is about 3 L in a 70-kg subject and is much smaller than \((V_D)_β\). The apparent volume of distribution, \((V_D)_β\), is also considerably larger than the volume of the plasma compartment (also referred to as the initial volume by some clinicians), which includes some extracellular fluid.
3. Etoposide is a drug that follows a two-compartment model with a beta elimination phase. Within the first few minutes after an intravenous bolus dose, most of the drug is distributed in the plasma fluid. Subsequently, the drug will diffuse into tissues and drug uptake may occur. Eventually, plasma drug levels will decline due to elimination, and some redistribution as etoposide in tissue diffuses back into the plasma fluid.

The real tissue drug level will differ from the plasma drug concentration, depending on the partitioning of drug in tissues and plasma. This allows the area under the curve, the volume distribution \((V_D)_β\), to be calculated, an area that has been related to toxicities associated with many cancer chemotherapy agents.

The two-compartment model allows continuous monitoring of the amount of the drug present in and out of the vascular system, including the amount of drug eliminated. This information is important in pharmacotherapy.

4. \((V_D)_β\) may be determined from the total drug clearance and beta:

\[
Cl = b \times (V_D)_β
\]

\((V_D)_β\) is also calculated from Equation 4.36 where

\[
(V_D)_β = (V_D)_area = \frac{D_0}{b[AUC]_0}
\]

This method for \((V_D)_β\) determination using \([AUC]_0\) is popular because \([AUC]_0\) is easily calculated using the trapezoidal rule. Many values for apparent volumes of distribution reported in the clinical literature are obtained using the area equation. In general, both volume terms reflect extravascular drug distribution. \((VD)_β\) appears to be affected by the dynamics of drug disposition in the beta phase. In clinical practice, many potent drugs are not injected by bolus dose. Instead, these drugs are infused over a short interval, making it difficult to obtain accurate information on the distributive phase. As a result, many drugs that follow a two-compartment model are approximated using a single compartment. It should be cautioned that there are substantial deviations in some cases. When in doubt, the full equation with all parameters should be applied for comparison. A small bolus (test) dose may be injected to obtain the necessary data if a therapeutic dose injected rapidly causes side effects or discomfort to the subject.

**Frequently Asked Questions**

- What is the error assumed in a one-compartment model compared to a two-compartment or multi-compartment model?
- What kind of improvement in terms of patient care or drug therapy is made using the compartment model?
Drugs B and C have different distributive profiles. Drug B has a gradual distributive phase followed by a slower elimination (beta phase). The pharmacokinetic profile for drug C shows a longer and steeper distributive phase. Both drugs are well described by the two-compartment model.

Assuming drugs A and B both have the same effective level of 0.1 μg/mL, which drug would you prefer for dosing your patient based on the above plasma profiles provided and assuming that both drugs have the same toxic endpoint (as measured by plasma drug level)?

At what time would you recommend giving a second dose for each drug? Please state your supportive reasons. Hints: Draw a line at 0.1 μg/mL and see how it intersects the plasma curve for drugs B and C.

If you ignore the distributive phase and dose a drug based only on clearance or the terminal half-life, how would this dose affect the duration above minimum effective drug concentration of 0.1 μg/mL for each drug after an IV bolus dose?

Drug A represents a drug that has limited tissue distribution with mostly a linear profile and is modeled by the one-compartment model. Simple one-compartment model assumptions are often made in practice and published in the literature for simplicity.
• Which drug is acceptable to be modeled by a simple one compartment model?
• When re-dosed (i.e., at 0.1 μg/mL), which drug was equilibrated with the tissue compartment?

Significance of Distribution Phase

With many drugs, the initial phase or transient concentration is not considered as important as the steady-state “trough” level during long-term drug dosing. However, for a drug with the therapeutic endpoint (e.g., target plasma drug concentration) that lies within the steep initial distributive phase, it is much harder to dose accurately and not overshoot the target endpoint. This scenario is particularly true for some drugs used in critical care where rapid responses are needed and IV bolus routes are used more often. Many new biotechnological drugs are administered intravenously because of instability by oral route. The choice of a proper dose and rate of infusion relative to the half-life of the drug is an important consideration for safe drug administration. Individual patients may behave very differently with regard to drug metabolism, drug transport, and drug efflux in target cell sites. Drug receptors can be genetically expressed differently making some people more prone to allergic reactions and side effects. Simple kinetic half-life determination coupled with a careful review of the patient’s chart by a pharmacist can greatly improve drug safety.

CLINICAL APPLICATION

Lidocaine is a drug with low toxicity and a long history of use for anesthetization and for treating ventricular arrhythmias. The drug has a steep distributive phase and is biphasic. The risk of adverse effects is dose related and increases at intravenous infusion rates of above 3 mg/min. Dosage and dose rate are important for proper use (Greenspon et al, 1989). A case of inappropriate drug use was reported (Avery, 1998).

An overdose of lidocaine was given to a patient to anesthetize the airway due to bronchoscopy by an inexperienced hospital personnel. The patient was then left unobserved and subsequently developed convulsions and cardiopulmonary arrest. He survived with severe cerebral damage. His lidocaine concentration was 24 μg/mL about 1 hour after initial administration (a blood concentration over 6 μg/mL is considered to be toxic). What is the therapeutic plasma concentration range according to the table in Appendix E of this book? Is the drug highly protein
bound? Is $V_D$ sufficiently large to show extravascular distribution?

A second case of adverse drug reaction (ADR) based on inappropriate use of this drug due to rapid absorption was reported by Pantuck AJ et al, 1997. A 40-year-old woman developed seizures after lidocaine gel 40 mL was injected into the ureter. Vascular absorption can apparently be very rapid depending on the site of application even if the route is not directly intravenous. It is important to note that for a drug with a steeply declining elimination plasma profile, it is harder to maintain a stable target level with dosing because a small change on the time scale ($x$ axis) can greatly alter the drug concentration ($y$ axis). Some drugs that have a steep distributive phase may easily cause a side effect in a susceptible subject.

Frequently Asked Questions

- A new experimental drug can be modeled by a two-compartment model. What potential adverse event could occur for this drug if given by single IV bolus injection?
- A new experimental drug can be modeled by a three-compartment model. What potential adverse event could occur for this drug if given by multiple IV bolus injections?

CHAPTER SUMMARY

Compartment is a term used in pharmacokinetic models to describe a theoretized region within the body in which the drug concentrations are presumed to be uniformly distributed.

- A two-compartment model typically shows a biexponential plasma drug concentration–time curve with an initial distributive phase and a later terminal phase.
- One or more tissue compartments may be present in the model depending on the shape of the polyexponential curve representing log plasma drug concentration versus time.
- The central compartment refers to the volume of the plasma and body regions that are in rapid equilibrium with the plasma.
- The amount of drug within each compartment after a given dose at a given time can be calculated once the model is developed and model parameters are obtained by data fitting.

A pharmacokinetic model is a quantitative description of how drug concentrations change over time. Pharmacokinetic parameters are numerical values of model descriptors derived from data that are fitted to a model. These parameters are initially estimated and later refined using computing curve-fitting techniques such as least squares.

- Mamillary models are pharmacokinetic models that are well connected or dynamically exchange drug concentration between compartments. The two- and three-compartment models are examples.
- Compartment models are useful for estimating the mass balance of the drug in the body. As more physiological and genetic information are known, the model may be refined. Efflux and special transporters are now known to influence drug distribution and plasma profile. The well-known ABC cassette transporters (eg, P-gp) are genetically expressed and vary among individuals. These drug transporters can be kinetically simulated using transfer constants in a compartment model designed to mimic drug efflux in and out of a cell or compartment model.

During curve fitting, simplifying the two-compartment model after an IV bolus dose and ignoring the presence of the distributive phase may cause serious errors unless the beta phase is very long relative to the distributive phase.

- An important consideration is whether the effective concentration lies near the distributive phase after the IV bolus dose is given.
LEARNING QUESTIONS

1. A drug was administered by rapid IV injection into a 70-kg adult male. Blood samples were withdrawn over a 7-hour period and assayed for intact drug. The results are tabulated below. Using the method of residuals, calculate the values for intercepts A and B and slopes a, b, k₁₂, and k₂₁.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Cₚ (μg/mL)</th>
<th>Time (hour)</th>
<th>Cₚ (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>70.0</td>
<td>2.5</td>
<td>14.3</td>
</tr>
<tr>
<td>0.25</td>
<td>53.8</td>
<td>3.0</td>
<td>12.6</td>
</tr>
<tr>
<td>0.50</td>
<td>43.3</td>
<td>4.0</td>
<td>10.5</td>
</tr>
<tr>
<td>0.75</td>
<td>35.0</td>
<td>5.0</td>
<td>9.0</td>
</tr>
<tr>
<td>1.00</td>
<td>29.1</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>1.50</td>
<td>21.2</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>2.00</td>
<td>17.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. A 70-kg male subject was given 150 mg of a drug by IV injection. Blood samples were removed and assayed for intact drug. Calculate the slopes and intercepts of the three phases of the plasma level–time plot from the results tabulated below. Give the equation for the curve.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Cₚ (μg/mL)</th>
<th>Time (hour)</th>
<th>Cₚ (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17</td>
<td>36.2</td>
<td>3.0</td>
<td>13.9</td>
</tr>
<tr>
<td>0.33</td>
<td>34.0</td>
<td>4.0</td>
<td>12.0</td>
</tr>
<tr>
<td>0.50</td>
<td>27.0</td>
<td>6.0</td>
<td>8.7</td>
</tr>
<tr>
<td>0.67</td>
<td>23.0</td>
<td>7.0</td>
<td>7.7</td>
</tr>
<tr>
<td>1.00</td>
<td>20.8</td>
<td>18.0</td>
<td>3.2</td>
</tr>
<tr>
<td>1.50</td>
<td>17.8</td>
<td>23.0</td>
<td>2.4</td>
</tr>
<tr>
<td>2.00</td>
<td>16.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Mitenko and Ogilvie (1973) demonstrated that theophylline followed a two-compartment pharmacokinetic model in human subjects. After administering a single intravenous dose (5.6 mg/kg) in nine normal volunteers, these investigators demonstrated that the equation best describing theophylline kinetics in humans was as follows:

\[ Cₚ = 12e^{-5.8t} + 18e^{-0.16t} \]

What is the plasma level of the drug 3 hours after the IV dose?

4. A drug has a distribution that can be described by a two-compartment open model. If the drug is given by IV bolus, what is the cause of the initial or rapid decline in blood levels (a phase)? What is the cause of the slower decline in blood levels (b phase)?

5. What does it mean when a drug demonstrates a plasma level–time curve that indicates a three-compartment open model? Can this curve be described by a two-compartment model?

6. A drug that follows a multicompartment pharmacokinetic model is given to a patient by rapid intravenous injection. Would the drug concentration in each tissue be the same after the drug equilibrates with the plasma and all the tissues in the body? Explain.

7. Park and associates (1983) studied the pharmacokinetics of amrinone after a single IV bolus injection (75 mg) in 14 healthy adult male volunteers. The pharmacokinetics of this drug followed a two-compartment open model and fit the following equation:

\[ Cₚ = Ae^{-at} + Be^{-bt} \]

where
\[ A = 4.62 \pm 12.0 \mu g/mL \]
\[ B = 0.64 \pm 0.17 \mu g/mL \]
\[ a = 8.94 \pm 13 h^{-1} \]
\[ b = 0.19 \pm 0.06 h^{-1} \]

From these data, calculate:

a. The volume of the central compartment
b. The volume of the tissue compartment
c. The transfer constants k₁₂ and k₂₁
d. The elimination rate constant from the central compartment
e. The elimination half-life of amrinone after the drug has equilibrated with the tissue compartment
8. A drug may be described by a three-compartment model involving a central compartment and two peripheral tissue compartments. If you could sample the tissue compartments (organs), in which organs would you expect to find a drug level corresponding to the two theoretical peripheral tissue compartments?

9. A drug was administered to a patient at 20 mg by IV bolus dose and the time–plasma drug concentration is listed below. Use a suitable compartment model to describe the data and list the fitted equation and parameters. What are the statistical criteria used to describe your fit?

<table>
<thead>
<tr>
<th>Hour</th>
<th>mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>3.42</td>
</tr>
<tr>
<td>0.40</td>
<td>2.25</td>
</tr>
<tr>
<td>0.60</td>
<td>1.92</td>
</tr>
<tr>
<td>0.80</td>
<td>1.80</td>
</tr>
<tr>
<td>1.00</td>
<td>1.73</td>
</tr>
<tr>
<td>2.00</td>
<td>1.48</td>
</tr>
<tr>
<td>3.00</td>
<td>1.28</td>
</tr>
<tr>
<td>4.00</td>
<td>1.10</td>
</tr>
<tr>
<td>6.00</td>
<td>0.81</td>
</tr>
<tr>
<td>8.00</td>
<td>0.60</td>
</tr>
<tr>
<td>10.00</td>
<td>0.45</td>
</tr>
<tr>
<td>12.00</td>
<td>0.33</td>
</tr>
<tr>
<td>14.00</td>
<td>0.24</td>
</tr>
<tr>
<td>18.00</td>
<td>0.13</td>
</tr>
<tr>
<td>20.00</td>
<td>0.10</td>
</tr>
</tbody>
</table>

10. The toxicokinetics of colchicine in seven cases of acute human poisoning was studied by Rochdi et al (1992). In three further cases, postmortem tissue concentrations of colchicine were measured. Colchicine follows the two-compartment model with wide distribution in various tissues. Depending on the time of patient admission, two disposition processes were observed. The first, in three patients, admitted early, showed a biexponential plasma colchicine decrease, with distribution half-lives of 30, 45, and 90 minutes. The second, in four patients, admitted late, showed a monoexponential decrease. Plasma terminal half-lives ranged from 10.6 to 31.7 hours for both groups.

11. Postmortem tissue analysis of colchicine showed that colchicine accumulated at high concentrations in the bone marrow (more than 600 ng/g), testicle (400 ng/g), spleen (250 ng/g), kidney (200 ng/g), lung (200 ng/g), heart (95 ng/g), and brain (125 ng/g). The pharmacokinetic parameters of colchicine are:

- Fraction of unchanged colchicine in urine = 30%
- Renal clearance = 13 L/h
- Total body clearance = 39 L/h
- Apparent volume of distribution = 21 L/kg

a. Why is colchicine described by a monoexponential profile in some subjects and a biexponential in others?

b. What is the range of distribution of half-life of colchicine in the subjects?

c. Which parameter is useful in estimating tissue drug level at any time?

d. Some clinical pharmacists assumed that, at steady state when equilibration is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?

e. Which tissues may be predicted by the tissue compartment?

REFERENCES


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**BIBLIOGRAPHY**


Intravenous Infusion

Chapter Objectives

- Describe the concept of steady-state and how it relates to continuous dosing.
- Determine optimum dosing for an infused drug by calculating pharmacokinetic parameters from clinical data.
- Calculate loading doses to be used with an intravenous infusion.
- Describe the purpose of a loading dose.
- Compare the pharmacokinetic outcomes and clinical implications after giving a loading dose for a drug that follows a one-compartment model to a drug that follows a two-compartment model.

Drugs may be administered to patients by one of various routes including oral, topical, or parenteral routes of administration. Examples of parenteral routes of administration include intravenous, subcutaneous, and intramuscular. Intravenous (IV) drug solutions may be given either as a bolus dose (injected all at once) or infused slowly through a vein into the plasma at a constant or zero-order rate. The main advantage for giving a drug by IV infusion is that IV infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient. For drugs with a narrow therapeutic window (eg, heparin), IV infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration. Moreover, the IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients. Furthermore, the duration of drug therapy may be maintained or terminated as needed using IV infusion.

The plasma drug concentration–time curve of a drug given by constant IV infusion is shown in Fig. 5-1. Because no drug was present in the body at zero time, drug level rises from zero drug concentration and gradually becomes constant when a plateau or steady-state drug concentration is reached. At steady state, the rate of drug leaving the body is equal to the rate of drug (infusion rate) entering the body. Therefore, at steady state, the rate of change in the plasma drug concentration \( \frac{dC_p}{dt} = 0 \), and

\[
\text{Rate of drug input} = \text{rate of drug output}
\]

(Infusion rate) (elimination rate)

Based on this simple mass balance relationship, a pharmacokinetic equation for infusion may be derived depending on whether the drug follows one- or two-compartment kinetics.

### ONE-COMPARTMENT MODEL DRUGS

The pharmacokinetics of a drug given by constant IV infusion follows a zero-order input process in which the drug is directly infused into the systemic blood circulation. Equation 5.2 gives the

91
plasma drug concentration at any time during the IV infusion where \( t \) is the time for infusion. The graph of Equation 5.2 appears in Fig. 5-1 and 5-2. For most drugs, elimination of drug from the plasma is a first-order process. Therefore, in this one-compartment model, the infused drug follows zero-order input and first-order output. The change in the amount of drug in the body at any time \( (dD_B/dt) \) during the infusion is the rate of input minus the rate of output.

\[
\frac{dD_B}{dt} = R - kD_B \quad (5.1)
\]

where \( D_B \) is the amount of drug in the body, \( R \) is the infusion rate (zero order), and \( k \) is the elimination rate constant (first order).

Integration of Equation 5.1 and substitution of \( D_B = C_pV_D \) gives:

\[
C_p = \frac{R}{V_Dk} (1 - e^{-kt}) \quad (5.2)
\]

As the drug is infused, the value for time \( (t) \) increases in Equation 5.2. At infinite time, \( t = \infty \) \( e^{-kt} \) approaches zero, and Equation 5.2 reduces to Equation 5.4.

\[
C_p = \frac{R}{V_Dk} e^{-\infty} \quad (5.3)
\]

\[
C_{ss} = \frac{R}{V_Dk} \quad (5.4)
\]

\[
C_{ss} = \frac{R}{V_Dk} = \frac{R}{Cl} \quad (5.5)
\]

**Steady-State Drug Concentration (\( C_{ss} \)) and Time Needed to Reach \( C_{ss} \)**

As stated earlier, the rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate) at steady state. In other words, there is no net change in the amount of drug in the body, \( D_B \), as a function of time during steady state. Drug elimination occurs according to first-order elimination kinetics. Whenever the infusion stops either at steady state, or before steady state is reached, the drug concentration declines according to first-order kinetics with the slope of the elimination curve equal to \(-k/2.3\) (Fig. 5-2). If the infusion is stopped before steady state is reached, the slope of the elimination curve remains the same (Fig. 5-2B).

Mathematically, the time to reach true steady-state drug concentrations, \( C_{ss} \), would take an infinite time. The time required to reach the steady-state drug concentration in the plasma is dependent on the elimination rate constant of the drug for a constant volume of distribution as shown in Equation 5.4. Because drug elimination is exponential (first order), the plasma drug concentration becomes asymptotic to the theoretical steady-state plasma drug concentration. For a zero-order elimination processes, if rate of input is greater than rate of elimination, plasma drug concentrations will keep increasing and no steady state will be reached. This is a potentially dangerous situation that will occur when saturation of metabolic process occurs.

**FIGURE 5-1**  Plasma level–time curve for constant IV infusion.

**FIGURE 5-2**  Plasma drug concentrations–time profiles after IV infusion. IV infusion is stopped at steady state (A) or prior to steady state (B). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope.
In clinical practice, a plasma drug concentration prior to, but asymptotically approaching, the theoretical steady-state is considered the steady state plasma drug concentration \( (C_{ss}) \). In a constant IV infusion, drug solution is infused at a constant or zero-order rate, \( R \). During the IV infusion, the drug concentration increases in the plasma and the rate of drug elimination increases because rate of elimination is concentration dependent (ie, rate of drug elimination \( = kC_p \)). \( C_p \) keeps increasing until steady state is reached at which time the rate of drug input (IV infusion rate) equals rate of drug output (elimination rate). The resulting plasma drug concentration at steady state \( (C_{ss}) \) is related to the rate of infusion and inversely related to the body clearance of the drug as shown in Equation 5.5.

In clinical practice, the activity of the drug will be observed when the drug concentration is close to the desired plasma drug concentration, which is usually the target or desired steady-state drug concentration. The time to reach 90%, 95%, and 99% of the steady-state drug concentration, \( C_{ss} \), may be calculated (Table 5-1). For therapeutic purposes, the time for the plasma drug concentration to reach more than 95% of the steady-state drug concentration in the plasma is often estimated. As detailed in Table 5-1, after IV infusion of the drug for 5 half-lives, the plasma drug concentration will be between 95% \((4.32 \, t_{1/2})\) and 99% \((6.65 \, t_{1/2})\) of the steady-state drug concentration. Thus, the time for a drug whose \( t_{1/2} \) is 6 hours to reach 95% of the steady-state plasma drug concentration will be \( 5 \, t_{1/2} \) or \( 5 \times 6 \, \text{hours} = 30 \, \text{hours} \). The calculation of the values in Table 5-1 is given in the example that follows.

### Table 5-1  Number of \( t_{1/2} \) to Reach a Fraction of \( C_{ss} \)

<table>
<thead>
<tr>
<th>Percent of ( C_{ss} ) Reached(^\text{a})</th>
<th>Number of Half-Lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>3.32</td>
</tr>
<tr>
<td>95</td>
<td>4.32</td>
</tr>
<tr>
<td>99</td>
<td>6.65</td>
</tr>
</tbody>
</table>

\(^{a}C_{ss}\) is the steady-state drug concentration in plasma.

An increase in the infusion rate will not shorten the time to reach the steady-state drug concentration. If the drug is given at a more rapid infusion rate, a higher steady-state drug level will be obtained, but the time to reach steady state is the same (Fig. 5-3). This equation may also be obtained with the following approach. At steady state, the rate of infusion equals the rate of elimination. Therefore, the rate of change in the plasma drug concentration is equal to zero.

\[
\frac{dC_p}{dt} = 0
\]

\[
\frac{dC_p}{dt} = \frac{R}{V_D} - kC_p = 0
\]

\[
(Rate_{in}) - (Rate_{out}) = 0
\]

\[
\frac{R}{V_D} = kC_p
\]

\[
C_{ss} = \frac{R}{V_D \cdot k} \tag{5.6}
\]

Equation 5.6 shows that the steady-state concentration \( (C_{ss}) \) is dependent on the volume of distribution, the elimination rate constant, and the infusion rate. Altering any one of these factors can affect steady-state concentration.
1. An antibiotic has a volume of distribution of 10 L and a $k$ of 0.2 h$^{-1}$. A steady-state plasma concentration of 10 μg/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows. Equation 5.6 can be rewritten as

$$ R = \frac{C_{ss} V_k}{k} $$

Assume the patient has a uremic condition and the elimination rate constant has decreased to 0.1 h$^{-1}$. To maintain the steady-state concentration of 10 μg/mL, we must determine a new rate of infusion as follows.

$$ R = (10 \text{ μg/mL}) (10) (1000 \text{ mL}) (0.1 \text{ h}^{-1}) = 10 \text{ mg/h} $$

When the elimination rate constant decreases, then the infusion rate must decrease proportionately to maintain the same $C_{ss}$. However, because the elimination rate constant is smaller (ie, the elimination $t_{1/2}$ is longer), the time to reach $C_{ss}$ will be longer.

2. An infinitely long period of time is needed to reach steady-state drug levels. However, in practice it is quite acceptable to reach 99% $C_{ss}$ (ie, 99% steady-state level). Using Equation 5.6, we know that the steady-state level is

$$ C_{ss} = \frac{R}{V_k} $$

and 99% steady-state level would be equal to

$$ 0.99 = \frac{R}{V_k} $$

Substituting into Equation 5.2 for $C_p$, we can find out the time needed to reach steady state by solving for $t$.

$$ 0.99 = \frac{R}{V_k} (1 - e^{-kt}) $$

$$ 0.99 = 1 - e^{-kt} $$

$$ e^{-kt} = 0.01 $$

Take the natural logarithm on both sides:

$$ -kt = \ln 0.01 $$

$$ t_{99\%} = \frac{-\ln 0.01}{-k} = \frac{-(-4.61)}{4.61} = \frac{-4.61}{k} $$

Substituting $0.693/t_{1/2}$ for $k$,

$$ t_{99\%} = \frac{4.61}{0.693 \times t_{1/2}} = 6.65 \times t_{1/2} $$

Notice that in the equation directly above, the time needed to reach steady state is not dependent on the rate of infusion, but only on the elimination half-life. Using similar calculations, the time needed to reach any percentage of the steady-state drug concentration may be obtained (Table 5.1).

IV infusion may be used to determine total body clearance if the infusion rate and steady-state level are known, as with Equation 5.6 repeated here:

$$ C_{ss} = \frac{R}{V_k} $$

Because total body clearance, $Cl_T$, is equal to $V_k/k$,

$$ Cl_T = \frac{R}{C_{ss}} $$

3. A patient was given an antibiotic ($t_{1/2} = 6$ hours) by constant IV infusion at a rate of 2 mg/h. At the end of 2 days, the serum drug concentration was 10 mg/L. Calculate the total body clearance $Cl_T$ for this antibiotic.

Solution

The total body clearance may be estimated from Equation 5.7. The serum sample was taken after 2 days or 48 hours of infusion, which time represents $8 \times t_{1/2}$; therefore, this serum drug concentration approximates the $C_{ss}$.

$$ Cl_T = \frac{R}{C_{ss}} \cdot \frac{2 \text{ mg/h}}{10 \text{ mg/L}} = 200 \text{ mL/h} $$
Frequently Asked Questions

INFUSION METHOD FOR CALCULATING PATIENT ELIMINATION HALF-LIFE

The $C_p$-versus-time relationship that occurs during an IV infusion (Equation 5.2) may be used to calculate $k$, or indirectly the elimination half-life of the drug in a patient. Some information about the elimination half-life of the drug in the population must be known, and one or two plasma samples must be taken at a known time after infusion. Knowing the half-life in the general population helps determine if the sample is taken at steady state in the patient. To simplify calculation, Equation 5.2 is arranged to solve for $k$:

$$C_p = \frac{R}{V_d k} (1 - e^{-kt})$$  \hspace{1cm} (5.2)

Since

$$C_{ss} = \frac{R}{V_d k}$$

substituting into Equation 5.2:

$$C_p = C_{ss} (1 - e^{-kt})$$

Rearranging and taking the log on both sides:

$$\log\left(\frac{C_{ss} - C_p}{C_{ss}}\right) = -\frac{kt}{2.3}$$ and

$$k = \frac{-2.3}{t} \log\left(\frac{C_{ss} - C_p}{C_{ss}}\right)$$  \hspace{1cm} (5.8)

where $C_p$ is the plasma drug concentration taken at time $t$, and $C_{ss}$ is the approximate steady-state plasma drug concentration in the patient.

EXAMPLE 1

An antibiotic has an elimination half-life of 3 to 6 hours in the general population. A patient was given an IV infusion of an antibiotic at an infusion rate of 15 mg/h. Blood samples were taken at 8 and at 24 hours and plasma drug concentrations were 5.5 and 6.5 mg/L, respectively. Estimate the elimination half-life of the drug in this patient.

Solution

Because the second plasma sample was taken at 24 hours, or $24/6 = 4$ half-lives after infusion, the plasma drug concentration in this sample is approaching 95% of the true plasma steady-state drug concentration assuming the extreme case of $t_{1/2} = 6$ hours. By substitution into Equation 5.8:

$$\log\left(\frac{6.5 - 5.5}{6.5}\right) = -k(8)\frac{2.3}{6.5}$$

$$k = 0.234 \text{ h}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.234} = 2.96 \text{ hours}$$

The elimination half-life calculated in this manner is not as accurate as the calculation of $t_{1/2}$ using multiple plasma drug concentration time points after a single IV bolus dose or after stopping the IV infusion. However, this method may be sufficient in clinical practice. As the second blood sample is taken closer to the time for steady state, the accuracy of this method improves. At the 30th hour, for example, the plasma concentration would be 99% of the true steady-state value (corresponding to 30/6 or 5 elimination half-lives), and less error would result in applying Equation 5.8.

When Equation 5.8 was used in the example above to calculate the drug $t_{1/2}$ of the patient, the second plasma drug concentration was assumed to be the theoretical $C_{ss}$. As demonstrated below, when $t_{1/2}$ and the corresponding values are substituted,

$$\log\left(\frac{C_{ss} - 5.5}{C_{ss}}\right) = -\frac{(0.234)(8)}{6.5} \frac{2.3}{6.5}$$

$$\frac{C_{ss} - 5.5}{C_{ss}} = 0.157$$
**LOADING DOSE PLUS IV INFUSION—ONE-COMPARTMENT MODEL**

The loading dose $D_L$, or initial bolus dose of a drug, is used to obtain desired concentrations as rapidly as possible. The concentration of drug in the body for a one-compartment model after an IV bolus dose is described by

$$C_1 = C_0 e^{-kt} = \frac{D_L}{V_D} e^{-kt} \quad (5.9)$$

and concentration by infusion at the rate $R$ is

$$C_2 = \frac{R}{V_D k} (1 - e^{-kt}) \quad (5.10)$$

Assume that an IV bolus dose $D_L$ of the drug is given and that an IV infusion is started at the same time. The total concentration $C_p$ at $t$ hours after the start of infusion would be equal to $C_1 + C_2$ due to the sum contributions of bolus and infusion, or

$$C_p = C_1 + C_2$$

$$C_p = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k} (1 - e^{-kt})$$

$$C_p = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k} - \frac{R}{V_D k} e^{-kt}$$

$$C_p = \frac{R}{V_D k} + \left( \frac{D_L}{V_D} e^{-kt} - \frac{R}{V_D k} e^{-kt} \right) \quad (5.11)$$

Let the loading dose ($D_L$) equal the amount of drug in the body at steady state

$$D_L = C_{ss} V_D$$

From Equation 5.4, $C_{ss} V_D = R/k$. Therefore,

$$D_L = \frac{R}{k} \quad (5.12)$$

Substituting $D_L = R/k$ in Equation 5.11 makes the expression in parentheses in Equation 5.11 cancel out. Equation 5.11 reduces to Equation 5.13, which is the same expression for $C_{ss}$ or steady-state plasma concentrations:

$$C_p = \frac{R}{V_D k} \quad (5.13)$$

---

**EXAMPLE 2**

If the desired therapeutic plasma concentration is 8 mg/L for the above patient (Example 1), what is the suitable infusion rate for the patient?

**Solution**

From Example 1, the trial infusion rate was 15 mg/h. Assuming the second blood sample is the steady-state level, 6.5 mg/mL, the clearance of the patient is

$$C_{ss} = \frac{R}{Cl}$$

$$Cl = \frac{R}{C_{ss}} = 15 / 6.5 = 2.31 \text{ L/h}$$

The new infusion rate should be

$$R = C_{ss} \times Cl = 8 \times 2.31 = 18.48 \text{ mg/h}$$

In this example, the $t_{1/2}$ of this patient is a little shorter, about 3 hours compared to 3 to 6 hours reported for the general population. Therefore, the infusion rate should be a little greater in order to maintain the desired steady-state level of 15 mg/L.

Equation 5.7 or the steady-state clearance method has been applied to the clinical infusion of drugs. The method was regarded as simple and accurate compared with other methods, including the two-point method (Hurley and McNeil, 1988).
By differentiating this equation at steady state, we obtain:

\[
\frac{dC}{dt} = 0 = -\frac{D_L k}{V_D} e^{-kt} + \frac{R k}{V_D} e^{-kt}
\]

(5.16)

\[
0 = e^{-kt}\left(-\frac{D_L k}{V_D} + \frac{R}{V_D}\right)
\]

(5.17)

\[
\frac{D_L k}{V_D} = \frac{R}{V_D}
\]

\[
D_L = \frac{R}{k} = \text{loading dose}
\]

In order to maintain instant steady-state level \([dCp/dt] = 0\), the loading dose should be equal to \(R/k\).

For a one-compartment drug, if the \(D_L\) and infusion rate are calculated such that \(C_o\) and \(C_{ss}\) and are the same and both \(D_L\) and infusion are started concurrently, then steady state and \(C_{ss}\) will be achieved immediately after the loading dose is administered (Fig. 5-4). Similarly, in Fig. 5-5, curve \(b\) shows the blood level after a single loading dose of \(R/k\) plus infusion from which the concentration desired at steady state is obtained. If the \(D_L\) is not equal to \(R/k\), then steady state will not occur immediately. If the loading dose given is larger than \(R/k\), the plasma drug concentration takes longer to decline to the concentration desired at steady state (curve \(a\)). If the loading dose is lower than \(R/k\), the plasma drug concentrations
will increase slowly to desired drug levels (curve c), but more quickly than without any loading dose.

Another method for the calculation of loading dose \( D_L \) is based on knowledge of the desired steady-state drug concentration \( C_{ss} \) and the apparent volume of distribution \( V_D \) for the drug, as shown in Equation 5.17.

\[
D_L = C_{ss} V_D \tag{5.18}
\]

For many drugs, the desired \( C_{ss} \) is reported in the literature as the effective therapeutic drug concentration. The \( V_D \) and the elimination half-life are also available for these drugs.

**PRACTICE PROBLEMS**

1. A physician wants to administer an anesthetic agent at a rate of 2 mg/h by IV infusion. The elimination rate constant is 0.1 h\(^{-1}\) and the volume of distribution (one compartment) is 10 L. What loading dose should be recommended if the doctor wants the drug level to reach 2 mg/mL immediately?

**Solution**

\[
C_{ss} = \frac{R}{V_D k} = \frac{2000}{(10 \times 10^3) (0.1)} = 2 \mu g/mL
\]

To reach \( C_{ss} \) instantly,

\[
D_L = \frac{R}{k} = \frac{2 \text{ mg/h}}{0.1 \text{/h}} \quad D_L = 20 \text{ mg}
\]

2. What is the concentration of a drug 6 hours after administration of a loading dose of 10 mg and simultaneous infusion at 2 mg/h (the drug has a \( t_{1/2} \) of 3 hours and a volume of distribution of 10 L)?

**Solution**

\[
k = \frac{0.693}{3 \text{ h}}
\]

\[
C_p = \frac{D_L}{V_D} e^{-kt'} + \frac{R}{V_D k} (1 - e^{-kt'})
\]

\[
C_p = \frac{10,000}{10,000} e^{-0.693(3/6)} + \frac{2000}{(10,000)(0.693/3)} (1 - e^{-0.693(3/6)})
\]

\[
C_p = 0.90 \mu g/mL
\]

3. Calculate the drug concentration in the blood after infusion has been stopped.

**Solution**

This concentration can be calculated in two parts (see Fig. 5-2A). First, calculate the concentration of drug during infusion, and second, calculate the concentration after the stop of the infusion, \( C \). Then use the IV bolus dose equation \( C = C_p e^{-kt'} \) for calculations for any further point in time. For convenience, the two equations can be combined as follows:

\[
C_p = \frac{R}{V_D k} \left( 1 - e^{-kt} \right) e^{-kt'} = \frac{R}{V_D k} \left( 1 - e^{-kt'} \right) \tag{5.19}
\]

where \( b = \) length of time of infusion period, \( t = \) total time (infusion and postinfusion), and \( t - b = \) length of time after infusion has stopped.

4. A patient was infused for 6 hours with a drug \( (k = 0.01 \text{ h}^{-1}; V_D = 10 \text{ L}) \) at a rate of 2 mg/h. What is the concentration of the drug in the body 2 hours after cessation of the infusion?

**Solution**

Using Equation 5.19,

\[
C_p = \frac{200}{(0.01)(10,000)} \left( 1 - e^{-0.01(12)} \right) e^{-0.01(18-6)}
\]

\[
C_p = 1.14 \mu g/mL
\]

Alternatively, when infusion stops, \( C_p' \) is calculated:

\[
C_p' = \frac{R}{V_D k} \left( 1 - e^{-kt} \right)
\]

\[
C_p' = \frac{2000}{0.01 \times 10,000} \left( 1 - e^{-0.01(12)} \right)
\]

\[
C = C_p' e^{-0.01(2)}
\]

\[
C = 1.14 \mu g/mL
\]

The two approaches should give the same answer.

5. An adult male asthmatic patient (78 kg, 48 years old) with a history of heavy smoking was given an IV infusion of aminophylline at a rate of 0.75 mg/kg/h. A loading dose of 6 mg/kg was given by IV bolus injection just prior to the start of the infusion. At 2 hours after the start of the IV infusion, the plasma theophylline...
Intravenous Infusion

99

0.65 mL/min/kg. Heavy smoking is known to increase \( C_l \) for theophylline.

The new IV infusion rate, \( R' \) in terms of theophylline, is calculated by

\[
R' = C_{\text{ss, desired}} C_l \times V_D = 10 \text{ mg/L} \times 8.07 \text{ L/h} = 80.7 \text{ mg/h or 1.03 mg/h/kg of theophylline which is equivalent to 1.29 mg/h/kg of aminophylline.}
\]

6. An adult male patient (43 years, 80 kg) is to be given an antibiotic by IV infusion. According to the literature, the antibiotic has an elimination \( t_{1/2} \) of 2 hours, \( V_D \) of 1.25 L/kg, and is effective at a plasma drug concentration of 14 mg/L. The drug is supplied in 5-mL ampuls containing 150 mg/mL.

a. Recommend a starting infusion rate in milligrams per hour and liters per hour.

Solution

Assume the effective plasma drug concentration is the target drug concentration or \( C_{\text{ss}} \).

\[
R = \frac{C_{\text{ss}} k V_D}{(S)(F)}
\]

where \( S \) is the salt form of the drug and \( F \) is the fraction of drug bioavailable. For aminophylline \( S \) is equal to 0.80 and for an IV bolus injection \( F \) is equal to 1.

\[
D_L = \frac{(0.45 \text{ L/kg})(78 \text{ kg})(10 - 5.8 \text{ mg/L})}{(0.8)(1)} = 0.6 \text{ mg/L/kg}
\]

\[
D_L = 184 \text{ mg aminophylline}
\]

The maintenance IV infusion rate may be calculated after estimation of the patient’s clearance, \( C_l \). Because a loading dose is given and an IV infusion of 0.75 mg/h aminophylline (equivalent to 0.75 \( \times \) 0.8 = 0.6 mg theophylline) per kg was given to the patient, the plasma theophylline concentration of 5.8 mg/L is the steady-state \( C_{\text{ss}} \). Total clearance may be estimated by

\[
C_l = \frac{R}{C_{\text{ss, present}}} = \frac{(0.6 \text{ mg/h/kg})(78 \text{ kg})}{5.8 \text{ mg/L}} = 8.07 \text{ L/h or 1.72 mL/min/kg}
\]

The usual \( C_l \) for adult, nonsmoking patients with uncomplicated asthma is approximately 0.65 mL/min/kg. Heavy smoking is known to increase \( C_l \) for theophylline.

The new IV infusion rate, \( R' \) in terms of theophylline, is calculated by

\[
R' = C_{\text{ss, desired}} C_l \times V_D = 10 \text{ mg/L} \times 8.07 \text{ L/h} = 80.7 \text{ mg/h or 1.03 mg/h/kg of theophylline which is equivalent to 1.29 mg/h/kg of aminophylline.}
\]

b. Blood samples were taken from the patient at 12, 16, and 24 hours after the start of the infusion. Plasma drug concentrations were as shown below:

<table>
<thead>
<tr>
<th>( t ) (hour)</th>
<th>( C_p ) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>16.1</td>
</tr>
<tr>
<td>16</td>
<td>16.3</td>
</tr>
<tr>
<td>24</td>
<td>16.5</td>
</tr>
</tbody>
</table>

From these additional data, calculate the total body clearance \( C_l \) for the drug in this patient.

Solution

Because the plasma drug concentrations at 12, 16, and 24 hours were similar, steady state has essentially been reached. (Note: The continuous increase in plasma drug concentrations could be caused by drug accumulation due to a second tissue compartment, or could be due to variation
in the drug assay. Assuming a \( C_{ss} \) of 16.3 mg/mL, \( Cl_t \) is calculated.

\[
Cl_t = \frac{R}{C_{ss}} = \frac{485.1 \text{ mg/h}}{16.3 \text{ mg/L}} = 29.8 \text{ L/h}
\]

c. From the above data, estimate the elimination half-life for the antibiotics in this patient.

**Solution**

Generally, the apparent volume of distribution \((V_D)\) is less variable than \( t_{1/2} \). Assuming that the literature value for \( V_D \) is 1.25 L/kg, then \( t_{1/2} \) may be estimated from the \( Cl_t \).

\[
Cl_t = kV_D
\]

\[
k = \frac{Cl_t}{V_D} = \frac{29.9 \text{ L/h}}{(1.25 \text{ L/kg})(80 \text{ kg})} = 0.299 \text{ h}^{-1}
\]

\[
t_{1/2} = \frac{0.693}{0.299 \text{ h}^{-1}} = 2.32 \text{ h}
\]

Thus the \( t_{1/2} \) for the antibiotic in this patient is 2.32 hours, which is in good agreement with the literature value of 2 hours.

d. After reviewing pharmacokinetics of the antibiotic in this patient, should the infusion rate for the antibiotic be changed?

**Solution**

To properly decide whether the infusion rate should be changed, the clinical pharmacist must consider the pharmacodynamics and toxicity of the drug. Assuming the drug has a wide therapeutic window and shows no sign of adverse drug toxicity, the infusion rate of 485.1 mg/h, calculated according to pharmacokinetic literature values for the drug, appears to be correct.

\[
C_p = \frac{R}{Cl} (1 - e^{-Cl/V_D})
\]

**ESTIMATION OF DRUG CLEARANCE AND \( V_D \) FROM INFUSION DATA**

The plasma concentration of a drug during constant infusion was described in terms of volume of distribution and elimination constant \( k \) in Equation 5.2. Alternatively, the equation may be described in terms of clearance by substituting for \( k \) into Equation 5.2 with \( k = Cl/V_D \):

\[
C_p = \frac{R}{Cl} (1 - e^{-Cl/V_D})
\]

The drug concentration in this physiologic model is described in terms of volume of distribution \((V_D)\) and total body clearance \((Cl)\). The independent parameters are clearance and volume of distribution; \( k \) is viewed as a dependent variable that depends on \( Cl \) and \( V_D \). In this model, the time for steady state and the resulting steady-state concentration will be dependent on both clearance and volume of distribution. When a constant volume of distribution is evident, the time for steady state is then inversely related to clearance. Thus, drugs with small clearance will take a long time to reach steady state. Although this newer approach is preferred by some clinical pharmacists, the alternative approach to parameter estimation was known for some time in classical pharmacokinetics. Equation 5.21 has been applied in population pharmacokinetics to estimate both \( Cl \) and \( V_D \) in individual patients with one or more data points. However, clearance in patients may differ greatly from subjects in the population, especially subjects with different renal functions. Unfortunately, the plasma samples taken at time equivalent to less than 1 half-life after infusion was started may not be very discriminating due to the small change in the drug concentration. Blood samples taken at 3 to 4 half-lives later are much more reflective of their difference in clearance.

**INTRAVENOUS INFUSION OF TWO-COMPARTMENT MODEL DRUGS**

Many drugs given by IV infusion follow two-compartment kinetics. For example, the respective distributions of theophylline and lidocaine in humans are described by the two-compartment open model. With two-compartment-model drugs, IV infusion requires a distribution and equilibration of the drug before a stable blood level is reached. During a constant IV infusion, drug in the tissue compartment is in distribution equilibrium with the plasma; thus, constant \( C_{ss} \) levels also result in constant drug concentrations in the tissue, that is, no net change in the amount of drug.
in the tissue occurs during steady state. Although some clinicians assume that tissue and plasma concentrations are equal when fully equilibrated, kinetic models only predict that the rate of drug transfer into and out of the compartments are equal at steady state. In other words, drug concentrations in the tissue are also constant, but may differ from plasma concentrations.

The time needed to reach a steady-state blood level depends entirely on the distribution half-life of the drug. The equation describing plasma drug concentration as a function of time is as follows:

\[ C_p = \frac{R}{V_p k} \left[ 1 - \left( \frac{k - b}{a - b} \right) e^{-at} - \left( \frac{a - k}{a - b} \right) e^{-bt} \right] \] (5.22)

where \( a \) and \( b \) are hybrid rate constants and \( R \) is the rate of infusion. At steady state (ie, \( t = \infty \)), Equation 5.22 reduces to

\[ C_{ss} = \frac{R}{V_p k} \] (5.23)

By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated.

\[ R = C_{ss} V_p k \] (5.24)

**Loading Dose for Two-Compartment Model Drugs**

Drugs with long half-lives require a loading dose to more rapidly attain steady-state plasma drug levels. It is clinically desirable to achieve rapid therapeutic drug levels by using a loading dose. However, for drugs that follow the two-compartment pharmacokinetic model, the drug distributes slowly into extravascular tissues (compartment 2). Thus, drug equilibrium is not immediate. The plasma drug concentration of a drug that follows a two-compartment model after various loading doses is shown in Fig. 5-6. If a loading dose is given too rapidly, the drug may initially give excessively high concentrations in the plasma (central compartment), which then decreases as drug equilibrium is reached (Fig. 5-6). It is not possible to maintain an instantaneous, stable steady-state blood level for a two-compartment model drug with a zero-order rate of infusion. Therefore, a loading dose produces an initial blood level either slightly higher or lower than the steady-state blood level. To overcome this problem, several IV bolus injections given as short intermittent IV infusions may be used as a method for administering a loading dose to the patient (see Chapter 8).

**Apparent Volume of Distribution at Steady State, Two-Compartment Model**

After administration of any drug that follows two-compartment kinetics, plasma drug levels will decline due to elimination, and some redistribution will occur as drug in tissue diffuses back into the plasma fluid. The volume of distribution at steady state, \( (V_D)_{ss} \), is the “hypothetical space” in which the drug is assumed to be distributed. The product of the plasma drug concentration with \( (V_D)_{ss} \) will give the total amount of drug in the body at that time period, such that \( C_{pss} \times (V_D)_{ss} = \) amount of drug in the body at steady state. At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment. These rates of drug transfer are described by the following expressions:

\[ D_1 k_{21} = D_p k_{12} \] (5.25)

\[ D_1 = k_{12} D_p \] (5.26)
Because the amount of drug in the central compartment, $D_p$, is equal to $V_p C_p$, by substitution in the above equation,

$$D_p = \frac{k_{12} C_p V_p}{k_{21}}$$  \hspace{1cm} (5.27)

The total amount of drug in the body at steady state is equal to the sum of the amount of drug in the tissue compartment, $D_t$, and the amount of drug in the central compartment, $D_p$. Therefore, the apparent volume of drug at steady state $(V_{D})_{ss}$ may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state:

$$(V_D)_{ss} = \frac{D_p + D_t}{C_p}$$  \hspace{1cm} (5.28)

Substituting Equation 5.27 into Equation 5.28, and expressing $D_p$ as $V_p C_p$, a more useful equation for the calculation of $(V_{D})_{ss}$ is obtained:

$$(V_D)_{ss} = \frac{C_p V_p + k_{12} V_p C_p / k_{21}}{C_p}$$  \hspace{1cm} (5.29)

which reduces to

$$(V_D)_{ss} = V_p + \frac{k_{12} V_p}{k_{21}}$$  \hspace{1cm} (5.30)

In practice, Equation 5.30 is used to calculate $(V_{D})_{ss}$. The $(V_{D})_{ss}$ is a function of the transfer constants, $k_{12}$ and $k_{21}$, which represent the rate constants of drug going into and out of the tissue compartment, respectively. The magnitude of $(V_{D})_{ss}$ is dependent on the hemodynamic factors responsible for drug distribution and on the physical properties of the drug, properties which, in turn, determine the relative amount of intra- and extravascular drug.

Another volume term used in two-compartment modeling is $(V_{D})_{b}$ (see Chapter 4). $(V_{D})_{b}$ is often calculated from total body clearance divided by $b$, unlike the steady-state volume of distribution, $(V_{D})_{ss}$, $(V_{D})_{b}$ is influenced by drug elimination in the beta “$b$” phase. Reduced drug clearance from the body may increase AUC, such that $(V_{D})_{b}$ is either reduced or unchanged depending on the value of $b$ as shown in Equation 4.30 (see Chapter 4):

$$(V_D)_b = (V_D)_{area} = \frac{D_p}{b[AUC]_0}$$  \hspace{1cm} (4.30)

Unlike $(V_{D})_{b}$, $(V_{D})_{ss}$ is not affected by changes in drug elimination. $(V_{D})_{ss}$ reflects the true distributional volume occupied by the plasma and the tissue pool when steady state is reached. Although this volume is not useful in calculating the amount of drug in the body during pre-steady state, $(V_{D})_{ss}$ multiplied by the steady-state plasma drug concentration, $C_{ss}$, yields the amount of drug in the body. This volume is often used to determine the loading drug dose necessary to upload the body to a desired plasma drug concentration. As shown by Equation 5.30, $(V_{D})_{ss}$ is several times greater than $V_p$, which represents the volume of the plasma compartment, but differs somewhat in value depending on the transfer constants.

**PRACTICAL FOCUS**

**Questions**

1. Do you agree with the following statements for a drug that is described by a two-compartment pharmacokinetic model? At steady state, the drug is well equilibrated between the plasma and the tissue compartment, $C_p = C_t$, and the rates of drug diffusion into and from the plasma compartment are equal. The steady-state volume of distribution is much larger than the initial volume, $V_i$, or the original plasma volume, $V_p$, of the central compartment. The loading dose is often calculated using the $(V_{D})_{ss}$ instead of $V_p$.

2. Azithromycin may be described by a plasma and a tissue compartment model (refer to Chapter 4).

3. “Rapid distribution of azithromycin into cells causes higher concentration in the tissues than
in the plasma. . . .” Does this statement conflict with the steady-state concept?

4. Why is a loading dose used?

Solutions

1. For a drug that follows a multiple-compartment model, the rates of drug diffusion into the tissues from the plasma and from the tissues into the plasma are equal at steady state. However, the tissue drug concentration is generally not equal to the plasma drug concentration.

2. When plasma drug concentration data are used alone to describe the disposition of the drug, no information on tissue drug concentration is known, and no model will predict actual tissue drug concentrations. To account for the mass balance (drug mass/volume = body drug concentration) of drug present in the body (tissue and plasma pool) at any time after dosing, the body drug concentration is assumed to be the plasma drug concentration. In reality, azithromycin tissue concentration is much higher. Therefore, the calculated volume of the tissue compartment is much bigger (31.1 L/kg) than its actual volume.

3. The product of the steady-state apparent \((V_D)_{ss}\) and the steady-state plasma drug concentration \((C_{SS})\) estimates the amount of drug present in the body. The amount of drug present in the body may be important information for toxicity considerations, but may be used as a therapeutic end point. In most cases, the therapeutic drug at the site of action accounts for only a small fraction of total drug in the tissue compartment. The pharmacodynamic profile may be described as a separate compartment (see effect compartment in Chapter 19). Based on pharmacokinetic and biopharmaceutic studies, the factors that account for high tissue concentrations include diffusion constant, lipid solubility, and tissue binding to cell components. A ratio measuring the relative drug concentration in tissue and plasma is the partition coefficient, which is helpful in predicting the distribution of a drug into tissues. Ultimately, studies of tissue drug distribution using radiolabeled drug are much more useful.

The real tissue drug level will differ from the plasma drug concentration depending on the partitioning of drug in tissues and plasma. \((V_D)_{b}\) is a volume of distribution often calculated because it is easier to calculate than \((V_D)_{ss}\). This volume of distribution, \((V_D)_{b}\), allows the area under the curve to be calculated, an area which has been related to toxicities associated with many cancer chemotherapy agents. Many values for apparent volumes of distribution reported in the clinical literature are obtained using the area equation. Some early pharmacokinetic literature only includes the steady-state volume of distribution, which approximates the \((V_D)_{b}\) but is substantially smaller in many cases. In general, both volume terms reflect extravascular drug distribution. \((V_D)_{b}\) appears to be much more affected by the dynamics of drug disposition in the beta phase, whereas \((V_D)_{ss}\) reflects more accurately the inherent distribution of the drug.

4. When drugs are given in a multiple-dose regimen, a loading dose may be given to achieve steady-state drug concentrations more rapidly.

Frequently Asked Questions

- **What is the main reason for giving a drug by slow IV infusion?**
- **Why do we use a loading dose to rapidly achieve therapeutic concentration for a drug with a long elimination half-life instead of increasing the rate of drug infusion or increasing the size of the infusion dose?**
- **Explain why the application of a loading dose as a single IV bolus injection may cause an adverse event or drug toxicity in the patient if the drug follows a two-compartment model with a slow elimination phase.**
- **What are some of the complications involved with IV infusion?**
LEARNING QUESTIONS

1. A female patient (35 years old, 65 kg) with normal renal function is to be given a drug by IV infusion. According to the literature, the elimination half-life of this drug is 7 hours and the apparent $V_d$ is 23.1% of body weight. The pharmacokinetics of this drug assumes a first-order process. The desired steady-state plasma level for this antibiotic is 10 $\mu$g/mL.
   a. Assuming no loading dose, how long after the start of the IV infusion would it take to reach 95% of the $C_{ss}$?
   b. What is the proper loading dose for this antibiotic?
   c. What is the proper infusion rate for this drug?
   d. What is the total body clearance?
   e. If the patient suddenly develops partial renal failure, how long would it take for a new steady-state plasma level to be established (assume that 95% of the $C_{ss}$ is a reasonable approximation)?
   f. If the total body clearance declined 50% due to partial renal failure, what new infusion rate would you recommend to maintain the desired steady-state plasma level of 10 $\mu$g/mL?

2. An anticonvulsant drug was given as (a) a single IV dose and (b) a constant IV infusion. The serum drug concentrations are as presented in Table 5-2.
   a. What is the steady-state plasma drug level?
   b. What is the time for 95% steady-state plasma drug level?
   c. What is the drug clearance?
   d. What is the plasma concentration of the drug 4 hours after stopping infusion (infusion was stopped after 24 hours)?
   e. What is the infusion rate for a patient weighing 75 kg to maintain a steady-state drug level of 10 $\mu$g/mL?

<table>
<thead>
<tr>
<th>TIME (hour)</th>
<th>Single IV Dose (1 mg/kg)</th>
<th>Constant IV Infusion (0.2 mg/kg per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>6</td>
<td>3.0</td>
<td>7.0</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>10</td>
<td>1.35</td>
<td>8.6</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>9.1</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>9.7</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>9.9</td>
</tr>
</tbody>
</table>
Intravenous Infusion

f. What is the plasma drug concentration 4 hours after an IV dose of 1 mg/kg followed by a constant infusion of 0.2 mg/kg/h?

3. An antibiotic is to be given by IV infusion. How many milliliters per hour should a sterile drug solution containing 25 mg/mL be given to a 75-kg adult male patient to achieve an infusion rate of 1 mg/kg/h?

4. An antibiotic drug is to be given to an adult male patient (75 kg, 58 years old) by IV infusion. The drug is supplied in sterile vials containing 30 mL of the antibiotic solution at a concentration of 125 mg/mL. What rate in milliliters per hour would you infuse this patient to obtain a steady-state concentration of 20 μg/mL? What loading dose would you suggest? Assume the drug follows the pharmacokinetics of a one-compartment open model. The apparent volume of distribution of this drug is 0.5 L/kg and the elimination half-life is 3 hours.

5. According to the manufacturer, a steady-state serum concentration of 17 mg/mL was measured when the antibiotic, cefradine (Velosef, Bristol-Meyers, Squibb) was given by IV infusion to 9 adult male volunteers (average weight, 71.7 kg) at a rate of 5.3 mg/kg/h for 4 hours.
   a. Calculate the total body clearance for this drug.
   b. When the IV infusion was discontinued, the cefradine serum concentration decreased exponentially, declining to 1.5 mg/mL at 6.5 hours after the start of the infusion. Calculate the elimination half-life.
   c. From the information above, calculate the apparent volume of distribution.
   d. Cefradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cefradine concentration. What is the probable mechanism for this interaction of probenecid with cefradine?

6. Calculate the excretion rate at steady state for a drug given by IV infusion at a rate of 30 mg/h. The \( C_{\text{ss}} \) is 20 μg/mL. If the rate of infusion were increased to 40 mg/h, what would be the new steady-state drug concentration, \( C_{\text{ss}}^* \)? Would the excretion rate for the drug at the new steady state be the same? Assume first-order elimination kinetics and a one-compartment model.

7. An antibiotic is to be given to an adult male patient (58 years, 75 kg) by IV infusion. The elimination half-life is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 60-mL ampules at a drug concentration of 15 mg/mL. The desired steady-state drug concentration is 20 μg/mL.
   a. What infusion rate in mg/h would you recommend for this patient?
   b. What loading dose would you recommend for this patient? By what route of administration would you give the loading dose? When?
   c. Why should a loading dose be recommended?
   d. According to the manufacturer, the recommended starting infusion rate is 15 mL/h. Do you agree with this recommended infusion rate for your patient? Give a reason for your answer.
   e. If you were to monitor the patient’s serum drug concentration, when would you request a blood sample? Give a reason for your answer.
   f. The observed serum drug concentration is higher than anticipated. Give two possible reasons based on sound pharmacokinetic principles that would account for this observation.

8. Which of the following statements (a–e) is/are true regarding the time to reach steady-state for the three drugs below?

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of infusion (mg/h)</td>
<td>10</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>( k ) (h⁻¹)</td>
<td>0.5</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>( Cl ) (L/h)</td>
<td>5</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

   a. Drug A takes the longest time to reach steady state.
   b. Drug B takes the longest time to reach steady state.
   c. Drug C takes the longest time to reach steady state.
d. Drug A takes 6.9 hours to reach steady state.
e. None of the above is true.

9. If the steady-state drug concentration of a cephalosporin after constant infusion of 250 mg/h is 45 \( \mu \)g/mL, what is the drug clearance of this cephalosporin?

10. Some clinical pharmacists assumed that, at steady state when equilibration is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?

**REFERENCE**


**BIBLIOGRAPHY**


Chapter Objectives

- Describe the main routes of drug elimination from the body including the model-dependent and model-independent approaches for drug elimination.
- Define the term “clearance” and its relationship to elimination half-life and volume of distribution.
- Differentiate between total body clearance and renal clearance.
- Describe the processes for renal drug excretion and explain which renal excretion process predominates in the kidney for a specific drug given its renal clearance.
- Describe the renal clearance model based on renal blood flow, glomerular filtration, and drug reabsorption.
- Describe organ drug clearance in terms of blood flow and extraction.
- Using graphical methods, determine whether clearance exhibits linear or nonlinear pharmacokinetics.

DRUG ELIMINATION

Drugs are removed from the body by various elimination processes. Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination. The declining plasma drug concentration observed after systemic drug absorption shows that the drug is being eliminated from the body but does not indicate which elimination processes are involved.

Drug elimination is usually divided into two major components: excretion and biotransformation. Drug excretion is the removal of the intact drug. Nonvolatile drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine. Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. Volatile drugs, such as gaseous anesthetics, alcohol, or drugs with high volatility, are excreted via the lungs into expired air.

Biotransformation or drug metabolism is the process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process. A few drugs may also be changed chemically by a nonenzymatic process (eg, ester hydrolysis). The enzymes involved in the biotransformation of drugs are located mainly in the liver (see Chapter 11). Other tissues such as kidney, lung, small intestine, and skin also contain biotransformation enzymes.

Drug elimination in the body involves many complex rate processes. Although organ systems have specific functions, the tissues within the organs are not structurally homogeneous, and elimination processes may vary in each organ. In Chapter 3, drug elimination was modeled by an overall first-order elimination rate process. In this chapter, drug elimination is described in terms of clearance from a hypothetical well-stirred compartment containing

1Nonenzymatic breakdown of drugs may also be referred to as degradation. For example, some drugs such as aspirin (acetylsalicylic acid) may break down in the stomach due to acid hydrolysis at pH 1–3.
uniform drug distribution. The term clearance describes the process of drug elimination from the body or from a single organ without identifying the individual processes involved. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. The units for clearance are milliliters per minute (mL/min) or liters per hour (L/h). The volume concept is simple and convenient, because all drugs are dissolved and distributed in the fluids of the body.

The advantage of the clearance approach is that clearance applies to all elimination rate processes, regardless of the mechanism for elimination. In addition, for first-order elimination processes, clearance is a constant, whereas the rate of drug elimination is not constant. For example, clearance considers that a certain portion or fraction (percent) of the distribution volume is cleared of drug over a given time period. This basic concept (see also Chapter 3) will be elaborated after a review of the anatomy and physiology of the kidney.

**Frequently Asked Questions**

- **What’s the difference between clearance and the rate of drug elimination?**
- **Why is clearance a useful pharmacokinetic parameter?**

**The Kidney**

The liver (see Chapter 11) and kidney are the two major drug elimination organs in the body, though drug elimination can also occur almost anywhere in the body. The kidney is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body. To maintain salt and water balance, the kidney excretes excess electrolytes, water, and waste products while conserving solutes necessary for proper body function. In addition, the kidney has two endocrine functions: (1) secretion of renin, which regulates blood pressure; and (2) secretion of erythropoietin, which stimulates red blood cell production.

**Anatomic Considerations**

The kidneys are located in the peritoneal cavity. A general view is shown in Fig. 6-1 and a longitudinal view in Fig. 6-2. The outer zone of the kidney is called the cortex, and the inner region is called the medulla. The nephrons are the basic functional units, collectively responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. Each kidney contains 1 to 1.5 million nephrons. The glomerulus of each nephron starts in the cortex. Cortical nephrons have short loops of Henle that
remain exclusively in the cortex; juxtamedullary nephrons have long loops of Henle that extend into the medulla (Fig. 6-3). The longer loops of Henle allow for a greater ability of the nephron to reabsorb water, thereby producing a more concentrated urine.

**Blood Supply**

The kidneys represent about 0.5% of the total body weight and receive approximately 20% to 25% of the cardiac output. The kidney is supplied by blood via the renal artery, which subdivides into the interlobar arteries penetrating within the kidney and branching farther into the afferent arterioles. Each afferent arteriole carries blood toward a single nephron into the glomerular portion of the nephron (Bowman’s capsule). The filtration of blood occurs in the glomeruli in Bowman’s capsule. From the capillaries (glomerulus) within Bowman’s capsule, the blood flows out via the efferent arterioles and then into a second capillary network that surrounds the tubules (peri-tubule capillaries and vasa recta), including the loop of Henle, where some water is reabsorbed.

The **renal blood flow** (RBF) is the volume of blood flowing through the renal vasculature per unit time. Renal blood flow exceeds 1.2 L/min or 1700 L/d. **Renal plasma flow** (RPF) is the renal blood flow minus the volume of red blood cells present. Renal plasma flow is an important factor in the rate of drug filtration at the glomerulus.

\[
RPF = RBF - (RBF \times Hct) \quad (6.1)
\]

where Hct is the hemocrit.

Hct is the fraction of blood cells in the blood, about 0.45% or 45% of the total blood volume. The relationship of renal blood flow to renal plasma flow is given by a rearrangement of Equation 6.1:

\[
RPF = RBF(1 - Hct) \quad (6.2)
\]

Assuming a hematocrit of 0.45 and a RBF of 1.2 L/min and using the above equation, \( RPF = 1.2 - (1.2 \times 0.45) = 0.66 \) L/min or 660 mL/min, approximately 950 L/d. The average glomerular filtration
rate (GFR) is about 120 mL/min in an average adult², or about 20% of the RPF. The ratio GFR/RPF is the filtration fraction.

Regulation of Renal Blood Flow

Blood flow to an organ is directly proportional to the arteriovenous pressure difference (perfusion pressure) across the vascular bed and indirectly proportional to the vascular resistance. The normal renal arterial pressure (Fig. 6-4) is approximately 100 mm Hg and falls to approximately 45 to 60 mm Hg in the glomerulus (glomerular capillary hydrostatic pressure). This pressure difference is probably due to the increasing vasculature resistance provided by the small diameters of the capillary network. Thus, the GFR is controlled by changes in the glomerular capillary hydrostatic pressure.

In the normal kidney, RBF and GFR remain relatively constant even with large differences in mean systemic blood pressure (Fig. 6-5). The term autoregulation refers to the maintenance of a constant blood flow in the presence of large fluctuations in arterial blood pressure. Because autoregulation maintains a relatively constant blood flow, the filtration fraction (GFR/RPF) also remains fairly constant in this pressure range.

Glomerular Filtration and Urine Formation

A normal adult male subject has a GFR of approximately 125 mL/min. About 180 L of fluid per day are filtered through the kidneys. In spite of this large filtration volume, the average urine volume is 1 to 1.5 L. Up to 99% of the fluid volume filtered at the glomerulus is reabsorbed. Besides fluid regulation, the kidney also regulates the retention or excretion of various solutes and electrolytes (Table 6-1). With the exception of proteins and protein-bound substances, most small molecules are filtered through the glomerulus from the plasma. The filtrate contains some ions, glucose, and essential nutrients as well as waste products, such as urea, phosphate, sulfate, and other substances. The essential nutrients and water are reabsorbed at various sites, including the proximal tubule, loops of Henle, and distal tubules. Both active reabsorption and secretion mechanisms are involved. The urine volume is reduced, and the urine generally contains a high concentration of metabolic wastes and eliminated drug products. Advances in molecular biology have shown that transporters such as P-glycoprotein and other efflux proteins are present in the kidney, and can influence urinary drug

²GFR is often based on average body surface, 1.73 m². GFR is less in women and also decreases with age.
excretion. Further, CYP isoenzyme may also be present in the kidney in addition to the liver, and can impact drug clearance by metabolism.

Renal Drug Excretion

Renal excretion is a major route of elimination for many drugs. Drugs that are nonvolatile, water soluble, have a low molecular weight (MW), or are slowly biotransformed by the liver are eliminated by renal excretion. The processes by which a drug is excreted via the kidneys may include any combination of the following:

- Glomerular filtration
- Active tubular secretion
- Tubular reabsorption

Glomerular filtration is a unidirectional process that occurs for most small molecules (MW < 500), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus. The major driving force for glomerular filtration is the hydrostatic pressure within the glomerular capillaries. The kidneys receive a large blood supply (approximately 25% of the cardiac output) via the renal artery, with very little decrease in the hydrostatic pressure.

Glomerular filtration rate (GFR) is measured by using a drug that is eliminated primarily by filtration only (ie, the drug is neither reabsorbed nor secreted). Examples of such drugs are inulin and creatinine. Therefore, the clearance of inulin is approximately equal to the GFR, which is equal to 125 to 130 mL/min. The value for the GFR correlates fairly well with body surface area. Glomerular filtration of drugs is directly related to the free or nonprotein-bound drug concentration in the plasma. As the free drug concentration in the plasma increases, the glomerular filtration for the drug increases proportionately, thus increasing renal drug clearance for some drugs.

Active tubular secretion is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system. Two active renal secretion

### TABLE 6-1 Quantitative Aspects of Urine Formation

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtered</th>
<th>Reabsorbed</th>
<th>Secreted</th>
<th>Excreted</th>
<th>Percent Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ion (mEq)</td>
<td>26,000</td>
<td>25,850</td>
<td>150</td>
<td></td>
<td>99.4</td>
</tr>
<tr>
<td>Chloride ion (mEq)</td>
<td>18,000</td>
<td>17,850</td>
<td>150</td>
<td></td>
<td>99.2</td>
</tr>
<tr>
<td>Bicarbonate ion (mEq)</td>
<td>4,900</td>
<td>4,900</td>
<td>0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>870</td>
<td>460</td>
<td></td>
<td>410</td>
<td>53</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>800</td>
<td>800</td>
<td>0</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Water (mL)</td>
<td>180,000</td>
<td>179,000</td>
<td>1000</td>
<td>99.4</td>
<td></td>
</tr>
<tr>
<td>Hydrogen ion</td>
<td>900</td>
<td>Variable</td>
<td>Variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium ion (mEq)</td>
<td>900</td>
<td>900d</td>
<td>100</td>
<td>100</td>
<td>100d</td>
</tr>
</tbody>
</table>

*Quantity of various plasma constituents filtered, reabsorbed, and excreted by a normal adult on an average diet.

*Urea diffuses into, as well as out of, some portions of the nephron.

*pH or urine is on the acid side (4.5–6.9) when all bicarbonate is reabsorbed.

*Potassium ion is almost completely reabsorbed before it reaches the distal nephron. The potassium ion in the voided urine is actively secreted into the urine in the distal tubule in exchange for sodium ion.

From Levine (1990), with permission.
systems have been identified, systems for (1) weak acids (organic anion transporter, OAT) and (2) weak bases (organic cation transporter, OCT). For example, probenecid competes with penicillin for the same carrier system (weak acids). Active tubular secretion rate is dependent on renal plasma flow. Drugs commonly used to measure active tubular secretion include $p$-amino-hippuric acid (PAH) and iodopyracet (Diodrast). These substances are both filtered by the glomeruli and secreted by the tubular cells. Active secretion is extremely rapid for these drugs, and practically all the drug carried to the kidney is eliminated in a single pass. The clearance for these drugs therefore reflects the effective renal plasma flow (ERPF), which varies from 425 to 650 mL/min. The ERPF is determined by both RPF and the fraction of drug that is effectively extracted by the kidney relative to the concentration in the renal artery.

For a drug that is excreted solely by glomerular filtration, the elimination half-life may change markedly in accordance with the binding affinity of the drug for plasma proteins. In contrast, drug protein binding has very little effect on the elimination half-life of the drug excreted mostly by active secretion. Because drug protein binding is reversible, drug bound to plasma protein rapidly dissociates as free drug is secreted by the kidneys. For example, some of the penicillins are extensively protein bound, but their elimination half-lives are short due to rapid elimination by active secretion.

Tubular reabsorption occurs after the drug is filtered through the glomerulus and can be an active or a passive process involving transporting back into the plasma. If a drug is completely reabsorbed (e.g., glucose), then the value for the clearance of the drug is approximately zero. For drugs that are partially reabsorbed, clearance values are less than the GFR of 120 mL/min.

The reabsorption of drugs that are acids or weak bases is influenced by the pH of the fluid in the renal tubule (i.e., urine pH) and the pK$_a$ of the drug. Both of these factors together determine the percentage of dissociated (ionized) and undissociated (nonionized) drug. Generally, the undissociated species is more lipid soluble (less water soluble) and has greater membrane permeability. The undissociated drug is easily reabsorbed from the renal tubule back into the body. This process of drug reabsorption can significantly reduce the amount of drug excreted, depending on the pH of the urinary fluid and the pK$_a$ of the drug. The pK$_a$ of the drug is a constant, but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. In addition, the initial morning urine generally is more acidic and becomes more alkaline later in the day. Vegetable and fruit diets (alkaline residue diet$^3$) result in higher urinary pH, whereas diets rich in protein result in lower urinary pH. Drugs such as ascorbic acid and antacids such as sodium carbonate may decrease (acidify) or increase (alkalinize) the urinary pH, respectively, when administered in large quantities. By far the most important changes in urine pH are caused by fluids administered intravenously. Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid–base therapy to alkalize or acidify the urine, respectively. Excretion of these solutions may drastically change urinary pH and alter drug reabsorption and drug excretion by the kidney.

The percentage of ionized weak acid drug corresponding to a given pH can be obtained from the Henderson–Hasselbalch equation.

$$\text{pH} = \text{pK}_a + \log \frac{[\text{ionized}]}{[\text{nonionized}]} \quad (6.3)$$

Rearrangement of this equation yields:

$$\frac{[\text{ionized}]}{[\text{nonionized}]} = 10^{\text{pH} - \text{pK}_a} \quad (6.4)$$

Fraction of drug ionized

$$= \frac{[\text{ionized}]}{[\text{ionized}]+[\text{nonionized}]} \quad (6.5) = \frac{10^{\text{pH} - \text{pK}_a}}{1 + 10^{\text{pH} - \text{pK}_a}}$$

$^3$The alkaline residue diet (also known as the alkaline ash diet) is a diet composed of foods, such as fruits and vegetables, from which the carbohydrate portion of the diet is metabolized in the body leaving an alkaline residue containing cations such as sodium, potassium, calcium, etc. These cations are excreted through the kidney and cause the urine to become alkaline.
The fraction or percent of weak acid drug ionized in any pH environment may be calculated with Equation 6.5. For acidic drugs with $pK_a$ values from 3 to 8, a change in urinary pH affects the extent of dissociation (Table 6-2). The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a $pK_a$ of 5 than with a $pK_a$ of 3. Weak acids with $pK_a$ values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations.

For a weak base drug, the Henderson–Hasselbalch equation is given as

$$pH = pK_{a, \text{nonionized}} + \log \left( \frac{\text{nonionized}}{\text{ionized}} \right)$$

and

$$\text{Percent of drug ionized} = \frac{10^{pK_a-pH}}{1 + 10^{pK_a-pH}}$$

The greatest effect of urinary pH on reabsorption occurs for weak base drugs with $pK_a$ values of 7.5 to 10.5.

From the Henderson–Hasselbalch relationship, a concentration ratio for the distribution of a weak acid or basic drug between urine and plasma may be derived. The urine–plasma ($U/P$) ratios for these drugs are as follows.

For weak acids,

$$\frac{U}{P} = \frac{1 + 10^{pH_{\text{urine}}-pK_a}}{1 + 10^{pH_{\text{plasma}}-pK_a}}$$

(6.8)

For weak bases,

$$\frac{U}{P} = \frac{1 + 10^{pK_a-pH_{\text{urine}}}}{1 + 10^{pK_a-pH_{\text{plasma}}}}$$

(6.9)

For example, amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipid-soluble nonionized species are formed. In contrast, acidification of the urine will cause the amphetamine to become more ionized (form a salt). The salt form is more water soluble, less likely to be reabsorbed, and tends to be excreted into the urine more quickly. In the case of weak acids (such as salicylic acid), acidification of the urine causes greater reabsorption of the drug and alkalinization of the urine causes more rapid excretion of the drug.

In summary, renal drug excretion is a composite of passive filtration at the glomerulus, active secretion in the proximal tubule and passive reabsorption in the distal tubule (Table 6-3). Active secretion is an enzyme (transporter)-mediated process that is saturable. Although reabsorption of drugs is a passive process, the extent of reabsorption of weak acid or weak base drugs is influenced by the pH of the urine.

### Table 6-2 Effect of Urinary pH and $pK_a$ on the Ionization of Drugs

<table>
<thead>
<tr>
<th>pH of Urine</th>
<th>Percent of Drug Ionized: $pK_{a,53}$</th>
<th>Percent of Drug Ionized: $pK_{a,55}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>100</td>
<td>99.6</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>50.0</td>
</tr>
<tr>
<td>4</td>
<td>91</td>
<td>9.1</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### Table 6-3 Properties of Renal Drug Elimination Processes

<table>
<thead>
<tr>
<th>Process</th>
<th>Active/Passive Transport</th>
<th>Location in Nephron</th>
<th>Drug Ionization</th>
<th>Drug Protein Binding</th>
<th>Influenced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration</td>
<td>Passive</td>
<td>Glomerulus</td>
<td>Either</td>
<td>Only free drug</td>
<td>Protein binding</td>
</tr>
<tr>
<td>Secretion</td>
<td>Active</td>
<td>Proximal tubule</td>
<td>Mostly weak acids and weak bases</td>
<td>No effect</td>
<td>Competitive inhibitors</td>
</tr>
<tr>
<td>Reabsorption</td>
<td>Passive</td>
<td>Distal tubule</td>
<td>Nonionized</td>
<td>Not applicable</td>
<td>Urinary pH and flow</td>
</tr>
</tbody>
</table>
and the degree of ionization of the drug. In addition, an increase in blood flow to the kidney, which may be due to diuretic therapy or large alcohol consumption, decreases the extent of drug reabsorption in the kidney and increases the rate of drug excreted in the urine.

**CLINICAL APPLICATION**

Both sulfisoxazole (Gantrisin) tablets and the combination product, sulfamethoxazole/trimethoprim (Bactrim) tablets, are used for urinary tract infections. Sulfisoxazole and sulfamethoxazole are sulfonamides that are well absorbed after oral administration and are excreted in high concentrations in the urine. Sulfonamides are N-acetylated to a less water-soluble metabolite. Both sulfonamides and their corresponding N-acetylated metabolite are less water soluble in acid and more soluble in alkaline conditions. In acid urine, renal toxicity can occur due to precipitation of the sulfonamides in the renal tubules. To prevent crystalluria and renal complications, patients are instructed to take these drugs with a high amount of fluid intake and to keep the urine alkaline.

**Frequently Asked Questions**

- Which renal elimination processes are influenced by protein binding?
- Is clearance a first-order process? Is clearance a better parameter to describe drug elimination than half-life? Why is it necessary to use both parameters in the literature?

**PRACTICE PROBLEMS**

Let $pK_a = 5$ for an acidic drug. Compare the $U/P$ at urinary pH (a) 3, (b) 5, and (c) 7.

**Solution**

a. At pH = 3,

$$\frac{U}{P} = \frac{1 + 10^{5-5}}{1 + 10^{7-5}} = \frac{1.01}{1.01} = \frac{1}{252}$$

b. At pH = 5,

$$\frac{U}{P} = \frac{1 + 10^{5-5}}{1 + 10^{7-5}} = \frac{2}{1 + 10^{2-5}} = \frac{2}{252}$$

c. At pH = 7,

$$\frac{U}{P} = \frac{1 + 10^{7-5}}{1 + 10^{7-5}} = \frac{101}{1 + 10^{2-5}} = \frac{101}{252}$$

In addition to the pH of the urine, the rate of urine flow influences the amount of filtered drug that is reabsorbed. The normal flow of urine is approximately 1 to 2 mL/min. Nonpolar and nonionized drugs, which are normally well reabsorbed in the renal tubules, are sensitive to changes in the rate of urine flow. Drugs that increase urine flow, such as ethanol, large fluid intake, and methylxanthines (such as caffeine or theophylline), decrease the time for drug reabsorption and promote their excretion. Thus, forced diuresis through the use of diuretics may be a useful adjunct for removing excessive drug in an intoxicated patient, by increasing renal drug excretion.

**DRUG CLEARANCE**

Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process. Drug clearance (body clearance, total body clearance, or $Cl_T$) considers the entire body as a single drug-eliminating system from which many unidentified elimination processes may occur. Instead of describing the drug elimination rate in terms of amount of drug removed per time unit (eg, mg/min), drug clearance is described in terms of volume of fluid clear of drug per time unit (eg, mL/min).

There are several definitions of clearance, which are similarly based on volume of drug removed per unit time. The simplest concept of clearance regards the body as a space that contains a definite volume of body fluid (apparent volume of distribution, $V_p$) in which the drug is dissolved. Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time. The units for...
clearance are volume/time (e.g., mL/min, L/h). For example, if the \( Cl_T \) of penicillin is 15 mL/min in a patient and penicillin has a \( V_D \) of 12 L, then from the clearance definition, 15 mL of the 12 L will be cleared of drug per minute.

Alternatively, \( Cl_T \) may be defined as the rate of drug elimination divided by the plasma drug concentration. This definition expresses drug elimination in terms of the volume of plasma eliminated of drug per unit time. This definition is a practical way to calculate clearance based on plasma drug concentration data.

\[
Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration}(C_p)} \quad (6.10)
\]

\[
Cl_T = \frac{dD_E}{dt} \frac{\mu g/min}{\mu g/mL} = mL/min \quad (6.11)
\]

where \( D_E \) is the amount of drug eliminated and \( dD_E/dt \) is the rate of elimination.


\[
\text{Elimination rate} = \frac{dD_E}{dt} = C_p Cl_T \quad (6.12)
\]

The two definitions for clearance are similar because dividing the elimination rate by the \( C_p \) yields the volume of plasma cleared of drug per minute, as shown in Equation 6.10.

As discussed in previous chapters, a first-order elimination rate, \( dD_E/dt \), is equal to \( kD_E \) or \( kC_pV_D \). Based on Equation 6.10, substituting elimination rate for \( kC_pV_D \),

\[
Cl_T = \frac{kC_p V_D}{C_p} = kV_D \quad (6.13)
\]

Equation 6.13 shows that clearance is the product of \( V_D \) and \( k \), both of which are constant. As the plasma drug concentration decreases during elimination, the rate of drug elimination, \( dD_E/dt \), decreases accordingly, but clearance remains constant. Clearance is constant as long as the rate of drug elimination is a first-order process.

EXAMPLE

Penicillin has a \( Cl_T \) of 15 mL/min. Calculate the elimination rate for penicillin when the plasma drug concentration, \( C_p \), is 2 \( \mu g/mL \).

Solution

Elimination rate = \( C_p \times Cl_T \) (from Equation 6.12)

\[
\frac{dD_e}{dt} = 2 \mu g/mL \times 15 mL/min = 30 \mu g/min
\]

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 \( \mu g/mL \). From Equation 6.11, the rate of drug elimination is

\[
\frac{dD_e}{dt} = 10 \mu g/mL \times 15 mL/min = 150 \mu g/min
\]

Thus, 150 \( \mu g/min \) of penicillin is eliminated from the body when the plasma penicillin concentration is 10 \( \mu g/mL \).

Clearance may be used to estimate the rate of drug elimination at any given concentration. Using the same example, if the elimination rate of penicillin was measured as 150 \( \mu g/min \) when the plasma penicillin concentration was 10 \( \mu g/mL \), then the clearance of penicillin is calculated from Equation 6.11:

\[
Cl_{\text{penicillin}} = \frac{150 \mu g/min}{10 \mu g/mL} = 15 mL/min
\]

Just as the elimination rate constant \( k \) represents the sum total of all the rate constants for drug elimination, including excretion and biotransformation, \( Cl_T \) is the sum total of all the clearance processes in the body, including clearance through the kidney (renal clearance), lung, and liver (hepatic clearance).

\[
\begin{align*}
\text{Renal clearance} &= k_v V_D \\
\text{Lung clearance} &= k_l V_D \\
\text{Hepatic clearance} &= k_m V_D \\
\text{Body clearance} &= (k_v + k_l + k_m) V_D = kV_D \quad (6.14)
\end{align*}
\]
Determine the total body clearance for a drug in a 70-kg male patient. The drug follows the kinetics of a one-compartment model and has an elimination half-life of 3 hours with an apparent volume of distribution of 100 mL/kg.

Solution
First determine the elimination rate constant \( k \) and then substitute properly into Equation 6.13.

\[
\frac{0.693}{t_{1/2}} = 0.693 \times \frac{3}{0.231} = 0.231 \text{ h}^{-1}
\]

\[
Cl_{T} = 0.231 \text{ h}^{-1} \times 100 \text{ mL/kg} = 23.1 \text{ mL kg}^{-1} \text{ h}^{-1}
\]

For a 70-kg patient,

\[
Cl_{T} = 23.1 \text{ mL/kg} \times 70 \text{ kg} = 1617 \text{ mL/h}
\]

**CLEARANCE MODELS**

The calculation of clearance from \( k \) and \( V_{D} \) assumes (sometimes incorrectly) a defined model, whereas clearance estimated directly from the plasma drug concentration–time curve does not assume any model. Although clearance may be regarded as the product of \( k \) and \( V_{D} \), Equation 6.10 is far more general because the reaction order for the rate of drug elimination, \( dD/dt \), is not specified, and the elimination rate may or may not follow first-order kinetics.

**Physiologic/Organ Clearance**

Clearance may be calculated for any organ involved in the irreversible removal of drug from the body. Many organs in the body have the capacity for drug elimination, including drug excretion and biotransformation. The kidneys and liver are the most common organs involved in excretion and metabolism, respectively. Physiologic pharmacokinetic models are based on drug clearance through individual organs or tissue groups (Fig. 6-6).

For any organ, clearance may be defined as the fraction of blood volume containing drug that flows through the organ and is eliminated of drug per unit time. From this definition, clearance is the product of the blood flow \( (Q) \) to the organ, and the extraction ratio (ER). The ER is the fraction of drug extracted by the organ as drug passes through.

\[
\text{Clearance} = Q(\text{ER}) \tag{6.15}
\]

If the drug concentration in the blood \( (C_{a}) \) entering the organ is greater than the drug concentration of blood \( (C_{v}) \) leaving the organ, then some of the drug has been extracted by the organ (Fig. 6-6). The ER is \( C_{a} - C_{v} \) divided by the entering drug concentration \( (C_{a}) \), as shown in Equation 6.16.

\[
\text{ER} = \frac{C_{a} - C_{v}}{C_{a}} \tag{6.16}
\]

**FIGURE 6-6** Drug clearance model. \( Q = \text{blood flow}, C_{a} = \text{incoming drug concentration [usually arterial drug concentration]}, C_{v} = \text{outgoing drug concentration [venous drug concentration]} \)
ER is a ratio with no units. The value of ER may range from 0 (no drug removed by the organ) to 1 (100% of the drug is removed by the organ). An ER of 0.25 indicates that 25% of the incoming drug concentration is removed by the organ as the drug passes through.

Substituting for ER into Equation 6.15 yields

$$Cl = Q \left( \frac{C_a - C_x}{C_a} \right)$$  \hspace{1cm} (6.17)

The physiologic approach to clearance shows that clearance depends on the blood flow rate and the ability of the organ to eliminate drug, whereas the classical definition of clearance is that a constant or static fraction of the volume in which the drug is contained is removed per unit time by the organ. However, clearance measurements using the physiologic approach require invasive techniques to obtain measurements of blood flow and extraction ratio. The physiologic approach has been used to describe hepatic clearance, which is discussed under hepatic elimination (Chapter 11). More classical definitions of clearance have been applied to renal clearance because direct measurements of plasma drug concentration and urinary drug excretion may be obtained. The various approaches for estimating clearance are described in Fig. 6-7.

**Frequently Asked Question**

How do you calculate body clearance using the physiologic approach based on organ clearance?

**Model-Independent Methods**

Clearance is commonly used to describe first-order drug elimination from compartment models such as the one-compartment model, \( C(t) = C_p = C_p e^{-kt} \) in which the distribution volume and elimination rate constant are well defined. Clearance estimated directly from area under the curve of the plasma drug concentration–time curve does not assume any model. Clearance does not easily relate to a compartment model particularly when an elimination process other than a first-order rate process is involved.

**Compartment model**

Static volume and first-order elimination are assumed. Plasma flow is not considered. \( Cl = k V_o \).

**Physiologic model**

Clearance is the product of the plasma flow \( Q \) and the extraction ratio \( ER \). Thus \( Cl = Q ER \).

**Model independent**

Volume and elimination rate constant not defined. \( Cl = \text{Dose}/[\text{AUC}] \).

**FIGURE 6-7** General approaches to clearance. Volume and elimination rate constant not defined.

**Model-independent methods** are noncompartment model approaches used to calculate certain pharmacokinetic parameters such as clearance and bioavailability \( (F) \). The major advantage of model-independent methods is that no assumption for a specific compartment model is required to analyze the data. Moreover, the volume of distribution and the elimination rate constant need not be determined directly from the equation that best fits the plasma drug concentration–time curve.

Clearance can be determined directly from the plasma–time concentration curve by

$$Cl = \int_0^\infty \frac{D_0}{C(t)} dt$$  \hspace{1cm} (6.18)

where \( D_0 \) is the dose and \( C(t) \) is an unknown function that describes the declining plasma drug concentrations.

In the compartment model, \( C(t) = C_p = C_p e^{-kt} \) can be different mathematical functions that describe the individual pharmacokinetics of the drug. Using
the noncompartment approach, the general equation uses area under the curve of the plasma drug concentration curve, $[\text{AUC}]_0^\infty$ for the calculation of clearance.

\[
\text{CL}_T = \frac{D_0}{[\text{AUC}]_0^\infty} \quad (6.19)
\]

where $D_0$ is the dose and $[\text{AUC}]_0^\infty = \int_0^\infty C \, dt$

Because $[\text{AUC}]_0^\infty$ is calculated from the plasma drug concentration–time curve from zero to infinity using the trapezoidal rule, no compartmental model is assumed. However, to extrapolate the data to infinity to obtain the residual $[\text{AUC}]_t^\infty$ or $(C_p/k)$, first-order elimination is usually assumed. This calculation of $\text{CL}_T$ is referred to as a noncompartment or model-independent method. In this case, if the drug follows the kinetics of a one-compartment model, the $\text{CL}_T$ is numerically similar to the product of $V_D$ and $k$ obtained by fitting the data to a one-compartment model.

### RENAL CLEARANCE

Renal clearance, $\text{Cl}_R$, is defined as the volume of plasma that is cleared of drug per unit of time through the kidney. Similarly, renal clearance may be defined as a constant fraction of the $V_D$ in which the drug is contained that is excreted by the kidney per unit of time. More simply, renal clearance is defined as the urinary drug excretion rate $(dD_u/dt)$ divided by the plasma drug concentration $(C_p)$.

\[
\text{Cl}_R = \frac{\text{excretion rate}}{\text{plasma concentration}} \Rightarrow \frac{dD_u/dt}{C_p} \quad (6.20)
\]

An alternative approach to obtaining Equation 6.20 is to consider the mass balance of drug cleared by the kidney and ultimately excreted in the urine. For any drug cleared through the kidney, the rate of the drug passing through kidney (via filtration, reabsorption, and/or active secretion) must equal the rate of drug excreted in the urine.

Rate of drug passing through kidney = rate of drug excreted

\[
\text{Cl}_R \times C_p = Q_u \times C_u \quad (6.21)
\]

mL/min $\times$ mg/mL = mL/min $\times$ mg/mL

where $\text{Cl}_R$ is renal clearance, $C_p$ is plasma drug concentration, $Q_u$ is the rate of urine flow, and $C_u$ is the urine drug concentration. Rearrangement of Equation 6.21 gives

\[
\text{Cl}_R = \frac{Q_u \times C_u}{C_p} \Rightarrow \frac{\text{excretion rate}}{C_p} \quad (6.22)
\]

Because the excretion rate $= Q_u C_u = dD_u/dt$, Equation 6.22 is the equivalent of Equation 6.20.

### Comparison of Drug Excretion Methods

Renal clearance may be measured without regard to the physiologic mechanisms involved in this process. From a physiologic viewpoint, however, renal clearance may be considered the ratio of the sum of the glomerular filtration and active secretion rates less the reabsorption rate divided by the plasma drug concentration:

\[
\text{Cl}_R = \frac{\text{filtration rate} \ + \text{secretion rate} \ - \text{reabsorption rate}}{C_p} \quad (6.23)
\]

The renal clearance of a drug is often related to the renal glomerular filtration rate, GFR, when reabsorption is negligible and the drug is not actively secreted. The renal clearance value for the drug is compared to that of a standard reference, such as inulin, which is cleared completely through the kidney by glomerular filtration only. The clearance ratio, which is the ratio of drug clearance to inulin clearance, may give an indication for the mechanism of renal excretion of the drug (Table 6-4). However, further renal drug excretion studies are necessary to confirm unambiguously the mechanism of excretion.
Drug Elimination and Clearance

TABLE 6-4 Comparison of Clearance of a Sample Drug to Clearance of a Reference Drug, Inulin

<table>
<thead>
<tr>
<th>Clearance Ratio</th>
<th>Probable Mechanism of Renal Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{Cl_{drug}}{Cl_{inulin}} &lt; 1$</td>
<td>Drug is partially reabsorbed</td>
</tr>
<tr>
<td>$\frac{Cl_{drug}}{Cl_{inulin}} = 1$</td>
<td>Drug is filtered only</td>
</tr>
<tr>
<td>$\frac{Cl_{drug}}{Cl_{inulin}} &gt; 1$</td>
<td>Drug is actively secreted</td>
</tr>
</tbody>
</table>

A method to quantify renal drug excretion is to consider the kinetic nature of the elimination processes. For this consideration, some of the detailed steps in the elimination process may be omitted or simplified. For example, assume that the body fluid volume is the $V_D$ and that the plasma drug concentration, $C_p$, is changing after an intravenous bolus injection.

**Filtration Only**

If glomerular filtration is the sole process for drug excretion and no drug is reabsorbed, then the amount of drug filtered at any time ($t$) will always be $C_p \times GFR$ (Table 6-5). Likewise, if the $Cl_R$ of the drug is by glomerular filtration only, as in the case of inulin, then $Cl_R = GFR$. Otherwise, $Cl_R$ represents all the processes by which the drug is cleared through the kidney, including any combination of filtration, reabsorption, and active secretion.

Note that the quantity of drug excreted per minute is always the plasma concentration ($C_p$) multiplied by a constant (eg, 125 mL/min), which in this case is also the renal clearance for the drug. The glomerular filtration rate may be treated as a first-order process relating to $C_p$. The rate of drug excretion using a compartment approach and physiologic approach are compared in Equations 6.24 and 6.25.

$$\frac{dD}{dt} = k_e V_D C_p \text{ (compartment)} \quad (6.24)$$

$$\frac{dD}{dt} = Cl_R C_p \text{ (physiologic)} \quad (6.25)$$

Equating 6.24 with 6.25,

$$k_e V_D C_p = Cl_R C_p$$

$$k_e = \frac{Cl_R}{V_D} \quad (6.26)$$

Equation 6.26 shows that, in the absence of other processes of drug elimination, the excretion rate constant is a fractional constant reflecting the volume pumped out per unit time due to GFR relative to the volume of the body compartment ($V_D$).

In the one-compartment model, a drug is assumed to be uniformly and instantly equilibrated. However, the renal plasma drug concentration entering the kidney (arterial drug concentration) is always higher than the venous plasma drug concentration leaving the kidney. In spite of this inconsistency, the rate of drug elimination is properly adjusted in the estimation of the first-order elimination rate constant ($k$) given in Equation 6.25 if the overall plasma drug concentration profile is adequately described. If the pharmacokinetic parameters are properly calculated to fit the data, the parameters $k$ and $V_D$ reflect the underlying kinetic processes.

**TABLE 6-5 Urinary Drug Excretion Rate**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>$C_p$ (μg/mL)</th>
<th>Excretion Rate (μg/min) (Drug filtered by GFR per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$C_{p0}$</td>
<td>$(C_{p0})_0 \times 125$</td>
</tr>
<tr>
<td>1</td>
<td>$(C_p)_1$</td>
<td>$(C_p)_1 \times 125$</td>
</tr>
<tr>
<td>2</td>
<td>$(C_p)_2$</td>
<td>$(C_p)_2 \times 125$</td>
</tr>
<tr>
<td>$t$</td>
<td>$(C_p)_t$</td>
<td>$(C_p)_t \times 125$</td>
</tr>
</tbody>
</table>

*Assumes that the drug is excreted by filtration only and that the GFR is 125 mL/min.
Filtration and Reabsorption

For a drug with a reabsorption fraction of \( fr \), the drug excretion rate is reduced, and Equation 6.25 is restated as Equation 6.27:

\[
\frac{dD}{dt} = C_l_r (1 - fr)C_p \quad (6.27)
\]

Equating the right sides of Equations 6.27 and 6.24 indicates that the first-order rate constant \( k_e \) in the compartment model is equivalent to \( C_l_r (1 - fr)/V_D \). In this case, the excretion rate constant is affected by the reabsorption fraction \( fr \) and the GFR. Because these two parameters generally remain constant, the general adoption of a first-order elimination process to describe renal drug excretion is a reasonable approach.

Filtration and Active Secretion

For a drug that is primarily filtered and secreted, with negligible reabsorption, the overall excretion rate will exceed GFR (Table 6-4). At low drug plasma concentrations, active secretion is not saturated, and the drug is excreted by filtration and active secretion. At high concentrations, the percentage of drug excreted by active secretion decreases due to saturation. Clearance decreases because excretion rate decreases (Fig. 6-8). Clearance decreases because the total excretion rate of the drug increases to the point where it is approximately equal to the filtration rate (Fig. 6-9).

The power of the kinetic approach is that, even lacking any knowledge of GFR, active secretion, or the reabsorption process, modeling the data allows the process of drug elimination to be described quantitatively. If a change to a higher-order elimination rate process occurs, then an additional process besides GFR may be involved. The compartmental analysis aids the ultimate development of a model consistent with physiologic functions of the body.

EXAMPLE

Two drugs, A and B, are entirely eliminated through the kidney by glomerular filtration (125 mL/min), with no reabsorption. Drug A has half the distribution volume of drug B, and the \( V_D \) of drug B is 20 L. What are the drug clearances for each drug based on the classical and physiologic approaches?

Solution

Since glomerular filtration of the two drugs is the same, and both drugs are not eliminated by other means, clearance for both drugs depends on renal plasma flow and extraction by the kidney only.
Drug Elimination and Clearance

that is excreted rapidly, \( dD/dt \) is large, the slope is steeper, and clearance is greater (Fig. 6-10, line A).

For a drug that is excreted slowly through the kidney, the slope is smaller (Fig. 6-10, line B).

From Equation 6.20,

\[
Cl = \frac{Q(C_a - C_0)}{C_a} = 125 \text{ mL/min}
\]

Interestingly, known drug clearance tells little about the dosing differences of the two drugs, although it helps identify the mechanism of drug elimination. In this example, both drugs have the same clearance.

Basing the calculation on the elimination concept and applying Equation 6.14, \( k \) is easily determined, resulting in an obvious difference in \( t_{1/2} \) between the two drugs—in spite of similar drug clearance.

\[
k_{\text{drugA}} = \frac{Cl}{V_D} = \frac{125 \text{ mL/min}}{10 \times 1000 \text{ mL}} = 0.0125 \text{ min}^{-1}
\]

\[
k_{\text{drugB}} = \frac{Cl}{V_D} = \frac{125 \text{ mL/min}}{20.0 \times 1000 \text{ mL}} = 0.00625 \text{ min}^{-1}
\]

Here \( k \) specifies the fraction of drug eliminated regardless of distributional differences of the drug.

In spite of identical drug clearances, \( k \) for drug A is twice that of drug B. Drug A has an elimination half-life of 55.44 minutes, while that of drug B is 110.88 minutes—much longer because of the bigger volume of distribution.

Frequently Asked Question

What is the difference between drug clearance and creatinine clearance?

DETERMINATION OF RENAL CLEARANCE

Graphical Methods

The clearance is given by the slope of the curve obtained by plotting the rate of drug excretion in urine (\( dD/dt \)) against \( C_p \) (Equation 6.28). For a drug that is excreted rapidly, \( dD/dt \) is large, the slope is steeper, and clearance is greater (Fig. 6-10, line A).

For a drug that is excreted slowly through the kidney, the slope is smaller (Fig. 6-10, line B).

From Equation 6.20,

\[
Cl = \frac{dD/dt}{C_p}
\]

Multiplying both sides by \( C_p \) gives

\[
Cl_c C_p = \frac{dD_c}{dt}
\]

By rearranging Equation 6.28 and integrating, one obtains

\[
\int_0^{t_1} dD_c = Cl_c \int_0^{t_1} C_p dt
\]

\[
[D_c]_1^1 = Cl_c[AUC_c]_1^1
\]

A graph is then plotted of cumulative drug excreted in the urine versus the area under the concentration–time curve (Fig. 6-11). Renal clearance is obtained from the slope of the curve. The area under the curve can be estimated by the trapezoidal rule or by other measurement methods. The disadvantage of
Chapter 6

this method is that if a data point is missing, the cumulative amount of drug excreted in the urine is difficult to obtain. However, if the data are complete, then the determination of clearance is more accurate by this method.

By plotting cumulative drug excreted in the urine from $t_1$ to $t_2$, $(D_u^*_{t_1}^t)$ versus $(\text{AUC}_{t_1}^t)^2$, one obtains an equation similar to that presented previously:

$$\int_{D_u^*_{t_1}^t} dD_u = Cl_R \int_{t_1}^{t_2} C_p dt$$ (6.31)

$$[D_u^*_{t_1}^t] = Cl_R [\text{AUC}_{t_1}^t]^2$$ (6.32)

The slope is equal to the renal clearance (Fig. 6-12).

**Model-Independent Methods**

Clearance rates may also be estimated by a single (nongraphical) calculation from knowledge of the $[\text{AUC}_{t_0}^t]$, the total amount of drug absorbed, $FD_{0}$, and the total amount of drug excreted in the urine, $D_u^*$. For example, if a single IV bolus drug injection is given to a patient and the $[\text{AUC}_{t_0}^t]$ is obtained from the plasma drug level–time curve, then total body clearance is estimated by

$$Cl_T = \frac{D_0}{[\text{AUC}_{t_0}^t]}$$ (6.33)

If the total amount of drug excreted in the urine, $D_u^*$, has been obtained, then renal clearance is calculated by

$$Cl_R = \frac{D_u^*}{[\text{AUC}_{t_0}^t]}$$ (6.34)

The calculations using Equations 6.33 and 6.34 allow for rapid and easily obtainable estimates of drug clearance. However, only a single-dose estimate is obtained; therefore, the calculations do not reflect nonlinear changes in the clearance rates, as indicated in Fig. 6-8.

Clearance can also be calculated from fitted parameters. If the volume of distribution and elimination constants are known, body clearance ($Cl_T$), renal clearance ($Cl_R$), and hepatic clearance ($Cl_h$) can be calculated according to the following expressions:

$$Cl_T = k V_D$$ (6.35)

$$Cl_R = k_e V_D$$ (6.36)

$$Cl_h = k_m V_D$$ (6.37)

**Total body clearance** ($Cl_T$) is equal to the sum of renal clearance and hepatic clearance and is based on the concept that the entire body acts as a drug-eliminating system.

$$Cl_T = Cl_R + Cl_h$$ (6.38)

Substituting Equations 6.35 and 6.36 into Equation 6.38,

$$k V_D = k_e V_D + k_m V_D$$ (6.39)
Dividing by \( V_D \) on both sides of Equation 6.39,

\[
k = k_e + k_m \quad (6.40)
\]

**Frequently Asked Question**

What is an independent parameter in a model? Is clearance an independent parameter of the physiologic model? How is clearance related to parameters in the compartment model?

**PRACTICE PROBLEM**

Consider a drug that is eliminated by first-order renal excretion and hepatic metabolism. The drug follows a one-compartment model and is given in a single intravenous or oral dose (Fig. 6-13). Working with the model presented in Fig. 6-13, assume that a single dose (100 mg) of this drug is given orally. The drug is 90% systemically available. The total amount of unchanged drug recovered in the urine is 60 mg, and the total amount of metabolite recovered in the urine is 30 mg (expressed as milligram equivalents to the parent drug). According to the literature, the elimination half-life for this drug is 3.3 hours and its apparent volume of distribution is 1000 L. From the information given, find (a) the total body clearance, (b) the renal clearance, and (c) the nonrenal clearance of the drug.

**Solution**

a. Total body clearance:

\[
Cl_T = kV_D
\]

\[
Cl_T = \frac{0.693}{3.3(1000)} = 210 \text{ L/h}
\]

b. Renal clearance. First find \( k_e \):

\[
\frac{k}{k} = \frac{D^u}{FD_0} = \frac{D^u}{M_u + D^u - M^m} \quad (6.41)
\]

\[
k_e = \left( \frac{0.693}{3.3} \right) \left( \frac{60}{30 + 60} \right) = 0.14 \text{ h}^{-1}
\]

Then, from Equation 6.36,

\[
Cl_R = k_e V_D
\]

\[
Cl_R = (0.14)(1000) = 140 \text{ mL/h}
\]

c. Nonrenal clearance:

\[
Cl_h = Cl_T - Cl_R
\]

\[
Cl_h = 210 - 140 = 70 \text{ mL/h}
\]

Alternatively,

\[
k_m = k - k_e
\]

\[
k_m = 0.21 - 0.14 = 0.07 \text{ h}^{-1}
\]

\[
k_m = k \left[ \frac{M^m}{M_u + D^u - M^m} \right]
\]

\[
k_m = 0.21 \left( \frac{30}{30 + 60} \right) = 0.07 \text{ h}^{-1}
\]

Applying Equation 6.37,

\[
Cl_h = k_m V_D
\]

\[
Cl_h = (0.07)(1000) = 70 \text{ mL/h}
\]
Fraction of Drug Excreted

For many drugs, the total amount of unchanged drug excreted in the urine \( D_u^- \), may be obtained by direct assay. The ratio of \( D_u^- \) to the fraction of the dose absorbed, \( D_u \), is equal to the ratio of drug excreted unchanged in the urine and is also equal to \( k_e/k \).

Fraction of drug excreted unchanged in the urine is

\[
f_u = \frac{D_u^-}{D_u} = \frac{k_e}{k}
\]  

(6.45)

Renal clearance may be determined from the fraction of unchanged drug excreted in the urine and the total body clearance.

\[
Cl_R = \frac{D_u^-}{FD_0} Cl_T = f_u Cl_T
\]  

(6.46)

Equation 6.46 can also be expressed as

\[
Cl_R = \frac{k_e}{k} Cl_T
\]  

(6.47)

PRACTICE PROBLEM

An antibiotic is given by IV bolus injection at a dose of 500 mg. The apparent volume of distribution was 21 L and the elimination half-life was 6 hours. Urine was collected for 48 hours, and 400 mg of unchanged drug was recovered. What is the fraction of the dose excreted unchanged in the urine? Calculate \( k, k_e, Cl_T, Cl_R, \) and \( Cl_h \).

Solution

Since the elimination half-life, \( t_{1/2} \), for this drug is 6 hours, a urine collection for 48 hours represents \( 8 \times t_{1/2} \), which allows for greater than 99% of the drug to be eliminated from the body. The fraction of drug excreted unchanged in the urine, \( f_u \), is obtained by using Equation 6.47 and recalling that \( f = 1 \) for drugs given by IV bolus injection.

\[
f_u = \frac{400}{500} = 0.8
\]
Therefore, 80% of the absorbed dose is excreted in the urine unchanged. Calculations for $k$, $k_e$, $Cl_T$, $Cl_R$, and $Cl_h$ are given here:

\[
k = \frac{0.693}{6} = 0.1155 \text{ h}^{-1}
\]

\[
k_e = f_kk = (0.8)(0.1155) = 0.0924 \text{ h}^{-1}
\]

\[
Cl_T = kV_D = (0.1155)(21) = 2.43 \text{ L/h}
\]

\[
Cl_R = f_k Cl_T = (0.8)(2.43) = 1.94 \text{ L/h}
\]

Alternatively,

\[
Cl_R = k_kV_D = (0.0924)(21) = 1.94 \text{ L/h}
\]

\[
Cl_h = Cl_T - Cl_R = 2.43 - 1.94 = 0.49 \text{ L/h}
\]

Protein-Bound Drugs

Protein-bound drugs are not eliminated by glomerular filtration. Therefore, Equation 6.18 for the calculation of renal clearance must be modified, because only the free drug is excreted by a linear process. The bound drugs are usually excreted by active secretion, following capacity-limited kinetics. The determination of clearance that separates the two components results in a hybrid clearance. There is no simple way to overcome this problem. Clearance values for a protein-bound drug are therefore calculated with the following equation:

\[
Cl_R = \frac{\text{rate of unbound drug excretion}}{\text{concentration of unbound drug in the plasma}}
\]

(6.48)

In practice, this equation is not easily applied because the rate of drug excretion is usually determined after collecting urine samples. The drug excreted in the urine is the sum of drug excreted by active tubular secretion and by passive glomerular filtration, minus drug that is reabsorbed. However, it is not possible to distinguish the amount of bound drug actively secreted or reabsorbed from the amount of drug excreted by glomerular filtration. Equation 6.48 can be used for drugs that are protein bound but not actively secreted. Nonlinear drug binding makes clearance less useful due to model complication.

Equation 6.48 is also used in the calculation of free drug concentration in the plasma, where $\alpha$ is the fraction of bound drug and $1 - \alpha$ is the fraction of free drug.

\[
(1 - \alpha) C_{p, total} = C_{p, free}
\]

For most drug studies, the total plasma drug concentration (free plus bound drug) is used in clearance calculations. If renal clearance is corrected for the fraction of drug bound to plasma proteins using Equation 6.48, then the renal clearance for the free drug concentration may have a higher value compared to the uncorrected renal clearance using the total plasma drug concentrations.

Plasma protein binding has very little effect on the renal clearance of actively secreted drugs such as penicillin. For these drugs, the free drug fraction is filtered at the glomerular, whereas the protein-bound drug appears to be stripped from the binding sites and actively secreted into the renal tubules.

RELATIONSHIP OF CLEARANCE TO ELIMINATION HALF-LIFE AND VOLUME OF DISTRIBUTION

The half-life of a drug can be determined if the clearance and $V_D$ are known. From Equation 6.35 we obtain

\[
Cl_T = kV_D
\]

and

\[
k = \frac{0.693}{t_{1/2}}
\]

Therefore, by substitution,

\[
Cl_T = \frac{0.693 \cdot V_D}{t_{1/2}}
\]

(6.50)

From Equation 6.50, as $Cl_T$ decreases, which might happen in the case of renal insufficiency, the $t_{1/2}$ for the drug increases. A good relationship of $V_D$, $k$, and $t_{1/2}$ is shown in Table 6-6.

Total body clearance, $Cl_T$, is a more useful index of measurement of drug removal compared to the
elimination half-life, $t_{1/2}$. Total body clearance takes into account changes in both the apparent volume of distribution, $V_D$, and $t_{1/2}$. In overt obesity or edematous conditions, the $V_D$ may change without a marked change in $t_{1/2}$. As will be shown in Chapters 10 and 11, $V_D$ is important in the calculation of the loading dose, whereas $Cl_T$ is important in the calculation of the maintenance dose.

Total body clearance may be calculated by the ratio, $FD_0/[AUC]_0$, which is considered a model-independent method and assumes no particular pharmacokinetic model for drug elimination.

$$Cl_T = \frac{FD_0}{[AUC]_0} \quad (6.51)$$

**Total Body Clearance of Drugs after Intravenous Infusion**

When drugs are administered by intravenous infusion (see Chapter 5), the total body clearance is obtained with the following equation:

$$Cl_T = \frac{R}{C_{ss}} \quad (6.52)$$

where $C_{ss}$ is the steady-state plasma drug concentration and $R$ is the rate of infusion. Equation 6.52 is valid for drugs that follow either the one- or the two-compartment open model (see Chapter 4).

**EXAMPLE**

A new antibiotic is actively secreted by the kidney; $V_D$ is 35 L in the normal adult. The clearance of this drug is 650 mL/min.

1. What is the usual $t_{1/2}$ for this drug?

   **Solution**

   $$t_{1/2} = \frac{0.693 \times 35,000 \text{mL}}{650 \text{mL/min}} = 37.3 \text{min}$$

2. What would be the new $t_{1/2}$ for this drug in an adult with partial renal failure whose clearance of the antibiotic was only 75 mL/min?

   **Solution**

   $$t_{1/2} = \frac{0.693 \times 35,000 \text{mL}}{75 \text{mL/min}} = 323 \text{min}$$

**TABLE 6-6 Relationships of Clearance, Rate Constant of Elimination, and Elimination Half-Life**

<table>
<thead>
<tr>
<th>Clearance*</th>
<th>Plasma Water (3000 mL)</th>
<th>Extracellular Fluid (12,000 mL)</th>
<th>Body Water (41,000 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial reabsorption (eg, 30 mL/min)</td>
<td>$1.00 \times 10^{-1}$</td>
<td>$2.50 \times 10^{-3}$</td>
<td>$7.32 \times 10^{-4}$</td>
</tr>
<tr>
<td>Glomerular filtration (eg, 130 mL/min)</td>
<td>$4.33 \times 10^{-1}$</td>
<td>$1.08 \times 10^{-2}$</td>
<td>$3.17 \times 10^{-3}$</td>
</tr>
<tr>
<td>Tubular secretion (eg, 650 mL/min)</td>
<td>$2.17 \times 10^{-1}$</td>
<td>$5.42 \times 10^{-2}$</td>
<td>$1.59 \times 10^{-2}$</td>
</tr>
</tbody>
</table>

*Entries are values for $k_e$, the rate constant of elimination (in units of min$^{-1}$); parenthetic entries are corresponding values of the elimination half-life. The clearance given under “partial reabsorption” is arbitrary; any clearance between 0 (complete reabsorption) and 650 mL/min is possible.

Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination. Drug elimination may be modeled in terms of renal and non renal drug elimination processes. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. Clearance is a constant for first-order rate processes. Clearance may also be considered the product of the elimination rate constant, \( k \) and the apparent volume of distribution. Thus, clearance is generally inversely related to elimination half-life of a drug. Physiological renal clearance is based on renal blood flow, glomerular filtration, and drug reabsorption. Renal drug excretion is a composite of passive filtration, active–passive reabsorption in the distal tubule. Active secretion is a transporter-mediated process that is saturable. Reabsorption of drugs is a passive process and the extent of reabsorption of weak acid or weak base drugs is influenced by the pH of the urine and the degree of ionization of the drug. In addition, an increase in blood flow to the kidney, which may be due to diuretic therapy or large beer consumption, decreases the extent of drug reabsorption in the kidney and increases the rate of drug excreted in the urine.

**CHAPTER SUMMARY**

Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination. Drug elimination may be modeled in terms of renal and non renal drug elimination processes. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. Clearance is a constant for first-order rate processes. Clearance may also be considered the product of the elimination rate constant, \( k \) and the apparent volume of distribution. Thus, clearance is generally inversely related to elimination half-life of a drug. Physiological renal clearance is based on renal blood flow, glomerular filtration, and drug reabsorption. Renal drug excretion is a composite of passive filtration, active–passive reabsorption in the distal tubule. Active secretion is a transporter-mediated process that is saturable. Reabsorption of drugs is a passive process and the extent of reabsorption of weak acid or weak base drugs is influenced by the pH of the urine and the degree of ionization of the drug. In addition, an increase in blood flow to the kidney, which may be due to diuretic therapy or large beer consumption, decreases the extent of drug reabsorption in the kidney and increases the rate of drug excreted in the urine.

**LEARNING QUESTIONS**

1. Explain why plasma protein binding will prolong the renal clearance of a drug that is excreted only by glomerular filtration but does not affect the renal clearance of a drug excreted by both glomerular filtration and active tubular secretion.
2. Explain the effect of alkalization or acidification of the urine on the renal clearance of dextroamphetamine sulfate. Dextroamphetamine sulfate is a weak base with a \( pK_a \) of 9.4.
3. Theophylline is effective in the treatment of bronchitis at a blood level of 10 to 20 \( \mu \)g/mL. At therapeutic range, theophylline follows first-order kinetics. The average \( t_{1/2} \) is 3.4 hours, and the range is 1.8 to 6.8 hours. The average volume of distribution is 30 L.
   a. What are the average upper and lower clearance limits for theophylline?
   b. The renal clearance of theophylline is 0.36 L/hr. What are the \( k_m \) and \( k_e \), assuming all nonrenal clearance (\( Cl_{NR} \)) is due to metabolism?
4. A single 250-mg oral dose of an antibiotic is given to a young man (age 32 years, creatinine clearance 122 mL/min, 78 kg). From the literature, the drug is known to have an apparent \( V_D \) equal to 21% of body weight and an elimination half-life of 2 hours. The dose is normally 90% bioavailable. Urinary excretion of the unchanged drug is equal to 70% of the absorbed dose.
   a. What is the total body clearance for this drug?
   b. What is the renal clearance for this drug?
   c. What is the probable mechanism for renal clearance of this drug?
5. A drug with an elimination half-life of 1 hour was given to a male patient (80 kg) by intravenous infusion at a rate of 300 mg/h. At 7 hours after infusion, the plasma drug concentration was 11 \( \mu \)g/mL.
   a. What is the total body clearance for this drug?
   b. What is the apparent \( V_D \) for this drug?
c. If the drug is not metabolized and is eliminated only by renal excretion, what is the renal clearance of this drug?

d. What is the probable mechanism for renal clearance of this drug?

6. In order to rapidly estimate the renal clearance of a drug in a patient, a 2-hour postdose urine sample was collected and found to contain 200 mg of drug. A midpoint plasma sample was taken (1 hour postdose) and the drug concentration in plasma was found to be 2.5 mg%. Estimate the renal clearance for this drug in the patient.

7. According to the manufacturer, after the antibiotic cephradine (Velosef), given by IV infusion at rate of 5.3 mg/kg/h to 9 adult male volunteers (average weight, 71.7 kg), a steady-state serum concentration of 17 µg/mL was measured. Calculate the average total body clearance for this drug in adults.

8. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for the interaction of probenecid with cephradine?

9. Why is clearance used as a measurement of drug elimination, rather than the excretion rate of the drug?

10. What is the advantage of using total body clearance as a measurement of drug elimination compared to using the elimination half-life of the drug?

11. A patient was given 2500 mg of a drug by IV bolus dose, and periodic urinary data were collected. (a) Determine the renal clearance of the drug using urinary data. (b) Determine total body clearance using the area method. (c) Is there any nonrenal clearance of the drug in this patient? What would be the nonrenal clearance, if any? How would you determine clearance using a compartmental approach and compare that with the area method?

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Plasma Urinary Concentration (µg/mL)</th>
<th>Urinary Volume (mL)</th>
<th>Urinary Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>250.00</td>
<td>100.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>198.63</td>
<td>125.00</td>
<td>2880.00</td>
</tr>
<tr>
<td>2</td>
<td>157.82</td>
<td>140.00</td>
<td>1901.20</td>
</tr>
<tr>
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<td>125.39</td>
<td>100.00</td>
<td>2114.80</td>
</tr>
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<tr>
<td>9</td>
<td>31.55</td>
<td>400.00</td>
<td>133.01</td>
</tr>
<tr>
<td>10</td>
<td>25.06</td>
<td>240.00</td>
<td>176.13</td>
</tr>
</tbody>
</table>

12. Ciprofloxacin hydrochloride (Cipro) is a fluoroquinolone antibacterial drug used to treat urinary tract infections. Ciprofloxacin contains several pKas (basic amine and carboxylic group) and may be considered a weak acid and eliminated primarily by renal excretion, although about 15% drug dose is metabolized. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. The renal clearance of ciprofloxacin is approximately 300 mL/min.

13. By what processes of renal excretion would you conclude that ciprofloxacin is excreted? Why?

14. If ciprofloxacin hydrochloride (Cipro) tablets are given to patients who are strict vegetarians, would you expect their renal drug clearance to be different from patients who consume a high meat diet?
REFERENCES


BIBLIOGRAPHY

Chapter Objectives

- Describe the oral one-compartment model and explain how this model simulates drug absorption from the gastrointestinal tract.
- Calculate the pharmacokinetic parameters of a drug that follows the oral one-compartment model.
- Calculate the fraction of drug absorbed in a one-compartment model using the Wagner–Nelson method.
- Calculate the fraction of drug absorbed in a two-compartment model using the Loo–Riegelman method.
- Describe the conditions that may lead to flip-flop of $k_a$ and $k$ during pharmacokinetic (PK) data analysis.
- Describe the model parameters that form the foundation of drug absorption and bioavailability of oral dosage forms.
- Discuss how $k_a$ and $k$ may influence $C_{max}$, $t_{max}$ and AUC and how changes in these parameters may affect drug safety in a clinical situation.

PHARMACOKINETICS OF DRUG ABSORPTION

The pharmacokinetics of drugs following intravenous drug administration are simpler to model compared to extravascular delivery (see Chapters 1–6). Extravascular delivery routes, particularly oral dosing, are important and popular means of drug administration. Unlike intravenous administration, in which the drug is injected directly into the plasma, pharmacokinetic models after extravascular drug administration must consider systemic drug absorption from the site of administration, for example, the lung, the gut, etc, into the plasma. Extravascular drug delivery is further complicated by variables at the absorption site, including possible drug degradation, metabolism, and significant inter- and intrapatient differences in the rate and extent of absorption. Absorption and metabolic variables are characterized using pharmacokinetic methods. The variability in systemic drug absorption can be minimized to some extent by proper biopharmaceutical design of the dosage form to provide predictable and reliable drug therapy (see Chapters 14–16). The major advantage of intravenous administration compared to extravascular drug absorption is that the rate and extent of systemic drug input are carefully controlled.

The systemic drug absorption from the gastrointestinal (GI) tract or from any other extravascular site is dependent on (1) the physicochemical properties of the drug, (2) the type and design of dosage form, and (3) the anatomy and physiology of the drug absorption site. Although this chapter will focus primarily on oral dosing, the concepts discussed here may be extrapolated to other extravascular routes. For oral dosing, such factors as surface area of the GI tract, stomach-emptying rate, GI mobility, and blood flow to the absorption site all affect the rate and the extent of drug absorption. In pharmacokinetics, the overall rate of drug absorption may be described as either a first-order or zero-order input process. Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

The rate of change in the amount of drug in the body, $dD_y/dt$, is dependent on the relative rates of drug absorption and elimination.
(Fig. 7-1). The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of drug elimination, regardless of whether absorption rate is zero order or first order.

\[
\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt}
\]  

(7.1)

where \(D_{GI}\) is the amount of drug in the gastrointestinal tract and \(D_E\) is the amount of drug eliminated. A plasma level–time curve showing drug absorption and elimination rate processes is given in Fig. 7-2. During the absorption phase of a plasma level–time curve (Fig. 7-2), the rate of drug absorption\(^1\) is greater than the rate of drug elimination.\(^2\) Note that during the absorption phase, elimination occurs whenever drug is present in the plasma, even though absorption predominates.

\[
\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}
\]  

(7.2)

At the peak drug concentration in the plasma (Fig. 7-2) the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

\[
\frac{dD_{GI}}{dt} = \frac{dD_E}{dt}
\]  

(7.3)

Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration).

However, the rate of drug elimination at this time is faster than the rate of absorption, as represented by the postabsorption phase in Fig. 7-2.

\[
\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}
\]  

(7.4)

When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero, or \(dD_{GI}/dt = 0\). The plasma level–time curve (now the elimination phase) then represents only the elimination of drug from the body, usually a first-order process. Therefore, during the elimination phase the rate of change in the amount of drug in the body is described as a first-order process:

\[
\frac{dD_B}{dt} = -kD_B
\]  

(7.5)

where \(k\) is the first-order elimination rate constant.

**Clinical application**

Manini et al (2005) reported a case of adverse drug reaction in a previously healthy young man who ingested a recommended dose of an over-the-counter (OTC) cold remedy containing pseudoephedrine. Forty-five minutes later, he had an acute myocardial infarction (MI). Elevations of cardiac-specific creatinine kinase and cardiac troponin I confirmed the
diagnosis. Cardiac magnetic resonance imaging (MRI) confirmed a regional MI. Cardiac catheterization 8 hours later revealed normal coronary arteries, suggesting a mechanism of vasospasm.

1. Could rapid drug absorption (large $k_a$) contribute to high-peak drug concentration of pseudoephedrine in this subject?
2. Can an adverse drug reaction (ADR) occur before absorption is complete or before $C_{\text{max}}$ is reached?
3. What is the effect of a small change in $k$ on the time and magnitude of $C_{\text{max}}$ (maximum plasma concentration)? (Remember to correctly assign $k_a$ and $k$ values when computing $k_a$ and $k$ from patient data. See flip-flop in oral absorption model in the next section.) In addition, see Chapter 12 for reasons why some subjects may have a smaller $k$.
4. Do you believe that therapeutic drug concentration and toxic plasma concentration are always clearly defined for individual subjects as introduced in Fig. 1-2 (see Chapter 1)?

**Discussion**

From past experience, generally transient high plasma drug concentrations are not considered unsafe as long as the steady-state plasma concentration is within a recommended range. This is generally true for OTC drugs. This case highlights a potential danger of some sympathomimetic drugs such as pseudoephedrine and should alert the pharmacist that even drugs with a long history of safe use may still exhibit dangerous ADRs in some susceptible subjects.

Do you believe that pseudoephedrine can be sold safely without advice from a pharmacist? What other types of medication are important to monitor where a large $k_a$ may present transient high drug concentrations in the blood?

A small elimination rate constant, $k$, may be caused by reduced renal drug excretion as discussed in Chapter 6, but a small $k$ may also be due to reduced hepatic clearance caused by relatively inactive metabolic enzymes such as CYPs for some patients (see Chapter 11). What are the kinetic tools that will allow one to make this differentiation?

The pharmacokinetic concepts presented in this chapter will allow you to decide whether an unusual peak plasma drug concentration, $C_{\text{max}}$, is caused by a large $k_a$, a small $k$ (or CI), both, or neither.

**SIGNIFICANCE OF ABSORPTION RATE CONSTANTS**

The overall rate of systemic drug absorption from an orally administered solid dosage form encompasses many individual rate processes, including dissolution of the drug, GI motility, blood flow, and transport of the drug across the capillary membranes and into the systemic circulation. The rate of drug absorption represents the net result of all these processes. The selection of a model with either first-order or zero-order absorption is generally empirical.

The actual drug absorption process may be zero order, first order, or a combination of rate processes that is not easily quantitated. For many immediate-release dosage forms, the absorption process is first order due to the physical nature of drug diffusion. For certain controlled-release drug products, the rate of drug absorption may be more appropriately described by a zero-order rate constant.

The calculation of $k_a$ is useful in designing a multiple-dosage regimen. Knowledge of the $k_a$ and $k$ values allow for the prediction of peak and trough plasma drug concentrations following multiple dosing. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic absorption may not differ markedly. Therefore, for these studies, $t_{\text{max}}$, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

**ZERO-ORDER ABSORPTION MODEL**

Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by a saturable process or a zero-order controlled-release delivery system is used (see Chapter 17). The pharmacokinetic model assuming zero-order absorption is described in Fig. 7-3. In this
model, drug in the gastrointestinal tract, $D_{GI}$, is absorbed systemically at a constant rate, $k_0$. Drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant, $k$. This model is analogous to that of the administration of a drug by intravenous infusion (see Chapter 5).

The rate of first-order elimination at any time is equal to $D_B k$. The rate of input is simply $k_0$. Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B \quad (7.6)$$

Integration of this equation with substitution of $V_p C_p$ for $D_B$ produces

$$C_p = \frac{k_0}{V_p k} (1 - e^{-kt}) \quad (7.7)$$

The rate of drug absorption is constant until the amount of drug in the gut, $D_{GI}$, is depleted. The time for complete drug absorption to occur is equal to $D_{GI}/k_0$. After this time, the drug is no longer available for absorption from the gut, and Equation 7.7 no longer holds. The drug concentration in the plasma subsequently declines in accordance with a first-order elimination rate process.

**CLINICAL APPLICATION—TRANSDERMAL DRUG DELIVERY**

The stratum corneum (horny layer) of the epidermis of the skin acts as a barrier and rate-limiting step for systemic absorption of many drugs. After application of a transdermal system (patch), the drug dissolves into the outer layer of the skin and is absorbed by a pseudo first-order process due to high concentration and is eliminated by a first-order process. Once the patch is removed the residual drug concentrations in the skin continue to decline by a first-order process.

Ortho Evra is a combination transdermal contraceptive patch with a contact surface area of 20 cm$^2$. Each patch contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE) and is designed to deliver 0.15 mg of NGMN and 0.02 mg EE to the systemic circulation daily. As shown in Fig. 7-4, serum EE (ethinyl estradiol) is absorbed from the patch at a zero-order rate.

**FIRST-ORDER ABSORPTION MODEL**

Although zero-order drug absorption can occur, systemic drug absorption after oral administration of a drug product (eg, tablet, capsule) is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body (Fig. 7-5). This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories. In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be described using a first-order process.
After oral administration of a drug product, the drug is released from the drug product and dissolves into the fluids of the GI tract. In the case of an immediate-release compressed tablet, the tablet first disintegrates into fine particles from which the drug then dissolves into the fluids of the GI tract. Only drug in solution is absorbed into the body. The rate of disappearance of drug from the gastrointestinal tract is described by

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F$$ \hspace{1cm} (7.8)

where $k_a$ is the first-order absorption rate constant from the GI tract, $F$ is the fraction absorbed, and $D_{GI}$ is the amount of drug in solution in the GI tract at any time $t$. Integration of the differential equation (7.8) gives

$$\frac{dD_{GI}}{dt} = D_0 e^{-k_d t}$$ \hspace{1cm} (7.9)

where $D_0$ is the dose of the drug.

The rate of drug elimination is described by a first-order reaction rate for most drugs and is equal to $-kD_B$. The rate of drug change in the body, $dD_B/dt$, is therefore the rate of drug in, minus the rate of drug out—as given by the differential equation, Equation 7.10:

$$\frac{dD_B}{dt} = \text{rate in} - \text{rate out}$$ \hspace{1cm} (7.10)

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B$$

where $F$ is the fraction of drug absorbed systemically. Since the drug in the gastrointestinal tract also follows a first-order decline (ie, the drug is absorbed across the gastrointestinal wall), the amount of drug in the gastrointestinal tract at any time $t$ is equal to $D_0 e^{-k_d t}$.

The value of $F$ may vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed. This equation can be integrated to give the general oral absorption equation for calculation of the drug concentration ($C_p$) in the plasma at any time $t$, as shown below.

$$C_p = \frac{Fk_a D_0}{V_d (k_a - k)} (e^{-kt} - e^{-k_d t})$$ \hspace{1cm} (7.11)

A typical plot of the concentration of drug in the body after a single oral dose is presented in Fig. 7-6.

The maximum plasma concentration after oral dosing is $C_{max}$, and the time needed to reach maximum concentration is $t_{max}$. The $t_{max}$ is independent of dose and is dependent on the rate constants for absorption ($k_a$) and elimination ($k$) (Equation 7.13). At $C_{max}$, sometimes called peak concentration, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. At $C_{max}$, the rate of concentration change can be obtained by differentiating Equation 7.11, as follows:

$$C_p = \frac{k_a D_0 F}{V_d (k_a - k)} (-ke^{-kt} + k_a e^{-k_d t}) = 0$$ \hspace{1cm} (7.12)
This can be simplified as follows:

\[-ke^{-kt} + k_a e^{-k_a t} = 0\] or \[ke^{-kt} = k_a e^{-k_a t}\]

\[\ln k - kt = \ln k_a - k_a t\]

\[t_{\text{max}} = \frac{\ln k - \ln k_a}{k_a - k} = \frac{\ln (k_a/k)}{k_a - k}\]

\[t_{\text{max}} = \frac{2.3 \log (k_a/k)}{k_a - k}\] (7.13)

As shown in Equation 7.13, the time for maximum drug concentration, \(t_{\text{max}}\), is dependent only on the rate constants \(k\) and \(k_a\). In order to calculate \(C_{\text{max}}\), the value for \(t_{\text{max}}\) is determined via Equation 7.13 and then substituted into Equation 7.11, solving for \(C_{\text{max}}\). Equation 7.11 shows that \(C_{\text{max}}\) is directly proportional to the dose of drug given (\(D_0\)) and the fraction of drug absorbed (\(F\)). Calculation of \(t_{\text{max}}\) and \(C_{\text{max}}\) is usually necessary, since direct measurement of the maximum drug concentration may not be possible due to improper timing of the serum samples.

The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve (Fig. 7-2). At later time intervals, when drug absorption has been completed, i.e., \(e^{-k_a t} = 0\), Equation 7.11 reduces to

\[C_p = \frac{F k_a D_0}{V_d (k_a - k)} e^{-k t}\] (7.14)

Taking the natural logarithm of this expression,

\[\ln C_p = \ln \left(\frac{F k_a D_0}{V_d (k_a - k)}\right) - kt\] (7.15)

Substitution of common logarithms gives

\[\log C_p = \log \left(\frac{F k_a D_0}{V_d (k_a - k)}\right) - \frac{kt}{2.3}\] (7.16)

With this equation, a graph constructed by plotting \(\log C_p\) versus time will yield a straight line with a slope of \(-k/2.3\) (Fig. 7-7A).

With a similar approach, urinary drug excretion data may also be used for calculation of the first-order elimination rate constant. The rate of drug excretion after a single oral dose of drug is given by

\[\frac{dD}{dt} = \frac{F k k_a D_0}{k_a - k} (e^{-k t} - e^{-k_a t})\] (7.17)

where \(\frac{dD}{dt}\) = rate of urinary drug excretion, \(k\) = first-order renal excretion constant, and \(F\) = fraction of dose absorbed.

A graph constructed by plotting \(\frac{dD}{dt}\) versus time will yield a curve identical in appearance to the plasma level–time curve for the drug (Fig. 7-8B). After drug absorption is virtually complete, \(-e^{-k_a t}\) approaches zero, and Equation 7.17 reduces to

\[\frac{dD}{dt} = \frac{F k k_a D_0}{k_a - k} e^{-k t}\] (7.18)
Taking the natural logarithm of both sides of this expression and substituting for common logarithms, Equation 7.18 becomes

$$\log \frac{dD_u}{dt} = \log \left( \frac{Fk_a k D_0}{k_a - k} \right) - \frac{kt}{2.3}$$  \hspace{1cm} (7.19)

When $\log(dD_u/dt)$ is plotted against time, a graph of a straight line is obtained with a slope of $-k/2.3$ (Fig. 7-7B). Because the rate of urinary drug excretion, $dD_u/dt$, cannot be determined directly for any given time point, an average rate of urinary drug excretion is obtained (see also Chapter 3), and this value is plotted against the midpoint of the collection period for each urine sample.
From this, one may also obtain the intercept of the y axis (Fig. 7-10).

\[ Fk D \quad \frac{Vk k}{a Da 0} \quad (7.22) \]

where \( A \) is a constant. Thus, Equation 7.22 becomes

\[ C_p = A e^{-kt} \quad (7.23) \]

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to \(-k/2.3\). The value for \( k_a \) can be obtained by using the method of residuals or a feathering technique, as described in Chapter 4. The value of \( k_a \) is obtained by the following procedure:

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis (Fig. 7-10).
2. Obtain the slope of the terminal phase (line BC, Fig. 7-10) by extrapolation.
3. Take any points on the upper part of line BC (eg, \( x_1', x_2', x_3' \), ...) and drop vertically to obtain corresponding points on the curve (eg, \( x_1, x_2, x_3 \), ...).
4. Read the concentration values at \( x_1 \) and \( x_1' \), \( x_2 \) and \( x_2' \), \( x_3 \) and \( x_3' \), and so on. Plot the values of the differences at the corresponding time points \( \Delta_1, \Delta_2, \Delta_3, \ldots \). A straight line will be obtained with a slope of \(-k/2.3\) (Fig. 7-10).

When using the method of residuals, a minimum of three points should be used to define the straight line. Data points occurring shortly after \( t_{\text{max}} \) may not be accurate, because drug absorption is still continuing at that time. Because this portion of the curve represents the postabsorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.

If drug absorption begins immediately after oral administration, the residual lines obtained by feathering the plasma level–time curve (as shown in Fig. 7-10) will intersect on the y axis at point A. The value of this y intercept, \( A \), represents a hybrid constant composed of \( k_a, k, V_D, \) and \( FD_0 \). The value of \( A \) has no direct physiologic meaning (see Equation 7.23).

\[ A = \frac{Fk D_0}{V_D (k_a - k)} \]

The value for \( A \), as well as the values for \( k \) and \( k_a \), may be substituted back into Equation 7.11 to obtain a general theoretical equation that will describe the plasma level–time curve.

**Lag Time**

In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility. The time delay prior to the commencement of first-order drug absorption is known as lag time.

The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level–time curve intersect at a point greater than \( t = 0 \) on the x axis. The time at the point of intersection on the x axis is the lag time (Fig. 7-11).

The lag time, \( t_{\text{lag}} \), represents the beginning of drug absorption and should not be confused with the pharmacologic term onset time, which represents latency, that is, the time required for the drug to reach minimum effective concentration.
the elimination rate constant $k$ obtained from oral absorption data does not agree with that obtained after intravenous bolus injection. For example, the $k$ obtained after an intravenous bolus injection of a bronchodilator was 1.72 h$^{-1}$, whereas the $k$ calculated after oral administration was 0.7 h$^{-1}$ (Fig. 7-12). When $k_a$ was obtained by the method of residuals, the rather surprising result was that the $k_a$ was 1.72 h$^{-1}$.

Apparently, the $k_a$ and $k$ obtained by the method of residuals have been interchanged. This phenomenon is called flip-flop of the absorption and elimination rate constants. Flip-flop, or the reversal of the rate constants, may occur whenever $k_a$ and $k$ are estimated from oral drug absorption data. Use of computer methods does not ensure against flip-flop of the two constants estimated.

In order to demonstrate unambiguously that the steeper curve represents the elimination rate for a drug given extravascularly, the drug must be given by intravenous injection into the same patient. After intravenous injection, the decline in plasma drug levels over time represents the true elimination rate. The relationship between $k_a$ and $k$ on the shape of the plasma drug concentration–time curve for a constant dose of drug given orally is shown in Fig. 7-12.

Most of the drugs observed to have flip-flop characteristics are drugs with fast elimination (ie, $k > k_a$). Drug absorption of most drug solutions or fast-dissolving products are essentially complete or at least half-complete within an hour (ie, absorption half-life of 0.5 or 1 hour, corresponding to a $k_a$ of 1.38 h$^{-1}$ or 0.69 h$^{-1}$). Because most of the drugs used orally have longer elimination half-lives compared to absorption half-lives, the assumption that the smaller slope or smaller rate constant (ie, the terminal

\[
\frac{Fk_aD}{V_p(k_a - k)} (e^{-k(t-t_0)} - e^{-k_a(t-t_0)}) \quad (7.24)
\]

where $Fk_aD/V_p(k_a - k)$ is the $y$ value at the point of intersection of the residual lines in Fig. 7-11.

The second expression that describes the curve in Fig. 7-11 omits the lag time, as follows:

\[
C_p = Be^{-kt} - Ae^{-k_a t} \quad (7.25)
\]

where $A$ and $B$ represents the intercepts on the $y$ axis after extrapolation of the residual lines for absorption and elimination, respectively.

**Frequently Asked Question**

**Flip-Flop of $k_a$ and $k$**

In using the method of residuals to obtain estimates of $k_a$ and $k$, the terminal phase of an oral absorption curve is usually represented by $k$, whereas the steeper slope is represented by $k_a$ (Fig. 7-12). In a few cases,
phase of the curve in Fig. 7-12) should be used as the elimination constant is generally correct.

For drugs that have a large elimination rate constant \( k > 0.69 \, \text{h}^{-1} \), the chance for flip-flop of \( k_a \) and \( k \) is much greater. The drug isoproterenol, for example, has an oral elimination half-life of only a few minutes, and flip-flop of \( k_a \) and \( k \) has been noted (Portmann, 1970). Similarly, salicyluric acid was flip-flopped when oral data were plotted. The \( k \) for salicyluric acid was much larger than its \( k_a \) (Levy et al, 1969). Many experimental drugs show flip-flop of \( k \) and \( k_a \), whereas few marketed oral drugs do. Drugs with a large \( k \) are usually considered to be unsuitable for an oral drug product due to their large elimination rate constant, corresponding to a very short elimination half-life. An extended-release drug product may slow the absorption of a drug, such that the \( k_a \) is smaller than the \( k \) and producing a flip-flop situation.

\[ \text{Determination of } k_a \text{ by Plotting Percent of Drug Unabsorbed versus Time (Wagner–Nelson Method)} \]

The Wagner–Nelson method may be used as an alternative means of calculating \( k_a \). This method estimates the loss of drug from the GI over time, whose slope is inversely proportional to \( k_a \). After a single oral dose of a drug, the total dose should be completely accounted for for the amount present in the body, the amount present in the urine, and the amount present in the GI tract. Therefore, dose \( (D_0) \) is expressed as follows:

\[ D_0 = D_{\text{GI}} + D_B + D_i \]  
\[ (7.26) \]

Let \( Ab = D_0 + D_a = \text{amount of drug absorbed} \) and let \( Ab^\infty = \text{amount of drug absorbed at } t = \infty \). At any given time the fraction of drug absorbed is \( Ab/Ab^\infty \), and the fraction of drug unabsorbed is \( 1 – (Ab/Ab^\infty) \). The amount of drug excreted at any time \( t \) can be calculated as

\[ D_u = kV_D[AUC]_D^0 \]  
\[ (7.27) \]

The amount of drug in the body \( (D_h) \) at any time is \( C_pV_D \). At any time \( t \), the amount of drug absorbed \( (Ab) \) is

\[ Ab = C_pV_D + kV_D[AUC]_D^t \]  
\[ (7.28) \]

At \( t = \infty \) \( C_pV_D = 0 \) (ie, plasma concentration is negligible), and the total amount of drug absorbed is

\[ Ab^\infty = 0 + kV_D[AUC]_D^\infty \]  
\[ (7.29) \]

The fraction of drug absorbed at any time is

\[ \frac{Ab}{Ab^\infty} = \frac{C_pV_D + k[AUC]_D^t}{k[AUC]_D^\infty} \]  
\[ (7.30) \]

The fraction unabsorbed at any time \( t \) is

\[ 1 - \frac{Ab}{Ab^\infty} = 1 - \frac{C_p + k[AUC]_D^t}{k[AUC]_D^\infty} \]  
\[ (7.32) \]

The drug remaining in the GI tract at any time \( t \) is

\[ D_{\text{GI}} = D_0 e^{-k_a t} \]  
\[ (7.33) \]

Therefore, the fraction of drug remaining is

\[ \frac{D_{\text{GI}}}{D_0} = e^{-k_a t} \quad \log \frac{D_{\text{GI}}}{D_0} = \frac{-k_a t}{2.3} \]  
\[ (7.34) \]

Because \( D_{\text{GI}}/D_0 \) is actually the fraction of drug unabsorbed—that is, \( 1 – (Ab/Ab^\infty) \)—a plot of \( 1 – (Ab/Ab^\infty) \) versus time gives \( -k_a t/2.3 \) as the slope (Fig. 7-13).

The following steps should be useful in determination of \( k_a \):

1. Plot log concentration of drug versus time.
2. Find \( k \) from the terminal part of the slope when the slope = \( -k/2.3 \).
3. Find \( [AUC]_D^t \) by plotting \( C_p \) versus \( t \).
4. Find \( k[AUC]_D^t \) by multiplying each \( [AUC]_D^t \) by \( k \).
5. Find \( k[AUC]_D^\infty \) by adding up all the [AUC] pieces, from \( t = 0 \) to \( t = \infty \).

Frequently Asked Question

1. Find \( k_a \) from the terminal part of the slope when the slope = \( -k/2.3 \).
2. Find \( [AUC]_D^t \) by multiplying each \( [AUC]_D^t \) by \( k \).
3. Find \( k[AUC]_D^\infty \) by adding up all the [AUC] pieces, from \( t = 0 \) to \( t = \infty \).
6. Determine the $1 - \left(\frac{\text{Ab}}{\text{Ab}^\infty}\right)$ value corresponding to each time point $t$ by using Table 7-1.

7. Plot $1 - \left(\frac{\text{Ab}}{\text{Ab}^\infty}\right)$ versus time on semilog paper, with $1 - \left(\frac{\text{Ab}}{\text{Ab}^\infty}\right)$ on the logarithmic axis.

If the fraction of drug unabsorbed, $1 - \frac{\text{Ab}}{\text{Ab}^\infty}$, gives a linear regression line on a semilog graph, then the rate of drug absorption, $dD_{GI}/dt$, is a first-order process. Recall that $1 - \frac{\text{Ab}}{\text{Ab}^\infty}$ is equal to $dD_{GI}/dt$ (Fig. 7-13).

As the drug approaches 100% absorption, $C_p$ becomes very small and difficult to assay accurately. Consequently, the terminal part of the line described

![Semilog graph of data in Table 7-2, depicting the fraction of drug unabsorbed versus time using the Wagner–Nelson method.](image)

**TABLE 7-1 Blood Concentrations and Associated Data for a Hypothetical Drug**

<table>
<thead>
<tr>
<th>Time $t_n$ (h)</th>
<th>Concentration $C_p$ (μg/mL)</th>
<th>$[\text{AUC}]_t^{\infty}$</th>
<th>$[\text{AUC}]_n^0$</th>
<th>$k[\text{AUC}]_t^0$</th>
<th>$C_p + k[\text{AUC}]_t^0$</th>
<th>$\frac{\text{Ab}}{\text{Ab}^\infty}$</th>
<th>(1 - \frac{\text{Ab}}{\text{Ab}^\infty})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
<td>3.13</td>
<td>1.57</td>
<td>1.57</td>
<td>0.157</td>
<td>3.287</td>
<td>0.328</td>
<td>0.672</td>
</tr>
<tr>
<td>2</td>
<td>4.93</td>
<td>4.03</td>
<td>5.60</td>
<td>0.560</td>
<td>5.490</td>
<td>0.548</td>
<td>0.452</td>
</tr>
<tr>
<td>3</td>
<td>5.86</td>
<td>5.40</td>
<td>10.99</td>
<td>1.099</td>
<td>6.959</td>
<td>0.695</td>
<td>0.305</td>
</tr>
<tr>
<td>4</td>
<td>6.25</td>
<td>6.06</td>
<td>17.05</td>
<td>1.705</td>
<td>7.955</td>
<td>0.794</td>
<td>0.205</td>
</tr>
<tr>
<td>5</td>
<td>6.28</td>
<td>6.26</td>
<td>23.31</td>
<td>2.331</td>
<td>8.610</td>
<td>0.856</td>
<td>0.140</td>
</tr>
<tr>
<td>6</td>
<td>6.11</td>
<td>6.20</td>
<td>29.51</td>
<td>2.951</td>
<td>9.061</td>
<td>0.905</td>
<td>0.095</td>
</tr>
<tr>
<td>7</td>
<td>5.81</td>
<td>5.96</td>
<td>35.47</td>
<td>3.547</td>
<td>9.357</td>
<td>0.934</td>
<td>0.066</td>
</tr>
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<td>8</td>
<td>5.45</td>
<td>5.63</td>
<td>41.10</td>
<td>4.110</td>
<td>9.560</td>
<td>0.955</td>
<td>0.045</td>
</tr>
<tr>
<td>9</td>
<td>5.06</td>
<td>5.26</td>
<td>46.35</td>
<td>4.635</td>
<td>9.695</td>
<td>0.968</td>
<td>0.032</td>
</tr>
<tr>
<td>10</td>
<td>4.66</td>
<td>4.86</td>
<td>51.21</td>
<td>5.121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3.90</td>
<td>8.56</td>
<td>59.77</td>
<td>5.977</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>3.24</td>
<td>7.14</td>
<td>66.91</td>
<td>6.691</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2.67</td>
<td>5.92</td>
<td>72.83</td>
<td>7.283</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>2.19</td>
<td>4.86</td>
<td>77.69</td>
<td>7.769</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.20</td>
<td>10.17</td>
<td>87.85</td>
<td>8.785</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>0.81</td>
<td>4.02</td>
<td>91.87</td>
<td>9.187</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>0.54</td>
<td>2.70</td>
<td>94.57</td>
<td>9.457</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>0.36</td>
<td>1.80</td>
<td>96.37</td>
<td>9.637</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>0.10</td>
<td>2.76</td>
<td>99.13</td>
<td>9.913</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$k = 0.1 \text{ h}^{-1}$. 

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by 1 – Ab/Ab∞ versus time tends to become scattered or nonlinear. This terminal part of the curve is excluded, and only the initial linear segment of the curve is used for the estimate of the slope.

**PRACTICE PROBLEM**

Drug concentrations in the blood at various times are listed in Table 7-1. Assuming the drug follows a one-compartment model, find the $k_a$ and compare it with the $k_a$ value obtained by the method of residuals.

**Solution**

The AUC is approximated by the trapezoidal rule. This method is fairly accurate when there are sufficient data points. The area between each time point is calculated as

$$[\text{AUC}]_{n-1} = \frac{C_n + C_{n-1}}{2} (t_n - t_{n-1}) \quad (7.35)$$

where $C_n$ and $C_{n-1}$ are concentrations. For example, at $n = 6$, the [AUC] is

$$\frac{6.28 + 6.11}{2} (6 - 5) = 6.20$$

To obtain [AUC]$_0^\infty$, add all the area portions under the curve from zero to infinity. In this case, 48 hours is long enough to be considered infinity, because the blood concentration at that point already has fallen to an insignificant drug concentration, 0.1 $\mu$g/mL. The rest of the needed information is given in Table 7-1. Notice that $k$ is obtained from the plot of log $C_p$ versus $t$; $k$ was found in this example to be 0.1 h$^{-1}$. The plot of $1 – (Ab/Ab^\infty)$ versus $t$ on semilog paper is shown in Fig. 7-13.

A more complete method of obtaining $k_s$ is to estimate the residual area from the last observed plasma concentration, $C_p$ at $t_a$ to time equal to infinity. This equation for the residual AUC from $C_p$ to time equal to infinity is

$$[\text{AUC}]_t = \frac{C_p}{k} \quad (7.36)$$

The total [AUC]$_0^\infty$ is the sum of the areas obtained by the trapezoidal rule, [AUC]$_0^t$, and the residual area, [AUC]$_t^\infty$, as described in the following expression:

$$[\text{AUC}]_0^\infty = [\text{AUC}]_0^t + [\text{AUC}]_t^\infty \quad (7.37)$$

**Estimation of $k_s$ from Urinary Data**

The absorption rate constant may also be estimated from urinary excretion data, using a plot of percent of drug unabsorbed versus time. For a one-compartment model:

$Ab = $ total amount of drug absorbed—that is, the amount of drug in the body plus the amount of drug excreted

$D_B = $ amount of drug in the body

$D_u = $ amount of unchanged drug excreted in the urine

$C_p = $ plasma drug concentration

$D_E = $ total amount of drug eliminated (drug and metabolites)

$$Ab = D_B + D_E \quad (7.38)$$

The differential of Equation 7.38 with respect to time gives

$$\frac{dAb}{dt} = \frac{dD_B}{dt} + \frac{dD_E}{dt} \quad (7.39)$$

Assuming first-order elimination kinetics with renal elimination constant $k_e$,

$$\frac{dD_u}{dt} = k_e D_B = k_e V_d C_p \quad (7.40)$$

Assuming a one-compartment model,

$$V_d C_p = D_B$$

Substituting $V_d C_p$ into Equation 7.39,

$$\frac{dAb}{dt} = V_d \frac{dC_p}{dt} + \frac{dD_E}{dt} \quad (7.41)$$

And rearranging Equation 7.40,

$$C_p = \frac{1}{k_e V_d} \left( \frac{dD_u}{dt} \right) \quad (7.42)$$
Pharmacokinetics of Oral Absorption

\[ \frac{dC_p}{dt} = \frac{d(D_e/\text{dt})}{dt} k_e V_D \]  
(7.43)

Substituting for \( dC_p/\text{dt} \) into Equation 7.41 and \( k_D/k_e \) for \( D_e \),

\[ \frac{dAb}{dt} = \frac{d(D_e/\text{dt})}{k_e dt} + \frac{k}{k_e} \left( \frac{D_u}{dt} \right) \]  
(7.44)

When the above expression is integrated from zero to time \( t \),

\[ Ab_t = \frac{1}{k_e} \left( \frac{D_u}{dt} \right) t + \frac{k}{k_e} (D_u)_t \]  
(7.45)

At \( t = \infty \), all the drug that is ultimately absorbed is expressed as \( Ab^\infty \) and \( dD_u/\text{dt} = 0 \). The total amount of drug absorbed is

\[ Ab^\infty = \frac{k}{k_e} D_u^\infty \]

where \( D_u^\infty \) is the total amount of unchanged drug excreted in the urine.

The fraction of drug absorbed at any time \( t \) is equal to the amount of drug absorbed at this time, \( Ab_t \), divided by the total amount of drug absorbed, \( Ab^\infty \).

\[ \frac{Ab_t}{Ab^\infty} \]

(7.46)

A plot of the fraction of drug unabsorbed, \( 1 - Ab/Ab^\infty \), versus time gives \(-k_a/2.3\) as the slope from which the absorption rate constant is obtained (Fig. 7-13; refer to Equation 7-34).

When collecting urinary drug samples for the determination of pharmacokinetic parameters, one should obtain a valid urine collection as discussed in Chapter 3. If the drug is rapidly absorbed, it may be difficult to obtain multiple early urine samples to describe the absorption phase accurately. Moreover, drugs with very slow absorption will have low concentrations, which may present analytical problems.

**Table 7-2 Effects of the Absorption Rate Constant and Elimination Rate**

<table>
<thead>
<tr>
<th>Absorption Rate Constant, ( k_a ) (h(^{-1}))</th>
<th>Elimination Rate Constant, ( k_e ) (h(^{-1}))</th>
<th>( t_{\max} ) (h)</th>
<th>( C_{\max} ) (( \mu )g/mL)</th>
<th>AUC (( \mu )g h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>6.93</td>
<td>2.50</td>
<td>50</td>
</tr>
<tr>
<td>0.2</td>
<td>0.1</td>
<td>6.93</td>
<td>5.00</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>0.1</td>
<td>5.49</td>
<td>5.77</td>
<td>100</td>
</tr>
<tr>
<td>0.4</td>
<td>0.1</td>
<td>4.62</td>
<td>6.29</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>0.1</td>
<td>4.02</td>
<td>6.69</td>
<td>100</td>
</tr>
<tr>
<td>0.6</td>
<td>0.1</td>
<td>3.58</td>
<td>6.99</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>0.1</td>
<td>5.49</td>
<td>5.77</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>0.2</td>
<td>4.05</td>
<td>4.44</td>
<td>50</td>
</tr>
<tr>
<td>0.3</td>
<td>0.3</td>
<td>3.33</td>
<td>3.68</td>
<td>33.3</td>
</tr>
<tr>
<td>0.3</td>
<td>0.4</td>
<td>2.88</td>
<td>3.16</td>
<td>25</td>
</tr>
<tr>
<td>0.3</td>
<td>0.5</td>
<td>2.55</td>
<td>2.79</td>
<td>20</td>
</tr>
</tbody>
</table>

\( t_{\max} \) = peak plasma concentration, \( C_{\max} \) = peak drug concentration, AUC = area under the curve. Values are based on a single oral dose (100 mg) that is 100% bioavailable (\( F = 1 \)) and has an apparent \( V_e \) of 10 L. The drug follows a one-compartment open model. \( t_{\max} \) is calculated by Equation 7.13 and \( C_{\max} \) is calculated by Equation 7.11. The AUC is calculated by the trapezoidal rule from 0 to 24 h.
and AUC are different. If the elimination rate constant is kept at 0.1 h\(^{-1}\) and the \(k_a\) changes from 0.2 to 0.6 h\(^{-1}\) (absorption rate increases), then the \(t_{\text{max}}\) becomes shorter (from 6.93 to 3.58 hours), the \(C_{\text{max}}\) increases (from 5.00 to 6.99 \(\mu\)g/mL), but the AUC remains constant (100 \(\mu\)g h/mL). In contrast, when the absorption rate constant is kept at 0.3 h\(^{-1}\) and \(k\) changes from 0.1 to 0.5 h\(^{-1}\) (elimination rate increases), then the \(t_{\text{max}}\) decreases (from 5.49 to 2.55 hours), the \(C_{\text{max}}\) decreases (from 5.77 to 2.79 \(\mu\)g/mL), and the AUC decreases (from 100 to 20 \(\mu\)g h/mL). Graphical representations for the relationships of \(k_a\) and \(k\) on the time for peak absorption and the peak drug concentrations are shown in Figs. 7-14 and 7-15.

**Modified Wagner–Nelson Method**

Hayashi et al (2001) introduced a modified Wagner–Nelson method to study the subcutaneous absorption of a drug with nonlinear kinetics from the central compartment. Nonlinear kinetics occurs in some drugs where the kinetic parameters such as \(k\) change with dose. The method was applicable to a biotechnological drug (recombinant human granulocyte-colony stimulating factors, rhG-CSF) which is eliminated nonlinearly. The drug was absorbed into the blood from the dermal site after subcutaneous injection. Because of nonlinear kinetics the extent of absorption was not easily determined. The amount of drug absorbed, \(A_{\text{ab}}\) for each time sample, \(t_n\), is given by Equation 7.47. \(V_1\) and \(V_{ss}\) are central compartment and steady-state volume of distribution, respectively.

\[
A_{\text{ab}}(t_n) = \sum_{i=1}^{n-1} \int_{t_i}^{t_{i+1}} \left[ \frac{V_{\text{max}} C(t)}{C(t) + K_m} + k V_s C(t) \right] dt + V_{ss} C(t_n)
\]

(7.47)

From the mass balance of the above equation, the authors did account for the amount of drug present in the tissue compartment. (Note the authors stated that the central compartment \(V_1\) is 4.56 L and that of \(V_{ss}\) is 4.90 L.) To simplify the model, the authors used convolution to show that the contribution of the tissue compartment is not significant and therefore may be neglected. Thus, the Loo–Riegelman method which requires a tissue compartment was not used by the authors. Convolution is an analytical method that predicts plasma time drug concentration using input and disposition functions for drugs with linear kinetics. The disposition function may be first
obtained by deconvolution of simple IV plasma drug concentration data or from the terminal phase of an oral solution. Alternatively, the method of Lockwood and Gillespie (1996) abbreviated the need for the simple solution.

**Models for Estimation of Drug Absorption**

There are many models and approaches that have been used to predict drug absorption since the introduction of the classical approaches by John Wagner (1967) and Jack Loo. Deconvolution and convolution approaches are used to predict plasma drug concentration of oral dosage forms. Several commercial software (eg, GastroPlus, iDEA, Intellipharm PK, and PK-Sim) are now available for formulation and drug development or to determine the extent of drug absorption. The new software allows the characteristics of the drug, physiologic factors, and the dosage form to be input into the software. An important class of programs involves the Compartmental Absorption and Transit (CAT) models. This model integrates the effect of solubility, permeability, and gastric emptying and GI transit time in the estimation of in vivo drug absorption. CAT models were successfully used to predict the fraction of drug oral absorption of 10 common drugs based on a small intestine transit time (Yu, 1999). The CAT models compared well overall with other plausible models such as the dispersion model, the single mixing tank model, and some flow models. It is important to note that the models discussed earlier in this chapter are used to compute extent of absorption after the plasma drug concentrations are measured. In contrast, the later models/software allow a comprehensive way to simulate or predict drug (product) performance in vivo. The subjects of dissolution, dosage form design, and drug absorption will be discussed in more detail in Chapters 13 and 14.

**Determination of $k_a$ from Two-Compartment Oral Absorption Data (Loo–Riegelman Method)**

Plotting the percent of drug unabsorbed versus time to determine $k_a$ may also be calculated for a drug exhibiting a two-compartment kinetic model. As in the method used previously to obtain an estimate of the $k_a$, no limitation is placed on the order of the absorption process. However, this method does require that the drug be given intravenously as well as orally to obtain all the necessary kinetic constants.

After oral administration of a dose of a drug that exhibits two-compartment model kinetics, the amount of drug absorbed is calculated as the sum of the amounts of drug in the central compartment ($D_p$), in the tissue compartment ($D_t$), and the amount of drug eliminated by all routes ($D_u$) (Fig. 7-16).

$$Ab = D_p + D_t + D_u$$

(7.48)

Each of these terms may be expressed in terms of kinetics constants and plasma drug concentrations, as follows:

$$D_p = V_p C_p$$

(7.49)

$$D_t = V_t C_t$$

(7.50)

$$\frac{dD_u}{dt} = k V_p C_p$$

(7.51)

$$D_u = k V_p [AUC]_0^t$$

Substituting the above expression for $D_p$ and $D_u$ into Equation 7.48,

$$Ab = V_p C_p + D_t + k V_p [AUC]_0^t$$

(7.52)

By dividing this equation by $V_p$ to express the equation on drug concentrations, we obtain

$$\frac{Ab}{V_p} = C_p + \frac{D_t}{V_p} + k [AUC]_0^t$$

(7.53)

At $t = \infty$, this equation becomes

$$\frac{Ab}{V_p} = k [AUC]_0^\infty$$

(7.54)
Equation 7.53 divided by Equation 7.54 gives the fraction of drug absorbed at any time as shown in Equation 7.55.

\[
\frac{A_b}{A_b^\infty} = C_p + \frac{(D_t/V_p)}{k[AUC]_0} + k[AUC]_0^\infty + \frac{k[12]}{k[21]} (C_p)_{t_{n-1}} (1 - e^{-k_2 t}) + (C_p)_{t_n} e^{-k_2 t}
\]

(7.55)

A plot of the fraction of drug unabsorbed, \(1 - A_b/A_b^\infty\), versus time gives \(-k_a/2.3\) as the slope from which the value for the absorption rate constant is obtained (refer to Equation 7.34).

The values for \(k[AUC]_0^\infty\) are calculated from a plot of \(C_p\) versus time. Values for \((D_t/V_p)\) can be approximated by the Loo–Riegelman method, as follows:

\[
(C_p)_{t_n} = \frac{k_{12} \Delta C_p \Delta t}{2} + \frac{k_{21}}{k_{21}} (C_p)_{t_{n-1}} (1 - e^{-k_2 t_{n-1}}) + (C_p)_{t_n} e^{-k_2 t_n}
\]

(7.56)

where \(C_i\) is \(D_t/V_p\), or apparent tissue concentration; \(t\) = time of sampling for sample \(n\); \(t_{n-1}\) = time of sampling for the sampling point preceding sample \(n\); and \((C_p)_{t_{n-1}}\) = concentration of drug at central compartment for sample \(n-1\).

Calculation of \(C_i\) values is shown in Table 7-3, using a typical set of oral absorption data. After calculation of \(C_i\) values, the percent of drug unabsorbed is calculated with Equation 7.55, as shown in Table 7-4. A plot of percent of drug unabsorbed versus time on semilog graph paper gives a \(k_a\) of approximately 0.5 h\(^{-1}\).

For calculation of \(k_a\) by this method, the drug must be given intravenously to allow evaluation of the distribution and elimination rate constants. For drugs that cannot be given by the IV route, the \(k_a\) cannot be calculated by the Loo–Riegelman method. For drugs that are given by the oral route only, the Wagner–Nelson method, which assumes a one-compartment model, is used for calculation of \(k_a\).

**TABLE 7-3  Calculation of \(C_i\) Values\(^a\)**

<table>
<thead>
<tr>
<th>((C_p)_{t_n})</th>
<th>((t)_{t_n})</th>
<th>(\Delta(C_p))</th>
<th>(\Delta t)</th>
<th>((k_{12} \Delta C_p \Delta t)/2)</th>
<th>((C_p)<em>{t</em>{n-1}})</th>
<th>((k_{12} / k_{21}) \times \frac{(1 - e^{-k_2 t_{n-1}})}{t_{n-1}})</th>
<th>((C_p)<em>{t</em>{n-1}})</th>
<th>((k_{12} / k_{21}) \times \frac{1}{t_{n}})</th>
<th>((C_p)_{t_n})</th>
<th>((C_p)_{t_n} e^{-k_2 t_n})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.00</td>
<td>0.5</td>
<td>3.0</td>
<td>0.5</td>
<td>0.218</td>
<td>0</td>
<td>0.134</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>5.20</td>
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<td>2.2</td>
<td>0.5</td>
<td>0.160</td>
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<td>0.134</td>
<td>0.402</td>
<td>0.187</td>
<td>0.749</td>
<td></td>
</tr>
<tr>
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<td>1.5</td>
<td>1.3</td>
<td>0.5</td>
<td>0.094</td>
<td>5.20</td>
<td>0.134</td>
<td>0.697</td>
<td>0.642</td>
<td>1.433</td>
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<td>0.5</td>
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<td>7.30</td>
<td>0.134</td>
<td>0.978</td>
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<tr>
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<td>3.0</td>
<td>0.15</td>
<td>0.5</td>
<td>0.011</td>
<td>7.60</td>
<td>0.134</td>
<td>1.018</td>
<td>2.442</td>
<td>3.471</td>
<td></td>
</tr>
<tr>
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<td>-0.05</td>
<td>0.5</td>
<td>-0.004</td>
<td>7.75</td>
<td>0.134</td>
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<td>2.976</td>
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<td></td>
</tr>
<tr>
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<td>4.0</td>
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<td>0.5</td>
<td>-0.007</td>
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<td>1.032</td>
<td>3.444</td>
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<td>-0.073</td>
<td>7.60</td>
<td>0.134</td>
<td>1.900</td>
<td>3.276</td>
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</tr>
<tr>
<td>6.60</td>
<td>6.0</td>
<td>-0.50</td>
<td>1.0</td>
<td>-0.073</td>
<td>7.10</td>
<td>0.250</td>
<td>1.775</td>
<td>3.740</td>
<td>5.442</td>
<td></td>
</tr>
<tr>
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<td>-0.60</td>
<td>1.0</td>
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<td>6.60</td>
<td>0.250</td>
<td>1.650</td>
<td>3.989</td>
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<td></td>
</tr>
<tr>
<td>5.10</td>
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<td>-0.90</td>
<td>2.0</td>
<td>-2.261</td>
<td>6.00</td>
<td>0.432</td>
<td>2.592</td>
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</tr>
<tr>
<td>4.40</td>
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<td>2.0</td>
<td>-0.203</td>
<td>5.10</td>
<td>0.432</td>
<td>2.203</td>
<td>2.861</td>
<td>4.861</td>
<td></td>
</tr>
<tr>
<td>3.30</td>
<td>15.0</td>
<td>-1.10</td>
<td>4.0</td>
<td>-0.638</td>
<td>4.40</td>
<td>0.720</td>
<td>3.168</td>
<td>1.361</td>
<td>3.891</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Calculated with the following rate constants: \(k_{12} = 0.29\) h\(^{-1}\), \(k_{21} = 0.31\) h\(^{-1}\).

Adapted with permission from Loo and Riegelman (1968).
model, may be used to provide an initial estimate of $k_a$. If the drug is given intravenously, there is no way of knowing whether there is any variation in the values for the elimination rate constant, $k$ and the distributive rate constants, $k_{12}$ and $k_{21}$. Such variations alter the rate constants. Therefore, a one-compartment model is frequently used to fit the plasma curves after an oral or intramuscular dose. The plasma level predicted from the $k_a$ obtained by this method does deviate from the actual plasma level. However, in many instances, this deviation is not significant.

**Cumulative Relative Fraction Absorbed**

The fraction of drug absorbed at any time $t$ (Equation 7.31) may be summed or cumulated for each time period for which a plasma drug sample was obtained. From Equation 7.31, the term $Ab/Ab_\infty$ becomes the **cumulative relative fraction absorbed** (CRFA).

$$CRFA = \frac{C_p}{k[AUC]_0^p} \left( \frac{1}{k[AUC]_0^p} \right)$$  \hspace{1cm} (7.57)$$

where $C_p$ is the plasma concentration at time $t$.

In the Wagner–Nelson equation, $Ab/Ab_\infty$ or CRFA will eventually equal unity, or 100%, even though the drug may not be 100% systemically bioavailable. The percent of drug absorbed is based on the total amount of drug absorbed ($Ab_\infty$) rather than the dose $D_0$. Because the amount of drug ultimately absorbed, $Ab_\infty$ in fractional term, is analogous to $k[AUC]_0$, the numerator will always equal the denominator at time infinity, whether the drug is 10%, 20%, or 100% bioavailable. The percent of drug absorbed based on $Ab/Ab_\infty$ is therefore different from the real percent of drug absorbed unless $F = 1$. However, for the calculation of $k_a$, the method is acceptable.

To determine the real percent of drug absorbed, a modification of the Wagner–Nelson equation was

### TABLE 7-4 Calculation of Percentage Unabsorbed

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$\left[C_p\right]_{tn}$</th>
<th>$\left[AUC\right]_{tn}$</th>
<th>$\left[AUC\right]_{tn}$</th>
<th>$k\left[AUC\right]_{tn}$</th>
<th>$\left[C_p\right]_{tn}$</th>
<th>$\frac{Ab}{V_p}$</th>
<th>$%\frac{Ab}{V_p}$</th>
<th>$100% - \frac{Ab}{V_p}$%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3.00</td>
<td>0.750</td>
<td>0.750</td>
<td>0.120</td>
<td>0.218</td>
<td>3.338</td>
<td>16.6</td>
<td>83.4</td>
</tr>
<tr>
<td>1.0</td>
<td>5.20</td>
<td>2.050</td>
<td>2.800</td>
<td>0.448</td>
<td>0.749</td>
<td>6.397</td>
<td>31.8</td>
<td>68.2</td>
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<tr>
<td>1.5</td>
<td>6.50</td>
<td>2.925</td>
<td>5.725</td>
<td>0.916</td>
<td>1.433</td>
<td>8.849</td>
<td>44.0</td>
<td>56.0</td>
</tr>
<tr>
<td>2.0</td>
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<td>3.450</td>
<td>9.175</td>
<td>1.468</td>
<td>2.157</td>
<td>10.925</td>
<td>54.3</td>
<td>45.7</td>
</tr>
<tr>
<td>2.5</td>
<td>7.60</td>
<td>3.725</td>
<td>12.900</td>
<td>2.064</td>
<td>2.849</td>
<td>12.513</td>
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</tr>
<tr>
<td>3.0</td>
<td>7.75</td>
<td>3.838</td>
<td>16.738</td>
<td>2.678</td>
<td>3.471</td>
<td>13.889</td>
<td>69.1</td>
<td>30.9</td>
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<tr>
<td>3.5</td>
<td>7.70</td>
<td>3.863</td>
<td>20.601</td>
<td>3.296</td>
<td>4.019</td>
<td>15.015</td>
<td>74.6</td>
<td>25.4</td>
</tr>
<tr>
<td>4.0</td>
<td>7.60</td>
<td>3.825</td>
<td>24.426</td>
<td>3.908</td>
<td>4.469</td>
<td>15.977</td>
<td>79.4</td>
<td>20.6</td>
</tr>
<tr>
<td>5.0</td>
<td>7.10</td>
<td>7.350</td>
<td>31.726</td>
<td>5.084</td>
<td>5.103</td>
<td>17.287</td>
<td>85.9</td>
<td>14.1</td>
</tr>
<tr>
<td>6.0</td>
<td>6.60</td>
<td>6.850</td>
<td>38.626</td>
<td>6.180</td>
<td>5.442</td>
<td>18.222</td>
<td>90.6</td>
<td>9.4</td>
</tr>
<tr>
<td>7.0</td>
<td>6.00</td>
<td>6.300</td>
<td>44.926</td>
<td>7.188</td>
<td>5.552</td>
<td>18.740</td>
<td>93.1</td>
<td>6.9</td>
</tr>
<tr>
<td>9.0</td>
<td>5.10</td>
<td>11.100</td>
<td>56.026</td>
<td>8.964</td>
<td>5.318</td>
<td>19.382</td>
<td>96.3</td>
<td>3.7</td>
</tr>
<tr>
<td>11.0</td>
<td>4.40</td>
<td>9.500</td>
<td>65.526</td>
<td>10.484</td>
<td>4.861</td>
<td>19.745</td>
<td>98.1</td>
<td>1.9</td>
</tr>
<tr>
<td>15.0</td>
<td>3.30</td>
<td>15.400</td>
<td>80.926</td>
<td>12.948</td>
<td>3.891</td>
<td>20.139</td>
<td>100.0</td>
<td>0</td>
</tr>
</tbody>
</table>

$\text{Ab/Ab}_\infty = (C_p) + \frac{k[\text{AUC}]_0^p}{C_p}$

$\left[C_p\right]_{tn} = k_{12}\Delta C_{0}^{tn/2} + k_{21}/k_{12} C_{tn}^{tn} (1 - e^{-k_{12}^{tn}}) + (C_p)_{tn} e^{-k_{21}^{tn}}$

$k = 0.16, k_{12} = 0.29, k_{21} = 0.31$
suggested by Welling (1986). A reference drug product was administered and plasma drug concentrations were determined over time. CRFA was then estimated by dividing \( Ab/Ab^\infty_{ref} \), where \( Ab \) is the cumulative amount of drug absorbed from the drug product and \( Ab^\infty_{ref} \) is the cumulative final amount of drug absorbed from a reference dosage form. In this case, the denominator of Equation 7.57 is modified as follows:

\[
CRFA = \frac{C_p + k[AUC]^p}{k_{ref}[AUC]^p_{ref}} \tag{7.58}
\]

where \( k_{ref} \) and \( [AUC]^p_{ref} \) are the elimination constant and the area under the curve determined from the reference product, respectively. The terms in the numerator of Equation 7.58 refer to the product, as in Equation 7.57.

Each fraction of drug absorbed is calculated and plotted against the time interval in which the plasma drug sample was obtained (Fig. 7-17). An example of the relationship of CRFA versus time for the absorption of tolazamide from four different drug products is shown in Fig. 7-18. The data for Fig. 7-19 were obtained from the serum tolazamide levels–time curves in Fig. 7-18. The CRFA–time graph provides a visual image of the relative rates of drug absorption from various drug products. If the CRFA–time curve is a straight line, then the drug was absorbed from the drug product at an apparent zero-order absorption rate.

The calculation of \( k_a \) is useful in designing a multiple-dosage regimen. Knowledge of the \( k_a \) and \( k \) allows for the prediction of peak and trough plasma drug concentrations following multiple dosing. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic absorption may not differ markedly. Therefore, for these studies, \( t_{max} \), or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

**Frequently Asked Questions**

![Fraction of drug absorbed](image)

**FIGURE 7-17** Fraction of drug absorbed. (Wagner–Nelson method.)

![Mean serum tolazamide levels](image)

**FIGURE 7-18** Mean cumulative relative fractions of tolazamide absorbed as a function of time. (From Welling et al, 1982, with permission.)

![Mean serum tolazamide levels](image)

**FIGURE 7-19** Mean serum tolazamide levels as a function of time. (From Welling et al, 1982, with permission.)
CHAPTER SUMMARY

The pharmacokinetics of drug absorption may be described by zero-order or first-order kinetics. Drug elimination from the body is generally described by first-order kinetics. Using the compartment model, various important pharmacokinetics parameters about drug absorption such as $k_a$, $k_c$, $C_{max}$, $t_{max}$, and other parameters may be computed from data by the method of residuals (feathering) or by computer modeling. The pharmacokinetic parameters are important in evaluating drug absorption and understanding how these parameters affect drug concentrations in the body. The fraction of drug absorbed may be computed in a one-compartment model using the Wagner–Nelson method or in a two-compartment model using the Loo–Riegelman method. The determination of the fraction of drug absorbed is an important tool in evaluating drug dosage form and design. The Wagner–Nelson method and Loo–Reigelman method are classical methods for determining absorption rate constants and fraction of drug absorbed. Convolution and deconvolution are powerful alternative tools used to predict a plasma drug concentration–time profile from dissolution of data during drug development.

The models presented in this chapter are very basic with simple assumptions. More sophisticated methods based on basic concepts may be extended to include physiological factors such as GI transit in the CAT models which represent the next stage of advance drug absorption model development. These models are also useful to predict drug absorption over time curves in designing oral dosage forms (see Chapters 13 and 14).

LEARNING QUESTIONS

1. Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>2.85</td>
</tr>
<tr>
<td>0.50</td>
<td>5.43</td>
</tr>
<tr>
<td>0.75</td>
<td>7.75</td>
</tr>
<tr>
<td>1.00</td>
<td>9.84</td>
</tr>
<tr>
<td>2.00</td>
<td>16.20</td>
</tr>
<tr>
<td>4.00</td>
<td>22.15</td>
</tr>
<tr>
<td>6.00</td>
<td>23.01</td>
</tr>
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<td>10.00</td>
<td>19.09</td>
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<td>14.00</td>
<td>13.90</td>
</tr>
<tr>
<td>20.00</td>
<td>7.97</td>
</tr>
</tbody>
</table>

From the above data:

a. Determine the elimination constant of the drug.

b. Determine $k_a$ by feathering.

c. Determine the equation that describes the plasma drug concentration of the new benzodiazepine.

2. Assuming that the drug in Question 1 is 80% absorbed, find (a) the absorption constant, $k_a$; (b) the elimination half-life, $t_{1/2}$; (c) the $t_{max}$, or time of peak drug concentration; and (d) the volume of distribution of the patient.

3. Contrast the percent of drug-unabsorbed methods for the determination of rate constant for absorption, $k_a$, in terms of (a) pharmacokinetic model, (b) route of drug administration, and (c) possible sources of error.

4. What is the error inherent in the measurement of $k_a$ for an orally administered drug that follows a two-compartment model when a one-compartment model is assumed in the calculation?

5. What are the main pharmacokinetic parameters that influence (a) time for peak drug concentration and (b) peak drug concentration?

6. Name a method of drug administration that will provide a zero-order input.
7. A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fits a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is

\[ C_p = 45(e^{-0.17t} - e^{-1.5t}) \]

From the equation above, calculate (a) \( t_{\text{max}} \), (b) \( C_{\text{max}} \), and (c) \( t_{1/2} \) for the drug in this patient. Assume \( C_p \) is in \( \mu g/mL \) and the first-order rate constants are in h\(^{-1}\).

8. Two drugs, A and B, have the following pharmacokinetic parameters after a single oral dose of 500 mg:

<table>
<thead>
<tr>
<th>Drug</th>
<th>( k_a (h^{-1}) )</th>
<th>( k (h^{-1}) )</th>
<th>( V_d (mL) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.0</td>
<td>0.2</td>
<td>10,000</td>
</tr>
<tr>
<td>B</td>
<td>0.2</td>
<td>1.0</td>
<td>20,000</td>
</tr>
</tbody>
</table>

Both drugs follow a one-compartment pharmacokinetic model and are 100% bioavailable.

a. Calculate the \( t_{\text{max}} \) for each drug.
b. Calculate the \( C_{\text{max}} \) for each drug.

d. From the above data, obtain the rate constant for absorption, \( k_a \), and the rate constant for elimination, \( k \), by the method of residuals.

b. Is it reasonable to assume that \( k_a > k \) for a drug in a solution? How would you determine unequivocally which rate constant represents the elimination constant \( k \)?
c. From the data, which method, Wagner–Nelson or Loo–Riegelman, would be more appropriate to determine the order of the rate constant for absorption?
d. From your values, calculate the theoretical \( t_{\text{max}} \). How does your value relate to the observed \( t_{\text{max}} \) obtained from the subjects?
e. Would you consider the pharmacokinetics of phenylpropanolamine HCl to follow a one-compartment model? Why?

9. The bioavailability of phenylpropanolamine hydrochloride was studied in 24 adult male subjects. The following data represent the mean blood phenylpropanolamine hydrochloride concentrations (ng/mL) after the oral administration of a single 25-mg dose of phenylpropanolamine hydrochloride solution.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Concentration (ng/mL)</th>
<th>Time (hour)</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>3</td>
<td>62.98</td>
</tr>
<tr>
<td>0.25</td>
<td>51.33</td>
<td>4</td>
<td>52.32</td>
</tr>
<tr>
<td>0.5</td>
<td>74.05</td>
<td>6</td>
<td>36.08</td>
</tr>
<tr>
<td>0.75</td>
<td>82.91</td>
<td>8</td>
<td>24.88</td>
</tr>
<tr>
<td>1.0</td>
<td>85.11</td>
<td>12</td>
<td>11.83</td>
</tr>
<tr>
<td>1.5</td>
<td>81.76</td>
<td>18</td>
<td>3.88</td>
</tr>
<tr>
<td>2</td>
<td>75.51</td>
<td>24</td>
<td>1.27</td>
</tr>
</tbody>
</table>

a. From the above data, obtain the rate constant for absorption, \( k_a \), and the rate constant for elimination, \( k \), by the method of residuals.
b. Is it reasonable to assume that \( k_a > k \) for a drug in a solution? How would you determine unequivocally which rate constant represents the elimination constant \( k \)?
c. From the data, which method, Wagner–Nelson or Loo–Riegelman, would be more appropriate to determine the order of the rate constant for absorption?
d. From your values, calculate the theoretical \( t_{\text{max}} \). How does your value relate to the observed \( t_{\text{max}} \) obtained from the subjects?
e. Would you consider the pharmacokinetics of phenylpropanolamine HCl to follow a one-compartment model? Why?

REFERENCES


BIBLIOGRAPHY


Chapter Objectives

- Define the index for measuring drug accumulation.
- Define drug accumulation and drug accumulation $t_{1/2}$.
- Explain the principle of superposition and its assumptions in multiple-dose regimens.
- Calculate the steady-state $C_{\text{max}}$ and $C_{\text{min}}$ after multiple IV bolus dosing of drugs.
- Calculate $k$ and $V_0$ of aminoglycosides in multiple-dose regimens.
- Adjust the steady-state $C_{\text{max}}$ and $C_{\text{min}}$ in the event the last dose is given too early, too late, or totally missed following multiple IV dosing.

Earlier chapters of this book discussed single-dose drug administration. Generally, drugs are given in multiple doses to treat chronic disease such as arthritis, hypertension, etc. After single-dose drug administration, the plasma drug level rises above and then falls below the minimum effective concentration (MEC), resulting in a decline in therapeutic effect. To treat chronic disease, multiple-dosage or IV infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window (eg, plasma drug concentrations above the MEC but below the minimum toxic concentration or MTC) to achieve optimal clinical effectiveness. These drugs may include antibacterials, cardiotonics, anticonvulsants, hypoglycemics, antihypertensives, hormones, and others. Ideally, a dosage regimen is established for each drug to provide the correct plasma level without excessive fluctuation and drug accumulation outside the therapeutic window.

For certain drugs, such as antibiotics, a desirable MEC can be determined. Some drugs that have a narrow therapeutic range (eg, digoxin and phenytoin) require definition of the therapeutic minimum and maximum nontoxic plasma concentrations (MEC and MTC, respectively). In calculating a multiple-dose regimen, the desired or target plasma drug concentration must be related to a therapeutic response, and the multiple-dose regimen must be designed to produce plasma concentrations within the therapeutic window.

There are two main parameters that can be adjusted in developing a dosage regimen: (1) the size of the drug dose and (2) $\tau$, the frequency of drug administration (ie, the time interval between doses).

**DRUG ACCUMULATION**

To calculate a multiple-dose regimen for a patient or patients, pharmacokinetic parameters are first obtained from the plasma level–time curve generated by single-dose drug studies. With these pharmacokinetic parameters and knowledge of the size of the dose and dosage interval ($\tau$), the complete plasma level–time curve or...
the plasma level may be predicted at any time after the beginning of the dosage regimen.

For calculation of multiple-dose regimens, it is necessary to decide whether successive doses of drug will have any effect on the previous dose. The principle of superposition assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or nth dose will overlay or superimpose the blood level attained after the (n – 1)th dose. In addition, the AUC = \( \int_{0}^{\infty} C_{d} dt \) for the first dose is equal to the steady-state area between doses, ie, \( \int_{t_{1}}^{t_{2}} C_{d} dt \) as shown in Fig. 8-1.

The principle of superposition allows the pharmacokineticist to project the plasma drug concentration–time curve of a drug after multiple consecutive doses based on the plasma drug concentration–time curve obtained after a single dose. The basic assumptions are: (1) that the drug is eliminated by first-order kinetics and (2) that the pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.

The plasma drug concentrations after multiple doses may be predicted from the plasma drug concentrations obtained after a single dose. In Table 8-1, the plasma drug concentrations from 0 to 24 hours are measured after a single dose. A constant dose of drug is given every 4 hours and plasma drug concentrations after each dose are generated using the data after the first dose. Thus, the predicted plasma drug concentration in the patient is the total drug concentration obtained by adding the residual drug concentration obtained after each previous dose. The superposition principle may be used to predict drug concentrations after multiple doses of many drugs. Because the superposition principle is an overlay method, it may be used to predict drug concentrations after multiple doses given at either equal or unequal dosage intervals. For example, the plasma drug concentrations may be predicted after a drug dose is given every 8 hours, or 3 times a day before meals at 8 AM, 12 noon, and 6 PM.

There are situations, however, in which the superposition principle does not apply. In these cases, the pharmacokinetics of the drug change after multiple dosing due to various factors, including changing pathophysiology in the patient, saturation of a drug carrier system, enzyme induction, and enzyme inhibition. Drugs that follow nonlinear pharmacokinetics (see Chapter 9) generally do not have predictable plasma drug concentrations after multiple doses using the superposition principle.

If the drug is administered at a fixed dose and a fixed dosage interval, as is the case with many multiple-dose regimens, the amount of drug in the body will increase and then plateau to a mean plasma level higher than the peak \( C_{p} \) obtained from the initial dose (Figs. 8-1 and 8-2). When the second dose is given after a time interval shorter than the time required to “completely” eliminate the previous dose, drug accumulation will occur in the body. In other words, the plasma concentrations following the second dose will be higher than corresponding plasma concentrations immediately following the first dose. However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, drug will not accumulate (see Table 8-1).

As repetitive equal doses are given at a constant frequency, the plasma level–time curve plateaus and a steady state is obtained. At steady state, the plasma drug levels fluctuate between \( C_{\max} \) and \( C_{\min} \). Once steady state is obtained, \( C_{\max} \) and \( C_{\min} \) are constant and remain unchanged from dose to dose. In addition, the AUC between \( \int_{t_{1}}^{t_{2}} C_{d} dt \) is constant during a dosing interval at steady state (see Fig. 8-1). The \( C_{\max} \) is important in determining drug safety. The \( C_{\max} \) should always remain below the minimum

![FIGURE 8-1](image-url) Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.
### Table 8-1: Predicted Plasma Drug Concentrations for Multiple-Dose Regimen Using the Superposition Principle

<table>
<thead>
<tr>
<th>Dose Number</th>
<th>Time (h)</th>
<th>Dose 1 (μg/mL)</th>
<th>Dose 2 (μg/mL)</th>
<th>Dose 3 (μg/mL)</th>
<th>Dose 4 (μg/mL)</th>
<th>Dose 5 (μg/mL)</th>
<th>Dose 6 (μg/mL)</th>
<th>Total (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>21.0</td>
<td>21.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21.0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>22.3</td>
<td>22.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22.3</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>19.8</td>
<td>19.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>19.8</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>16.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16.9</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>14.3</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35.3</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>12.0</td>
<td>22.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
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<td>7</td>
<td>10.1</td>
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<td>0</td>
<td>0</td>
<td>29.9</td>
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<tr>
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<td>0</td>
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<td>11</td>
<td>5.06</td>
<td>10.1</td>
<td>19.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35.0</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>4.25</td>
<td>8.50</td>
<td>16.9</td>
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<td>0</td>
<td>0</td>
<td>29.7</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>3.58</td>
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<td>14.3</td>
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<td>0</td>
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<td>6.01</td>
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<td>43.3</td>
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<tr>
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<td>15</td>
<td>2.53</td>
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<td>0</td>
<td>37.5</td>
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<tr>
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<td>16</td>
<td>2.13</td>
<td>4.25</td>
<td>8.50</td>
<td>16.9</td>
<td>0</td>
<td>0</td>
<td>31.8</td>
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<tr>
<td>17</td>
<td>17</td>
<td>1.79</td>
<td>3.58</td>
<td>7.15</td>
<td>14.3</td>
<td>21.0</td>
<td>0</td>
<td>47.8</td>
</tr>
<tr>
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<td>1.51</td>
<td>3.01</td>
<td>6.01</td>
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<td>22.3</td>
<td>0</td>
<td>44.8</td>
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<td>2.53</td>
<td>5.06</td>
<td>10.1</td>
<td>19.8</td>
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<td>38.8</td>
</tr>
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<td>1.07</td>
<td>2.13</td>
<td>4.25</td>
<td>8.50</td>
<td>16.9</td>
<td>0</td>
<td>32.9</td>
</tr>
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<td>0.90</td>
<td>1.79</td>
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<td>7.15</td>
<td>14.3</td>
<td>21.0</td>
<td>48.7</td>
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<tr>
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<td>0.75</td>
<td>1.51</td>
<td>3.01</td>
<td>6.01</td>
<td>12.0</td>
<td>22.3</td>
<td>45.6</td>
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<td>23</td>
<td>0.63</td>
<td>1.27</td>
<td>2.53</td>
<td>5.06</td>
<td>10.1</td>
<td>19.8</td>
<td>39.4</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
<td>0.53</td>
<td>1.07</td>
<td>2.13</td>
<td>4.25</td>
<td>8.50</td>
<td>16.9</td>
<td>33.4</td>
</tr>
</tbody>
</table>

* A single oral dose of 350 mg was given and the plasma drug concentrations were measured for 0–24 h. The same plasma drug concentrations are assumed to occur after doses 2–6. The total plasma drug concentration is the sum of the plasma drug concentrations due to each dose. For this example, $V_d = 10$ L, $t_{1/2} = 4$ h, and $k_a = 1.5$ h$^{-1}$. The drug is 100% bioavailable and follows the pharmacokinetics of a one-compartment open model.
toxic concentration. The $C_{\text{max}}^\infty$ is also a good indication of drug accumulation. If a drug produces the same $C_{\text{max}}^\infty$ at steady state, compared with the $(C_{n=1})_{\text{max}}$ after the first dose, then there is no drug accumulation. If $C_{\text{max}}^\infty$ is much larger than $(C_{n=1})_{\text{max}}$, then there is significant accumulation during the multiple-dose regimen. Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation $R$ is

$$R = \frac{(C_{\text{max}}^\infty)}{(C_{n=1})_{\text{max}}}$$  \hspace{1cm} (8.1)$$

Substituting for $C_{\text{max}}$ after the first dose and at steady state yields

$$R = \frac{D/V}{D/V_D}$$

$$R = \frac{1}{1-e^{-k\tau}}$$  \hspace{1cm} (8.2)$$

Equation 8.2 shows that drug accumulation measured with the $R$ index depends on the elimination constant and the dosing interval and is independent of the dose. For a drug given in repetitive oral doses, the time required to reach steady state is dependent on the elimination half-life of the drug and is independent of the size of the dose, the length of the dosing interval, and the number of doses. For example, if the dose or dosage interval of the drug is altered as shown in Fig. 8-2, the time required for the drug to reach steady state is the same, but the final steady-state plasma level changes proportionately. Furthermore, if the drug is given at the same dosing rate but as an infusion (eg, 25 mg/h), the average plasma drug concentrations ($C_{\text{av}}^\infty$) will be the same but the fluctuations between $C_{\text{max}}^\infty$ and $C_{\text{min}}^\infty$ will vary (Fig. 8-3). An average steady-state plasma drug concentration is obtained by dividing the area under the curve (AUC) for a dosing period (ie, $\int C_{\text{av}}^\infty dt$) by the dosing interval $\tau$, at steady state.

An equation for the estimation of the time to reach one-half of the steady-state plasma levels or the accumulation half-life has been described by van Rossum and Tomey (1968).

$$\text{Accumulation } t_{1/2} = t_{1/2} \left[1 + 3.3 \log \frac{k_a}{k_a - k}\right]$$  \hspace{1cm} (8.3)$$

![FIGURE 8-2](image-url) Amount of drug in the body as a function of time. Equal doses of drug were given every 6 hours (upper curve) and every 8 hours (lower curve). $k_a$ and $k$ remain constant.

![FIGURE 8-3](image-url) Simulated plasma drug concentration–time curves after IV infusion and oral multiple doses for a drug with an elimination half-life of 4 hours and apparent $V_D$ of 10 L. IV infusion given at a rate of 25 mg/hr; oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.
For IV administration, $k_a$ is very rapid (approaches $\infty$); $k$ is very small in comparison to $k_a$ and can be omitted in the denominator of Equation 8.3. Thus, Equation 8.3 reduces to

$$\text{Accumulation} \ t_{1/2} = t_{1/2} \left(1 + 3.3 \log \frac{k_a}{k} \right)$$

Because $k_a/k = 1$ and $\log 1 = 0$, the accumulation $t_{1/2}$ of a drug administered intravenously is the elimination $t_{1/2}$ of the drug. From this relationship, the time to reach 50% steady-state drug concentrations is dependent on the elimination $t_{1/2}$ and not on the dose or dosage interval.

As shown in Equation 8.4, the accumulation $t_{1/2}$ is directly proportional to the elimination $t_{1/2}$. Table 8-2 gives the accumulation $t_{1/2}$ of drugs with various elimination half-lives given by multiple oral doses (see Table 8-2).

From a clinical viewpoint, the time needed to reach 90% of the steady-state plasma concentration is 3.3 times the elimination half-life, whereas the time required to reach 99% of the steady-state plasma concentration is 6.6 times the elimination half-life (Table 8-3). It should be noted from Table 8-3 that at a constant dose size, the shorter the dosage interval, the larger the dosing rate (mg/h), and the higher the steady-state drug level.

The number of doses for a given drug to reach steady state is dependent on the elimination half-life of the drug and the dosage interval $\tau$ (see Table 8-3). If the drug is given at a dosage interval equal to the half-life of the drug, then 6.6 doses are required to reach 99% of the theoretical steady-state plasma drug concentration. The number of doses needed to reach steady state is $6.6 \ t_{1/2}/\tau$, as calculated in the far right column of Table 8-3. As discussed in Chapter 5, Table 5.1, it takes 4.32 half-lives to reach 95% of steady state.

**CLINICAL EXAMPLE**

Paroxetine (Prozac) is an antidepressant drug with a long elimination half-life of 21 hours. Paroxetine is well absorbed after oral administration and has a $t_{\text{max}}$ of about 5 hours, longer than most drugs. Slow elimination may cause the plasma curve to peak slowly. The $t_{\text{max}}$ is affected by $k$ and $k_a$, as discussed in Chapter 7. The $C_{\text{max}}$ for paroxetine after multiple dosing of 30 mg of paroxetine for 30 days in one study ranged from 8.6 to 105 ng/mL among 15 subjects. Clinically it is important to achieve a stable

<table>
<thead>
<tr>
<th>Elimination Half-Life (h)</th>
<th>Elimination Rate Constant $\frac{\text{h}}{\text{h}}$</th>
<th>Absorption Rate Constant $\frac{\text{h}}{\text{h}}$</th>
<th>Accumulation Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.173</td>
<td>1.50</td>
<td>4.70</td>
</tr>
<tr>
<td>8</td>
<td>0.0866</td>
<td>1.50</td>
<td>8.67</td>
</tr>
<tr>
<td>12</td>
<td>0.0578</td>
<td>1.50</td>
<td>12.8</td>
</tr>
<tr>
<td>24</td>
<td>0.0289</td>
<td>1.50</td>
<td>24.7</td>
</tr>
<tr>
<td>4</td>
<td>0.173</td>
<td>1.00</td>
<td>5.09</td>
</tr>
<tr>
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<td>0.0866</td>
<td>1.00</td>
<td>8.99</td>
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<td>0.0578</td>
<td>1.00</td>
<td>13.0</td>
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<tr>
<td>24</td>
<td>0.0289</td>
<td>1.00</td>
<td>25.0</td>
</tr>
</tbody>
</table>

$^a$Accumulation half-life is calculated by Equation 8.3, and is the half-time for accumulation of the drug to 90% of the steady-state plasma drug concentration.
steady-state level in multiple dosing that does not “under dose” or overdose the patient. The pharmacist should advise the patient to follow the prescribed dosing interval and dose as accurately as possible. Taking a dose too early or too late contributes to variation. Individual variation in metabolism rate can also cause variable blood levels, as discussed later in Chapter 12.

REPETITIVE INTRAVENOUS INJECTIONS

The maximum amount of drug in the body following a single rapid IV injection is equal to the dose of the drug. For a one-compartment open model, the drug will be eliminated according to first-order kinetics.

\[ D_B = D_0 e^{-kt} \]  

(8.5)

If \( \tau \) is equal to the dosage interval (ie, the time between the first dose and the next dose), then the amount of drug remaining in the body after several hours can be determined with

\[ D_B = D_0 e^{-k\tau} \]  

(8.6)

The fraction \( f \) of the dose remaining in the body is related to the elimination constant \( k \) and the dosage interval \( \tau \) as follows:

\[ f = \frac{D_B}{D_0} = e^{-k\tau} \]  

(8.7)

With any given dose, \( f \) depends on \( k \) and \( \tau \). If \( \tau \) is large, \( f \) will be smaller because \( D_B \) (the amount of drug remaining in the body) is smaller.

TABLE 8-3  Interrelation of Elimination Half-Life, Dosage Interval, Maximum Plasma Concentration, and Time to Reach Steady-State Plasma Concentration

<table>
<thead>
<tr>
<th>Elimination Half-Life, h</th>
<th>Dosage Interval, h</th>
<th>( C_{\text{max}} ), ( \mu g/mL )</th>
<th>Time for ( C_{\text{av}} ) to Reach 99% Steady State, h</th>
<th>NO. Doses to Reach 99% Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>200</td>
<td>3.3</td>
<td>6.6</td>
</tr>
<tr>
<td>0.5</td>
<td>1.0</td>
<td>133</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>1.0</td>
<td>0.5</td>
<td>341</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>200</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
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<td>2.0</td>
<td>133</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>1.0</td>
<td>4.0</td>
<td>107</td>
<td>6.6</td>
<td>1.65</td>
</tr>
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<td>0.66</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
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<td>13.2</td>
<td>13.2</td>
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<tr>
<td>2.0</td>
<td>2.0</td>
<td>200</td>
<td>13.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

\( a \) A single dose of 1000 mg of three hypothetical drugs with various elimination half-lives but equal volumes of distribution \( (V_D = 10 \text{ L}) \) were given by multiple IV doses at various dosing intervals. All time values are in hours; \( C_{\text{max}} = \) maximum steady-state concentration; \( \bar{C}_{\text{av}} \) = average steady-state plasma concentration; the maximum plasma drug concentration after the first dose of the drug is \( (C_{\text{max}})_{\text{max}} = 100 \mu g/mL \).

\( b \) Time to reach 99% of steady-state plasma concentration.

\( c \) Since the dosage interval \( \tau \) is very large compared to the elimination half-life, no accumulation of drug occurs.
EXAMPLES

1. A patient receives 1000 mg every 6 hours by repetitive IV injection of an antibiotic with an elimination half-life of 3 hours. Assume the drug is distributed according to a one-compartment model and the volume of distribution is 20 L.

   a. Find the maximum and minimum amount of drug in the body.
   b. Determine the maximum and minimum plasma concentration of the drug.

Solution

a. The fraction of drug remaining in the body is estimated by Equation 8.7. The concentration of the drug declines to one-half after 3 hours ($t_{1/2} = 3$ h), after which the amount of drug will again decline by one-half at the end of the next 3 hours. Therefore, at the end of 6 hours only one-quarter, or 0.25, of the original dose remains in the body. Thus $f$ is equal to 0.25.

   To use Equation 8.7, we must first find the value of $k$ from the $t_{1/2}$:

   \[
   k = \frac{0.693}{t_{1/2}} = \frac{0.693}{3} = 0.231 \text{ h}^{-1}
   \]

   The time interval $\tau$ is equal to 6 hours. From Equation 8.7,

   \[
   f = e^{-(0.231)(6)} = 0.25
   \]

   In this example, 1000 mg of drug is given intravenously, so the amount of drug in the body is immediately increased by 1000 mg. At the end of the dosage interval (ie, before the next dose), the amount of drug remaining in the body is 25% of the amount of drug present just after the previous dose, because $f = 0.25$. Thus, if the value of $f$ is known, a table can be constructed relating the fraction of the dose in the body before and after rapid IV injection (Table 8-4).

   From Table 8-4 the maximum amount of drug in the body is 1333 mg and the minimum amount of drug in the body is 333 mg. The difference between the maximum and minimum values, $D_{av}$, will always equal the injected dose.

   \[
   D_{max} - D_{min} = D_0 \quad (8.8)
   \]

   In this example,

   \[
   1333 - 333 = 1000 \text{ mg}
   \]

   $D_{max}$ can also be calculated directly by the relationship

   \[
   D_{max} = \frac{D_0}{1-f} \quad (8.9)
   \]

   Substituting known data, we obtain

   \[
   D_{max} = \frac{1000}{1-0.25} = 1333 \text{ mg}
   \]

   Then, from Equation 8.8,

   \[
   D_{min} = 1333 - 1000 = 333 \text{ mg}
   \]

   The average amount of drug in the body at steady state, $D_{av}$, can be found by Equation 8.10 or Equation 8.11. $F$ is the fraction of dose absorbed. For an IV injection, $F$ is equal to 1.0.

   \[
   D_{av} = \frac{FD_0}{k\tau} \quad (8.10)
   \]

   \[
   D_{av} = \frac{FD_0}{k\tfrac{1}{2}} \quad (8.11)
   \]
Equations 8.10 and 8.11 can be used for repetitive dosing at constant time intervals and for any route of administration as long as elimination occurs from the central compartment. Substitution of values from the example into Equation 8.11 gives

\[
D_{av} = \frac{(1)(1000)(1.44)(3)}{6} = 720 \text{ mg}
\]

Since the drug in the body declines exponentially (i.e., first-order drug elimination), the value \( D_{av} \) is not the arithmetic mean of \( D_{\text{max}} \) and \( D_{\text{min}} \). The limitation of using \( D_{av} \) is that the fluctuations of \( D_{\text{max}} \) and \( D_{\text{min}} \) are not known.

b. To determine the concentration of drug in the body after multiple doses, divide the amount of drug in the body by the volume in which it is dissolved. For a one-compartment model, the maximum, minimum, and steady-state concentrations of drug in the plasma are found by the following equations:

\[
C_{\text{av}} = \frac{D_{av}}{V_d}
\]

\[
C_{\text{min}} = \frac{D_{\text{min}}}{V_d}
\]

\[
C_{\text{av}} = \frac{D_{\text{av}}}{V_d}
\]

A more direct approach to finding \( C_{\text{max}} \), \( C_{\text{min}} \), and \( C_{\text{av}} \) is

\[
C_{\text{max}} = \frac{C_0}{1 - e^{-k V_d}}
\]

where \( C_0 \) is equal to \( D_0/V_d \).

\[
C_{\text{min}} = \frac{C_0 e^{-k \tau}}{1 - e^{-k \tau}}
\]

\[
C_{\text{av}} = \frac{F D_0}{V_d k \tau}
\]

For this example, the values for \( C_{\text{max}} \), \( C_{\text{min}} \), and \( C_{\text{av}} \) are 66.7, 16.7, and 36.1 \( \mu \text{g/mL} \), respectively.

As mentioned, \( C_{\text{av}} \) is not the arithmetic mean of \( C_{\text{max}} \) and \( C_{\text{min}} \) because plasma drug concentration declines exponentially. The \( C_{\text{av}} \) is equal to \( \{\text{AUC}\}^2_{t_1} \) or \( (\int_{t_1}^{t_2} C_d \, dt) \) for a dosage interval at steady state divided by the dosage interval \( \tau \).

\[
C_{\text{av}} = \frac{\{\text{AUC}\}^2_{t_1}}{\tau}
\]

\( C_{\text{av}} \) gives an estimate of the mean plasma drug concentration at steady state. The \( C_{\text{av}} \) is often the target drug concentration for optimal therapeutic effect and gives an indication as to how long this plasma drug concentration is maintained during the dosing interval (between doses). The \( C_{\text{av}} \) is dependent on both \( \text{AUC} \) and \( \tau \). The \( C_{\text{av}} \) reflects drug exposure after multiple doses. Drug exposure is often related to drug safety and efficacy as discussed later in Chapter 19. For example, drug exposure is closely monitored when a cytotoxic or immunosuppressive, anti cancer drug is administered during therapy. AUC may be estimated by sampling several plasma drug concentrations over time. Theoretically, AUC is superior to sampling just the \( C_{\text{max}} \) or \( C_{\text{min}} \). For example, when cyclosporine dosing is clinically evaluated using AUC, the AUC is approximately estimated by two or three points. Dosing error is less than using AUC compared to the trough method alone (Primmett, D et al, 1998). In general, \( C_{\text{min}} \) or trough level is more frequently used than \( C_{\text{max}} \). \( C_{\text{min}} \) is the drug concentration just before the next dose is given and is less variable than peak drug concentration, \( C_{\text{max}} \). The sample time for \( C_{\text{av}} \) is approximated and the true \( C_{\text{av}} \) may not be accurately estimated. In some cases, the plasma trough level, \( C_{\text{min}} \) is considered by some investigators as a more reliable sample since the drug is equilibrate with the surrounding tissues although this may also depend on other factors.

The AUC is related to the amount of drug absorbed divided by total body clearance (\( Cl \)), as shown in the following equation.

\[
\{\text{AUC}\}^2_{t_1} = \frac{F D_0}{Cl} = \frac{F D_0}{k V_d}
\]
Substitution of $FD_0/kV_o$ for AUC in Equation 8.18 gives Equation 8.17. Equation 8.17 or 8.18 can be used to obtain $C_{av}$ after a multiple-dose regimen regardless of the route of administration.

It is sometimes desirable to know the plasma drug concentration at any time after the administration of $n$ doses of drug. The general expression for calculating this plasma drug concentration is

$$C_p = \frac{D_0}{V_o} \left( \frac{1 - e^{-nt}}{1 - e^{-xt}} \right) e^{-kt}$$

(8.20)

where $n$ is the number of doses given and $t$ is the time after the $n$th dose.

At steady state, $e^{-nt}$ approaches zero and Equation 8.20 reduces to

$$C_p = \frac{D_0}{V_o} e^{-kt}$$

(8.21)

where $C_p$ is the steady-state drug concentration at time $t$ after the dose.

2. The patient in the previous example received 1000 mg of an antibiotic every 6 hours by repetitive IV injection. The drug has an apparent volume of distribution of 20 L and elimination half-life of 3 hours. Calculate (a) the plasma drug concentration, $C_p$ at 3 hours after the second dose, (b) the steady-state plasma drug concentration, $C_p^\infty$ at 3 hours after the last dose, (c) $C_{max}$, (d) $C_{min}$, and (e) $C_{av}$.

Solution

a. The $C_p$ at 3 hours after the second dose—use Equation 8.20 and let $n = 2$, $t = 3$ hours, and make other appropriate substitutions.

$$C_p = \frac{1000}{20} \left( \frac{1 - e^{-12/6}}{1 - e^{-36/6}} \right) e^{-3/3}$$

$C_p = 31.3$ mg/L

b. The $C_p^\infty$ at 3 hours after the last dose—because steady state is reached, use Equation 8.21 and perform the following calculation.

$$C_p^\infty = \frac{1000}{20} \left( \frac{1}{1 - e^{-36/6}} \right) e^{-3/3}$$

$C_p^\infty = 33.3$ mg/L

c. The $C_{max}$ is calculated from Equation 8.15.

$$C_{max} = \frac{1000/20}{1 - e^{-0.23(20)}} = 66.7$$ mg/L

d. The $C_{min}$ may be estimated as the drug concentration after the dosage interval $\tau$, or just before the next dose.

$$C_{min} = C_{max} e^{-kt} = 66.7 e^{-0.23(20)/6} = 16.7$$ mg/L

e. The $C_{av}$ is estimated by Equation 8.17—because the drug is given by IV bolus injections, $F = 1$.

$$C_{av} = \frac{1000}{(0.23/20)(6)} = 36.1$$ mg/L

$C_{av}$ is represented as $C_{SS}$ in some references.

**Problem of a Missed Dose**

Equation 8.22 describes the plasma drug concentration $t$ hours after the $n$th dose is administered; the doses are administered $\tau$ hours apart according to a multiple-dose regimen:

$$C_p = \frac{D_0}{V_o} \left( \frac{1 - e^{-nt}}{1 - e^{-xt}} \right) e^{-kt}$$

(8.22)

Concentration contributed by the missing dose is

$$C' = \frac{D_0}{V_o} e^{-kt_{miss}}$$

(8.23)

in which $t_{miss} = \text{time elapsed since the scheduled dose was missed}$. Subtracting Equation 8.23 from Equation 8.20 corrects for the missing dose as shown in Equation 8.24.

$$C_p = \frac{D_0}{V_o} \left[ \left( \frac{1 - e^{-nt}}{1 - e^{-xt}} \right) e^{-kt} - \frac{D_0}{V_o} e^{-kt_{miss}} \right]$$

(8.24)
Note: If steady state is reached (i.e., either $n = \text{large}$ or after many doses), the equation simplifies to Equation 8.25. Equation 8.25 is useful when steady state is reached.

$$C_p = \frac{D_t}{V_D} \left( e^{-kt} \right) - e^{-kt_{\text{miss}}} \quad (8.25)$$

Generally, if the missing dose is recent, it will affect the present drug level more. If the missing dose is several half-lives later (>5 $t_{1/2}$), the missing dose may be omitted because it will be very small. Equation 8.24 accounts for one missing dose, but several missing doses can be subtracted in a similar way if necessary.

EXAMPLE

A cephalosporin ($k = 0.2 \text{ h}^{-1}$, $V_D = 10 \text{ L}$) was administered by IV multiple dosing; 100 mg was injected every 6 hours for 6 doses. What was the plasma drug concentration 4 hours after the sixth dose (i.e., 40 hours later) if (a) the fifth dose was omitted, (b) the sixth dose was omitted, (c) the fourth dose was omitted?

**Solution**

Substitute $k = 0.2 \text{ h}^{-1}$, $V_D = 10 \text{ L}$, $D = 100 \text{ mg}$, $n = 6$, $t = 4 \text{ h}$, and $\tau = 6 \text{ h}$ into equation 8.20 and evaluate:

$$C_p = 6.425 \text{ mg/L}$$

If no dose was omitted, then 4 hours after the sixth injection, $C_p$ would be 6.425 mg/L.

(a) Missing the fifth dose, its contribution must be subtracted off, $t_{\text{miss}} = 6 + 4 = 10 \text{ hours}$ (the time elapsed since missing the dose) using the steady-state equation:

$$C_p = \frac{D_t}{V_D} \left( e^{-kt_{\text{miss}}} \right) = 10 \left( 1 - e^{-0.2 \times 10} \right)
= 10 \times 0.1353 = 1.353 \text{ mg/L}$$

Drug concentration correcting for the missing dose = 6.425 – 1.353 = 5.072 mg/L.

(b) If the sixth dose is missing, $t_{\text{miss}} = 4 \text{ hours}$:

$$C_p = \frac{D_t}{V_D} \left( e^{-kt_{\text{miss}}} \right) = \frac{100}{10} e^{-0.2 \times 4} = 4.493 \text{ mg/L}$$

Drug concentration correcting for the missing dose = 6.425 – 4.493 = 1.932 mg/L.

(c) If the fourth dose is missing, $t_{\text{miss}} = 12 + 4 = 16 \text{ hours}$:

$$C_p = \frac{D_t}{V_D} \left( e^{-kt_{\text{miss}}} \right) = \frac{100}{10} e^{-0.2 \times 16} = 0.408 \text{ mg/L}$$

The drug concentration corrected for the missing dose = 6.425 – 0.408 = 6.017 mg/L.

Note: The effect of a missing dose becomes less pronounced at a later time. A strict dose regimen compliance is advised for all drugs. With some drugs, missing a dose can have a serious effect on therapy. For example, compliance is important for the anti-HIV1 drugs such as the protease inhibitors.

**Early or Late Dose Administration during Multiple Dosing**

When one of the drug doses is taken earlier or later than scheduled, the resulting plasma drug concentration can still be calculated based on the principle of superposition. The dose can be treated as missing, with the late or early dose added back to take into account the actual time of dosing, using Equation 8.26.

$$C_p = \frac{D_t}{V_D} \left( 1 - e^{-kt_{\text{miss}}} - e^{-kt_{\text{miss}}} + e^{-kt_{\text{actual}}} \right) \quad (8.26)$$

in which $t_{\text{miss}}$ = time elapsed since the dose (late or early) is scheduled, and $t_{\text{actual}}$ = time elapsed since the dose (late or early) is actually taken. Using a similar approach, a second missed dose can be subtracted from Equation 8.20. Similarly, a second late/early dose may be corrected by subtracting the scheduled dose followed by adding the actual dose. Similarly, if a different dose is given, the regular dose may be subtracted and the new dose added back.
Multiple-Dosage Regimens

involving short IV infusion, the drug may not reach steady state. The rationale for intermittent IV infusion is to prevent transient high drug concentrations and accompanying side effects. Many drugs are better tolerated when infused slowly over time compared to IV bolus dosing.

Administering One or More Doses by Constant Infusion: Superposition of Several IV Infusion Doses

For a continuous IV infusion (see Chapter 6):

$$C_p = \frac{R}{kV_D} (1 - e^{-kt})$$

Equation 8.27 may be modified to determine drug concentration after one or more short IV infusions for a specified time period (Equation 8.28).

$$C_p = \frac{D}{t_{int} V_D k} (1 - e^{-kt})$$

where $R = \text{rate of infusion} = Dt_{int}$, $D = \text{size of infusion dose}$, and $t_{int} = \text{infusion period}$.

After the infusion is stopped, the drug concentration post-IV infusion is obtained using the first-order equation for drug elimination:

$$C_p = C_{stop} e^{-kt}$$

where $C_{stop} = \text{concentration when infusion stops}$, $t = \text{time elapsed since infusion stopped}$.

**EXAMPLE**

Assume the same drug as above (i.e., $k = 0.2$ h$^{-1}$, $V_D = 10$ L) was given by multiple IV bolus injections and that at a dose of 100 mg every 6 hours for six doses. What is the plasma drug concentration 4 hours after the sixth dose, if the fifth dose were given an hour late?

Substitute into Equation 8.26 for all unknowns:

- $k = 0.2$ h$^{-1}$, $V_D = 10$ L,
- $D = 100$ mg,
- $n = 6$,
- $\tau = 6$ h,
- $t_{miss} = 6 + 4 = 10$ h,
- $t_{actual} = 9$ h (taken 1 hour late, i.e., 5 hours before the sixth dose).

$$C_p = \frac{D}{V_D} \left( \frac{1 - e^{-kt}}{1 - e^{-kt_{miss}}} \right)$$

$$C_p = 6.425 - 1.353 + 1.653 = 6.725 \text{ mg/L}$$

Note: 1.353 mg/L was subtracted and 1.653 mg/mL was added because the fifth dose was not given as planned, but was given 1 hour later.

**INTERMITTENT INTRAVENOUS INFUSION**

Intermittent IV infusion is a method of successive short IV drug infusions in which the drug is given by IV infusion for a short period of time followed by a drug elimination period, then followed by another short IV infusion (Fig. 8-4). In drug regimens involving short IV infusion, the drug may not reach steady state. The rationale for intermittent IV infusion is to prevent transient high drug concentrations and accompanying side effects. Many drugs are better tolerated when infused slowly over time compared to IV bolus dosing.

**EXAMPLE**

An antibiotic was infused with a 40-mg IV dose over 2 hours. Ten hours later, a second dose of 40 mg was infused, again over 2 hours. (a) What is the plasma drug concentration 2 hours after the start of the first infusion? (b) What is the plasma drug concentration 5 hours after the second dose infusion was started? Assume $k = 0.2$ h$^{-1}$, $V_D = 10$ L for the antibiotic.
Solution

The predicted plasma drug concentrations after the first and second IV infusions are shown in Table 8-5. Using the principle of superposition, the total plasma drug concentration is the sum of the residual drug concentrations due to the first IV infusion (column 3) and the drug concentrations due to the second IV infusion (column 4). A graphical representation of these data is shown in Fig. 8-4.

a. The plasma drug concentration at 2 hours after the first IV infusion starts is calculated from Equation 8.28.

\[ C_p = \frac{40/2}{10 \times 0.2} (1 - e^{-0.2 \times 2}) = 3.30 \text{ mg/L} \]

b. From Table 8-5, the plasma drug concentration at 15 hours (i.e., 5 hours after the start of the second IV infusion) is 2.06 µg/mL. At 5 hours after the second IV infusion starts, the plasma drug concentration is the sum of the residual plasma drug concentrations from the first 2-hour infusion according to first-order elimination and the residual plasma drug concentrations from the second 2-hour IV infusion as shown in the following scheme:

<table>
<thead>
<tr>
<th>First infusion for 2 hours</th>
<th>Second infusion for 8 hours</th>
<th>10 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronized infusion</td>
<td>Synchronized infusion</td>
<td>10 hours</td>
</tr>
<tr>
<td>Not synchronized infusion</td>
<td>Not synchronized infusion</td>
<td></td>
</tr>
</tbody>
</table>

The plasma drug concentration is calculated using the first-order elimination equation, where \( C_{\text{stop}} \) is the plasma drug concentration at the stop of the 2-hour IV infusion.

The plasma drug concentration after the completion of the first IV infusion, when \( t = 15 \) hours is

\[ C_p = C_{\text{stop}} \times e^{-kt} = 3.30 e^{-0.2 \times 15} = 0.25 \text{ µg/L} \]

The plasma drug concentration 5 hours after the second IV infusion is

\[ C_p = C_{\text{stop}} \times e^{-kt} = 3.30 e^{-0.2 \times 3} = 1.81 \text{ µg/mL} \]

The total plasma drug concentration 5 hours after the start of the second IV infusion is

\[ 0.25 \text{ mg/L} + 1.81 \text{ mg/L} = 2.06 \text{ mg/L} \]

CLINICAL EXAMPLE

Gentamicin sulfate was given to an adult male patient (57 years old, 70 kg) by intermittent IV infusions. One-hour IV infusions of 90 mg of gentamicin were given at 8-hour intervals. Gentamicin clearance is similar to creatinine clearance and was estimated as 7.2 L/h with an elimination half-life of 3 hours.

a. What is the plasma drug concentration after the first IV infusion?

b. What is the peak plasma drug concentration, \( C_{\text{max}} \), and the trough plasma drug concentration, \( C_{\text{min}} \), at steady state?

Solution

a. The plasma drug concentration directly after the first infusion is calculated from Equation 8.27, where \( R = 90 \text{ mg/h} \), \( Cl = 7.2 \text{ L/h} \), and \( k = 0.231 \text{ h}^{-1} \). The time for infusion, \( t_{\text{inf}} \), is 1 hour.

\[ C_p = \frac{90}{7.2} (1 - e^{-(0.231)(1)}) = 2.58 \text{ mg/L} \]

b. The \( C_{\text{max}} \) at steady state may be obtained from Equation 8.30.

\[ C_{\text{max}} = \frac{R(1 - e^{-k_{\text{inf}}})}{Cl} \frac{1}{(1 - e^{-kt})} \quad (8.30) \]

where \( C_{\text{max}} \) is the peak drug concentration following the \( n \)th infusion, at steady state, \( t_{\text{inf}} \) is the time period of infusion, and \( t \) is the dosage interval. The term \( 1/(1 - e^{-kt}) \) is the accumulation factor for repeated drug administration.

Substitution in Equation 8.30 gives

\[ C_{\text{max}} = \frac{90(1 - e^{-(0.231)(1)})}{7.2} \times \frac{1}{(1 - e^{-0.231(8)})} = 3.06 \text{ mg/L} \]

The plasma drug concentration \( C_{\text{p}} \) at any time \( t \) after the last infusion ends when steady state is obtained by Equation 8.31 and assumes that plasma drug concentrations decline according to first-order elimination kinetics.
where $t_{\text{inf}}$ is the time for infusion and $t$ is the time period after the end of the infusion.

The trough plasma drug concentration, $C_{\text{min}}^\infty$, at steady state is the drug concentration just before the start of the next IV infusion or after a dosage interval equal to 8 hours after the last infusion stopped. Equation 8.31 can be used to determine the plasma drug concentration at any time after the last infusion is stopped (after steady state has been reached).

$$C_{\text{min}}^\infty = \frac{R(1-e^{-kt_{\text{inf}}})}{CI} \times \frac{1}{(1-e^{-k(t)})} \times e^{-kt} \quad (8.31)$$

where $t_{\text{inf}}$ is the time for infusion and $t$ is the time period after the end of the infusion.

The trough plasma drug concentration, $C_{\text{min}}^\infty$, at steady state is the drug concentration just before the start of the next IV infusion or after a dosage interval equal to 8 hours after the last infusion stopped. Equation 8.31 can be used to determine the plasma drug concentration at any time after the last infusion is stopped (after steady state has been reached).

$$C_{\text{min}}^\infty = \frac{90(1-e^{-(0.231)(1)})}{7.2} \times \frac{e^{-(0.231)(8)}}{(1-e^{-(0.231)(8)})} = 0.48 \, \text{mg/L}$$

### ESTIMATION OF $k$ AND $V_D$ OF AMINOGLYCOSIDES IN CLINICAL SITUATIONS

As illustrated above, antibiotics are often infused intravenously by multiple doses, so it is desirable to adjust the recommended starting dose based on the patient’s individual $k$ and $V_D$ values. According to Sawchuk and Zaske (1976), individual parameters for aminoglycoside pharmacokinetics may be determined in a patient by using a limited number of plasma drug samples taken at appropriate time intervals. The equation was simplified by replacing an elaborate model with the one-compartment model to describe drug elimination and appropriately avoiding

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**TABLE 8-5  Drug Concentration after Two Intravenous Infusions**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma Drug Concentration after Infusion 1</th>
<th>Plasma Drug Concentration after Infusion 2</th>
<th>Total Plasma Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.81</td>
<td>1.81</td>
<td>3.62</td>
</tr>
<tr>
<td>2</td>
<td>3.30</td>
<td>1.81</td>
<td>5.11</td>
</tr>
<tr>
<td>3</td>
<td>2.70</td>
<td>1.81</td>
<td>4.51</td>
</tr>
<tr>
<td>4</td>
<td>2.21</td>
<td>1.81</td>
<td>4.02</td>
</tr>
<tr>
<td>5</td>
<td>1.81</td>
<td>1.81</td>
<td>3.62</td>
</tr>
<tr>
<td>6</td>
<td>1.48</td>
<td>1.81</td>
<td>3.29</td>
</tr>
<tr>
<td>7</td>
<td>1.21</td>
<td>1.81</td>
<td>2.82</td>
</tr>
<tr>
<td>8</td>
<td>0.99</td>
<td>1.81</td>
<td>2.78</td>
</tr>
<tr>
<td>9</td>
<td>0.81</td>
<td>1.81</td>
<td>2.62</td>
</tr>
<tr>
<td>10</td>
<td>0.67</td>
<td>0</td>
<td>0.67</td>
</tr>
<tr>
<td>11</td>
<td>0.55</td>
<td>1.81</td>
<td>2.36</td>
</tr>
<tr>
<td>12</td>
<td>0.45</td>
<td>3.30</td>
<td>3.74</td>
</tr>
<tr>
<td>13</td>
<td>0.37</td>
<td>2.70</td>
<td>3.07</td>
</tr>
<tr>
<td>14</td>
<td>0.30</td>
<td>2.21</td>
<td>2.51</td>
</tr>
<tr>
<td>15</td>
<td>0.25</td>
<td>1.81</td>
<td>2.06</td>
</tr>
</tbody>
</table>

*Drug is given by a 2-hour infusion separated by a 10-hour drug elimination interval. All drug concentrations are in mg/mL. The declining drug concentration after the first infusion dose and the drug concentration after the second infusion dose give the total plasma drug concentration.
the distributive phase. The plasma sample should be collected 15 to 30 minutes postinfusion (with infusion lasting about 60 minutes) and, in patients with poor renal function, 1 to 2 hours postinfusion, to allow adequate tissue distribution. The second and third blood samples should be collected about 2 to 3 half-lives later, in order to get a good estimation of the slope. The data may be determined graphically or by regression analysis using a scientific calculator or computer program.

\[ V_D = \frac{R(1-e^{-kt_{inf}})}{[C_{\text{max}} - C_{\text{min}} e^{-kt_{inf}}]} \]  

(8.32)

The dose of aminoglycoside is generally fixed by the desirable peak, \( C_{\text{max}} \), and trough plasma concentration, \( C_{\text{min}} \). For example, \( C_{\text{min}} \) for gentamicin may be set at 6 to 10 \( \mu \)g/mL with the steady-state trough level, \( C_{\text{min}} \), generally about 0.5 to 2 \( \mu \)g/mL, depending on the severity of the infection and renal considerations. The upper range is used only for life-threatening infections. The infusion rate for any desired peak drug concentration may be calculated using Equation 8.33.

\[ R = \frac{V_D k C_{\text{max}} (1-e^{-kt})}{(1-e^{-k t_{\text{inf}}})} \]  

(8.33)

The dosing interval \( \tau \) between infusions may be adjusted to obtain a desired concentration.

**Frequently Asked Questions**

- Why is the accumulation index, \( R \), not affected by the trough level, \( C_{\text{min}} \)?
- How is the drug accumulation index, \( R \), much greater than 1?
- Would it be possible to give a drug with a short half-life to have dose or clearance of a drug?
- Why are drugs eliminated slowly from the body?

**MULTIPLE-ORAL-DOSE REGIMEN**

Figures 8-1 and 8-2 present typical cumulation curves for the concentration of drug in the body after multiple oral doses given at a constant dosage interval. The plasma concentration at any time during an oral or extravascular multiple-dose regimen, assuming a one-compartment model and constant doses and dose interval, can be determined as follows:

\[ C_p = \frac{F k_D D_0}{V_D (k - k_t)} \left[ \frac{1-e^{-nk_{t}}}{1-e^{-k_{t} \tau}} \right] e^{-k_{t} t} - \left[ \frac{1-e^{-nk_{t}}}{1-e^{-k_{t} \tau}} \right] e^{-k_{t} \tau} \]  

(8.34)

where \( n \) = number of doses, \( \tau \) = dosage interval, \( F \) = fraction of dose absorbed, and \( t \) = time after administration of \( n \) doses.

The mean plasma level at steady state, \( C_{av}^{\infty} \), is determined by a similar method to that employed for repeat IV injections. Equation 8.17 can be used for finding \( C_{av}^{\infty} \) for any route of administration.

\[ C_{av}^{\infty} = \frac{F D_0}{V_D k_t} \]  

(8.17)

Because proper evaluation of \( F \) and \( V_D \) requires IV data, the AUC of a dosing interval at steady state may be substituted in Equation 8.17 to obtain

\[ C_{av}^{\infty} = \int_0^\infty \frac{C_p dt}{\tau} = \frac{[\text{AUC}]_0}{\tau} \]  

(8.35)

One can see from Equation 8.17 that the magnitude of \( C_{av}^{\infty} \) is directly proportional to the size of the dose and the extent of drug absorbed. Furthermore, if the dosage interval (\( \tau \)) is shortened, then the value for \( C_{av}^{\infty} \) will increase. The \( C_{av}^{\infty} \) will be predictably higher for drugs distributed in a small \( V_D \) (eg, plasma water) or that have long elimination half-lives than for drugs distributed in a large \( V_D \) (eg, total body water) or that have very short elimination half-lives. Because body clearance (\( Cl_D \)) is equal to \( k V_D \), substitution into Equation 8.17 yields

\[ C_{av}^{\infty} = \frac{F D_0}{Cl_D \tau} \]  

(8.36)

Thus, if \( Cl_D \) decreases, \( C_{av}^{\infty} \) will increase.
The $C^\text{av}_\infty$ does not give information concerning the fluctuations in plasma concentration ($C^\text{max}_\infty$ and $C^\text{min}_\infty$). In multiple-dose regimens, $C_p$ at any time can be obtained using Equation 8.34, where $n = nth$ dose. At steady state, the drug concentration can be determined by letting $n$ equal infinity. Therefore, $e^{-nk\tau}$ becomes approximately equal to zero and Equation 8.22 becomes

$$C_p = \frac{k_p FD_0}{V_0(k_a - k)} \left[ \frac{1}{1 - e^{-k\tau}} e^{-kt} - \left( \frac{1}{1 - e^{-k\tau}} e^{-k\tau} \right) \right]$$

(8.37)

The maximum and minimum drug concentrations ($C^\text{max}_\infty$ and $C^\text{min}_\infty$) can be obtained with the following equations:

$$C^\text{max}_\infty = \frac{FD_0}{V_0} \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-kt}$$

(8.38)

$$C^\text{min}_\infty = \frac{k_p FD_0}{V_0(k_a - k)} \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau}$$

(8.39)

The time at which maximum (peak) plasma concentration (or $t^\text{max}$) occurs following a single oral dose is

$$t^\text{max} = \frac{2.3}{k_a - k} \log \frac{k}{k}$$

(8.40)

whereas the peak plasma concentration, $t_p$, following multiple doses is given by Equation 8.41.

$$t_p = \frac{1}{k_a - k} \ln \left[ \frac{k_a (1 - e^{-k\tau})}{k (1 - e^{-k\tau})} \right]$$

(8.41)

Large fluctuations between $C^\text{max}_\infty$ and $C^\text{min}_\infty$ can be hazardous, particularly with drugs that have a narrow therapeutic index. The larger the number of divided doses, the smaller the fluctuations in the plasma drug concentrations. For example, a 500-mg dose of drug given every 6 hours will produce the same $C^\text{av}_\infty$ value as a 250-mg dose of the same drug given every 3 hours, while the $C^\text{max}_\infty$ and $C^\text{min}_\infty$ fluctuations for the latter dose will be decreased by one-half (see Fig. 8.3). With drugs that have a narrow therapeutic index, the dosage interval should not be longer than the elimination half-life.

**EXAMPLE**

An adult male patient (46 years old, 81 kg) was given 250 mg of tetracycline hydrochloride orally every 8 hours for 2 weeks. From the literature, tetracycline hydrochloride is about 75% bioavailable and has an apparent volume of distribution of 1.5 L/kg. The elimination half-life is about 10 hours. The absorption rate constant is 0.9 h$^{-1}$. From this information, calculate (a) $C^\text{max}$ after the first dose, (b) $C^\text{min}$ after the first dose, (c) plasma drug concentration $C_p$ at 4 hours after the seventh dose, (d) maximum plasma drug concentration at steady-state $C^\text{max}_s$, (e) minimum plasma drug concentration at steady-state $C^\text{min}_s$, and (f) average plasma drug concentration at steady-state $C^\text{av}_s$.

**Solution**

a. $C^\text{max}$ after the first dose occurs at $t^\text{max}$—therefore, using Equation 8.40,

$$t^\text{max} = \frac{2.3}{k_a - k} \log \frac{k}{k}$$

$$t^\text{max} = 3.07$$

Then substitute $t^\text{max}$ into the following equation for a single oral dose (one-compartment model) to obtain $C^\text{max}$.

$$C^\text{max} = \frac{FD_0 k_p}{V_0(k_a - k)} (e^{-k\tau + k\tau} - e^{-k\tau})$$

$$C^\text{max} = \frac{(0.75)(250)(0.9)}{((10.0)(0.9 - 0.07))(e^{-0.07(3.07)} - e^{-0.9(3.07)})}$$

$$C^\text{max} = 1.28 \text{ mg/L}$$
b. $C_{\text{min}}$ after the first dose occurs just before the administration of the next dose of drug—therefore, set $t = 8$ hours and solve for $C_{\text{min}}$.

\[
C_{\text{min}} = \frac{(0.75)(250)(0.9)}{121.5(0.9 - 0.07)} e^{-0.07(8)} - e^{-0.9(8)} = 0.95 \text{ mg/L}
\]

c. $C_\text{p}$ at 4 hours after the seventh dose may be calculated using Equation 8.34, letting $n = 7, t = 4, \tau = 8$, and making the appropriate substitutions.

\[
C_\text{p} = \frac{(0.75)(250)(0.9)}{121.5(0.9 - 0.07 - 0.9)} \times \left[\frac{1 - e^{-7(0.9)(8)}}{1 - e^{-0.9(8)}}\right] e^{-0.9(4)} - \left(\frac{1 - e^{-7(0.07)(8)}}{1 - e^{-0.07(8)}}\right) e^{-0.07(4)} = 2.86 \text{ mg/L}
\]

d. $C_{\text{max}}$ at steady state; $t_p$ at steady state is obtained from Equation 8.41.

\[
t_p = \frac{1}{k_a - k} \ln \left[\frac{k_a(1 - e^{-\tau})}{k(1 - e^{-\tau})}\right]
\]

\[
t_p = \frac{1}{0.9 - 0.07} \ln \left[\frac{0.9(1 - e^{-0.07(8)})}{0.07(1 - e^{-0.9(8)})}\right] = 2.05 \text{ hours}
\]

Then $C_{\text{max}}$ is obtained using Equation 8.38.

\[
C_{\text{max}} = \frac{0.75(250)}{121.5} \left(\frac{1}{1 - e^{-0.07(8)}}\right) e^{-0.07(2.05)} = 3.12 \text{ mg/L}
\]

e. $C_{\text{min}}$ at steady state is calculated from Equation 8.39.

\[
C_{\text{min}} = \frac{(0.9)(0.75)(250)}{121.5(0.9 - 0.07)} \left(\frac{1}{1 - e^{-0.07(8)}}\right) e^{-0.7(8)} = 2.23 \text{ mg/L}
\]

f. $C_{\text{min}}$ at steady state is calculated from Equation 8.17.

\[
C_{\text{min}} = \frac{(0.75)(250)}{121.5(0.07)(8)} = 2.76 \text{ mg/L}
\]

**LOADING DOSE**

Since extravascular doses require time for absorption into the plasma to occur, therapeutic effects are delayed until sufficient plasma concentrations are achieved. To reduce the onset time of the drug—that is, the time it takes to achieve the minimum effective concentration (assumed to be equivalent to the $C_{\text{av}}^\infty$) of a loading (priming) or initial dose of drug is given. The main objective of the loading dose is to achieve desired plasma concentrations, $C_{\text{av}}^\infty$, as quickly as possible. If the drug follows one-compartment pharmacokinetics, then in theory, steady state is also achieved immediately following the loading dose. Thereafter, a maintenance dose is given to maintain $C_{\text{av}}^\infty$ and steady state so that the therapeutic effect is also maintained. In practice, a loading dose may be given as a bolus dose or a short-term loading IV infusion.

As discussed earlier, the time required for the drug to accumulate to a steady-state plasma level is dependant mainly on its elimination half-life. The time needed to reach 90% of $C_{\text{av}}^\infty$ is approximately 3.3 half-lives, and the time required to reach 99% of $C_{\text{av}}^\infty$ is equal to approximately 6.6 half-lives. For a drug with a half-life of 4 hours, it will take approximately 13 and 26 hours to reach 90% and 99% of $C_{\text{av}}^\infty$, respectively.

For drugs absorbed rapidly in relation to elimination ($k_a >> k$) and that are distributed rapidly, the loading dose $D_L$ can be calculated as follows:

\[
\frac{D_L}{D_0} = \frac{1}{(1 - e^{-k\tau})(1 - e^{-k\tau})} \quad (8.42)
\]

For extremely rapid absorption, as when the product of $k\tau$ is large or in the case of IV infusion, $e^{-k\tau}$ becomes approximately zero and Equation 8.42 reduces to

\[
\frac{D_L}{D_0} = \frac{1}{1 - e^{-k\tau}} \quad (8.43)
\]

The loading dose should approximate the amount of drug contained in the body at steady state.
The dose ratio is equal to the loading dose divided by the maintenance dose.

\[
\text{Dose ratio} = \frac{D_L}{D_m} \quad (8.44)
\]

As a general rule, the dose ratio should be equal to 2.0 if the selected dosage interval is equal to the elimination half-life. Figure 8-5 shows the plasma level–time curve for dosage regimens with equal maintenance doses but different loading doses. A rapid approximation of loading dose, \(D_L\), may be estimated from

\[
D_L = \frac{V_d C_{av}^{\infty}}{(S)(F)} \quad (8.45)
\]

where \(C_{av}^{\infty}\) is the desired plasma drug concentration, \(S\) is the salt form of the drug, and \(F\) is the fraction of drug bioavailability.

Equation 8.45 assumes very rapid drug absorption from an immediate-release dosage form. The \(D_L\) calculated by this method has been used in clinical situations for which only an approximation of the \(D_L\) is needed.

These calculations for loading doses are not applicable to drugs that demonstrate multicompartment kinetics. Such drugs distribute slowly into extravascular tissues, and drug equilibration and steady state may not occur until after the apparent plateau is reached in the vascular (central) compartment.

**DOSEAGE REGIMEN SCHEDULES**

Predictions of steady-state plasma drug concentrations usually assume the drug is given at a constant dosage interval throughout a 24-hour day. Very often, however, the drug is given only during the waking hours (Fig. 8-6). Niebergall and associates (1974) discussed the problem of scheduling dosage regimens and particularly warned against improper timing of the drug dosage. For drugs with a narrow therapeutic index such as theophylline (Fig. 8-7), large fluctuation between the maximum and minimum plasma levels are undesirable and may lead to subtherapeutic plasma drug concentrations and/or to high, possibly toxic drug concentrations. These wide fluctuations occur if larger doses are given at wider dosage intervals (see Fig. 8-3). For example, Fig. 8-7 shows procainamide given with a 1.0-g loading dose on the first day followed by maintenance doses of 0.5-g four times a day. On the second, third, and
subsequent days, the procainamide plasma levels did not reach the therapeutic range until after the second dose of drug.

Ideally, drug doses should be given at evenly spaced intervals. However, to improve patient compliance, dosage regimens may be designed to fit with the lifestyle of the patient. For example, the patient is directed to take a drug such as amoxicillin four times a day (QID), before meals and at bedtime, for a systemic infection. This dosage regimen will produce unequal dosage intervals during the day, because the patient takes the drug before breakfast, at 0800 hours (8 AM), before lunch, at 1200 hours (12 noon), before dinner, at 1800 hours (6 PM), and before bedtime, at 2300 hours (11 PM). For these drugs, evenly spaced dosage intervals are not that critical to the effectiveness of the antibiotic as long as the plasma drug concentrations are maintained above the minimum inhibitory concentration (MIC) for the microorganism. In some cases, a drug may be given at a larger dose allowing for a longer duration above MIC if fluctuation is less critical. In Augmentin Bid-875 (amoxicillin/clavulanate tablets), the Amoxicillin/clavulanate tablet is administered twice daily.

Patient compliance with multiple dose regimens may be a problem for the patient in following the prescribed dosage regimen. Occasionally, a patient may miss taking the drug dose at the prescribed dosage interval. For drugs with long elimination half-lives (e.g., levothyroxine sodium or oral contraceptives), the consequences of one missed dose are minimal, since only a small fraction of drug is lost between daily dosing intervals. The patient should either take the next drug dose as soon as the patient remembers or continue the dosing schedule starting at the next prescribed dosing period. If it is almost time for the next dose, then the skipped dose should not be taken and the regular dosing schedule should be maintained. Generally, the patient should not double the dose of the medication. For specific drug information on missed doses, USP DI II, Advice for the Patient, published annually by the United States Pharmacopeia, is a good source of information.

The problems of widely fluctuating plasma drug concentrations may be prevented by using a controlled-release formulation of the drug, or a drug in the same therapeutic class that has a long elimination half-life. The use of extended-release dosage forms allows for less frequent dosing and prevents undermedication between the last evening dose and the first morning dose. Extended-release drug products may improve patient compliance by decreasing the number of doses within a 24-hour period that the patient needs to take. Patients generally show better compliance with a twice-a-day (BID) dosage regimen compared to a three-times-a-day (TID) dosage schedule.

CLINICAL EXAMPLE

Bupropion hydrochloride (Wellbutrin) is a noradrenergic/dopaminergic antidepressant. Bupropion hydrochloride is available in 3 oral formulations. The immediate-release (IR) tablet is given 3 times a day, the sustained-release tablet (Wellbutrin SR) is given twice a day, and the extended-release tablet (Wellbutrin XL) is given once a day.

The total daily dose was 300 mg bupropion HCl. The area under the curve, AUC, for each dose treatment was similar showing that the formulations were bioequivalent based on extent of absorption. The fluctuations between peak and trough levels were greatest for the IR product given three times a day and least for the once-a-day XL product. According to the manufacturer, all three dosage regimens
Multiple-Dosage Regimens

171

will depend on the bioavailability of the drug from the drug product, the desired therapeutic drug level, and the dosage interval chosen. Assume that the antibiotic is 90% bioavailable and that the physician would like to continue oral medication every 6 hours.

The average or steady-state plasma drug level is given by

$$C_{av}^{\infty} = \frac{F D_0}{V_d k_\alpha \tau}$$

$$D_0 = \frac{(15 \mu g/mL)(196 mL/kg)(0.693)(6 h)}{(0.9)(3 h)}$$

D_0 = 454 mg/kg

Because patient C.S. weighs 76.6 kg, he should be given the following dose:

$$D_0 = (4.54 \text{ mg/kg})(76.6 \text{ kg})$$

$$D_0 = 348 \text{ mg every 6 h}$$

For drugs with equal absorption but slower absorption rates (F is the same but k_\alpha is smaller), the initial dosing period may show a lower blood level; however, the steady-state blood level will be unchanged.

2. In practice, drug products are usually commercially available in certain specified strengths. Using the information provided in the preceding problem, assume that the antibiotic is available in 125-, 250-, and 500-mg tablets. Therefore, the pharmacist or prescriber must now decide which tablets are to be given to the patient. In this case, it may be possible to give the patient 375 mg (eg, one 125-mg tablet and one 250-mg tablet) every 6 hours. However, the C_{av}^{\infty} should be calculated to determine if the plasma level is approaching a toxic value. Alternatively, a new dosage interval might be appropriate for the patient. It is very important to design the dosage interval and the dose to be as simple as possible, so that the patient will not be confused and will be able to comply with the medication program properly.

a. What is the new C_{av}^{\infty} if the patient is given 375 mg every 6 hours?
Is it possible to take a single blood sample to measure the steady-state peak plasma drug concentration measured sometime after an IV dose is given in a clinical situation?

**Solution**

\[ C_{av}^\infty = \frac{(0.9)(375,000)(3)}{(196)(76.6)(6)(0.693)} \]

\[ C_{av}^\infty = 16.2 \, \mu g/mL \]

Because the therapeutic objective was to achieve a minimum effective concentration (MEC) of 15 \( \mu g/mL \), a value of 16.2 \( \mu g/mL \) is reasonable.

b. The patient has difficulty in distinguishing tablets of different strengths. Can the patient take a 500-mg dose (eg, two 250-mg tablets)?

**Solution**

The dosage interval (\( \tau \)) for the 500-mg tablet would have to be calculated as follows:

\[ \tau = \frac{(0.9)(500,000)(3)}{(196)(76.6)(15)(0.693)} \]

\[ \tau = 8.63 \, h \]

c. A dosage interval of 8.63 hours is difficult to remember. Is a dosage regimen of 500 mg every 8 hours reasonable?

**Solution**

\[ C_{av}^\infty = \frac{(0.9)(500,000)(3)}{(196)(76.6)(8)(0.693)} \]

\[ C_{av}^\infty = 16.2 \, \mu g/mL \]

Notice that a larger dose is necessary if the drug is given at longer intervals.

In designing a dosage regimen, one should consider a regimen that is practical and convenient for the patient. For example, for good compliance, the dosage interval should be spaced conveniently for the patient. In addition, one should consider the commercially available dosage strengths of the prescribed drug product.

The use of Equation 8.17 to estimate a dosage regimen initially has wide utility. The \( C_{av}^\infty \) is equal to the dosing rate divided by the total body clearance of the drug in the patient:

\[ C_{av}^\infty = \frac{FD_0 \times 1}{\tau \times Cl_T} \] (8.47)

where \( FD_0/\tau \) is equal to the dosing rate \( R \), and \( 1/Cl_T \) is equal to \( 1/kV_D \).

In designing dosage regimens, the dosing rate \( D_0/\tau \) is adjusted for the patient’s drug clearance to obtain the desired \( C_{av}^\infty \). For an IV infusion, the zero-order rate of infusion \( (R) \) is used to obtain the desired steady-state plasma drug concentration \( C_{SS} \). If \( R \) is substituted for \( FD_0/\tau \) in Equation 8.47, then the following equation for estimating \( C_{SS} \) after an IV infusion is obtained:

\[ C_{SS} = \frac{R}{Cl_T} \] (8.48)

From Equations 8.47 and 8.48, all dosage schedules having the same dosing rate \( D_0/\tau \), or \( R \), will have the same \( C_{av}^\infty \) or \( C_{SS} \), whether the drug is given by multiple doses or by IV infusion. For example, dosage schedules of 100 mg every 4 hours, 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours will yield the same \( C_{av}^\infty \) in the patient. An IV infusion rate of 25 mg/h in the same patient will give a \( C_{SS} \) equal to the \( C_{av}^\infty \) obtained with the multiple-dose schedule (see Fig. 8-3; Table 8-6).
Multiple-Dosage Regimens

173

1 parameter compares the steady-state concentration with drug concentration after the initial dose. The plasma concentration at any time during an oral or extravascular multiple-dose regimen, for a one-compartment model and constant doses and dose interval, is dependent on 

\[ n = \text{number of doses}, \]

\[ \tau = \text{dosage interval}, \]

\[ F = \text{fraction of dose absorbed}, \]

and \[ t = \text{time after administration of } n \text{ doses}. \]

The trough steady-state concentration after multiple oral dosing is

\[ C_{\text{min}} = \frac{k_a F D_0}{\text{V}_{\text{D}} (k - k_a)} \left( \frac{1}{1 - e^{-\tau k a}} \right) e^{-\tau k_a} \]

The relationship between average steady-state concentration is related to the AUC and dosing interval.

\[ C_{\text{av}} = \frac{\int_0^\infty C_p \, dt}{\tau} = \frac{[\text{AUC}]_0}{\tau} \]

This parameter is a good measure of drug exposure.

### CHAPTER SUMMARY

The purpose of giving a loading dose is to achieve desired (therapeutic) plasma concentrations as quickly as possible. For a drug with long elimination half-life, it may take a long time (several half-lives) to achieve steady-state levels. The loading dose must be calculated appropriately based on pharmacokinetic parameters to avoid overdosing. When several doses are administered for a drug with linear kinetics, drug accumulation may occur according to the principle of superposition. Superposition allows the derivation of equations that predict the plasma drug peak and trough concentrations of a drug at steady state and the theoretical drug concentrations at any time after the dose is given. The principle of superposition is used to examine the effect of an early, late, or missing dose on steady-state drug concentration.

\[ C_{\text{max}}, C_{\text{min}}, \text{ and } C_{\text{av}} \text{ are useful parameters for monitoring the safety and efficacy of a drug during multiple dosing. A clinical example of multiple dosing using short, intermittent intravenous infusions has been applied to the aminoglycosides and is based on pharmacokinetics and clinical factors for safer dosing. The index for measuring drug accumulation during multiple dosing, } R, \text{ is related to the dosing interval and the half-life of the drug, but not the dose. This parameter compares the steady-state concentration with drug concentration after the initial dose. The plasma concentration at any time during an oral or extravascular multiple-dose regimen, for a one-compartment model and constant doses and dose interval, is dependent on } n \text{ number of doses, } \tau \text{ dosage interval, } F \text{ fraction of dose absorbed, and } t \text{ time after administration of } n \text{ doses.} \]

\[ C_p = \frac{Fk_a D_0}{\text{V}_{\text{D}} (k - k_a)} \left[ 1 - \frac{1 - e^{-\tau k a}}{1 - e^{-\tau k a}} \right] e^{-\tau k a} \]

\[ C_{\text{min}} = \frac{k_a F D_0}{\text{V}_{\text{D}} (k - k_a)} \left( \frac{1}{1 - e^{-\tau k a}} \right) e^{-\tau k_a} \]

The trough steady-state concentration after multiple oral dosing is

\[ C_{\text{av}} = \frac{\int_0^\infty C_p \, dt}{\tau} = \frac{[\text{AUC}]_0}{\tau} \]

This parameter is a good measure of drug exposure.
LEARNING QUESTIONS

1. Gentamicin has an average elimination half-life of approximately 2 hours and an apparent volume of distribution of 20% of body weight. It is necessary to give gentamicin, 1 mg/kg every 8 hours by multiple IV injections, to a 50-kg woman with normal renal function. Calculate (a) \( C_{\text{max}} \), (b) \( C_{\text{min}} \), and (c) \( C_{\text{av}} \).

2. A physician wants to give theophylline to a young male asthmatic patient (age 29, 80 kg). According to the literature, the elimination half-life for theophylline is 5 hours and the apparent \( V_D \) is equal to 50% of the body weight. The plasma level of theophylline required to provide adequate airway ventilation is approximately 10 \( \mu \)g/mL.
   a. The physician wants the patient to take medication every 6 hours around the clock. What dose of theophylline would you recommend (assume theophylline is 100% bioavailable)?
   b. If you were to find that theophylline is available to you only in 225-mg capsules, what dosage regimen would you recommend?

3. What pharmacokinetic parameter is most important in determining the time at which the steady-state plasma drug level \( (C_{\text{av}}^\infty) \) is reached?

4. Name two ways in which the fluctuations of plasma concentrations (between \( C_{\text{max}} \) and \( C_{\text{min}} \)) can be minimized for a person on a multiple-dose drug regimen without altering the \( C_{\text{av}}^\infty \).

5. What is the purpose of giving a loading dose?

6. What is the loading dose for an antibiotic \((k = 0.23 \text{ h}^{-1})\) with a maintenance dose of 200 mg every 3 hours?

7. What is the main advantage of giving a potent drug by IV infusion as opposed to multiple IV injections?

8. A drug has an elimination half-life of 2 hours and a volume of distribution of 40 L. The drug is given at a dose of 200 mg every 4 hours by multiple IV bolus injections. Predict the plasma drug concentration at 1 hour after the third dose.

9. The elimination half-life of an antibiotic is 3 hours and the apparent volume of distribution is 20% of the body weight. The therapeutic window for this drug is from 2 to 10 \( \mu \)g/mL. Adverse toxicity is often observed at drug concentrations above 15 \( \mu \)g/mL. The drug will be given by multiple IV bolus injections.
   a. Calculate the dose for an adult male patient (68 years old, 82 kg) with normal renal function to be given every 8 hours.
   b. Calculate the anticipated \( C_{\text{max}}^\infty \) and \( C_{\text{min}}^\infty \) values.
   c. Calculate the \( C_{\text{av}}^\infty \) value.
   d. Comment on the adequacy of your dosage regimen.

10. Tetracycline hydrochloride (Achromycin V, Lederle) is prescribed for a young adult male patient (28 years old, 78 kg) suffering from gonorrhea. According to the literature, tetracycline HCl is 77% orally absorbed, is 65% bound to plasma proteins, has an apparent volume of distribution of 0.5 L/kg, has an elimination half-life of 10.6 hours, and is 58% excreted unchanged in the urine. The minimum inhibitory drug concentration (MIC) for gonorrhea is 25 to 30 \( \mu \)g/mL.
   a. Calculate an exact maintenance dose for this patient to be given every 6 hours around the clock.
   b. Achromycin V is available in 250- and 500-mg capsules. How many capsules (state dose) should the patient take every 6 hours?
   c. What loading dose using the above capsules would you recommend for this patient?

11. The body clearance of sumatriptan (Imitrex) is 250 mL/min. The drug is about 14% bioavailable. What would be the average plasma drug concentration after 5 doses of 100 mg PO every 8 hours in a patient? (Assume steady state was reached.)

12. Cefotaxime has a volume of distribution of 0.17 L/kg and an elimination half-life of 1.5 hours. What is the peak plasma drug concentration in a patient weighing 75 kg after receiving 1 g IV of the drug 3 times daily for 3 days?
REFERENCES


BIBLIOGRAPHY


Chapter Objectives

- Describe the differences between linear pharmacokinetics and nonlinear pharmacokinetics.
- Illustrate nonlinear pharmacokinetics with drug disposition examples.
- Discuss some potential risks in dosing drugs that follow nonlinear kinetics.
- Explain how to detect nonlinear kinetics using AUC versus doses plots.
- Apply the appropriate equation and graphical methods, to calculate the $V_{\text{max}}$ and $k_M$ parameters after multiple dosing in a patient.
- Describe the use of the Michaelis–Menten equation to simulate the elimination of a drug by a saturable enzymatic process.
- Estimate the dose for a nonlinear drug such as phenytoin in multiple-dose regimens.
- Describe chronopharmacokinetics, time-dependent pharmacokinetics, and its influence on drug disposition.

Previous chapters discussed linear pharmacokinetic models using simple first-order kinetics to describe the course of drug disposition and action. These linear models assumed that the pharmacokinetic parameters for a drug would not change when different doses or multiple doses of a drug were given. With some drugs, increased doses or chronic medication can cause deviations from the linear pharmacokinetic profile previously observed with single low doses of the same drug. This nonlinear pharmacokinetic behavior is also termed dose-dependent pharmacokinetics.

Many of the processes of drug absorption, distribution, biotransformation, and excretion involve enzymes or carrier-mediated systems. For some drugs given at therapeutic levels, one of these specialized processes may become saturated. As shown in Table 9-1, various causes of nonlinear pharmacokinetic behavior are theoretically possible. Besides saturation of plasma protein-binding or carrier-mediated systems, drugs may demonstrate nonlinear pharmacokinetics due to a pathologic alteration in drug absorption, distribution, and elimination. For example, aminoglycosides may cause renal nephrotoxicity, thereby altering renal drug excretion. In addition, gallstone obstruction of the bile duct will alter biliary drug excretion. In most cases, the main pharmacokinetic outcome is a change in the apparent elimination rate constant.

A number of drugs demonstrate saturation or capacity-limited metabolism in humans. Examples of these saturable metabolic processes include glycine conjugation of salicylate, sulfate conjugation of salicylamide, acetylation of $p$-aminobenzoic acid, and the elimination of phenytoin (Tozer et al, 1981). Drugs that demonstrate saturation kinetics usually show the following characteristics.

1. Elimination of drug does not follow simple first-order kinetics—that is, elimination kinetics are nonlinear.
2. The elimination half-life changes as dose is increased. Usually, the elimination half-life increases with increased dose due to saturation of an enzyme system. However, the elimination half-life might decrease due to “self”-induction of liver biotransformation enzymes, as is observed for carbamazepine.
3. The area under the curve (AUC) is not proportional to the amount of bioavailable drug.
4. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (i.e., competition effects).
5. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose.

### TABLE 9-1 Examples of Drugs Showing Nonlinear Kinetics

<table>
<thead>
<tr>
<th>Cause</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl Absorption</td>
<td></td>
</tr>
<tr>
<td>Saturable transport in gut wall</td>
<td>Riboflavin, gabapentin, l-dopa, baclofen, ceftibuten</td>
</tr>
<tr>
<td>Intestinal metabolism</td>
<td>Salicylamide, propranolol</td>
</tr>
<tr>
<td>Drugs with low solubility in GI but relatively high dose</td>
<td>Chorothiazide, griseofulvin, danazol</td>
</tr>
<tr>
<td>Saturable gastric or GI decomposition</td>
<td>Penicillin G, omeprazole, saquinavir</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>Saturable plasma protein binding</td>
<td>Phenylbutazone, lidocaine, salicylic acid, ceftriaxone, diazoxide, phenytoin, warfarin, disopyramide</td>
</tr>
<tr>
<td>Cellular uptake</td>
<td>Methicillin (rabbit)</td>
</tr>
<tr>
<td>Tissue binding</td>
<td>Imiprimine (rat)</td>
</tr>
<tr>
<td>CSF transport</td>
<td>Benzylpenicillins</td>
</tr>
<tr>
<td>Saturable transport into or out of tissues</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Renal Elimination</td>
<td></td>
</tr>
<tr>
<td>Active secretion</td>
<td>Mezlocillin, para-aminohippuric acid</td>
</tr>
<tr>
<td>Tubular reabsorption</td>
<td>Riboflavin, ascorbic acid, cephaolin</td>
</tr>
<tr>
<td>Change in urine pH</td>
<td>Salicylic acid, dextroamphetamine</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
</tr>
<tr>
<td>Saturable metabolism</td>
<td>Phenytoin, salicylic acid, theophylline, valproic acid(^b)</td>
</tr>
<tr>
<td>Cofactor or enzyme limitation</td>
<td>Acetaminophen, alcohol</td>
</tr>
<tr>
<td>Enzyme induction</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Altered hepatic blood flow</td>
<td>Propranolol, verapamil</td>
</tr>
<tr>
<td>Metabolite inhibition</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Biliary Excretion</td>
<td></td>
</tr>
<tr>
<td>Biliary secretion</td>
<td>Iodipamide, sulfochromophthalein sodium</td>
</tr>
<tr>
<td>Enterohepatic recycling</td>
<td>Cimetidine, isotretinoin</td>
</tr>
</tbody>
</table>

\(^a\) Hypothermia, metabolic acidosis, altered cardiovascular function, and coma are additional causes of dose and time dependencies in drug overdose.

\(^b\) In guinea pig and probably in some younger subjects.

Because these drugs have a changing apparent elimination constant with larger doses, prediction of drug concentration in the blood based on a single small dose is difficult. Drug concentrations in the blood can increase rapidly once an elimination process is saturated. In general, metabolism (biotransformation) and active tubular secretion of drugs by the kidney are the processes most usually saturated. Figure 9-1 shows plasma level–time curves for a drug that exhibits saturable kinetics. When a large dose is given, a curve is obtained with an initial slow elimination phase followed by a much more rapid elimination at lower blood concentrations (curve A). With a small dose of the drug, apparent first-order kinetics is observed, because no saturation kinetics occurs (curve B). If the pharmacokinetic data were estimated only from the blood levels described by curve B, then a twofold increase in the dose would give the blood profile presented in curve C, which considerably underestimates the drug concentration as well as the duration of action.

In order to determine whether a drug is following dose-dependent kinetics, the drug is given at various dosage levels and a plasma level–time curve is obtained for each dose. The curves should exhibit parallel slopes if the drug follows dose-independent kinetics. Alternatively, a plot of the areas under the plasma level–time curves at various doses should be linear (Fig. 9-2).

**SATURABLE ENZYMATIC ELIMINATION PROCESSES**

The elimination of drug by a saturable enzymatic process is described by Michaelis–Menten kinetics. If \( C_p \) is the concentration of drug in the plasma, then

\[
\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{\text{max}} C_p}{K_M + C_p} \quad (9.1)
\]

where \( V_{\text{max}} \) is the maximum elimination rate and \( K_M \) is the Michaelis constant that reflects the capacity of the enzyme system. It is important to note that \( K_M \) is not an elimination constant, but is actually a hybrid rate constant in enzyme kinetics, representing both the forward and backward reaction rates and equal to the drug concentration or amount of drug in the body at \( 0.5V_{\text{max}} \). The values for \( K_M \) and \( V_{\text{max}} \) are dependent on the nature of the drug and the enzymatic process involved.

The elimination rate of a hypothetical drug with a \( K_M \) of 0.1 µg/mL and a \( V_{\text{max}} \) of 0.5 µg/mL per hour is calculated in Table 9-2 by means of Equation 9.1. Because the ratio of the elimination rate to drug concentration changes as the drug concentration changes (ie, \( dC / dt \) is not constant, Equation 9.1), the rate of drug elimination also changes and is not a first-order or linear process. In contrast, a first-order elimination process would yield the same elimination rate constant at all plasma drug concentrations. At drug concentrations of 0.4 to 10 µg/mL, the enzyme system is not saturated and the rate of elimination is a
PRACTICE PROBLEM

Using the hypothetical drug considered in Table 9-2 ($V_{\text{max}} = 0.5 \mu g/mL$ per hour, $K_M = 0.1 \mu g/mL$), how long would it take for the plasma drug concentration to decrease from 20 to 12 $\mu g/mL$?

Solution

Because 12 $\mu g/mL$ is above the saturable level, as indicated in Table 9-2, elimination occurs at a zero-order rate of approximately 0.5 $\mu g/mL$ per hour.

Time needed for the drug to decrease to

$$12 \mu g/mL = \frac{20 - 12 \mu g}{0.5 \mu g/h} = 16 \text{ h}$$

A saturable process can also exhibit linear elimination when drug concentrations are much less than enzyme concentrations. When the drug concentration $C_p$ is small in relation to $K_M$ ($C_p \ll K_M$), the rate of drug elimination becomes a first-order process. The data generated from Equation 9.2 ($C_p \leq 0.05 \mu g/mL$, Table 9-3) using $K_M = 0.8 \mu g/mL$ and $V_{\text{max}} = 0.9 \mu g/mL$.

### Table 9-2: Effect of Drug Concentration on the Elimination Rate and Rate Constant

<table>
<thead>
<tr>
<th>Drug Concentration ($\mu g/mL$)</th>
<th>Elimination Rate ($\mu g/mL/h$)</th>
<th>Elimination Rate/Concentration ($h^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.400</td>
<td>1.000</td>
</tr>
<tr>
<td>0.8</td>
<td>0.444</td>
<td>0.556</td>
</tr>
<tr>
<td>1.2</td>
<td>0.462</td>
<td>0.385</td>
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<tr>
<td>1.6</td>
<td>0.472</td>
<td>0.294</td>
</tr>
<tr>
<td>2.0</td>
<td>0.476</td>
<td>0.238</td>
</tr>
<tr>
<td>2.4</td>
<td>0.480</td>
<td>0.200</td>
</tr>
<tr>
<td>2.8</td>
<td>0.483</td>
<td>0.172</td>
</tr>
<tr>
<td>3.2</td>
<td>0.485</td>
<td>0.152</td>
</tr>
<tr>
<td>10.0</td>
<td>0.495</td>
<td>0.0495</td>
</tr>
<tr>
<td>10.4</td>
<td>0.495</td>
<td>0.0476</td>
</tr>
<tr>
<td>10.8</td>
<td>0.495</td>
<td>0.0459</td>
</tr>
<tr>
<td>11.2</td>
<td>0.496</td>
<td>0.0442</td>
</tr>
<tr>
<td>11.6</td>
<td>0.496</td>
<td>0.0427</td>
</tr>
</tbody>
</table>

$aK_M = 0.1 \mu g/mL, V_{\text{max}} = 0.5 \mu g/mL/h.$

$b$The ratio of the elimination rate to the concentration is equal to the rate constant.

### Table 9-3: Effect of Drug Concentration on the Elimination Rate and Rate Constant

<table>
<thead>
<tr>
<th>Drug Concentration ($C_p$) ($\mu g/mL$)</th>
<th>Elimination Rate ($\mu g/mL/h$)</th>
<th>Elimination Rate Concentration ($h^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.011</td>
<td>1.1</td>
</tr>
<tr>
<td>0.02</td>
<td>0.022</td>
<td>1.1</td>
</tr>
<tr>
<td>0.03</td>
<td>0.033</td>
<td>1.1</td>
</tr>
<tr>
<td>0.04</td>
<td>0.043</td>
<td>1.1</td>
</tr>
<tr>
<td>0.05</td>
<td>0.053</td>
<td>1.1</td>
</tr>
<tr>
<td>0.06</td>
<td>0.063</td>
<td>1.0</td>
</tr>
<tr>
<td>0.07</td>
<td>0.072</td>
<td>1.0</td>
</tr>
<tr>
<td>0.08</td>
<td>0.082</td>
<td>1.0</td>
</tr>
<tr>
<td>0.09</td>
<td>0.091</td>
<td>1.0</td>
</tr>
</tbody>
</table>

$aK_M = 0.8 \mu g/mL, V_{\text{max}} = 0.9 \mu g/mL/h.$

$b$The ratio of the elimination rate to the concentration is equal to the rate constant.

mixed or nonlinear process (Table 9-2). At higher drug concentrations, 11.2 $\mu g/mL$ and above, the elimination rate approaches the maximum velocity ($V_{\text{max}}$) of approximately 0.5 $\mu g/mL$ per hour. At $V_{\text{max}}$, the elimination rate is a constant and is considered a zero-order process.

Equation 9.1 describes a nonlinear enzyme process that encompasses a broad range of drug concentrations. When the drug concentration $C_p$ is large in relation to $K_M$ ($C_p \gg K_M$), saturation of the enzymes occurs and the value for $K_M$ is negligible. The rate of elimination proceeds at a fixed or constant rate equal to $V_{\text{max}}$. Thus, elimination of drug becomes a zero-order process and Equation 9.1 becomes:

$$-\frac{dC_p}{dt} = \frac{V_{\text{max}}C_p}{C_p} = V_{\text{max}}$$  \hspace{1cm} (9.2)
per hour shows that enzymatic drug elimination can change from a nonlinear to a linear process over a restricted concentration range. This is evident because the rate constant (or elimination rate/drug concentration) values are constant. At drug concentrations below 0.05 μg/mL, the ratio of elimination rate to drug concentration has a constant value of 1.1 h⁻¹. Mathematically, when \( C_p \) is much smaller than \( K_M \), \( C_p \) in the denominator is negligible and the elimination rate becomes first order.

\[
\frac{-dC_p}{dt} = \frac{V_{\text{max}} C_p}{C_p + K_M} = \frac{V_{\text{max}}}{K_M} C_p
\]

(9.3)

The first-order rate constant for a saturable process, \( k' \), can be calculated from Equation 9.3:

\[
k' = \frac{V_{\text{max}}}{K_M} = 0.9 \quad \rightarrow \quad 1.1 \text{ h}^{-1}
\]

This calculation confirms the data in Table 9-3, because enzymatic drug elimination at drug concentrations below 0.05 μg/mL is a first-order rate process with a rate constant of 1.1 h⁻¹. Therefore, the \( t_{1/2} \) due to enzymatic elimination can be calculated:

\[
t_{1/2} = \frac{0.693}{1.1} = 0.63 \text{ h}
\]

**PRACTICE PROBLEM**

How long would it take for the plasma concentration of the drug in Table 9-3 to decline from 0.05 to 0.005 μg/mL?

**Solution**

Because drug elimination is a first-order process for the specified concentrations,

\[
C_p = C_p^0 e^{-kt}
\]

\[
\log C_p = C_p^0 - \frac{kt}{2.3}
\]

\[
t = \frac{\log C - \log C_p^0}{k}
\]

Because \( C_p^0 = 0.05 \) μg/mL, \( k = 1.1 \) h⁻¹, and \( C_p = 0.005 \) μg/mL,

\[
t = \frac{2.3(\log 0.05 - \log 0.005)}{1.1}
\]

\[
= \frac{2.3(-1.30 + 2.3)}{1.1}
\]

\[
= \frac{2.3}{1.1} = 2.09 \text{ h}
\]

When given in therapeutic doses, most drugs produce plasma drug concentrations well below \( K_M \) for all carrier-mediated enzyme systems affecting the pharmacokinetics of the drug. Therefore, most drugs at normal therapeutic concentrations follow first-order rate processes. Only a few drugs, such as salicylate and phenytoin, tend to saturate the hepatic mixed-function oxidases at higher therapeutic doses. With these drugs, elimination kinetics is first-order with very small doses, mixed order at higher doses, and may approach zero-order with very high therapeutic doses.

**Frequently Asked Questions**

**What kinetic processes in the body can be considered saturable?**

**Why is it important to monitor drug levels carefully for dose dependency?**

**DRUG ELIMINATION BY CAPACITY-LIMITED PHARMACOKINETICS: ONE-COMPARTMENT MODEL, IV BOLUS INJECTION**

The rate of elimination of a drug that follows capacity-limited pharmacokinetics is governed by the \( V_{\text{max}} \) and \( K_M \) of the drug. Equation 9.1 describes the elimination of a drug that distributes in the body as a single compartment and is eliminated by Michaelis–Menten or capacity-limited pharmacokinetics. If a single IV bolus injection of drug (\( D_p \)) is given at \( t = 0 \), the drug concentration (\( C_p \)) in the plasma at any
Chapter 9

time $t$ may be calculated by an integrated form of Equation 9.1 described by

$$\frac{C_0 - C_p}{t} = V_{\text{max}} \left( -\frac{K_M}{t} \ln \left( \frac{C_0}{C_p} \right) \right)$$  (9.4)

Alternatively, the amount of drug in the body after an IV bolus injection may be calculated by the following relationship. Equation 9.5 may be used to simulate the decline of drug in the body after various size doses are given, provided the $K_M$ and $V_{\text{max}}$ of drug are known.

$$\frac{D_0 - D_t}{t} = V_{\text{max}} \left( -\frac{K_M}{t} \ln \frac{D_0}{D_t} \right)$$  (9.5)

where $D_0$ is the amount of drug in the body at $t = 0$.

In order to calculate the time for the dose of the drug to decline to a certain amount of drug in the body, Equation 9.5 must be rearranged and solved for time $t$:

$$t = \frac{1}{V_{\text{max}}} \left( D_0 - D_t + K_M \ln \frac{D_0}{D_t} \right)$$  (9.6)

The relationship of $K_M$ and $V_{\text{max}}$ to the time for an IV bolus injection of drug to decline to a given amount of drug in the body is illustrated in Figs. 9-3 and 9-4. Using Equation 9.6, the time for a single 400-mg dose given by IV bolus injection to decline to 20 mg was calculated for a drug with a $K_M$ of 38 mg/L and a $V_{\text{max}}$ that varied from 200 to 100 mg/h (Table 9-4). With a $V_{\text{max}}$ of 200 mg/h, the time for the 400-mg dose to decline to 20 mg in the body is 2.46 hours, whereas when the $V_{\text{max}}$ is decreased to 100 mg/h, the time for the 400-mg dose to decrease to 20 mg is increased to 4.93 hours (see Fig. 9-3). Thus, there is an inverse relationship between the time for the dose to decline to a certain amount of drug in the body and the $V_{\text{max}}$ as shown in Equation 9.6.

Using a similar example, the effect of $K_M$ on the time for a single 400-mg dose given by IV bolus injection to decline to 20 mg in the body is described in Table 9-5 and Fig. 9-4. Assuming $V_{\text{max}}$ is constant at 200 mg/h, the time for the drug to decline from 400 to 20 mg is 2.46 hours when $K_M$ is 38 mg/L, whereas when $K_M$ is 76 mg/L, the time for the drug dose to decline to 20 mg is 3.03 hours. Thus, an increase in $K_M$ (with no change in $V_{\text{max}}$) will increase the time for the drug to be eliminated from the body.

The one-compartment open model with capacity-limited elimination pharmacokinetics adequately describes the plasma drug concentration–time profiles for some drugs. The mathematics needed to describe nonlinear pharmacokinetic behavior of drugs that follow two-compartment models and/or have both combined capacity-limited and first-order kinetic profiles are very complex and have little practical application for dosage calculations and therapeutic drug monitoring.
Nonlinear Pharmacokinetics

183

injection, calculate the time for 50% of the dose to be eliminated. Explain why there is a difference in the time for 50% elimination of a 400-mg dose compared to a 320-mg dose.

Solution

Use Equation 9.6 to calculate the time for the dose to decline to a given amount of drug in the

### TABLE 9-4 Capacity-Limited Pharmacokinetics: Effect of $V_{\text{max}}$ on the Elimination of Drug

<table>
<thead>
<tr>
<th>Amount of Drug in Body (mg)</th>
<th>$V_{\text{max}} = 200$ mg/h</th>
<th>$V_{\text{max}} = 100$ mg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>380</td>
<td>0.109</td>
<td>0.219</td>
</tr>
<tr>
<td>360</td>
<td>0.220</td>
<td>0.440</td>
</tr>
<tr>
<td>340</td>
<td>0.330</td>
<td>0.661</td>
</tr>
<tr>
<td>320</td>
<td>0.442</td>
<td>0.884</td>
</tr>
<tr>
<td>300</td>
<td>0.554</td>
<td>1.10</td>
</tr>
<tr>
<td>280</td>
<td>0.667</td>
<td>1.33</td>
</tr>
<tr>
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<td>1.56</td>
</tr>
<tr>
<td>240</td>
<td>0.897</td>
<td>1.79</td>
</tr>
<tr>
<td>220</td>
<td>1.01</td>
<td>2.02</td>
</tr>
<tr>
<td>200</td>
<td>1.13</td>
<td>2.26</td>
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<td>180</td>
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<td>120</td>
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<tr>
<td>100</td>
<td>1.76</td>
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<tr>
<td>40</td>
<td>2.23</td>
<td>4.47</td>
</tr>
<tr>
<td>20</td>
<td>2.46</td>
<td>4.93</td>
</tr>
</tbody>
</table>

### TABLE 9-5 Capacity-Limited Pharmacokinetics: Effects of $K_M$ on the Elimination of Drug

<table>
<thead>
<tr>
<th>Amount of Drug in Body (mg)</th>
<th>$K_M = 38$ mg/L</th>
<th>$K_M = 76$ mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>380</td>
<td>0.109</td>
<td>0.119</td>
</tr>
<tr>
<td>360</td>
<td>0.220</td>
<td>0.240</td>
</tr>
<tr>
<td>340</td>
<td>0.330</td>
<td>0.361</td>
</tr>
<tr>
<td>320</td>
<td>0.442</td>
<td>0.484</td>
</tr>
<tr>
<td>300</td>
<td>0.554</td>
<td>0.609</td>
</tr>
<tr>
<td>280</td>
<td>0.667</td>
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</tr>
<tr>
<td>20</td>
<td>2.46</td>
<td>3.03</td>
</tr>
</tbody>
</table>

*A single 400-mg dose is given by IV bolus injection. The drug is distributed into a single compartment and is eliminated by capacity-limited pharmacokinetics. $K_M$ is 38 mg/L. The time for drug to decline from 400 to 20 mg is calculated from Equation 9.6 assuming the drug has $V_{\text{max}} = 200$ mg/h or $V_{\text{max}} = 100$ mg/h.

*A single 400-mg dose is given by IV bolus injection. The drug is distributed into a single compartment and is eliminated by capacity-limited pharmacokinetics. $V_{\text{max}}$ is 200 mg/h. The time for drug to decline from 400 to 20 mg is calculated from Equation 9.6 assuming the drug has $K_M = 38$ mg/L or $K_M = 76$ mg/L.

### PRACTICE PROBLEMS

1. A drug eliminated from the body by capacity-limited pharmacokinetics has a $K_M$ of 100 mg/L and a $V_{\text{max}}$ of 50 mg/h. If 400 mg of the drug is given to a patient by IV bolus injection, calculate the time for the drug to be 50% eliminated. If 320 mg of the drug is to be given by IV bolus injection, calculate the time for 50% of the dose to be eliminated. Explain why there is a difference in the time for 50% elimination of a 400-mg dose compared to a 320-mg dose.

Solution

Use Equation 9.6 to calculate the time for the dose to decline to a given amount of drug in the
body. For this problem, $D_t$ is equal to 50% of the dose $D_0$.

If the dose is 400 mg,
$$t = \frac{1}{50} \left( 400 - 200 + 100 \ln \frac{400}{200} \right) = 5.39 \text{ h}$$

If the dose is 320 mg,
$$t = \frac{1}{50} \left( 320 - 160 + 100 \ln \frac{320}{160} \right) = 4.59 \text{ h}$$

For capacity-limited elimination, the elimination half-life is dose dependent, because the drug elimination process is partially saturated. Therefore, small changes in the dose will produce large differences in the time for 50% drug elimination. The parameters $K_M$ and $V_{\text{max}}$ determine when the dose is saturated.

2. Using the same drug as in Problem 1, calculate the time for 50% elimination of the dose when the doses are 10 and 5 mg. Explain why the times for 50% drug elimination are similar even though the dose is reduced by one-half.

**Solution**

As in Practice Problem 1, use Equation 9.6 to calculate the time for the amount of drug in the body at zero time ($D_0$) to decline 50%.

If the dose is 10 mg,
$$t = \frac{1}{50} \left( 10 - 5 + 100 \ln \frac{10}{5} \right) = 1.49 \text{ h}$$

If the dose is 5 mg,
$$t = \frac{1}{50} \left( 5 - 2.5 + 100 \ln \frac{5}{2.5} \right) = 1.44 \text{ h}$$

Whether the patient is given a 10- or a 5-mg dose by IV bolus injection, the times for the amount of drug to decline 50% are approximately the same. For 10- and 5-mg doses the amount of drug in the body is much less than the $K_M$ of 100 mg. Therefore, the amount of drug in the body is well below saturation of the elimination process and the drug declines at a first-order rate.

---

**Determination of $K_M$ and $V_{\text{max}}$**

Equation 9.1 relates the rate of drug biotransformation to the concentration of the drug in the body. The same equation may be applied to determine the rate of enzymatic reaction of a drug in vitro (Equation 9.7). When an experiment is performed with solutions of various concentration of drug $C$, a series of reaction rates ($\nu$) may be measured for each concentration. Special plots may then be used to determine $K_M$ and $V_{\text{max}}$ (see also Chapter 11).

Equation 9.7 may be rearranged into Equation 9.8.

$$\nu = \frac{V_{\text{max}} C}{K_M + C} \quad (9.7)$$

$$\frac{1}{\nu} = \frac{1}{V_{\text{max}}} \frac{1}{C} + \frac{1}{V_{\text{max}}} \quad (9.8)$$

Equation 9.8 is a linear equation when $1/\nu$ is plotted against $1/C$. The y intercept for the line is $1/V_{\text{max}}$, and the slope is $K_M/V_{\text{max}}$. An example of a drug reacting enzymatically with rate ($\nu$) at various concentrations $C$ is shown in Table 9-6 and Fig. 9-5. A plot of $1/\nu$ versus $1/C$ is shown in Fig. 9-6. A plot of $1/\nu$ versus $1/C$ is linear with an intercept of 0.33 mmol.

Thus, $K_M/V_{\text{max}} = 0.33 \text{ mmol}$, because the slope is $1.65 = K_M/V_{\text{max}} = K_M/3$ or $K_M = 3 \times 1.65 \mu\text{mol/mL} = 5 \mu\text{mol/mL}$. Alternatively, $K_M$
Nonlinear Pharmacokinetics

\[ \frac{C}{v} = \frac{1}{V_{\text{max}}} C + \frac{K_m}{V_{\text{max}}} \]  

\[ 9.9 \]

A plot of \( C/v \) versus \( C \) would yield a straight line with \( 1/V_{\text{max}} \) as slope and \( K_m/V_{\text{max}} \) as intercept (Equation 9.9). A plot of \( v \) versus \( v/C \) would yield a slope of \(-K_m\) and an intercept of \( V_{\text{max}} \) (Equation 9.10).

The necessary calculations for making the above plots are shown in Table 9-7. The plots are shown in Figs. 9-7 and 9-8. It should be noted that the data are spread out better by the two latter plots. Calculations from the slope show that the same \( K_m \) and \( V_{\text{max}} \) are obtained as in Fig. 9-6. When the data are more spread out, the latter methods are preferable.

\[ v = -K_m \frac{v}{C} + V_{\text{max}} \]  

\[ 9.10 \]

### TABLE 9-6 Information Necessary for Graphic Determination of \( V_{\text{max}} \) and \( K_m \)

<table>
<thead>
<tr>
<th>Observation Number</th>
<th>( C ) (μM/mL)</th>
<th>( V ) (μM/mL/min)</th>
<th>( 1/V ) (mL/min/μM)</th>
<th>( 1/C ) (mL/μM)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>0.500</td>
<td>2.000</td>
<td>1.000</td>
</tr>
<tr>
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<td>6</td>
<td>1.636</td>
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</tr>
<tr>
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Chapter 9

compartment in which the drug is dissolved. The rate of drug metabolism will vary depending on the concentration of drug \( C_p \) as well as on the metabolic rate constants \( K_M \) and \( V_{max} \) of the drug in each individual.

An example for the determination of \( K_M \) and \( V_{max} \) is given for the drug phenytoin. Phenytoin undergoes capacity-limited kinetics at therapeutic drug concentrations in the body. To determine \( K_M \) and \( V_{max} \), two different dose regimens are given at different times, until steady state is reached. The steady-state drug concentrations are then measured by assay. At steady state, the rate of drug metabolism (\( v \)) is assumed to be the same as the rate of drug input \( R \) (dose/day). Therefore Equation 9.11 may be written for drug metabolism in the body similar to the way drugs are metabolized in vitro (Eq. 9.7). However, steady state will not be reached if the drug input rate, \( R \), is greater than the \( V_{max} \); instead, drug accumulation will continue to occur without reaching a steady-state plateau.

\[
R = \frac{V_{max} C_{SS}}{K_M + C_{SS}} \tag{9.11}
\]

where \( R \) = dose/day or dosing rate, \( C_{SS} \) = steady-state plasma drug concentration, \( V_{max} \) = maximum metabolic rate constant in the body, and \( K_M \) = Michaelis–Menten constant of the drug in the body.

### Example

Phenytoin was administered to a patient at dosing rates of 150 and 300 mg/d, respectively. The steady-state plasma drug concentrations were 8.6 and 25.1 mg/L, respectively. Find the \( K_M \) and \( V_{max} \) of this patient. What dose is needed to achieve a steady-state concentration of 11.3 mg/L?

**Solution**

There are three methods for solving this problem, all based on the same basic equation (Equation 9.11).

**Method A**

Inverting Equation 9.11 on both sides yields

\[
\frac{1}{R} = \frac{K_M}{V_{max} C_{SS}} + \frac{1}{V_{max}} \tag{9.12}
\]
Multiply both sides by $C_{ss} V_{\text{max}}$

$$ \frac{V_{\text{max}} C_{ss}}{R} = K_M + C_{ss} $$

Rearrange.

$$ C_{ss} = \frac{V_{\text{max}} C_{ss}}{R} - K_M $$

(9.13)

A plot of $C_{ss}$ versus $C_{ss}/R$ is shown in Fig. 9-9. $V_{\text{max}}$ is equal to the slope, 630 mg/d, and $K_M$ is found from the $y$ intercept, 27.6 mg/L (note the negative intercept).

**Method B**

From Equation 9.11,

$$ R K_M + R C_{ss} = V_{\text{max}} C_{ss} $$

Dividing both sides by $C_{ss}$ yields

$$ R = V_{\text{max}} - \frac{K_M R}{C_{ss}} $$

(9.14)

A plot of $R$ versus $R/C_{ss}$ is shown in Fig. 9-10. The $K_M$ and $V_{\text{max}}$ found are similar to those calculated by the previous method (Fig. 9-9).

**Method C**

A plot of $R$ versus $C_{ss}$ is shown in Fig. 9-11. To determine $K_M$ and $V_{\text{max}}$

1. Mark points for $R$ of 300 mg/d and $C_{ss}$ of 25.1 mg/L as shown. Connect with a straight line.
2. Mark points for $R$ of 150 mg/d and $C_{ss}$ of 8.6 mg/L as shown. Connect with a straight line.
3. The point where lines from the first two steps cross is called point A.
4. From point A, read $V_{\text{max}}$ on the $y$ axis and $K_M$ on the $x$ axis. (Again, $V_{\text{max}}$ of 630 mg/d and $K_M$ of 27 mg/L are found.)

This $V_{\text{max}}$ and $K_M$ can be used in Equation 9.11 to find an $R$ to produce the desired $C_{ss}$ of 11.3 mg/L. Alternatively, join point A on the graph to meet 11.3 mg/L on the $x$ axis; $R$ can be read where this line meets the $y$ axis (190 mg/d).

To calculate the dose needed to keep steady-state phenytoin concentration of 11.3 mg/L in this patient, use Equation 9.7.

$$ R = \frac{(630 \text{ mg/d})(11.3 \text{ mg/L})}{27 \text{ mg/L} + 11.3 \text{ mg/L}} $$

$$ = \frac{7119}{38.3} = 186 \text{ mg/day} $$

This answer compares very closely with the value obtained by the graphic method. All three methods have been used clinically. Vozeh et al (1981) introduced a method that allows for an estimation of phenytoin dose based on steady-state concentration resulting from one dose. This method is based on a statistically compiled nomogram that makes it possible to project a most likely dose for the patient.

**Determination of $K_M$ and $V_{\text{max}}$ by Direct Method**

When steady-state concentrations of phenytoin are known at only two dose levels, there is no advantage...
Combining the two equations yields Equation 9.15.

\[ R_2 = \frac{V_{\text{max}} C_2}{K_M + C_2} \]

where \( C_1 \) is steady-state plasma drug concentration after dose 1, \( C_2 \) is steady-state plasma drug concentration after dose 2, \( R_1 \) is the first dosing rate, and \( R_2 \) is the second dosing rate. To calculate \( K_M \) and \( V_{\text{max}} \), use Equation 9.15 with the values \( C_1 = 8.6 \) mg/L, \( C_2 = 25.1 \) mg/L, \( R_1 = 150 \) mg/d, and \( R_2 = 300 \) mg/d. The results are

\[ K_M = \frac{300 - 150}{(150/8.6) - (300/25.1)} = 27.3 \text{ mg/L} \]

Substitute \( K_M \) into either of the two simultaneous equations to solve for \( V_{\text{max}} \).

\[ 150 = \frac{V_{\text{max}} (8.6)}{27.3 + 8.6} \]
\[ V_{\text{max}} = 626 \text{ mg/d} \]

**Interpretation of \( K_M \) and \( V_{\text{max}} \)**

An understanding of Michaelis–Menten kinetics provides insight into the nonlinear kinetics and helps avoid dosing a drug at a concentration near enzyme saturation. For example, in the above phenytoin dosing example, since \( K_M \) occurs at 0.5\( V_{\text{max}} \), \( K_M = 27.3 \) mg/L, the implication is that at a plasma concentration of 27.3 mg/L, enzymes responsible for phenytoin metabolism are eliminating the drug at 50% \( V_{\text{max}} \), i.e., 0.5 \times 626 mg/day or 313 mg/day. When the subject is receiving 300 mg of phenytoin per day, the plasma drug concentration of phenytoin is 8.6 mg/L, which is considerably below the \( K_M \) of 27.3 mg/L. In practice, the \( K_M \) in patients can range from 1 to 15 mg/L, \( V_{\text{max}} \) can range from 100 to 1000 mg/d. Patients with a low \( K_M \) tend to have greater changes in plasma concentrations during dosing adjustments. Patients with a smaller \( K_M \) (same \( V_{\text{max}} \)) will show a greater change in the rate of elimination when plasma drug concentration changes compared to
Nonlinear Pharmacokinetics

189

because the elimination half-life is not constant. Clinically, if the half-life is increasing as plasma concentration increases, and there is no apparent change in metabolic or renal function, then there is a good possibility that the drug may be metabolized by nonlinear kinetics.

Dependence of Clearance on Dose

The total body clearance of a drug given by IV bolus injection that follows a one-compartment model with Michaelis–Menten elimination kinetics changes with respect to time and plasma drug concentration. Within a certain drug concentration range, an average or mean clearance ($Cl_{av}$) may be determined. Because the drug follows Michaelis–Menten kinetics, $Cl_{av}$ is dose dependent. $Cl_{av}$ may be estimated from the area under the curve and the dose given (Wagner et al, 1985).

According to the Michaelis–Menten equation,

$$\frac{dC_p}{dt} = \frac{V_{max} C_p}{K_{M} + C_p} \quad (9.17)$$

Inverting Equation 9.17 and rearranging yields

$$C_p dt = \frac{V_{max} C_p}{K_{M}} dC_p - \frac{C_p}{V_{max}} dC_p \quad (9.18)$$

The area under the curve, [AUC]$_{tu}$, is obtained by integration of Equation 9.18 (ie, [AUC]$_{tu}$ = $\int_0^t C_p dt$).

$$\int_0^{\infty} C_p dt = \int_{C_p^{\beta}}^{K_{M}} dC_p \frac{K_{M}}{V_{max}} - \int_{C_p^{\beta}}^{V_{max}} dC_p \frac{C_p}{V_{max}} \quad (9.19)$$

where $V'$ is the maximum velocity for metabolism. Units for $V_{max}^{\max}$ are mass/compartment volume per unit time. $V_{max}^{max} = V_{max}/V_D$. Wagner et al (1985) used $V_{max}$ in Equation 9.20 as mass/time to be consistent with biochemistry literature, which considers the initial mass of the substrate reacting with the enzyme.

Integration of Equation 9.18 from time 0 to infinity gives Equation 9.20.

$$[\text{AUC}]_{tu} = \frac{C_p^\beta}{V_{max}/V_D} \left( \frac{C_p^\beta}{2} + K_{M} \right) \quad (9.20)$$

where $V_D$ is the apparent volume of distribution.

Dependence of Elimination Half-Life on Dose

For drugs that follow linear kinetics, the elimination half-life is constant and does not change with dose or drug concentration. For a drug that follows nonlinear kinetics, the elimination half-life and drug clearance both change with dose or drug concentration. Generally, the elimination half-life becomes longer, clearance becomes smaller, and the area under the curve becomes disproportionately larger with increasing dose. The relationship between elimination half-life and drug concentration is shown in Equation 9.16. The elimination half-life is dependent on the Michaelis–Menten parameters and concentration.

$$t_{1/2} = \frac{0.693}{V_{max}} (K_{M} + C_p) \quad (9.16)$$

Some pharmacokineticists prefer not to calculate the elimination half-life of a nonlinear drug because the elimination half-life is not constant. Clinically, if the half-life is increasing as plasma concentration increases, and there is no apparent change in metabolic or renal function, then there is a good possibility that the drug may be metabolized by nonlinear kinetics.

![Diagram showing the rate of metabolism when $V_{max}$ is constant (8 μg/ml/h) and $K_{M}$ is changed ($K_{M} = 2$ μg/ml for top curve and $K_{M} = 4$ μg/ml for bottom curve). Note the rate of metabolism is faster for the lower $K_{M}$, but saturation starts at lower concentration.](image)

**FIGURE 9-12** Diagram showing the rate of metabolism when $V_{max}$ is constant (8 μg/ml/h) and $K_{M}$ is changed ($K_{M} = 2$ μg/ml for top curve and $K_{M} = 4$ μg/ml for bottom curve). Note the rate of metabolism is faster for the lower $K_{M}$, but saturation starts at lower concentration.
Because the dose $D_0 = C_p^0 V_p$, Equation 9.20 may be expressed as

$$\text{[AUC]}_0^\infty = \frac{D_0}{V_{\max}} \left( \frac{C_p^0}{2} + K_M \right)$$  \hspace{1cm} (9.21)

To obtain mean body clearance, $Cl_{av}$ is then calculated from the dose and the AUC.

$$Cl_{av} = \frac{D_0}{[\text{AUC}]}_0^\infty = \frac{V_{\max}}{(C_p^0/2) + K_M}$$  \hspace{1cm} (9.22)

$$Cl_{av} = \frac{V_{\max}}{(D_p/2V_p) + K_M}$$  \hspace{1cm} (9.23)

Alternatively, dividing Equation 9.17 by $C_p$ gives Equation 9.24, which shows that the clearance of a drug that follows nonlinear pharmacokinetics is dependent on the plasma drug concentration $C_p$, $K_M$, and $V_{\max}$.

$$Cl = \frac{V_0(dC_p/dt)}{C_p} = \frac{V_{\max}}{K_M + C_p}$$  \hspace{1cm} (9.24)

Equation 9.22 or 9.23 calculates the average clearance $Cl_{av}$ for the drug after a single IV bolus dose over the entire time course of the drug in the body. For any time period, clearance may be calculated (see Chapters 6 and 11) as

$$Cl = \frac{dD_p/dt}{C_p}$$  \hspace{1cm} (9.25)

In Chapter 11, the physiologic model based on blood flow and intrinsic clearance is used to describe drug metabolism. The extraction ratios of many drugs are listed in the literature. Actually, extraction ratios are dependent on dose, enzymatic system, and blood flow, and for practical purposes, they are often assumed to be constant at normal doses.

Except for phenytoin, there is a paucity of $K_M$ and $V_{\max}$ data defining the nature of nonlinear drug elimination in patients. However, abundant information is available supporting variable metabolism due to genetic polymorphism (Chapter 11). The clearance (apparent) of many of these drugs in patients who are slow metabolizers changes with dose, although these drugs may exhibit linear kinetics in subjects with the “normal” phenotype. Metoprolol and many $\beta$-adrenergic antagonists are extensively metabolized. The plasma levels of metoprolol in slow metabolizers (Lennard et al, 1986) were much greater than other patients, and the AUC, after equal doses, is several times greater among slow metabolizers of metoprolol (Fig. 9-13). A similar picture is observed with another $\beta$-adrenergic antagonist, timolol. These drugs have smaller clearance than normal.

**FIGURE 9-13** Mean plasma drug concentration versus time profiles following administration of single oral doses of (A) metoprolol tartrate 200 mg to six extensive metabolizers (EMs) and six poor metabolizers (PMs) and (B) timolol maleate 20 mg to six EMs (O) and four PMs (•). (Data from Lennard MJS, et al: Oxidation Phenotype—A Major Determinant of Metoprolol Metabolism and Response, NEJM 1982; Dec 16;307:1558-1560; Lennard MJS, et al: The relationship between debrisoquine oxidation phenotype and the pharmacokinetics and pharmacodynamics of propranolol, Br J Clin Pharmac, June;17(6):679-685, 1984; Lewis RV: Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics, Br J Clin Pharmac, Mar;19(3):329-333, 1985.)
CLINICAL FOCUS

The dose-dependent pharmacokinetics of sodium valproate (VPA) was studied in guinea pigs at 20, 200, and 600 mg/kg by rapid intravenous infusion. The area under the plasma concentration−time curve increased out of proportion at the 600-mg/kg dose level in all groups (Yu et al, 1987). The total clearance (\(Cl_p\)) was significantly decreased and the beta elimination half-life (\(t_{1/2}\)) was significantly increased at the 600-mg/kg dose level. The dose-dependent kinetics of VPA were due to saturation of metabolism. Metabolic capacity was greatly reduced in young guinea pigs.

Clinically, similar enzymatic saturation may be observed in infants and in special patient populations, whereas drug metabolism may be linear with dose in normal subjects. These patients have lower \(V_{\text{max}}\) and longer elimination half-life. Variability in drug metabolism is described in Chapters 11 and 12.

Frequently Asked Questions

- What is the Michaelis–Menten equation? How are \(K_m\) and \(V_{\text{max}}\) obtained? What are the units for \(K_m\) and \(V_{\text{max}}\)?
- What is the relevance of \(K_m\)?
- What are the main differences in pharmacokinetic parameters between a drug that follows linear and a nonlinear model?

Nonlinear Pharmacokinetics

Paroxetine hydrochloride (Paxil) is an orally administered psychotropic drug. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine exhibits autoinhibition. The major pathway for paroxetine metabolism is by CYP2D6. The elimination half-life is about 21 hours. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug−drug interactions. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including itself, desipramine, risperidone, and atomoxetine.

Paroxetine hydrochloride is known to inhibit metabolism of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) producing “serotonin syndrome” (hyperthermia, muscle rigidity, and rapid changes in vital signs). Three cases of accidental overdosing with paroxetine hydrochloride were reported (Vermeulen, 1998). In the case of overdose, high liver drug concentrations and an extensive tissue distribution (large \(V_d\)) made the drug difficult to remove. Vermeulen (1998) reported that saturation of CYP2D6 could result in a disproportionally higher plasma level than could be expected from an increase in dosage. These high plasma drug concentrations may be outside the range of 20 to 50 mg normally recommended. Since publication of this article, more is known about genotype CYP2D6*10 (Yoon, 2000), which may contribute to inter-subject variability in metabolism of this drug (see also Chapter 12).

DRUGS DISTRIBUTED AS ONE-COMPARTMENT MODEL AND ELIMINATED BY NONLINEAR PHARMACOKINETICS

The equations presented thus far in this chapter have been formulated for drugs given by IV bolus, distributed as a one-compartment model, and eliminated only by nonlinear pharmacokinetics. The following are useful
equations describing other possible routes of drug administration and including mixed drug elimination, by which the drug may be eliminated by both nonlinear (Michaelis–Menten) and linear (first-order) processes.

Mixed Drug Elimination

Drugs may be metabolized to several different metabolites by parallel pathways. At low drug doses corresponding to low drug concentrations at the site of the biotransformation enzymes, the rates of formation of metabolites are first order. However, with higher doses of drug, more drug is absorbed and higher drug concentrations are presented to the biotransformation enzymes. At higher drug concentrations, the enzyme involved in metabolite formation may become saturated, and the rate of metabolite formation becomes nonlinear and approaches zero order. For example, sodium salicylate is metabolized to both a glucuronide and a glycine conjugate (hippurate). The rate of formation of the glycine conjugate is limited by the amount of glycine available. Thus, the rate of formation of the glucuronide continues as a first-order process, whereas the rate of conjugation with glycine is capacity limited.

The equation that describes a drug that is eliminated by both first-order and Michaelis–Menten kinetics after IV bolus injection is given by

\[
-\frac{dC_p}{dt} = kC_p + \frac{V'_\text{max} C_p}{K_m + C_p} \tag{9.26}
\]

where \( k \) is the first-order rate constant representing the sum of all first-order elimination processes, while the second term of Equation 9.26 represents the saturable process. \( V'_\text{max} \) is simply \( V_\text{max} \) expressed as concentration by dividing by \( V_D \).

CLINICAL FOCUS

The pharmacokinetic profile of niacin is complicated due to extensive first-pass metabolism that is dosing-rate specific. In humans, one metabolic pathway is through a conjugation step with glycine to form nicotinuric acid (NUA). NUA is excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other metabolic pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least \( N \)-methylnicotinamide (MNA) and nicotinamide-\( N \)-oxide (NNO). MNA is further metabolized to two other compounds, \( N \)-methyl-2-pyridone-5-carboxamide (2PY) and \( N \)-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma drug concentrations following multiple-doses of Niaspan (niacin) extended-release tablets (Niaspan, FDA-approved label, 2009).

Zero-Order Input and Nonlinear Elimination

The usual example of zero-order input is constant IV infusion. If the drug is given by constant IV infusion and is eliminated only by nonlinear pharmacokinetics, then the following equation describes the rate of change of the plasma drug concentration:

\[
\frac{dC_p}{dt} = k_0 - \frac{V'_\text{max} C_p}{K_m + C_p} \tag{9.27}
\]

where \( k_0 \) is the infusion rate and \( V_D \) is the apparent volume of distribution.

First-Order Absorption and Nonlinear Elimination

The relationship that describes the rate of change in the plasma drug concentration for a drug that is given extravascularly (eg, orally), absorbed by first-order absorption, and eliminated only by nonlinear pharmacokinetics, is given by the following equation. \( C_{\text{Gi}} \) is concentration in the GI tract.

\[
\frac{dC_p}{dt} = k_a C_{\text{Gi}} e^{-k_a t} - \frac{V'_\text{max} C_p}{K_m + C_p} \tag{9.28}
\]

where \( k_a \) is the first-order absorption rate constant.
If the drug is eliminated by parallel pathways consisting of both linear and nonlinear pharmacokinetics, Equation 9.28 may be extended to Equation 9.29.

\[
\frac{dC_1}{dt} = k_1 C_1 e^{-k_\frac{t-t_0}{V_1}} - \frac{V_{\text{max}} C_1}{K_M + C_p} - kC_p \quad (9.29)
\]

where \( k \) is the first-order elimination rate constant.

**Two-Compartment Model with Nonlinear Elimination**

RhG-CSF is a glycoprotein hormone (recombinant human granulocyte-colony stimulating factors, rhG-CSF, MW about 20,000) that stimulates the growth of neutrophoietic cells and activates mature neutrophils. The drug is used in neutropenia occurring during chemotherapy or radiotherapy. Similar to many biotechnological drugs, RhG-CSF is administered by injection. The drug is administered subcutaneously and the drug is absorbed into the blood from the dermis site. This drug follows a two-compartment model with two elimination processes: (1) a saturable process of receptor-mediated elimination in the bone marrow and (2) a nonsaturable process of elimination. The model is described by two differential equations as shown below:

\[
\frac{dC_1}{dt} = -\left( k_{12} + k + \frac{V_{\text{max}}}{V_1(C_1 + K_M)} \right) C_1 + \frac{k_2 X_2}{V_1} \quad (9.29a)
\]

\[
\frac{dX_2}{dt} = k_{21} C_1 V_1 - k_{12} X_2 \quad (9.29b)
\]

where \( k_{12} \) and \( k_{21} \) are first-order transfer constants between the central and peripheral compartments; \( k \) is the first-order elimination constant from the central compartment; \( V_1 \) is the volume of the central compartment and the steady-state volume of distribution is \( V' = V_1 X_2 \); \( X_2 \) is the amount in the peripheral compartment; \( C_1 \) is the drug concentration in the central compartments at time \( t \); and \( V_{\text{max}}, K_M \) are Michaelis-Menten parameters that describe the saturable elimination.

The pharmacokinetics of this drug was described by Hayashi et al (2001). Here, \( \alpha \) is a function of dose with no dimensions and granulocyte colony-stimulating factor (G-CSF) takes a value from 0 to 1. When the dose approaches 0, \( \alpha = 1 \); when the dose approaches \( \infty \), \( \alpha = 0 \).

According to Hayashi et al. (2001), the drug clearance may be considered as two parts as shown below:

\[
\text{Dose/AUC} = \alpha Cl_{\text{int}} + Cl = Cl \quad (9.29c)
\]
\[
\int_0^\infty \frac{CK_M}{C+K_M} dt = \int_0^\infty C dt \quad (9.29d)
\]

where \( Cl_{\text{int}} \) is intrinsic clearance for the saturable pathway; \( Cl \) is nonsaturable clearance; and \( C \) is serum concentration.

**CHRONOPHARMACOKINETICS AND TIME-DEPENDENT PHARMACOKINETICS**

*Chronopharmacokinetics* broadly refers to a temporal change in the rate process (such as absorption or elimination) of a drug. The temporal changes in drug absorption or elimination can be cyclical over a constant period (e.g., 24-hour interval), or they may be noncyclical, in which drug absorption or elimination changes over a longer period of time. Chronopharmacokinetics is an important consideration during drug therapy.

*Time-dependent pharmacokinetics* generally refers to a noncyclical change in the drug absorption or drug elimination rate process over a period of time. Time-dependent pharmacokinetics leads to nonlinear pharmacokinetics. Unlike dose-dependent pharmacokinetics, which involves a change in the rate process when the dose is changed, time-dependent pharmacokinetics may be the result of alteration in the physiology or biochemistry in an organ or a region in the body that influences drug disposition (Levy, 1983).

Time-dependent pharmacokinetics may be due to auto-induction or auto-inhibition of biotransformation
enzymes. For example, Pitlick and Levy (1977) have shown that repeated doses of carbamazepine induce the enzymes responsible for its elimination (ie, auto-induction), thereby increasing the clearance of the drug. Auto-inhibition may occur during the course of metabolism of certain drugs (Perrier et al, 1973). In this case, the metabolites formed increase in concentration and further inhibit metabolism of the parent drug. In biochemistry, this phenomenon is known as product inhibition. Drugs undergoing time-dependent pharmacokinetics have variable clearance and elimination half-lives. The steady-state concentration of a drug that causes auto-induction may be due to increased clearance over time. Some anticancer drugs are better tolerated at certain times of the day; for example, the antimetabolite drug fluorouracil (FU) was least toxic when given in the morning to rodents (Von Roemeling, 1991). A list of drugs that demonstrate time dependence is shown in Table 9-8.

In pharmacokinetics, it is important to recognize that many isozymes (CYPs) are involved in drug metabolisms. A drug may competitively influence the metabolism of another drug within the same CYP subfamily. Sometimes, an unrecognized effect from the presence of another drug may be misjudged as a time-dependent pharmacokinetics. Drug metabolism and pharmacogenetics are discussed more extensively in Chapter 12.

### Circadian Rhythms and Influence on Drug Response

Circadian rhythms are rhythmic or cyclical changes in plasma drug concentrations that may occur daily, due to normal changes in body functions. Some rhythmic changes that influence body functions and drug response are controlled by genes and subject to modification by environmental factors. The mammalian circadian clock is a self-sustaining oscillator, usually within a period of ~24 hours, that cyclically controls many physiological and behavioral systems. The biological clock attempts to synchronize and respond to changes in length of the daylight cycle and optimize body functions.

Circadian rhythms are regulated through periodic activation of transcription by a set of clock genes. For example, melatonin onset is associated with onset of the quiescent period of cortisol secretion that regulates many functions. Some well-known circadian physiologic parameters are core body temperature (CBT), heart rate (HR), and other cardiovascular parameters. These fundamental physiologic factors can affect disease states, as well as toxicity and therapeutic response to drug therapy. The toxic dose of a drug may vary as much as several-fold, depending on the time of drug administration—during either sleep or wake cycle.

For example, the effects of timing of aminoglycoside administration on serum aminoglycoside levels and the incidence of nephrotoxicity were studied in 221 patients (Prins et al, 1997). Each patient received an IV injection of 2 to 4 mg/kg gentamicin or tobramycin once daily at: (1) between midnight and 7:30 AM, (2) between 8 AM and 3:30 PM, or (3) between 4 PM and 11:30 PM. In this study, no statistically significant differences in drug trough levels (0–4.2 mg/L) or peak drug levels (3.6–26.8 mg/L) were found for the three time periods of drug administration. However, nephrotoxicity occurred significantly more frequently when the aminoglycosides were given during the rest period (midnight–7:30 AM). Many factors contributing to nephrotoxicity were discussed; the time of administration was considered to be an independent risk factor in the multivariate statistical analysis. Time-dependent pharmacokinetics/pharmacodynamics is important, but it may be difficult to detect the clinical difference in drug concentrations due to multivariates.

Another example of circadian changes on drug response involves observations with chronic obstructive pulmonary disease (COPD) patients. Symptoms of hypoxemia may be aggravated in some COPD patients due to changes in respiration during the sleep cycle. Circadian variations have been reported

### TABLE 9-8 Drugs Showing Circadian or Time-Dependent Disposition

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<tr>
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<th>Fluorouracil</th>
<th>Ketoprofen</th>
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<td>Cisplatin</td>
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</table>

Data from Reinberg (1991).
inhibitors. There is clinical evidence that antihypertensive drugs should be dosed in the early morning in patients who are hypertensive “dippers,” whereas for patients who are non-dippers, it may be necessary to add an evening dose or even to use a single evening dose not only to reduce high blood pressure (BP) but also to normalize a disturbed non-dipping 24-hour BP profile. However, for practical purposes, some investigators found diurnal BP monitoring in many individuals too variable to distinguish between dippers and non-dippers (Lemmer, 2006).

The issue of time-dependent pharmacokinetics/pharmacodynamics (PK/PD) may be an important issue in some antihypertensive care. Pharmacists should recognize drugs that exhibit this type of time-dependent PK/PD.

Another example of time-dependent pharmacokinetics involves ciprofloxacin. Circadian variation in the urinary excretion of ciprofloxacin was investigated in a crossover study in 12 healthy male volunteers, ages 19 to 32 years. A significant decrease in the rate and extent of the urinary excretion of ciprofloxacin was observed following administrations at 2200 versus 1000 hours, indicating that the rate of excretion during the night time was slower (Sarveshwer Rao et al, 1997).

Clinical and Adverse Toxicity due to Nonlinear Pharmacokinetics

The presence of nonlinear or dose-dependent pharmacokinetics, whether due to saturation of a process involving absorption, first-pass metabolism, binding, or renal excretion, can have significant clinical consequences. However, nonlinear pharmacokinetics may not be noticed in drug studies that use a narrow dose range in patients. In this case, dose estimation may result in disproportionate increases in adverse reactions but insufficient therapeutic benefits. Nonlinear pharmacokinetics can occur anywhere above, within, or below the therapeutic window.

The problem of a nonlinear dose relationship in population pharmacokinetics analysis has been investigated using simulations (Hashimoto et al, 1994, 1995; Jonsson et al, 2000). For example, nonlinear fluvoxamine pharmacokinetics was reported (Jonsson et al, 2000) to be present even at subtherapeutic

**CLINICAL FOCUS**

Hypertensive patients are sometimes characterized as “dippers” if their nocturnal blood pressure drops below their daytime pressure. Non-dipping patients appear to be at an increased risk of cardiovascular morbidity. Blood pressure and cardiovascular events have a diurnal rhythm, with a peak of both in the morning hours, and a decrease during the night. The circadian variation of blood pressure provides assistance in predicting cardiovascular outcome (de la Sierra et al, 2009).

The pharmacokinetics of many cardiovascular acting drugs have a circadian phase-dependency (Lemmer, 2006). Examples include β-blockers, calcium channel blockers, oral nitrates, and ACE inhibitors.
doses. By using simulated data and applying nonlinear mixed-effects models using NONMEM, the authors also demonstrated that use of nonlinear mixed-effect models in population pharmacokinetics has an important application in the detection and characterization of nonlinear processes (pharmacokinetic and pharmacodynamic). Both first-order (FO) and FO conditional estimation (FOCE) algorithms were used for the population analyses. Population pharmacokinetics is discussed further in Chapter 22.

**NONLINEAR PHARMACOKINETICS DUE TO DRUG–PROTEIN BINDING**

Protein binding may prolong the elimination half-life of a drug. Drugs that are protein bound must first dissociate into the free or nonbound form to be eliminated by glomerular filtration. The nature and extent of drug–protein binding affects the magnitude of the deviation from normal linear or first-order elimination rate process.

For example, consider the plasma level–time curves of two hypothetical drugs given intravenously in equal doses (Fig. 9-14). One drug is 90% protein bound, whereas the other drug does not bind plasma protein. Both drugs are eliminated solely by glomerular filtration through the kidney.

The plasma curves in Fig. 9-14 demonstrate that the protein-bound drug is more concentrated in the plasma than a drug that is not protein bound, and the protein-bound drug is eliminated at a slower, nonlinear rate. Because the two drugs are eliminated by identical mechanisms, the characteristically slower elimination rate for the protein-bound drug is due to the fact that less free drug is available for glomerular filtration in the course of renal excretion.

The concentration of free drug, \( C_f \), can be calculated at any time, as follows.

\[
C_f = C_p (1 - \text{fraction bound}) \quad (9.30)
\]

**BIOAVAILABILITY OF DRUGS THAT FOLLOW NONLINEAR PHARMACOKINETICS**

The bioavailability of drugs that follow nonlinear pharmacokinetics is difficult to estimate accurately. As shown in Table 9-1, each process of drug absorption, distribution, and elimination is potentially saturable. Drugs that follow linear pharmacokinetics follow the principle of superposition (Chapter 8). The assumption in applying the rule of superposition is that each dose of drug superimposes on the previous dose. Consequently, the bioavailability of subsequent doses is predictable and not affected by the previous dose. In the presence of a saturable pathway for drug absorption, distribution, or elimination, drug bioavailability will change within a single dose or with subsequent (multiple) doses. An example of a drug with dose-dependent absorption is chlorothiazide (Hsu et al, 1987).

The extent of bioavailability is generally estimated using \([\text{AUC}]_{f}\). If drug absorption is saturation limited in the gastrointestinal tract, then a smaller fraction of drug is absorbed systemically when the gastrointestinal drug concentration is high. A drug with a saturable elimination pathway may also have a concentration-dependent AUC affected by the magnitude of \( K_M \) and \( V_{\text{max}} \) of the enzymes involved in drug elimination (Equation 9.21). At low \( C_p \), the rate of elimination is first order, even at the beginning of drug absorption from the gastrointestinal tract. As more drug is absorbed, either from a single dose or after multiple doses, systemic drug concentrations increase to levels that saturate the enzymes involved in drug elimination. The body drug clearance changes and the AUC increases disproportionately to the increase in dose (see Fig. 9-2).

**FIGURE 9-14** Plasma curve comparing the elimination of two drugs given in equal IV doses. Curve A represents a drug 90% bound to plasma protein. Curve B represents a drug not bound to plasma protein.
For any protein-bound drug, the free drug concentration \((C_f)\) will always be less than the total drug concentration \((C_p)\).

A careful examination of Fig. 9-14 shows that the slope of the bound drug decreases gradually as the drug concentration decreases. This indicates that the percent of drug bound is not constant. In vivo, the percent of drug bound usually increases as the plasma drug concentration decreases (see Chapter 10). Since protein binding of drug can cause nonlinear elimination rates, pharmacokinetic fitting of protein-bound drug data to a simple one-compartment model without accounting for binding results in erroneous estimates of the volume of distribution and elimination half-life. Sometimes plasma drug data for drugs that are highly protein bound have been inappropriately fitted to two-compartment models.

Valproic acid (Depakene) shows nonlinear pharmacokinetics that may be due partially to nonlinear protein binding. The free fraction of valproic acid is 10% at a plasma drug concentration of 40 \(\mu\)g/mL and 18.5% at a plasma drug level of 130 \(\mu\)g/mL. In addition, higher-than-expected plasma drug concentrations occur in the elderly, hyperlipidemic patients, and in patients with hepatic or renal disease.

**One-Compartment Model**

**Drug with Protein Binding**

The process of elimination of a drug distributed in a single compartment with protein binding is illustrated in Fig. 9-15. The one compartment contains both free drug and bound drug, which are dynamically interconverted with rate constants \(k_1\) and \(k_2\). Elimination of drug occurs only with the free drug, at a first-order rate. The bound drug is not eliminated. Assuming a saturable and instantly reversible drug-binding process, where \(P = \) protein concentration in plasma, \(C_f = \) plasma concentration of free drug, \(k_d = k_2/k_1 = \) dissociation constant of the protein drug complex, \(C_p = \) total plasma drug concentration, and \(C_b = \) plasma concentration of bound drug,

\[
\frac{C_b}{P} = \frac{(1/k_d)C_f}{1 + (1/k_d)C_f} \quad (9.31)
\]

This equation can be rearranged as follows:

\[
C_b = \frac{PC_f}{k_d + C_f} = C_p - C_f \quad (9.32)
\]

Solving for \(C_f\),

\[
C_f = \frac{1}{2} \left[ -(P + k_d - C_p) + \sqrt{(P + k_d - C_p)^2 + 4k_pC_p} \right] \quad (9.33)
\]

Because the rate of drug elimination is \(dC_p/dt\),

\[
\frac{dC_p}{dt} = -kC_f
\]

\[
\frac{dC_p}{dt} = -\frac{k}{2} \left[ -(P + k_d - C_p) + \sqrt{(P + k_d - C_p)^2 + 4k_pC_p} \right] \quad (9.34)
\]

This differential equation describes the relationship of changing plasma drug concentrations during elimination. The equation is not easily integrated but can be solved using a numerical method. Figure 9-16

![FIGURE 9-15](image1.png)

**FIGURE 9-15** One-compartment model with drug–protein binding.

![FIGURE 9-16](image2.png)

**FIGURE 9-16** Plasma drug concentrations for various doses of a one-compartment model drug with protein binding. (Adapted from Coffey et al, 1971, with permission.)
shows the plasma drug concentration curves for a one-compartment protein-bound drug having a volume of distribution of 50 mL/kg and an elimination half-life of 30 minutes. The protein concentration is 4.4% and the molecular weight of the protein is 67,000 Da. At various doses, the pharmacokinetics of elimination of the drug, as shown by the plasma curves, ranges from linear to nonlinear, depending on the total plasma drug concentration.

Nonlinear drug elimination pharmacokinetics occurs at higher doses. Because more free drug is available at higher doses, initial drug elimination occurs more rapidly. For drugs demonstrating nonlinear pharmacokinetics, the free drug concentration may increase slowly at first, but when the dose of drug is raised beyond the protein-bound saturation point, free plasma drug concentrations may rise abruptly. Therefore, the concentration of free drug should always be calculated to make sure the patient receives a proper dose.

**Determination Linearity in Data Analysis**

During new drug development, the pharmacokinetics of the drug is examined for linear or nonlinear pharmacokinetics. A common approach is to give several graded doses to human volunteers and obtain plasma drug concentration curves for each dose. From these data, a graph of AUC versus dose is generated as shown in Fig. 9-2. The drug is considered to follow linear kinetics if AUC versus dose for various doses is proportional (ie, linear relationship). In practice, the experimental data presented may not be very clear, especially when oral drug administration data are presented and there is considerable variability in the data. For example, the AUC versus three-graded doses of a new drug is shown in Figure 9-17. A linear regression line was drawn through the three data points. The conclusion is that the drug follows dose-independent (linear) kinetics based upon a linear regression line through the data and a correlation coefficient, $R^2 = 0.97$.

- Do you agree with this conclusion after inspecting the graph?

The conclusion for linear pharmacokinetics in Fig. 9-17 seems reasonable based on the estimated regression line drawn through the data points.

However, another pharmacokineticist noticed that the regression line in Fig. 9-17 does not pass through the origin point (0,0). This pharmacokineticist considered the following questions:

- Are the patients in the study receiving the drug doses well separated by a washout period during the trial such that no residual drug remained in the body and carried to the present dose when plasma samples are collected?
- Is the method for assaying the samples validated? Could a high sample blank or interfering material be artificially adding to elevate 0 time drug concentrations?
- How does the trend line look if the point (0,0) is included?

When the third AUC point is above the trend line, it is risky to draw a conclusion. One should verify that the high AUC is not due to a lower elimination or clearance due to saturation.

In Fig. 9-18, a regression line was obtained by forcing the same data through point (0,0). The linear
Nonlinear Pharmacokinetics

regression analysis and estimated $R^2$ appears to show that the drug followed nonlinear pharmacokinetics. The line appears to have a curvature upward and the possibility of some saturation at higher doses. This pharmacokineticist recommends additional study by adding a higher dose to more clearly check for dose dependency.

What is your conclusion?

Considerations

The experimental data is composed of three different drug doses.

- The regression line shows that the drug follows linear pharmacokinetics from the low dose to the high dose.
- The use of a (0.0) value may provide additional information concerning the linearity of the pharmacokinetics. However, extrapolation of curves beyond the actual experimental data can be misleading.
- The conclusion in using the (0.0) time point shows that the pharmacokinetics is nonlinear below the lowest drug dose. This may occur after oral dosing because at very low drug doses some of the drug is decomposed in the gastrointestinal tract or metabolized prior to systemic absorption. With higher doses, the small amount of drug loss is not observed systemically.

Note if $V_D$ of the drug is known, determining $k$ from the terminal slope of the oral data provides another way of calculating $Cl$ ($Cl = V_D k$) to check whether clearance has changed at higher doses due to saturation. Some common issues during data analysis for linearity are listed below.

Note: In some cases, with certain drugs, the oral absorption mechanism is quite unique and drug clearance by the oral route may involve absorption site-specific enzymes or transporters located on the brush border. Extrapolating pharmacokinetic information from IV dosing dose data should be done cautiously only after a careful consideration of these factors. It is helpful to know whether nonlinearity is caused by distribution, or absorption factors.

Unsuspected nonlinear drug disposition is one of the biggest issues concerning drug safety. Although pharmacokinetic tools are useful, nonlinearity can be easily missed during data analysis when there are outliers or extreme data scattering due to individual patient factors such as genetics, age, sex, and other unknown factors in special populations.

**TABLE 9-9 Some Common Issues during Data Analysis for Linearity**

<table>
<thead>
<tr>
<th>Oral Data</th>
<th>Issues during Data Analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last data point may be below the LOD or limit of detection. What should the AUC tail piece be?</td>
<td>Last sample point scheduled too late in the study protocol.</td>
<td></td>
</tr>
<tr>
<td>Last data point still very high, much above the LOD. What should be the AUC tail piece?</td>
<td>Last sample point scheduled too early. A substantial number of data points may be incorrectly estimated by the tail piece method.</td>
<td></td>
</tr>
<tr>
<td>Incomplete sample spacing around peak.</td>
<td>Total AUC estimated may be quite variable or unreliable.</td>
<td></td>
</tr>
<tr>
<td>Oral AUC data are influenced by $F$, $D$, and $Cl$.</td>
<td>When examining $D_0/Cl$ vs $D_0$, $F$ must be held constant. Any factor causing change in $F$ during the trial will introduce uncertainty to AUC.</td>
<td></td>
</tr>
<tr>
<td>$F$ may be affected by efflux, transporters (see Chapter 13), and GI CYP enzymes. An increase in $F$ and decrease in $Cl$ or vice versa over doses may mask each other.</td>
<td>Nonlinearity of AUC vs $D_0$ may not be evident and one may incorrectly conclude a drug follows linear kinetics when it is does not.</td>
<td></td>
</tr>
<tr>
<td>IV data</td>
<td>AUC data by IV are influenced by $D_0$ and $Cl$ only.</td>
<td>When examining $D_0/Cl$ vs $D_0$, $F$ is always constant. Therefore, it is easier to see changes in AUC when $Cl$ changes by IV route.</td>
</tr>
</tbody>
</table>

LOD, limit of detection.
While statistical analysis can help minimize this, it is extremely helpful to survey for problems (eg, epidemiological surveillance) and have a good understanding of how drugs are disposed in various parts of the body in the target populations.

### POTENTIAL REASONS FOR UNSUSPECTED NONLINEARITY

1. Nonlinearity caused by membrane resident transporters
2. Nonlinearity caused by membrane CYPs

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### CHAPTER SUMMARY

Nonlinear pharmacokinetics refers to kinetic processes that result in disproportional changes in plasma drug concentrations when the dose is changed. This is also referred to as dose-dependent pharmacokinetics or saturation pharmacokinetics. Clearance and half-life are usually not constant with dose-dependent pharmacokinetics. Carrier-mediated processes and processes that depend on the binding of the drug to a macromolecule resulting in drug metabolism, protein binding, active absorption, and some transporter-mediated processes can potentially exhibit dose-dependent kinetics, especially at higher doses. The Michaelis–Menten kinetic equation may be applied in vitro or in vivo to describe drug disposition, eg, phenytoin.

An approach to determine nonlinear pharmacokinetics is to plot AUC versus doses and observe for nonlinearity curving. A common cause of overdosing in clinical practice is undetected saturation of a metabolic enzyme due to genotype difference in a subject, eg, CYP2D6. A second common cause of overdosing in clinical practice is undetected saturation of a metabolic enzyme due to coadministration of a second drug/agent that alters the original linear elimination process.

### LEARNING QUESTIONS

1. Define nonlinear pharmacokinetics. How do drugs that follow nonlinear pharmacokinetics differ from drugs that follow linear pharmacokinetics?
   a. What is the rate of change in the plasma drug concentration with respect to time, \( dC_p/dt \), when \( C_p \ll K_M \)?
   b. What is the rate of change in the plasma drug concentration with respect to time, \( dC_p/dt \), when \( C_p \gg K_M \)?

2. What processes of drug absorption, distribution, and elimination may be considered “capacity limited,” “saturated,” or “dose dependent”?
3. Drugs, such as phenytoin and salicylates, have been reported to follow dose-dependent elimination kinetics. What changes in pharmacokinetic parameters, including $t_{1/2}$, $V_D$, AUC, and $C_p$, could be predicted if the amounts of these drugs administered were increased from low pharmacologic doses to high therapeutic doses?

4. A given drug is metabolized by capacity-limited pharmacokinetics. Assume $K_M$ is 50 μg/mL, $V_{max}$ is 20 μg/mL per hour, and the apparent $V_p$ is 20 L/kg.
   a. What is the reaction order for the metabolism of this drug when given in a single intravenous dose of 10 mg/kg?
   b. How much time is necessary for the drug to be 50% metabolized?

5. How would induction or inhibition of the hepatic enzymes involved in drug biotransformation theoretically affect the pharmacokinetics of a drug that demonstrates nonlinear pharmacokinetics due to saturation of its hepatic elimination pathway?

6. Assume that both the active parent drug and its inactive metabolites are excreted by active tubular secretion. What might be the consequences of increasing the dosage of the drug on its elimination half-life?

7. The drug isoniazid was reported to interfere with the metabolism of phenytoin. Patients taking both drugs together show higher phenytoin levels in the body. Using the basic principles in this chapter, do you expect $K_M$ to increase or decrease in patients taking both drugs? (Hint: see Fig. 9-4.)

8. Explain why $K_M$ sometimes has units of mM/mL and sometimes mg/L.

9. The $V_{max}$ for metabolizing a drug is 10 mmol/h. The rate of metabolism ($v$) is 5 μmol/h when drug concentration is 4 μmol. Which of the following statements is/are true?
   a. $K_M$ is 5 μmol for this drug.
   b. $K_M$ cannot be determined from the information given.
   c. $K_M$ is 4 μmol for this drug.

10. Which of the following statements is/are true regarding the pharmacokinetics of diazepam (98% protein bound) and propranolol (87% protein bound)?
   a. Diazepam has a long elimination half-life because it is difficult to be metabolized due to extensive plasma–protein binding.
   b. Propranolol is an example of a drug with high protein binding but unrestricted (unaffected) metabolic clearance.
   c. Diazepam is an example of a drug with low hepatic extraction.
   d. All of the above.
   e. a and c.
   f. b and c.

11. Which of the following statements describe(s) correctly the properties of a drug that follows nonlinear or capacity-limited pharmacokinetics?
   a. The elimination half-life will remain constant when the dose changes.
   b. The area under the plasma curve (AUC) will increase proportionally as dose increases.
   c. The rate of drug elimination = $C_p \times K_M$.
   d. All of the above.
   e. a and b.
   f. None of the above.

12. The hepatic intrinsic clearances of two drugs are
drug A: 1300 mL/min
drug B: 26 mL/min
Which drug is likely to show the greatest increase in hepatic clearance when hepatic blood flow is increased from 1 L/min to 1.5 L/min?
   a. Drug A
   b. Drug B
   c. No change for both drugs
REFERENCES


Chapter Objectives

- Describe the physiology of drug distribution in the body.
- Explain how drug distribution is affected by blood flow, protein, and tissue binding.
- Describe how drug distribution can affect the apparent volume of distribution.
- Explain how volume of distribution, drug clearance, and half-life can be affected by protein binding.
- Evaluate the impact of change in drug–protein binding or displacement on free drug concentration.

PHYSIOLOGIC FACTORS OF DISTRIBUTION

After a drug is absorbed systemically from the site of administration, the drug molecules are distributed throughout the body by the systemic circulation. The location, extent, and degree of distribution are dependent on the drug’s properties and individual patient characteristics such as organ perfusion and blood flow. The drug molecules are carried by the blood to the target site (receptor) for drug action and to other (nonreceptor) tissues as well, where side effects or adverse reactions may occur. These sites may be intracellular and/or extracellular. Drug molecules are distributed to eliminating organs, such as the liver and kidney, and to noneliminating tissues, such as the brain, skin, and muscle. In pregnancy, drugs cross the placenta and may affect the developing fetus. Drugs can also be secreted in milk via the mammary glands, into the saliva and into other secretory pathways. A substantial portion of the drug may be bound to proteins in the plasma and/or in the tissues. Lipophilic drugs deposit in fat, from which the drug may be slowly released.

Drug distribution throughout the body occurs primarily via the circulatory system, which consists of a series of blood vessels that carry the drug in the blood; these include the arteries that carry blood to tissues, and the veins that return the blood back to the heart. An average subject (70 kg) has about 5 L of blood, which is equivalent to about 3 L of plasma (Fig. 10-1). About 50% of the blood is in the large veins or venous sinuses. The volume of blood pumped by the heart per minute—the cardiac output—is the product of the stroke volume of the heart and the number of heartbeats per minute. An average cardiac output is 0.08 L/left ventricle contraction × 69 contractions (heart beats)/min, or about 5.5 L/min in subjects at rest. The cardiac output may be five to six times higher during exercise. Left ventricular contraction may produce a systolic blood pressure of 120 mm Hg, and moves blood at a linear speed of 300 mm/s through the aorta. Mixing of a drug solution in the blood occurs rapidly at this flow rate. Drug molecules rapidly diffuse through a network of fine capillaries to the tissue spaces filled with interstitial fluid (Fig. 10-2). The interstitial fluid plus the plasma water is termed extracellular water, because these fluids...
Drug molecules may further diffuse from the interstitial fluid across the cell membrane into the cell cytoplasm.

Drug distribution is generally rapid, and most small drug molecules permeate capillary membranes easily. The passage of drug molecules across a cell membrane depends on the physicochemical nature of both the drug and the cell membrane. Cell membranes are composed of protein and a bilayer of phospholipid, which act as a lipid barrier to drug uptake. Thus, lipid-soluble drugs generally diffuse across cell membranes more easily than highly polar or water-soluble drugs. Small drug molecules generally diffuse more rapidly across cell membranes than large drug molecules. If the drug is bound to a plasma protein such as albumin, the drug–protein complex becomes too large for easy diffusion across the cell or even capillary membranes. A comparison of diffusion rates for water-soluble molecules is given in Table 10-1.

**Diffusion and Hydrostatic Pressure**

The processes by which drugs transverse capillary membranes into the tissue include passive diffusion and hydrostatic pressure. Passive diffusion is the main process by which most drugs cross cell membranes. Passive diffusion (see Chapter 13) is the process by which drug molecules move from an area of high concentration to an area of low concentration.
Physiologic Drug Distribution and Protein Binding

207

Concentration. Passive diffusion is described by Fick’s law of diffusion:

\[
\text{Rate of drug diffusion} = \frac{dQ}{dt} = \frac{-DKA(C_p - C_t)}{h}
\]

(10.1)

where \( C_p - C_t \) is the difference between the drug concentration in the plasma \( (C_p) \) and in the tissue \( (C_t) \), respectively; \( A \) is the surface area of the membrane; \( h \) is the thickness of the membrane; \( K \) is the lipid–water partition coefficient; and \( D \) is the diffusion constant. The negative sign denotes net transfer of drug from inside the capillary lumen into the tissue and extracellular spaces. Diffusion is spontaneous and temperature dependent. Diffusion is distinguished from blood flow–initiated mixing, which involves hydrostatic pressure.

Hydrostatic pressure represents the pressure gradient between the arterial end of the capillaries entering the tissue and the venous capillaries leaving the tissue. Hydrostatic pressure is responsible for penetration of water-soluble drugs into spaces between endothelial cells and possibly into lymph. In the kidneys, high arterial pressure creates a filtration pressure that allows small drug molecules to be filtered in the glomerulus of the renal nephron (see Chapter 6).

Blood flow–induced drug distribution is rapid and efficient, but requires pressure. As blood pressure gradually decreases when arteries branch into the small arterioles, the speed of flow slows and diffusion into the interstitial space becomes diffusion or concentration driven and facilitated by the large surface area of the capillary network. The average pressure of the blood capillary is higher (+18 mm Hg) than the mean tissue pressure (–6 mm Hg), resulting in a net total pressure of 24 mm Hg higher in the capillary over the tissue. This pressure difference is offset by an average osmotic pressure in the blood of 24 mm Hg, pulling the plasma fluid back into the capillary. Thus, on average, the pressures in the tissue and most parts of the capillary are equal, with no net flow of water.

At the arterial end, as the blood newly enters the capillary (Fig. 10-2A), however, the pressure of the capillary blood is slightly higher (about 8 mm Hg) than that of the tissue, causing fluid to leave the capillary and enter the tissues. This pressure is called hydrostatic or filtration pressure. This filtered fluid (filtrate) is later returned to the venous capillary

### TABLE 10-1 Permeability of Molecules of Various Sizes to Capillaries

<table>
<thead>
<tr>
<th>Molecular Weight</th>
<th>Radius of Equivalent Sphere A (0.1 mm)</th>
<th>Diffusion Coefficient In Water (cm²/s) × 10⁵</th>
<th>Across Capillary (cm²/s × 100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>18</td>
<td>3.20</td>
<td>3.7</td>
</tr>
<tr>
<td>Urea</td>
<td>60</td>
<td>1.95</td>
<td>1.83</td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>0.91</td>
<td>0.64</td>
</tr>
<tr>
<td>Sucrose</td>
<td>342</td>
<td>0.74</td>
<td>0.35</td>
</tr>
<tr>
<td>Raffinose</td>
<td>594</td>
<td>0.56</td>
<td>0.24</td>
</tr>
<tr>
<td>Inulin</td>
<td>5,500</td>
<td>0.21</td>
<td>0.036</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,000</td>
<td>0.15</td>
<td>0.005</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>68,000</td>
<td>0.094</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>69,000</td>
<td>0.085</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Chapter 10

(Fig. 10-2B) due to a lower venous pressure of about the same magnitude. The lower pressure of the venous blood compared with the tissue fluid is termed as absorptive pressure. A small amount of fluid returns to the circulation through the lymphatic system.

**Distribution Half-Life, Blood Flow, and Drug Uptake by Organs**

Because the process of drug transfer from the capillary into the tissue fluid is mainly diffusional, according to Fick’s law, the membrane thickness, diffusion coefficient of the drug, and concentration gradient across the capillary membrane are important factors in determining the rate of drug diffusion. Kinetically, if a drug diffuses rapidly across the membrane in such a way that blood flow is the rate-limiting step in the distribution of drug, then the process is perfusion or flow limited. A person with congestive heart failure has a decreased cardiac output, resulting in impaired blood flow, which may reduce renal clearance through reduced filtration pressure and blood flow. In contrast, if drug distribution is limited by the slow diffusion of drug across the membrane in the tissue, then the process is termed diffusion or permeability limited (Fig. 10-3). Drugs that are permeability limited may have an increased distribution volume in disease conditions that cause inflammation and increased capillary membrane permeability. The delicate osmotic pressure balance may be altered due to changes in albumin and/or blood loss or due to changes in electrolyte levels in renal and hepatic disease, resulting in net flow of plasma water into the interstitial space (edema). This change in fluid distribution may partially explain the increased extravascular drug distribution during some disease states.

Blood flow, tissue size, and tissue storage (partitioning and binding) are also important in determining the time it takes the drug to become fully distributed. Table 10-2 lists the blood flow and tissue mass for many tissues in the human body. Drug affinity for a tissue or organ refers to the partitioning and accumulation of the drug in the tissue. The time for drug distribution is generally measured by the distribution half-life or the time for 50% distribution. The factors that determine the distribution constant of a drug into an organ are related to the blood flow to the organ, the volume of the organ, and

**TABLE 10-2 Blood Flow to Human Tissues**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Percent Body Weight</th>
<th>Percent Cardiac Output</th>
<th>Blood Flow (mL/100 g tissue/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.02</td>
<td>1</td>
<td>550</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.4</td>
<td>24</td>
<td>450</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.04</td>
<td>2</td>
<td>400</td>
</tr>
<tr>
<td>Liver</td>
<td>2.0</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2.0</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Portal</td>
<td>2.0</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Portal-drained viscera</td>
<td>2.0</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Heart (basal)</td>
<td>0.4</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>Brain</td>
<td>2.0</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Skin</td>
<td>7.0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Muscle (basal)</td>
<td>40.0</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>7.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fat</td>
<td>15.0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

the partitioning of the drug into the organ tissue, as shown in Equation 10.2.

\[ k_d = \frac{Q}{VR} \]  

(10.2)

where \( k_d \) = first-order distribution constant, \( Q \) = blood flow to the organ, \( V \) = volume of the organ, \( R \) = ratio of drug concentration in the organ tissue to drug concentration in the blood (venous). The *distribution half-life* of the drug to the tissue, \( t_{d1/2} \), may easily be determined from the distribution constant, \( t_{d1/2} = \frac{0.693}{k_d} \).

The ratio \( R \) must be determined experimentally from tissue samples. With many drugs, however, only animal tissue data are available. Pharmacokineticists have estimated the ratio \( R \) based on knowledge of the partition coefficient of the drug. The *partition coefficient* is a physical property that measures the ratio of the solubility of the drug in the oil phase and in aqueous phase. The partition coefficient (\( P_{o/w} \)) is defined as a ratio of the drug concentration in the oil phase (usually represented by octanol) divided by the drug concentration in the aqueous phase measured at equilibrium under specified temperature *in vitro* in an oil/water two-layer system (Fig. 10-4). The partition coefficient is one of the most important factors that determine the tissue distribution of a drug.

If each tissue has the same ability to store the drug, then the distribution half-life is governed by the blood flow, \( Q \), and volume (size), \( V \), of the organ. A large blood flow, \( Q \), to the organ decreases the distribution time, whereas a large organ size or volume, \( V \), increases the distribution time because a longer time is needed to fill a large organ volume with drug. Figure 10-5 illustrates the distribution time (for 0%, 50%, 90%, and 95% distribution) for the adrenal gland, kidney, muscle (basal), skin, and fat tissue in an average human subject (ideal body weight, IBW, = 70 kg). In this illustration, the blood drug concentration is equally maintained at 100 \( \mu \)g/mL, and the drug is assumed to have equal distribution between all the tissues and blood, ie, when fully equilibrated, the partition or drug concentration ratio (\( R \)) between the tissue and the plasma will equal 1. Vascular tissues such as the kidneys and adrenal glands achieve 95% distribution in less than 2 minutes. In contrast, drug distribution time in fat tissues takes 4 hours, and less in vascular tissues, such as the skin and muscles, between 2 and 4 hours (Fig. 10-5). When drug partition of the tissues is the same, the distribution time is dependent only on the tissue volume and its blood flow.

Blood flow is an important consideration in determining how rapid and how much drug reaches the receptor site. Under normal conditions, limited blood flow reaches the muscles. During exercise, the increase in blood flow may change the fraction of drug reaching the muscle tissues. Diabetic patients

![Diagram showing equilibration of drug between oil and water layer *in vitro*.](image1)

![Drug distribution in five groups of tissues at various rate of equilibration (1 = adrenal, 2 = kidney, 3 = skin, 4 = muscle (basal), 5 = fat).](image2)
receiving intramuscular injection of insulin may experience the effects of changing onset of drug action during exercise. Normally, the blood reserve of the body stays mostly in the large veins and sinuses in the abdomen. During injury or when blood is lost, constriction of the large veins redirects more blood to needed areas and therefore affects drug distribution. Accumulation of carbon dioxide may lower the pH of certain tissues and may affect the level of drugs reaching those tissues.

Figure 10-6 illustrates the distribution of a drug to three different tissues when the partition of the drug for each tissue varies. For example, the drug partition ($R = 5$) shows that the drug concentration in the adrenal glands is five times more than the drug concentration in the plasma, while the drug partition for the kidney is $R = 3$, and for basal muscle, $R = 1$. In this illustration, the adrenal gland and kidney take five and three times as long to be equilibrated with drug. Thus, it can be seen that, even for vascular tissues, high drug partition can take much more time for the tissue to become fully equilibrated. In the example in Fig. 10-6, drug administration is continuous (as in IV infusion), since tissue drug levels remain constant after equilibrium.

Some tissues have great ability to store and accumulate drug, as shown by large $R$ values. For example, the anti-androgen drug flutamide and its active metabolite are highly concentrated in the prostate. The prostate drug concentration is 20 times that of the plasma drug concentration; thus, the anti-androgen effect of the drug is not fully achieved until distribution to this receptor site is complete. Digoxin is highly bound to myocardial membranes. Digoxin has a high tissue/plasma concentration ratio ($R = 60 – 130$) in the myocardium. This high $R$ ratio for digoxin leads to a long distributional phase (see Chapter 4) despite abundant blood flow to the heart. It is important to note that if a tissue has a long distribution half-life, a long time is needed for the drug to leave the tissue as the blood level decreases. Understanding drug distribution is important because the activities of many drugs are not well correlated with plasma drug levels. Kinetically, both drug–protein binding or favorable drug solubility in the tissue site lead to longer distribution times.

Chemical knowledge in molecular structure often helps estimate the lipid solubility of a drug. A drug with large oil/water partition coefficient tends to have high $R$ values in vivo. A reduction in the partition coefficient of a drug often reduces the rate of drug uptake into the brain. This may decrease drug distribution into the central nervous system and decrease undesirable central nervous system side effects. Extensive tissue distribution is kinetically evidenced by an increase in the volume of distribution. A secondary effect is a prolonged drug elimination half-life, since the drug is distributed within a larger volume (thus, the drug is more diluted) and therefore, less efficiently removed by the kidney or the liver. For example, etretinate (a retinoate derivative) for acne treatment has an unusually long elimination half-life of about 100 days (Chien et al, 1992), due to its extensive distribution to body fats. Newly synthesized agents have been designed to reduce the lipophilicity and drug distribution. These new agents have less accumulation and less potential for teratogenicity.

**Drug Accumulation**

The deposition or uptake of the drug into the tissue is generally controlled by the diffusional barrier of the capillary membrane and other cell membranes.
For example, the brain is well perfused with blood, but many drugs with good aqueous solubility have high kidney, liver, and lung concentrations and yet little or negligible brain drug concentration. The brain capillaries are surrounded by a layer of tightly joined glial cells that act as a lipid barrier to impede the diffusion of polar or highly ionized drugs. A diffusion-limited model may be necessary to describe the pharmacokinetics of these drugs that are not adequately described by perfusion models.

Tissues receiving high blood flow equilibrate quickly with the drug in the plasma. However, at steady state, the drug may or may not accumulate (concentrate) within the tissue. The accumulation of drug into tissues is dependent on both the blood flow and the affinity of the drug for the tissue. Drug affinity for the tissue depends on partitioning and also binding to tissue components, such as receptors. Drug uptake into a tissue is generally reversible. The drug concentration in a tissue with low capacity equilibrates rapidly with the plasma drug concentration and then declines rapidly as the drug is eliminated from the body.

In contrast, drugs with high tissue affinity tend to accumulate or concentrate in the tissue. Drugs with a high lipid/water partition coefficient are very fat soluble and tend to accumulate in lipid or adipose (fat) tissue. In this case, the lipid-soluble drug partitions from the aqueous environment of the plasma into the fat. This process is reversible, but the extraction of drug out of the tissue is so slow that the drug may remain for days or even longer in adipose tissues, long after the drug is depleted from the blood. Because the adipose tissue is poorly perfused with blood, drug accumulation is slow. However, once the drug is concentrated in fat tissue, drug removal from fat may also be slow. For example, the insecticide chlorinated hydrocarbon DDT (dichlorodiphenyltrichloroethane) is highly lipid soluble and remains in fat tissue for years.

In addition to partitioning, drugs may accumulate in tissues by other processes. For example, drugs may accumulate by binding to proteins or other macromolecules in a tissue. Digoxin is highly bound to proteins in cardiac tissue, leading in a large volume of distribution (440 L/70 kg) and long elimination $t_{1/2}$ (approximately 40 hours). Some drugs may complex with melanin in the skin and eye, as observed after long-term administration of high doses of phenothiazine to chronic schizophrenic patients. The antibiotic tetracycline forms an insoluble chelate with calcium. In growing teeth and bones, tetracycline will complex with the calcium and remain in these tissues.

Some tissues have enzyme systems that actively transport natural biochemical substances into the tissues. For example, various adrenergic tissues have a specific uptake system for catecholamines, such as norepinephrine. Thus, amphetamine, which has a phenylethylamine structure similar to norepinephrine, is actively transported into adrenergic tissue. Other examples of drug accumulation are well documented. For some drugs, the actual mechanism for drug accumulation may not be clearly understood.

In a few cases, the drug is irreversibly bound into a particular tissue. Irreversible binding of drug may occur when the drug or a reactive intermediate metabolite becomes covalently bound to a macromolecule within the cell, such as to a tissue protein. Many purine and pyrimidine drugs used in cancer chemotherapy are incorporated into nucleic acids, causing destruction of the cell.

**Permeability of Cell and Capillary Membranes**

Cellular and plasma membranes vary in their permeability characteristics, depending on the tissue. For example, capillary membranes in the liver and kidneys are more permeable to transmembrane drug movement than capillaries in the brain. The sinusoidal capillaries of the liver are very permeable and allow the passage of large-molecular-weight molecules. In the brain and spinal cord, the capillary endothelial cells are surrounded by a layer of glial cells, which have tight intercellular junctions. This added layer of cells around the capillary membranes acts effectively to slow the rate of drug diffusion into the brain by acting as a thicker lipid barrier. This lipid barrier, which slows the diffusion and penetration of water-soluble and polar drugs into the brain and spinal cord, is called the blood–brain barrier.

Under certain pathophysiologic conditions, the permeability of cell membranes, including capillary
cell membranes, may be altered. For example, burns will alter the permeability of skin and allow drugs and larger molecules to permeate inward or outward. In meningitis, which involves inflammation of the membranes of the spinal cord and/or brain, drug uptake into the brain will be enhanced.

The diameters of the capillaries are very small and the capillary membranes are very thin. The high blood flow within a capillary allows for intimate contact of the drug molecules with the plasma membrane, providing for rapid drug diffusion. For capillaries that perfuse the brain and spinal cord, the layer of glial cells functions effectively to increase the thickness term $h$ in Equation 10.1, thereby slowing the diffusion and penetration of water-soluble and polar drugs into the brain and spinal cord.

**Drug Distribution within Cells and Tissues**

Pharmacokinetic models generally provide a good estimation of plasma drug concentrations in the body based on dose, volume of distribution, and clearance. However, drug concentrations within the cell or within a special region in the body are also governed by special efflux and metabolizing enzyme systems that prevent and detoxify foreign agents entering the body. Some proteins are receptors on cell surfaces that react specifically with a drug. The transporters are specialized proteins in the body that can associate transiently with a substrate drug through the hydrophobic region in the molecule, eg, P-glycoprotein, P-gP or Pgp. Drug-specific transporters are very important in preventing drug accumulation in cells and may cause drug tolerance or drug resistance. Transporters can modulate drug absorption and disposition (see Chapters 12 and 13). Special families of transporters are important and well documented (You and Morris, 2007). For example, monocarboxylate transporters, organic cation transporters, organic anion transporters, oligopeptide transporters, nucleoside transporters, bile acid transporters, and multidrug resistance protein (eg, P-gP) that modulate distribution of many types of drugs. Drug transporters in the liver, kidney, brain, and gastrointestinal are discussed by You and Morris (2007) (see also Chapter 12 and Fig. 13-1 in Chapter 13). When considering drug utilization and drug–drug interactions, it is helpful to know whether the drug is a substrate for any of the transporters or enzyme systems. It is also important to determine whether the pharmacokinetic models have adequately taken transporter information into consideration.

**Drug Distribution to Cerebral Spinal Fluid, CSF, and Brain: Blood–Brain Barrier**

The blood–brain barrier permits selective entry of drugs into the brain and spinal cord due to (1) anatomical features (as mentioned above) and (2) due to the presence of cellular transporters. Anatomically, the layer of cells around the capillary membranes of the brain acts effectively as a thicker lipid barrier that slows the diffusion and penetration of water-soluble and polar drugs into the brain and spinal cord. However, some small hydrophilic molecules may cross the blood–brain barrier by simple diffusion. Efflux transporter is often found at the entry point into vital organs in the body. P-glycoprotein expression in the endothelial cells of human capillary blood vessels at the blood–brain was detected by special antibodies against the human multidrug-resistance gene product. P-glycoprotein may have a physiological role in regulating the entry of certain molecules into the central nervous system and other organs (Cordoncardo et al, 1989). P-gP substrate examples include doxorubicin, inmervectin, and others. Knocking out P-gP expression can increase brain toxicity with inmervectin in probe studies. Kim et al (1998) studied transport characteristics of protease inhibitor drugs, indinavir, neflfnavir, and saquinavir in vitro using the model P-glycoprotein expressing cell lines and in vivo administration in the mouse model. After IV administration, plasma concentrations of the drug in mdr1a (−/−) mice, the brain concentrations were elevated 7- to 36-fold. These data demonstrate that P-glycoprotein can limit the penetration of these drugs into the brain. Efflux transporters (ie, P-glycoprotein) effectively prevent certain small drug substances to enter into the brain, whereas influx transporters enable small nutrient molecules such as glucose to be actively taken into the brain. There is much interest in understanding the mechanisms for drug uptake into brain in order to deliver therapeutic and diagnostic agents into specific regions of the brain.


**CLINICAL FOCUS**

Jaundice is a condition marked by high levels of bilirubin in the blood. Newborn infants with jaundice are particularly sensitive to the effects of bilirubin since their blood–brain barrier is not well formed at birth. The increased bilirubin, if untreated, may cause jaundice and damage the brain centers of infants caused by increased levels of unconjugated, indirect bilirubin which is free (not bound to albumin). This syndrome is also known as *kernicterus*. Depending on the level of exposure to bilirubin, the effects range from unnoticeable to severe brain damage. Treatment in some cases may require phototherapy that requires a special blue light that helps break down bilirubin in the skin.

**Frequently Asked Questions**

- How does a physical property, such as partition coefficient, affect drug distribution?
- Why do some tissues rapidly take up drugs, whereas for other tissues, drug uptake is slower?
- Does rapid drug uptake into a tissue mean that the drug will accumulate into that tissue?
- What physical and chemical characteristics of a drug would increase or decrease the uptake of the drug into the brain or cerebral spinal fluid?

**APPARENT VOLUME DISTRIBUTION**

The concentration of drug in the plasma or tissues depends on the amount of drug systemically absorbed and the volume in which the drug is distributed. The *apparent volume of distribution*, $V_D$, in a pharmacokinetic model, is used to estimate the extent of drug distribution in the body (see Chapters 3 and 4). Although the apparent volume of distribution does not represent a true anatomical or physical volume, the $V_D$ represents the result of dynamic drug distribution between the plasma and the tissues and accounts for the mass balance of the drug in the body. To illustrate the use of $V_D$, consider a drug dissolved in a simple solution. A volume term is needed to relate drug concentration in the system (or human body) to the amount of drug present in that system. The volume of the system may be estimated if the amount of drug added to the system and the drug concentration after equilibrium in the system are known.

\[
\text{Volume (L)} = \frac{\text{amount (mg) of drug added to system}}{\text{drug concentration (mg/L) in system after equilibrium}}
\]  

(10.3)

Equation 10.3 describes the relationship of concentration, volume, and mass, as shown in Equation 10.4.

\[
\text{Concentration (mg/L) \times volume (L) = mass (mg)}
\]  

(10.4)

**Considerations in the Calculation of Volume of Distribution: A Simulated Example**

The objective of this exercise is to calculate the fluid volume in each beaker and to compare the calculated volume to the real volume of water in the beaker. Assume that three beakers are each filled with 100 mL of aqueous fluid. Beaker 1 contains water only; beakers 2 and 3 each contain aqueous fluid and a small compartment filled with cultured cells. The cells in beaker 2 can bind the drug, while the cells in beaker 3 can metabolize the drug. The three beakers represent the following, respectively:

- **Beaker 1.** Drug distribution in a fluid (water) compartment only, without drug binding and metabolism
- **Beaker 2.** Drug distribution in a fluid compartment containing cell clusters that reversibly bind drugs
- **Beaker 3.** Drug distribution in a fluid compartment containing cell clusters (similar to tissues *in vivo*) in which the drug may be metabolized and the metabolites bound to cells

Suppose 100 mg of drug is then added to each beaker (Fig. 10-7). After the fluid concentration of drug in each beaker is at equilibrium, and the concentration of drug in the water (fluid) compartment has been sampled and assayed, the volume of water may be computed.

![Image](97x326 to 296x333)

**Frequently Asked Questions**

- How does a physical property, such as partition coefficient, affect drug distribution?
- Why do some tissues rapidly take up drugs, whereas for other tissues, drug uptake is slower?
- Does rapid drug uptake into a tissue mean that the drug will accumulate into that tissue?
- What physical and chemical characteristics of a drug would increase or decrease the uptake of the drug into the brain or cerebral spinal fluid?
Case 1

The volume of water in beaker 1 is calculated from the amount of drug added (100 mg) and the equilibrated drug concentration using Equation 10.3. After equilibration, the drug concentration was measured to be 1 mg/mL.

\[
\text{Volume} = \frac{100 \text{ mg}}{1 \text{ mg/mL}} = 100 \text{ mL}
\]

The calculated volume in beaker 1 confirms that the system is a simple, homogeneous system and, in this case, represents the “true” fluid volume of the beaker.

Case 2

Beaker 2 contains cell clusters stuck to the bottom of the beaker. Binding of drug to the proteins of the cells occurs on the surface and within the cytoplasmic interior. This case represents a heterogeneous system consisting of a well-stirred fluid compartment and a tissue (cell). To determine the volume of this system, more information is needed than in Case 1:

1. The amount of drug dissolved in the fluid compartment must be determined. Because some of the drug will be bound within the cell compartment, the amount of drug in the fluid compartment will be less than the 100 mg placed in the beaker.
2. The amount of drug taken up by the cell cluster must be known to account for the entire amount of drug in the beaker. Therefore, both the cell and the fluid compartments must be sampled and assayed to determine the drug concentration in each compartment.
3. The volume of the cell cluster must be determined.

Assume that the above measurements were made and that the following information was obtained:

- Drug concentration in fluid compartment = 0.5 mg/mL
- Drug concentration in cell cluster = 10 mg/mL
- Volume of cell cluster = 5 mL
- Amount of drug added = 100 mg
- Amount of drug taken up by the cell cluster = 10 mg/mL × 5 mL = 50 mg
- Amount of drug dissolved in fluid (water) compartment = 100 mg (total) − 50 mg (in cells) = 50 mg (in water)

Using the above information, the true volume of the fluid (water) compartment is calculated using Equation 10.3.

\[
\text{Volume of fluid compartment} = \frac{50 \text{ mg}}{0.5 \text{ mg/mL}} = 100 \text{ mL}
\]

The value of 100 mL agrees with the volume of fluid we put into the beaker.

If the tissue cells were not accessible for sampling as in the case of in vivo drug administration, the volume of the fluid (water) compartment is calculated using Equation 10.3, assuming the system is homogeneous and that 100 mg drug was added to the system.

\[
\text{Apparent volume} = \frac{100 \text{ mg}}{0.5 \text{ mg/mL}} = 200 \text{ mL}
\]

The value of 200 mL is a substantial overestimation of the true volume (100 mL) of the system.

When a heterogeneous system is involved, the real or true volume of the system may not be accurately calculated by monitoring only one compartment. Therefore, an apparent volume of distribution is calculated and the infrastructure of the system is ignored. The term apparent volume of distribution refers to the lack of true volume characteristics. The apparent volume of distribution is used in pharmacokinetics because the tissue (cellular) compartments are not easily sampled and the true volume is not known. When the experiment in beaker 2 is performed with an equal volume of cultured cells that have different binding affinity for the drug, then the apparent volume of distribution is very much affected by the extent of cellular drug binding (Table 10-3).
As shown in Table 10-3, as the amount of drug in the cell compartment increases (column 3), the apparent \( V_D \) of the fluid compartment increases (column 6). Extensive cellular drug binding effectively pulls drug molecules out of the fluid compartment, decreases the drug concentration in the fluid compartment, and increases \( V_D \). In biological systems, the quantity of cells, cell compartment volume, and extent of drug binding within the cells affect \( V_D \). A large cell volume and/or extensive drug binding in the cells reduce the drug concentration in the fluid compartment and increase the apparent volume of distribution.

In this example, the fluid compartment is comparable to the *central compartment* and the cell compartment is analogous to the peripheral or *tissue compartment*. If the drug is distributed widely into the tissues or concentrates unevenly into the tissues, the \( V_D \) for a drug may exceed the physical volume of the body (about 70 L of total volume or 42 L of body water for a 70-kg subject). Besides cellular protein binding, partitioning of drug into lipid cellular components may greatly inflate \( V_D \). Many drugs have oil/water partition coefficients above 10,000. These lipophilic drugs are mostly concentrated in the lipid phase of adipose tissue, resulting in a very low drug concentration in the extracellular water. Generally, drugs with very large \( V_D \) values have very low drug concentrations in plasma.

A large \( V_D \) is often interpreted as broad drug distribution for a drug, even though many other factors also lead to the calculation of a large apparent volume of distribution. A true \( V_D \) that exceeds the volume of the body is physically impossible. Only if the drug concentrations in both the tissue and plasma compartments are sampled, and the volumes of each compartment are clearly defined, can a true physical volume be calculated.

**Case 3**

The drug in the cell compartment in beaker 3 decreases due to undetected metabolism because the metabolite formed is bound to be inside the cells. Thus, the apparent volume of distribution is also greater than 100 mL. Any unknown source that decreases the drug concentration in the fluid compartment will increase the \( V_D \), resulting in an overestimated apparent volume of distribution. This is illustrated with the experiment in beaker 3. In beaker 3, the cell cluster metabolizes the drug and binds the metabolite to the cells. Therefore, the drug is effectively removed from the fluid concentration. The data for this experiment (note that metabolite is expressed as equivalent intact drug) are as follows:

- Total drug placed in beaker = 100 mg
- Cell compartment:
  - Drug concentration = 0.2 mg/mL
  - Metabolite-bound concentration = 9.71 mg/mL
  - Metabolite-free concentration = 0.29 mg/mL
  - Cell volume = 5 mL
- Fluid (water) compartment:
  - Drug concentration = 0.2 mg/mL
  - Metabolite concentration = 0.29 mg/mL

### Table 10-3: Relationship of Volume of Distribution and Amount of Drug in Tissue (Cellular) Compartment

<table>
<thead>
<tr>
<th>Total Drug (mg)</th>
<th>Volume of Cells (mL)</th>
<th>Drug in Cells (mg)</th>
<th>Drug in Water (mg)</th>
<th>Drug Concentration in Water (mg/mL)</th>
<th>Apparent ( V_D ) in Water (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>15</td>
<td>75</td>
<td>25</td>
<td>0.25</td>
<td>400</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>50</td>
<td>50</td>
<td>0.50</td>
<td>200</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>25</td>
<td>75</td>
<td>0.75</td>
<td>133</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>5</td>
<td>95</td>
<td>0.95</td>
<td>105</td>
</tr>
</tbody>
</table>

*For each condition, the true water (fluid) compartment is 100 mL. Apparent volume of distribution \( (V_D) \) is calculated according to Equation 10.3.*
To calculate the total amount of drug and metabolite in the cell compartment, Equation 10.3 is rearranged as shown:

Total drug and metabolite in cells = 5 mL
\(\times (0.2 + 9.96 + 0.29 \text{ mg/mL}) = 52.45 \text{ mg}\)

Therefore, the total drug and metabolites in the fluid compartment is 100 - 52.45 mg = 47.55 mg.

If only the intact drug is considered, \(V_D\) is calculated using Equation 10.3:

\[V_D = \frac{100 \text{ mg}}{0.2 \text{ mg/mL}} = 500 \text{ mL}\]

Considering that only 100 mL of water was placed into beaker 3, the calculated apparent volume of distribution of 500 mL is an overestimate of the true fluid volume of the system.

The following conclusions can be drawn from this beaker exercise:

1. Drug must be at equilibrium in the system before any drug concentration is measured. In nonequilibrium conditions, the sample removed from the system for drug assay does not represent all parts of the system.
2. Drug binding distorts the true physical volume of distribution when all components in the system are not properly sampled and assayed. Extravascular drug binding increases the apparent \(V_D\).
3. Both intravascular and extravascular drug binding must be determined to calculate meaningful volumes of distribution.
4. The apparent \(V_D\) is essentially a measure of the relative extent of drug distribution outside the plasma compartment. Greater tissue drug binding and drug accumulation increases \(V_D\), whereas greater plasma protein drug binding decreases the \(V_D\) distribution.
5. Undetected cellular drug metabolism increases \(V_D\).
6. An apparent \(V_D\) larger than the combined volume of plasma and body water is indicative of (4) and (5), or both, above.
7. Although the \(V_D\) is not a true physiologic volume, the \(V_D\) is useful to relate the plasma drug concentration to the amount of drug in the body (Equation 10.3). This relationship of the product of the drug concentration and volume to equal the total mass of drug is important in pharmacokinetics.

**PRACTICE PROBLEM**

The amount of drug in the system calculated from \(V_D\) and the drug concentration in the fluid compartment is shown in Table 10-3. Calculate the amount of drug in the system using the true volume and the drug concentration in the fluid compartment.

**Solution**

In each case, the product of the drug concentration (column 5) times the apparent volume of distribution (column 6) yields 100 mg of drug, accurately accounting for the total amount of drug present in the system. For example, 0.25 mg/mL \(\times 400 \text{ mL} = 100 \text{ mg}\). Notice that the total amount of drug present cannot be determined using the true volume and the drug concentration (column 5).

The physiologic approach requires detailed information, including (1) cell drug concentration, (2) cell compartment volume, and (3) fluid compartment volume. Using the physiologic approach, the total amount of drug is equal to the amount of drug in the cell compartment and the amount of drug in the fluid compartment.

\[(15 \text{ mg/mL} \times 5 \text{ mL}) + (100 \text{ mL} \times 0.25 \text{ mg/mL}) = 100 \text{ mg}\]

Each of the two approaches shown above accounts correctly for the amount of drug present in the system. However, the second approach requires more information than is commonly available. The second approach does, however, make more physiologic sense. Most physiologic compartment spaces are not clearly defined for measuring drug concentrations.

**Complex Biological Systems and \(V_D\)**

The above example illustrates how the \(V_D\) represents the apparent volume into which a drug appears to distribute, whether into a beaker of fluid or the
Physiologic Drug Distribution and Protein Binding

Physiologic Drug Distribution and Protein Binding

The human body is a much more complex system than even a beaker of water containing drug-metabolizing cells. Many components within cells, tissues, or organs can bind to or metabolize drug, thereby influencing the apparent $V_D$. Only free, unbound drug diffuses between the plasma and tissue fluids. The tissue fluid, in turn, equilibrates with the intracellular water inside the tissue cells. The tissue drug concentration is influenced by the partition coefficient (lipid/water affinity) of the drug and tissue protein drug binding. The distribution of drug in a biological system is illustrated by Fig. 10-8.

Apparent Volume of Distribution

The apparent volume of distribution in general relates the plasma drug concentration to the amount of drug present in the body. In classical compartment models, $V_{DSS}$ is the volume of distribution determined at steady state when the drug concentration in the tissue compartment is at equilibrium with the drug concentration in the plasma compartment (Fig. 10-9A). In a physiological system involving a drug distributed to a given tissue from the plasma fluid (Fig. 10-9B), the two-compartment model is not assumed, and drug distribution from the plasma to a tissue is equilibrated by perfusion with arterial blood and returned by venous blood. The model parameter $V_{app}$ is used to represent the apparent distribution volume in this model, which is different from $V_{DSS}$ used in the compartment model. Similar to the apparent volume simulated in the beaker experiment in Equation 10.3, $V_{app}$ is defined by Equation 10.5, and the amount of drug in the body is given by Equation 10.6.

\[
V_{app} = \frac{D_B}{C_p} \quad (10.5)
\]

\[
D_B = V_p C_p + V_t C_t \quad (10.6)
\]

where $D_B$ is the amount of drug in the body, $V_p$ is the plasma fluid volume, $V_t$ is the tissue volume, $C_p$ is

![FIGURE 10-8](image.png)  
**FIGURE 10-8** Effect of reversible drug–protein binding on drug distribution and elimination. Drugs may bind reversibly with proteins. Free (nonbound) drugs penetrate cell membranes, distributing into various tissues including those tissues involved in drug elimination, such as kidney and liver. Active renal secretion, which is a carrier-mediated system, may have a greater affinity for free drug molecules compared to plasma proteins. In this case, active renal drug excretion allows for rapid drug excretion despite drug–protein binding. If a drug is displaced from the plasma proteins, more free drug is available for distribution into tissues and interaction with the receptors responsible for the pharmacologic response. Moreover, more free drug is available for drug elimination.
the plasma drug concentration, and $C_t$ is the tissue drug concentration.

For many protein-bound drugs, the ratio of $D_B / C_p$ is not constant over time, and this ratio depends on the nature of dissociation of the protein–drug complex and how the free drug is distributed; the ratio is best determined at steady state. Protein binding to tissue has an apparent effect of increasing the apparent volume of distribution. Several $V_D$ terms were introduced in the classical compartment models (see Chapter 4). However, protein binding was not introduced in those models.

Equation 10.6 describes the amount of drug in the body at any time point between a tissue and the plasma fluid. Instead of assuming the drug distributes to a hypothetical compartment, it was assumed that, after injection, the drug diffuses from the plasma to the extracellular fluid/water, where it further equilibrates with the given tissue. One or more tissue types may be added to the model if needed. If the drug penetrates inside the cell, distribution into the intracellular water may occur. If the volume of body fluid and the protein level are known, this information may be incorporated into the model. Such a model may be more compatible with the physiology and anatomy of the human body.

When using pharmacokinetic parameters from the literature, it is important to note that most calculations of steady-state $V_D$ involve some assumptions on how and where the drug distributes in the body; it could involve a physiologic or a compartmental approach.

For a drug that involves protein binding, some models assume that the drug distributes from the plasma water into extracellular tissue fluids, where the drug binds to extravascular proteins, resulting in a larger $V_D$ due to extravascular protein binding. Unfortunately, drug binding and distribution to lipid tissues are generally not distinguishable. If the pharmacokineticist suspects distribution to body lipids because the drug involved is very lipophilic, he or she may want to compare results simulated with different models before making a final conclusion.

Figure 10-10 lists the steady-state volume of distribution of 10 common drugs in ascending order. Most of these drugs follow multicompartment kinetics with various tissue distribution phases. The physiologic volumes of an ideal 70-kg subject are also plotted for comparison: (1) the plasma (3 L), (2) the extracellular fluid (15 L), and (3) the intracellular fluid (27 L). Drugs such as penicillin, cephalosporin, valproic acid, and furosemide are polar compounds that stay mostly within the plasma and extracellular fluids and therefore have a relatively low $V_D$.

In contrast, drugs with smaller distribution to the extracellular water are more extensively distributed inside the tissues and tend to have a large $V_D$. An excessively high volume of distribution (greater than the body volume of 70 L) is due mostly to special tissue storage, tissue protein binding, carrier, or efflux system which removes drug from the plasma fluid. Digoxin, for example, is bound to myocardial membrane that has drug levels that are 60 and 130 times the serum drug level in adults and children, respectively (Park et al, 1982). The high tissue binding is responsible for the large steady-state volume of distribution (see Chapter 4). The greater drug affinity also results in longer distribution $\alpha$ half-life in spite of the heart’s great vascular blood perfusion. Imipramine is a drug that is highly protein bound and concentrated in the plasma, yet its favorable tissue partition and binding accounts for a large volume of distribution. Several tricyclic antidepressants (TCAs) also have large volumes of distribution due to tissue (CNS) penetration and binding.
**Physiologic Drug Distribution and Protein Binding**

**Frequently Asked Questions**

- Why is the volume of distribution, $V_D$, considered an "apparent" volume and not a "true" anatomic or physiologic volume?
- Can the $V_D$ have a volume equal to a true anatomic volume in the body?

**PROTEIN BINDING OF DRUGS**

Many drugs interact with plasma or tissue proteins or with other macromolecules, such as melanin and DNA, to form a drug–macromolecule complex. The formation of a drug–protein complex is often named drug–protein binding. Drug–protein binding may be a reversible or an irreversible process. **Irreversible** drug–protein binding is usually a result of chemical activation of the drug, which then attaches strongly to the protein or macromolecule by covalent chemical bonding. Irreversible drug binding accounts for certain types of drug toxicity that may occur over a long time period, as in the case of chemical carcinogenesis, or within a relatively short time period, as in the case of drugs that form reactive chemical intermediates. For example, the hepatotoxicity of high doses of acetaminophen is due to the formation of reactive metabolite intermediates that interact with liver proteins.

Most drugs bind or complex with proteins by a reversible process. **Reversible drug–protein binding** implies that the drug binds the protein with weaker chemical bonds, such as hydrogen bonds or van der Waals forces. The amino acids that compose the protein chain have hydroxyl, carboxyl, or other sites available for reversible drug interactions.

Reversible drug–protein binding is of major interest in pharmacokinetics. The protein-bound drug is a large complex that cannot easily transverse the capillary wall and therefore has a restricted distribution (Fig. 10-11). Moreover, the protein-bound...
drug is usually pharmacologically inactive. In contrast, the free or unbound drug crosses cell membranes and is therapeutically active. Studies that critically evaluate drug–protein binding are usually performed *in vitro* using a purified protein such as albumin. Methods for studying protein binding, including equilibrium dialysis and ultrafiltration, make use of a semipermeable membrane that separates the protein and protein-bound drug from the free or unbound drug (Table 10-4). By these *in vitro* methods, the concentrations of bound drug, free drug, and total protein may be determined. Each method for the investigation of drug–protein binding *in vitro* has advantages and disadvantages in terms of cost, ease of measurement, time, instrumentation, and other considerations. Various experimental factors for the measurement of protein binding are listed in Table 10-5.

Drugs may bind to various macromolecular components in the blood, including albumin, α₁-acid glycoprotein, lipoproteins, immunoglobulins (IgG), and erythrocytes (RBC).

*Albumin* is a protein with a molecular weight of 65,000 to 69,000 Da that is synthesized in the liver and is the major component of plasma proteins responsible for reversible drug binding (Table 10-6). In the body, albumin is distributed in the plasma and extracellular water.

### Figure 10-11
Diagram showing that bound drugs will not diffuse across membrane but free drug will diffuse freely between the plasma and extracellular water.

### Table 10-4 Methods for Studying Drug–Protein Binding

<table>
<thead>
<tr>
<th>Method</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibrium dialysis</td>
<td>Gel chromatography</td>
</tr>
<tr>
<td>Dynamic dialysis</td>
<td>Spectrophotometry</td>
</tr>
<tr>
<td>Dialfiltration</td>
<td>Electrophoresis</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Optical rotatory dispersion and circulatory dichroism</td>
</tr>
</tbody>
</table>

### Table 10-5 Considerations in the Study of Drug–Protein Binding

- Equilibrium between bound and free drug must be maintained.
- The method must be valid over a wide range of drug and protein concentrations.
- Extraneous drug binding or drug adsorption onto the apparatus walls, membranes, or other components must be avoided or considered in the method.
- Denaturation of the protein or contamination of the protein must be prevented.
- The method must consider pH and ionic concentrations of the media and Donnan effects due to the protein.
- The method should be capable of detecting both reversible and irreversible drug binding, including fast- and slow-phase associations and dissociations of drug and protein.
- The method should not introduce interfering substances, such as organic solvents.
- The results of the *in vitro* method should allow extrapolation to the *in vivo* situation.

Adapted with permission from Bridges and Wilson (1976).

### Table 10-6 Major Proteins to Which Drugs Bind in Plasma

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular Weight (Da)</th>
<th>Normal Range of Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>65,000</td>
<td>35–50 5–7.5 × 10⁻⁴</td>
</tr>
<tr>
<td>α₁-Acid glycoprotein</td>
<td>44,000</td>
<td>0.4–1.0 0.9–2.2 × 10⁻⁵</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>200,000–3,400,000</td>
<td>Variable</td>
</tr>
</tbody>
</table>

From Tozer (1984), with permission.
in the extracellular fluids of skin, muscle, and various other tissues. Interstitial fluid albumin concentration is about 60% of that in the plasma. The elimination half-life of albumin is 17 to 18 days. Normally, albumin concentration is maintained at a relatively constant level of 3.5% to 5.5% (weight per volume) or 4.5 mg/dL. Albumin is responsible for maintaining the osmotic pressure of the blood and for the transport of endogenous and exogenous substances in the plasma. Albumin complexes with endogenous substances such as free fatty acids (FFAs), bilirubin, various hormones (eg, cortisone, aldosterone, thyroxine, tryptophan), and other compounds. Many weak acidic (anionic) drugs bind to albumin by electrostatic and hydrophobic bonds. Weak acidic drugs such as salicylates, phenylbutazone, and penicillins are highly bound to albumin. However, the strength of the drug binding is different for each drug.

Alpha-1-acid glycoprotein (AAGP) also known as orosomucoid, is a globulin with a molecular weight of about 44,000 Da. The plasma concentration of AAG is low (0.4%–1%) and binds primarily basic (cationic) drugs such as saquinavir, propranolol, imipramine, and lidocaine (see below).

Globulins (α-, β-, γ-globulins) may be responsible for the plasma transport of certain endogenous substances such as corticosteroids. These globulins have a low capacity but high affinity for the binding of these endogenous substances.

**CLINICAL EXAMPLES**

**Case 1**

Dexmedetomidine hydrochloride injection (Precedex®) is an α-2-adrenergic agonist with sedative and analgesic properties that is given intravenously using a controlled infusion device. The pharmacokinetics of dexmedetomidine was studied in volunteers with and without severe renal impairment (De Wolf et al, 2001). The pharmacokinetics of dexmedetomidine differed little in the two groups and there were no significant differences in the hemodynamic responses. The elimination half-life in subjects with renal disease was significantly shorter than in normal subjects: (113.4 ± 11.3 minutes vs 136.5 ± 13.0 minutes; p < 0.05). However, dexmedetomidine resulted in more prolonged sedation in subjects with renal disease. The authors postulated that reduced protein binding in the renal disease patients may be responsible for the prolonged sedation. The drug is mainly cleared by hepatic metabolism and is highly protein bound. The example indicates that simple kinetic extrapolation may be inappropriate in many clinical situations.

- Could reduced protein binding change the concentration of the active drug in the central nervous system, CNS?
- Is the drug a substrate for a transporter?

**Case 2**

Diazepam (Valium) is a benzodiazepine derivative for anxiolytic, sedative, muscle-relaxant, and anticonvulsant effects. Diazepam is highly protein bound (98.7%) in plasma. Ochs et al (1981) examined the effect of changing protein binding on diazepam distribution in subjects with normal renal function versus patients with renal failure. The authors found no significant change in clearance of unbound drug in the subjects with renal failure. Previous studies have suggested that changes in protein binding may be associated with altered drug disposition for some drugs. Ochs et al (1981) also studied diazepam disposition in hyperthyroidism and found no significant difference in diazepam disposition in hyperthyroid patients versus matched controls.

It is important to remember that each drug has a unique molecular structure. Although one drug may have comparable protein binding, the capacity to bind proteins and the drug–protein binding constant may be different among similar drugs, as discussed later in this chapter. Individual patient characteristics and kinetic parameters are also very important. Qin et al (1999) reported great variation in clearance of diazepam among fast and slow metabolizers due to polymorphism of the cytochrome gene (see Chapter 12) that regulates CYP2C19, which is responsible for variation in the half-life of this drug.

**Lipoproteins** are macromolecular complexes of lipids and proteins and are classified according to their density and separation in the ultracentrifuge. The terms VLDL, LDL, and HDL are abbreviations for very-low-density, low-density, and high-density lipoproteins.
The hepatic expression of MDR1 in females was reported as about one-third to one-half of the hepatic P-gP level measured in men. However, another study reported no difference in MDR1 between females and males. Low P-gP activity in the liver was suggested to increase hepatic CYP3A metabolism in some cases. The important point is that a protein such as P-gP can translocate a drug away or closer to the site of the hepatic enzyme and therefore affect the rate of metabolism. A similar situation can occur within the GI tract. This situation explains why first-pass effect is often quite erratic. Pharmacokineticists now use in vitro methods to study both “apical to basolateral” and “basolateral to apical” drug transport to determine if the drug favors mucosal to serosal movement or vice versa.

**EFFECT OF PROTEIN BINDING ON THE APPARENT VOLUME OF DISTRIBUTION**

The extent of drug protein binding in the plasma or tissue affects $V_{D}$. Drugs that are highly bound to plasma proteins have a low fraction of free drug ($f_u = \text{unbound or free drug fraction}$) in the plasma water. The plasma protein–bound drug does not diffuse easily and is therefore less extensively distributed to tissues (see Fig. 10-11). Drugs with low plasma protein binding have larger $f_u$, generally diffuse more easily into tissues, and have a greater volume of distribution. Since the apparent volume of distribution is influenced by lipid solubility in addition to protein binding, there are some exceptions to this rule. However, when several drugs are selected from a single family with close physical and lipid partition characteristics, the apparent volume of distribution may be explained by the relative degree of drug binding to tissue and plasma proteins.

The $V_{D}$ of four cephalosporin antibiotics (Fig. 10-12) in humans and mice (Sawada et al, 1984) demonstrates that the differences in volume of distribution of cefazolin, cefotetan, moxalactam, and cefoperazone are due mostly to differences in the degree of protein binding. For example, the fraction of unbound drug, $f_u$, in the plasma is the highest for lipoproteins, respectively. Lipoproteins are responsible for the transport of plasma lipids to the liver and may be responsible for the binding of drugs if the albumin sites become saturated.

**Gender Differences in Drug Distribution**

Gender differences in drug distribution are now known for many drugs (Anderson, 2005). For example, Meibohm et al (2002) discussed the physiologic impact of P-gP binding to substrate drugs. The human multidrug-resistance gene 1 (MDR1) gene product P-gP are now known to play a major role in absorption, distribution, and/or renal and hepatic excretion of therapeutic agents.
Physiologic Drug Distribution and Protein Binding

223

Cefoperazone in humans and mice, and the volume of distribution is also the highest among the four drugs in both humans and mice. Conversely, cefazolin has the lowest unbound fraction ($f_u$) in humans and is correlated with the lowest volume of distribution. Differences in $V_D$ and $t_{1/2}$ among various species may be due to differences in drug–protein binding. Interestingly, the volume of distribution per kilogram in humans ($V_{human}$) is generally higher than that in mice ($V_{mouse}$) because the fraction of unbound drug is also greater, resulting in a greater volume of distribution. Differences in $V_D$ and $t_{1/2}$ among various species may be due to differences in drug–protein binding. An equation (Equation 10.12) relating quantitatively the effect of protein binding on apparent volume of distribution is derived in the next section.

Drugs such as furosemide, sulfisoxazole, tolbutamide, and warfarin are bound greater than 90% to plasma proteins and have a $V_D$ value ranging from 7.7 to 11.2 L per 70-kg body weight (see Appendix E). Basic drugs such as imipramine, nortriptyline, and propranolol are extensively bound to both tissue and plasma proteins and have very large $V_D$ values. Displacement of drugs from plasma proteins can affect the pharmacokinetics of a drug in several ways: (1) directly increase the free (unbound) drug concentration as a result of reduced binding in the blood; (2) increase the free drug concentration that reaches the receptor sites directly, causing a more intense pharmacodynamic (or toxic) response; (3) increase the free drug concentration, causing a transient increase in $V_D$ and decreasing partly some of the increase in free plasma drug concentration; (4) increase the free drug concentration, resulting in more drug diffusion into tissues of eliminating organs, particularly the liver and kidney, resulting in a transient increase in drug elimination. The ultimate drug concentration reaching the target depends on one or more of these four factors dominating in the clinical situation. The effect of drug–protein binding must be evaluated carefully before dosing changes are made (see below).

**Effect of Changing Plasma Protein: An Example**

The effect of increasing the plasma α1-acid glycoprotein (AAG) level on drug penetration into tissues may be verified with cloned transgenic animals that have 8.6 times the normal AAG levels. In an experiment investigating the activity of the tricyclic antidepressant drug imipramine, equal drug doses were administered to both normal and transgenic mice. Since imipramine is highly bound to AAG, the steady-state imipramine serum level was greatly increased in the blood due to protein binding.

- **Imipramine serum level (transgenic mouse):** 859 ng/mL
- **Imipramine serum level (normal mouse):** 319.9 ng/mL
- **Imipramine brain level (transgenic mouse):** 3862.6 ng/mL
- **Imipramine brain level (normal mouse):** 7307.7 ng/mL

However, the imipramine concentration was greatly reduced in the brain tissue because of higher degree of binding to AAG in the serum, resulting in reduced drug penetration into the brain tissue. The volume of distribution of the drug was reported to be reduced in the transgenic mice. The antidepressant effect was observed to be lower in the transgenic mouse due to lower brain imipramine levels. This experiment illustrates that high drug–protein binding in the serum can reduce drug penetration to tissue receptors for some drugs (Holladay et al, 1996).

**FIGURE 10.12** Plot of $V_D$ of four cephalosporin antibiotics in humans and mice showing the relationship between the fraction of unbound drug ($f_u$) and the volume of distribution. (Data from Sawada et al, 1984.)
Saquinavir mesylate (Invirase) is an inhibitor of the human immunodeficiency virus (HIV) protease. Saquinavir is approximately 98% bound to plasma proteins over a concentration range of 15 to 700 ng/mL. Saquinavir binding in human plasma and control mouse plasma are similar and approximately 2% to 3% unbound. Saquinavir is highly bound to AAG and has reduced free drug concentrations in transgenic mice that express elevated AAG (Holladay et al, 2001). In this study, the drug was bound to both albumin and AAG (2.1% to AAG vs 11.5% to albumin). Elevated AAG caused saquinavir’s volume of distribution to be reduced in this study. In AAG-overexpressing transgenic mice, AAG is genetically increased such that most saquinavir is bound in plasma and only 1.5% is free to be metabolized. The result is a decrease in systemic clearance of saquinavir. His conclusion is consistent with the observations that systemic exposure to saquinavir in HIV-1 subjects is greater than that in healthy subjects and that AAG levels increase with the degree of HIV infection.

According to the approved label, HIV-infected patients administered Invirase (600-mg TID) had AUC and maximum plasma concentration (\(C_{\text{max}}\)) values approximately 2 to 2.5 times those observed in healthy volunteers receiving the same treatment regimen.

For a drug that distributes into the plasma and a given tissue in the body, the amount of drug bound may be found by Equation 10.7. Because drug may bind to both plasma and tissue proteins, the bound and unbound drug concentrations must be considered. At steady state, unbound drug in plasma and tissue are in equilibrium.

\[
D_B = V_p C_p + V_i C_i \tag{10.7}
\]

\[
C_u = C_{\text{ut}}
\]

Alternatively,

\[
C_p f_u = C_i f_{\text{ui}} \tag{10.8}
\]

or

\[
C_i = C_p \frac{f_u}{f_{\text{ui}}} \tag{10.9}
\]

where all terms refer to steady-state conditions: \(f_u\) is the unbound (free) drug fraction in the plasma, \(f_{\text{ui}}\) is the unbound drug fraction in the tissue, \(C_p\) is the unbound drug concentration in the plasma, and \(C_{\text{ut}}\) is the unbound drug concentration in the tissues. Substituting for \(C_i\) in Equation 10.7 using Equation 10.9 results in

\[
D_B = V_p C_p + V_i \left[ C_p \left( \frac{f_u}{f_{\text{ui}}} \right) \right] \tag{10.10}
\]

Rearranging,

\[
\frac{D_B}{C_p} = V_p + V_i \left( \frac{f_u}{f_{\text{ui}}} \right) \tag{10.11}
\]

Because \(D_B/C_p = V_{\text{app}}\), by substitution into Equation 10.11, \(V_{\text{app}}\) may be estimated by Equation 10.12:

\[
V_{\text{app}} = V_p + V_i \left( \frac{f_u}{f_{\text{ui}}} \right) \tag{10.12}
\]

Equation 10.12 relates the amount of drug in the body to plasma volume, tissue volume, and fraction of free plasma and tissue drug in the body. Equation 10.12 may be expanded to include several tissue organs with \(V_i\) each with unbound tissue fraction \(f_{\text{ui}}\).

\[
V_{\text{app}} = V_p + \sum V_i \left( \frac{f_u}{f_{\text{ui}}} \right)
\]

where \(V_i = \) tissue volume of the \(i\)th organ and \(f_{\text{ui}} = \) unbound fraction of the \(i\)th organ.

The following are important considerations in the calculation of \(V_{\text{app}}\):

1. The volume of distribution is a constant only when the drug concentrations are in equilibrium between the plasma and tissue.
2. Values of \(f_u\) and \(f_{\text{ui}}\) are concentration dependent and must also be determined at equilibrium conditions.
3. Equation 10.12 shows that \(V_{\text{app}}\) is an indirect measure of drug binding in the tissues rather than a measurement of a true anatomic volume.
4. When \(f_u\) and \(f_{\text{ui}}\) are unity, Equation 10.12 is simplified to

\[
\frac{D_B}{C_p} = V_p + V_i
\]

When no drug binding occurs in tissue and plasma, the volume of distribution will not exceed the real
anatomic volume. Only at steady state are the unbound plasma drug concentration, \( C_u \), and the tissue drug concentration, \( C_t \), equal. At any other time, \( C_u \) may not equal to \( C_t \). The amount of drug in the body, \( D_b \), cannot be calculated easily from \( V_{app} \) and \( C_u \) under nonequilibrium conditions. For simplicity, some models assume that the drug distributed to a tissue is approximated by the drug present in the fluid of that tissue. The tissue fluid volume is then represented by the volume of the extracellular/intracellular fluid, depending on drug penetration. Such a model fails to consider drug partition into fatty tissues/lipids, and simulates extravascular drug distribution based solely on protein binding. A number of drugs have a large volume of distribution despite high protein binding to plasma proteins. Some possible reasons for this high volume of distribution could be due to strong tissue drug partition and/or high intracellular or receptor binding within the tissue. Under these situations, the model discussed above does not adequately describe the in vivo drug distribution.

In contrast, when the data are analyzed by the compartmental model, no specific binding interpretation is made. The analyst may interpret a large apparent volume due to either partition to fatty tissues or extravascular binding based on other observations. Compartment models are based on mass balance and focus on the amount of drug in each compartment and not on the tissue volume or tissue drug concentration. The tissue volume and drug concentrations are theoretical and do not necessarily reflect true physiologic values. Even the \( C_t \) may not be uniform in local tissues and under disease conditions.

**Frequently Asked Questions**

- Is it possible for \( V_p \) to exceed a patient’s actual physiologic volume? If so, why?
- How does protein binding influence \( V_p \)?
- What are \( f_{ut} \) and \( f_u \)? Are they constant?

**PRACTICE PROBLEM**

Drug A and drug B have \( V_{app} \) of 20 and 100 L, respectively. Both drugs have a \( V_p \) of 4 L and a \( V_t \) of 10 L, and they are 60% bound to plasma protein. What is the fraction of tissue binding of the two drugs? Assume that \( V_p \) is 4 L and \( V_t \) is 10 L.

**Solution**

**Drug A**

Applying Equation 10.12,

\[
V_{app} = V_p + V_t \left( \frac{f_u}{f_{ut}} \right)
\]

Because drug A is 60% bound, the drug is 40% free, or \( f_u = 0.4 \).

\[
20 = 4 + 10 \left( \frac{0.4}{f_{ut}} \right)
\]

\[
f_{ut} = \frac{4}{16} = 0.25
\]

The fraction of drug bound to tissues is \( 1 - 0.25 = 0.75 \) or 75%.

**Drug B**

\[
100 = 4 + 10 \left( \frac{0.4}{f_{ut}} \right)
\]

\[
f_{ut} = 0.042
\]

The fraction of drug bound to tissues is \( 1 - 0.042 = 0.958 = 95.8\% \).

In this problem, the percent free (unbind) drug for drug A is 25% and the percent free drug for drug B is 4.2% in plasma fluid. Drug B is more highly bound to tissue, which results in a larger apparent volume of distribution. This approach assumes a pooled tissue group because it is not possible to identify physically the tissue group to which the drug is bound.

Equation 10.12 may explain the wide variation in the apparent volumes of distribution for drugs observed in the literature (Tables 10-7–10-9). Drugs in Table 10-7 have small apparent volumes of distribution due to plasma drug binding (less than 10 L when extrapolated to a 70-kg subject). Drugs in Table 10-8 show that, in general, as the fraction of unbound drug, \( f_u \), in the plasma increases, the apparent volume increases. Reduced drug binding in the plasma results in increased free drug concentration, which diffuses into the extracellular water. Drugs showing exceptionally large volumes of distribution...
may have unusual tissue binding. Some drugs move into the interstitial fluid but are unable to diffuse across the plasma membrane into the intracellular fluids, thereby reducing the volume of distribution. Drugs in Table 10-9 apparently do not obey the general binding rule, because their volumes of distribution are not related to plasma drug binding. These drugs have very large volumes of distribution and may have undiscovered tissue binding or tissue metabolism. Based on their pharmacologic activities, presumably all these drugs penetrate into the intracellular space.

### CLINICAL EXAMPLE

The serum protein binding of azithromycin is concentration dependent, ranging from 51% at 0.02 µg/mL to 7% at 2.0 µg/mL as reported in the literature. Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Higher azithromycin concentrations in tissues than in plasma or serum have been observed.

- What is the apparent $V_D$ for a subject weighing 70 kg?
- Is the apparent greater or lower than the plasma volume of the body for this subject?
- Do you think protein binding affects the distribution of this drug?

#### Solution

\[ V_D = 70 \times 31.1 = 2191 \text{ L} \]
Electrolyte Balance

Electrolyte balance affects the movement of fluid in the body. The kidney is the main regulator of electrolyte balance. Albumin is synthesized in the liver and is the main component of plasma proteins. The plasma albumin concentration contributes to osmotic pressure in the blood. Plasma albumin concentration may be increased during hypovolemia (loss of plasma volume due to movement fluid into extracellular fluid and other various factors such as dehydration, shocks, excessive blood loss, etc) or decreased during hypervolemia (increase in plasma volume due to various causes such as excessive fluid intake, sodium retention, congestive heart failure, etc). Changes in plasma protein concentration and in plasma drug–protein binding may occur to various degrees, thus affecting drug disposition. Disease conditions may cause changes in protein concentration and drug–protein binding, thus altering the protein distribution in the body. An altered protein concentration and binding may result in more non protein-bound drug resulting in a more intense pharmacodynamic effect and a change in the rate of drug elimination.

### RELATIONSHIP OF PLASMA DRUG–PROTEIN BINDING TO DISTRIBUTION AND ELIMINATION

In general, drugs that are highly bound to plasma protein have reduced overall drug clearance. For a drug that is metabolized mainly by the liver, binding to plasma proteins prevents the drug from entering the hepatocytes, resulting in reduced hepatic drug metabolism. In addition, bound drugs may not be available as substrates for liver enzymes, thereby further reducing the rate of metabolism.

Protein-bound drugs act as larger molecules that cannot diffuse easily through the capillary membranes in the glomeruli. The elimination half-lives of some drugs such as the cephalosporins, which are excreted mainly by renal excretion, are generally increased when the percent of drug bound to plasma proteins increases (Table 10-10). The effect of serum protein binding on the renal clearance and elimination half-life on several tetracycline analogs is shown in Table 10-11. For example, doxycycline, which is 93% bound to serum proteins, has an elimination half-life of 15.1 hours, whereas oxytetracycline,

<table>
<thead>
<tr>
<th>Protein Bound (%)</th>
<th>$t_{1/2}$ (h)</th>
<th>Renal Clearance (mL/min/1.73 m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>96</td>
<td>8.0</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>90</td>
<td>1.8</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>85</td>
<td>3.3</td>
</tr>
<tr>
<td>Ceforanide</td>
<td>81</td>
<td>3.0</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>70</td>
<td>1.7</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>52</td>
<td>2.3</td>
</tr>
<tr>
<td>Cefsulodin</td>
<td>26</td>
<td>1.5</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>22</td>
<td>1.9</td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>21</td>
<td>1.5</td>
</tr>
</tbody>
</table>

From Houin (1985), with permission.
which is 35.4% bound to serum proteins, has an elimination half-life of 9.2 hours. On the other hand, drug that is both extensively bound and actively secreted by the kidneys, such as penicillin, has a short elimination half-life, because active secretion takes preference in removing or stripping the drug from the proteins as the blood flows through the kidney.

Some cephalosporins are excreted by both renal and biliary secretion. The half-lives of drugs that are significantly excreted in the bile do not correlate well with the extent of plasma protein binding.

**Relationship between \( V_D \) and Drug Elimination Half-Life**

Drug elimination is governed mainly by renal and various metabolic processes in the body. However, extensive drug distribution has the effect of diluting the drug in a large volume, making it harder for the kidney to filter the drug by glomerular filtration. Thus, the \( t_{1/2} \) of the drug is prolonged if clearance (\( CL \)) is constant and \( V_D \) is increased according to Equation 10.13. \( CL \) is related to apparent volume of distribution, \( V_D \), and the elimination constant \( k \), as shown in Equation 10.13 (see also Chapter 3).

\[
CL = kV_D \quad (10.13)
\]

For a first-order process, \( CL \) is the product of \( V_D \) and the elimination rate constant, \( k \), according to Equation 10.13. The equation is derived for a given drug dose distributed in a single volume of body fluid without protein binding. The equation basically describes the empirical observation that either a large clearance or large volume of distribution leads to low plasma drug concentrations after a given dose. Mechanistically, a relatively low plasma drug concentration from a given dose may be due to (1) extensive distribution into tissues due to favorable lipophilicity, (2) extensive distribution into tissues due to protein binding in peripheral tissues, and/or (3) lack of drug plasma protein binding.

Two drug examples are selected to illustrate further the relationship between elimination half-life, clearance, and the volume of distribution. Although the kinetic relationship is straightforward, there is more than one way of explaining the observations.

**CLINICAL EXAMPLES**

**Drug with a Large Volume of Distribution and a Long Elimination \( t_{1/2} \)**

The macrolide antibiotic dirithromycin is extensively distributed in tissues, resulting in a large steady-state volume of distribution of about 800 L (range 504–1041 L). The elimination \( t_{1/2} \) in humans is about 44 hours (range 16–65 h). The drug has a relatively large total body clearance of 226 to 1040 mL/min (13.6–62.4 L/hours) and is given once daily. In this case, clearance is large due to a large \( V_D \), whereas \( k \) is relatively small. In this case, \( CL \) is large but the elimination half-life is longer because of the large \( V_D \). Intuitively, the drug will take a long time to be removed when the drug is distributed extensively over a large volume; despite a relatively large clearance, \( t_{1/2} \) accurately describes drug elimination alone.
Drug with a Small Volume of Distribution and a Long Elimination $t_{1/2}$

Tenoxicam is a nonsteroidal anti-inflammatory drug (Nilsen, 1994) that is about 99% bound in human plasma protein. The drug has low lipophilicity, is highly ionized (approximately 99%), and is distributed in blood. Because tenoxicam is very polar, the drug penetrates cell membranes slowly. The synovial fluid peak drug level is only one-third of that of the plasma drug concentration and occurs 20 hours (range 10–34 h) later than the peak plasma drug level. In addition, the drug is poorly distributed to body tissues and has an apparent volume of distribution, $V_D$, of 9.6 L (range 7.5–11.5 L). Tenoxicam has a low total plasma clearance of 0.106 L/h (0.079–0.142 L/h) and an elimination half-life of 67 hours (range 49–81 hours), undoubtedly related to the extensive drug binding to plasma proteins.

According to Equation 10.13, drug clearance from the body is small if $V_D$ is small and $k$ is not too large. This relationship is consistent with a small $Cl$ and a small $V_D$ observed for tenoxicam. Equation 10.4, however, predicts that a small $V_D$ would result in a small elimination $t_{1/2}$. In this case, the actual elimination half-life is long (67 hours) because the plasma tenoxicam clearance is so low that it dominates in Equation 10.4. The long elimination half-life of tenoxicam is better explained by restrictive drug clearance due to its binding to plasma protein, making it difficult for the drug to clear rapidly.

Clearance

Some pharmacokineticists regard $Cl$ and $V_D$, as independent model variables based on Equation 10.14. Equation 10.13 and its equivalent, Equation 10.14, are rooted in classical pharmacokinetics. Initially, it may be difficult to understand why a drug such as dirithromycin, with a rapid clearance of 226 to 1040 mL/min, has a long half-life. In pharmacokinetics, the elimination constant $k = 0.0156$ h$^{-1}$ implies that 1/64 (ie, 0.0156 h$^{-1}$ = 1/64) of the drug is cleared per hour (a low-efficiency elimination factor). From the elimination rate constant $k$, one can estimate that it takes 44 hours ($t_{1/2} = 44$ hours) to eliminate half the drug in the body, regardless of $V_D$. While $t_{1/2}$ is dependent on clearance and $V_D$ as shown by Equation 10.4, clearance is clearly affected by the volume of distribution and by many variables of the drug in the biological system. In patients with ascites, clearance is increased but with no increase in half-life, reflecting the increase in volume of distribution in ascitic patients (Stoeckel et al, 1983).

Frequently Asked Questions

- Does a large value for clearance always result in a short half-life? Explain.
- What are the causes of a long distribution half-life for a body organ if blood flow to the tissue is rapid?
- How long does it take for a tissue organ to be fully equilibrated with the plasma? How long for a tissue organ to be half-equilibrated?
- When a body organ is equilibrated with drug from the plasma, is the drug concentration in that organ the same as that of the plasma?
- What is the parameter that tells when half of the protein binding sites are occupied?

Elimination of Protein-Bound Drug: Restrictive versus Nonrestrictive Elimination

When a drug is tightly bound to a protein, only the unbound drug is assumed to be metabolized; drugs belonging to this category are described as restrictively eliminated. On the other hand, some drugs may be eliminated even when they are protein bound; drugs in this category are described as nonrestrictively eliminated. Nonrestrictively cleared drugs are normally rapidly eliminated since protein binding does not impede the elimination process. Examples of nonrestrictively cleared drugs include morphine, metoprolol, and propranolol. Para-aminohippuratic acid is also nonrestrictively cleared by the kidney and useful as a marker for renal blood flow.

If a clinician fails to consider the role of restrictive versus nonrestrictive elimination, serious dosage miscalculations may be made with regard in response to the addition of inhibitors or changes in protein concentration. Nonrestrictively cleared drugs are less influenced by changes in protein binding since drug elimination is not affected. However, free drug diffusion
may be affected by a change in free fraction. Therefore, when some drugs with varying fractions of plasma protein binding are compared, the expected reduction in clearance for drugs with low protein binding is sometimes absent or very minor. However, restrictively cleared drugs will exhibit a relationship between total drug concentration and protein concentration, though the free drug concentration may not change because of the resulting proportional changes in elimination. Therefore, whether a drug is restrictively or nonrestrictively eliminated must be considered when determining the role of changes in protein binding or inhibitors. The effect of protein binding on the kinetics of drug clearance in an organ system is discussed in detail in Chapter 11.

In practice, the molecular effect of protein binding on elimination is not always predictable. Drugs with restrictive elimination are recognized by very small plasma clearances and extensive plasma protein binding. The hepatic extraction ratios (ERs) for drugs that are restrictively eliminated are generally small, because of strong protein binding. Their hepatic extraction ratios are generally smaller than their unbound fractions in plasma (ie, ER < \( f_u \)). For example, phenylbutazone and the oxicams, including piroxicam, isoxicam, and tenoxicam, all have hepatic extraction ratios smaller than their unbound fraction in plasma (Verbeeck and Wallace, 1994). The hepatic elimination for these drugs is therefore restrictive. A series of nonsteroid anti-inflammatory drugs (NSAIDs) were reported by the same authors to be nonrestrictive with the following characteristics: (1) drug elimination is exclusively hepatic, (2) bioavailability of the drug from an oral dosage form is complete, and (3) these drugs do not undergo extensive reversible biotransformation or enterohepatic circulation.

Propranolol is a drug that has low bioavailability with a hepatic extraction ratio, ER, of 0.7 to 0.9. Propranolol is 89% bound, ie, 11% free (or \( f_u = 0.11 \)) so that ER > \( f_u \). Thus, propranolol is considered to be nonrestrictively eliminated. The bioavailability of propranolol is very low because of the large first-pass effect, and its elimination half-life is relatively short.

In contrast, highly bound drugs such as warfarin (99% bound) and diazepam (98% bound) have an average long half-life of about 37 hours (see Appendix E). Reasons for a long half-life drug in the body may include a high degree of protein binding, a lower fraction of drug metabolized, and having drug molecular properties (eg, lipophilicity) that favor extravascular partitioning into tissues.

**CLINICAL EXAMPLE**

Diazepam (Valium®) has an average elimination half-life of 37 hours and \( V_d \) of 77 L and is mainly eliminated by demethylation.

- Is diazepam slowly eliminated due to the extensive binding to protein, a large \( V_d \) or simply because diazepam has a low metabolic rate (or low extraction ratio, ER)?

Recent studies with CYP 2C9 have shown that drug protein binding is not the only reason for small clearance and a long \( t_{1/2} \) of diazepam (Qin et al, 1999). Diazepam demethylation varies greatly among individuals due to genetic polymorphism (see Chapter 12). In some subjects, slow metabolism is the main cause for a longer elimination half-life. The half-lives of diazepam ranged from 20 to 84 hours (Qin et al, 1999). Clearance ranged from 2.8 ± 0.9 mL/min (slow metabolizer) to the fast metabolizers (19.5 ± 9.8 mL/min). The long half-life is, in part, due to the small ER in some subjects. The elimination half-lives are shorter in subjects who are fast metabolizers, although the elimination half-lives are still quite long due to the large volume of distribution of this drug (small \( k \) and large \( V_d \)). It is important to keep in mind that free drug concentration and how it sustains ultimately determines pharmacologic effect and duration of action. Based on a well-stirred venous equilibrium model (Benet and Hoener, 2002), and a given set of assumptions, one can predict that the free AUC or systemic exposure of an orally administered drug will not be affected by protein binding despite its high degree of binding since the free AUC is not affected by \( f_u \). In general, the approach is quite useful for many drugs with receptor sites within the plasma compartment discussed earlier. In the case of diazepam, pharmacological effect occurs in the brain and penetration across the CNS may not be adequately considered by the equations of one-compartment model. The risk of unknown metabolism or uptake within cells outside
Physiologic Drug Distribution and Protein Binding

the plasma compartment is always present. (See illustrated in vitro examples for \( V_D \) in the beginning of this chapter).

Schmidt et al (2010) recently reviewed the effect of protein binding of various drugs, and they characterized various situations in which steady-state free drug concentrations may or may not be affected by protein binding. The article discussed a group of benzodiazepines with different degrees of protein binding and reported that penetration into CNS is better related to the free drug concentration, ie, after correcting for protein binding. The benzodiazepines studied were (1) flunitrazepam, 85% bound, (2) midazolam, 96%, (3) oxazepam, 91%, and (4) clobazam, 69%. The authors concluded that for each drug, the pharmacokinetics and pharmacodynamics should be considered instead of a generalized “one-size-fit-all” approach. Schmidt et al (2010) also discuss various situations that may cause changes in half-life as a result of changes in protein–drug binding. Furthermore, Schmidt et al (2010) conclude that “plasma protein binding can have multiple effects on the pharmacokinetics and pharmacodynamics of a drug and a simple, generalized guideline for the evaluation of the clinical significance of protein binding frequently cannot be applied.” These authors propose that a careful analysis of protein-binding effects must be made on a drug-by-drug basis.

**Frequently Asked Question**

Why is it important to report detailed information of the pharmacokinetics of a drug including the number and demographics of the subjects and the nature of drug elimination when citing mean clearance or half-life data from a table in the literature?

**DETERMINANTS OF PROTEIN BINDING**

Drug–protein binding is influenced by a number of important factors, including the following:

1. The drug
   - Physicochemical properties of the drug
   - Total concentration of the drug in the body

2. The protein
   - Quantity of protein available for drug–protein binding
   - Quality or physicochemical nature of the protein synthesized

3. The affinity between drug and protein
   - Includes the magnitude of the association constant

4. Drug interactions
   - Competition for the drug by other substances at a protein-binding site
   - Alteration of the protein by a substance that modifies the affinity of the drug for the protein; for example, aspirin acetylates lysine residues of albumin

5. The pathophysiologic condition of the patient
   - For example, drug–protein binding may be reduced in uremic patients and in patients with hepatic disease

Plasma drug concentrations are generally reported as the total drug concentration in the plasma, including both protein-bound drug and unbound (free) drug concentrations. Most literature values for the therapeutic effective drug concentrations refer to the total plasma or serum drug concentration. For therapeutic drug monitoring, the total plasma drug concentrations are generally used in the development of the appropriate drug dosage regimen for the patient. In the past, measurement of free drug concentration was not routinely performed in the laboratory. More recently, free drug concentrations may be measured quickly using ultrafiltration thereby allowing the measure of the drug concentration available to the drug receptor. Because of the high plasma protein binding of phenytoin and the narrow therapeutic index of the drug, more hospital laboratories are measuring both free and total phenytoin plasma levels.

**CLINICAL EXAMPLE**

Macfie et al (1992) studied the disposition of intravenous dosing of alfentanil in six patients who suffered 10% to 30% surface area burns compared with a control group of six patients matched for age, sex, and weight. Alfentanil binding to plasma proteins was measured by equilibrium dialysis. The burn
patients had significantly greater concentrations of AAG and smaller concentrations of albumin. The mean protein binding of alfentanil was 94.2% ± 0.05 (SEM) in the burn group and 90.7% ± 0.4 in the control group (p = 0.004). A good correlation was found between AAG concentration and protein binding. The greater AAG concentrations in the burn group corresponded with significantly reduced volume of distribution and total clearance of alfentanil. The clearance of the unbound fraction and the elimination half-life of alfentanil were not decreased significantly.

KINETICS OF PROTEIN BINDING

The kinetics of reversible drug–protein binding for a protein with one simple binding site can be described by the law of mass action, as follows:

\[
\text{Protein} + \text{drug} \rightleftharpoons \text{drug–protein complex}
\]

or

\[
[P] + [D] \rightleftharpoons [PD]
\]  
(10.15)

From Equation 10.15 and the law of mass action, an association constant, \( K_a \) (also called the affinity constant), can be expressed as the ratio of the molar concentration of the products and the molar concentration of the reactants. This equation assumes only one binding site per protein molecule.

\[
K_a = \frac{[PD]}{[P][D]}
\]  
(10.16)

The extent of the drug–protein complex formed is dependent on the association binding constant, \( K_a \). The magnitude of \( K_a \) yields information on the degree of drug–protein binding. Drugs strongly bound to protein have a very large \( K_a \) and exist mostly as the drug–protein complex. With such drugs, a large dose may be needed to obtain a reasonable therapeutic concentration of free drug.

Most kinetic studies in vitro use purified albumin as a standard protein source because this protein is responsible for the major portion of plasma drug–protein binding. Experimentally, both the free drug \([D]\) and the protein-bound drug \([PD]\), as well as the total protein concentration \([P] + [PD]\), may be determined. To study the binding behavior of drugs, a determinable ratio \( r \) is defined, as follows:

\[
r = \frac{\text{moles of drug bound}}{\text{total moles of protein}}
\]

Because moles of drug bound is \([PD]\) and the total moles of protein is \([P] + [PD]\), this equation becomes

\[
r = \frac{[PD]}{[PD]+[P]}
\]  
(10.17)

According to Equation 10.16, \([PD] = K_a [P] [D]\); by substitution into Equation 10.17, the following expression is obtained:

\[
r = \frac{K_a [P][D]}{K_a [P][D]+[P]}
\]  
(10.18)

This equation describes the simplest situation, in which 1 mole of drug binds to 1 mole of protein in a 1:1 complex. This case assumes only one independent binding site for each molecule of drug. If there are \( n \) identical independent binding sites per protein molecule, then the following is used:

\[
r = \frac{nK_A[D]}{1+K_A[D]}
\]  
(10.19)

In terms of \( K_d \), which is \( 1/K_a \), Equation 10.19 reduces to

\[
r = \frac{n[D]}{K_d + [D]}
\]  
(10.20)

Protein molecules are quite large compared to drug molecules and may contain more than one type of binding site for the drug. If there is more than one type of binding site and the drug binds independently to each binding site with its own association constant, then Equation 10.20 expands to

\[
r = \frac{n_1K_{1}[P]}{1+K_{1}[D]} + \frac{n_2K_{2}[P]}{1+K_{2}[D]} + \ldots
\]  
(10.21)

where the numerical subscripts represent different types of binding sites, the \( Ks \) represent the binding constants, and the \( ns \) represent the number of binding sites per molecule of albumin.

These equations assume that each drug molecule binds to the protein at an independent binding site,
and the affinity of a drug for one binding site does not influence binding to other sites. In reality, drug–protein binding sometimes exhibits a phenomenon of cooperativity. For these drugs, the binding of the first drug molecule at one site on the protein molecule influences the successive binding of other drug molecules. The binding of oxygen to hemoglobin is an example of drug cooperativity.

Each method for the investigation of drug–protein binding in vitro has advantages and disadvantages in terms of cost, ease of measurement, time, instrumentation, and other considerations. Drug–protein binding kinetics yield valuable information concerning proper therapeutic use of the drug and predictions of possible drug interactions.

PRACTICAL FOCUS

1. How is \( r \) related to the fraction of drug bound \( \left( f_u \right) \), a term that is often of clinical interest?

Solution

\( r \) is the ratio of number of moles of drug bound/number of moles of albumin. \( r \) determines the fraction of drug binding sites that are occupied. \( f_u \) is based on the fraction of drug which is free in the plasma. The value of \( f_u \) is often assumed to be fixed. However, \( f_u \) may change, with changes in drug concentration, especially with drugs that have therapeutic levels close to \( K_d \). (See examples on diazoxide.)

2. At maximum drugs binding, the number of binding sites is \( n \) (see Equation 10.21). The drug disopyramide has a \( K_d = 1 \times 10^{-6} \) M/L. How close to saturation is the drug when the free drug concentration is \( 1 \times 10^{-6} \) M/L?

Solution

Substitution for \( [D] = 1 \times 10^{-6} \) M/L and \( K_d = 1 \times 10^{-6} \) M/L in Equation 10.21 gives

\[
 r = \frac{n}{2}
\]

When \( n = 1 \) and the unbound (free) drug concentration is equal to \( K_d \), the protein binding of the drug is half-saturated. Interestingly, when \( [D] \) is much greater than \( K_d \), \( K_d \) is negligible in

Equation 10.21, and \( r = n \) (ie, \( r \) is independent of concentration or fully saturated).

When \( K_d > [D] \), \([D]\) is negligible in the denominator of Equation 10.21, and \( r \) is dependent on \( n/K_d[D] \), or \( nK_d[D] \). In this case, the number of sites bound is directly proportional to \( n \), \( K_d \), and the free drug concentration \([D]\). This relationship also explains why a drug with a higher \( K_d \) may not necessarily have a higher percent of drug bound, because the number of binding sites, \( n \), may be different from one drug to another. At higher \([D]\), the relationship between \([PD]\) and \([D]\) may no longer be linear.

DETERMINATION OF BINDING CONSTANTS AND BINDING SITES BY GRAPHIC METHODS

In Vitro Methods (Known Protein Concentration)

A plot of the ratio of \( r \) (moles of drug bound per mole of protein) versus free drug concentration \([D]\) is shown in Fig. 10-13. Equation 10.20 shows that as free drug concentration increases, the number of moles of drug bound per mole of protein becomes saturated and plateaus. Thus, drug protein binding resembles a Langmuir adsorption isotherm, which is also similar to the process where adsorption of a drug to an adsorbent becomes saturated as the drug concentration increases. Because of nonlinearity in
drug–protein binding, Equation 10.20 is rearranged for the estimation of \( n \) and \( K_a \), using various graphic methods as discussed in the next section.

The values for the association constants and the number of binding sites are obtained by various graphic methods. The reciprocal of Equation 10.20 gives the following equation:

\[
\frac{1}{r} = \frac{1}{n K_a[D]} + \frac{1}{nK_D} \tag{10.22}
\]

A graph of \( 1/r \) versus \( 1/[D] \) is called a double reciprocal plot. The \( y \) intercept is \( 1/n \) and the slope is \( 1/nK_a \). From this graph (Fig. 10-14), the number of binding sites may be determined from the \( y \) intercept, and the association constant may be determined from the slope, if the value for \( n \) is known.

If the graph of \( 1/r \) versus \( 1/[D] \) does not yield a straight line, then the drug–protein binding process is probably more complex. Equation 10.20 assumes one type of binding site and no interaction among the binding sites. Frequently, Equation 10.22 is used to estimate the number of binding sites and binding constants, using computerized iteration methods.

Another graphic technique called the Scatchard plot, is a rearrangement of Equation 10.20. The Scatchard plot spreads the data to give a better line for the estimation of the binding constants and binding sites. From Equation 10.20, we obtain

\[
\frac{r}{D} = \frac{nK_a[D]}{1 + K_a[D]}
\]

\[
r + rK_a[D] = nK_a[D]
\]

\[
r = nK_a[D] - rK_a[D]
\]

\[
\frac{r}{D} = nK_a - rK_a
\]

A graph constructed by plotting \( r/D \) versus \( r \) yields a straight line with the intercepts and slope shown in Figs. 10-15 and 10-16.

Some drug–protein binding data produce Scatchard graphs of curvilinear lines (Figs. 10-17 and 10-18). The curvilinear line represents the summation of two straight lines that collectively form the curve. The binding of salicylic acid to albumin is an example of this type of drug–protein binding in which there are at least two different, independent binding sites (\( n_1 \) and \( n_2 \)), each with its own independent association constant (\( k_1 \) and \( k_2 \)). Equation 10.21 best describes this type of drug–protein interaction.

**In Vivo Methods (Unknown Protein Concentration)**

Reciprocal and Scatchard plots cannot be used if the exact nature and amount of protein in the experimental system is unknown. The percent of drug bound is often used to describe the extent of drug–protein binding in the plasma. The fraction of drug bound, \( \beta \), can be determined experimentally and is equal to the ratio of the concentration of bound drug, \([D]_p\), and the total drug concentration, \([D]_t\), in the plasma, as follows:

\[
\beta = \frac{[D]_p}{[D]_t}
\]

A graph constructed by plotting \( r/D \) versus \( r \) yields a straight line with the intercepts and slope shown in Figs. 10-15 and 10-16.

Some drug–protein binding data produce Scatchard graphs of curvilinear lines (Figs. 10-17 and 10-18). The curvilinear line represents the summation of two straight lines that collectively form the curve. The binding of salicylic acid to albumin is an example of this type of drug–protein binding in which there are at least two different, independent binding sites (\( n_1 \) and \( n_2 \)), each with its own independent association constant (\( k_1 \) and \( k_2 \)). Equation 10.21 best describes this type of drug–protein interaction.
The value of the association constant $K_a$ can be determined, even though the nature of the plasma proteins binding the drug is unknown, by rearranging Equation 10.24 into Equation 10.25:

$$ r \frac{[D_b]}{[D_T]} = \frac{nK_a[D]}{1 + K_a[D]} $$

where $[D_b]$ is the bound drug concentration; $[D]$ is the free drug concentration; and $[P_T]$ is the total protein concentration. Rearrangement of this equation gives the following expression, which is analogous to the Scatchard equation:

$$ \frac{[D_b]}{[D]} = nK_a[P_T] - K_a[D_b] $$

Concentrations of both free and bound drug may be found experimentally, and a graph obtained by plotting $[D_b]/[D]$ versus $[D_b]$ will yield a straight line for which the slope is the association constant $K_a$. Equation 10.26 shows that the ratio of bound $C_p$ to free $C_p$ is influenced by the affinity constant, the protein concentration, $[P_T]$, which may change during disease states, and the drug concentration in the body.

The values for $n$ and $K_a$ give a general estimate of the affinity and binding capacity of the drug, as plasma contains a complex mixture of proteins. The drug–protein binding in plasma may be influenced by...
competing substances such as ions, free fatty acids, drug metabolites, and other drugs. Measurements of drug–protein binding should be obtained over a wide drug concentration range, because at low drug concentrations a high-affinity, low-capacity binding site might be missed or, at a higher drug concentration, saturation of protein-binding sites might occur.

**Relationship between Protein Concentration and Drug Concentration in Drug–Protein Binding**

The drug concentration, the protein concentration, and the association (affinity) constant, $K_a$, influence the fraction of drug bound (Equation 10.24). With a constant concentration of protein, only a certain number of binding sites are available for a drug. At low drug concentrations, most of the drug may be bound to the protein, whereas at high drug concentrations, the protein-binding sites may become saturated, with a consequent rapid increase in the free drug concentrations (Fig. 10-19).

To demonstrate the relationship of the drug concentration, protein concentration, and $K_a$, the following expression can be derived from Equations 10.24 and 10.25.

$$\beta = \frac{1}{1 + ([D]/n[P_T]) + (1/nK_a[P_T])} \quad (10.27)$$

From Equation 10.27, both the free drug concentration, $[D]$, and the total protein concentration, $[P_T]$, have important effects on the fraction of drug bound. Any factors that suddenly increase the fraction of free drug concentration in the plasma will cause a change in the pharmacokinetics of the drug.

Because protein binding is nonlinear in most cases, the percent of drug bound is dependent on the concentrations of both the drug and proteins in the plasma. In disease situations, the concentration of protein may change, thus affecting the percent of drug bound. As the protein concentration increases, the percent of drug bound increases to a maximum. The shapes of the curves are determined by the association constant of the drug–protein complex and the drug concentration. The effect of protein concentration on drug binding is demonstrated in Fig. 10-20.

**CLINICAL SIGNIFICANCE OF DRUG–PROTEIN BINDING**

Most drugs bind reversibly to plasma proteins to some extent. When the clinical significance of the fraction of drug bound is considered, it is important to know whether the study was performed using pharmacologic or therapeutic plasma drug concentrations. As mentioned previously, the fraction of drug bound can change with plasma drug concentration and dose of drug administered. In addition, the patient’s plasma protein concentration should be considered. If a patient has a low plasma protein concentration, then, for any given dose of drug, the
concentration of free (unbound) bioactive drug may be higher than anticipated. The plasma protein concentration is controlled by a number of variables, including (1) protein synthesis, (2) protein catabolism, (3) distribution of the protein between intravascular and extravascular space, and (4) excessive elimination of plasma protein, particularly albumin. A number of diseases, age, trauma, and related circumstances affect the plasma protein concentration (Tables 10-12–10-14).

For example, liver disease results in a decrease in plasma albumin concentration due to decreased protein synthesis. In nephrotic syndrome, an accumulation of waste metabolites, such as urea and uric acid, as well as an accumulation of drug metabolites, may alter protein binding of drugs. Severe burns may cause an increased distribution of albumin into the extracellular fluid, resulting in a smaller plasma albumin concentration. In certain genetic diseases, the quality of the protein that is synthesized in the plasma may be altered due to a change in the amino acid sequence. Both chronic liver disease and renal disease, such as uremia, may cause an alteration in the quality of plasma protein synthesized. An alteration in the protein quality may be demonstrated by an alteration in the association constant or affinity of the drug for the protein.

**Drug Interactions—Competition for Binding Sites**

When a highly protein-bound drug is displaced from binding by a second drug or agent, a sharp increase in the free drug concentration in the plasma may occur, leading to toxicity. For example, an increase in free warfarin level was responsible for an increase in bleeding when warfarin was co-administered with phenylbutazone, which competes for the same protein-binding site (O’Reilly, 1973; Udall, 1970; Sellers and Koch-Weser, 1971). Recently, studies and reviews have shown that the clinical significance of warfarin protein binding and its impact on bleeding are less prominent, adding other factors and explanations (Sands et al, 2002; Chan, 1995; Benet and Hoener, 2002). Since protein binding and metabolism both occur in vivo and can both influence the rate of metabolism in a patient, it is not always clear whether to attribute the cause of a change in metabolism based on kinetic observations alone. Change in CYP enzymes may occur in genetic polymorphism and at the same time change in protein may occur due to a number of causes. Van Steeg et al (2009) recently reviewed the effect of protein binding on drug pharmacokinetics and on pharmacodynamics. The authors discussed many important aspects of protein binding and drug disposition using beta-blocker as examples. Schmidt et al (2010) reviewed many examples of drug–protein binding and concluded that appropriate analysis requires careful consideration of both pharmacokinetic and pharmacodynamic processes, as they both contribute to the safety and efficacy of drugs. Ideally, the free drug concentrations at the receptor site should be used for making inferences about a drug’s pharmacological activity.

Albumin has two known binding sites that share the binding of many drugs (MacKichan, 1992). Binding site I is shared by phenylbutazone, sulfonamides, phenytoin, and valproic acid. Binding site II is shared by the semisynthetic penicillins, probenecid, medium-chain fatty acids, and the benzodiazepines. Some drugs bind to both sites. Displacement occurs when a second drug is taken that competes for the same binding site in the protein as the initial drug.

Although it is generally assumed that binding sites are preformed, there is some evidence pointing to the allosteric nature of protein binding. This means that the binding of a drug modifies the conformation of protein in such a way that the drug binding influences the nature of binding of further molecules of the drug. The binding of oxygen to hemoglobin is a well-studied biochemical example
<table>
<thead>
<tr>
<th>Condition</th>
<th>Albumin</th>
<th>a1-Glycoprotein</th>
<th>Lipoprotein</th>
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<tr>
<td><strong>Decreasing</strong></td>
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<td></td>
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<td>Hyperthyroidism</td>
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<td>GI disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leprosy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver abscess</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition (severe)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis (acute)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increasing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign tumor</td>
<td>Age (geriatric)</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>Celiac disease</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Crohn's disease</td>
<td>Liver disease?</td>
<td></td>
</tr>
<tr>
<td>Neurological disease?</td>
<td>Injury</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Neurosis</td>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In the conditions listed, the protein concentrations are altered, on average, by 30% or more, and in some cases by more than 100%.

### TABLE 10-14  Protein Binding in Normal (Norm) Renal Function, End-Stage Renal Disease (ESRD), during Hemodialysis (HD), and in Nephrotic Syndrome (NS)

<table>
<thead>
<tr>
<th></th>
<th>Norm (% Bound)</th>
<th>ESRD (% Bound)</th>
<th>HD (% Bound)</th>
<th>NS (% Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azlocillin</td>
<td>28</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>24</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>84</td>
<td>73</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>73</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>53</td>
<td>45</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>98</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofibrate</td>
<td>96</td>
<td></td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo red</td>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>80</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Desmethyldiazepam</td>
<td>98</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmethylimipramine</td>
<td>89</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>99</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazoxide (30 μg/mL)</td>
<td>92</td>
<td>86</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(300 μg/mL)</td>
<td>77</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>96</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diflunisal</td>
<td>88</td>
<td>56</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Digitoxin</td>
<td>97</td>
<td>96</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>Digoxin</td>
<td>25</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>88</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>75</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etomidate</td>
<td>75</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescein</td>
<td>86</td>
<td>Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemid</td>
<td>96</td>
<td>94</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td>90</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Methyldigoxin</td>
<td>30</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl orange</td>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl red</td>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>35</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>88</td>
<td>81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
TABLE 10-14  Protein Binding in Normal (Norm) Renal Function, End-Stage Renal Disease (ESRD), during Hemodialysis (HD), and in Nephrotic Syndrome (NS) (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Norm (% Bound)</th>
<th>ESRD (% Bound)</th>
<th>HD (% Bound)</th>
<th>NS (% Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>75</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>95</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>97</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>72</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>66</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>55</td>
<td>Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol red</td>
<td></td>
<td></td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>97</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90</td>
<td>80</td>
<td>93 81</td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>41</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>95</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone (50 mg)</td>
<td>74</td>
<td>65 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(15 mg)</td>
<td>87</td>
<td>88</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>d-Proxymethanol</td>
<td>76</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>88</td>
<td>89 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>88</td>
<td>86 88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylate</td>
<td>94</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td></td>
<td></td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>74</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td></td>
<td></td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Strophanthin</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Theophylline</td>
<td>60</td>
<td>Decreased</td>
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<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>72</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroxine</td>
<td></td>
<td></td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Triamterene</td>
<td>81</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>70</td>
<td>68</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>75</td>
<td>Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td>44</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>85</td>
<td>Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>90</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>99</td>
<td>98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Keller et al (1984), with permission.
in which the initial binding of other oxygen to the iron in the heme portion influences the binding of other oxygen molecules.

**Effect of Change in Protein Binding**

Most studies of the kinetics of drug–protein binding consider binding to plasma proteins. However, certain drugs may also bind specific tissue proteins or other macromolecules, such as melanin or DNA, drug receptors or transiently to transport proteins. Most literature excludes drug binding to other macromolecules and is limited to discussing the effect of drug binding to plasma albumin and AAG only. Since many drugs are eliminated by the liver, it is relevant to discuss the effect of protein binding after oral drug administration or by parenteral administration, after which the drug bypasses first-pass hepatic elimination.

After IV drug administration, displacement of drugs from plasma protein binding causing an increase in $f_u$ or increased free drug concentration, may potentially facilitate extravascular drug distribution and an increase in the apparent volume of distribution. The increased distribution results in a smaller plasma $C_p$ due to wider distribution, making drug elimination more difficult ($k = Cl/V_D$). This is analogous to reducing the fraction of free drug presented for elimination per unit time based on a one-compartment model. Consequently, a longer elimination half-life is expected due to wider tissue drug distribution. The relationship is expressed by Equation 10.28 in order to assess the distribution effect due to protein binding.

$$Cl = \frac{0.693 \cdot V_D}{t_{1/2}} = kV_D \quad (10.28)$$

Drug clearance may remain unaffected or only slightly changed if the decrease in the elimination rate constant is not compensated by an increase in $V_D$ as shown by Equation 10.28. The mean steady-state total drug concentration will remain unchanged based on no change in $Cl$ or $kV_D$. Whether the change in plasma drug–protein binding has pharmacodynamic significance or not depends on whether the drug is highly potent and has a narrow therapeutic window. Protein–drug binding has the buffering effect of preventing an abrupt rise in free drug concentration in the body. For orally administered drugs, the liver provides a good protection against drug toxicity because of hepatic portal drug absorption and metabolism. For a highly extracted drug orally administered, an increase in $f_u$ (more free drug) causes hepatic clearance to increase (ie, $f_uCl_{oral}$), thus reducing total $AUC_{oral}$ but not changing free drug $AUC_{oral}$ due to the compensatory effect of $f_u AUC_{oral}$ (ie, decrease in $AUC_{oral}$ is compensated by the same increase in free $AUC_u = f_u AUC_{oral}$) (see derivation of Equation 10.34 based on Benet and Hoener [2002] under **Protein Binding and Drug Exposure**).

The assumptions and derivation should be carefully observed before applying the concept to individual drugs. Most important of all, the model assumes a simple well-stirred hepatic model and excludes drugs involving transporters, which is now known to be common. A recent review (Schmidt et al, 2010) further discussed the issue of protein binding and its effect on pharmacokinetics and pharmacodynamics. The author discussed the effect of changing $V_D$ on the elimination half-life of drugs using Equation 10.14, which can be obtained by rearranging Equation 10.28

$$t_{1/2} = \frac{0.693 \cdot V_D}{Cl} \quad (10.14)$$

**Drug Distribution, Drug Binding, Displacement, and Pharmacodynamics**

The relationship of reversible drug–protein binding in the plasma and drug distribution and elimination is shown in Fig. 10-8. A decrease in protein binding that results in increased free drug concentration will allow more drug to cross cell membranes and distribute into all tissues, as discussed above. More drug will therefore be available to interact at a receptor site to produce a more intense pharmacologic effect, at least temporarily. The increased free concentration also may cause an increased rate of metabolism and decreased half-life which then may produce a lower total steady-state drug concentration but similar steady-state free drug concentration.
Clinically, the pharmacodynamic response is influenced by both the distribution of the drug and the concentration of the unbound drug fraction. The drug dose and the dosage form must be chosen to provide sufficiently high unbound drug concentrations so that an adequate amount of drug reaches the site of drug action (receptor). The onset of drug action depends on the rate of the free (unbound) drug that reaches the receptor and produces a minimum effective concentration (MEC) to produce a pharmacodynamic response (see Chapters 1 and 19). The onset time is often dependent on the rate of drug uptake and distribution to the receptor site. The intensity of a drug action depends on the total drug concentration at the receptor site and the number of receptors occupied by drug. To achieve a pharmacodynamic response with the initial (priming) dose, the amount (mass) of drug when dissolved in the volume of distribution must give a drug concentration ≥ MEC at the receptor site. Subsequent drug doses maintain the pharmacodynamic effect by sustaining the drug concentration at the receptor site. Subsequent doses are given at a dose rate (eg, 250 mg every 6 hours) that replaces drug loss from the receptor site, usually by elimination. However, redistributional factors may also contribute to the loss of drug from the receptor site.

A less understood aspect of protein binding is the effect of binding on the intensity and pharmacodynamics of the drug after intravenous administration. Rapid IV injection may increase the free drug concentration of some highly protein-bound drugs and therefore increase its intensity of action. Sellers and Koch-Weser (1973) reported a dramatic increase in hypotensive effect when diazoxide was injected rapidly IV in 10 seconds versus a slower injection of 100 seconds. Diazoxide was 9.1% and 20.6% free when the serum levels were 20 and 100 µg/mL, respectively. Figure 10-21 shows a transient high free diazoxide concentration that resulted after a rapid IV injection, causing maximum arterial dilation and hypotensive effect due to initial saturation of the protein-binding sites. In contrast, when diazoxide was injected more slowly over 100 seconds, free diazoxide serum level was low, due to binding and drug distribution. The slower injection of diazoxide produced a smaller fall in blood pressure, even though the total drug dose injected was the same. Although most drugs have linear binding at therapeutic dose, in some patients, free drug concentration can increase rapidly with rising drug concentration as binding sites become saturated. An example is illustrated in Fig. 10-22 for lidocaine (MacKichan, 1992).
The nature of drug–drug and drug–metabolite interactions is also important in drug–protein binding. In this case, one drug may displace a second bound drug from the protein, causing a sudden increase in pharmacologic response due to an increase in free drug concentration.

Frequently Asked Questions

What happens to the pharmacokinetic parameters of a drug when a displacing agent is given? What kind of drugs are most susceptible to clinically relevant changes in pharmacokinetics? Does the rate of administration matter?

**EXAMPLE**

Compare the percent of change in free drug concentration when two drugs, A (95% bound) and B (50% bound), are displaced by 5% from their respective binding sites by the administration of another drug (Table 10-15). For a highly bound drug A, a displacement of 5% of free drug is actually a 100% increase in free drug level. For a weakly bound drug like drug B, a change of 5% in free concentration due to displacement would cause only a 10% increase in free drug level over the initially high (50%) free drug concentration. For a patient medicated with drug B, a 10% increase in free drug level would probably not affect the therapeutic outcome. However, a 100% increase in active drug, as occurs with drug A, might be toxic. Although this example is based on one drug displacing another drug, nutrients, physiologic products, and the waste products of metabolism may cause displacement from binding in a similar manner.

As illustrated by this example, displacement is most important with drugs that are more than 95% bound and have a narrow therapeutic index. Under normal circumstances, only a small proportion of the total drug is active. Consequently, a small displacement of bound drug causes a disproportionate increase in the free drug concentration, which may cause drug intoxication.

With drugs that are not as highly bound to plasma proteins, a small displacement from the protein causes a transient increase in the free drug concentration, which may cause a transient increase in pharmacologic activity. However, more free drug is available for both renal excretion and hepatic biotransformation, which may be demonstrated by a transient decreased elimination half-life. Drug displacement from protein by a second drug can occur by competition of the second drug for similar binding sites. Moreover, any alteration of the protein structure may also change the capacity of the protein to bind drugs. For example, aspirin acetylates the lysine residue of albumin, which changes the binding capacity of this protein for certain other anti-inflammatory drugs, such as phenylbutazone.

The displacement of endogenous substances from plasma proteins by drugs is usually of little consequence. Some hormones, such as thyroid and cortisol, are normally bound to specific plasma proteins. A small displacement of these hormones rarely causes problems because physiologic feedback control mechanisms take over. However, in infants, the displacement of bilirubin by drugs can cause mental retardation and even death, due to the difficulty of bilirubin elimination in newborns.

Finally, the binding of drugs to proteins can affect the duration of action of the drug. A drug that is extensively but reversibly bound to protein may have a long duration of action due to a depot effect of the drug–protein complex.

While a change in free drug concentration due to changing protein binding can potentially change the pharmacologic response of a drug, many drugs with a change in protein binding did not show a significant change in clinical effect (Benet and Hoener, 2002), as discussed in the next section. The important question to ask is: Will the increase in free drug concentration due to reduced binding elicit a rapid pharmacologic response before the temporary increase in free drug is diluted by a rapid distribution and/or elimination due to a greater fraction of free drug? Kruger and Figg (2001)
observed that the angiogenesis activity of suramin, an inhibitor of blood vessel proliferation, is greatly altered by protein binding. In biological assays with aorta rings of rats, the effect is measured \textit{ex vivo} at the site directly, and the degree of protein binding was reported to be important. In the body, the pathways to reach the receptor, distribution, and elimination are factors that complicate the effect of a rise in free drug due to displacement from binding. In general, the outcome of a change in protein binding \textit{in vivo} may be harder to measure depending on where the site of action is located. The onset of a drug, and its distribution half-life to the site of action, may need to be considered. In the next section, this subject is further discussed based on the recent concept of drug exposure. The concept of drug exposure is important because many vital organs and adverse reactions are related to their exposure to plasma drug concentration.

\section*{Protein Binding and Drug Exposure}

The impact of protein binding on clinical drug efficacy and safety has long been recognized (Koch-Weser and Sellers, 1976; Greenblatt et al, 1982) but has received renewed literature discussion recently (Sands et al, 2002; Chan, 1995; Benet and Hoener, 2002, van Steeg et al, 2009, Schmidt et al, 2010). Free plasma drug concentration or free drug concentration at the site of action is generally considered to be more relevant than total plasma drug concentration. When considering drug safety, how high and how long the free plasma drug level will be sustained are also important to a toxicokineticist. This is often measured by the AUC for the free plasma drug concentration.

Based on the well-stirred venous equilibration model incorporating protein binding (Benet and Hoener, 2002), organ clearance for a drug (\(Cl\)) is expressed as

\[ Cl = \frac{Q_{\text{organ}} f_u Cl_{\text{int}}}{Q_{\text{organ}} + f_u Cl_{\text{int}}} \]  

(10.29)

For a low-extraction drug, where \(Q\) is blood flow, \(f_u\) is fraction of drug unchanged and \(Cl_{\text{int}}\) is intrinsic clearance, \(Q_{\text{organ}} \gg f_u Cl_{\text{int}}\), the equation simplifies to

\[ Cl = f_u Cl_{\text{int}} \]  

(10.30)

Clearance depends on \(f_u\) and intrinsic clearance. Intrinsic clearance is flow independent, whereas hepatic clearance, \(Cl_H\), is flow dependent for a high extraction drug.

Hepatic bioavailability of a drug, \(F_H\), is expressed as

\[ F_H = \frac{Q_H}{Q_H + f_u Cl_{\text{int}}} \]  

(10.31)

Let \(F_{abs}\) be the fraction of drug absorbed to the gut wall and \(F_G\) be the fraction that gets through the gut wall unchanged (ie, \(F_{oral} = F_{abs} F_G F_H\)). The systemic AUC after an oral dose is

\[ \text{AUC}_{\text{oral}} = \frac{F_{abs} F_G \text{Dose}}{f_u Cl_{\text{int}}} \]  

(10.32)

\begin{table}[h]
\centering
\caption{Comparison of Effects of 5\% Displacement from Binding on Two Hypothetical Drugs}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Drug A} & \multicolumn{2}{c|}{\textbf{Before Displacement}} & \textbf{Percent Increase in Free Drug} \\
\hline
Percent drug bound & 95 & 90 & +100 \\
Percent drug free & 5 & 10 & \\
\hline
\textbf{Drug B} & \multicolumn{2}{c|}{\textbf{After Displacement}} & \\
\hline
Percent drug bound & 50 & 45 & \\
Percent drug free & 50 & 55 & +10 \\
\hline
\end{tabular}
\end{table}
For an unbound drug, \( \text{AUC}^u_{\text{oral}} = (f_u) \text{AUC}^u_{\text{oral}} \) \hspace{1cm} (10.33)

When substituted for \( \text{AUC}^u_{\text{oral}} \) using Equation 10.32 into Equation 10.33, \( f_u \) cancels out, and the equation becomes

\[
\text{AUC}^u_{\text{oral}} = \frac{F_{\text{abs}} F_{G} \text{Dose}}{Cl_{\text{int}}} \hspace{1cm} (10.34)
\]

Equation 10.34 above shows that for low-extraction drugs, unbound drug exposure as measured by unbound plasma drug area under the curve is independent of \( f_u \).

For a low-extraction drug, given IV or orally, changes in protein binding are generally not important. For a high-extraction drug after IV administration, changes in protein binding are clinically important whether metabolism is hepatic or nonhepatic. For a drug that is administered IV and is highly extracted by the liver \( (Q_{\text{organ}} \ll f_u \cdot Cl_{\text{int}}) \), \( \text{AUC}^u_{\text{IV}} \) or unbound drug systemic exposure is expressed by

\[
\text{AUC}^u_{\text{IV}} = f_u \text{AUC}^u_{\text{IV}} = f_u \frac{\text{Dose}}{Q_{\text{int}}} \hspace{1cm} (10.35)
\]

In this case, changes in binding may be clinically important, as shown by the change of \( f_u \) in Equation 10.35.

The derivation of Equation 10.33 into Equation 10.34 is dependent on the fact that \( f_u \) is constant as a function of \( t \). If unbound drug concentration \( C_u \) is changing at various \( C_{p} \), i.e., concentration-dependent binding, then \( C_u = F(t) \) is time dependent, and in fact, AUC will be nonlinear with dose and Equation 10.34 will be different for different doses (see Chapter 9). Within therapeutic drug concentrations, the effect of changes in \( f_u \) is apparently not sufficient to change the efficacy of most drugs and is not of clinical concern. However, as more potent biological drugs with short elimination half-lives are used, plasma drug concentrations may potentially fall several fold and \( f_u \) may change significantly at various plasma concentrations. An anatomic-physiologic approach to evaluating drug concentrations (Mather, 2001) may be helpful in understanding how drug efficacy and safety change in protein binding and clearances in local tissues (see Chapter 12).

### Frequently Asked Questions

- Do all drugs that bind proteins lead to clinically significant interactions?
- What macromolecules participate in drug–protein binding?
- How does drug–protein binding affect drug elimination?
- What are the factors to consider when adjusting the drug dose for a patient whose plasma protein concentration decreases to half that of normal?
- \( f_u \) is used to represent the fraction of free drug in the plasma (Equations 10.30 and 10.33). Is \( f_u \) always a constant?
- Can a protein-bound drug be metabolized?

### Clinical Examples

Protein concentration may change during some acute disease states. For example, plasma AAG levels in patients may increase due to the host’s acute-phase response to infection, trauma, inflammatory processes, and some malignant diseases. The acute-phase response is a change in various plasma proteins that is observed within hours or days following the onset of infection or injury. The acute-phase changes also may be indicative of chronic disease (Kremer et al, 1988).

AAG binds to many basic drugs, and a change in AAG protein concentration can contribute to more fluctuation in free drug concentrations among patients during various stages of infection or disease. Amprenavir (Agenerase), a protease inhibitor of human immunodeficiency virus type 1 (HIV-1), is highly bound to human plasma proteins, mostly to AAG (approximately 90%). AAG levels are known to vary with infection, including HIV disease. Sadler et al (2001) showed a significant inverse linear relationship between AAG levels and amprenavir clearance as estimated by \( Cl/F \). Unbound, or free, amprenavir concentrations were not affected by AAG concentrations even though the apparent total drug clearance was increased.
The understanding of the molecular interactions of drug binding to proteins is essential to explain the clinical pharmacology and toxicology in the body. Drug–protein binding is generally assumed to be reversible as modeled in later sections of this chapter. Taheri et al (2003) studied the binding and displacement of several local anesthetics, such as lidocaine, mepivacaine, and bupivacaine with human α1-acid glycoprotein (AGP). These investigators used a special molecular probe to see how local anesthetics behave during equilibrium-competitive displacement from AGP. The change in recovery of AGP’s fluorescence as the quenching probe was displaced from its high-affinity site was used to observe change in dissociation constants for the various local anesthetics. The study demonstrated that the AGP-binding site has a strong positive correlation between hydrophobicity of the local anesthetics and their free energies of dissociation. The effect of pH and electrostatic forces on binding was also explored. Studies by other investigators of these molecular factors’ influence on binding were done previously with albumin binding to different agents. More sophisticated models may be needed as the understanding of molecular interactions of a drug with a substrate protein improves. Theoretically, a change in molecular conformation or allosteric binding may change the activity of a drug but requires clinically demonstrated.

**CLINICAL EXAMPLE**

A drug–drug interaction derived from the displacement of lidocaine from tissue binding sites by mexiletine that resulted in the increased plasma lidocaine concentrations was reported by Maeda et al (2002). A case of an unexpected increase in plasma lidocaine concentration accompanied by severe side effects was observed when mexiletine was administered to a patient with dilated cardiomyopathy. Maeda et al (2002) further studied this observation in rabbits and *in vitro*. Mexiletine significantly reduced the tissue distribution of lidocaine to the kidneys and lungs. Lidocaine plasma levels were higher. Mexiletine had a strong displacing effect of lidocaine binding to the membrane component phosphatidylserine.
Drug distribution may change in many disease and physiologic states, making it difficult to predict the concentration of drug that reaches the site of drug action (receptor). Pharmacokinetic models can be used to predict these pharmacokinetic changes due to changes in physiologic states. The model should consider free and bound drug equilibration and metabolism at the apparent site of action, and transient changes due to disease state (eg, pH change or impaired perfusion).

In pharmacokinetics, perfusion and rapid equilibration within a region form the basis for the well-stirred models that are used in many classical compartment models as well as some physiologic pharmacokinetic models. The concept of body or organ drug clearance both assume that uniform drug concentration is rapidly established within a given biological region \( C_{\text{organ}} \) or \( C_{\text{plasma}} \) at a given time point. The model also allows: (1) the mass of drug present in the region can be monitored by multiplying the concentration with its volume at a given time; and (2) the rate of drug elimination from the site can be calculated by the product of clearance times drug concentration.

Model simplicity using the well-stirred approach has advanced the concept of drug clearance and allowed practical drug concentration to be estimated based on body clearance and drug dose. The approach has generally provided more accurate dosing for many drugs for which drug action is determined mostly by steady-state concentration, and a transient change in concentration of short duration is not critical. However, caution should be exercised in equating model-predicted concentration to drug concentration at a given site in the body.

**Arterial and Venous Differences in Drug Concentrations**

Most pharmacokinetic studies are modeled based on blood samples drawn from various venous sites after either IV or oral dosing. Physiologists have long recognized the unique difference between arterial and venous blood. For example, arterial tension (pressure) of oxygen drives the distribution of oxygen to vital organs. Chiou (1989) and Mather (2001) have discussed the pharmacokinetic issues when differences in drug concentrations \( C_p \) in arterial and venous are observed. These reviewers question the validity of the assumption of the well-stirred condition or rapid mixing within the blood or plasma pool when there is gradual permeation into tissues in which the drug may then be metabolized. Indeed, some drug markers have shown that rapid mixing may not be typical, except when the drug is essentially confined to the blood pool due to protein binding.

Differences ranging as high as several hundred-fold for griseofulvin due to differences in arterial and venous blood levels have been reported. Forty compounds have been shown to exhibit marked site dependence in plasma or blood concentration after dosing in both humans and animals. In some cases, differences are due mostly to large extraction of drug in poorly perfused local tissues, such as with nitroglycerin (3.8-fold arteriovenous difference) and procainamide (234%-arteriovenous difference, venous being higher). The classical assumption in pharmacokinetics of rapid mixing within minutes in the entire blood circulation therefore may not be applicable to some drugs. Would the observed sampling differences result in significant difference between the AUCs between arterial and venous blood, or in prediction of toxicity or adverse effects of drugs? No such differences were observed in the reviews by Chiou and Mather, although the significance of these differences on drug therapy and toxicity has not been fully explored.

**Frequently Asked Questions**

- Why are most of the plasma drug concentration data reported without indicating the sampling site when there is a substantial difference in arterial and venous blood drug concentrations for many drugs?
- Does the drug concentration in the terminal phase of the curve show less dependency on site of sampling?
The processes by which drugs transverse capillary membranes include passive diffusion and hydrostatic pressure. Passive diffusion is generally governed by Fick’s law of diffusion. Hydrostatic pressure represents the pressure gradient between the arterial end of the capillaries entering the tissue and the venous capillaries leaving the tissue. Not all tissues have the same drug permeability. In addition, permeability of tissues may change under various disease states, such as inflammation.

Drug distribution can be perfusion or flow limited or diffusion or permeability limited depending on the nature of the drug. Drug distribution into cells is also controlled by efflux and influx transporters. The factors that determine the distribution constant, \( k_d \), of a drug into an organ are related to the blood flow to the organ, the volume of the organ, and the partitioning of the drug into the organ tissue, ie, \( k_d = Q / VR \). The distribution half-life is inversely related to \( k_d \).

The equation \( t_{1/2} = 0.693 \left( V_D / CL \right) \) relates the elimination half-life to the apparent volume of distribution and clearance. A large apparent volume of distribution leads to low plasma drug concentrations, making it harder to remove the drug by the kidney or liver. Mechanistically, a low plasma drug concentration may be due to (1) extensive distribution into tissues due to favorable lipophilicity, (2) extensive distribution into tissues due to protein binding in peripheral tissues, or (3) lack of drug plasma protein binding. The equation is the basis for considering that \( CL \) and \( V_D \) are both independent variables in contrast to \( CL = kV_D \) which depicts \( CL \) as proportional to \( V_D \) with a constant, \( k \) specific for the drug.

Plasma protein binding of a drug generally serves to retain the drug intravascularly, whereas tissue drug binding generally pulls the drug away from the vascular compartment. The two main proteins in the plasma that are involved in drug–protein binding are albumin and \( \alpha_1 \)-acid glycoprotein, AAG. AAG tends to bind mostly basic drugs. Protein-bound drugs are generally not considered to be pharmacodynamically active. Protein-bound drugs are slower to diffuse and are not eliminated easily. For highly extractable drugs, the bound drug may be dissociated to the unbound drug in the liver for metabolism or in the kidney for excretion. These drugs are observed to have an ER >> \( f_u \).

The pathophysiologic condition of the patient can affect drug–protein binding. Drug–protein binding may be reduced in uremic patients and in patients with hepatic disease. During infection, stress, trauma, and severe burn, AAG levels may change and affect drug disposition.

Lipophilic (hydrophobic) drugs may accumulate in adipose or other tissues, which have a good affinity for the drug.

The equation \( V_{app} = V_p + V_t (f_u / f_u) \) defines \( V_{app} \) which is related to plasma volume, tissue volume, and fraction of free plasma and tissue drug in the body. The term \( V_{app} \) allows the amount of drug in the body to be calculated.

When a drug is tightly bound to a protein, only the unbound drug is assumed to be metabolized; drugs belonging to this category are described as restrictively eliminated. Some drugs may be eliminated even when they are protein bound and are described as nonrestrictively eliminated.

The extent of drug binding to protein may be determined by two common in vitro methods: ultrafiltration and equilibrium dialysis. The number of binding sites and the binding constant can be determined using a graphic technique called the Scatchard plot. A drug tightly bound to protein has a large association binding constant which is derived based on the law of mass action.

Based on a “well-stirred venous equilibration” model and hepatic clearance during absorption, many orally given drugs do not result in clinically significant changes in drug exposure when protein binding (ie, \( f_u \)) changes. The drug elimination rate increases in the liver when \( f_u \) (free drug fraction) is increased for many drugs given orally at doses below saturation. In contrast, drugs administered by IV injection and a few orally administered drugs can have significant changes in free drug concentration when protein binding changes. The clinical significance of changes in protein binding must be
considered on individual drug basis and cannot be over generalized.

An important consideration regarding the effect of change in drug–protein binding is the pharmacodynamics (PD) of the individual drug involved, ie, how and where the drug exerts its action because drug penetration to the site of action is important. Recent reviews indicate that simple hepatic flow/intrinsic clearance-based analysis may sometimes be inadequate to predict drug effect due to protein-binding changes.

**LEARNING QUESTIONS**

1. Why is the zone of inhibition in an antibiotic disc assay larger for the same drug concentration (10 μg/mL) in water than in serum? See Fig. 10-23.

2. Determine the number of binding sites (n) and the association constant ($K_a$) from the following data using the Scatchard equation.

<table>
<thead>
<tr>
<th>r</th>
<th>$(D \times 10^{-4}$ M)</th>
<th>r/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>0.80</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>1.20</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>1.60</td>
<td>5.33</td>
<td></td>
</tr>
</tbody>
</table>

Can n and $K_a$ have fractional values? Why?

3. Discuss the clinical significance of drug–protein binding on the following:
   a. Drug elimination
   b. Drug–drug interactions
   c. “Percent of drug-bound” data
   d. Liver disease
   e. Kidney disease

4. Vallner (1977) reviewed the binding of drugs to albumin or plasma proteins. The following data were reported:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Drug Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>53</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>70</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>93</td>
</tr>
<tr>
<td>Morphine</td>
<td>38</td>
</tr>
</tbody>
</table>

Which drug listed above might be predicted to cause an adverse response due to the concurrent administration of a second drug such as sulfisoxazole (Gantrisin)? Why?

5. What are the main factors that determine the uptake and accumulation of a drug into tissues? Which tissues would have the most rapid drug uptake? Explain your answer.

6. As a result of edema, fluid may leave the capillary into the extracellular space. What effect does edema have on osmotic pressure in the blood and on drug diffusion into extracellular space?

7. Explain the effects of plasma drug–protein binding and tissue drug–protein binding on (a) the apparent volume of distribution and (b) drug elimination.

8. Naproxen (Naprosyn, Syntex) is a nonsteroidal anti-inflammatory drug (NSAID) that is highly bound to plasma proteins, > 99%. Explain why the plasma concentration of free (unbound) naproxen increases in patients with chronic alcoholic liver disease and probably other forms of cirrhosis, whereas the total plasma drug concentration decreases.

9. Most literature references give an average value for the percentage of drug bound to plasma proteins.
   a. What factors influence the percentage of drug bound?
b. How does renal disease affect the protein binding of drugs?

c. How does hepatic disease affect the protein binding of drugs?

10. It is often assumed that linear binding occurs at therapeutic dose. What are the potential risks of this assumption?

11. When a drug is 99% bound, it means that there is a potential risk of saturation. True or false?

12. Adenosine is a drug used for termination of tachycardia. The $t_{1/2}$ after IV dose is only 20 to 30 seconds according to product information. Suggest a reason for such a short half-life based on your knowledge of drug distribution and elimination.

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Chapter 10


Chapter Objectives

► Describe the pathways for drug elimination in the body.
► Compare the clinical implications of hepatic and renal disease on drug therapy.
► Describe the role of hepatic blood flow, drug protein binding, and intrinsic clearance on hepatic clearance.
► Explain how the rate of drug elimination may change from first-order elimination to zero-order elimination and the clinical implications of this occurrence.
► Describe the biotransformation of drugs in the liver and which enzymatic processes are considered “phase I reactions” and “phase II reactions.”
► List the organs involved in drug elimination and the significance of each.
► Discuss the relationship between metabolic pathways and enzyme polymorphisms on intrasubject variability and drug–drug interactions.
► Describe how the exposure of a drug is changed when co-administered with another drug that shares the same metabolic pathway.

ROUTE OF DRUG ADMINISTRATION AND EXTRAHEPATIC DRUG METABOLISM

The decline from peak plasma concentrations after drug administration results from drug elimination or removal by the body. The elimination of most drugs from the body involves the processes of both metabolism (biotransformation) and renal excretion (see Chapter 6). For many drugs, the principal site of metabolism is the liver. However, other tissues or organs, especially those tissues associated with portals of drug entry into the body, may also be involved in drug metabolism. These sites include the lung, skin, gastrointestinal mucosal cells, microbiological flora in the distal portion of the ileum, and large intestine. The kidney may also be involved in certain drug metabolism reactions.

Whether a change in drug elimination is more likely to be affected by renal disease, hepatic disease, or a drug–drug interaction may be predicted by measuring the fraction of the drug that is eliminated by either metabolism or excretion. Drugs that are highly metabolized (such as phenytoin, theophylline, and lidocaine) often demonstrate large intersubject variability in elimination half-lives and are dependent on the intrinsic activity of the biotransformation enzymes, which may vary by genetic and environmental factors. Intersubject variability in elimination half-lives is less for drugs that are eliminated primarily by renal drug excretion. Renal drug excretion is highly dependent on the glomerular filtration rate (GFR) and blood flow to the kidney. Since GFR is relatively constant among individuals with normal renal function, the elimination of drugs that are primarily excreted unchanged in the urine is also less variable.

First-Order Elimination

The rate constant of elimination (k) is the sum of the first-order rate constant for metabolism (k_m) and the first-order rate constant for excretion (k_e):

\[ k = k_e + k_m \]  

(11.1)
Define Michaelis–Menton kinetics and capacity-mediated metabolism.

Calculate drug and metabolite concentrations for drugs that undergo both hepatic and biliary elimination.

Define first-pass metabolism and describe the relationship between first-pass metabolism and oral drug bioavailability.

Use urine data to calculate fraction of drug excreted and metabolized.

Explain how Michaelis–Menton kinetics can be used to determine the mechanism of enzyme inhibition and transporter inhibition.

Describe biliary drug excretion and define enterohepatic drug elimination.

Discuss the reasons why bioavailability is variable and can be less than 100%.

Describe the BDDCS—Biological Drug Disposition Classification System.

In practice, the excretion rate constant \( k_e \) is easily evaluated for drugs that are primarily renally excreted. Nonrenal drug elimination is usually assumed to be due for the most part to hepatic metabolism, though metabolism or degradation can occur in any organ or tissue that contains metabolic enzymes or is in a degradative condition. Therefore, the rate constant for metabolism \( k_m \) is difficult to measure directly and is usually found from the difference between \( k \) and \( k_e \).

\[
k_m = k - k_e
\]

A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc); thus, the metabolism rate constant \( k_m \) is the sum of the rate constants for the formation of each metabolite:

\[
k_m = k_{m_A} + k_{m_B} + k_{m_C} + \cdots + k_{m_{D}}
\]

(11.2)

The relationship in this equation assumes that the process of metabolism is first order and that the substrate (drug) concentration is very low. Drug concentrations at therapeutic plasma levels for most drugs are much lower than the Michaelis–Menten constant, \( K_M \), and do not saturate the enzymes involved in metabolism. Nonlinear Michaelis–Menten kinetics must be used when drug concentrations saturate metabolic enzymes (see also Chapter 19).

Because these rates of elimination at low drug concentration are considered first-order processes, the percentage of total drug metabolized may be found by the following expression:

\[
\% \text{ drug metabolized} = \frac{k_m}{k} \times 100
\]

(11.3)

**Fraction of Drug Excreted Unchanged \( f_u \) and Fraction of Drug Metabolized \( 1-f_u \)**

For most drugs, the fraction of dose eliminated unchanged \( f_u \) and the fraction of dose eliminated as metabolites can be determined. For example, consider a drug that has two major metabolites and is also eliminated by renal excretion (Fig. 11-1). Assume that 100 mg of the drug was given to a patient and the drug was completely absorbed (bioavailability factor \( F = 1 \)). A complete (cumulative) urine collection was obtained, and the quantities in parentheses in Fig. 11-1 indicate the amounts of each metabolite and unchanged drug that were recovered. The overall elimination half-life \( t_{1/2} \) for this drug was 2.0 hours \( (k = 0.347 \text{ h}^{-1}) \).
To determine the renal excretion rate constant, the following relationship is used:

\[ k_e = \frac{\text{total dose excreted in urine}}{\text{total dose absorbed}} = \frac{D_u}{FD_0} \quad (11.4) \]

where \( D_u \) is the total amount of unchanged drug recovered in the urine. In this example, \( k_e \) is found by proper substitution into Equation 11.4:

\[ k_e = (0.347) \frac{70}{100} = 0.243 \text{ h}^{-1} \]

To find the percent of drug eliminated by renal excretion, the following approach may be used:

\[ \% \text{ drug excretion} = \frac{k_e}{k} \times 100 = \frac{0.243}{0.347} \times 100 = 70\% \]

Alternatively, because 70 mg of unchanged drug was recovered from a total dose of 100 mg, the percent of drug excretion may be found by

\[ \% \text{ drug excretion} = \frac{70}{100} \times 100 = 70\% \]

Therefore, the percent of drug metabolized is 100\% – 70\%, or 30\%.

For many drugs, the literature has approximate values for the fraction of drug (\( f_e \)) excreted unchanged in the urine. In this example, the value of \( k_e \) may be estimated from the literature values for the elimination half-life of the drug and \( f_e \). Assuming that the elimination half-life of the drug is 2 hours and \( f_e \) is 0.7, then \( k_e \) is estimated by Equation 11.5.

\[ k_e = f_e k \quad (11.5) \]

Because \( t_{1/2} \) is 2 hours, \( k \) is 0.693/2 h = 0.347 h\(^{-1}\), and \( k_e \) is

\[ k_e = (0.7) (0.347) = 0.243 \text{ h}^{-1} \]

**PRACTICAL FOCUS**

The percentages of drug excreted and metabolized are clinically useful information. If the renal excretion pathway becomes impaired, as in certain kidney disorders, then less drug will be excreted renally and hepatic metabolism may become the primary drug elimination route. The reverse is true if liver function declines. For example, if in the above situation renal excretion becomes totally impaired (\( k_e \approx 0 \)), the elimination \( t_{1/2} \) can be determined as follows:

\[ k = k_m + k_e \]

but

\[ k_e = 0 \]

Therefore,

\[ k = k_m = 0.104 \text{ h}^{-1} \]

The new \( t_{1/2} \) (after complete renal shutdown) is

\[ t_{1/2} = \frac{0.693}{0.104} = 6.7 \text{ h} \]

In this example, renal impairment caused the drug elimination \( t_{1/2} \) to be prolonged from 2 to 6.7 hours. Clinically, the dosage of this drug must be lowered to prevent the accumulation of toxic drug levels. Methods for adjusting the dose for renal impairment are discussed in Chapter 21.

**HEPATIC CLEARANCE**

The clearance concept may be applied to any organ and is used as a measure of drug elimination by the organ (see Chapter 6). Hepatic clearance may be
defined as the volume of blood that perfuses the liver which is cleared of drug per unit of time. As discussed in Chapter 6, total body clearance is composed of all the clearances in the body:

\[ Cl_T = Cl_{nr} + Cl_r \]  

(11.6)

where, \( Cl_T \) is total body clearance, \( Cl_{nr} \) is nonrenal clearance (often equated with hepatic clearance, \( Cl_h \)), and \( Cl_r \) is renal clearance. Hepatic clearance (\( Cl_h \)) is also equal to total body clearance (\( Cl_T \)) minus renal clearance (\( Cl_R \)) assuming no other organ metabolism, as shown by rearranging Equation 11.6 to

\[ Cl_h = Cl_T - Cl_R \]  

(11.6a)

**Extrahepatic Metabolism**

A few drugs (e.g., nitroglycerin) are metabolized extensively outside the liver. This is known as extrahepatic metabolism. A simple way to assess extrahepatic metabolism is to calculate hepatic (metabolic) and renal clearance of the drug and compare these clearances to total body clearance.

**EXAMPLE S**

1. The total body clearance for a drug is 15 mL/min/kg. Renal clearance accounts for 10 mL/min/kg. What is the hepatic clearance for the drug?

   **Solution**
   Hepatic clearance = 15 – 10 = 5 mL/min/kg

   Sometimes the renal clearance is not known, in which case hepatic clearance and renal clearance may be calculated from the percent of intact drug recovered in the urine.

2. The total body clearance of a drug is 10 mL/min/kg. The renal clearance is not known. From an urinary drug excretion study, 60% of the drug is recovered intact and 40% is recovered as metabolites. What is the hepatic clearance for the drug assuming that metabolism occurs in the liver?

   **Solution**
   Hepatic clearance = total body clearance \( \times (1 - f_e) \)

   \[ Cl_h = 10 \times (1 - 0.6) = 4 \text{ mL/min/kg} \]

   where, \( f_e \) = fraction of intact drug recovered in the urine.

   In this example, the metabolites are recovered completely and hepatic clearance may be calculated as total body clearance times the percent of dose recovered as metabolites. Often, the metabolites are not completely recovered, thus precluding the accuracy of this approach. In this case, hepatic clearance is estimated as the difference between body clearance and renal clearance.

**EXAMPLE S**

1. Morphine clearance, \( Cl_p \), for a 75-kg male patient is 1800 mL/min. After an oral dose, 4% of the drug is excreted unchanged in the urine (\( f_e = 0.04 \)). The fraction of drug absorbed after an oral dose of morphine sulfate is 24% (\( F = 0.24 \)). Hepatic blood flow is about 1500 mL/min. Does morphine have any extrahepatic metabolism?

   **Solution**
   Since \( f_e = 0.04 \), renal clearance \( Cl_r = 0.04 Cl_T \) and nonrenal clearance \( Cl_{nr} = (1 - 0.04) Cl_T = 0.96 Cl_T \). Therefore, \( Cl_{nr} = 0.96 \times 1800 \text{ mL/min} = 1728 \text{ mL/min} \). Since hepatic blood flow is about 1500 mL/min, the drug appears to be metabolized faster than the rate of hepatic blood flow. Thus, at least some of the drug must be metabolized outside the liver. The low fraction of drug absorbed after an oral dose indicates that much of the drug is metabolized before reaching the systemic circulation.
2. Flutamide (Eulexin®, Schering), used to treat prostate cancer, is rapidly metabolized in humans to an active metabolite, α-hydroxyflutamide. The steady-state level is 51 ng/mL (range 24–78 ng/mL) after oral multiple doses of 250 mg of flutamide given three times daily or every 8 hours (manufacturer-supplied information). Calculate the total body clearance and hepatic clearance assuming that flutamide is 90% metabolized, and is completely (100%) absorbed.

Solution
From Chapters 6 and 8, total body clearance, $C_l_T$, can be calculated by

$$C_l_T = \frac{F D_0}{C_{st}}$$

$$C_l_T = \frac{250 \times 1,000,000}{51 \times 8}$$

$$= 6.127 \times 10^5 \text{ mL/h}$$

$$= 10,200 \text{ mL/min}$$

$$C_{l,nr} = 10,200 \text{ mL/min} \times 0.9$$

$$= 9,180 \text{ mL/min}$$

The $C_{l,nr}$ of flutamide is far greater than the rate of hepatic blood flow (about 1500 mL/min), indicating extensive extrahepatic clearance.

ENZYME KINETICS

The process of biotransformation or metabolism is the enzymatic conversion of a drug to a metabolite. In the body, the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary. When the drug concentration is low relative to the enzyme concentration, there are abundant enzymes to catalyze the reaction, and the rate of metabolism is a first-order process. Saturation of the enzyme usually occurs when the plasma drug concentration is relatively high, all the enzyme molecules become complexed with drug, and the reaction rate is at a maximum rate; the rate process then becomes a zero-order process (Fig. 11-2). The maximum reaction rate is known as $V_{max}$, and the substrate or drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter $K_M$. These two parameters determine the profile of a simple enzyme reaction rate at various drug concentrations. The relationship of these parameters is described by the Michaelis–Menten equation (see Chapter 9).

Enzyme kinetics generally considers that 1 mole of drug interacts with 1 mole of enzyme to form an enzyme–drug (ie, enzyme–substrate) intermediate. The enzyme–drug intermediate further reacts to yield a reaction product or a drug metabolite (Fig. 11-3). The rate process for drug metabolism is described by the Michaelis–Menten equation which assumes that the rate of an enzymatic reaction is dependent on the concentrations of both the enzyme and the

**FIGURE 11-2** Michaelis–Menten enzyme kinetics. The hyperbolic relationship between enzymatic reaction velocity and the drug substrate concentration is described by Michaelis–Menten enzyme kinetics. The $K_M$ is the substrate concentration when the velocity of the reaction is at 0.5$V_{max}$. 

Frequently Asked Questions

- How does the route of drug administration affect drug elimination?
- Why does the rate of drug elimination for some drugs change from first-order elimination to zero-order elimination?
- What organs are involved in drug elimination?
- How are zero- or first-order elimination processes related to either linear or nonlinear drug metabolism?
drug and that an energetically favored drug–enzyme intermediate is initially formed, followed by the formation of the product and regeneration of the enzyme.

Each rate constant in Fig. 11-3 is a first-order reaction rate constant. The following rates may be written:

\[
\text{Rate of intermediate } [ED] \text{ formation } = k_1 [E][D]
\]

\[
\text{Rate of intermediate } [ED] \text{ decomposition } = -k_2 [ED] + k_3 [ED]
\]

By mass balance, the total enzyme concentration \([E_t]\) is the sum of the free enzyme concentration \([E]\) and the enzyme–drug intermediate concentration \([ED]\):

\[
[E_t] = [E] + [ED]
\]  \hspace{1cm} (11.9)

Rearranging,

\[
[E] = [E_t] - [ED]
\]  \hspace{1cm} (11.10)

Substituting for \([E]\) in Equation 11.8,

\[
\frac{d[ED]}{dt} = k_1 ([E_t] - [ED]) - k_2 [ED] - k_3 [ED]
\]  \hspace{1cm} (11.11)

At steady state, the concentration \([ED]\) is constant with respect to time, because the rate of formation of the drug–enzyme intermediate equals the rate of decomposition of the drug–enzyme intermediate. Thus, \(d[ED]/dt = 0\), and

\[
k_1 [E_t][D] = [ED] (k_1 [D] + (k_2 + k_3))
\]  \hspace{1cm} (11.12)

\[
[E_t][D] = [ED] \left( [D] + \frac{k_2 + k_3}{k_1} \right)
\]  \hspace{1cm} (11.13)

Let

\[
K_M = \frac{k_2 + k_3}{k_1}
\]  \hspace{1cm} (11.14)

\[
[E_t][D] = [ED] ([D] + K_M)
\]  \hspace{1cm} (11.15)

Solving for \([ED]\),

\[
[ED] = \frac{[D][E_t]}{[D] + K_M}
\]  \hspace{1cm} (11.16)

Multiplying by \(k_3\) on both sides,

\[
\frac{k_3 [E_t][D]}{[D] + K_M} = k_3 [ED]
\]  \hspace{1cm} (11.17)

The velocity or rate \((v)\) of the reaction is the rate for the formation of the product (metabolite) of the reaction, which is also the forward rate of decomposition of the enzyme–drug \([ED]\) intermediate (see Fig. 11-3).

\[
v = k_3 [ED]
\]  \hspace{1cm} (11.18)

When all the enzyme is saturated (i.e., all the enzyme is in the form of the \(ED\) intermediate due to the large drug concentration), the reaction rate is dependent on the availability of free enzyme, and the reaction rate proceeds at zero-order maximum velocity, \(V_{max}\).

\[
V_{max} = k_3 [E_t]
\]  \hspace{1cm} (11.19)

Therefore, the velocity of metabolism is given by the equation

\[
v = \frac{V_{max} [D]}{[D] + K_M}
\]  \hspace{1cm} (11.20)

Equation 11.20 describes the rate of metabolite formation, or the Michaelis–Menten equation. The maximum velocity \((V_{max})\) corresponds to the rate when all available enzymes are in the form of the drug–enzyme \((ED)\) intermediate. At \(V_{max}\), the drug (substrate) concentration is in excess, and the forward reaction,
Drug Elimination and Hepatic Clearance

$k_3[ED]$, is dependent on the availability of more free enzyme molecules. The Michaelis constant, $K_M$, is defined as the substrate concentration when the velocity ($v$) of the reaction is equal to one-half the maximum velocity, or $0.5V_{\text{max}}$ (see Fig. 11-2). The $K_M$ is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half $V_{\text{max}}$. In general, for a drug with a large $K_M$, a higher concentration will be necessary before saturation is reached.

The Michaelis–Menten equation assumes that one drug molecule is catalyzed sequentially by one enzyme at a time. However, enzymes may catalyze more than one drug molecule (multiple sites) at a time, which may be demonstrated in vitro. In the body, drug may be eliminated by enzymatic reactions (metabolism) to one or more metabolites and by the excretion of the unchanged drug via the kidney. In Chapter 9, the Michaelis–Menten equation is used for modeling drug conversion in the body.

The relationship of the rate of metabolism to the drug concentration is a nonlinear, hyperbolic curve (see Fig. 11-2). To estimate the parameters $V_{\text{max}}$ and $K_M$, the reciprocal of the Michaelis–Menten equation is used to obtain a linear relationship.

\[
\frac{1}{v} = \frac{K_M}{V_{\text{max}}} \frac{1}{[D]} + \frac{1}{V_{\text{max}}} \quad (11.21)
\]

Equation 11.21 is known as the Lineweaver–Burk equation, in which $K_M$ and $V_{\text{max}}$ may be estimated from a plot of $1/v$ versus $1/[D]$ (Fig. 11-4). Although the Lineweaver–Burk equation is widely used, other rearrangements of the Michaelis–Menten equation have been used to obtain more accurate estimates of $V_{\text{max}}$ and $K_M$. In Chapter 9, drug concentration $[D]$ is replaced by $C$, which represents drug concentration in the body.

**Frequently Asked Questions**

- **How does one determine whether a drug follows Michaelis–Menten kinetics?**
- **When does the rate of drug metabolism approach $V_{\text{max}}$?**
- **What is the difference between $v$ and $V_{\text{max}}$?**

**Kinetics of Enzyme Inhibition**

Many compounds (eg, cimetidine) may inhibit the enzymes that metabolize other drugs in the body. An inhibitor may decrease the rate of drug metabolism by several different mechanisms. The inhibitor may combine with a cofactor such as NADPH$_2$ needed for enzyme activity, interact with the drug or substrate, or interact directly with the enzyme. Enzyme inhibition may be reversible or irreversible. The mechanism of enzyme inhibition is usually classified...
Chapter 11

by enzyme kinetic studies and observing changes in the $K_M$ and $V_{max}$ (see Fig. 11-4).

In the case of competitive enzyme inhibition, the inhibitor and drug–substrate compete for the same active site on the enzyme. The drug and the inhibitor may have similar chemical structures. An increase in the drug (substrate) concentration may displace the inhibitor from the enzyme and partially or fully reverse the inhibition. Competitive enzyme inhibition is usually observed by a change in the $K_M$, but the $V_{max}$ remains the same.

The reaction velocity $V_I$ for competitive inhibition in the presence of an inhibitor is given by Equation 11.22.

$$V_I = \frac{V_{max}[D]}{[D] + K_M(1 + [I]/K_i)}$$

(11.22)

where $[I]$ is the inhibitor concentration and is the dissociation constant of the inhibitor which can be determined experimentally. For a competitive reaction as shown in Fig. 11-5, $K_i$ is $k_{-i}/k_i$.

In noncompetitive enzyme inhibition, the inhibitor may inhibit the enzyme by combining at a site on the enzyme that is different from the active site (ie, an allosteric site). In this case, enzyme inhibition depends only on the inhibitor concentration. In non-competitive enzyme inhibition, $K_M$ is not altered, but $V_{max}$ is lower. Noncompetitive enzyme inhibition cannot be reversed by increasing the drug concentration, because the inhibitor will interact strongly with the enzyme and will not be displaced by the drug. The reaction velocity in the presence of a noncompetitive inhibitor is given by Equation 11.23

For a noncompetitive reaction,

$$V_I = \frac{V_{max}[D]}{(1+[I]/K_i)([D]+K_M)}$$

(11.23)

FIGURE 11-4(B and C) Agonist effect (E) versus agonist concentration for a competitive antagonist and a noncompetitive antagonist. (Reproduced with permission from Bertram G. Katzung (Editor): Basic & Clinical Pharmacology, 11 ed, 2009, McGraw Hill, Inc.)

FIGURE 11-5 Diagram showing competitive inhibition of an enzyme [E] or a macromolecule (eg, a transport protein) with an inhibitor [I], respectively, $K_i = k_{-i}/k_i$, or [D] refers to the substrate concentration (ie, [D]). In the case of an interaction with a macromolecule, [D] is referred to as ligand concentration and [E] would correspond to the macromolecule concentration. [ED] is the enzyme drug complex and [EI] is the enzyme-inhibitor complex.
Equation (11.23B) relates $K_i$ to $[D]$, $K_M$ and $[I]$ for a general competitive reaction. $V_i$ and $V$ are the reaction velocity with and without inhibitor present, respectively.

$$K_i = \frac{[I]}{[D]} \left( \frac{V}{V_i} - 1 \right)$$  \hspace{1cm} (11.23a)

Experimentally, $IC_{50}$, is determined at 50% inhibition. $V_i$ and $V$ are the velocity with and without inhibitor, respectively, ie, $V/V_i = 2/1$. Substituting into Equation (11.23a) for $V/V_i = 2/1$ yields the familiar Chang–Prusoff equation in the next section.

$$K_i = \frac{IC_{50}}{[D]} \left( \frac{V}{V_i} - 1 \right)$$  \hspace{1cm} (11.23b)

Other types of enzyme inhibition, such as mixed enzyme inhibition and enzyme uncompetitive inhibition, have been described by observing changes in $K_M$ and $V_{max}$.

**CLINICAL EXAMPLE**

Pravastatin sodium (Pravachol®) is an HMG-CoA reductase inhibitor ("statin") which reduces cholesterol biosynthesis, thereby reducing cholesterol. The FDA-approved label states, “The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates.” However, neither myopathy nor significant increases in creatine phosphokinase, CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to 2 years concurrently with pravastatin 10–40 mg and cyclosporine.” Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation (CV), based on between-subject variability, was 50% to 60% for AUC. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance.

- How does cyclosporine change the pharmacokinetics of pravastatin?
- Is pravastatin uptake involved?

**Solution**

Pravastatin and other statins have variable inter- and intra-individual pharmacokinetics after oral dosing due to a large first-pass effect. A drug that is metabolized and also subject to the efflux effect of hepatic transporters can affect overall plasma drug concentrations and liver drug concentrations. It is important to examine the drug dose used in the patient and carefully assess if the dose range is adequately documented by clinical data in a similar patient population, especially if an inhibitor is involved. Finally, it is important to understand the pharmacokinetics, pharmacodynamics, and risk-benefit involved for the drug. Plasma drug concentrations are NOT the only consideration. An oversimplification is often assumed by considering only AUC and $C_{max}$ (ie, drug bioavailability). In this example, the site of action is in the liver. The therapeutic goal should always be to optimize drug concentrations at the site of action and to avoid or minimize drug exposure at unintended sites where adverse effects occur. In this case, adverse drug reactions, ADR, occurs at the heart (eg, myopathy). Whenever possible, a critical drug–drug interaction, DDI, should be avoided or minimized with a washout period during drug co-administration. Alternative therapeutic agents with less liability for DDI may be recommended to clinicians if feasible. A very useful integrated approach and model was recently published about hepatic drug level of pravastatin. Watanabe et al (2009) discussed the simulated plasma concentrations of pravastatin with a detailed physiological model in human and animals. Sensitivity analyses showed that changes in the hepatic uptake ability altered the plasma concentration of pravastatin markedly but had a minimal effect on the liver concentration, whereas changes in canalicular efflux altered the liver concentration of pravastatin markedly but had a small effect on the plasma concentration. In conclusion, the model allowed the prediction of the disposition of pravastatin in humans.

This study suggested that changes in the OATP1B1 (transporter) activities may have a small
and a large impact on the therapeutic efficacy and side effect (myopathy) of pravastatin, respectively, whereas changes in MRP2 activities may have opposite impacts (ie, large and small impacts on the therapeutic efficacy and side effect, respectively).

Kinetics of Enzymatic Inhibition or Macromolecule-Binding Inhibition In Vitro

When an interaction involves competitive inhibition of an enzyme \([E]\) or a macromolecule (eg, a transport protein with a inhibitor \([I]\) as shown in Fig. 11-5), in vitro screening assays are commonly used to evaluate potential inhibitors of enzymatic activity or macromolecule-ligand binding. \(IC_{S0}\) is the total inhibitor concentration that reduces enzymatic or macromolecule-ligand binding activities by 50% \((IC_{S0})\). However, measured \(IC_{S0}\) values depend on concentrations of the enzyme (or target macromolecule), the inhibitor, and the substrate (or ligand) along with other experimental conditions. An accurate determination of the \(K_i\) value requires an intrinsic, thermodynamic quantity that is independent of the substrate (ligand) but depends on the enzyme and inhibitor. The relationship for various types of drug binding may be complex. Cer et al (2009) developed a software for computation of \(K_i\) for various types of inhibitions from \(IC_{S0}\) measurements.

**IC\(_{S0}\) and Affinity**

The relationship between the 50% inhibition concentration and the inhibition constant is given by the Cheng–Prusoff equation below:

\[
K_i = \frac{IC_{S0}}{[D] + 1} \tag{11.23b}
\]

where \(K_i\) shows the binding affinity of the inhibitor, \(IC_{S0}\) is the functional strength of the inhibitor, and \([D]\) is substrate (drug) concentration. Equation 11.23b was published by Cheng and Prusoff (1973). From Equation 11.23b, when \([D]\) is \(<< K_M\), \(K_i = IC_{S0}/[D]\). When \([D] = K_M\), \(K_i = IC_{S0}/2\)

Whereas the \(IC_{S0}\) value for a compound may vary between experiments depending on experimental conditions, the \(K_i\) is an absolute value. \(K_i\) is the inhibition constant of the inhibitor; the concentration of competing ligand in a competition assay which would occupy 50% of the enzyme if no ligand was present. Pharmacologists often use this relationship to determine the \(K_i\) of a competitive inhibitor on an enzyme or a macromolecule such as a transporter. Since there are many drug inhibition interactions, it is important to consider the ratio of inhibition concentration (eg, steady-state plasma concentration \(in vivo\) to the \(IC_{S0}\)). In general, if \([I]/IC_{S0} > 0.1\), the interaction involved should be investigated during early drug development in order to understand the important interaction issue and assess how significant the potential interaction might be clinically. Information on how to study drug metabolism inhibition/induction during development is available on the FDA web. Subclasses of CYP enzymes and transporters are also updated for DDI information (see FDA Guidance, 2006).

**Metabolite Pharmacokinetics for Drugs That Follow a One-Compartment Model**

The one-compartment model may be used to estimate simultaneously both metabolite formation and drug decline in the plasma. For example, a drug is given by intravenous bolus injection and then metabolized by parallel pathways (Fig. 11-6). Assume that both metabolite formation and metabolite and parent drug elimination follow linear (first-order) pharmacokinetics at therapeutic concentrations. The elimination rate constant and the volume of distribution for each metabolite and the parent drug are obtained from curve fitting of the plasma drug concentration–time and each metabolite concentration–time curve. If purified metabolites are available, each metabolite...
Drug Elimination and Hepatic Clearance

should be administered IV separately, to verify the pharmacokinetic parameters independently.

The rate of elimination of the metabolite may be faster or slower than the rate of formation of the metabolite from the drug. Generally, metabolites such as glucuronide, sulfate, or glycine conjugates are more polar or more water soluble than the parent drug and will be eliminated more rapidly than the parent drug. Therefore, the rate of elimination of each of these metabolites is relatively more rapid than the rate of formation. In contrast, if the drug is acetylated or metabolized to a less-polar or less-water-soluble metabolite, then the rate of elimination of the metabolite is relatively slower than the rate of formation of the metabolite. In this case, metabolite accumulation will occur.

Compartment modeling of drug and metabolites is relatively simple and practical. The major shortcoming of compartment modeling is the lack of realistic physiologic information when compared to more sophisticated models that take into account spatial location of enzymes and flow dynamics. However, compartment models are useful for predicting drug and metabolite plasma levels.

For a drug given by IV bolus injection, the metabolite concentration exhibiting linear pharmacokinetics may be predicted from the following equation:

\[ C_m = \frac{k_f D_0}{V_m (k_e - k_{em})} \left( e^{-k_{em}t} - e^{-k_et} \right) \] (11.24)

where \( C_m \) is the metabolite concentration in plasma, \( k_{em} \) is the metabolite elimination rate constant, \( k_e \) is the metabolite formation rate constant, \( V_m \) is the metabolite volume of distribution, \( D_0 \) is the dose of drug, and \( V_D \) is the apparent volume of distribution of drug. All rate constants are first order.

**Frequently Asked Questions**

- Which first-order rate constants will be affected by the addition of an enzyme inhibitor?
- Will \( V_m \) (metabolite) differ from \( V_p \) (parent drug)? If so, why?
- What is the relationship, if any, between \( k_f \), \( k_{em} \), \( k_{m} \), and \( k_e \)?

**PRACTICE PROBLEM**

A drug is eliminated primarily by biotransformation (metabolism) to a glucuronide conjugate and a sulfate conjugate. A single dose (100 mg) of the drug is given by IV bolus injection, and all elimination processes of the drug follow first-order kinetics. The \( V_D \) is 10 L and the elimination rate constant for the drug is 0.9 h\(^{-1}\). The rate constant \((k_e)\) for the formation of the glucuronide conjugate is 0.6 h\(^{-1}\), and the rate constant for the formation of the sulfate conjugate is 0.2 h\(^{-1}\).

a. Predict the drug concentration 1 hour after the dose.

b. Predict the concentration of glucuronide and sulfate metabolites 1 hour after the dose, if the \( V_m \) for both metabolites is the same as for the parent drug and the \( k_{em} \) for both metabolites is 0.4 h\(^{-1}\). (**Note**: \( V_m \) and \( k_{em} \) usually differ between metabolites and parent drug.) In this example, \( V_m \) and \( k_{em} \) are assumed to be the same for both metabolites, so that the concentration of the two metabolites may be compared by examining the formation constants.

**Solution**

The plasma drug concentration 1 hour after the dose may be estimated using the following equation for a one-compartment model, IV bolus administration:

\[ C_p = C_p e^{-kt} = \frac{D_0}{V_D} e^{-kt} \]

\[ C_m = \frac{100}{10} e^{-0.9(1)} = 4.1 \text{ mg/L} \]

The plasma concentrations for the glucuronide and sulfate metabolites 1 hour postdose are estimated after substitution into Equation 11.24.

**Glucuronide:**

\[ C_m = \frac{(0.6)(100)}{10(0.6 - 0.4)} \left( e^{-0.4(1)} - e^{-0.6(1)} \right) \]

\[ C_m = 3.6 \text{ mg/L} \]

**Sulfate:**

\[ C_m = \frac{(0.2)(100)}{10(0.2 - 0.4)} \left( e^{-0.4(1)} - e^{-0.2(1)} \right) \]

\[ C_m = 1.5 \text{ mg/L} \]
Chapter 11

After an IV bolus dose of a drug, the equation describing metabolite concentration formation and elimination by first-order processes is kinetically analogous to drug absorption after oral administration (see Chapter 7). Simulated plasma concentration–time curves were generated using Equation 11.24 for the glucuronide and sulfate metabolites, respectively (Fig. 11-7). The rate constant for the formation of the glucuronide is faster than the rate constant for the formation of the sulfate. Therefore, the time for peak plasma glucuronide concentrations is shorter compared to the time for peak plasma sulfate conjugate concentrations. Equation 11.24 cannot be used if drug metabolism is nonlinear because of enzyme saturation (ie, if metabolism follows Michaelis–Menten kinetics).

Metabolite Pharmacokinetics for Drugs That Follow a Two-Compartment Model

Cephalothin is an antibiotic drug that is metabolized rapidly by hydrolysis in both humans and rabbits. The metabolite desacetylcephalothin has less antibiotic activity than the parent drug. In urine, 18% to 33% of the drug was recovered as desacetylcephalothin metabolite in a human. The time course of both the drug and the metabolite may be predicted after a given dose from the distribution kinetics of both the drug and the metabolite. Cephalothin follows a two-compartment model after IV bolus injection in a rabbit, whereas the desacetylcephalothin metabolite follows a one-compartment model (Fig. 11-8). After a single IV bolus dose of cephalothin (20 mg/kg) to a rabbit, cephalothin declines as a result of excretion and metabolism to desacetylcephalothin. The plasma levels of both cephalothin and desacetylcephalothin may be calculated using equations based on a model with linear metabolism and excretion.

The equations for cephalothin plasma and tissue levels are the same as those derived in Chapter 4 for a simple two-compartment model, except that the elimination constant $k_e$ for the drug now consist of $k_c + k_p$, representing the rate constants for parent drug excretion and metabolite formation constant, respectively.

$$C_p = D_b \left[ \frac{k_{21} - a}{V_p (b-a)} e^{-at} + \frac{k_{21} - b}{V_p (a-b)} e^{-bt} \right]$$ (11.25)

$$C_i = D_b \left[ \frac{k_{12}}{V_i (b-a)} e^{-at} + \frac{k_{12}}{V_i (a-b)} e^{-bt} \right]$$ (11.26)

$$a + b = k + k_{12} + k_{21}$$ (11.27)

$$ab = kk_{21}$$ (11.28)

$$k = k_i + k_e$$ (11.29)

The equation for metabolite plasma concentration, $C_m$, is triexponential, with three preexponential coefficients ($C_s$, $C_t$, and $C_y$) calculated from the various kinetic constants, $V_m$, and the dose of the drug.

$$C_m = C_s e^{-kt} + C_t e^{-at} + C_y e^{-by}$$ (11.30)
For example, after the IV administration of cephalothin to a rabbit, both metabolite and plasma cephalothin concentration may be fitted to Equations 11.25 and 11.30 simultaneously (Fig. 11-9), with the following parameters obtained using a regression computer program (all rate constants in min$^{-1}$).

\[
C_5 = \frac{k_1 D_0 k_{21} - k_1 D_0 k_a}{V_m (b - k_u)(a - k_u)} \quad (11.31)
\]

\[
C_6 = \frac{k_1 D_0 k_{21} - k_1 D_0 a}{V_m (b - a)(k_u - a)} \quad (11.32)
\]

\[
C_7 = \frac{k_1 D_0 k_{21} - k_1 D_0 b}{V_m (k_u - b)(a - b)} \quad (11.33)
\]

For example, after the IV administration of cephalothin to a rabbit, both metabolite and plasma cephalothin concentration may be fitted to Equations 11.25 and 11.30 simultaneously (Fig. 11-9), with the following parameters obtained using a regression computer program (all rate constants in min$^{-1}$).

\[
k_{12} = 0.052 \quad k_{21} = 0.009 \quad V_m = 285 \text{ mL/kg}
\]

\[
k_u = 0.079 \quad k = 0.067 \quad D_0 = 20 \text{ mg/kg}
\]

\[
k_i = 0.045 \quad V_p = 548 \text{ mL/kg} \quad k_a = 0.022
\]

**ANATOMY AND PHYSIOLOGY OF THE LIVER**

The liver is the major organ responsible for drug metabolism. However, intestinal tissues, lung, kidney, and skin also contain appreciable amounts of biotransformation enzymes, as reflected by animal data (Table 11-1). Metabolism may also occur in other tissues to a lesser degree depending on drug properties and route of drug administration.

The liver is both a synthesizing and an excreting organ. The basic anatomical unit of the liver is the liver lobule, which contains parenchymal cells in a network of interconnected lymph and blood vessels. The liver consists of large right and left lobes that merge in the middle. The liver is perfused by blood from the hepatic artery; in addition, the large hepatic portal vein that collects blood from various segments of the GI tract also perfuses the liver (Fig. 11-10). The hepatic artery carries oxygen to the liver and accounts for about 25% of the liver blood supply. The hepatic portal vein carries nutrients to the liver and accounts for about 75% of liver blood flow. The terminal branches of the hepatic artery and portal vein fuse within the liver and mix with the large vascular capillaries known as sinusoids (Fig. 11-11). Blood leaves the liver via the hepatic vein, which empties into the vena cava (see Fig. 11-10). The liver also secretes bile acids within the liver lobes, which flow through a network of channels and eventually empty into the common bile duct (Figs. 11-11 and 11-12). The common bile duct drains bile and biliary excretion products from both lobes into the gallbladder.

**TABLE 11-1 Distribution of Cytochrome P-450 and Glutathione S-Transferase in the Rat**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>CYT P-450$^a$</th>
<th>GSH Transferase$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.73</td>
<td>599</td>
</tr>
<tr>
<td>Lung</td>
<td>0.046</td>
<td>61</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.135</td>
<td>88</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.042</td>
<td>103</td>
</tr>
<tr>
<td>Colon</td>
<td>0.016</td>
<td>—$^c$</td>
</tr>
<tr>
<td>Skin</td>
<td>0.12</td>
<td>—$^c$</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>0.5</td>
<td>308</td>
</tr>
</tbody>
</table>

$^a$Cytochrome P-450, nmole/mg microsome protein.

$^b$Glutathione S-transferase, nmole conjugate formed/min/mg cytosolic protein.

$^c$Values not available.

Data from Wolf (1984).
Chapter 11

FIGURE 11-10 The large hepatic portal vein that collects blood from various segments of the GI tract also perfuses the liver.

FIGURE 11-11 Intrahepatic distribution of the hepatic and portal veins.
Although the principal sites of liver metabolism are the hepatocytes, drug transporters are also present in the hepatocyte besides CYP isoenzymes. Transporters can efflux drug either in or out of the hepatocytes, thus influencing the rate of metabolism. In addition, drug transporters are also present in the bile canaliculi which can eliminate drug by efflux.

Sinusoids are blood vessels that form a large reservoir of blood, facilitating drug and nutrient removal before the blood enters the general circulation. The sinusoids are lined with endothelial cells, or Kupffer cells. Kupffer cells are phagocytic tissue macrophages that are part of the reticuloendothelial system (RES). Kupffer cells engulf worn-out red blood cells and foreign material.

Drug metabolism in the liver has been shown to be flow and site dependent. Some enzymes are reached only when blood flow travels from a given direction. The quantity of enzyme involved in metabolizing drug is not uniform throughout the liver. Consequently, changes in blood flow can greatly affect the fraction of drug metabolized. Clinically, hepatic diseases, such as cirrhosis, can cause tissue fibrosis, necrosis, and hepatic shunt, resulting in changing blood flow and changing bioavailability of drugs (see Chapter 21). For this reason, and in part because of genetic differences in enzyme levels among different subjects and environmental factors, the half-lives of drugs eliminated by drug metabolism are generally very variable.

A pharmacokinetic model simulating hepatic metabolism should involve several elements, including the heterogeneity of the liver, the hydrodynamics of hepatic blood flow, the nonlinear kinetics of drug metabolism, and any unusual or pathologic condition of the subject. Most models in practical use are simple or incomplete models, however, because insufficient information is available about an individual patient. For example, the average hepatic blood flow is usually cited as 1.3–1.5 L/min. Hepatic arterial blood flow and hepatic venous (portal) blood enter the liver at different flow rates, and their drug concentrations are different. It is possible that a toxic metabolite may be transiently higher in some liver tissues and not in others. The pharmacokinetic challenge is to build models that predict regional (organ) changes from easily accessible data, such as plasma drug concentration.

### HEPATIC ENZYMES INVOLVED IN THE BIOTRANSFORMATION OF DRUGS

#### Mixed-Function Oxidases

The liver is the major site of drug metabolism, and the type of metabolism is based on the reaction involved. Oxidation, reduction, hydrolysis, and conjugation are the most common reactions, as discussed under phase I and phase II reactions in the next two sections. The enzymes responsible for oxidation and reduction of drugs (xenobiotics) and certain natural
metabolites, such as steroids, are monoxygenase enzymes known as mixed-function oxidases (MFOs). The hepatic parenchymal cells contain MFOs in association with the endoplasmic reticulum, a network of lipoprotein membranes within the cytoplasm and continuous with the cellular and nuclear membranes. If hepatic parenchymal cells are fragmented and differentially centrifuged in an ultracentrifuge, a microsomal fraction, or microsome, is obtained from the postmitochondrial supernatant. The microsomal fraction contains fragments of the endoplasmic reticulum.

The mixed-function oxidase enzymes are structural enzymes that constitute an electron-transport system that requires reduced NADPH (NADPH$_2$), molecular oxygen, cytochrome P-450, NADPH–cytochrome P-450 reductase, and phospholipid. The phospholipid is involved in the binding of the drug molecule to the cytochrome P-450 and coupling the NADPH–cytochrome P-450 reductase to the cytochrome P-450. Cytochrome P-450 is a heme protein with iron protoporphyrin IX as the prosthetic group. Cytochrome P-450 is the terminal component of an electron-transfer system in the endoplasmic reticulum and acts as both an oxygen- and a substrate-binding locus for drugs and endogenous substrates in conjunction with a flavoprotein reductase, NADPH–cytochrome P-450 reductase. Many lipid-soluble drugs bind to cytochrome P-450, resulting in oxidation (or reduction) of the drug. Cytochrome P-450 consists of closely related isoenzymes (isozymes) that differ somewhat in amino acid sequence and drug specificity (see Chapter 12). A general scheme for MFO drug oxidation is described in Fig. 11-13.

In addition to the metabolism of drugs, the CYP monooxygenase enzyme system catalyzes the biotransformation of various endogenous compounds such as steroids. The CYP monooxygenase enzyme system is also located in other tissues such as kidney, GI tract, skin, and lungs.

A few enzymatic oxidation reactions involved in biotransformation do not include the CYP monooxygenase enzyme system. These include monoamine oxidase (MAO) that deaminates endogenous substrates including neurotransmitters (dopamine, serotonin, norepinephrine, epinephrine, and various drugs with a similar structure); alcohol and aldehyde dehydrogenase in the soluble fraction of liver are involved in the metabolism of ethanol and xanthine oxidase which converts hypoxanthine to xanthine and then to uric acid. Drug substrates for xanthine oxidase include theophylline and 6-mercaptopurine. Allopurinol is a substrate and inhibitor of xanthine oxidase and also delays metabolism of other substrates used in the treatment of gout.

**FIGURE 11-13** Electron flow pathway in the microsomal drug-oxidizing system. (From Alvares and Pratt, 1990, with permission.)
DRUG BIOTRANSFORMATION REACTIONS

The hepatic biotransformation enzymes play an important role in the inactivation and subsequent elimination of drugs that are not easily cleared through the kidney. For these drugs—theophylline, phenytoin, acetaminophen, and others—there is a direct relationship between the rate of drug metabolism (biotransformation) and the elimination half-life for the drug.

For most biotransformation reactions, the metabolite of the drug is more polar than the parent compound. The conversion of a drug to a more polar metabolite enables the drug to be eliminated more quickly than if the drug remained lipid soluble. A lipid-soluble drug crosses cell membranes and is easily reabsorbed by the renal tubular cells, exhibiting a consequent tendency to remain in the body. In contrast, the more polar metabolite does not cross cell membranes easily, is filtered through the glomerulus, is not readily reabsorbed, and is more rapidly excreted in the urine.

Both the nature of the drug and the route of administration may influence the type of drug metabolite formed. For example, isoproterenol given orally forms a sulfate conjugate in the gastrointestinal mucosal cells, whereas after IV administration, it forms the 3-O-methylated metabolite due to S-adenosylmethionine and catechol-O-methyltransferase. Azo drugs such as sulfasalazine are poorly absorbed after oral administration. However, the azo group of sulfasalazine is cleaved by the intestinal microflora, producing 5-aminosalicylic acid and sulfapyridine, which is absorbed in the lower bowel.

The biotransformation of drugs may be classified according to the pharmacologic activity of the metabolite or according to the biochemical mechanism for each biotransformation reaction. For most drugs, biotransformation results in the formation of a more polar metabolite that is pharmacologically inactive and is eliminated more rapidly than the parent drug (Table 11-2).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Drug to Inactive Metabolite</strong></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Deamination → Phenylacetone</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Hydroxylation → Hydroxyphenobarbital</td>
</tr>
<tr>
<td><strong>Active Drug to Active Metabolite</strong></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Demethylation → Morphone</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Acetylation → N-acetylprocainamide</td>
</tr>
<tr>
<td>Phenybutazone</td>
<td>Hydroxylation → Oxyphenbutazone</td>
</tr>
<tr>
<td><strong>Inactive Drug to Active Metabolite</strong></td>
<td></td>
</tr>
<tr>
<td>Hetacillin</td>
<td>Hydrolysis → Ampicillin</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Azoreduction → Sulfapyridine + 5-aminosalicylic acid</td>
</tr>
<tr>
<td><strong>Active Drug to Reactive Intermediate</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Aromatic Hydroxylation → Reactive metabolite (hepatic necrosis)</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>Aromatic Hydroxylation → Reactive metabolite (carcinogenic)</td>
</tr>
</tbody>
</table>
For some drugs the metabolite may be pharmacologically active or produce toxic effects. Prodrugs are inactive and must be biotransformed in the body to metabolites that have pharmacologic activity. Initially, prodrugs were discovered by serendipity, as in the case of prontosil, which is reduced to the antibacterial agent sulfanilamide. More recently, prodrugs have been intentionally designed to improve drug stability, increase systemic drug absorption, or prolong the duration of activity. For example, the antiparkinsonian agent levodopa crosses the blood–brain barrier and is then decarboxylated in the brain to l-dopamine, an active neurotransmitter. l-Dopamine does not easily penetrate the blood–brain barrier into the brain and therefore cannot be used as a therapeutic agent.

### PATHWAYS OF DRUG BIOTRANSFORMATION

Pathways of drug biotransformation may be divided into two major groups of reactions, phase I and phase II reactions. **Phase I,** or asynthetic reactions, include oxidation, reduction, and hydrolysis. **Phase II,** or synthetic reactions, include conjugations. A partial list of these reactions is presented in Table 11-3. In addition, a number of drugs that resemble natural biochemical molecules are able to utilize the metabolic pathways for normal body compounds. For example, isoproterenol is methylated by catechol O-methyl transferase (COMT), and amphetamine is deaminated by monamine oxidase (MAO). Both COMT and MAO are enzymes involved in the metabolism of noradrenaline.

### Phase I Reactions

Usually, phase I biotransformation reactions occur first and introduce or expose a functional group on the drug molecules. For example, oxygen is introduced into the phenyl group on phenylbutazone by aromatic hydroxylation to form oxyphenbutazone, a more polar metabolite. Codeine is demethylated to form morphine. In addition, the hydrolysis of esters, such as aspirin or benzocaine, will yield more polar products, such as salicylic acid and p-aminobenzoic acid, respectively. For some compounds, such as acetaminophen, benzo[a]pyrene, and other drugs containing aromatic rings, reactive intermediates, such as epoxides, are formed during the hydroxylation reaction. These aromatic epoxides are highly reactive and will react with macromolecules, possibly causing liver necrosis (acetaminophen) or cancer (benzo[a]pyrene). The biotransformation of salicylic acid (Fig. 11-14) demonstrates the variety of possible metabolites that may be formed. It should be noted that salicylic acid is also conjugated directly (phase II reaction) without a preceding phase I reaction.

### Conjugation (Phase II) Reactions

Once a polar constituent is revealed or placed into the molecule, a phase II or conjugation reaction may occur. Common examples include the conjugation of acetanilide with sulphate or glucuronic acid to form more soluble metabolites (see Fig. 11-14).

Conjugation reactions use conjugating reagents, which are derived from biochemical compounds.
involved in carbohydrate, fat, and protein metabolism. These reactions may include an active, high-energy form of the conjugating agent, such as uridine diphosphoglucuronic acid (UDPGA), acetyl CoA, 3′-phosphoadenosine-5′-phosphosulfate (PAPS), or S-adenosylmethionine (SAM), which, in the presence of the appropriate transferase enzyme, combines with the drug to form the conjugate. Conversely, the drug may be activated to a high-energy compound that then reacts with the conjugating agent in the presence of a transferase enzyme (Fig. 11-15). The major conjugation (phase II) reactions are listed in Tables 11-3 and 11-4.

Some of the conjugation reactions may have limited capacity at high drug concentrations, leading to nonlinear drug metabolism. In most cases, enzyme activity follows first-order kinetics with low drug (substrate) concentrations. At high doses, the drug concentration may rise above the Michaelis–Menten rate constant ($K_M$), and the reaction rate approaches zero order ($V_{max}$). Glucuronidation reactions have a high capacity and may demonstrate nonlinear (saturation) kinetics at very high drug concentrations. In contrast, glycine, sulfate, and glutathione conjugations show lesser capacity and demonstrate nonlinear kinetics at therapeutic drug concentrations (Caldwell, 1980). The limited capacity of certain conjugation pathways may be due to several factors, including

(1) limited amount of the conjugate transferase,
(2) limited ability to synthesize the active nucleotide intermediate, or
(3) limited amount of conjugating agent, such as glycine.

### TABLE 11-4 Phase II Conjugation Reactions

<table>
<thead>
<tr>
<th>Conjugation Reaction</th>
<th>Conjugating Agent</th>
<th>High-Energy Intermediate</th>
<th>Functional Groups Combined with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucuronidation</td>
<td>Glucuronic acid</td>
<td>UDPGA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—OH, —COOH, —NH&lt;sub&gt;2&lt;/sub&gt;, SH</td>
</tr>
<tr>
<td>Sulfation</td>
<td>Sulfate</td>
<td>PAPS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—OH, —NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Amino acid conjugation</td>
<td>Glycine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Coenzyme A thioesters</td>
<td>—COOH</td>
</tr>
<tr>
<td>Acetylation</td>
<td>Acetyl CoA</td>
<td>Acetyl CoA</td>
<td>—OH, —NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Methylation</td>
<td>CH₃ from S-adenosylmethionine</td>
<td>S-adenosylmethionine</td>
<td>—OH, —NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Glutathione (mercapturine acid conjugation)</td>
<td>Glutathione</td>
<td>Arene oxides, epoxides</td>
<td>Aryl halides, epoxides, arene oxides</td>
</tr>
</tbody>
</table>

<sup>a</sup>UDPGA = uridine diphosphoglucuronic acid.
<sup>b</sup>PAPS = 3′-phosphoadenosine-5′-phosphosulfate.
<sup>c</sup>Glycine conjugates are also known as hippurates.
In addition, the $N$-acetylated conjugation reaction shows genetic polymorphism: for certain drugs, the human population may be divided into fast and slow acetylators. Finally, some of these conjugation reactions may be diminished or defective in cases of inborn errors of metabolism.

Glucuronidation and sulfate conjugation are very common phase II reactions that result in watersoluble metabolites being rapidly excreted in bile (for some high-molecular-weight glucuronides) and/or urine. Acetylation and mercapturic acid synthesis are conjugation reactions that are often implicated in the toxicity of the drug; they will now be discussed more fully.

**Acetylation**

The acetylation reaction is an important conjugation reaction for several reasons. First, the acetylated product is usually less polar than the parent drug. The acetylation of such drugs as sulfanilamide, sulfadiazine, and sulfisoxazole produces metabolites that are less water soluble and that in sufficient concentration precipitate in the kidney tubules, causing kidney damage and crystaluria. In addition, a less-polar metabolite is reabsorbed in the renal tubule and has a longer elimination half-life. For example, procainamide (elimination half-life of 3 to 4 hours) has an acetylated metabolite, $N$-acetylprocainamide, which is biologically active and has an elimination half-life of 6 to 7 hours. Lastly, the $N$-acetyltransferase enzyme responsible for catalyzing the acetylation of isoniazid and other drugs demonstrates a genetic polymorphism. Two distinct subpopulations have been observed to inactivate isoniazid, including the “slow inactivators” and the “rapid inactivators” (Evans, 1968). Therefore, the former group may demonstrate an adverse effect of isoniazide, such as peripheral neuritis, due to the longer elimination half-life and accumulation of the drug.

**Glutathione and Mercapturic Acid Conjugation**

Glutathione (GSH) is a tripeptide of glutamyl-cysteine-glycine that is involved in many important biochemical reactions. GSH is important in the detoxification of reactive oxygen intermediates into nonreactive metabolites and is the main intracellular molecule for protection of the cell against reactive electrophilic compounds. Through the nucleophilic sulfhydryl group of the cysteine residue, GSH reacts nonenzymatically and enzymatically via the enzyme glutathione S-transferase, with reactive electrophilic oxygen intermediates of certain drugs, particularly aromatic hydrocarbons formed during oxidative biotransformation. The resulting GSH conjugates are precursors for a group of drug conjugates known as mercapturic acid ($N$-acetylcysteine) derivatives. The formation of a mercapturic acid conjugate is shown in Fig. 11-16.

The enzymatic formation of GSH conjugates is saturable. High doses of drugs such as acetaminophen (APAP) may form electrophilic intermediates and deplete GSH in the cell. The reactive intermediate covalently bonds to hepatic cellular macromolecules, resulting in cellular injury and necrosis. The suggested antidote for intoxication (overdose) of acetaminophen is the administration of $N$-acetylcysteine (Mucomyst), a drug molecule that contains available sulfhydryl (R–SH) groups.

**FIGURE 11-16** Mercapturic acid conjugation.
Metabolism of Enantiomers

Many drugs are given as mixtures of stereoisomers. Each isomeric form may have different pharmacologic actions and different side effects. For example, the natural thyroid hormone is \( l \)-thyroxine, whereas the synthetic \( d \) enantiomer, \( d \)-thyroxine, lowers cholesterol but does not stimulate basal metabolic rate like the \( l \) form. Since enzymes as well as drug receptors demonstrate stereoselectivity, isomers of drugs may show differences in biotransformation and pharmacokinetics (Tucker and Lennard, 1990). With improved techniques for isolating mixtures of enantiomers, many drugs are now available as pure enantiomers. The rate of drug metabolism and the extent of drug protein binding are often different for each stereoisomer. For example, \((S)-(+)\)disopyramide is more highly bound in humans than \((R)-(\_)\)disopyramide. Carprofen, a nonsteroidal anti-inflammatory drug, also exists in both an \( S \) and an \( R \) configuration. The predominate activity lies in the \( S \) configuration. The clearance of the \( S \)-carprofen glucuronide through the kidney was found to be faster than that of the \( R \) form, 36 versus 26 mL/min (Iwakawa et al, 1989). A list of some common drugs with enantiomers is given in Table 11-5. A review (Ariens and Wuis, 1987) shows that of 475 semisynthetic drugs derived from natural sources, 469 were enantiomers, indicating that the biologic systems are very stereospecific.

The anticonvulsant drug mephenytoin is another example of a drug that exists as \( R \) and \( S \) enantiomers. Both enantiomers are metabolized by hydroxylation in humans (Wilkinson et al, 1989). After an oral dose of 300 mg of the racemic or mixed form, the plasma concentration of the \( S \) form in most subjects was only about 25% of that of the \( R \) form. The elimination half-life of the \( S \) form (2.13 hours) was much faster than that of the \( R \) form (76 hours) in these subjects (Fig. 11-17A). The severity of the sedative side effect of this drug was also less in subjects with rapid metabolism. Hydroxylation reduces the lipophilicity of the metabolite and may reduce the partition of the metabolite into the CNS. Interestingly, some subjects do not metabolize the \( S \) form of mephenytoin well, and the severity of sedation in these subjects was increased. The plasma level of the \( S \) form was much higher in these subjects (Fig. 11-17B). The variation in metabolic rate was attributed to genetically controlled enzymatic differences within the population.

Regioselectivity

In addition to stereoselectivity, biotransformation enzymes may also be regioselective. In this case, the enzymes catalyze a reaction that is specific for a particular region in the drug molecule. For example, isoproterenol is methylated via catechol-\(O\)-methyltransferase and \( S\)-adenosylmethionine primarily in the meta position, resulting in a 3-\(O\)-methylated metabolite. Very little methylation occurs at the hydroxyl group in the para position.

Species Differences in Hepatic Biotransformation Enzymes

The biotransformation activity of hepatic enzymes can be affected by a variety of factors (Table 11-6). During the early preclinical phase of drug development, drug metabolism studies attempt to identify the major metabolic pathways of a new drug through the use of animal models. For most drugs, different animal species may have different metabolic pathways. For example, amphetamine is mainly hydroxylated in rats, whereas in humans and dogs it is largely deaminated. In many cases, the rates of metabolism may differ among different animal species even though the biotransformation pathways are the same. In other cases, a specific pathway may be absent in a particular species. Generally, the researcher tries to

### TABLE 11-5 Common Drug Enantiomers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enantiomer</th>
<th>Enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>( l )</td>
<td>( d )</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>( l )</td>
<td>( d )</td>
</tr>
<tr>
<td>Cocaine</td>
<td>( l )</td>
<td>( d )</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Propranolol</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Nadolol</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Verapamil</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Tocainide</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Morphine</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Warfarin</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Throxine</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Flecainide</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Atenolol</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Subutamol</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>( S )</td>
<td>( R )</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>( S )</td>
<td>( R )</td>
</tr>
</tbody>
</table>
find the best animal model that will be predictive of the metabolic profile in humans.

In recent years, in vitro drug screening with human liver microsomes or with hepatocytes has helped confirm whether a given CYP isoenzyme is important in human drug metabolism. Animal models also provide some supportive evidence.

**TABLE 11-6  Sources of Variation in Intrinsic Clearance**

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic differences within population</td>
<td></td>
</tr>
<tr>
<td>Racial differences among different populations</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental factors and drug interactions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme induction</td>
<td></td>
</tr>
<tr>
<td>Enzyme inhibition</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiologic conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Diet/nutrition</td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug dosage regimen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of drug administration</td>
<td></td>
</tr>
<tr>
<td>Dose-dependent (nonlinear) pharmacokinetics</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL EXAMPLE**

Lovastatin (Mevacor®) is a cholesterol-lowering agent and was found to be metabolized by human liver microsomes to two major metabolites: 6’β-hydroxy (Michaelis-Menten constant $[K_M]$: 7.8 ± 2.7 μM) and 6’-exomethylene lovastatin ($[K_M]$, 10.3 ± 2.6 μM). 6’β-Hydroxylovastatin formation in the liver was inhibited by the specific CYP3A inhibitors cyclosporine ($[K_i]$, 7.6 ± 2.3 μM), ketoconazole ($[K_i]$, 0.25 ± 0.2 μM), and troleandomycin ($[K_i]$, 26.6 ± 18.5 μM).

Hydroxylation of lovastatin is a phase I reaction and catalyzed by a specific cytochrome P-450 enzyme commonly referred to as CYP3A. Ketoconazole and cyclosporine are CYP3A inhibitors and therefore affect lovastatin metabolism. Lovastatin is referred to as a substrate. Substrate concentrations are expressed as $[S]$ ($[D]$ in Fig. 11-4A), preferably in (μM). The Michaelis–Menten constant ($[K_M]$) of the enzyme is expressed in micromoles (μM) because most new drugs have different MW, making it easier to compare by expressing them in moles. Cyclosporine would be expected to produce a significant drug–drug interaction in the body based a review of the $[K_i]$ values. In addition to inhibiting the cytochrome P-450 enzyme pathway, an efflux transporter can deplete the drug before significant biotransformation occurs. Efflux
inhibition would have the opposite effect. Thus, location (time and place) issues are important when DDI involves a CYP and a transporter.

A systems biology approach that takes into account all aspects of ADME processes integrated with pharmacogenetics is needed to properly address various pharmacokinetic, pharmacodynamic, and clinical issues of risk/benefit. The interplay among the various processes including influx and efflux transporters may sometimes outweigh any single process when complex drug–drug interactions are involved. For most drugs, metabolism has multiple pathways are inherently complicated. Many pharmacodynamic drug actions in patients encounter the issue of responder and nonresponder, which may be genetically defined or totally obscured.

Knowledge of drug transport of drug from one site can make the hepatic intrinsic clearance concept obsolete in some simple physiological blood flow models. Macro models based on mass balance are kinetically based and the amount of drug in the plasma pool can still be computed and properly tracked. A drug–drug interaction between lovastatin and cyclosporine occurs because cyclosporine is a CYP3A and transport inhibitor in the liver.

### Frequently Asked Questions

**Variation of Biotransformation Enzymes**

Variation in metabolism may be caused by a number of biologic and environmental variables (see Table 11-6). **Pharmacogenetics** is the study of genetic differences in pharmacokinetics and pharmacodynamics, including drug elimination (see Chapter 12). For example, the N-acetylation of isoniazid is genetically determined, with at least two identifiable groups, including rapid and slow acetylators (Evans et al, 1968). The difference is referred to as **genetic polymorphism**. Individuals with slow acetylation are prone to isoniazid-induced neurotoxicity. Procainamide and hydralazine are other drugs that are acetylated and demonstrate genetic polymorphism.

Another example of genetic differences in drug metabolism is glucose 6-phosphate-dehydrogenase deficiency, which is observed in approximately 10% of African Americans. A well-documented example of genetic polymorphism with this enzyme was observed with phenytoin (Wilkinson et al, 1989). Two phenotypes, EM (efficient metabolizer) and PM (poor metabolizer), were identified in the study population. The PM frequency in Caucasians was about 4% and in Japanese was about 16%. Variation in metabolic rate was also observed with mephobarbital. The incidence of side effects was higher in Japanese subjects, possibly due to a slower oxidative metabolism. Variations in propranolol metabolism due to genetic difference among Chinese populations was also reported (Lai et al, 1995). Some variations in metabolism may also be related to geographic rather than racial differences (Bertilsson, 1995).

Besides genetic influence, the basal level of enzyme activity may be altered by environmental factors and exposure to chemicals. Shorter theophylline elimination half-life due to smoking was observed in smokers. Apparently, the aromatic hydrocarbons, such as benzpyrene, that are released during smoking stimulate the enzymes involved in theophylline metabolism. Young children are also known to eliminate theophylline more quickly. Phenobarbital is a potent inducer of a wider variety of hepatic enzymes. Polycyclic hydrocarbons such as 3-methylcholanthrene and benzpyrene also induce hepatic enzyme formation. These compounds are carcinogenic.

Hepatic enzyme activity may also be inhibited by a variety of agents including carbon monoxide, heavy metals, and certain imidazole drugs such as cimetidine. Enzyme inhibition by cimetidine may lead to higher plasma levels and longer elimination of co-administered phenytoin or theophylline. The physiologic condition of the host—including age, gender, nutrition, diet, and pathophysiology—also affects the level of hepatic enzyme activities.

**Genetic Variation of Cytochrome P-450 (CYP) Isozymes**

The most important enzymes accounting for variation in phase I metabolism of drugs is the cytochrome P-450 enzyme group, which exists in many
Drug Elimination and Hepatic Clearance

forms among individuals because of genetic differences (May, 1994; Tucker, 1994; Parkinson, 1996; see also Chapter 12). Initially, the cytochrome P-450 enzymes were identified according to the substrate that was biotransformed. More recently, the genes encoding many of these enzymes have been identified. Multiforms of cytochrome P-450 are referred to as isozymes, and are classified into families (originally denoted by Roman numerals: I, II, III, etc) and subfamilies (denoted by A, B, C, etc) based on the similarity of the amino acid sequences of the isozymes. If an isozyme amino acid sequence is 60% similar or more, it is placed within a family. Within the family, isozymes with amino acid sequences of 70% or more similarity are placed into a subfamily, and an Arabic number follows for further classification. Further information on the CYP enzymes including drug interactions, classification, table of substrates, inhibitors, and inducers have been published by Nelson (2009) and the US FDA. Nebert et al (1989) and Hansch and Zhang (1993) have reviewed the nomenclature of the P-450 family of enzymes. A new nomenclature starts with CYP as the root denoting cytochrome P-450, and an Arabic number now replaces the Roman numeral (Table 11-7). The CYP3A subfamily of CYP3 appears to be responsible for the metabolism of a large number of structurally diverse endogenous agents (eg, testosterone, cortisol, progesterone, estradiol) and xenobiotics (eg, nifedipine, lovastatin, midazolam, terfenadine, erythromycin).

The substrate specificities of the P-450 enzymes appear to be due to the nature of the amino acid residues, the size of the amino acid side chain, and the polarity and charge of the amino acids (Negishi et al, 1996). The individual gene is denoted by an Arabic number (last number) after the subfamily. For example, cytochrome P-450 IA2 (CYP1A2) is involved in the oxidation of caffeine and CYP2D6 is involved in the oxidation of drugs, such as codeine, propranolol, and dextromethorphan. The well-known CYP2D6 is responsible for debrisoquine metabolism among individuals showing genetic polymorphism. The vinca alkaloids used in cancer treatment have shown great inter- and intra-individual variabilities. CYP3A enzymes are known to be involved in the metabolism of vindesine, vinblastine, and other vinca alkaloids (Rahmani and Zhou, 1993). Failing to recognize variations in drug clearance in cancer chemotherapy may result in greater toxicity or even therapeutic failure.

There are now at least eight families of cytochrome isozymes known in humans and animals. CYP 1–3 are best known for metabolizing clinically useful drugs in humans. Variation in isozyme distribution and content in the hepatocytes may affect intrinsic hepatic clearance of a drug. The levels and activities of the cytochrome P-450 isozymes differ among individuals as a result of genetic and environmental factors. Clinically, it is important to look for evidence of unusual metabolic profiles in patients before dosing. Pharmacokinetic experiments using a “marker” drug such as antipyrine or dextromethorphan may be used to determine if the intrinsic hepatic clearance of the patient is significantly different from that of an average subject.

The metabolism of debrisoquin is polymorphic in the population, with some individuals having extensive metabolism (EM) and other individuals having poor metabolism (PM). Those individuals who are PM lack functional CYP2D6 (P-450IID6). In EM individuals, quinidine will block CYP2D6 so that genotypic EM individuals appear to be phenotypic PM individuals (Caraco et al, 1996). Some drugs metabolized by CYP2D6 (P-450IID6) are codeine, flecainide, dextromethorphan, imipramine, and other cyclic antidepressants that undergo ring

### TABLE 11-7 Comparison of P-450 Nomenclatures Currently in Use

<table>
<thead>
<tr>
<th>P-450 Gene Family/Subfamily</th>
<th>New Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-450I</td>
<td>CYP1</td>
</tr>
<tr>
<td>P-450IIA</td>
<td>CYP2A</td>
</tr>
<tr>
<td>P-450IIB</td>
<td>CYP2B</td>
</tr>
<tr>
<td>P-450IIC</td>
<td>CYP2C</td>
</tr>
<tr>
<td>P-450IID</td>
<td>CYP2D</td>
</tr>
<tr>
<td>P-450IIIE</td>
<td>CYP2E</td>
</tr>
<tr>
<td>P-450III</td>
<td>CYP3</td>
</tr>
<tr>
<td>P-450IV</td>
<td>CYP4</td>
</tr>
</tbody>
</table>

hydroxylation. The inability to metabolize substrates for CYP2D6 results in increased plasma concentrations of the parent drug in PM individuals.

**Drug Interactions Involving Drug Metabolism**

The enzymes involved in the metabolism of drugs may be altered by diet and the co-administration of other drugs and chemicals. *Enzyme induction* is a drug- or chemical-stimulated increase in enzyme activity, usually due to an increase in the amount of enzyme present. Enzyme induction usually requires some onset time for the synthesis of enzyme protein. For example, rifampin induction occurs within 2 days, while phenobarbital induction takes about 1 week to occur. Enzyme induction for carbamazepine begins after 3 to 5 days and is not complete for approximately 1 month or longer. Smoking can change the rate of metabolism of many cyclic antidepressant drugs (CAD) through enzyme induction (Toney and Ereshefsky, 1995). Agents that induce enzymes include aromatic hydrocarbons (such as benzopyrene, found in cigarette smoke), insecticides (such as chlor dane), and drugs such as carbamazepine, rifampin, and phenobarbital (see also Chapter 20). *Enzyme inhibition* may be due to substrate competition or direct inhibition of drug-metabolizing enzymes, particularly one of several of the cytochrome P-450 enzymes. Many widely prescribed antidepressants generally known as selective serotonin reuptake inhibitors (SSRIs) have been reported to inhibit the CYP2D6 system, resulting in significantly elevated plasma concentration of co-administered psychotropic drugs. Fluoxetine causes a ten-fold decrease in the clearance of imipramine and desipramine because of its inhibitory effect on hydroxylation (Toney and Ereshefsky, 1995).

A few clinical examples of enzyme inhibitors and inducers are listed in Table 11-8. Diet also affects drug-metabolizing enzymes. For example, plasma theophylline concentrations and theophylline clearance in patients on a high-protein diet are lower than in subjects whose diets are high in carbohydrates. Sucrose or glucose plus fructose decrease the activity of mixed-function oxidases, an effect related to a slower metabolism rate and a prolongation in hexobarbital sleeping time in rats. Chronic administration of 5% glucose was suggested to affect sleeping time in subjects receiving barbiturates. A decreased intake of fatty acids may lead to decreased basal MFO activities (Campbell, 1977) and affect the rate of drug metabolism.

The protease inhibitor saquinavir mesylate (Invirase®, Roche) has very low bioavailability—

---

**TABLE 11-8 Examples of Drug Interactions Affecting Mixed Function Oxidase Enzymes**

<table>
<thead>
<tr>
<th>Inhibitors of Drug Metabolism</th>
<th>Example</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Ethanol</td>
<td>Increased hepatotoxicity in chronic alcoholics</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Warfarin</td>
<td>Prolongation of prothrombin time</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Carbamazepine</td>
<td>Decreased carbazepine clearance</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Imipramine (IMI)</td>
<td>Decreased clearance of CAD</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Desipramine (DMI)</td>
<td>Decreased clearance of CAD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inducers of Drug Metabolism</th>
<th>Example</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Acetaminophen</td>
<td>Increased acetaminophen metabolism</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Methadone</td>
<td>Increased methadone metabolism, may precipitate opiate withdrawal</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Dexamethasone</td>
<td>Decreased dexamethasone elimination half-life</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Prednisolone</td>
<td>Increased elimination of prednisolone</td>
</tr>
</tbody>
</table>

---
only about 4%. In studies conducted by Hoffmann-La Roche, the area under the curve (AUC) of saquinavir was increased to 150% when the volunteers took a 150-mL glass of grapefruit juice with the saquinavir, and then another 150-mL glass an hour later. Concentrated grapefruit juice increased the AUC up to 220%. Naringin, a bioflavonoid in grapefruit juice, was found to be at least partially responsible for the inhibition of saquinavir metabolism by CYP3A4, present in the liver and the intestinal wall, which metabolizes saquinavir, resulting in an increase in its AUC. Ketoconazole and ranitidine (Zantac®) may also increase the AUC of saquinavir by inhibiting the cytochrome P-450 enzymes. In contrast, rifampin greatly reduces the AUC of saquinavir, apparently due to enzymatic stimulation. Other drugs recently shown to have increased bioavailability when taken with grapefruit juice include several sedatives and the anticoagulant coumarin (Table 11-9). Increases in drug levels may be dangerous, and the pharmacokinetics of drugs with potential interactions should be closely monitored. More complete tabulations of the cytochrome P-450s are available (Flockhart, 2003; Parkinson, 1996; Cupp and Tracy, 1998); some examples are given in Table 11-10.

### Auto-Induction and Time-Dependent Pharmacokinetics

Many drugs enhance the activity of cytochrome P-450 (CYP) enzymes and thereby change their own metabolism (auto-induction) or the metabolism of other compounds. When assessing induction, the enzyme activity is usually measured before and after a period of treatment with the inducing agent. Thus, the induction magnitude of various CYP enzymes is well known for several inducing agents.

The time-dependent pharmacokinetics have been described with a model where the production rates of the affected enzymes were proportional to the amounts of the inducing agents and the time course of the induction process was described by the turnover model. An example of a drug with time-dependent pharmacokinetics is carbamazepine.

For new drugs, the potential for drug metabolism/interaction is studied in vitro and/or in vivo by identifying whether the drug is a substrate for the common CYP450 subfamilies (FDA Guidance for Industry, 1999, 2006). An understanding of the mechanistic basis of metabolic drug–drug interactions enables the prediction of whether the coadministration of two or more drugs may have clinical consequences affecting safety and efficacy. In practice, an investigational drug under development is co-administered with an approved drug (interacting drug) which utilizes similar CYP pathways. Examples of substrates include (1) midazolam for CYP3A; (2) theophylline for CYP1A2; (3) repaglinide for CYP2C8; (4) warfarin for CYP2C9 (with the evaluation of S-warfarin); (5) omeprazole for CYP2C19; and (6) desipramine for CYP2D6. Additional examples of substrates, along with inhibitors and inducers of specific CYP enzymes, are listed in Table A-2 in Appendix A in the FDA draft guidance (2006). Examples of substrates include, but are not limited to, (1) midazolam, buspirone, felodipine, simvastatin, or lovastatin for CYP3A4; (2) theophylline for CYP1A2; (3) S-warfarin for CYP2C9; and (4) desipramine for CYP2D6.

Since metabolism usually occurs in the liver (some enzymes such as CYP3A4 are also important in gut metabolism), human liver microsomes provide a convenient way to study CYP450 metabolism. Microsomes are a subcellular fraction of tissue obtained by differential high-speed centrifugation. The key CYP450 enzymes are collected in the microsomal fraction. The CYP450 enzymes retain their activity for many years in microsomes or whole liver stored at low temperature. Hepatic microsomes can be obtained commercially, with or without prior phenotyping, for most important CYP450 enzymes.

---

**TABLE 11-9 Change in Drug Availability due to Oral Coadministration of Grapefruit Juice**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>Hukkanen et al, 1995</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Kupferschmidt et al, 1995</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Yee et al, 1995</td>
</tr>
<tr>
<td>Coumarin</td>
<td>Merkel et al, 1994</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Baily DG et al, 1993a</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Baily DG et al, 1993b</td>
</tr>
</tbody>
</table>
The cDNAs for the common CYP450s have been cloned, and the recombinant human enzymatic proteins have been expressed in a variety of cells. These recombinant enzymes provides an excellent way to confirm results using microsomes. Pharmacokinetic endpoints recommended for assessment of the substrate are (1) exposure measures such as AUC, \(C_{\text{max}}\), time to \(C_{\text{max}}\) (\(T_{\text{max}}\)), and others as appropriate; and (2) pharmacokinetic parameters such as clearance, volumes of distribution, and half-lives (FDA Guidance for Industry, 1999). For metabolism induction studies, in vivo studies are more relied upon because enzyme induction may not be well predicted from in vitro results. Considerations in drug-metabolizing/drug interaction studies include: (1) acute or chronic use of the substrate and/or interacting drug; (2) safety considerations, including whether a drug is likely to be an NTR (narrow therapeutic range) or non-NTR drug; (3) pharmacokinetic and pharmacodynamic characteristics of the substrate and interacting drugs; and (4) the need to assess induction as well as inhibition. The inhibiting/inducing drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their clinical use.

**Transporter-Based Drug–Drug Interactions**

Transporter-based interactions have been increasingly documented. Examples include the inhibition or induction of transport proteins, such as P-glycoprotein (P-gp), organic anion transporter (OAT), organic anion transporting polypeptide (OATP), organic cation transporter (OCT), multidrug resistance–associated proteins (MRP), and breast cancer–resistant protein (BCRP). Examples of transporter-based interactions include the interactions

<table>
<thead>
<tr>
<th>Table 11-10 Cytochrome P450 Isoforms and Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
</tr>
<tr>
<td><strong>CYP2B6</strong></td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
</tr>
<tr>
<td><strong>CYP2D6</strong></td>
</tr>
<tr>
<td><strong>CYP2E1</strong></td>
</tr>
<tr>
<td><strong>CYP3A4, 5, 6</strong></td>
</tr>
</tbody>
</table>

Examples based on Flockhart (2003), Cupp and Tracy (1998), and Desta et al (2002).
between digoxin and quinidine, fexofenadine and ketoconazole (or erythromycin), penicillin and probenecid, and dofetilide and cimetidine. Of the various transporters, P-gp is the best understood and may be appropriate to evaluate during drug development. Table 11-11 lists some of the major human transporters and known substrates, inhibitors, and inducers.

In the simple hepatic clearance model, intrinsic clearance is assumed to be constant within the same subject. This model describes how clearance can change in response to physiologic changes such as blood flow or enzymatic induction. Patient variability and changes in intrinsic clearance may be due to (1) patient factors such as age and genetic polymorphism, (2) enzymatic induction or inhibition due to co-administered drugs, (3) modification of influx and efflux transporters in the liver and the bile canaliculi.

Some hepatic transporters in the liver include P-gp and OATPs (Huang et al, 2009). When a

<table>
<thead>
<tr>
<th>Gene</th>
<th>Aliases</th>
<th>Tissue</th>
<th>Drug Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>P-gp,</td>
<td>Intestine, liver, kidney,</td>
<td>Digoxin, fexofenadine,</td>
<td>Ritonavir, cyclosporine, verapamil, erythromycin,</td>
<td>Rifampin, St John’s wort</td>
</tr>
<tr>
<td></td>
<td>MDR1</td>
<td>brain, placenta, adrenal,</td>
<td>indinavir, vincristine,</td>
<td>ketoconazole, itraconazole, quinidine, elacridar (GF120918)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>tests</td>
<td>colchicine, topotecan, paclitaxel</td>
<td>LY335979 valsapodar (PSC833)</td>
<td></td>
</tr>
<tr>
<td>ABCB4</td>
<td>MDR3</td>
<td>Liver</td>
<td>Digoxin, paclitaxel, vinblastine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCB11</td>
<td>BSEP</td>
<td>Liver</td>
<td>Vinceblastine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCC1</td>
<td>MRP1</td>
<td>Intestine, liver, kidney,</td>
<td>Adefovir, indinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCC2</td>
<td>MRP2,</td>
<td>Intestine, liver, kidney,</td>
<td>Indinavir, cisplatin</td>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMOAT</td>
<td>brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCC3</td>
<td>MRP3,</td>
<td>Intestine, liver, kidney,</td>
<td>Etoposide, methotrexate,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMOAT2</td>
<td>placenta, adrenal</td>
<td>tenoposide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCC4</td>
<td>MRP4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC5</td>
<td>MRP5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC6</td>
<td>MRP6</td>
<td>Liver, kidney</td>
<td>Cisplatin, daunorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCG2</td>
<td>BCRP</td>
<td>Intestine, liver, breast,</td>
<td>Daunorubicin, doxorubicin,</td>
<td>Elacridar (GF120918), gefitinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>placenta</td>
<td>topotecan, rosuvastatin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sulfasalazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC01B1</td>
<td>OATP1B1,</td>
<td>Liver</td>
<td>Rifampin, rosuvastatin,</td>
<td>Cyclosporine, rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OATP-C</td>
<td></td>
<td>methotrexate, pravastatin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OATP2</td>
<td></td>
<td>thyroxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC01B3</td>
<td>OATP1B3</td>
<td>Liver</td>
<td>Digoxin, methotrexate, rifampin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC02B1</td>
<td>SLC21A9,</td>
<td>Intestine, liver, kidney,</td>
<td>Pravastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OATP-B</td>
<td>brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC10A1</td>
<td>NTCP</td>
<td>Liver, pancreas</td>
<td>Rosuvastatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

transporter is known to play a major role in translocating drug in and out of cells and organelles within the liver, the simple hepatic clearance model may not adequately describe the pharmacokinetics of the drug within the liver. Micro constants may be needed to describe how the drug moves kinetically in and out within a group of cells or compartment. Canalicular transporters are present for many drugs. Biliary excretion should also be incorporated into the model as needed. For this reason, local drug concentration in the liver may be very high, leading to serious liver toxicity. Huang et al (2009) have discussed the importance of drug transporters, drug disposition, and how to study drug interaction in the new drugs.

Knowledge of drug transporters and CYPs can help predict whether many drug interactions have clinical significance. Pharmacists should realize that the combined effect of efflux and CYP inhibition can cause serious or even fatal adverse reaction due to severalfold increase in AUC or \( C_{\text{max}} \). Impairment of bile flow, saturation of conjugation enzymes (phase II) such as glucoronide, and sulfate conjugate formation can lead to adverse toxicity.

**CLINICAL EXAMPLE**

Digoxin is a MDR1/P-gp substrate.

1. Which of the following sites is an important influence on the plasma levels of digoxin after oral administration?
   a. Hepatocyte (canalicular)
   b. Hepatocyte (sinusoidal)
   c. Intestinal enterocyte

2. Ritonavir and quinidine are examples of P-gp inhibitors. What changes in AUC or \( C_{\text{max}} \) would you expect for digoxin when co-administered with either one of these two inhibitors?

3. Using your knowledge of drug transporters and their substrate inhibitors, can you determine whether the above change in digoxin plasma level is due to a change in metabolism or distribution?

**Solution**

1. According to Table 11-11, MDR1 is an efflux transporter for digoxin in the liver (canaliculi) and enterocyte. Digoxin is also a substrate for MDR3, SLC01B1, and other transporters. MDR1 is inhibited by quinidine and ritonavir.

2. A literature search shows that digoxin transport by P-gp occurs at the liver canaliculi and P-gp will interact with ritonavir or quinidine with co-administration (both are inhibitors of MDR1). Inhibition of efflux will increase the plasma level of digoxin. Other effects may also occur since most transport inhibitors are not 100% specific and may affect metabolism/disposition in other ways.

3. The package insert should be consulted on drug distribution and drug interaction. A pharmacist should realize that although either one of the two inhibitors can increase AUC of digoxin (by 1.5–2 \( x \)) in this hypothetical case, in reality, a comprehensive evaluation of pharmacokinetics and pharmacodynamics of the drug doses involved and the medical profile of the patient is needed to determine if an interaction is clinically significant.

**FIRST-PASS EFFECTS**

For some drugs, the route of administration affects the metabolic rate of the compound. For example, a drug given parenterally, transdermally, or by inhalation may distribute within the body prior to metabolism by the liver. In contrast, drugs given orally are normally absorbed in the duodenal segment of the small intestine and transported via the mesenteric vessels to the hepatic portal vein and then to the liver before entering the systemic circulation. Drugs that are highly metabolized by the liver or by the intestinal mucosal cells demonstrate poor systemic availability when given orally. This rapid metabolism of an orally administered drug before reaching the general circulation is termed **first-pass effect** or **pre-systemic elimination**.

**Evidence of First-Pass Effects**

First-pass effects may be suspected when there is relatively low concentrations of parent (or intact) drug in the systemic circulation after oral compared
Drug Elimination and Hepatic Clearance

283
to IV administration. In such a case, the AUC for a drug given orally is also less than the AUC for the same dose of drug given intravenously. From experimental findings in animals, first-pass effects may be assumed if the intact drug appears in a cannulated hepatic portal vein but not in general circulation.

For an orally administered drug that is chemically stable in the gastrointestinal tract and is 100% systemically absorbed ($F = 1$), the area under the plasma drug concentration curve, $AUC_{0, \text{oral}}$, should be the same when the same drug dose is given intravenously, $AUC_{0, \text{IV}}$. Therefore, the absolute bioavailability ($F$) may reveal evidence of drug being removed by the liver due to first-pass effects as follows:

$$F = \frac{[AUC]_{0, \text{oral}}/D_{0, \text{oral}}}{[AUC]_{0, \text{IV}}/D_{0, \text{IV}}}$$  (11.34)

For drugs that undergo first-pass effects, $AUC_{0, \text{oral}}$ is smaller than $AUC_{0, \text{IV}}$ and $F < 1$. Drugs such as propranolol, morphine, and nitroglycerin have $F$ values less than 1 because these drugs undergo significant first-pass effects.

Liver Extraction Ratio

Because there are many other reasons for a drug to have a reduced $F$ value, the extent of first-pass effects is not precisely measured from the $F$ value. The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug.

$$\text{ER} = \frac{C_a - C_v}{C_a}$$  (11.35)

where $C_a$ is the drug concentration in the blood entering the liver and $C_v$ is the drug concentration leaving the liver.

Because $C_a$ is usually greater than $C_v$, ER is usually less than 1. For example, for propranolol, ER or $[E]$ is about 0.7—that is, about 70% of the drug is actually removed by the liver before it is available for general distribution to the body. By contrast, if the drug is injected intravenously, most of the drug would be distributed before reaching the liver, and less of the drug would be metabolized the first time the drug reaches the liver.

The ER may vary from 0 to 1.0. An ER of 0.25 means that 25% of the drug is removed by the liver. If both the ER for the liver and the blood flow to the liver are known, then hepatic clearance $Cl_h$, may be calculated by the following expression:

$$Cl_h = \frac{Q(C_a - C_v)}{C_a} = Q \times ER$$  (11.36)

where $Q$ is the effective hepatic blood flow.

Relationship Between Absolute Bioavailability and Liver Extraction

Liver ER provides a measurement of liver extraction of a drug orally administered. Unfortunately, sampling of drug from the hepatic portal vein and artery is difficult and performed mainly in animals. Animal ER values may be quite different from those in humans. The following relationship between bioavailability and liver extraction enables a rough estimate of the extent of liver extraction:

$$F = 1 - \text{ER} - F''$$  (11.37)

where $F$ is the fraction of bioavailable drug, ER is the drug fraction extracted by the liver, and $F''$ is the fraction of drug removed by nonhepatic process prior to reaching the circulation.

If $F''$ is assumed to be negligible—that is, there is no loss of drug due to chemical degradation, gut metabolism, and incomplete absorption—ER may be estimated from

$$F = 1 - \text{ER}$$  (11.38)

After substitution of Equation 11.34 into Equation 11.38,

$$\text{ER} = 1 - \frac{[AUC]_{0, \text{oral}}/D_{0, \text{oral}}}{[AUC]_{0, \text{IV}}/D_{0, \text{IV}}}$$  (11.39)

ER is a rough estimation of liver extraction for a drug. Many other factors may alter this estimation: the size of the dose, the formulation of the drug, and the pathophysiologic condition of the patient all may affect the ER value obtained.

Liver ER provides valuable information in determining the oral dose of a drug when the intra-
venous dose is known. For example, propranolol requires a much higher oral dose compared to an IV dose to produce equivalent therapeutic blood levels, because of oral drug extraction by the liver. Because liver extraction is affected by blood flow to the liver, oral dosing of drug with extensive liver metabolism may produce erratic plasma drug levels. Formulation of this drug into an oral dosage form requires extensive, careful testing.

Estimation of Reduced Bioavailability due to Liver Metabolism and Variable Blood Flow

Blood flow to the liver plays an important role in the amount of drug metabolized after oral administration. Changes in blood flow to the liver may substantially alter the percentage of drug metabolized and therefore alter the percentage of bioavailable drug. The relationship between blood flow, hepatic clearance, and percent of drug bioavailable is

$$F^* = 1 - \frac{Cl_h}{Q} = 1 - ER$$

where $Cl_h$ is the hepatic clearance of the drug and $Q$ is the effective hepatic blood flow. $F^*$ is the bioavailability factor obtained from estimates of liver blood flow and hepatic clearance, ER.

This equation provides a reasonable approach for evaluating the reduced bioavailability due to first-pass effect. The usual effective hepatic blood flow is 1.5 L/min, but it may vary from 1 to 2 L/min depending on diet, food intake, physical activity, or drug intake (Rowland, 1973). For the drug propoxyphene hydrochloride, $F^*$ has been calculated from hepatic clearance (990 mL/min) and an assumed liver blood flow of 1.53 L/min:

$$F^* = 1 - \frac{0.99}{1.53} = 0.35$$

The results, showing that 35% of the drug is systemically absorbed after liver extraction, are reasonably compared with the experimental values for propranolol.

Presystemic elimination or first-pass effect is a very important consideration for drugs that have a high extraction ratio (Table 11-12). Drugs with low extraction ratios, such as theophylline, have very little presystemic elimination, as demonstrated by complete systemic absorption after oral administration. In contrast, drugs with high extraction ratios have poor bioavailability when given orally. Therefore, the oral dose must be higher than the intravenous dose to achieve the same therapeutic response. In some cases, oral administration of a drug with high presystemic elimination, such as nitroglycerin, may be impractical due to very poor oral bioavailability, and thus a sublingual, transdermal, or nasal route of administration may be preferred.

Furthermore, if an oral drug product has slow dissolution characteristics or release rate, then more of the drug will be subject to first-pass effect compared to doses of drug given in a more bioavailable

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**TABLE 11-12 Hepatic and Renal Extraction Ratios of Representative Drugs**

<table>
<thead>
<tr>
<th>Extraction Ratios</th>
<th>Low (&lt;0.3)</th>
<th>Intermediate (0.3–0.7)</th>
<th>High (&gt;0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATIC EXTRACTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amobarbital</td>
<td>Aspirin</td>
<td>Arabinosylcytosine</td>
<td></td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Quinidine</td>
<td>Encainide</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Desipramine</td>
<td>Isoproterenol</td>
<td></td>
</tr>
<tr>
<td>Chlor Diazepoxide</td>
<td>Nortriptyline</td>
<td>Meperidine</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Nitroglycerin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Pentazocine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Propoxyphene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Salicylaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Tocainide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tolbutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
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<td></td>
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</tbody>
</table>

Drug Elimination and Hepatic Clearance

form (such as a solution). In addition, drugs with high presystemic elimination tend to demonstrate more variability in drug bioavailability between and within individuals. Finally, the quantity and quality of the metabolites formed may vary according to the route of drug administration, which may be clinically important if one or more of the metabolites has pharmacologic or toxic activity.

To overcome first-pass effect, the route of administration of the drug may be changed. For example, nitroglycerin may be given sublingually or topically, and xylocaine may be given parenterally to avoid the first-pass effects. Another way to overcome first-pass effects is to either increase the dose or change the drug product to a more rapidly absorbable dosage form. In either case, a large amount of drug is presented rapidly to the liver, and some of the drug will reach the general circulation in the intact state.

Although Equation 11.40 seems to provide a convenient way of estimating the effect of liver blood flow on bioavailability, this estimation is actually more complicated. A change in liver blood flow may alter hepatic clearance and $F'$. A large blood flow may deliver enough drug to the liver to alter the rate of metabolism. In contrast, a small blood flow may decrease the delivery of drug to the liver and become the rate-limiting step for metabolism (see below). The hepatic clearance of a drug is usually calculated from plasma drug data rather than whole-blood data. Significant nonlinearity may be the result of drug equilibration due to partitioning into the red blood cells.

**EXAMPLES**

1. A new propranolol 5-mg tablet was developed and tested in volunteers. The bioavailability of propranolol from the tablet was 70%, compared to an oral solution of propranolol, and 21.6%, compared to an intravenous dose of propranolol. Calculate the relative and absolute bioavailability of the propranolol tablet. Comment on the feasibility of further improving the absolute bioavailability of the propranolol tablet.

Solution

The relative bioavailability of propranolol from the tablet compared to the solution is 70% or 0.7. The absolute bioavailability, $F$, of propranolol from the tablet compared to the IV dose is 21.6%, or $F = 0.216$. From the table of ER values (Table 11-13), the ER for propranolol is 0.6 to 0.8. If the product is perfectly formulated, i.e., the tablet dissolves completely and all the drug is released from the tablet, the fraction of drug absorbed after deducting for the fraction of drug extracted by the liver is

$$F' = 1 - ER$$

$$F' = 1 - 0.7 \quad (\text{mean } ER = 0.7)$$

$$F' = 0.3$$

Thus, under normal conditions, total systemic absorption of propranolol from an oral tablet would be about 30% ($F = 0.3$). The measurement of relative bioavailability for propranolol is always performed against a reference standard given by the same route of administration and can have a value greater than 100%.

The following shows a method for calculating the absolute bioavailability from the relative bioavailability provided the ER is accurately known. Using the above example,

Absolute availability of the solution = 1 – ER

$= 1 - 0.7 = 0.3 = 30\%$

Relative availability of the solution = 100%

Absolute availability of the tablet = $x\%$

Relative availability of the tablet = 70%

$$x = \frac{30 \times 70}{100} = 21\%$$

Therefore, this product has a theoretical absolute bioavailability of 21%. The small difference of calculated and actual (the difference between 21.6% and 21%) absolute bioavailability is due largely to liver extraction fluctuation. All calculations are performed with the assumption of linear pharmacokinetics, which is generally a good approximation. ER may deviate significantly with changes in blood flow or other factors.
Fluvastatin sodium (Lescol®, Novartis) is a drug used to lower cholesterol. The absolute bioavailability after an oral dose is reported to be 19% to 29%. The drug is rapidly and completely absorbed (manufacturer’s product information). What are the reasons for the low oral bioavailability in spite of reportedly good absorption? What is the extraction ratio of fluvastatin? (The absolute bioavailability, $F$, is 46%, according to values reported in the literature.)

**Solution**

Assuming the drug to be completely absorbed as reported, using Equation 11.38,

$$ER = 1 - 0.46 = 0.54$$

Thus, 54% of the drug is lost due to first-pass effect because of a relatively large extraction ratio. Since bioavailability is only 19% to 29%, there is probably some nonhepatic loss, according to Equation 11.37. Fluvastatin sodium was reported to be extensively metabolized, with some drug excreted in feces.

### Relationship Between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

Although Equation 11.40 seems to provide a convenient way of estimating the effect of liver blood flow on bioavailability, this estimation is actually more complicated. For example, factors that affect the hepatic clearance of a drug include (1) blood flow to the liver, (2) intrinsic clearance, and (3) the fraction of drug bound to protein.

A change in liver blood flow may alter hepatic clearance and $F'$. A large blood flow may deliver enough drug to the liver to alter the rate of metabolism. In contrast, a small blood flow may decrease the delivery of drug to the liver and become the rate-limiting step for metabolism. The hepatic clearance of a drug is usually calculated from plasma drug data rather than whole-blood data. Significant nonlinearity

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Extraction Ratio (Approx.)</th>
<th>Percent Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow Limited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.83</td>
<td>45–80</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.6–0.8</td>
<td>93</td>
</tr>
<tr>
<td>Pethidine (meperidine)</td>
<td>0.60–0.95</td>
<td>60</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.8</td>
<td>—</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>0.95</td>
<td>—</td>
</tr>
<tr>
<td>Nortriptiline</td>
<td>0.5</td>
<td>95</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.5–0.75</td>
<td>35</td>
</tr>
<tr>
<td>Capacity Limited, Binding Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.03</td>
<td>90</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.03</td>
<td>98</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>0.02</td>
<td>98</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.003</td>
<td>99</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.22</td>
<td>91–99</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.23</td>
<td>94</td>
</tr>
<tr>
<td>Quinidine</td>
<td>0.27</td>
<td>82</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>0.005</td>
<td>97</td>
</tr>
<tr>
<td>Capacity Limited, Binding Insensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>0.09</td>
<td>59</td>
</tr>
<tr>
<td>Hexobarbital</td>
<td>0.16</td>
<td>—</td>
</tr>
<tr>
<td>Amobarbital</td>
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</tr>
<tr>
<td>Antipyrine</td>
<td>0.07</td>
<td>10</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.28</td>
<td>60–80</td>
</tr>
<tr>
<td>Thiopental</td>
<td>0.28</td>
<td>72</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.43</td>
<td>5</td>
</tr>
</tbody>
</table>

*Concentration dependent in part.
From Blaschke (1977), with permission.
may be the result of drug equilibration due to partitioning into the red blood cells.

**High-Extraction Ratio Drugs**

For some drugs (such as isoproterenol, lidocaine, and nitroglycerin), the extraction ratio is high (>0.7), and the drug is removed by the liver almost as rapidly as the organ is perfused by blood in which the drug is contained. For drugs with very high extraction ratios, the rate of drug metabolism is sensitive to changes in hepatic blood flow. Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ. Propranolol, a β-adrenergic blocking agent, decreases hepatic blood flow by decreasing cardiac output. In such a case, the drug decreases its own clearance through the liver when given orally. Many drugs that demonstrate first-pass effects are drugs that have high extraction ratios with respect to the liver.

Intrinsic clearance ($Cl_{int}$) is used to describe the total ability of the liver to metabolize a drug in the absence of flow limitations, reflecting the inherent activities of the mixed-function oxidases and all other enzymes. Intrinsic clearance is a distinct characteristic of a particular drug, and as such, it reflects the inherent ability of the liver to metabolize the drug. Intrinsic clearance may be shown to be analogous to the ratio $V_{max}/K_M$ for a drug that follows Michaelis–Menten kinetics. Hepatic clearance is a concept that characterizes drug elimination based on both blood flow and the intrinsic clearance of the liver, as shown in Equation 11.41.

$$Cl_h = \frac{QCl_{int}}{Q + Cl_{int}} \quad (11.41)$$

**Low-Extraction Ratio Drugs**

When the blood flow to the liver is constant, hepatic clearance is equal to the product of blood flow ($Q$) and the extraction ratio ($ER$) (Equation 11.36). However, the hepatic clearance of a drug is not constant. Hepatic clearance changes with blood flow and the intrinsic clearance of the drug are described in Equation 11.41. For drugs with low extraction ratios (e.g., theophylline, phenylbutazone, and procainamide), the hepatic clearance is less affected by hepatic blood flow. Instead, these drugs are more affected by the intrinsic activity of the mixed-function oxidases. Describing clearance in terms of all the factors in a physiologic model allows drug clearance to be estimated when physiologic or disease conditions cause changes in blood flow or intrinsic enzyme activity. Smoking, for example, can increase the intrinsic clearance for the metabolism of many drugs.

Changes or alterations in mixed-function oxidase activity or biliary secretion can affect the intrinsic clearance and thus the rate of drug removal by the liver. Drugs that show low extraction ratios and are eliminated primarily by metabolism demonstrate marked variation in overall elimination half-lives within a given population. For example, the elimination half-life of theophylline varies from 3 to 9 hours. This variation in $t_{1/2}$ is thought to be due to genetic differences in intrinsic hepatic enzyme activity. Moreover, the elimination half-lives of these same drugs are also affected by enzyme induction, enzyme inhibition, age of the individual, nutritional, and pathologic factors.

Clearance may also be expressed as the rate of drug removal divided by plasma drug concentration:

$$Cl_h = \frac{\text{rate of drug removed by the liver}}{C_a} \quad (11.42)$$

Because the rate of drug removal by the liver is usually the rate of drug metabolism, Equation 11.42 may be expressed in terms of hepatic clearance and drug concentration entering the liver ($C_a$):

$$\text{Rate of liver drug metabolism} = Cl_hC_a \quad (11.43)$$

**HEPATIC CLEARANCE OF A PROTEIN-BOUND DRUG: RESTRICTIVE AND NONRESTRICTIVE CLEARANCE FROM BINDING**

It is generally assumed that protein-bound drugs are not easily metabolized (restrictive clearance), while free (unbound) drugs are subject to metabolism. Protein-bound drugs do not easily diffuse through
cell membranes, while free drugs can reach the site of the mixed-function oxidase enzymes easily. Therefore, an increase in the free drug concentration in the blood will make more drug available for hepatic extraction. The concept is discussed under restrictive and nonrestrictive clearance (Gillette, 1973) of protein-bound drugs (see Chapter 10).

Most drugs are restrictively cleared, for example, diazepam, quinidine, tolbutamide, and warfarin. The clearance of these drugs is proportional to the fraction of unbound drug ($f_u$). However, some drugs, such as propranolol, morphine, and verapamil, are nonrestrictively extracted by the liver regardless of drug bound to protein or free. Kinetically, a drug is nonrestrictively cleared if its hepatic extraction ratio (ER) is greater than the fraction of free drug ($f_u$), and the rate of drug clearance is unchanged when the drug is displaced from binding. Mechanistically, the protein binding of a drug is a reversible process and for a nonrestrictively bound drug, the free drug gets “stripped” from the protein relatively easily compared to a restrictively bound drug during the process of drug metabolism. The elimination half-life of a nonrestrictively cleared drug is not significantly affected by a change in the degree of protein binding. This is an analogous situation to a protein-bound drug that is actively secreted by the kidney.

For a drug with restrictive clearance, the relationship of blood flow, intrinsic clearance, and protein binding is

$$Cl_h = Q \left( \frac{f_u Cl{'}_{int}}{Q + f_u Cl{'}_{int}} \right)$$

(11.44)

where $f_u$ is the fraction of drug unbound in the blood and $Cl{'}_{int}$ is the intrinsic clearance of free drug. Equation 11.44 is derived by substituting $f_u Cl{'}_{int}$ for $Cl{'}_{int}$ in Equation 11.41.

From Equation 11.44, when $Cl{'}_{int}$ is very small in comparison to hepatic blood flow (ie, $Q > Cl{'}_{int}$), then Equation 11.45 reduces to Equation 11.46.

$$Cl_h = \frac{Q f_u Cl{'}_{int}}{Q}$$

(11.45)

$$Cl_h = f_u Cl{'}_{int}$$

(11.46)

As shown in Equation 11.46, a change in $Cl{'}_{int}$ or $f_u$ will cause a proportional change in $Cl_h$ for drugs with protein binding.

In the case where $Cl{'}_{int}$ for a drug is very large in comparison to flow ($Cl{'}_{int} >> Q$), Equation 11.47 reduces to Equation 11.48.

$$Cl_h = \frac{Q f_u Cl{'}_{int}}{f_u Cl{'}_{int}}$$

(11.47)

$$Cl_h = Q$$

(11.48)

Thus, for drugs with a very high $Cl{'}_{int}$, $Cl_h$ is dependent on hepatic blood flow and independent of protein binding.

For restrictively cleared drugs, change in binding generally alters drug clearance. For a drug with low hepatic extraction ratio and low plasma binding, clearance will increase, but not significantly, when the drug is displaced from binding. For a drug highly bound to plasma proteins (more than 90%), a displacement from these binding sites will significantly increase the free concentration of the drug, and clearance (both hepatic and renal clearance) will increase (see Chapter 10). There are some drugs that are exceptional and show a paradoxical increase in hepatic clearance despite an increase in protein binding. In one case, increased binding to AAG ($\alpha$ acid glycoprotein) was found to concentrate drug in the liver, leading to an increased rate of metabolism because the drug was nonrestrictively cleared in the liver.

**EFFECT OF CHANGING INTRINSIC CLEARANCE AND/OR BLOOD FLOW ON HEPATIC EXTRACTION AND ELIMINATION HALF-LIFE AFTER IV AND ORAL DOSING**

The effects of altered hepatic intrinsic clearance and liver blood flow on the blood level–time curve have been described by Wilkinson and Shand (1975) after both IV and oral dosing. These investigators show how changes in intrinsic clearance and blood flow affect the elimination half-life, first-pass effects, and
bioavailability of the drug as represented by the area under the curve.

**Effect of Changing Intrinsic Clearance**

The elimination half-life of a drug with a low extraction ratio is decreased significantly by an increase in hepatic enzyme activity. In contrast, the elimination half-life of a drug with a high extraction ratio is not markedly affected by an increase in hepatic enzyme activity because enzyme activity is already quite high. In both cases, an orally administered drug with a higher extraction ratio results in a greater first-pass effect as shown by an increase in hepatic clearance.

**Effect of Changing Blood Flow**

Drug clearance and elimination half-life as simulated by Wilkinson et al. are both affected by changing blood flow to the liver. For drugs with low extraction ($E = 0.1$), a decrease in hepatic blood flow from normal (1.5 L/min) to one-half decreases clearance only slightly, and blood level is slightly higher. In contrast, for a drug with high extraction ratio ($E = 0.9$), decreasing the blood flow to one-half of normal greatly decreases clearance, and the blood level is much higher.

Alterations in hepatic blood flow significantly affect the elimination of drugs with high extraction ratios (eg, propranolol) and have very little effect on the elimination of drugs with low extraction ratios (eg, theophylline). For drugs with low extraction ratios, any concentration of drug in the blood that perfuses the liver is more than the liver can eliminate. Consequently, small changes in hepatic blood flow do not affect the removal rate of such drugs. In contrast, drugs with high extraction ratios are removed from the blood as rapidly as they are presented to the liver. If the blood flow to the liver decreases, then the elimination of these drugs is prolonged. Therefore, drugs with high extraction ratios are considered to be flow dependent. A number of drugs have been investigated and classified according to their extraction by the liver.

**Effect of Changing Protein Binding on Hepatic Clearance**

The effect of protein binding on hepatic clearance is often difficult to quantitate precisely, because it is not always known whether the bound drug is restrictively or nonrestrictively cleared. For example, animal tissue levels of imipramine, a nonrestrictively cleared drug, were shown to change as the degree of plasma protein binding changes (see Chapter 10). As discussed, drug protein binding is not a factor in hepatic clearance for drugs that have high extraction ratios. These drugs are considered to be flow limited. In contrast, drugs that have low extraction ratios may be affected by plasma protein binding, depending on the fraction of drug bound. For a drug that has a low extraction ratio and is less than 75% to 80% bound, small changes in protein binding will not produce significant changes in hepatic clearance. These drugs are considered capacity-limited, binding-insensitive drugs (Blaschke, 1977) and are listed in Table 11-13. Drugs that are highly bound to plasma protein but with low extraction ratios are considered capacity limited and binding sensitive, because a small displacement in the protein binding of these drugs will cause a very large increase in the free drug concentration. These drugs are good examples of restrictively cleared drugs. A large increase in free drug concentration will cause an increase in the rate of drug metabolism, resulting in an overall increase in hepatic clearance. Figure 11-18 illustrates the relationship of protein binding, blood flow, and extraction.

**BILIARY EXCRETION OF DRUGS**

The biliary system of the liver is an important system for the secretion of bile and the excretion of drugs. Anatomically, the intrahepatic bile ducts join outside the liver to form the common hepatic duct (Fig. 11-19). The bile that enters the gallbladder becomes highly concentrated. The hepatic duct, containing hepatic bile, joins the cystic duct that drains the gallbladder to form the common bile duct. The common bile duct then empties into the duodenum. Bile consists primarily of water, bile salts, bile pigments, electrolytes, and, to a lesser extent, cholesterol and fatty acids. The hepatic cells lining the bile canaliculi are responsible for the production of bile. The production of bile appears to be an active secretion process. Separate active biliary secretion processes have been reported for organic anions, organic cations, and for polar, uncharged molecules.
Drugs that are excreted mainly in the bile have molecular weights in excess of 500. Drugs with molecular weights between 300 and 500 are excreted both in urine and in bile. For these drugs, a decrease in one excretory route results in a compensatory increase in excretion via the other route. Compounds with molecular weights of less than 300 are excreted almost exclusively via the kidneys into urine.

In addition to relatively high molecular weight, drugs excreted into bile usually require a strongly polar group. Many drugs excreted into bile are metabolites, very often glucuronide conjugates. Most metabolites are more polar than the parent drug. In addition, the formation of a glucuronide increases the molecular weight of the compound by nearly 200, as well as increasing the polarity.

Drugs excreted into the bile include the digitalis glycosides, bile salts, cholesterol, steroids, and indomethacin (Table 11-14). Compounds that enhance bile production stimulate the biliary excretion of drugs normally eliminated by this route. Furthermore, phenobarbital, which induces many mixed-function oxidase activities, may stimulate the biliary excretion of drugs by two mechanisms: by an increase in the formation of the glucuronide metabolite and by an increase in bile flow. In contrast, compounds that decrease bile flow or pathophysiologic conditions that cause cholestasis decrease biliary drug excretion. The route of administration may also influence the amount of the drug excreted into bile. For example,
Drug Elimination and Hepatic Clearance

291

**Enterohepatic Circulation**

A drug or its metabolite is secreted into bile and upon contraction of the gallbladder is excreted into the duodenum via the common bile duct. Subsequently, the drug or its metabolite may be excreted into the feces or the drug may be reabsorbed and become systemically available. The cycle in which the drug is absorbed, excreted into the bile, and reabsorbed is known as enterohepatic circulation. Some drugs excreted as a glucuronide conjugate become hydrolyzed in the gut back to the parent drug by the action of a β-glucuronidase enzyme present in the intestinal bacteria. In this case, the parent drug becomes available for reabsorption.

**Significance of Biliary Excretion**

When a drug appears in the feces after oral administration, it is difficult to determine whether this presence of drug is due to biliary excretion or incomplete absorption. If the drug is given parenterally and then observed in the feces, one can conclude that some of the drug was excreted in the bile. Because drug secretion into bile is an active process, this process can be saturated with high drug concentrations. Moreover, other drugs may compete for the same carrier system.

Enterohepatic circulation after a single dose of drug is not as important as after multiple doses or a very high dose of drug. With a large dose or multiple doses, a larger amount of drug is secreted in the bile, from which drug may then be reabsorbed. This reabsorption process may affect the absorption and elimination rate constants. Furthermore, the biliary secretion process may become saturated, thus altering the plasma level–time curve.

**TABLE 11-14 Examples of Drugs Undergoing Enterohepatic Circulation and Biliary Excretion**

<table>
<thead>
<tr>
<th>Enterohepatic Circulation</th>
<th>Biliary Excretion (intact or as metabolites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>Cefamandole</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Cefoperazone</td>
</tr>
<tr>
<td>Morphine</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>Diazepam</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
</tr>
<tr>
<td></td>
<td>Estradiol</td>
</tr>
<tr>
<td></td>
<td>Fluvalinatin</td>
</tr>
<tr>
<td></td>
<td>Lovastatin</td>
</tr>
<tr>
<td></td>
<td>Moxalactam</td>
</tr>
<tr>
<td></td>
<td>Practolol</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Testosterone</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
</tr>
</tbody>
</table>

drugs given orally may be extracted by the liver into the bile to a greater extent than the same drugs given intravenously.

**Estimation of Biliary Clearance**

In animals, bile duct cannulation allows both the volume of the bile and the concentration of drug in the bile to be measured directly using a special intubation technique that blocks off a segment of the gut with an inflating balloon. The rate of drug elimination may then be measured by monitoring the amount of drug secreted into the GI perfusate.

Assuming an average bile flow of 0.5 to 0.8 mL/min in humans, biliary clearance can be calculated if the bile concentration, \( C_{\text{bile}} \), is known.

\[
Cl_{\text{biliary}} = \frac{\text{bile flow} \times C_{\text{bile}}}{C_p} \quad (11.49)
\]

Alternatively, using the perfusion technique, the amount of drug eliminated in bile is determined from the GI perfusate, and \( Cl_{\text{biliary}} \) may be calculated without the bile flow rate, as follows.

\[
Cl_{\text{biliary}} = \frac{\text{amount of drug secreted from bile per minute}}{C_p} \quad (11.50)
\]

To avoid any complication of unabsorbed drug in the feces, the drug should be given by parenteral administration (eg, IV) during biliary determination experiments. The amount of drug in the GI perfusate recovered periodically may be determined. The extent of biliary elimination of digoxin has been determined in humans using this approach.

**Examples of Drugs Undergoing Enterohepatic Circulation and Biliary Excretion**

- Cefamandole
- Cefoperazone
- Chloramphenicol
- Diazepam
- Digoxin
- Doxorubicin
- Doxycycline
- Estradiol
- Fluvastatin
- Lovastatin
- Moxalactam
- Practolol
- Spironolactone
- Testosterone
- Tetracycline
- Vincristine

\[
Cl_{\text{biliary}} = \frac{\text{amount of drug secreted from bile per minute}}{C_p} \quad (11.50)
\]
Drugs that undergo enterohepatic circulation sometimes show a small secondary peak in the plasma drug–concentration curve. The first peak occurs as the drug in the GI tract is depleted; a small secondary peak then emerges as biliary-excreted drug is reabsorbed. In experimental studies involving animals, bile duct cannulation provides a means of estimating the amount of drug excreted through the bile. In humans, a less accurate estimation of biliary excretion may be made from the recovery of drug excreted through the feces. However, if the drug was given orally, some of the fecal drug excretion could represent unabsorbed drug.

**CLINICAL EXAMPLE**

Leflunomide, an immunomodulator for rheumatoid arthritis, is metabolized to a major active metabolite and several minor metabolites. Approximately 48% of the dose is eliminated in the feces due to high biliary excretion. The active metabolite is slowly eliminated from the plasma. In the case of serious adverse toxicity, the manufacturer recommends giving cholestyramine or activated charcoal orally to bind the active metabolite in the GI tract to prevent drug reabsorption and to facilitate drug elimination. The use of cholestyramine or activated charcoal reduces the plasma levels of the active metabolite by approximately 40% in 24 hours and by about 50% in 48 hours.

**ROLE OF TRANSPORTERS IN HEPATIC CLEARANCE AND BIOAVAILABILITY**

In the simple hepatic clearance model, intrinsic clearance is assumed to be constant within the same subject. This model describes how clearance can change in response to physiologic changes such as blood flow or enzymatic induction. Patient variability and changes in intrinsic clearance may be due to (1) patient factors such as age and genetic polymorphism, (2) enzymatic induction or inhibition due to co-administered drugs, and (3) modification of influx and efflux transporters in the liver and the bile canaliculi. When a transporter is known to play a major role in translocating drug in and out of cells and organelles within the liver, the simple hepatic clearance model may not adequately describe the pharmacokinetics of the drug within the liver. Micro constants may be needed to describe how the drug moves kinetically in and out within a group of cells or compartment. Biliary excretion should also be incorporated into the model as needed. Since the development of the hepatic model based on intrinsic clearance, much more information is now known about the interplay between transporters and strategically located CYP isoenzymes in the GI, the hepatocytes in various parts of the liver (see Figs. 11-11 and 11-12). More elaborate models are now available to relate transporters to drug disposition. Huang et al (2009) have discussed the importance of drug transporters and drug disposition, and how to study drug interaction of the new drugs. The interplay between transporters, drug permeability in GI, and hepatic drug extraction are important to the bioavailability and the extent of drug metabolism.

It appears that drugs may be divided into several classes to facilitate prediction of drug disposition. A drug substance is considered to be “highly permeable” when the extent of the absorption (parent drug plus metabolites) in humans is determined to be 90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. Drugs may be classified into four BCS (biopharmaceutical classification system) classes. With respect to oral bioavailability,
elimination, effects of efflux, and absorptive transporters on oral absorption, when transporter–enzyme interplay will yield clinically significant effects such as low bioavailability and drug–drug interactions (DDI), the direction and importance of food effects, and transporter effects on postabsorption systemic levels following oral and intravenous dosing.

Figure 11-20 provides a good summary of how various physiologic and physiochemical factors influence drug disposition. For example, Class 1 drugs are not so much affected by transporters because absorption is generally good already due to high solubility and permeability. Class 2 drugs are very much affected by efflux transporters because of low solubility and high permeability. The limited amount of drug solubilized and absorbed could efflux back into the GI lumen due to efflux transporters, thus resulting in low plasma level. Further, efflux transporter may pump drug into bile if located in the liver canaliculi.

**Frequently Asked Questions**

```
What are the effects of metabolism on Class 1 and 2 drugs?

What are the effects of transporters on Class 3 and 4 drugs?
```

Wu and Benet (2005) proposed categorizing drugs into the four classes based on solubility and permeability because these criteria may provide significant new insights into predicting routes of elimination, metabolism, and excretion. The classification system, known as the Biopharmaceutics Drug Disposition Classification System (BDDCS), helps to understand the importance of these factors in drug disposition. The BDDCS divides drugs into four classes based on their solubility and permeability:

- **Class 1**: High solubility and high permeability. Metabolism effects are minimal.
- **Class 2**: Low solubility and high permeability. Efflux transporter effects predominate.
- **Class 3**: Low solubility and low permeability. Absorptive transporter effects predominate.
- **Class 4**: Low solubility and high permeability. Absorptive and efflux transporter effects could be important.

**CHAPTER SUMMARY**

The elimination of most drugs from the body involves the processes of both metabolism (biotransformation) and renal excretion. Drugs that are highly metabolized often demonstrate large intersubject variability in elimination half-lives and are dependent on the intrinsic activity of the biotransformation enzymes. Renal drug excretion is highly dependent on the glomerular filtration rate (GFR) and blood flow to the kidney.

Hepatic clearance is influenced by hepatic blood flow, drug–protein binding, and intrinsic clearance. The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug. Drugs that are metabolized by the liver enzymes follow Michaelis–Menton kinetics. At low drug concentrations, the rate of metabolism is first order, whereas at very high drug concentrations, the rate of drug metabolism may approach zero-order pharmacokinetics. Phase 1 reactions are generally oxidation and reduction reactions and involve the mixed function oxidases or cytochrome enzymes. These enzymes may be altered by genetic and environmental factors. Phase 2 reactions are generally conjugation reactions such as the formation of glucuronide and sulfate conjugations. Cytochrome-mediated and acetylation reactions demonstrate polymorphic variability in humans.
First-pass effects or presystemic elimination may occur after oral drug administration in which some of the drug may be metabolized or not absorbed prior to reaching the general circulation. Alternate routes of drug administration are often used to circumnavigate presystemic elimination. High-molecular-weight, polar drugs may be eliminated by biliary drug excretion.

**LEARNING QUESTIONS**

1. A drug fitting a one-compartment model was found to be eliminated from the plasma by the following pathways with the corresponding elimination rate constants.
   - Metabolism: $k_m = 0.200 \text{ h}^{-1}$
   - Kidney excretion: $k_e = 0.250 \text{ h}^{-1}$
   - Biliary excretion: $k_b = 0.150 \text{ h}^{-1}$
   a. What is the elimination half-life of this drug?
   b. What would be the half-life of this drug if biliary secretion was completely blocked?
   c. What would be the half-life of this drug if drug excretion through the kidney was completely impaired?
   d. If drug-metabolizing enzymes were induced so that the rate of metabolism of this drug doubled, what would be the new elimination half-life?

2. A new broad-spectrum antibiotic was administered by rapid intravenous injection to a 50-kg woman at a dose of 3 mg/kg. The apparent volume of distribution of this drug was equivalent to 5% of body weight. The elimination half-life for this drug is 2 hours.
   a. If 90% of the unchanged drug was recovered in the urine, what is the renal excretion rate constant?
   b. Which is more important for the elimination of the drugs, renal excretion or biotransformation? Why?

3. Explain briefly:
   a. Why does a drug that has a high extraction ratio (e.g., propranolol) demonstrate greater differences between individuals after oral administration than after intravenous administration?
   b. Why does a drug with a low hepatic extraction ratio (e.g., theophylline) demonstrate greater differences between individuals after hepatic enzyme induction than a drug with a high hepatic extraction ratio?

4. A drug is being screened for antihypertensive activity. After oral administration, the onset time is 0.5 to 1 hour. However, after intravenous administration, the onset time is 6 to 8 hours.
   a. What reasons would you give for the differences in the onset times for oral and intravenous drug administration?
   b. Devise an experiment that would prove the validity of your reasoning.

5. Calculate the hepatic clearance for a drug with an intrinsic clearance of 40 mL/min in a normal adult patient whose hepatic blood flow is 1.5 L/min.
   a. If the patient develops congestive heart failure that reduces hepatic blood flow to 1.0 L/min but does not affect the intrinsic clearance, what is the hepatic drug clearance in this patient?
   b. If the patient is concurrently receiving medication, such as phenobarbital, which increases the $Cl_{int}$ to 90 mL/min but does not alter the hepatic blood flow (1.5 L/min), what is the hepatic clearance for the drug in this patient?

6. Calculate the hepatic clearance for a drug with an intrinsic clearance of 12 L/min in a normal adult patient whose hepatic blood flow is 1.5 L/min. If this same patient develops congestive heart failure that reduces his hepatic blood flow to 1.0 L/min but does not affect
intrinsic clearance, what is the hepatic drug clearance in this patient?

a. Calculate the extraction ratio for the liver in this patient before and after congestive heart failure develops.

b. From the above information, estimate the fraction of bioavailable drug, assuming the drug is given orally and absorption is complete.

7. Why do elimination half-lives of drugs eliminated primarily by hepatic biotransformation demonstrate greater intersubject variability than those drugs eliminated primarily by glomerular filtration?

8. A new drug demonstrates high presystemic elimination when taken orally. From which of the following drug products would the drug be most bioavailable? Why?

a. Aqueous solution
b. Suspension
c. Capsule (hard gelatin)
d. Tablet
e. Sustained release

9. For a drug that demonstrated presystemic elimination, would you expect qualitative and/or quantitative differences in the formation of metabolites from this drug given orally compared to intravenous injection? Why?

10. The bioavailability of propranolol is 26%. Propranolol is 87% bound to plasma proteins and has an elimination half-life of 3.9 hours. The apparent volume of distribution of propranolol is 4.3 L/kg. Less than 0.5% of the unchanged drug is excreted in the urine.

a. Calculate the hepatic clearance for propranolol in an adult male patient (43 years old, 80 kg).

b. Assuming the hepatic blood flow is 1500 mL/min, estimate the hepatic extraction ratio for propranolol.

c. Explain why hepatic clearance is more important than renal clearance for the elimination of propranolol.

d. What would be the effect of hepatic disease such as cirrhosis on the (1) bioavailability of propranolol and (2) hepatic clearance of propranolol?

e. Explain how a change in (1) hepatic blood flow, (2) intrinsic clearance, or (3) plasma protein binding would affect hepatic clearance of propranolol.

f. What is meant by first-pass effects? From the data above, why is propranolol a drug with first-pass effects?

11. The following pharmacokinetic information for erythromycin was reported by Gilman et al, 1990, p. 1679:

Bioavailability: 35%
Urinary excretion: 12%
Bound in plasma: 84%
Volume of distribution: 0.78 L/kg
Elimination half-life: 1.6 hours

An adult male patient (41 years old, 81 kg) was prescribed 250 mg of erythromycin base every 6 hours for 10 days. From the data above, calculate the following:

a. Total body clearance
b. Renal clearance
c. Hepatic clearance

d. Why would you expect hepatic clearance of theophylline in identical twins to be less variable compared to hepatic clearance in fraternal twins?

13. Which of the following statements describe(s) correctly the properties of a drug that follows nonlinear or capacity-limited pharmacokinetics?

a. The elimination half-life will remain constant when the dose changes.

b. The area under the plasma curve (AUC) will increase proportionately with an increase in dose.

c. The rate of drug elimination = \( C_p \times K_M \).

d. At maximum saturation of the enzyme by the substrate, the reaction velocity is at \( V_{max} \).

e. At very low substrate concentrations, the reaction rate approximates a zero-order rate.

14. The \( V_{max} \) for metabolizing a drug is 10 \( \mu \)m/h. The rate of metabolism (\( \nu \)) is 5 \( \mu \)m/h when drug concentration is 4 \( \mu \)m. Which of the following statements is/are true?

a. \( K_M \) is 5 \( \mu \)m for this drug.

b. \( K_M \) cannot be determined from the information given.

c. \( K_M \) is 4 \( \mu \)m for this drug.
15. Which of the following statements is/are true regarding the pharmacokinetics of diazepam (98% protein bound) and propranolol (87% protein bound)?
   a. Diazepam has a long elimination half-life due to its lack of metabolism and its extensive plasma protein binding.
   b. Propranolol is a drug with high protein binding but unrestricted (unaffected) metabolic clearance.
   c. Diazepam exhibits low hepatic extraction.

16. The hepatic intrinsic clearance of two drugs are as follows:
   Drug A: 1300 mL/min
   Drug B: 26 mL/min

Which drug is likely to show the greatest increase in hepatic clearance when hepatic blood flow is increased from 1 L/min to 1.5 mL/min? Which drug will likely be blood-flow limited?

17. Pravastatin is a statin drug commonly prescribed. The package insert (approved labeling) states that, “The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin or cyclosporine.” How does cyclosporine change the pharmacokinetics of pravastatin? Is pravastatin uptake involved?

Pravastatin is 18% oral bioavailability and 17% urinary excreted (see Appendix E).
Flockhart: Drug interaction table maintained by David Flockhart.
Chapter 11

BIBLIOGRAPHY


Chapter Objectives

- Define pharmacogenetics and pharmacogenomics.
- Define genetic polymorphism and explain the difference between genotype and phenotype.
- Define gene expression and provide examples that explain how gene expression may affect pharmacodynamics of a drug.
- Explain with relevant examples how genetic variability influences drug response, pharmacokinetics, and dosing regimen design.
- Describe the relevance of CYP enzymes and their genetic variability to pharmacokinetics and dosing.
- List what types of technologies have enabled the field of pharmacogenetics and pharmacogenomics, and discuss how these technologies will impact the future of medicine and pharmacy.

The genetic basis underlying variation in drug response among individuals has become evident with the introduction of modern analytical methods for the analysis of gene sequence and expression. The goal of pharmacogenetics is to stratify drug therapy into groups of individual patients based on their genetic makeup. Additional factors such as the environment, diet, age, lifestyle, and state of health can influence a person’s response to medicine. An understanding of an individual’s genetic makeup is thought to be the key to drug selection, drug design, and dosage regimen development. Greater efficacy and safety in drug therapy is based on stratification of patients into groups based on their relevant phenotypes (Phillips et al, 2001; Mancinelli et al, 2000).

Pharmacogenetics is the study of the genetic basis of interindividual patient variability in the response to drug therapy. Pharmacogenetics allows for individualization of drug therapy. In contrast, pharmacokinetics provides a means for estimating kinetic parameters of the drug absorption, distribution, metabolism, and excretion in various population subgroups and then applying the information to drug therapy for the average patient.

Pharmacogenomics is closely related to pharmacogenetics and is considered to be an equivalent or overlapping field. Pharmacogenomics involves study of the role of genes and their genetic variations (DNA, RNA level) in the molecular basis of disease and the resulting pharmacologic impact of drugs on that disease. Pharmacogenomics is sometimes defined to include drug design aimed at variants of a pharmacologic target. Pharmacogenetics and pharmacogenomics are both important disciplines involved in the study of genes that code for drug-metabolizing enzymes (see Chapter 11), drug receptors (see Chapter 19), drug transporters, and ion channels or efflux systems (see Chapter 13). Many of the above are relatively new factors involved in determining how genetic variation contributes to diversity in the response to drugs, including the ultimate fate of the drug and its ability to exert a therapeutic response without undue side effects.

Application of pharmacogenetics to pharmacokinetics and pharmacodynamics helps in development of models that predict an individual’s risk to an adverse drug event and therapeutic
Discuss the main issues in applying genomic data to patient care, e.g., clinical interpretation of data from various laboratories and accuracy of record keeping of large amounts of genomic data.

List the major drug transporters and describe how their genetic variability can impact pharmacokinetics.

response. With some drugs, pharmacogenetics allows the recognition of subgroups or strata based on differences in genetic makeup in drug receptor sequences and are therefore characterized by predictable changes in pharmacodynamic response to drugs. Understanding the genetic and molecular differences in disease etiology, individual pharmacokinetics, and drug mechanism produce insight on how a patient will respond to a given drug. For example, the monoclonal antibody Herceptin was designed to treat a subset of breast cancer patients who overexpress the HER-2 (human epidermal growth factor receptor-2) gene. Patients who lack HER-2 overexpression are considered to be nonresponders to Herceptin therapy. In the past, such differences would be apparent only after a trial-and-error period. This genetic knowledge improves our ability to select or design the proper drug for individuals suffering from a disease with a varying range of molecular defects.

Pharmacogenetics provides justification for individualized dosing for many drugs known to be highly variable in their effects. The outcome of disease, resistance to treatment, and adverse reactions are increasingly recognized as an interaction of the individual’s genes and the environment. A review of the role of genes in human susceptibility to infection predicted that recent advances in genetics and high-throughput genotyping technology will enable screening of the whole genome for genetic factors that determine susceptibility to HIV and AIDS, malaria, and tuberculosis (Kwiatkowski, 2000). Kwiatkowski (2000) listed many genes and their encoded proteins that play roles in immunity and disease fighting. Examples include genes with alleles that affect susceptibility to hepatitis B, HIV, and other known infections. Susceptibility to the AIDS virus includes proteins that bind the receptor (such as HLA, human leukocyte antigen) and immune response amplification such as chemokine and cytokine response (Kaur and Mehra, 2009). Besides host factors, progress has been even faster for genes of microbes that play roles in the efflux of drugs out of the organism, a principal factor for antibiotic resistance in many pathogens. The study of efflux drug pumps in microbes and other organisms have been reviewed by Franke et al (2010).

Pharmacogenetics (PGt) or pharmacogenomics (PGx), a term preferred by some researchers, is of interest to the pharmaceutical industry and regulatory agencies. These groups tried to generate a consensus on how and to what extent should PGx or PGt information be applied to improve drug therapy and safety of both old and new drugs (Lesko and Woodcock, 2002). The FDA has since provided guidance on PGx (FDA Guidance, 2005) to help sponsors determine whether submission of PGx data will likely be required or voluntary for investigational, biological, or new drug applications including the type of PGt data needed in the product label.
Drugs such as irinotecan, mercaptopurine, and warfarin contain pharmacogenetic information on their labels.

PGt’s and PGx’s central role in medicine has been enabled by high-throughput technology that allows rapid screening of tens of thousands of genes rapidly and simultaneously. For example, the DNA chip is a microchips that uses hybridization technology to concurrently detect the presence of tens of thousands of sequences in a small sample. The probes (of known sequence) are spotted onto discreet locations on the chip, so cDNA (complementary DNA) hybridization from the patient’s sample to a probe residing in a defined location indicates the presence of a specific sequence. Other rapid and low-cost sequencing technologies such as ULCS (ultra-low-cost sequencing) or cyclic array technologies will also permit rapid and high-volume sequencing and/or sequencing of individual genomes. These technologies usually rely on some combination of miniaturization, multiplex or parallel assays, analyte amplification and/or concentration, and detection signal amplification.

This chapter will focus on variations in pharmacokinetics due to PGx. However, variation in drug response is also in large part due to nongenetic factors, as listed in Table 12-1. Variations in drug response due to polymorphisms (genetic variations) in the drug’s receptor or downstream processes can also be identified using PGx principles and screening, with the number of examples growing rapidly each year (Table 12-2). The challenge in PGx is to distinguish clinically significant haplotypes (common patterns of polymorphic variation) from the thousands of co-existing polymorphisms that have been identified in either disease etiology or treatment. Polymorphisms in a gene may have several possible outcomes including no change in phenotype (as in a silent mutation), a nonclinically significant change in phenotype, a clinically significant change in phenotype that may or may not represent a possible drug target or potential biomarker for diagnosis, prognosis, or other types of treatment. For example, Brouwers et al (2006) examined over 34,000 genes in pheochromocytoma, and found that 2246 genes had differential gene expression between noradrenergic and adrenergic tumors, and 636 genes were differentially expressed when comparing malignant and benign tumors. An important follow-up from this study is to determine which of these polymorphisms are most relevant for diagnosis, prognosis, and treatment and how to use this information most effectively for treatment design.

Scientists compared the genetic signatures of drugs in patients who are or are not responsive to drug treatments (such as hormone therapy for prostate cancer, or imatinib for acute lymphocytic leukemia) to find which genetic determinants enable a positive (or even a negative) drug response. Chemicals with genetic signatures that are similar to effective drugs also suggest that the compound may have potential therapeutic activity. Such discoveries may someday improve the efficiency of drug selection and discovery.

**POLYMORPHISM**

A well-studied example of genetic polymorphism is the variable metabolic acetylation of drugs among patients resulting in different drug responses. Patients’ ability to metabolize certain drugs such as hydralazine, procainamide, and isoniazid are categorized as either fast acetylators, normal acetylators, or slow acetylators. Acetylation status is dependent on the patient’s genetic composition, which determines the activity of the acetylation enzyme N-acetyltransferase. Acetylation status determines whether a patient is dosed with a correspondingly higher or lower dose compared to “normal acetylators.”

Although acetylation status in humans has been well described, other metabolic or pharmacologic variations have been poorly understood until recently. Genetic variations are well known in bacteria and other microorganisms because rapid changes in these organisms are easily observed. In humans, mutations and related changes occur to different degrees in thousands of proteins and other macromolecules.

Polymorphisms, genetic variations with a frequency of greater than 1% of the population, or mutations, a change in genetic sequences in less than 1% of the population, can affect patient therapeutic response or metabolism of a given drug (Meyer, 2000). Genetic polymorphism may also refer to the occurrence in a population of more than one allele at
Chapter 12

Among individuals, groups, or populations that gives rise to different phenotypic forms such as the human blood groups or other body characteristics. Genetic polymorphism can occur with drug metabolism at the same locus with the least frequent allele occurring more frequently than can be accounted for by mutation alone. Less precisely, genetic polymorphism is described as differences in DNA sequence among individuals, groups, or populations that gives rise to different phenotypic forms such as the human blood groups or other body characteristics. Genetic polymorphism can occur with drug metabolism

### TABLE 12-1  Pharmacogenetic and Nongenetic Influences on Variations in Disease and Drug Therapy

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Example</th>
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<tbody>
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</tr>
<tr>
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<td>P-glycoprotein or other drug transporter (difference in genetic expression)</td>
</tr>
<tr>
<td>Drug receptor (PD)</td>
<td>Variation in receptor number, affinity, or response to drug</td>
</tr>
<tr>
<td>Indirect drug response (PD)</td>
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</tr>
<tr>
<td>Nongenetic influences</td>
<td>Environmental (PK, PD, or disease prognosis)</td>
</tr>
<tr>
<td>Mixed covariates (gender, age, body weight/surface)</td>
<td>Male, female, infant, young adult, or geriatric patient</td>
</tr>
<tr>
<td>Pathophysiology (PK/PD)</td>
<td>Renal, hepatic, cardiovascular, or other disease</td>
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<tr>
<td>Drug–drug interactions (PK/PD)</td>
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#### TABLE 12-2  Genetic Polymorphisms in Disease

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<th>Gene</th>
<th>Implications</th>
<th>Reference</th>
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<td>5-lipoxygenase-activating protein (FLAP)</td>
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<td>Hakonarson et al 293:2245–2256, 2005</td>
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Environmental factors may switch on genes, and the nongenetic category may not be absolute. The two primary independent variables in life processes are genetics and environment.

Examples of diet: Atkins diet, vegetarian, diabetic, and other hospital diets, etc. Foods rich in carbohydrates/protein may have an effect on urinary pH and affect renal tubular drug reabsorption. Diet can also affect PK drug absorption; certain groups lack or have abundant GI enzymes, lactase, etc (even though it might be genetic rather than adaptive, arguably).

Examples of nutrients include vitamins, antioxidants, fortified fruit drinks, and supplements taken regularly, other than meals.

Some genetic/environmental outcomes may become a covariate for a new pharmacogenetic response.

Some examples partially adapted from Evans and McLeod (2003).

#### TABLE 12-2  Genetic Polymorphisms in Disease

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Pharmacogenetics

305

enzymes, drug transporters, and even drug receptors that govern therapeutic responses of drugs. Therefore, it is rational to individualize dose regimens based on pharmacokinetic data obtained from different polymorphic groups. Many alleles encoding different drug receptors are being discovered and studied with increasing frequency. Pharmacokinetic parameters influenced by genetic differences include drug bioavailability, distribution, metabolism, and tissue binding. Environmental factors (eg, smoking, drug–drug interactions, nutritional status) and pathophysiology of the patient (eg, cardiovascular disease, age, hepatic and renal disease) can also influence the pharmacokinetics of a drug. Our understanding of the impact of these genetic differences on clinical pharmacokinetics and pharmacodynamics is in its infancy.

Polymorphism in cytochrome isozymes has been demonstrated in drug metabolism along with their corresponding allele genes. The clinical significance of certain polymorphic forms with regard to drug metabolism has been reported for many drugs. Genetic tests are available to screen polymorphisms for cytochrome P-450 drug-metabolizing enzymes in an individual. Prior knowledge of an individual’s metabolic capability can reduce the risk of adverse drug reactions by adjustment of the dose regimens according to an individual patient’s metabolic capability. The types of genetic mutations affecting metabolic enzymes are illustrated in Fig. 12-1.

Genetic polymorphism within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors. The probability of carrying a specific allele varies among different subjects depending on whether the dominating factor is geographic or ethnic. In practice, genetic polymorphisms with higher frequencies are more important because they are likely to affect more people. However, some rare mutations are important because they cause extreme medical consequences or may be fatal for the individual.

Using genetic polymorphism considerations, drugs may be developed for groups of patients who are genetically comparable to improve efficacy and reduce risk of an adverse event. Drugs may also be developed only for patients who express a particular genetic profile to provide a desired level of safety or efficacy. In addition, doses for patients can be based on their metabolic capacity by determining whether they are “poor metabolizers” or “ultrarapid metabolizers.” Molecular studies in pharmacogenetics began with cloning of CYP2D6 and now have been
extended to more than two dozen drug-metabolizing enzymes and several drug transport systems (Meyer, 2000). The most important isozymes with genetic polymorphism involved in drug metabolism are shown in Fig. 12-2.

Recognition of the genotypes associated with drug disposition and metabolism and the ability to obtain a "specific pharmacogenetic profile" for the patient will allow individualization of drug therapy and reduction of drug interactions (Evans and Relling, 1999; Roses, 2000, 2001). PGx research aims to eludicate these polygenic (multiple-gene) determinants of drug effects. The interplay of genetic polymorphism with interindividual differences in pharmacokinetics and pharmacodynamics has been well reviewed (Evans and Johnson, 2001; McLeod and Evans, 2001). The ultimate goal is to provide new strategies for optimizing drug efficacy and toxicity based on groups of patient’s genetic determinants.

PHARMACOGENOMICS

Pharmacogenomics, PGx, developed rapidly as a result of advances in molecular genetics and genomics employing high-throughput tests such as microarray technology. The previously held notion of the monogenic nature of disease (one gene causing one disorder) is yielding to the concept of polygenic disorders, by which dozens or even thousands of genes may be differentially expressed compared to normal, healthy tissue. As such new information arises, new challenges and opportunities also emerge for novel drug development.
The coordinated goal to sequence the 30,000 or more human genes via the Human Genome Project has also fueled progress in PGx. Many new genes or gene products have emerged from the Human Genome Project as new potential drug targets. These new targets may be receptors, membrane proteins, enzymes, or ion channels that may be directly or indirectly involved in disease pathogenesis. While these newly discovered receptors or target enzymes can be exploited as new drug targets, polymorphic variations of those genes must be considered when developing new drugs that target these proteins.

Unique genetic sequences have been identified for thousands of proteins and endogenous substances that support normal cellular functions. The genetic information is coded in the two helical strands of DNA. DNA consists of four basic nitrogenous substances or bases (C, cytosine; A, adenine; T, thymine; and G, guanine), which combine with deoxyribose and phosphate to form the respective nucleotides. The four nucleotides are combined in unique sequences for each gene. Genes are coded in a special region or locus in the DNA.

A change or mutation in gene sequence may or may not result in a change in phenotype such as chronically reduced or increased level or activity of a protein or an essential enzyme. In some cases, such changes result in an exaggerated or reduced therapeutic response to a drug. The cell is homozygous if the genetic sequences occupying the locus are the same on the maternal and paternal chromosome; if they are different, the cell is heterozygous. When more than one alternative forms of a gene exist, the alternative genes are referred to as alleles of the gene. The identity of the alleles carried by an individual at a given gene locus is referred to as the genotype. Alleles that vary by a single nucleotide change can now be characterized rapidly at the DNA level by single-nucleotide polymorphism (SNP) screening. SNPs occur in about one of every 100 to 1500 base pairs (bp) between two unrelated individuals. Any two individuals may differ by 0.1% of their more than 3 billion base pairs. Common or informative SNPs are those that occur at frequencies of greater than 1% (Meyer, 2000). The physical effect observed as a result of genotype difference is referred to as phenotype. Haplotypes, in contrast, are groups of SNPs that vary together to influence a phenotype.

The International HapMap Project is an international collaboration to provide a respository of haplotype information (www.hapmap.org). Haplotypes are identified by examining gene expression patterns for commonality. For example, high-throughput data may be converted to visual information (eg, red for higher expression, green for lower expression) and organized by patient, expression level, phenotype and/or gene in a two- or three-dimensional grid in attempt to detect patterns in gene expression. The most relevant genes involved in disease etiology or classification have been determined for tumors such as AML (acute myeloid leukemia) and menangioma.

Genes are considered functionally polymorphic when allelic variants exist stably in the population and their gene products exhibit altered activity in relation to the wild type (“normal”). Ideally, variation in drug response can be predicted by monitoring differences in phenotype or genotype for a single patient or a group of patients. Often, a surrogate chemical measure for a physiologic condition or response called a biomarker may be used for this purpose. Biomarkers may also be used to identify disease susceptibility and diagnose or monitor disease or response to treatment.

To determine whether a patient is a rapid or slow metabolizer, the patient is given a known substrate for that enzyme and the patient’s intrinsic clearance (see Chapter 11) is measured. Traditionally, inter-subject variation in metabolism has been investigated by the use of known substrates followed by in vitro verification of the enzyme level. Alternatively, the metabolic-status genotype may be determined directly from subjects’ DNA. The latter approach is more definitive and offers much insight during drug development into how genes affect the metabolism of drugs. The mechanism of metabolism has been elucidated for many drugs using both approaches. In practice, fragments of DNA samples are compared based on SNPs or haplotypes. If the patient’s genotype and its functional activity are known, the probable individual drug response can be predicted.

In the future, rapid sequencing, use of biomarkers, and/or measuring associated phenotypes will play a major role in detecting unusual variations in heritable clinical phenotypes of drug response. Once a large number of these genetic variations and their frequencies in
different populations are known, they can be used to correlate a patient’s genetic “fingerprint” to the patient’s probable individual drug response. This genetic or biomarker information can then be used to group patients into genetic groups or “strata” to personalize drug treatment for these patient subgroups. For example, patients with chronic myeloid leukemia who are BCR-ABL (a tyrosine kinase) positive are good candidates for Gleevec (imatinib mesylate), a tyrosine-kinase inhibitor.

SNP and haplotype variations in coding regions of genes (about 30,000–100,000 per genome) cause variations in amino acid sequence and protein function. Genetic variations in gene regulatory regions can cause differences in protein expression that may affect drug response. Genetic profiles of individuals may be analyzed to determine disease susceptibility as well as predisposition to PGt considerations in drug efficacy or toxicity.

**Frequently Asked Questions**

- What are the differences between pharmacogenetics and pharmacogenomics? How are PGx and PGt used to improve healthcare?
- What is the difference between a polymorphism, SNP, and haplotype? Why are these distinctions important for individualizing drug therapy?
- What types of genes are important to drug therapy? How would variability in these genes impact drug therapy?
- How common and clinically relevant are metabolic polymorphisms?
- How can genetic information be used to improve drug therapy for individuals and/or groups of patients?

**ADVERSE DRUG REACTIONS ATTRIBUTED TO GENETIC DIFFERENCES**

Variations in drug pharmacokinetics and pharmacodynamics are due largely to genetic polymorphism in genes involved in drug metabolism, absorption, disposition, and disease pathogenesis. As early as the 1950s, researchers realized that some adverse drug reactions were caused by genetically determined variations in enzyme activity. Adverse drug reactions of debrisoquin have led to the discovery of the genetic polymorphism of this drug-metabolizing enzyme, debrisoquine hydroxylase CYP2D6. More recently, a review of the PGt literature showed that a sizable portion of ADRs (~30%) involved in drug therapy implicated drug metabolism polymorphisms in CYP2D6 (Sadee, 2002). In CYP2D6-deficient patients, dosing of antiarrhythmic drug sparteine causes more nausea, diplopia, and blurred vision adverse reactions. The presence of four phenotypic subpopulations for CYP2D6 ensures genetic variation in the population and thus in part accounts for interindividual differences in adverse drug response between patients: 3% to 10% of whites, 6% to 8% of African Americans, and less than 2% of Asians are poor 2D6 metabolizers. As a result, these groups are more prone to adverse effects from 2D6 substrates such as SSRIs (selective serotonin reuptake inhibitors), tricyclic antidepressants, and metoprolol, and are more likely to be unresponsive to codeine, which requires 2D6 activation to its active metabolite. Other examples of adverse reactions caused by genetic polymorphisms include prolonged muscle relaxation in some subjects suffering from an inherited deficiency of a plasma cholinesterase after receiving a cholinergic drug. Hemolysis caused by antimalarial drugs is recognized as being caused by inherited variants of glucose 6-phosphate dehydrogenase. Slow acetylation status of isoniazid in some patients causes increased risk for peripheral neuropathy.

It is important to determine whether the variation in ADR is truly genetic or due to other factors. A method used to distinguish hereditary and environmental components of variability is the comparison of monozygotic and dizygotic twins, or pharmacokinetically by repeated drug administration and comparison of the variability of the responses within and between individuals. The National Institutes of Health (NIH), wants to identify genetic risk factors and biomarkers that predict drug response. NIH has organized the Pharmacogenomics Knowledge Base, a nationwide collaboration to study genes, drugs, and disease (www.pharmgkb.org). Examples of genetic polymorphism affecting drug response/side effect are listed in Table 12-3.
<table>
<thead>
<tr>
<th>Enzyme/Receptor</th>
<th>Frequency of Polymorphism</th>
<th>Drug</th>
<th>Drug Effect/Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>14%–28% (heterozygotes)</td>
<td>Warfarin, Tolbutamide, Phenytoin, Glipizide, Losartan</td>
<td>Hemorrhage, Hypoglycemia, Phenytoin toxicity, Hypoglycemia, Decreased antihypertensive effect</td>
</tr>
<tr>
<td></td>
<td>0.2%–1% (homozygotes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>5%–10% (poor metabolizers)</td>
<td>Antiarrhythmics</td>
<td>Proarrhythmic and other toxic effects, Toxicity in poor metabolizers</td>
</tr>
<tr>
<td></td>
<td>1%–10% (ultrarapid</td>
<td>Antidepressants</td>
<td>Inefficacy in ultrarapid metabolizers</td>
</tr>
<tr>
<td></td>
<td>metabolizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antipsychotics, Opioids</td>
<td>Tardive dyskinesia, Inefficacy of codeine as analgesic, narcotic side effects,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin, β-Adrenoceptor</td>
<td>Higher risk of hemorrhage, Increased—blockade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>antagonists</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>3%–6% (whites)</td>
<td>Omeprazole</td>
<td>Higher cure rates when given with clarithromycin</td>
</tr>
<tr>
<td></td>
<td>8%–23% (Asians)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diazepam</td>
<td>Prolonged sedation</td>
</tr>
<tr>
<td>Dihydropyrimidine</td>
<td>0.1%</td>
<td>Fluorouracil</td>
<td>Myelotoxicity, Neurotoxicity</td>
</tr>
<tr>
<td>dehydrogenase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma pseudo-cholinesterase</td>
<td>1.5%</td>
<td>Succinylcholine</td>
<td>Prolonged apnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-acetyltransferase</td>
<td>40%–70% (whites)</td>
<td>Sulphonamides, Amonafide,</td>
<td>Hypersensitivity, Myleotoxicity, Drug-induced lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>10%–20% (Asians)</td>
<td>Procainamide, hydralazine,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>isoniazid</td>
<td></td>
</tr>
<tr>
<td>Thiopurine methyltransferase</td>
<td>0.3%</td>
<td>Mercaptopurine, thioguanine,</td>
<td>Myelotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azothioprine</td>
<td></td>
</tr>
<tr>
<td>UDP-glucuronosyl-transferase</td>
<td>10%–15%</td>
<td>Iринотекан</td>
<td>Diarrhea, myelosuppression</td>
</tr>
<tr>
<td>ACE</td>
<td></td>
<td>Enalapril, lisinapril</td>
<td>Renoprotective effect, cardiac indexes, blood pressure</td>
</tr>
<tr>
<td>Potassium channels</td>
<td></td>
<td>Quinidine</td>
<td>Drug-induced QT syndrome</td>
</tr>
<tr>
<td>HERG</td>
<td></td>
<td>Cisapride</td>
<td>Drug-induced torsade de pointes</td>
</tr>
<tr>
<td>KvLQT1</td>
<td></td>
<td>Terfenadine disopyramide</td>
<td>Drug-induced long-QT syndrome</td>
</tr>
<tr>
<td>VKORC</td>
<td></td>
<td>Warfarin</td>
<td>Over-anticoagulation</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
<td></td>
<td>Gefitinib</td>
<td>Certain polymorphs susceptible</td>
</tr>
<tr>
<td>receptor (EGFR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKCNE2</td>
<td></td>
<td>Mefloquine clarithromycin</td>
<td>Drug-induced arrhythmia</td>
</tr>
</tbody>
</table>

*From Meyer (2000) with permission, and from Evans and Relling (1999), Limdi and Veenstra (2010).*
Chapter 12

GENETIC POLYMORPHISM IN DRUG METABOLISM: CYTOCHROME P-450 ISOZYMES

As discussed in Chapter 11, cytochrome P-450 enzymes (CYPs) are a family of oxidative enzymes involved in phase I metabolism of many drugs. The most important families for drug metabolism are CYP1, CYP2, and CYP3, with CYP3 arguably the most important for drug elimination. CYP-metabolized drugs often act as a substrate for more than one CYP enzyme, resulting in redundancy if a specific CYP enzyme is a slow metabolizer due to genetics (CYP3A varies approximately fivefold) and/or inhibitors (can increase variability to 400-fold).

Polymorphisms in CYP and other metabolic enzymes can affect the clearance of a drug and thus the overall pharmacokinetics for a given patient. Advanced knowledge of a patient’s polymorph status could therefore be used to design optimum dosing regimens before an adverse reaction or subtherapeutic response occurs clinically. However, given the redundancy of drug metabolism and the contribution from environmental factors (such as diet, other drugs, age, weight, etc), the use of enzyme status data may be difficult to translate to a clinical decision. For example, warfarin metabolism is highly variable and results from a combination of factors including CYP2C9 (2%–10%), VKORC1 (10%–25%), and environmental factors (20%–25%). Algorithms for warfarin dosing are available which are particularly effective for patients requiring either less than 3 mg per day or more than 7 mg per day (Limdi and Veenstra, 2010). The significance of CYPs and transporters, and potential for interaction have great impact on drug efficacy and safety (Huang et al, 2008).

CYP2D6

CYP2D6 (see Chapter 11) is a large isozyme family that affects metabolism of many drugs. CYP2D6 is highly polymorphic. More than 70 variant alleles of the CYP2D6 locus have been reported. The metabolism of the tricyclic antidepressants amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline, and the tetracyclic compounds maprotiline and mianserin is influenced by the CYP2D6 polymorphism to various degrees. Genetic polymorphism of CYP2D6 was first investigated with debrisoquine (Gonzalez et al, 1988). Poor metabolizers often carry two nonfunctional alleles of this gene, resulting in reduced drug clearance.

Since about 10% of the population are poor CYP2D6 metabolizers, drug candidates that are CYP2D6 substrates are often dropped from further development by researchers in favor of others (Sadee, 2002). Poor metabolizers have increased plasma concentrations of tricyclic antidepressants when given recommended doses of the drug. Adverse effects may occur more frequently in poor metabolizers and may be misinterpreted as symptoms of depression and may further lead to erroneous increases in the dose. When determining CYP2D6 metabolic status (slow vs fast metabolizers) in patients on tricyclic antidepressants, co-administration of other CYP2D6 substrates such as serotonin selective reuptake inhibitors may result in erroneously concluding poor CYP2D6 metabolic status.

In contrast, ultrarapid metabolizers have relatively fast drug metabolism due to the presence of more enzyme or increased enzyme activity. Patients in this group are prone to therapeutic failure due to the resulting subtherapeutic drug concentrations when “normal” doses are given. PGx studies have revealed that some fast metabolizers of CYP2D6 are the result of gene duplication present among different racial groups. Depending on the population studied, 5% to 20% of patients can be classified as either rapid or poor metabolizers.

Polymorphic drug metabolism is found in a large number of drugs used in psychiatric patients. Retrospective analysis of psychiatric patients treated with substrates of CYP2D6 strongly indicates that genotyping can improve the likelihood of preventing adverse drug reactions and decrease the costs of therapy.

The polymorphic O-demethylation of codeine is of clinical importance for drug activation when this drug is given as an analgesic. About 10% of codeine is O-demethylated by CYP2D6 to morphine, and this conversion is deficient in poor metabolizers.
Poor metabolizers therefore experience no analgetic effects of codeine.

**CYP1A2**

Another isozyme, CYP1A2, which metabolizes 5% of randomly selected drugs, may also be considered during development, since up to 15% of a patient population can be classified as poor metabolizers, according to Sadee (2002). Fluvoxamine is a substrate and potent inhibitor of CYP1A2, causing important interactions with drugs such as amitriptyline, clomipramine, imipramine, clozapine, and theophylline that are partly metabolized by this cytochrome P-450 enzyme.

**CYP2C9**

Still another example of a clinically important drug metabolism polymorphism is the association of variant alleles of CYP2C9 with the requirement for lower warfarin dose. In a retrospective study of a population from an anticoagulant clinic, the CYP2C9 alleles associated with decreased enzyme activity (*2 and *3) are overrepresented in patients stabilized on low doses of warfarin. These patients had an increased incidence of major and minor hemorrhage.

**CYP2C19**

The 4′-hydroxylation of the (S)-enantiomer of mephenytoin is catalyzed by CYP2C19. The polymorphic enzyme has a poor metabolizer (PM) frequency of about 3% in Caucasians, 15% to 25% among Asians, and 4% to 7% among Black Africans (Dahl, 2002). The major defective allele responsible for the PM phenotype is CYP2C19*2, which is found in 13% and 32% of Caucasians and Asians, respectively. A second allele, CYP2C19*3, is found mostly among Asians and rarely in Caucasians.

Interestingly, few polymorphisms are reported for the isozyme subfamily CYP3A. This isozyme is involved in the metabolism of endogenous steroid and testosterone. Mutations of this vital enzyme may not be compatible with life.

Not all therapeutic variations and side effects result from genetic differences in the receptor or drug metabolism. Drug response (including therapeutic and unintended side effects) is influenced by many direct and indirect factors, including modifying effects from environmental factors on the disease process and drug disposition. As a result, some researchers are unsure whether prescribing drugs based on a PGt profile will significantly reduce side effects for most drugs, since many side effects and therapeutic failures may be the result of incorrect diagnosis or failure to account for other influencing variables such as the nature and severity of the disease, the individual’s age and race, organ function, concomitant therapy, drug interactions, and concomitant illnesses.

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**GENETIC POLYMORPHISM IN DRUG TRANSPORT: MDR1 (P-GLYCOPROTEIN) AND MULTIDRUG RESISTANCE**

*Transporter pharmacogenetics* is a rapidly developing field that is concerned with drug uptake and efflux into or through tissues. Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability and high intra- and interindividual variation in pharmacokinetics. Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action (Borst et al, 2000).

*Drug efflux* is an important cause of drug resistance in certain types of cells. In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in the case of *intrinsic* or *acquired multidrug resistance*, usually highly effective antineoplastic compounds, eg, vincristine, vinblastine, daunorubicin, or doxorubicin, fail to produce response. One of the many causes of such multidrug resistance (MDR) is the appearance of special efflux proteins, eg, the *P-glycoprotein can transport drug out in some cells* and result in low drug levels in targeted cells. The commonly known P-gp is an example of many MDR-associated proteins. P-gp is genetically designated as ABCB1 or MDR1. Genetic variants of P-gp/ABCB1 are found in approximately 5% of Caucasians (Sharom et al, 1999) and usually associated with impaired function in vitro. Transporter
polymorphism has important effects on *in vivo* drug pharmacokinetics. ABCB1 haplotypes have been proposed to predict the kinetics of drugs such as digoxin, cyclosporine, and fexofenadine. P-gp *substrates and inhibitors* are discussed in Chapter 13.

**ABC Transporters**

The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently, of which MRP1 (ABCC1), MRP2 (ABCC2), and MRP3 (ABCC3) are commonly known to affect drug disposition. MRP1 is ubiquitous in the body. Substrates for MRP1 include glutathione, glucuronide, adefovir, ciprofloxacin, paclitaxel, saquinavir, and sulfate; inhibitors include cyclosporine, glyburide, indo -methacin, sulfinpyrazone, and verapamil. MRP1 is expressed basolaterally in the intestine, although its role in extruding drugs out of the enterocytes is still uncertain. There is some substrate overlap between MRP1 and apically located P-gp (see Chapter 13).

**Solute Carrier Transporters**

Another important class of drug carriers is the solute carriers (SLCs) such as the organic anion transporter protein (OATP) and organic cation transporter (OCT). SLCs are membrane transporters that may function as passive transporters, ion-coupled transporters, or exchangers with organic anions and cations, respectively, as their substrates. For example, OATP1B1 (SLCO1B1) has at least 17 SNPs identified and transports drugs such as statin drugs, rifampicin, enalapril, and methotrexate, but is inhibited by erythromycin, thryoxine, and rifampin. Changes in AUC and plasma concentrations have been reported for patients expressing OATP1B1 variants.

**GENETIC POLYMORPHISM IN DRUG TARGETS**

In the future, proteins involved in disease will increasingly become identified as important biomarkers for pharmacodynamic studies. Genomics has led to the development of proteomics, which involves the study of biologically interesting proteins and their variants. Proteins such as cell surface proteins (eg, COX-2, D-2R), intracellular proteins (eg, troponin I), and secreted proteins (eg, MCP-1) can be used as probes for drug discovery or as biomarkers for drug safety.

The physiologic response of the body to a drug is generally the result of interaction of the drug at a specific target site in the body. It is estimated that about 50% of drugs act on membrane receptors, about 30% act on enzymes, and about 5% act on ion channels (Meyer, 2000). Many of the genes encoding these target proteins exhibit polymorphisms that may alter drug response. Clinically relevant examples of polymorphism leading to variable responses are listed in Table 12-4. For example, the β2-adrenergic receptor, and its common mutation of Arg→Gly at amino acid 16, greatly reduces the bronchodilator response of albuterol (Ligget, 2000). In addition, mutations in the angiotensin-converting enzyme (ACE) gene have been proposed to account for variations in the response to ACE inhibitors. Another study has shown that a combination of two mutations in the gene encoding a high-affinity sulphonylurea receptor leads to a 40% reduction in the insulin response to tolbutamide (Hansen et al, 1998). The response to clozapine in patients with schizophrenia appears to involve genetic polymorphisms in the 5-hydroxytryptamine (serotonin) receptor, HTR2A.

Mutations in five genes involved in the cardiac ion channels affect the risk of drug-induced long-QT syndrome (Priori et al, 1999), a potential cause of sudden cardiac death in young individuals without structural heart disease. The prevalence of long-QT syndrome is about 1 in 10,000. All five genes code for membrane ion channels affecting sodium or potassium transport and are influenced by antiarrhythmics and other drugs (Evans and Relling, 1999). Examples such as these are reported in the biomedical literature, yet the data are often conflicting, and the clinical implications of such findings are often unclear.

The systematic identification and functional analysis of human genes is changing the study of disease processes and drug development. PGx potentially enables clinicians to make reliable assessments of an individual’s risk of acquiring a particular disease, increase specificity in drug targeting, and account for individual variation of therapeutic response and toxicity of drugs. Polymorphic alleles are the best-studied individual risk factors for adverse drug reactions,
Pharmacogenetics

including the genes for N-acetyltransferase, thiopurine methyltransferase, dihydropyrimidine dehydrogenase, and the cytochrome P-450 isozymes. Genotyping can predict phenotype extremes in these situations and identify metabolic status in individual patients. Genomics is providing the information and technology needed to analyze the complex multifactorial situations involved in drug therapy (Fig. 12-3).

Awareness of inherited variations of drug response can lead to dose adjustment on the basis of the patient’s genetic makeup and provides a promising approach to reducing adverse drug reactions (Evans and Johnson, 2001; Roses, 2000). Dahl (2002), deLeon (2009), and others have reviewed the issues involving PGx and the prescribing of antipsychotic drugs.

RELATIONSHIP OF PHARMACOKINETICS / PHARMACODYNAMICS AND PHARMACOGENETICS / PHARMACOMICROBIOMICS

The study of drug interactions and PGx has revealed that many unexpected pharmacodynamic responses and pharmacokinetic variations among individuals during drug therapy involve genetic factors. These genetic factors contribute to variation at many levels, including drug transport, metabolism, and interaction at the receptor site.

TABLE 12-4 Clinically Important Genetic Polymorphisms of Drug Targets and Drug Transporters

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Drug</th>
<th>Drug Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug-resistance gene (MDR1)</td>
<td>24%</td>
<td>Digoxin</td>
<td>Increased concentrations of digoxin in plasma</td>
</tr>
<tr>
<td>β2 Adrenergic receptor gene (2AR)</td>
<td>37%</td>
<td>Albuterol</td>
<td>Decreased response to β2-adrenergic agonists</td>
</tr>
<tr>
<td>Sulphonylurea receptor gene (SUR1)</td>
<td>2%–3%</td>
<td>Tolbutamide</td>
<td>Decreased insulin response</td>
</tr>
<tr>
<td>Five genes coding for cardiac ion channels</td>
<td>1%–2%</td>
<td>Antiarrhythmics, terfenadine, many other drugs</td>
<td>Sudden cardiac death due to long-QT syndrome</td>
</tr>
<tr>
<td>Serotonin transporter (SLC6A4)</td>
<td></td>
<td>Antidepressants</td>
<td>Better response to SSRIs (L-allele); higher incidence of adverse events (S-allele)</td>
</tr>
<tr>
<td>Serotonin receptor S-HT2C</td>
<td></td>
<td>Antipsychotics Clozapine</td>
<td>Weight gain; No treatment response in schizophrenia</td>
</tr>
<tr>
<td>Dopamine receptor DRD3</td>
<td></td>
<td>Antipsychotics Clozapine</td>
<td>Lower treatment response, movement disorders; Better response in schizophrenia</td>
</tr>
</tbody>
</table>

that information linked to a clearance prediction for the patient? Recognizing the allele that predisposes the patient to a severe adverse reaction or toxic plasma concentration may allow the dose to be reduced or the drug to be avoided entirely. Similarly, if a patient is known to be a nonresponder or at high risk for adverse reactions due to genetic variation, that information can be used to select an alternate drug a priori. Table 12-5 lists FDA black box warnings for drugs that have been identified with a serious adverse reaction associated with a polymorphism.

In Chapter 20, a mixed-effect model is described that takes into account the effect of enzyme induction due to concomitant administration of a drug that induces enzyme. Should new models be developed, or will an extension of some of the mixed-effect models suffice? Advances in PGt will no doubt stimulate developments in pharmacokinetics and pharmacodynamics.

The successful application of genetic screening tests to identify patients with specific risks in drug response or drug toxicity depends on many factors. Large amounts of relevant genetic information might be monitored. Robust, high-throughput, high-positive and low-negative predictive tests must be developed and implemented. Such an endeavor will also involve considerable training, adaptation, and acceptance of the new technology by physicians and other healthcare personnel. With genetic diagnostic tests becoming more common and affordable, it is expected that individual drug dosing will become more accurate and ultimately result in vast improvements in therapeutic

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**FIGURE 12-3** Molecular diagnostics of pharmacogenomic traits. DNA arrays are being made for automated, high-throughput detection of functionally important mutations in genes that are important determinants of drug effects, such as drug-metabolizing enzymes, drug targets (receptors), disease pathogenesis, and other polymorphic genes that influence an individual's susceptibility to drug toxicities or environmental exposures (such as pathogens, carcinogens, and others). This figure exemplifies components of a potential diagnostic DNA array for genes that could influence a patient's response to chemotherapy for acute lymphoblastic leukemia, including genes that determine drug metabolism, disease sensitivity, and the risk of adverse effects of treatment (cardiovascular or endocrine toxicities, infections, etc). (From Evans and Relling, 1999, with permission.)
response and better drug tolerance. Researchers have high expectations that the use of diagnostic DNA microarrays or gene chips will simplify and expand testing and have clinical applications in diagnosis, disease prevention, drug selection, and dose calculation. The challenge to pharmacokinetics is to integrate all the relevant information into a model that is accurate and simple enough for practical application.

**CLINICAL EXAMPLE**

How useful are the average pharmacokinetic parameters obtained from a pharmacokinetic model in a drug study population that does not incorporate parameters accounting for genomic determinants?

- Average pharmacokinetic parameters are generally estimated by regression methods to minimize deviations from the data iteration within a group. These pharmacokinetic parameters are estimated for an average individual such that most subjects in the study population resemble the mean within a group. However, for a subject with the unusual allele, the underlying genetic factors contribute parameter differences that are the result of genetic expression. *(Note: An attempt to force data fitting the mean would seriously error for a few individuals, ie, fit most subjects well, but will err badly for the few, on the basis of minimization of the sum of squared deviations.)*

- Diazepam (Valium®) is highly metabolized in the body. Qin XP et al (1999) demonstrated that it is important to obtain individual PK parameters for patients using the drug diazepam. The presence of a single-nucleotide polymorphism (G681A) of the CYP2C19 gene cosegregates with the impaired metabolism of diazepam and desmethyldiazepam among Chinese subjects. The mean plasma elimination half-life value of diazepam is $84.0 \pm 13.7$ hours in homozygotes subjects. The corresponding half-life is much longer, $20.0 \pm 10.8$ hours for diazepam in wild-type homozygotes subjects. The longer half-life values in subjects of m1/m1 are also reflected by slow clearance of diazepam ($2.8 \pm 0.9$ mL/min). However, diazepam disposition may be affected by protein binding besides CYP enzyme levels. This example shows the important contribution by pharmacogenetic polymorphism of CYPs.

### Frequently Asked Questions

- **Why is the frequency of genetic polymorphisms of CYP2C9 much higher in heterozygotes (14%–28%) than in homozygotes (0.2%–1%)?**

- **How do drug efflux transporters affect the rate and extent of drug absorption and the bioavailability of a drug?**

- **Which human ABC-transport protein may influence the activation of transcription factors such as PXR in the liver, and which nuclear hormone receptors regulate drug detoxification genes?**

- **How is biliary excretion affected if genetic expression of a transport protein is enhanced?**

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**TABLE 12-5**  Black Box Warnings Based on Genetic Polymorphisms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Problem</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec)</td>
<td>UGT1A1</td>
<td>Treatment-emergent suicide ideation</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>GR1A3, GR1K3 (glutamate receptors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>CYP2C19 loss of function</td>
<td>Cardiovascular events</td>
<td></td>
</tr>
<tr>
<td>Thioridazine (Mellari)</td>
<td>CYP2D6 poor metabolizers</td>
<td></td>
<td>Avoid use</td>
</tr>
<tr>
<td>Carbamazepine and other anti-epileptic drugs</td>
<td>HLA-B*1502</td>
<td>Potentially fatal skin reaction</td>
<td>Genotype Asian patients</td>
</tr>
</tbody>
</table>
Genetic polymorphism can occur with drug metabolic enzymes, drug transporters, and drug receptors that govern therapeutic responses of drugs. Genetic polymorphism that occurs with minor allele frequency of $\geq 1\%$ in the population are very common (see Table 12-3). Phenotype is defined as the observable expression of a particular gene or genes. A deletion, insertion, or substitution can result in a loss or increase of a DNA sequence, which can lead to changes in copy-number or activity of the gene. Any of these genetic events can cause important changes in drug metabolism (eg, slow drug metabolizer or rapid-drug metabolizer phenotype), as shown in Fig. 12-1.

**SUMMARY**

Pharmacogenetics and pharmacogenomics involve the investigation and understanding of the role of genetics in drug therapy and therapeutic response, respectively. High-throughput technologies such as diagnostic microarrays have allowed the rapid sequencing of human genetic variability involved in drug transport, metabolism, and receptors, now exposing a complex interplay between these often highly variable genes. Clinically useful tools such as arrays and other sequencing technologies used to translate polymorphism data into effective recommendations are used to improve drug development and to individualize therapy for the patient.

Genetic polymorphism can occur with drug metabolic enzymes, drug transporters, and drug receptors that govern therapeutic responses of drugs. Genetic polymorphism that occurs with minor allele frequency of $\geq 1\%$ in the population are very common (see Table 12-3). Phenotype is defined as the observable expression of a particular gene or genes. A deletion, insertion, or substitution can result in a loss or increase of a DNA sequence, which can lead to changes in copy-number or activity of the gene. Any of these genetic events can cause important changes in drug metabolism (eg, slow drug metabolizer or rapid-drug metabolizer phenotype), as shown in Fig. 12-1.

**GLOSSARY**

- **Allele**: An alternative form of a gene at a given locus.
  - **Minor allele**: A less common allele at a polymorphic locus.

- **Biological marker (biomarker)**: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- **Genetic polymorphism**: Minor allele frequency of $\geq 1\%$ in the population.

- **Genome**: The complete DNA sequence of an organism.

- **Genotype**: The alleles at a specific locus an individual carries.

- **Haplotype**: A group of alleles from two or more loci on a chromosome, inherited as a unit.

- **Pharmacogenetic test**: An assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics), including polymorphic variation in the genes that encode the

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functions of transporters, metabolizing enzymes, receptors, and other proteins.

**Pharmacogenetics**: A study of genetic causes of individual variations in drug response. In this review, the term “pharmacogenetics” is interchangeable with “pharmacogenomics.”

**Pharmacogenomic test**: An assay intended to study interindividual variations in whole-genome or candidate gene, single-nucleotide polymorphism (SNP) maps, haplotype markers, or alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response. In some cases, the pattern or profile of change is the relevant biomarker, rather than changes in individual markers.

**Pharmacogenomics**: Genome-wide analysis of the genetic determinants of drug efficacy and toxicity. Pharmacogenomics focuses on a single gene while pharmacogenomics studies multiple genes.

**Phenotype**: Observable expression of a particular gene or genes.

**Promoter**: A segment of DNA sequence that controls initiation of transcription of the gene and is usually located upstream of the gene.

**ABBREVIATIONS**

**ABC transporters**: ATP-binding cassette transporter

**OATP**: Organic anion transporter protein

**OCT**: Organic cation transporter

**P-gp**: P-glycoprotein, MDR1, ABCB1

**PGt**: Pharmacogenetics

**PM**: Poor metabolizer

**SNP**: A single-nucleotide polymorphism is a DNA sequence variation occurring when a single nucleotide—A, T, C, or G—in the genome (or other shared sequence) differs between members of a species or paired chromosomes in an individual.

**REFERENCES**


Meyer UA: Pharmacogenomics Knowledge Base, Pharm GKB (www.pharmgkb.org).


The FDA has constructed a website called Genomics at FDA (www.fda.gov/cder/genomics) for individuals who would like to understand the agency’s current thinking on pharmacogenetics. The site also provides education materials on pharmacogenetics.

The table of valid genomic biomarkers in the context of approved drug labels (www.fda.gov/cder/genomics/genomic_biomarkers_table.htm) summarizes all pharmacogenetic discoveries included on current drug labeling with a link to the approved package insert.
Chapter Objectives

- Define passive and active drug absorption.
- Explain how Fick’s law of diffusion relates to passive drug absorption.
- Calculate the percent of drug nonionized and ionized for a weak acid or weak-base drug using the Henderson-Hasselbalch equation, and explain how this may affect drug absorption.
- Define transcellular and paracellular drug absorption and explain using drug examples.
- Describe the anatomy and physiology of the GI tract and explain how stomach emptying time and GI transit time can alter the rate and extent of drug absorption.
- Explain the effect of food on gastrointestinal physiology and systemic drug absorption.
- Describe the various transporters and how they influence the pharmacokinetics of drug disposition in the GI tract.

DRUG ABSORPTION AND DESIGN OF A DRUG PRODUCT

Major considerations in the design of a drug product include the therapeutic objective, the application site, and systemic drug absorption from the application site. If the drug is intended for systemic activity, the drug should ideally be completely and consistently absorbed from the application site. In contrast, if the drug is intended for local activity, then systemic absorption from the application should be minimal to prevent systemic drug exposure and possible systemic side effects. For extended-release drug products, the drug product should remain at or near the application site and then slowly release the drug for the desired period of time. The systemic absorption of a drug is dependent on (1) the physicochemical properties of the drug, (2) the nature of the drug product, and (3) the anatomy and physiology of the drug absorption site.

In order to develop a drug product that elicits the desired therapeutic objective, the pharmaceutical scientist must have a thorough understanding of the biopharmaceutic properties of the drug and drug product and the physiologic and pathologic factors affecting drug absorption from the application site. Pharmacists must also understand the relationship of drug dosage to therapeutic efficacy and adverse reactions and the potential for drug–drug and drug–nutrient interactions. This chapter will focus on the anatomic and physiologic considerations for the systemic absorption of a drug, whereas Chapter 14 will focus on the biopharmaceutic aspects of the drug and drug-product design including considerations in manufacturing and performance tests. Since the major route of drug administration is the oral route, major emphasis in the chapter will be on gastrointestinal drug absorption.

ROUTE OF DRUG ADMINISTRATION

Drugs may be given by parenteral, enteral, inhalation, intranasal, transdermal (percutaneous), or intranasal route for systemic absorption. Each route of drug administration has certain advantages and
Chapter 13

► Explain the pH-partition hypothesis and how gastrointestinal pH and the pKₐ of a drug may influence systemic drug absorption. Describe how drug absorption may be affected by a disease that causes changes in intestinal blood flow and/or motility.

► List the major factors that affect drug absorption from oral and nonoral routes of drug administration.

► Describe various methods that may be used to study oral drug absorption from the gastrointestinal transit.

disadvantages. Some characteristics of the more common routes of drug administration are listed in Table 13-1. The systemic availability and onset of drug action are affected by blood flow at the administration site, the physicochemical characteristics of the drug and the drug product, and by any pathophysiologic condition at the absorption site. After a drug is systemically absorbed, drug distribution and clearance follow normal physiological conditions of the body. Drug distribution and clearance are not usually altered by the drug formulation but may be altered by pathology, genetic polymorphism, and drug–drug interactions, as discussed in other chapters.

Many drugs are not administered orally because of insufficient systemic absorption from the GI tract. The diminished oral drug absorption may be due to drug instability in the gastrointestinal tract, drug degradation by the digestive enzymes in the intestine, high hepatic clearance (first-pass effect), and efflux transporters such as P-glycoprotein resulting in poor and/or erratic systemic drug availability. Some orally administered drugs, such as cholestyramine and others (Table 13-2), are not intended for systemic absorption but may be given orally for local activity in the gastrointestinal tract. However, some oral drugs such as mesalamine and balsalazide that are intended for local activity in the GI tract may also have a significant amount of systemic drug absorption. Small, highly lipid-soluble drugs such as nitroglycerin and fentanyl that are subject to high first-pass effects if swallowed but may be given by buccal or sublingual routes to by-pass degradation in the GI tract and/or first-pass effects. Insulin is an example of protein peptide drug generally not given orally due to degradation and inadequate absorption in the GI tract.

Biotechnology-derived drugs (see Chapter 18) are usually given by the parenteral route because they are too labile in the GI tract to be administered orally. For example, erythropoietin and human growth hormone (somatropin) are administered intramuscularly, and insulin is given subcutaneously or intramuscularly. Subcutaneous injection results in relatively slow absorption from the site of administration compared to intravenous injection which provides immediate delivery to the plasma. Pathophysiologic conditions such as burns will increase the permeability of drugs across the skin compared with normal intact skin. Currently, pharmaceutical research is being directed to devise approaches for the oral absorption of various protein drugs such as insulin (Dhawan et al, 2009). Recently, inhaled insulin was approved for use by the FDA but the product was fairly quickly discontinued by the manufacturer because of poor patient and physician acceptance of this new route of administration. Biotechnology-derived drugs are discussed more fully in Chapter 18.

When a drug is administered by an extravascular route of administration (eg, oral, topical, intranasal, inhalation, rectal), the
<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral Routes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous bolus (IV)</td>
<td>Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.</td>
<td>Drug is given for immediate effect.</td>
<td>Increased chance for adverse reaction. Possible anaphylaxis.</td>
</tr>
<tr>
<td>Intravenous infusion (IV inf)</td>
<td>Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.</td>
<td>Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.</td>
<td>Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).</td>
</tr>
<tr>
<td>Subcutaneous injection (SC)</td>
<td>Prompt from aqueous solution. Slow absorption from repository formulations.</td>
<td>Generally, used for insulin injection.</td>
<td>Rate of drug absorption depends on blood flow and injection volume. Insulin formulation can vary from short to intermediate and long acting.</td>
</tr>
<tr>
<td>Intradermal injection</td>
<td>Drug injected into surface area (dermal) of skin.</td>
<td>Often used for allergy and other diagnostic tests, such as tuberculosis.</td>
<td>Some discomfort at site of injection.</td>
</tr>
<tr>
<td>Intramuscular injection (IM)</td>
<td>Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.</td>
<td>Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.</td>
<td>Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.</td>
</tr>
<tr>
<td>Intra-arterial injection</td>
<td>100% of solution is absorbed.</td>
<td>Used in chemotherapy to target drug to organ.</td>
<td>Drug may also distribute to other tissues and organs in the body.</td>
</tr>
<tr>
<td>Intrathecal injection</td>
<td>100% of solution is absorbed.</td>
<td>Drug is directly injected into cerebrospinal fluid (CSF) for uptake into brain.</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal injection</td>
<td>In laboratory animals, (eg, rat) drug absorption resembles oral absorption.</td>
<td>Used more in small laboratory animals. Less common injection in humans. Used for renally impaired patients on peritoneal dialysis who develop peritonitis.</td>
<td>Drug absorption via mesenteric veins to liver, may have some hepatic clearance prior to systemic absorption.</td>
</tr>
<tr>
<td><strong>Enteral Routes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal or sublingual (SL)</td>
<td>Rapid absorption from lipid-soluble drugs.</td>
<td>No “first-pass” effects. Buccal route may be formulated for local prolonged action. Eg, adhere to the buccal mucosa with some antifungal. Buccal is different from sublingual which is usually placed “under tongue.”</td>
<td>Some drugs may be swallowed. Not for most drugs or drugs with high doses.</td>
</tr>
<tr>
<td>Oral (PO)</td>
<td>Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.</td>
<td>Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.</td>
<td>Some drugs may have erratic absorption, be unstable in the gastrointestinal tract, or be metabolized by liver prior to systemic absorption.</td>
</tr>
</tbody>
</table>

(Continued)
Chapter 13

The drug must first be absorbed into the systemic circulation and then diffuse or be transported to the site of action before eliciting biological and therapeutic activity. The general principles and kinetics of absorption from these extravascular sites follow the same principles as oral dosing, although the physiology of the site of administration differs.

### Table 13-1 Common Routes of Drug Administration (Continued)

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enteral Routes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Absorption may vary from suppository. More reliable absorption from enema (solution).</td>
<td>Useful when patient cannot swallow medication. Used for local and systemic effects.</td>
<td>Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.</td>
</tr>
<tr>
<td><strong>Other Routes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Slow absorption, rate may vary. Increased absorption with occlusive dressing.</td>
<td>Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW (molecular weight).</td>
<td>Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.</td>
</tr>
<tr>
<td>Inhalation and intranasal</td>
<td>Rapid absorption. Total dose absorbed is variable.</td>
<td>May be used for local or systemic effects.</td>
<td>Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.</td>
</tr>
</tbody>
</table>

### Table 13-2 Drugs Given Orally for Local Drug Activity in the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Questran</td>
<td>Cholestyramine resin is the chloride salt of a basic anion exchange resin, a cholesterol-lowering agent. Cholestyramine resin is hydrophilic, but insoluble in water and not absorbed from the digestive tract.</td>
</tr>
<tr>
<td>Balsalazide disodium</td>
<td>Colazal</td>
<td>Balsalazide disodium is a prodrug that is enzymatically cleaved in the colon to produce mesalamine, an anti-inflammatory drug. Balsalazide disodium is intended for local action in the treatment of mildly to moderately active ulcerative colitis. Balsalazide disodium and its metabolites are absorbed from the lower intestinal tract and colon.</td>
</tr>
<tr>
<td>Mesalamine(^a) delayed-release tablet</td>
<td>Asacol HD tablet</td>
<td>Asacol HD delayed-release tablets have an outer protective coat and an inner coat which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum for topical anti-inflammatory action in the colon.</td>
</tr>
<tr>
<td>Mesalamine controlled-release capsule</td>
<td>Pentasa capsule</td>
<td>Pentasa capsule is an ethylcellulose-coated, controlled-release capsule formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract.</td>
</tr>
</tbody>
</table>

\(^a\)Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA). Although mesalamine is indicated for local anti-inflammatory activity in the lower GI tract, mesalamine is systemically absorbed from the GI tract.

**Nature of Cell Membranes**

Many drugs administered by extravascular routes are intended for local effect. Other drugs are designed to be absorbed from the site of administration into the systemic circulation. For systemic drug absorption, the drug may cross cellular membranes. After oral...
administration, drug molecules must cross the intestinal epithelium by going either through or between the epithelial cells to reach the systemic circulation. The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure and properties of the drug and to the physical and biochemical properties of the cell membranes. Once in the plasma, the drug may act directly or have to cross biological membranes to reach the site of action. Therefore, biological membranes potentially pose a significant barrier to drug delivery.

Transcellular absorption is the process of drug movement across a cell. Some polar molecules may not be able to traverse the cell membrane but, instead, go through gaps or tight junctions between cells, a process known as paracellular drug diffusion. Figure 13-1 shows the difference between the two processes. Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Membranes are major structures in cells, surrounding the entire cell (plasma membrane) and acting as a boundary between the cell and the interstitial fluid. In addition, membranes enclose most of the cell organelles (eg, the mitochondrion membrane). Functionally, cell membranes are semipermeable partitions that act as selective barriers to the passage of molecules. Water, some selected small molecules, and lipid-soluble molecules pass through such membranes, whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

The transmembrane movement of drugs is influenced by the composition and structure of the plasma membranes. Cell membranes are generally thin, approximately 70 to 100 Å in thickness. Cell membranes are composed primarily of phospholipids in the form of a bilayer interdispersed with carbohydrates and protein groups. There are several theories as to the structure of the cell membrane. The lipid bilayer or unit membrane theory, originally proposed by Davson and Danielli (1952), considers the plasma membrane to be composed of two layers of phospholipid between two surface layers of proteins, with the hydrophilic “head” groups of the phospholipids facing the protein layers and the hydrophobic “tail” groups of the phospholipids aligned in the interior. The lipid bilayer theory explains the observation that lipid-soluble drugs tend to penetrate cell membranes more easily than polar molecules. However, the bilayer cell membrane structure does not account for the diffusion of water, small-molecular-weight molecules such as urea, and certain charged ions.
Chapter 13

The fluid mosaic model, proposed by Singer and Nicolson (1972), explains the transcellular diffusion of polar molecules. According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix (Fig. 13-2). These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier. As shown in Fig. 13-2, transmembrane proteins are interdispersed throughout the membrane. Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane transport studies (Pratt and Taylor, 1990). These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

**FIGURE 13-2** Model of the plasma membrane including proteins and carbohydrates as well as lipids. Integral proteins are embedded in the lipid bilayer; peripheral proteins are merely associated with the membrane surface. The carbohydrate consists of monosaccharides, or simple sugars, strung together in chains attached to proteins (forming glycoproteins) or to lipids (forming glycolipids). The asymmetry of the membrane is manifested in several ways. Carbohydrates are always on the exterior surface and peripheral proteins are almost always on the cytoplasmic, or inner, surface. The two lipid monolayers include different proportions of the various kinds of lipid molecules. Most important, each species of integral protein has a definite orientation, which is the same for every molecule of that species. (©George V. Kelvin.)

**PASSAGE OF DRUGS ACROSS CELL MEMBRANES**

**Passive Diffusion**

Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is passive because no external energy is expended. In Fig. 13-3, drug molecules move forward and back across a membrane. If the two sides have the same drug concentration, forward-moving drug molecules are balanced by molecules moving...
Physiologic Factors Related to Drug Absorption

back, resulting in no net transfer of drug. When one side is higher in drug concentration at any given time, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules; the net result will be a transfer of molecules to the alternate side downstream from the concentration gradient, as indicated in the figure by the big arrow. The rate of transfer is called flux, and is represented by a vector to show its direction in space. The tendency of molecules to move in all directions is natural, because molecules possess kinetic energy and constantly collide with one another in space. Only left and right molecule movements are shown in Fig. 13-3, because movement of molecules in other directions will not result in concentration changes because of the limitation of the container wall.

Passive diffusion is the major absorption process for most drugs. The driving force for passive diffusion is higher drug concentrations, typically on the mucosal side compared to the blood as in the case of oral drug absorption. According to Fick’s law of diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

\[
\frac{dQ}{dt} = \frac{DAK}{h} (C_{\text{GI}} - C_p)
\]

(13.1)

where \(dQ/dt\) = rate of diffusion, \(D\) = diffusion coefficient, \(K\) = lipid–water partition coefficient of drug in the biologic membrane that controls drug permeation, \(A\) = surface area of membrane, \(h\) = membrane thickness, and \(C_{\text{GI}} - C_p\) = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

Because the drug distributes rapidly into a large volume after entering the blood, the concentration of drug in the blood initially will be quite low with respect to the concentration at the site of drug absorption. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the microgram-per-milliliter or nanogram-per-milliliter range. If the drug is given orally, then \(C_{\text{GI}} >> C_p\) and a large concentration gradient is maintained until most of the drug is absorbed, thus driving drug molecules into the plasma from the gastrointestinal tract.

Given Fick’s law of diffusion, several other factors can be seen to influence the rate of passive diffusion of drugs. For example, the degree of lipid solubility of the drug influences the rate of drug absorption. The partition coefficient, \(K\), represents the lipid–water partitioning of a drug across the hypothetical membrane in the mucosa. Drugs that are more lipid soluble have a larger value of \(K\). The surface area, \(A\), of the membrane also influences the rate of absorption. Drugs may be absorbed from most areas of the gastrointestinal tract. However, the duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.

The thickness of the hypothetical model membrane, \(h\), is a constant for any particular absorption site. Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain. In the brain, the capillaries are densely lined with glial cells, so a drug diffuses slowly into the brain as if a thick lipid membrane exists. The term blood–brain barrier is used to describe the poor diffusion of water-soluble molecules across capillary plasma membranes into the brain. However, in certain disease states such as meningitis these membranes may be disrupted or become more permeable to drug diffusion.

The diffusion coefficient, \(D\), is a constant for each drug and is defined as the amount of a drug that
diffuses across a membrane of a given unit area per unit time when the concentration gradient is unity. The dimensions of $D$ are area per unit time—for example, cm$^2$/sec.

Because $D$, $A$, $K$, and $h$ are constants under usual conditions for absorption, a combined constant $P$ or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \quad (13.2)$$

Furthermore, in Equation 13.1 the drug concentration in the plasma, $C_p$, is extremely small compared to the drug concentration in the gastrointestinal tract, $C_{GI}$. If $C_p$ is negligible and $P$ is substituted into Equation 13.1, the following relationship for Fick’s law is obtained:

$$\frac{dQ}{dt} = P(C_{GI}) \quad (13.3)$$

Equation 13.3 is an expression for a first-order process. In practice, the extravascular absorption of most drugs tends to be a first-order absorption process. Moreover, because of the large concentration gradient between $C_{GI}$ and $C_p$, the rate of drug absorption is usually more rapid than the rate of drug elimination.

Many drugs have both lipophilic and hydrophilic chemical substituents. Those drugs that are more lipid soluble tend to traverse cell membranes more easily than less lipid-soluble or more water-soluble molecules. For drugs that act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the rate of drug transport. The ionized species of the drug contains a charge and is more water soluble than the nonionized species of the drug, which is more lipid soluble. The extent of ionization of a weak electrolyte will depend on both the $pK_a$ of the drug and the pH of the medium in which the drug is dissolved. *Henderson and Hasselbalch* used the following expressions pertaining to weak acids and weak bases to describe the relationship between $pK_a$ and pH:

For weak acids,

$$\text{Ratio} = \frac{[\text{salt}]}{[\text{acid}]} = \frac{[A^-]}{[HA]} = 10^{\phi H-pK_a} \quad (13.4)$$

For weak bases,

$$\text{Ratio} = \frac{[\text{base}]}{[\text{salt}]} = \frac{[RNH_2]}{[RNH_3^+]} = 10^{\phi H-pK_a} \quad (13.5)$$

With Equations 13.4 and 13.5, the proportion of free acid or free base existing as the nonionized species may be determined at any given pH, assuming the $pK_a$ for the drug is known. For example, at a plasma pH of 7.4, salicylic acid ($pK_a = 3.0$) exists mostly in its ionized or water-soluble form, as shown below:

$$\text{Ratio} = \frac{[\text{salt}]}{[\text{acid}]} = 10^{7.4-3.0}$$

$$\log \frac{[\text{salt}]}{[\text{acid}]} = 7.4 - 3.0 = 4.4$$

$$\frac{[\text{salt}]}{[\text{acid}]} = 2.51 \times 10^4$$

In a simple system, the total drug concentration on either side of a membrane should be the same at equilibrium, assuming Fick’s law of diffusion is the only distribution factor involved. For diffusible drugs, such as nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium. However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane. For example, consider the concentration of salicylic acid ($pK_a = 3.0$) in the stomach (pH 1.2) as opposed to its concentration in the plasma (pH 7.4) (Fig. 13-4). According to the Henderson–Hasselbalch equation (Equation 13.4) for weak acids, at pH 7.4 and at pH 1.2, salicylic acid exists in the ratios that follow.

In the plasma, at pH 7.4:

$$\text{Ratio} = \frac{(RCOO^-)}{(RCOOH)} = 2.51 \times 10^4$$

In gastric juice, at pH 1.2

$$\text{Ratio} = \frac{(RCOO^-)}{(RCOOH)} = 10^{1.2-3.0} = 1.58 \times 10^{-2}$$
Physiologic Factors Related to Drug Absorption

The total drug concentration on either side of the membrane is determined as shown in Table 13-3.

Thus, the pH affects distribution of salicylic acid (RCOOH) and its salt (RCOO⁻) across cell membranes. It is assumed that the acid, RCOOH, is freely permeable and the salt, RCOO⁻, is not permeable across the cell membrane. In this example the total concentration of salicylic acid at equilibrium is approximately 25,000 times greater in the plasma than in the stomach (see Table 13-3). These calculations can also be applied to weak bases, using Equation 13.5.

According to the pH–partition hypothesis, if the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then (1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane; (2) the total drug concentrations (ionized plus nonionized drug) on either side of the membrane will be unequal; and (3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration. For these reasons, a weak acid (such as salicylic acid) will be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) will be poorly absorbed from the stomach.

Another factor that can influence drug concentrations on either side of a membrane is a particular affinity of the drug for a tissue component, which prevents the drug from moving freely back across the cell membrane. For example, a drug such as dicumarol binds to plasma protein, and digoxin binds to tissue protein. In each case, the protein-bound drug does not move freely across the cell membrane. Drugs such as chlordane are very lipid soluble and will partition into adipose (fat) tissue. In addition, a drug such as tetracycline might form a complex with calcium in the bones and teeth. Finally, a drug may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines into adrenergic storage sites. Such drugs may have a higher total drug concentration on the side where binding occurs, yet the free drug concentration that diffuses across cell membranes will be the same on both sides of the membrane.

Instead of diffusing into the cell, drugs can also diffuse into the spaces around the cell as an absorption mechanism. In paracellular drug absorption, drug molecules smaller than 500 MW diffuse into the tight junctions, or spaces between intestinal epithelial cells.

### Carrier-Mediated Transport

Theoretically, a lipophilic drug may either pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism. Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

### Active Transport

Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites. A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are

---

**TABLE 13-3** Relative Concentrations of Salicylic Acid as Affected by pH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gastric Juice (pH 1.2)</th>
<th>Plasma (pH 7.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCOOH</td>
<td>1.0000</td>
<td>1</td>
</tr>
<tr>
<td>RCOO⁻</td>
<td>0.0158</td>
<td>25,100</td>
</tr>
<tr>
<td>Total drug concentration</td>
<td>1.0158</td>
<td>25,101</td>
</tr>
</tbody>
</table>
absorbed from the gastrointestinal tract by this process. Active transport is characterized by the ability to transport drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high drug concentrations. Therefore, this is an energy-consuming system. In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane (Fig. 13-5).

The carrier molecule may be highly selective for the drug molecule. If the drug structurally resembles a natural substrate that is actively transported, then it is likely to be actively transported by the same carrier mechanism. Therefore, drugs of similar structure may compete for sites of adsorption on the carrier. Furthermore, because only a fixed number of carrier molecules are available, all the binding sites on the carrier may become saturated if the drug concentration gets very high. A comparison between the rate of drug absorption and the concentration of drug at the absorption site is shown in Fig. 13-6. Notice that for a drug absorbed by passive diffusion, the rate of absorption increases in a linear relationship to drug concentration (first-order rate). In contrast, for drugs that are absorbed by a carrier-mediated process, the rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated. At higher drug concentrations, the rate of drug absorption remains constant, or zero order.

Facilitated Diffusion

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (ie, moves from a region of high drug concentration to a region of low drug concentration). Therefore, this system does not require energy input. However, because this system is carrier mediated, it is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure. In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Transporters and Carrier-Mediated Intestinal Absorption

Various carrier-mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body (Tsuji and Tamai, 1996). Both influx and efflux transporters are present in the brush border and basolateral membrane that will increase drug absorption (influx transporter) or decrease drug absorption (efflux transporter).

Influx transporters. For convenience, influx transporters were referred to as those that enhance absorption as influx transporters and those that cause drug outflow as efflux transporters. However, this concept is too simple and inadequate to describe the roles of many transporters which have bidirectional efflux and other functions related to their location in the membrane. Recent progress has been made in understanding the genetic role of membrane transporters in drug safety and efficacy. In particular, more than 400 membrane transporters in two major superfamilies—ATP-binding cassette (ABC) and solute carrier (SLC)—have been annotated in the
Physiologic Factors Related to Drug Absorption

Many of these transporters have been cloned, characterized, and location found in the human body including the GI tract. The subject was reviewed recently by The International Transporter Consortium (ITC) (Giacomini et al, 2010).

Many drugs are absorbed by carrier system because of the structural similarity to natural substrates or simply because they encounter the transporters located in specific part of the GI tract (Table 13-4). The small intestine expresses a variety of influx transporters (see Fig. 13-1) for amino acids, peptides, hexose, organic anions, organic cations, nucleosides, and other nutrients (Tsuji and Tamai, 1996, Giacomini et al, 2010). Among these influx (absorptive) transporters are the intestinal oligopeptide transporter, or di-/tripeptide transporter, PepT1 has potential for enhancing intestinal absorption of peptide drugs. The expression and function of PepT1 are now well analyzed for this application. Proteins given orally are digested in the gastrointestinal tract to produce a variety of short-chain peptides; these di- and tripeptides could be taken up by enterocytes and the proton/p

**Efflux transporters.** Many of the efflux transporters in the GI tract are membrane proteins located strategically in membranes to protect the body from influx of undesirable substrates. A common example is MDR1 or P-gp (alias) which is also named ABCB1. P-gp is an example of the ATP-binding cassette (ABC) subfamily. MDR1 is one of the many proteins known as multidrug-resistance associated protein. It is important in effluxing drug out and causing treatment resistance in some cell lines (see Chapter 12).

P-gp has been identified in the intestine and reduces apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid transporter</td>
<td>Gabapentin, d-Cycloserine</td>
</tr>
<tr>
<td></td>
<td>Methyldopa, Baclofen</td>
</tr>
<tr>
<td></td>
<td>l-dopa</td>
</tr>
<tr>
<td>Oligopeptide transporter</td>
<td>Cefadroxil, Cephradine</td>
</tr>
<tr>
<td></td>
<td>Cefixime, Cefitibuten</td>
</tr>
<tr>
<td></td>
<td>Cephalexin, Captopril</td>
</tr>
<tr>
<td></td>
<td>Lisinopril, Thrombin inhibitor</td>
</tr>
<tr>
<td>Phosphate transporter</td>
<td>Fostomycin, Foscarnet</td>
</tr>
<tr>
<td>Bile acid transporter</td>
<td>S3744</td>
</tr>
<tr>
<td>Glucose transporter</td>
<td>p-Nitrophenyl-β-d-glucopyranoside</td>
</tr>
<tr>
<td>P-glycoprotein efflux</td>
<td>Etoposide, Vinblastine</td>
</tr>
<tr>
<td></td>
<td>Cyclosporin A</td>
</tr>
<tr>
<td>Monocarboxylic acid transporter</td>
<td>Salicylic acid, Benzoic acid</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
</tr>
</tbody>
</table>

Data from Tsuji and Tamai (1996).
cytotoxic drugs. P-gp is highly expressed on the apical surface of superficial columnar epithelial cells of the ileum and colon, and expression decreases proximally into the jejunum, duodenum, and stomach (Ho et al, 2003; Takano et al, 2006). Takano et al (2006) reported that P-gp is present in various human tissues and ranked as follows: (1) Adrenal medulla (relative level to that in KB-3-1 cells, > 500-fold); (2) adrenal (160-fold); (3) kidney medulla (75-fold); (4) kidney (50-fold); (5) colon (31-fold); (6) liver (25-fold); (7) lung, jejunum, and rectum (20-fold); (8) brain (12-fold); (9) prostate (8-fold); and so on, including skin, esophagus, stomach, ovary, muscle, heart, and kidney cortex. The widespread presence of P-gp in the body appears to be related to its defensive role in effluxing drugs and other xenobiotics out of different cells and vital body organs. This transporter is sometimes called an efflux transporter while others are better described as “influx” proteins. P-gp has the remarkable ability to efflux drug out of many types of cells including endothelial lumens of capillaries. The expression of P-gp is often triggered in many cancer cells making them drug resistant due to drug efflux.

For many GI transporters, the transport of a drug is often bidirectional (Fig. 13-7), and whether the transporter causes drug absorption or exsorption depends on which direction the flux dominates with regard to a particular drug at a given site. An example of how P-gp affects drug absorption can be seen with the drug digoxin. P-gp is present in the liver and the GI tract. In Caco-2 cells and other model systems, P-gp is known to efflux drug out of the enterocyte. Digoxin was previously known to have erratic/incomplete absorption or bioavailability problems. While reported bioavailability issues were attributed to formulation or other factors, it is now known that knocking out the P-gp gene in mice increases bioavailability of the drug. In addition, human P-gp genetic polymorphisms occur. Hoffmeyer et al (2000) demonstrated that a polymorphism in exon 26 (C3435T) resulted in reduced intestinal P-gp, leading to increased oral bioavailability of digoxin in the subject involved. However, direct determination of P-gp substrate in vivo is not always readily possible. Most early determinations are done using in vitro cell assay methods, or in vivo studies involving a cloned animal with the gene knocked out such as the P-gp, a KO (knock out) mouse, eg, P-gp (−/−) which is the most sensitive method to identify P-gp substrates. Cross-species studies should be substantiated using human studies. The expression of P-gp is triggered by disease or other conditions, contributing to efflux and variability of plasma drug concentrations after a given dose is administered.

Enterocytes are intestinal absorptive cells that express the transport proteins. Enterocytes are simple columnar epithelial cells that line the intestinal wall and are found in the small intestine and colon. Influx transporters move drug molecules into the blood and increase plasma drug concentration, whereas efflux transporters move drug molecules back into the gut lumen and reduce systemic drug absorption.

**FIGURE 13-7** Diagram showing possible directional movement of a substrate drug by a transporter.
Physiologic Factors Related to Drug Absorption

Table 13-5  Reported Substrates of P-gp—A Member of ATP-Binding Cassette (ABC) Transporters

<table>
<thead>
<tr>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol, acetaminophen, actinomycin d, h-acetyl digoxin, amitriptyline, ampirnavir, apafant, asimadoline, atenolol, atorvastatin, azidopine, azidopracainamide, methiodide, azithromycin</td>
</tr>
<tr>
<td>Benzo[a]pyrene, betamethasone, bisantrene, bromocriptine, bunitrolol, calcein-AM</td>
</tr>
<tr>
<td>Camptothecin, carbamazepine, carvedilol, cephalothin, cerivastatin, chloroquine, chlorpromazine, chlorothiazide, Clarithromycin, colchicine, corticosterone, cortisol, cyclosporin A</td>
</tr>
<tr>
<td>Daunorubicin (daunomycin), debrisoquine, desoxycorticoster one, dexamethasone, digitoxin, Digoxin, diltiazem, dipyriramole, docetaxel, dolastatin 10, domperidone, doxorubicin (adriamycin)</td>
</tr>
<tr>
<td>Eletriptan, emetine, endosulfan, erythromycin, estradiol, estradiol-17-h-d-glucuronide, etoposide (VP-16)</td>
</tr>
<tr>
<td>Fexofenadine, gf120918, gregapoxacin</td>
</tr>
<tr>
<td>Hoechst 33342, hydroxyrubcin, imatinib, indinavir, ivermectin</td>
</tr>
<tr>
<td>Levofoxacin, loperamide, losartan, lovastatin</td>
</tr>
<tr>
<td>Methadone, methotrexate, methylprednisolone, metoprolol, mitoantrone, monensin</td>
</tr>
<tr>
<td>Morphine, N-desmethytamoxifen, nadolol, nelfinavir, nicardipine, nifedipine, nitrendipine, norverapamil</td>
</tr>
<tr>
<td>Olanzapine, omeprazole</td>
</tr>
<tr>
<td>PSC-833 (valspodar), perphenazine, prazosin, prednisone, pristinamycin IA, puromycin</td>
</tr>
<tr>
<td>Quetiapine, quinidine, quinine</td>
</tr>
<tr>
<td>Ranitidine, reserpine</td>
</tr>
<tr>
<td>Rhodamine 123, risperdone, ritonavir, roxithromycin</td>
</tr>
<tr>
<td>Saquinavir, sirolimus, sparfloxacin, sumatriptan, Tacrolimus, talinolol, tamoxifen, Taxol (paclitaxel), telithromycin, terfenadine, timolol, toremifene</td>
</tr>
<tr>
<td>Tributylmethylammonium, trimethoprim</td>
</tr>
<tr>
<td>Valinomycin, vecuronium, verapamil, vinblastine</td>
</tr>
<tr>
<td>Vincristine, vindoline, vinorelbine</td>
</tr>
</tbody>
</table>

(Adapted from Takano et al (2006).

P-gp affects the bioavailability of many substrate drugs listed in Table 13-5. P-gp inhibitors should be carefully evaluated before coadministration with a P-gp substrate drug. Other transporters are also present in the intestines (Tsuji and Tamai, 1996). For example, many oral cephalosporins are absorbed through the amino acid transporter. Cefazolin, a parenteral-only cephalosporin, is not available orally because it cannot be absorbed to a significant degree through this mechanism.

Frequently Asked Questions

The bioavailability of an antitumor drug is provided in the package insert. Why is it important to know whether the drug is a P-gp substrate or not?

Can the expression of P-gp in a cell change as the disease progresses?

Why is blockade of P-gp efflux of a drug, its glucuronide, or sulfate metabolite into the liver or bile/canniculi clinically important?

ORAL DRUG ABSORPTION DURING DRUG PRODUCT DEVELOPMENT

Prediction of Oral Drug Absorption

During the screening of new chemical entities for possible therapeutic efficacy, some drugs might not be discovered due to lack of systemic absorption after oral administration. Lipinski et al (1997, 2001) reviewed the chemical structure of many orally administered drugs and published the Rule of Five. During drug screening, “Rule of Five” predicts that poor drug absorption or permeation is more likely when there are more than five H-bond donors. For
10 H-bond (hydrogen-bond) acceptors, the molecular weight (MWT) is greater than 500 and the calculated $\log P$ (Clog $P$) is greater than 5 (or $M\log P > 4.15$). The rule is based on molecular computation and simulation and the effect of hydrophobicity, hydrogen bond, molecular size, and other relevant factors in assessing absorption using computational methods. The method is not applicable to drugs whose absorption involves transporters. These rules were developed to avoid types of chemical structures during early drug development that are unlikely to have adequate bioavailability. These rules have been modified by others (Takano et al, 2006). Rules for drug molecules that would improve the chance for oral absorption would include:

- Molecular weight $\leq 500$ Da
- Not more than five H-bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms) (O–H or N–H group)
- Not more than 10 H-bond acceptors (nitrogen or oxygen atoms)
- An octanol–water partition coefficient, $\log P \leq 5.0$.
- Number of H-bond donors $\leq 5$ (O–H or N–H group) stated above
- Number of H-bond acceptors $\leq 10$ (O or N) stated above

These rules only help predict adequate drug absorption and do not predict adequate pharmacodynamic activity. Moreover, some chemical structures do not follow the above rules, but may have good therapeutic properties.

Burton et al (2002) reviewed the difficulty in predicting drug absorption based only on physicochemical activity of drug molecules and discussed other factors that can affect oral drug absorption. Burton et al state that drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors, and physiological variables, including regional permeability differences, pH, mucosal enzymology, and intestinal motility, among others. These investigators point out that intestinal drug absorption, permeability, fraction absorbed, and, in some cases, even bioavailability are not equivalent properties and can be used interchangeably. Often these properties are influenced by the nature of the drug product and physical and chemical characteristics of the drug.

Software programs, such as GastroPlus™, have recently been developed to predict oral drug absorption, pharmacokinetics, and pharmacodynamic drugs in human and preclinical species. Simulation programs may use physicochemical data, such as molecular weight, $pK_a$, solubility at various pH, $\log P/\log D$, type of dosage form, $in vitro$ inputs such as dissolution, permeability/Caco-2, CYP metabolism (gut/liver), transporter rates, and $in vivo$ inputs such as drug clearance and volume of distribution.

### DRUG INTERACTIONS IN THE GASTROINTESTINAL TRACT

Many agents (drug or chemical substances) may have dual roles as substrate and/or inhibitor between CYP3A4 and P-glycoprotein, P-gp. Simultaneous administration of these agents results in an increase in the oral drug bioavailability of one or both of the drugs. Various drug–drug and drug–nutrient interactions involving oral bioavailability have been reported in human subjects (Thummel and Wilkinson, 1998, DiMarco et al, 2002, von Richter et al, 2004).

Many commonly used medications (eg, dextromethorphan hydrobromide) and certain food groups (eg, grapefruit juice) are substrates for both the efflux transporter, P-gp, and for the CYP3A enzymes involved in biotransformation of drugs (see Chapter 11). Grapefruit juice also affects drug transport in the intestinal wall. Certain components of grapefruit juice (such as citrus psoralens) are responsible for the inhibition of P-gp. DiMarco et al, (2002) demonstrated the inhibitory effect of grapefruit and Seville orange juice on the pharmacokinetics of dextromethorphan. Using dextromethorphan as the substrate, these investigators showed that grapefruit juice inhibits both CYP3A activity as well as P-gp resulting in an increased bioavailability of dextromethorphan. Grapefruit juice has been shown to increase the oral bioavailability of many drugs, such as cyclosporine or saquinavir, by inhibiting intestinal metabolism.

Esomeprazole (Nexium) and omeprazole (Prilosec) are proton pump inhibitors that inhibit
gastric acid secretion, resulting an increased stomach pH. Esomeprazole and omeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts, and digoxin). Both esomeprazole and omeprazole are extensively metabolized in the liver by CYP2C19 and CYP3A4. The prodrug clopidogrel (Plavix) inhibits platelet aggregation entirely due to an active metabolite. Co-administration of clopidogrel with omeprazole, an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel if given either concomitantly or 12 hours apart.

The dual effect of a CYP isoenzyme and a transporter on drug absorption is not always easy to determine or predict based on pharmacokinetic studies alone. A well-studied example is the drug digoxin. Digoxin is metabolized (CYP3A4), orally absorbed (Suzuki and Sugiyama, 2000), and a substrate for P-gp based on:

1. Human polymorphism single-nucleotide polymorphism (SNP) in exon 26 (C3435T) results in a reduced intestinal expression level of P-gp, along with increased oral bioavailability of digoxin.
2. Ketoconazole increases the oral bioavailability and shortens mean absorption time from 1.1 to 0.3 hour. Ketoconazole is a substrate and inhibitor of P-gp; P-gp can subsequently influence bioavailability. The influence of P-gp is not always easily detected unless studies are designed to investigate its presence.

For this analysis, a drug is given orally and intravenously before and after administration of an inhibitor drug. The AUC of the drug is calculated for each case. For example, ketoconazole causes an increase in the oral bioavailability of the immunosuppressant tacrolimus from 0.14 to 0.30, without affecting hepatic bioavailability (0.96–0.97) (Suzuki and Sugiyama, 2000). Since hepatic bioavailability is similar, the increase in bioavailability from 0.14 to 0.30 is the result of ketoconazole suppression on P-gp.

Mouly and Paine (2003) reported P-gp expression determined by Western blotting along the entire length of the human small intestine. They found that relative P-gp levels increased progressively from the proximal to the distal region. von Richter et al (2004) measured P-gp as well as CYP3A4 in paired human small intestine and liver specimens obtained from 15 patients. They reported that much higher levels of both P-gp (about seven times) and CYP3A4 (about three times) were found in the intestine than in the liver, suggesting the critical participation of intestinal P-gp in limiting oral drug bioavailability.

**Frequently Asked Questions**

**Vesicular Transport**

Vesicular transport is the process of engulfing particles or dissolved materials by the cell. Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested. Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages. Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

During pinocytosis, phagocytosis or transcytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it inside the cell (Fig. 13-8). Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell. Transcytosis is the process by which various macromolecules are transported across the interior of a cell. In transcytosis, the vesicle fuses with the plasma membrane to release the encapsulated material to another side of the cell. Vesicles are employed to intake the macromolecules on one side of the cell, draw them across the cell, and eject them on the other side. Transcytosis (sometimes referred to as vesicular transport) is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.
Pinocytosis is a cellular process that permits the active transport of fluid from outside the cell through the membrane surrounding the cell into the inside of the cell. In pinocytosis, tiny incippings called caveolae (little caves) in the surface of the cell close and then pinch off to form pinosomes, little fluid-filled bubbles, that are free within the cytoplasm of the cell.

An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

**Pore (Convective) Transport**

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. Although such pores have never been directly observed by microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.

A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell (see Fig. 13-1). Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

**Ion-Pair Formation**

Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme \( \text{pK}_a \) values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane. For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pairs with hexylsalicylate (Nienbert, 1989).

An interesting application of ion pairs is the complexation of amphotericin B and DSPG (distearylphosphatidylglycerol) in some amphotericin B/liposome products. Ion pairing may transiently alter distribution, reduce high plasma free drug concentration, and reduce renal toxicity.

**ORAL DRUG ABSORPTION**

The oral route of administration is the most common and popular route of drug dosing. The oral dosage form must be designed to account for extreme pH ranges, the presence or absence of food, degradative enzymes, varying drug permeability in the different regions of the intestine, and motility of the gastrointestinal tract. In this chapter we will discuss intestinal variables that affect absorption; dosage-form considerations are discussed in Chapters 14 to 17.

**Anatomic and Physiologic Considerations**

The normal physiologic processes of the alimentary canal may be affected by diet, contents of the gastrointestinal (GI) tract, hormones, the visceral nervous system, disease, and drugs. Thus, drugs given by the enteral route for systemic absorption may be affected by the anatomy, physiologic functions, and contents of the alimentary tract. Moreover, the physical, chemical, and pharmacologic properties of the drug and the formulation of the drug product will also affect systemic drug absorption from the alimentary canal.
The enteral system consists of the alimentary canal from the mouth to the anus (Fig. 13-9). The major physiologic processes that occur in the GI system are secretion, digestion, and absorption. Secretion includes the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are also involved in the digestion of carbohydrates and proteins. Other secretions, such as mucus, protect the linings of the lumen of the GI tract. Digestion is the breakdown of food constituents into smaller structures in preparation for absorption. Food constituents are mostly absorbed in the proximal area (duodenum) of the small intestine. The process of absorption is the entry of constituents from the lumen of the gut into the body. Absorption may be considered the net result of both lumen-to-blood and blood-to-lumen transport movements.

Drugs administered orally pass through various parts of the enteral canal, including the oral cavity, esophagus, and various parts of the gastrointestinal tract. Residues eventually exit the body through the anus. The total transit time, including gastric emptying, small intestinal transit, and colonic transit, ranges from 0.4 to 5 days (Kirwan and Smith, 1974). The small intestine, particularly, the duodenum area is the most important site for drug absorption. Small intestine transit time (SITT) ranges from 3 to 4 hours for most healthy subjects. If absorption is not completed by the time a drug leaves the small intestine, absorption may be erratic or incomplete. The small intestine is normally filled with digestive juices and liquids, keeping the lumen contents fluid. In contrast, the fluid in the colon is reabsorbed, and the luminal content in the colon is either semisolid or solid, making further drug dissolution and absorption erratic and difficult. The lack of the solubilizing effect of the chyme and digestive fluid contributes to a less favorable environment for drug absorption.

**Oral Cavity**

Saliva is the main secretion of the oral cavity, and it has a pH of about 7. Saliva contains ptyalin (salivary amylase), which digests starches. Mucin, a glycoprotein that lubricates food, is also secreted and may interact with drugs. About 1500 mL of saliva is secreted per day.

The oral cavity can be used for the buccal absorption of lipid-soluble drugs such as fentanyl citrate (Actiq®) and nitroglycerin, also formulated for sublingual routes. Recently, orally disintegrating tablets, ODT, have become available. These ODT tablets, such as aripiprazole (Abilify Discmelt®), orally disintegrating tablets rapidly disintegrate in the oral cavity in the presence of saliva. The resulting fragments which are suspended in the saliva are swallowed and the drug is then absorbed from the gastrointestinal tract. A major advantage for ODTs is that the drug may be taken without water. In the case of the antipsychotic drug, aripiprazole, a nurse may give the drug in the form of an ODT (Abilify Discmelt) to a schizophrenic patient. The nurse can easily ascertain that the drug was taken and swallowed.

**Esophagus**

The esophagus connects the pharynx and the cardiac orifice of the stomach. The pH of the fluids in the
esophagus is between 5 and 6. The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach. Tablets or capsules may lodge in this area, causing local irritation. Very little drug dissolution occurs in the esophagus.

**Stomach**

The stomach is innervated by the vagus nerve. However, local nerve plexus, hormones, mechanoreceptors sensitive to the stretch of the GI wall, and chemoreceptors control the regulation of gastric secretions, including acid and stomach emptying. The fasting pH of the stomach is about 2 to 6. In the presence of food, the stomach pH is about 1.5 to 2, due to hydrochloric acid secreted by parietal cells. Stomach acid secretion is stimulated by gastrin and histamine. Gastrin is released from G cells, mainly in the antral mucosa and also in the duodenum. Gastrin release is regulated by stomach distention (swelling) and the presence of peptides and amino acids. A substance known as intrinsic factor enhances vitamin B-12 (cyanocobalamin) absorption and various gastric enzymes, such as pepsin, which initiates protein digestion, are secreted into the gastric lumen to initiate digestion.

Basic drugs are solubilized rapidly in the presence of stomach acid. Mixing is intense and pressurized in the antral part of the stomach, a process of breaking down large food particles described as antral milling. Food and liquid are emptied by opening the pyloric sphincter into the duodenum. Stomach emptying is influenced by the food content and osmolality. Fatty acids and mono- and diglycerides delay gastric emptying (Hunt and Knox, 1968). High-density foods generally are emptied from the stomach more slowly. The relation of gastric emptying time to drug absorption is discussed more fully in the next section.

Stomach pH may be increased due to the presence of food and certain drugs such as omeprazole, a proton pump inhibitor used in gastroesophageal reflux disease (GERD). Increasing stomach pH may cause a drug interaction with an enteric-coated drug product (e.g., diclofenac enteric-coated tablets, Voltaren) which requires acid pH for drug release.

A few fat-soluble, acid-stable drugs may be absorbed from the stomach by passive diffusion. Ethanol is completely miscible with water, easily crosses cell membranes, and is efficiently absorbed from the stomach (Welling, 2002). Ethanol is more rapidly absorbed from the stomach in the fasting state compared to the fed state (Levitt et al, 1997).

**Duodenum**

A common duct from both the pancreas and the gall-bladder enters into the duodenum. The duodenal pH is about 6 to 6.5, because of the presence of bicarbonate that neutralizes the acidic chyme emptied from the stomach. The pH is optimum for enzymatic digestion of protein and peptide-containing food. Pancreatic juice containing enzymes is secreted into the duodenum from the bile duct. Trypsin, chymotrypsin, and carboxypeptidase are involved in the hydrolysis of proteins into amino acids. Amylase is involved in the digestion of carbohydrates. Pancreatic lipase secretion hydrolyzes fats into fatty acid. The complex fluid medium in the duodenum helps dissolve many drugs with limited aqueous solubility.

The duodenum is the major site for passive drug absorption due to both its anatomy, which creates a high surface area, and high blood flow. The duodenum is a site where many ester prodrugs are hydrolyzed during absorption. Proteolytic enzymes in the duodenum degrade many protein drugs preventing adequate absorption of the intact protein drug.

**Jejunum**

The jejunum is the middle portion of the small intestine, between the duodenum and the ileum. Digestion of protein and carbohydrates continues after addition of pancreatic juice and bile in the duodenum. This portion of the small intestine generally has fewer contractions than the duodenum and is preferred for in vivo drug absorption studies.

**Ileum**

The ileum is the terminal part of the small intestine. This site also has fewer contractions than the duodenum and may be blocked off by catheters with an inflatable balloon and perfused for drug absorption studies. The pH is about 7, with the distal part as high as 8. Due to the presence of bicarbonate secretion, acid drugs will dissolve in the ileum. Bile
secretion helps dissolve fats and hydrophobic drugs. The ileocecal valve separates the small intestine from the colon.

**Colon**
The colon lacks villi and has limited drug absorption due to lack of large surface area, blood flow, and the more viscous and semisolid nature of the lumen contents. The colon is lined with mucin that functions as lubricant and protectant. The pH in this region is 5.5 to 7 (Shareef et al, 2003). A few drugs, such as theophylline and metoprolol, are absorbed in this region. Drugs that are absorbed well in this region are good candidates for an oral sustained-release dosage form. The colon contains both aerobic and anaerobic microorganisms that may metabolize some drugs. For example, l-dopa and lactulose are metabolized by enteric bacteria. Crohn’s disease affects the colon and thickens the bowel wall. The microflora also become more anaerobic. Absorption of clindamycin and propranolol are increased, whereas other drugs have reduced absorption with this disease (Rubinstein et al, 1988). A few delayed-release drug products such as mesalamine (Asacol tablets, Pentasa capsules) have a pH-sensitive coating that dissolves in the higher pH of the lower bowel, releasing the mesalamine to act locally in Crohn’s disease. Balsalazide disodium capsules (Colazal), also used in Crohn’s disease, is a prodrug containing an azo group that is cleaved by anaerobic bacteria in the lower bowel to produce mesalamine (5-aminosalicylic acid or 5-ASA), an anti-inflammatory drug.

**Rectum**
The rectum is about 15 cm long, ending at the anus. In the absence of fecal material, the rectum has a small amount of fluid (approximately 2 mL) with a pH of about 7. The rectum is perfused by the superior, middle, and inferior hemorrhoidal veins. The inferior hemorrhoidal vein (closest to the anal sphincter) and the middle hemorrhoidal vein feed into the vena cava and back to the heart. The superior hemorrhoidal vein joins the mesenteric circulation, which feeds into the hepatic portal vein and then to the liver. The small amount of fluid present in the rectum has virtually no buffer capacity; as a consequence, the dissolving drug(s) or even excipients can have a determining effect on the existing pH in the anorectal area. Drug absorption after rectal administration may be variable, depending on the placement of the suppository or drug solution within the rectum. A portion of the drug dose may be absorbed via the lower hemorrhoidal veins, from which the drug feeds directly into the systemic circulation; some drugs may be absorbed via the superior hemorrhoidal vein, which feeds into the mesenteric veins to the hepatic portal vein to the liver, and be metabolized before systemic absorption.

**Drug Absorption in the Gastrointestinal Tract**
Drugs may be absorbed by passive diffusion from all parts of the alimentary canal including sublingual, buccal, GI, and rectal absorption. For most drugs, the optimum site for drug absorption after oral administration is the upper portion of the small intestine or duodenum region. The unique anatomy of the duodenum provides an immense surface area for the drug to diffuse passively (Fig. 13-10). The large surface area of the duodenum is due to the presence of valve-like folds in the mucous membrane on which are small projections known as villi. These villi contain even smaller projections known as microvilli, forming a brush border. In addition, the duodenal region is highly perfused with a network of capillaries, which helps maintain a concentration gradient from the intestinal lumen and plasma circulation.

**Gastrointestinal Motility**
Once a drug is given orally, the exact location and/or environment of the drug product within the GI tract is difficult to discern. GI motility tends to move the drug through the alimentary canal, so the drug may not stay at the absorption site. For drugs given orally, an anatomic absorption window may exist within the GI tract in which the drug is efficiently absorbed. Drugs contained in a nonbiodegradable controlled-release dosage form should be completely released into this absorption window to be absorbed before the movement of the dosage form into the large bowel.

The transit time of the drug in the GI tract depends on the physicochemical and pharmacologic properties of the drug, the type of dosage form, and
various physiologic factors. Movement of the drug within the GI tract depends on whether the alimentary canal contains recently ingested food (digestive or fed state) or is in the fasted or interdigestive state (Fig. 13-11). During the fasted or interdigestive state, alternating cycles of activity known as the migrating motor complex (MMC) act as a propulsive movement that empties the upper GI tract to the cecum. Initially, the alimentary canal is quiescent. Then, irregular contractions followed by regular

**FIGURE 13-10** Three mechanisms for increasing surface area of the small intestine. The increase in surface area is due to folds of Kerkring, villi, and microvilli. (From Wilson, 1962, with permission.)

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>INCREASE IN SURFACE AREA (relative to cylinder)</th>
<th>SURFACE AREA (sq cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of simple cylinder</td>
<td>1</td>
<td>3300</td>
</tr>
<tr>
<td>Folds of Kerkring (valvulae conniventes)</td>
<td>3</td>
<td>10,000</td>
</tr>
<tr>
<td>Villi</td>
<td>30</td>
<td>100,000</td>
</tr>
<tr>
<td>Microvilli</td>
<td>600</td>
<td>2,000,000</td>
</tr>
</tbody>
</table>

**FIGURE 13-11** A pictorial representation of the typical motility patterns in the interdigestive (fasted) and digestive (fed) state. (From Rubinstein et al, 1988, with permission.)
contractions with high amplitude (housekeeper waves) push any residual contents distally or farther down the alimentary canal. In the fed state, the migrating motor complex is replaced by irregular contractions, which have the effect of mixing intestinal contents and advancing the intestinal stream toward the colon in short segments (Table 13-6). The pylorus and ileocecal valves prevent regurgitation or movement of food from the distal to the proximal direction.

**Gastric Emptying Time**

Anatomically, a swallowed drug rapidly reaches the stomach. Eventually, the stomach empties its contents into the small intestine. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug. Some drugs, such as penicillin, are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

A number of factors affect gastric emptying time. Some factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs (Burks et al, 1985; Rubinstein et al, 1988). Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum. Different constituents of a meal empty from the stomach at different rates. Feldman and associates (1984) observed that 10 oz of liquid soft drink, scrambled egg (digestible solid), and a radio-opaque marker (undigestible solid) were 50% emptied from the stomach in 30 minutes, 154 minutes, and 3 to 4 hours, respectively. Thus, liquids are generally emptied faster than digested solids from the stomach (Fig. 13-12).

**Table 13-6 Characteristics of the Motility Patterns in the Fasted Dog**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasted State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>30–60 min</td>
<td>Quiescence.</td>
</tr>
<tr>
<td>II</td>
<td>20–40 min</td>
<td>• Irregular contractions&lt;br&gt;• Medium amplitude but can be as high as phase III&lt;br&gt;• Bile secretion begins&lt;br&gt;• Onset of gastric discharge of administered fluid of small volume usually occurs before that of particle discharge&lt;br&gt;• Onset of particle and mucus discharge may occur during the latter part of phase II</td>
</tr>
<tr>
<td>III</td>
<td>5–15 min</td>
<td>• Regular contractions (4–5 contractions/min) with high amplitude&lt;br&gt;• Mucus discharge continues&lt;br&gt;• Particle discharge continues</td>
</tr>
<tr>
<td>IV</td>
<td>0–5 min</td>
<td>• Irregular contractions&lt;br&gt;• Medium descending amplitude&lt;br&gt;• Sometimes absent</td>
</tr>
<tr>
<td><strong>Fed State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One phase only</td>
<td>As long as food is present in the stomach</td>
<td>• Regular, frequent contractions.&lt;br&gt;• Amplitude is lower than phase III&lt;br&gt;• 4–5 contractions/min</td>
</tr>
</tbody>
</table>

From Rubinstein et al (1988), with permission.
Large particles, including tablets and capsules, are delayed from emptying for 3 to 6 hours by the presence of food in the stomach. Indigestible solids empty very slowly, probably during the interdigestive phase, a phase in which food is not present and the stomach is less motile but periodically empties its content due to housekeeper wave contraction (Fig. 13-13).

**Intestinal Motility**

Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells. The drug must have a sufficient time (residence time) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

The average normal small intestine transit time (SITT) was about 7 hours as measured in early studies using indirect methods based on the detection of hydrogen after an oral dose of lactulose (fermentation of lactulose by colon bacteria yields hydrogen in the breath). Newer studies using gamma scintigraphy have shown SITT to be about 3 to 4 hours. Thus a drug may take about 4 to 8 hours to pass through the stomach and small intestine during the fasting state. During the fed state, SITT may take 8 to 12 hours. For modified-release or controlled-dosage forms, which slowly release the drug over an extended period of time, the dosage form must stay within a certain segment of the intestinal tract so that the drug contents are released and absorbed before loss of the dosage form in the feces. Intestinal transit is discussed further in relation to the design of sustained-release products in Chapter 17.

In one study reported by Shareef et al (2003), utilizing a radio-opaque marker, mean mouth-to-anus transit time was 53.3 hours. The mean colon transit time was 35 hours, with 11.3 hours for the right (ascending transverse portion), 11.4 hours for the left (descending and portion of the transverse), and 12.4 hours for the recto sigmoid colon. Dietary fiber has the greatest effect on colonic transit. Dietary fiber increases fecal weight, partly by retaining water and partly by increasing bacterial mass (Shareef et al, 2003).

**Perfusion of the Gastrointestinal Tract**

The blood flow to the GI tract is important in carrying absorbed drug to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the duodenal region and peritoneum. The splanchnic circulation receives about 28% of the
Physiologic Factors Related to Drug Absorption

Cardiac output and is increased after meals. Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic-portal vein and the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability (Benet et al, 1976).

The role of the lymphatic circulation in drug absorption is well established. Drugs are absorbed through the lacteal or lymphatic vessels under the microvilli. Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism, because drug absorption through the hepatic-portal vein is avoided. The lymphatics are important in the absorption of dietary lipids and may be partially responsible for the absorption of some lipophilic drugs. Many poorly water-soluble drugs are soluble in oil and lipids, which may dissolve in chylomicrons and be absorbed systemically via the lymphatic system. Bleomycin or aclarubicin were prepared in chylomicrons to improve oral absorption through the lymphatic system (Yoshikawa et al, 1983, 1989).

Effect of Food on Gastrointestinal Drug Absorption

The presence of food in the GI tract can affect the bioavailability of the drug from an oral drug product (Table 13-7). Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs. The effects of food are not always predictable and can have clinically significant consequences. Some effects of food on the bioavailability of a drug from a drug product include (US Food and Drug Administration, Guidance for Industry, December 2002):

- Delay in gastric emptying
- Stimulation of bile flow
- A change in the pH of the GI tract
- An increase in splanchnic blood flow
- A change in luminal metabolism of the drug substance
- Physical or chemical interaction of the meal with the drug product or drug substance

Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiologic changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. The FDA recommends the use of high-calorie and high-fat meals to study the effect of food on the bioavailability and bioequivalence of drug products (FDA Guidance for Industry, 2002; see also Chapter 15).

The absorption of some antibiotics, such as penicillin and tetracycline and certain hydrophilic drugs, is decreased with food; whereas other drugs, particularly lipid-soluble drugs such as griseofulvin, metaxalone and metazaalone, are better absorbed when given with food containing a high-fat content (Fig. 13-14). The presence of food in the GI lumen stimulates the flow of bile. Bile contains bile acids, which are surfactants involved in the digestion and solubilization of fats, and also increases the solubility of fat-soluble drugs through micelle formation. For some basic drugs (eg, cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the pH, causing more rapid dissolution of the drug and better absorption. Absorption of this basic drug is reduced when gastric acid secretion is reduced (Ogata et al, 1986).

Most drugs should be taken with a full glass (approximately 8 fluid oz or 250 mL) of water to ensure that drugs will wash down the esophagus and be more available for absorption. Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Fig. 13-15). The solubility of many drugs is limited, and sufficient fluid is necessary for dissolution of the drug. Some patients may be on several drugs that are dosed frequently for months. These patients are often nauseous and are reluctant to take a lot of fluid. For example, HIV patients with active viral counts may be on an AZT or DDI combination with one or more of
<table>
<thead>
<tr>
<th>Drug</th>
<th>Food Affect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased bioavailability with food</strong></td>
<td></td>
</tr>
<tr>
<td>Doxycycline Hyclate Delayed-Release Tablets</td>
<td>The mean Cmax and AUC$_{0-\infty}$ of doxycycline are 24% and 13% lower, respectively, following single dose administration with a high-fat meal (including milk) compared to fasted conditions.</td>
</tr>
<tr>
<td>Atorvastatin calcium tablets</td>
<td>Food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC.</td>
</tr>
<tr>
<td>Clopidogrel bisulfate tablets</td>
<td>Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites. The active metabolite AUC$_{0-24}$ was unchanged in the presence of food, while there was a 57% decrease in active metabolite Cmax.</td>
</tr>
<tr>
<td>Naproxen delayed-release tablets</td>
<td>Naproxen delayed-release tablets are enteric coated tablets with a pH-sensitive coating. The presence of food prolonged the time the tablets remained in the stomach. Tmax is delayed but peak naproxen levels, Cmax was not affected.</td>
</tr>
<tr>
<td>Alendronate sodium tablets</td>
<td>Bioavailability was decreased by approximately 40% when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast. Alendronate must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food, and some medications are likely to reduce drug absorption.</td>
</tr>
<tr>
<td>Tamsulosin HCl capsules</td>
<td>Taking tamsulosin capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C$_{max}$) compared to fed conditions.</td>
</tr>
<tr>
<td><strong>Increased bioavailability with food</strong></td>
<td></td>
</tr>
<tr>
<td>Oxycodone HCl CR tablets</td>
<td>Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg tablet was administered with a high-fat meal.</td>
</tr>
<tr>
<td>Metaxalone Tablets</td>
<td>A high-fat meal increased Cmax by 177.5% and increased AUC (AUC$<em>{0-t}$ AUC$</em>{\infty}$) by 123.5% and 115.4%, respectively. Tmax was delayed (4.3 h versus 3.3 h) and terminal t$_{1/2}$ was decreased (2.4 h versus 9.0 h).</td>
</tr>
<tr>
<td>Spironolactone tablets</td>
<td>Food increased the bioavailability of unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known</td>
</tr>
<tr>
<td><strong>Food has very little affect on bioavailability</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentin capsules</td>
<td>Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C$_{max}$).</td>
</tr>
<tr>
<td>Tramadol HCl tablets</td>
<td>Oral administration of Tramadol hydrochloride tablets with food does not significantly affect its rate or extent of absorption.</td>
</tr>
<tr>
<td>Digoxin tablets</td>
<td>When digoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced.</td>
</tr>
<tr>
<td>Bupropion HCl ER tablets</td>
<td>Food did not affect the C$_{max}$ or AUC of bupropion.</td>
</tr>
<tr>
<td>Methylphenidate HCl ER tablets (Concerta®)</td>
<td>In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of Concerta® when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.</td>
</tr>
<tr>
<td>Fluoxetine HCl capsules</td>
<td>Food does not appear to affect the 846 systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.</td>
</tr>
<tr>
<td>Dutasteride soft gelatin capsules</td>
<td>Food reduces the Cmax by 10% to 15%. This reduction is of no clinical significance.</td>
</tr>
</tbody>
</table>

Food can affect bioavailability of the drug by affecting the rate and/or extent of drug absorption. In some cases, food may delay the Tmax for enteric coated drugs due to a delay in stomach emptying time. For each drug, the clinical importance of the change in bioavailability due to food must be assessed.
Physiologic Factors Related to Drug Absorption

**FIGURE 13-14** A comparison of the effects of different types of food intake on the serum griseofulvin levels following a 1.0-g oral dose. (From Crouse, 1961, with permission.)

the protease inhibitors, Invirase (Hoffmann-La Roche), Crixivan (Merck), or Norvir (Abbott). These HIV treatments appear to be better than any previous treatments but depend on patient compliance in taking up to 12 to 15 pills daily for weeks. Any complications affecting drug absorption can influence the outcome of these therapies. With antibiotics, unabsorbed drug may influence the GI flora. For drugs that cause GI disturbances, residual drug dose in the GI tract can potentially aggravate the incidence of diarrhea.

Some drugs, such as erythromycin, iron salts, aspirin, and nonsteroidal anti-inflammatory agents (NSAIDs), are irritating to the GI mucosa and are given with food to reduce this irritation. For these drugs, the rate of absorption may be reduced in the presence of food, but the extent of absorption may be the same and the efficacy of the drug is retained.

The GI transit time for enteric-coated and nondisintegrating drug products may also be affected by the presence of food. Enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying. Thus, the enteric-coated tablet does not reach the duodenum rapidly, delaying drug release and systemic drug absorption. The presence of food may delay stomach emptying of enteric-coated tablets or nondisintegrating dosage forms for several hours. In contrast, since enteric-coated beads or microparticles disperse in the stomach, stomach emptying of the particles is less affected by food, and these preparations demonstrate more consistent drug absorption from the duodenum. Fine granules (smaller than 1 to 2 mm in size) and tablets that disintegrate are not significantly delayed from emptying from the stomach in the presence of food.

Food can also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24 controlled-release tablets is much more rapid when given to a subject in the fed rather than fasted state because of dosage form failures, known as dose-dumping (Fig.13-16).

Timing of drug administration in relation to meals is often important. Pharmacists regularly advise patients to take a medication either 1 hour before or 2 hours after meals to avoid any delay in drug absorption.

Alendronate sodium (Fosamax®) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption used to prevent osteoporosis. Bisphosphonates are very soluble in water and their systemic oral absorption is greatly reduced in the presence of food. The approved labeling for alendronate sodium states that (Fosamax) “must be taken

![Figure 13-16](image-url)
Physiologic Factors Related to Drug Absorption

347

at least one-half hour before the first food, beverage, or medication of the day with plain water only.”

Since fatty foods may delay stomach emptying time beyond 2 hours, patients who have just eaten a heavy, fatty meal should take these drugs 3 hours or more after the meal, whenever possible. Products that are used to curb stomach acid secretion are usually taken before meals, in anticipation of acid secretion stimulated by food. Famotidine (Pepcid), and cimetidine (Tagamet) are taken before meals to curb excessive acid production. In some cases, drugs are taken directly after a meal or with meals to increase the systemic absorption of the drug (eg, itraconazole, metaxalone) or with food to decrease gastric irritation of the drug (eg, ibuprofen). Many lipophilic drugs have increased bioavailability with food possibly due to formation of micelles in the GI tract and some lymphatic absorption.

Fluid volume tends to distend the stomach and speed up stomach emptying; however, large volume of nutrients with high caloric content supersedes that faster rate and delays stomach emptying time. Reduction in drug absorption may be caused by several other factors. For example, tetracycline hydrochloride absorption is reduced by milk and food that contains calcium, due to tetracycline chelation. However, significant reduction in absorption may simply be the result of reduced dissolution due to increased pH. Co-administration of sodium bicarbonate raises the stomach pH and reduces tetracycline dissolution and absorption (Barr et al, 1971).

Ticlopidine (Ticlid®) is an antiplatelet agent that is commonly used to prevent thromboembolic disorders. Ticlopidine has enhanced absorption after a meal. The absorption of ticlopidine was compared in subjects who received either an antacid or food or were in a control group (fasting). Subjects who received ticlopidine 30 minutes after a fatty meal had an average increase of 20% in plasma concentrations over fasting subjects, whereas antacid reduced ticlopidine plasma concentrations by approximately the same amount. There was a higher incidence of gastrointestinal complaint in the fasting group. Many other drugs have reduced gastrointestinal side effects when taken with food. The decreased gastrointestinal side effects associated with food consumption may greatly improve tolerance and compliance in patients.

Double-Peak Phenomenon

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks (Fig. 13-17). This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients. The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form.

The double-peak phenomenon observed for cimetidine (Oberle and Amidon, 1987) may be due to variability in stomach emptying and intestinal flow rates during the entire absorption process after a single dose. For many drugs, very little absorption

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**FIGURE 13-17** Serum concentrations of dipyridamole in three groups of four volunteers each. **A.** After taking 25 mg as tablet intact. **B.** As crushed tablet. **C.** As tablet intact 2 hours before lunch. (From Mellinger TJ, Bohorofoush JG: Blood levels of dipyridamole (Persantine) in humans. Arch Int Pharmacodyn Ther 163:471–480, 1966, with permission.)
occurs in the stomach. For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

In contrast, ranitidine (Miller, 1984) produces a double peak after both oral or parenteral (IV bolus) administration. Ranitidine is apparently concentrated in the bile within the gallbladder from the general circulation after IV administration. When stimulated by food, the gallbladder contracts and bile-containing drug is released into the small intestine. The drug is then reabsorbed and recycled (enterohepatic recycling).

Tablet integrity may also be a factor in the production of a double-peak phenomenon. Mellinger and Bohorfoush (1966) compared a whole tablet or a crushed tablet of dipyridamole in volunteers and showed that a tablet that does not disintegrate or incompletely disintegrates may have delayed gastric emptying, resulting in a second absorption peak.

**METHODS FOR STUDYING FACTORS THAT AFFECT DRUG ABSORPTION**

**Gamma Scintigraphy to Study Site of Drug Release**

Gamma scintigraphy is a technique commonly used to track drug dosage form movement from one region to another within the GI tract after oral administration. Gamma scintigraphy also has many research applications and is widely used for formulation studies, such as the mechanism of drug release from a hydrophilic matrix tablet (Abrahamsson et al, 1998). Generally a nonabsorbable radionuclide that emits gamma rays is included as marker in the formulation. In some studies, two radiolabels may be used for simultaneous detection of liquid and solid phases. One approach is to use labeled technesium ($^{99m}$Tc) in a capsule matrix to study how a drug is absorbed. The image of the capsule breaking up in the stomach or the GI tract is monitored using a gamma camera. Simultaneously, blood levels or urinary excretion of the drug may be measured. This study can be used to correlate residence time of the drug in a given region after capsule breakup to drug absorption. The same technique is used to study drug absorption mechanisms in different regions of the GI tract before a drug is formulated for extended release.

Gamma scintigraphy has been used to study the effect of transit time on the absorption of theophylline (Sournac et al, 1988). *In vitro* drug release characteristics were correlated with total gastrointestinal transit time. The results showed a significant correlation between the *in vitro* release of theophylline and the percent of the total amount of theophylline absorbed *in vivo*. This study illustrates the importance of gamma scintigraphy for the development of specialized drug dosage forms.

**Markers to Study Effect of Gastric and GI Transit Time on Absorption**

Many useful agents are available that may be used as tools to study absorption and understand the mechanism of the absorptive process. For example, mannitol has a concentration-dependent effect on small intestinal transit. Adkin et al (1995) showed that small concentrations of mannitol included in a pharmaceutical formulation could lead to reduced uptake of many drugs absorbed exclusively from the small intestine. No significant differences between the gastric emptying times of the four solutions of different concentrations tested were observed.

Similarly, Hebden et al (1999) demonstrated that codeine slowed GI transit, decreased stool water content, and diminished drug absorption when compared to controls. The results indicated that stool water content may be an important determinant in colonic drug absorption. In contrast, the sugar lactulose accelerated GI transit, increased stool water content, and enhanced drug absorption from the distal gut. Quinine absorption was greater when given with lactulose compared to no lactulose.

Riley et al (1992) studied the effects of gastric emptying and GI transit on the absorption of several drug solutions (furosemide, atenolol, hydrochlorothiazide, and salicylic acid) in healthy subjects. These drugs may potentially be absorbed differently at various sites in the GI system. Subjects were given 20 mg oral metoclopramide or 60 mg oral codeine.
physiologic factors related to drug absorption. The study showed that gastric emptying affects the absorption of salicylic acid, but not that of furosemide, hydrochlorothiazide, or atenolol. In vivo experiments are needed to determine the effect of changing transit time on drug absorption.

**Remote Drug Delivery Capsules (RDDCs)**

Drug absorption in vivo may be studied either directly by an intubation technique that directly takes samples from the GI tract, or remotely with a special device, such as the Heidelberg capsule. The Heidelberg capsule (Baine, 1999) is a device used to determine the pH of the stomach. The capsule contains a pH sensor and a miniature radio transmitter (invented by H. G. Noeller and used at Heidelberg University in Germany decades ago). The capsule is about 2 cm × 0.8 cm and can transmit data to outside after the device is swallowed and tethered to the stomach. Other, newer telemetric methods may be used to take pictures of various regions of the GI tract.

An interesting remote drug delivery capsule (RDDC) with electronic controls for noninvasive regional drug absorption study was reported by Parr et al (1999). This device was used to study absorption of ranitidine hydrochloride solution in 12 healthy male volunteers. Mean gastric emptying of the RDDC was 1.50 hours, and total small intestine transit was 4.79 hours. The capsule was retrieved from the feces at 30.25 hours. The onset of ranitidine serum levels depended on the time of capsule activation and the site of drug release.

**Osmotic Pump Systems**

The osmotic pump system is a drug product that contains a small hole from which dissolved drug is released (pumped out) at a rate determined by the rate of entrance of water from the GI tract across a semipermeable membrane due to osmotic pressure (see Chapter 17). The drug is either mixed with an osmotic agent or is located in a reservoir. Osmotic pump systems may be used to study drug absorption in different parts of the GI tract because the rate of drug release is constant (zero order) and generally not altered by the environment of the gastrointestinal tract. The constant rate of drug release provides relatively constant blood concentrations.

**In Vivo GI Perfusion Studies**

In the past, segments of guinea pig or rat ileums were cut and used to study drug absorption; however, we now know that many of the isolated preparations were not viable shortly after removal, making the absorption data collected either invalid or difficult to evaluate. In addition, the differences among species make it difficult to extrapolate animal data to humans.

GI perfusion is an in vivo method used to study absorption and permeability of a drug in various segments of the GI tract. A tube is inserted from the mouth or anus and placed in a specific section of the GI tract. A drug solution is infused from the tube at a fixed rate, resulting in drug perfusion of the desired GI region. The jejunal site is peristaltically less active than the duodenum, making it easier to intubate, and therefore it is often chosen for perfusion studies. Perfusion studies in other sites such as the duodenum, ileum, and even the colon have also been performed by gastroenterologists and pharmaceutical scientists.

Lennernas et al (1992, 1995) have applied perfusion techniques in humans to study permeability in the small intestine and the rectum. These methods yield direct absorption information in various segments of the GI tract. The regional jejunal perfusion method was reported to have great potential for mechanistic evaluations of drug absorption.

Buch and Barr (1998) evaluated propranolol HCl in the proximal and distal intestine in humans (n = 7 subjects) using direct intubation. Propranolol HCl is a beta blocker that has high inter- and intrasubject variability in absorption and metabolism. These investigators showed that propranolol was better absorbed from a solution in the distal region of the intestine. This study is difficult to relate to the propranolol extended-release oral products for which differences in drug release rates and GI transit time may also influence inter- and intrasubject variability in bioavailability.

**Intestinal Permeability to Drugs**

Drugs that are completely absorbed (F > 90%) after oral administration generally demonstrate high permeability in models in vitro. Previously, poor drug
absorption was mostly attributed to poor dissolution, slow diffusion, degradation, or poor intestinal permeation. Modern technology has shown that poor or variable oral drug bioavailability among individuals is also the result of individual genetic differences in intestinal absorption (see Chapter 12). Interindividual differences in membrane proteins, ion channels, transporters, and antiporters (such as P-glycoprotein, P-gp) that mediate directional transport of drugs and their metabolites across biological membranes can change the extent of drug absorption, or even transport to the site of action elsewhere in the body. It is now clear that the behavior of drugs in the body is the result of an intricate interplay between these receptors, drug transporters, and the drug-metabolizing systems. This insight provides another explanation for erratic drug absorption beyond poor formulation and first-pass metabolism.

Alternative methods to study intestinal drug permeability include *in vivo* or *in situ* intestinal perfusion in a suitable animal model (e.g., rats), and/or *in vitro* permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells such as Caco-2 cells. In addition, the physicochemical characterization of a drug substance (e.g., oil/water partition coefficient) provides useful information to predict a drug’s permeability.

**Caco-2 Cells for In-Vitro Permeability Studies**

Although *in vivo* studies yield much definitive information about drug permeability in humans, they are tedious and costly to perform. The *Caco-2* cell line is a human colon adenocarcinoma cell line that differentiates in culture and resembles the epithelial lining of the human small intestine. The permeability of the cellular monolayer may vary with the stage of cell growth and the cultivation method used. However, using monolayers of Caco-2 cells under controlled conditions, the permeability of a drug may be determined. Caco-2 cells can also be used to study interactions of drugs with the transporter P-gp discussed below.

Drug permeability using the Caco-2 cell line has been suggested as an *in vitro* method for passively transported drugs. In some cases, the drug permeability may appear to be low due to efflux of drugs via membrane transporters such as P-gp. Permeability studies using the Caco-2 cell line have been suggested as a method for classifying the permeability of a drug according to the Biopharmaceutics Classification System, BCS (Tolle-Sander and Polli, 2001; US FDA, Guidance 2003, August 2002; Sun and Pang, 2007). The main purpose of the BCS classification is to identify a drug as having high or low permeability as a predictor of systemic drug absorption from the GI tract (see Chapter 15).

**Drug Transporters**

Several transport proteins are expressed in the intestinal epithelial cells (Suzuki and Sugiyama et al, 2000; Takano et al, 2006) (Fig. 13-18). Although some transporters facilitate absorption, other transporters,
such as P-gp may effectively inhibit drug absorption. P-gp (also known as MDR1), an energy-dependent, membrane-bound protein, is an efflux transporter that mediates the secretion of compounds from inside the cell back out into the intestinal lumen, thereby limiting overall absorption (see Chapter 12). Thus, drug absorption may be reduced or increased by the presence or absence of efflux proteins. The role of efflux proteins is generally believed to be a defense mechanism for the body to excrete and reduce drug accumulation.

P-gp is expressed also in other tissues such as the blood–brain barrier, liver, and kidney, where it limits drug penetration into the brain, mediates biliary drug secretion, and renal tubular drug secretion, respectively. Efflux pumps are present throughout the body and are involved in transport of a diverse group of hydrophobic drugs, natural products, and peptides. Many drugs and chemotherapeutic agents, such as cyclosporin A, verapamil, terfenadine, fexofenadine, and most HIV-1 protease inhibitors are substrates of P-gp (see Chapter 12). In addition, individual genetic differences in intestinal absorption may be the result of genetic differences in P-gp and other transporters.

**CLINICAL EXAMPLES**

Multidrug resistance (MDR) to cancer cells has been linked to efflux transporter proteins such as P-gp that can efflux or pump out chemotherapeutic agents from the cells (Sauna et al, 2001). Paclitaxel (Taxol) is an example of coordinated metabolism, efflux, and triggering of hormone nuclear receptor to induce efflux protein (Fig. 13-19). P-gp (see MDR1 in Fig. 13-1) is responsible for 85% of paclitaxel excretion back into the GI tract (Synold et al, 2001). Paclitaxel induces the steroid xenobiotic receptor SXR (also known as PXR), which in turn activates MDR1 transcription and P-gp expression, resulting in even further excretion of paclitaxel into the intestinal fluid. Paclitaxel also induces CYP3A4 and CYP2C8 transcription, resulting in increased paclitaxel metabolism. Thus, in response to a xenobiotic challenge, SXR can induce both a first line of defense (intestinal excretion) and a backup system (hepatic drug inactivation) that limits exposure to potentially toxic compounds. In contrast to paclitaxel, docetaxel is a closely related antineoplastic agent that does not activate SXR but has a much better absorption profile.

Mutations of other transporters, particularly those involved in reuptake of serotonin, dopamine, and gamma-aminobutyric acid (GABA), are presently being studied with regard to clinically relevant changes in drug response. Pharmacogenetic variability in these transporters is an important consideration in patient dosing. When therapeutic failures occur, the following questions should be asked: (1) Is the drug a substrate for P-gp and/or CYP3A4? (2) Is the drug being co-administered with anything that inhibits either P-gp and/or CYP3A4? For example, grapefruit juice and many drugs can affect drug metabolism and oral absorption.

**EFFECT OF DISEASE STATES ON DRUG ABSORPTION**

Drug absorption may be affected by any disease that causes changes in (1) intestinal blood flow,
(2) gastrointestinal motility, (3) changes in stomach emptying time, (4) gastric pH that affects drug solubility, (5) intestinal pH that affects the extent of ionization, (6) the permeability of the gut wall, (7) bile secretion, (8) digestive enzyme secretion, or (9) alteration of normal GI flora. Some factors may dominate, while other factors sometimes cancel the effects of one another. Pharmacokinetic studies comparing subjects with and without the disease are generally necessary to establish the effect of the disease on drug absorption. Patients in an advanced stage of Parkinson’s disease may have difficulty swallowing and greatly diminished gastrointestinal motility.

Patients on tricyclic antidepressants (imipramine, amitriptyline, and nortriptyline) and antipsychotic drugs (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delays in drug absorption, especially with slow-release products, have occurred.

Achlorhydric patients may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases. Many weak-base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out due to the weak basicity.

Dapsone, itraconazole, and ketoconazole may also be less well absorbed in the presence of achlorhydria. In patients with acid reflux disorders, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption. Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.

HIV–AIDS patients are prone to a number of gastrointestinal (GI) disturbances, such as increased gastric transit time, diarrhea, and achlorhydria. Rapid gastric transit time and diarrhea can alter the absorption of orally administered drugs. Achlorhydria may or may not decrease absorption, depending on the acidity needed for absorption of a specific drug. Indinavir, for example, requires a normal acidic environment for absorption. The therapeutic window of indinavir is extremely narrow, so optimal serum concentrations are critical for this drug to be efficacious.

Congestive heart failure (CHF) patients with persistent edema have reduced splanchnic blood flow and develop edema in the bowel wall. In addition, intestinal motility is slowed. The reduced blood flow to the intestine and reduced intestinal motility results in a decrease in drug absorption. For example, furosemide (Lasix), a commonly used loop diuretic, has erratic and reduced oral absorption in patients with CHF and a delay in the onset of action.

As discussed above, Crohn’s disease is an inflammatory disease of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel. The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of reduced surface area and thicker gut wall for diffusion. For example, higher plasma propranolol concentration has been observed in patients with Crohn’s disease after oral administration of propranolol. Serum α-1-acid glycoprotein levels are increased in Crohn’s disease patients and may affect the protein binding and distribution of propranolol in the body and result in higher plasma concentrations.

Celiac disease is an inflammatory disease affecting mostly the proximal small intestine. Celiac disease is caused by sensitization to gluten, a viscous protein found in cereals and grains. Patients with celiac disease generally have an increased rate of stomach emptying and increased permeability of the small intestine. Cephalexin absorption appears to be increased in celiac disease, although it is not possible to make general predictions about these patients. Other intestinal conditions that may potentially affect drug absorption include corrective surgery involving peptic ulcer, antrectomy with gastroduodenostomy, and selective vagotomy.

Drugs That Affect Absorption of Other Drugs

Anticholinergic drugs in general may reduce stomach acid secretion. Propantheline bromide is an anticholinergic drug that may also slow stomach emptying and motility of the small intestine. Tricyclic
antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract. Slower stomach emptying may cause delay in drug absorption.

Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis, which may reduce the effective time for the absorption of some drugs and thereby decrease the peak drug concentration and the time to reach peak drug concentration. For example, digoxin absorption from a tablet is reduced by metoclopramide but increased by an anticholinergic drug, such as propantheline bromide. Allowing more time in the stomach for the tablet to dissolve generally helps with the dissolution and absorption of a poorly soluble drug, but would not be helpful for a drug that is not soluble in stomach acid.

Antacids should not be given with cimetidine, because antacids may reduce drug absorption. Antacids containing aluminum, calcium, or magnesium may complex with drugs such as tetracycline, ciprofloxacin, and indinavir, resulting in a decrease in drug absorption. To avoid this interaction, antacids should be taken 2 hours before or 6 hours after drug administration.

Proton pump inhibitors such as omeprazole (Prilosec®), lansoprazole (Prevacid®), pantoprazole (Protonix®), and others decrease gastric acid production, thereby raising gastric pH. These drugs may interfere with drugs for which gastric pH affects bioavailability (eg, ketoconazole, iron salts, ampicillin esters, and digoxin) and enteric-coated drug products (eg, aspirin, diclofenac) in which the pH-dependent enteric coating may dissolve in the higher gastric pH and release drug prematurely (“dose-dumping”).

Cholestyramine is a nonabsorbable ion-exchange resin for the treatment of hyperlipemia. Cholestyramine binds warfarin, thyroxine, and laparadime, similar to activated charcoal, thereby reducing absorption of these drugs.

**Nutrients That Interfere with Drug Absorption**

Many nutrients substantially interfere with the absorption or metabolism of drugs in the body (Anderson, 1988; Kirk, 1995). The effect of food on bioavailability was discussed earlier. Oral drug–nutrient interactions are often drug specific and can result in either an increase or decrease in drug absorption.

Absorption of water-soluble vitamins, such as vitamin B-12 and folic acid, are aided by special absorption mechanisms. Vitamin B-12 absorption in the stomach is facilitated by intrinsic factors. B-12 forms a complex with the factor and is carried in the intestinal stream to the ileum, where it then binds to a specific receptor. Vitamin B-12 then ultimately dissociates from the complex and is absorbed.

Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin D deficiency states. It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

Grapefruit juice often increases bioavailability, as observed by an increase in plasma levels of many drugs that are substrates for cytochrome P-450 (CYP) 3A4 (see Chapter 11). Grapefruit juice contains various flavonoids such as naringin, which inhibits certain cytochrome P-450 enzymes involved in drug metabolism. In this case, the observed increase in the plasma drug–blood levels is due to decreased presystemic elimination in the GI tract and/or liver. Indirectly, the amount of drug absorbed systemically from the drug product is increased. Grapefruit juice can also block drug efflux by inhibiting P-gp for some drugs.

**MISCELLANEOUS ROUTES OF DRUG ADMINISTRATION**

For systemic drug absorption, the oral route is the easiest, safest, and most popular route of drug administration. Alternate routes of drug administration have been used successfully to improve systemic drug absorption or to localize drug effects in order to minimize systemic drug exposure and adverse events. Increasingly popular nonparenteral alternatives to oral drug delivery for systemic drug absorption include nasal, inhalation, and transdermal drug delivery. Nasal, inhalation, and topical drug delivery may also be used for local drug action.
Nasal Drug Delivery

Nasal drug delivery may be used for either local or systemic effects. Because the nasal region is richly supplied with blood vessels, nasal administration is also useful for systemic drug delivery. However, the total surface area in the nasal cavity is relatively small, retention time in the nasal cavity is generally short, and some drug may be swallowed. These factors may limit the nose's capacity for systemic delivery of drugs requiring large doses. Surfactants are often used to increase systemic penetration, although the effect of chronic drug exposure on the integrity of nasal membranes must also be considered. In general, a drug must be sufficiently lipophilic to cross the membranes of the nasal epithelium in order to be absorbed. Small molecules with balanced lipophilic and hydrophilic properties tend to be absorbed more easily. This observation poses a challenge for nasal delivery of larger molecules such as proteins and peptides, which would benefit from delivery routes that avoid the degradative environment of the intestine. Dosage forms intended for nasal drug delivery include nasal drops, nasal sprays, aerosols, and nebulizers (Su and Campanale, 1985).

Depending on the metabolic absorption, and chemical profile of the drug, some drugs are rapidly absorbed through the nasal membrane and can deliver rapid therapeutic effect. Various hormones and insulin have been tested for intranasal delivery. In some cases the objective is to improve availability, and in other cases it is to reduce side effects. Vasopressin and oxytocin are older examples of drugs marketed as intranasal products. In addition, many opioids are known to be rapidly absorbed from the nasal passages and can deliver systemic levels of the drug almost as rapidly as an intravenous injection (Dale et al, 2002). A common problem with nasal drug delivery is the challenge of developing a formulation with nonirritating ingredients. Many surfactants that facilitate absorption tend to be moderately or very irritating to the nasal mucosa.

Intranasal corticosteroids for treatment of allergic and perennial rhinitis have become more popular since intranasal delivery is believed to reduce the total dose of corticosteroid required. A lower dose also leads to minimization of side effects such as growth suppression. This logic has led to many second-generation corticosteroids such as beclometasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide that are being considered or developed for intranasal delivery (Szefler, 2002). However, the potential for growth suppression in children varies. In one study, beclometasone dipropionate reduced growth in children, but mometasone furoate nasal spray used for 1 year showed no signs of growth suppression. Overall, the second-generation corticosteroids are given by nasal delivery to cause minimal systemic side effects (Szefler, 2002).

Inhalation Drug Delivery

Inhalation drug delivery may also be used for local or systemic drug effects. The lung has a potential absorption surface of some 70 m², a much larger surface than the small intestine or nasal passages. When a substance is inhaled, it is exposed to membranes of the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar sacs, and alveoli. The lungs and their associated airways are designed to remove foreign matter from the highly absorptive peripheral lung surfaces via mucociliary clearance. However, if compounds such as aerosolized drug can reach the peripheral region of the lung, absorption can be very efficient.

Particle (droplet) size and velocity of application control the extent to which inhaled substances penetrate into airway spaces. Optimum size for deep airway penetration of drug particles is 3 to 5 μm. Large particles tend to deposit in upper airways, whereas very small molecules (<3 μm) are exhaled before absorption can occur. Most inhalation devices deliver approximately 10% of the administered dose to the lower respiratory tract. A number of devices such as spacers (to reduce turbulence and improve deep inhalation) have been developed to increase lung delivery. An in-vitro device useful to measure the particle size emitted from an aerosol or a mechanically produced fine mist is the cascade impacter.

Recently, recombinant human insulin for inhalation (Exubera®) was approved by the FDA, demonstrating the viability of this delivery route even for large biological drugs. Insulin inhalation was
withdrawn from the US market in 2007 due to lack of consumer demand for the product.

**Topical and Transdermal Drug Delivery**

Topical drug delivery is generally used for local drug effects at the site of application. Dosing is dependent upon the concentration of the drug in the topical product (e.g., cream, ointment) and the total surface area applied. Drug may be applied as an ointment or cream to the skin or various mucous membranes such as intravaginally. Even though the objective is to obtain a local drug effect, some of the drug may be absorbed systemically.

Transdermal products are generally used for systemic drug absorption. For transdermal drug delivery the drug is incorporated into a transdermal therapeutic system or patch, but it may be incorporated into an ointment as well (see Chapter 14). The advantages of transdermal delivery include continuous release of drug over a period of time, low presystemic clearance, and good patient compliance.

Other routes of drug administration are discussed elsewhere and in Chapter 14.

**CHAPTER SUMMARY**

Systemic drug absorption is a complex process dependent upon many biopharmaceutic factors including (1) the physicochemical properties of the drug, (2) the nature of the drug product, (3) the anatomy and physiology of the drug absorption site and (4) type and amount of food or other drugs present in the gut. Most drugs are passively absorbed as described by Fick’s law of diffusion according to the pH–partition hypothesis which may be a first-order process depending on permeability and how much drug is dissolved at the absorption site. Orally administered drugs may not be absorbed all along the gastrointestinal tract. The duodenum affords the optimum area for absorption due to the high surface area and blood flow. Many substrate-specific transporters may be the dominant factor responsible for bioavailability of some drugs. These drugs are absorbed by active transport which is a carrier-mediated process that requires energy and transports the drug against a concentration gradient. Active drug absorption may be saturable depending on the carrier protein involved and is often site specific. Influx and efflux transporters in the gastrointestinal tract influence systemic drug absorption. A well-known class of transporters in the GI tract is known as the ABC-cassette family. MDR1 (alias P-gp) is an example. P-gp reduces drug absorption by effluxing the drug out of the enterocytes and back into the gut lumen. When the absorption process becomes saturated, the rate of drug absorption no longer follows a first-order process. Many efflux transporters in the GI and other parts of the body are now recognized and their presence and quantity are genetically expressed and may be activated by certain diseases, such as cancer. P-glycoprotein is a common efflux transporter in the GI tract which may be inhibited by co-administered drugs and nutrients leading to enhanced systemic absorption. In addition to normal gastrointestinal and physiologic factors such as stomach emptying time, small intestine transit time, local pH, content of the GI tract, presystemic metabolism, and drug dosage form factors jointly influence systemic drug absorption.

Biopharmaceutic factors such as drug aqueous solubility, permeability of cell membranes, the degree of ionization, molecular size, particle size, and nature of the dosage form will also affect systemic
drug absorption. The prediction of drug absorption based on physico-chemical activity of drug molecules and other factors have been attempted during drug screening and discovery. Often these properties are influenced by biopharmaceutic factors such as formulation, physiological variables, pH, intestinal regional permeability differences, lumenal contents, transporters, and intestinal motility. Drug absorption is greatly dependent on routes of administration. Parenteral, inhalation, transdermal, and intranasal routes all present physiologic and biopharmaceutic issues that must be understood in order to develop an optimum formulation that is consistently absorbed systemically. Various methods are used to study drug absorption depended on the route involved. Gamma scintigraphy and marker methods are used to study stomach emptying time and GI transit time. GI perfusion methods are used to determine the influence of transporters and the effect of presystemic clearance and regional drug absorption.

**LEARNING QUESTIONS**

1. A recent bioavailability study in adult human volunteers demonstrated that after the administration of a single enteric-coated aspirin granule product given with a meal, the plasma drug levels resembled the kinetics of a sustained-release drug product. In contrast, when the product was given to fasted subjects, the plasma drug levels resembled the kinetics of an immediate-release drug product. Give a plausible explanation for this observation.

2. The aqueous solubility of a weak-base drug is poor. In an intubation (intestinal perfusion) study, the drug was not absorbed beyond the jejunum. Which of the following would be the correct strategy to improve drug absorption from the intestinal tract?
   a. Give the drug as a suspension and recommend that the suspension be taken on an empty stomach.
   b. Give the drug as a hydrochloride salt.
   c. Give the drug with milk.
   d. Give the drug as a suppository.

3. What is the primary reason that protein drugs such as insulin are not given orally for systemic absorption?

4. Which of the following statements is true regarding an acidic drug with a \( \text{pK}_a \) of 4?
   a. The drug is more soluble in the stomach when food is present.
   b. The drug is more soluble in the duodenum than in the stomach.
   c. The drug is more soluble when dissociated.

5. Which region of the gastrointestinal tract is most populated by bacteria? What types of drugs might affect the gastrointestinal flora?

6. Discuss methods by which the first-pass effect (presystemic absorption) may be circumvented.

7. Misoprostol (Cytotec, GD Searle) is a synthetic prostaglandin E1 analog. According to the manufacturer, the following information was obtained when misoprostol was taken with an antacid or high-fat breakfast:

<table>
<thead>
<tr>
<th>Condition</th>
<th>( C_{\text{max}} ) (pg/mL)</th>
<th>( \text{AUC}_{0-24} ) hour (pg h/mL)</th>
<th>( t_{\text{max}} ) (minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>811 ± 317*</td>
<td>417 ± 135</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>With antacid</td>
<td>689 ± 315</td>
<td>349 ± 108b</td>
<td>20 ± 14</td>
</tr>
<tr>
<td>With high-fat breakfast</td>
<td>303 ± 176b</td>
<td>373 ± 111b</td>
<td>64 ± 79b</td>
</tr>
</tbody>
</table>

*Results are expressed as the mean ± SD (standard deviation).  
Comparisons with fasting results statistically significant, \( p < 0.05 \).

What is the effect of antacid and high-fat breakfast on the bioavailability of misoprostol? Comment on how these factors affect the rate and extent of systemic drug absorption.

8. Explain why the following occur.
   a. Drug A is given by IV bolus injection and the onset of the pharmacodynamic effect is immediate. When Drug A is given orally in
the same dose, the onset of the pharmacodynamic effect is delayed and the intensity of the pharmacodynamic effect is less than the drug given by IV bolus injection. 

b. Drug B is given by IV bolus injection and the onset of the pharmacodynamic effect is delayed. When Drug B is given orally in the same dose to fasted subjects, the onset of the pharmacodynamic effect is shorter and the pharmacodynamic effect is more intense after IV bolus injection.

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Physiologic Factors Related to Drug Absorption


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Biopharmaceutics Considerations in Drug Product Design and *In Vitro* Drug Product Performance

**Chapter Objectives**

- **Define biopharmaceutics and explain how biopharmaceutic principles relate to drug product performance, *in vitro* and *in vivo*.**
- **Define the term “rate-limiting step” and discuss how the rate-limiting step relates to the bioavailability of a drug.**
- **Differentiate between the terms, solubility, and dissolution.**
- **Differentiate between the concept of drug absorption and bioavailability.**
- **Describe the various *in vitro* and *in vivo* tests commonly used to evaluate drug products.**
- **Describe the multivariate considerations in developing a dissolution method (eg, media type, volume, operation principle, and equipment type). Discuss how successfully the method will perform by evaluating the variables that share or do not share the real processes in the body (*in vivo*).**
- **Explain the rationale involved in quantifying bioavailability or drug product performance based on dissolution profile alone (eg, $Q = 75\%$ in 30 minutes or dissolution rate at several time points)?**

*Biopharmaceutics* is the study of the physicochemical properties of the drug and the drug product, *in vitro*, on the bioavailability of the drug, *in vivo*, to produce a desired therapeutic effect. Biopharmaceutics links the physical and chemical properties of the drug and the drug product to their performance, *in vivo*. A primary concern in biopharmaceutics is the bioavailability of drugs. Bioavailability refers to the measurement of the rate and extent of active drug that becomes available at the site of action. Oral drug absorption involves at least three distinct steps: drug release and dissolution from the drug product, permeation of the drug across the gastrointestinal (GI) linings, and drug disposition during GI transit. Additional drug disposition may occur in the body. Because the systemic blood circulation delivers therapeutically active drug to the tissues and to the site of action of the drug, changes in bioavailability affect changes in the pharmacodynamics and toxicity of a drug. The aim of biopharmaceutics is to adjust the delivery of drug from the drug product in such a manner as to provide optimal therapeutic activity and safety for the patient.

**BIOPHARMACEUTIC FACTORS AFFECTING DRUG BIOAVAILABILITY**

Drugs are not usually given as a pure chemical drug substances, but are formulated into a finished dosage forms (drug products), such as tablets, capsules, ointments, solutions, etc, which are then administered to patients. Drug products are designed to deliver the drug for local or systemic effects. The design of the dosage form, the formulation of the drug product, and the manufacturing process requires a thorough understanding of the biopharmaceutic principles of drug delivery. Considerations in the design of a drug product to deliver the active drug with the desired bioavailability characteristics and therapeutic objectives include (1) the physicochemical properties of the drug molecule, (2) the type of drug product (eg, tablet, capsule, transdermal delivery system, topical ointment, parenteral solution), (3) the nature of the excipients in the drug product, (4) the method of manufacturing, and (5) the route of drug administration.
Drug products include the active drug substance combined with selected additional ingredients (*excipients*) that make up the dosage form. Common drug products include liquids, tablets, capsules, injectables, suppositories, transdermal systems, and topical products such as creams and ointments. These finished dosage forms or drug products are then given to patients to achieve a specific therapeutic objective. Although excipients are considered inert with respect to pharmacodynamic activity, excipients are important in the manufacture of the drug product and provide functionality to the drug product with respect to drug release and dissolution (see also Chapter 16).

Biopharmaceutics allows for the rational design of drug products and is based on:

- The physical and chemical properties of the drug substance
- The route of drug administration, including the anatomic and physiologic nature of the application site (e.g., oral, topical, injectable, implant, transdermal patch, etc)
- Desired pharmacodynamic effect (e.g., immediate or prolonged activity)
- Toxicologic properties of the drug
- Safety of excipients
- Effect of excipients and dosage form on drug product performance
- Manufacturing processes

Some drugs are intended for topical or local therapeutic action at the site of administration. For these locally acting drugs, systemic drug absorption is undesirable. Drugs intended for local activity are designed to have a direct pharmacodynamic action without affecting other body organs. These drugs may be applied topically to the skin, nose, eye, mucous membranes, buccal cavity, throat, or rectum. A drug intended for local activity may be given intravaginally, into the urethral tract, intranasally, inhaled into the lungs, applied into the ear, on the eye, or orally. Examples of drugs used for local action include anti-infectives, antifungals, local anesthetics, antacids, astringents, vasoconstrictors, antihistamines, bronchodilators, and corticosteroids. However, some systemic drug absorption may occur with drugs used for local activity.

Each route of drug application presents special biopharmaceutical considerations in drug product design. For example, the design of a vaginal tablet formulation for the treatment of a fungal infection must use ingredients compatible with vaginal anatomy and physiology. An eye medication may require special biopharmaceutical considerations, including appropriate pH, isotonicity, sterility, minimization of local irritation to the cornea, draining by tears, and concern for systemic drug absorption.

Explain the term *discriminating dissolution test* and how a discriminating dissolution test relates to drug product quality and drug product performance.

List the USP dissolution apparatus and provide examples of drug products for which the dissolution apparatus might be appropriate.

Define sink conditions and explain why dissolution medium must maintain sink conditions.

Define *in vitro–in vivo correlation* (IVIVC) and explain why a Level A correlation is the most important correlation for IVIVC.

Explain the biopharmaceutic classification system and how solubility, dissolution, and permeation apply to BCS classification.

Provide a method for comparing two dissolution profiles for similarity.

Provide a description of some common oral drug products and explain how biopharmaceutic principles may be used to formulate a product that will extend the duration of activity of the active drug.
For a drug administered by an extravascular route (e.g., intramuscular injection), local irritation, drug dissolution at the application site and drug absorption from the intramuscular site are some of the factors that must be considered. The systemic absorption of a drug from an extravascular site is influenced by the anatomic and physiologic properties of the site and the physicochemical properties of the drug and the drug product. If the drug is given by an intravascular route (e.g., IV administration), systemic drug absorption is considered complete or 100% bioavailable, because the drug is placed directly into the general circulation.

In some cases, a drug product is designed so that it may be used in conjunction with a specialized medical device or packaging component. For example, a drug solution or suspension may be formulated to work with a nebulizer or metered-dose inhaler for administration into the lungs. Both the physical characteristics of the nebulizer and the formulation of the drug product can influence the droplet particles and the spray pattern (plume geometry) that the patient receives upon inhalation of the drug product.

By choosing the route of drug administration carefully and properly designing the drug product, the bioavailability of the active drug can be varied from rapid and complete absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. Once the drug is systemically absorbed, normal physiologic processes for drug distribution and elimination occur. The normal physiologic processes are not usually influenced by the specific formulation of the drug. The rate of drug release from the product and the rate and extent of drug absorption are important in determining the onset, intensity, and duration of drug action.

Biopharmaceutic considerations often determine the ultimate dose and dosage form of a drug product. For example, the dosage for a drug intended for local activity, such as a topical drug product (e.g., ointment), is often expressed in concentration or as percentage of the active drug in the formulation (e.g., 0.5% hydrocortisone ointment). The amount of drug applied is not specified because the concentration of the drug at the active site relates to the pharmacodynamic action. However, biopharmaceutic studies must be performed to ensure that the drug product does not irritate, cause an allergic response, or allow significant systemic drug absorption. In contrast, the dosage of a drug intended for systemic absorption is given on the basis of mass, such as milligrams or grams. In this case, dosage is based on the amount of drug that is absorbed systemically and dissolved in an apparent volume of distribution to produce a desired drug concentration at the target site. The therapeutic dose may be based on the weight or surface area of the patient, to account for the differences in the apparent volume of distribution. Thus, doses are expressed as mass per unit of body weight (mg/kg) or mass per unit of body surface area (mg/m²).

For many commercial drug products, the dose is determined based on average body weights and may be available in several dose strengths, such as 10-mg, 5-mg, and 2.5-mg tablets, to accommodate differences in body weight and possibly to titrate the dose in the patient.

**Frequently Asked Questions**

- How do excipients improve the manufacturing of an oral drug product?
- If excipients do not have pharmacodynamic activity, how do excipients affect the performance of the drug product?

**RATE-LIMITING STEPS IN DRUG ABSORPTION**

Systemic drug absorption from a drug product consists of a succession of rate processes (Fig. 14-1). For solid oral, immediate-release drug products (e.g., tablets, capsules), the rate processes include (1) disintegration of the drug product and subsequent release of the drug, (2) dissolution of the drug in an aqueous environment, and (3) absorption across cell membranes into the systemic circulation. In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence. The slowest step in a series of kinetic processes is called the rate-limiting step. Except for controlled-release products, disintegration of a solid oral drug...
product is usually more rapid than drug dissolution and drug absorption. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid, and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

**Disintegration**

For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug. To monitor uniform tablet disintegration, the *United States Pharmacopeia* (USP) has established an official disintegration test (Fig. 14-2). Solid drug products exempted from disintegration tests include troches, tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.

The process of disintegration does not imply complete dissolution of the tablet and/or the drug. Complete disintegration is defined by the USP-NF as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus in the soft mass have no palpably firm core.” The official apparatus for the disintegration test and procedure is described in the USP-NF. Separate specifications are given for drug products that are designed not to disintegrate. These products include troches, chewable tablets, and modified-release drug products.

Although disintegration tests allow for measurement of the formation of fragments, granules, or aggregates from solid dosage forms, no information is obtained from these tests on the rate of dissolution of the active drug. However, there has been some interest in using only the disintegration test and no dissolution test for drug products that meet the Biopharmaceutical Classification System (BCS) for highly soluble and highly permeable drugs (Chapter 15). In general, the disintegration test serves as a component in the overall quality control of tablet manufacture.

**Dissolution and Solubility**

*Dissolution* is the process by which a solid drug substance becomes dissolved in a solvent. *Solubility* is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25°C).

---

1For certain immediate release, drug products that contain a highly soluble, rapidly dissolving, and highly permeable active drug (BCS1), the rate of disintegration may be the rate-limiting step if the tablet has been compressed too high, producing a very hard tablet.
Solubility is a static property, whereas dissolution is a dynamic property. In biologic systems, drug dissolution in an aqueous medium is an important prior condition for predicting systemic drug absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug. Thus, dissolution tests may be used to predict bioavailability and may be used to discriminate formulation factors that affect drug bioavailability. The dissolution test is required for all US Food and Drug Administration (FDA)-approved solid oral drug products.

Noyes and Whitney (1897) and other investigators studied the rate of dissolution of solid drugs. According to their observations, the steps in dissolution include the process of drug dissolution at the surface of the solid particle, thus forming a saturated solution around the particle. The dissolved drug in the saturated solution, known as the stagnant layer, diffuses to the bulk of the solvent from regions of high drug concentration to regions of low drug concentration (Fig. 14-3).

The overall rate of drug dissolution may be described by the Noyes–Whitney equation (Equation 14.1):

$$\frac{dC}{dt} = \frac{DA}{h} (C_s - C)$$  \hspace{1cm} (14.1)

where $dC/dt$ = rate of drug dissolution at time $t$, $D$ = diffusion rate constant, $A$ = surface area of the particle, $C_s$ = concentration of drug (equal to solubility of drug) in the stagnant layer, $C$ = concentration of drug in the bulk solvent, and $h$ = thickness of the stagnant layer. The rate of dissolution, $dC/dt$, is the rate of drug dissolved per time expressed as concentration change in the dissolution fluid.

The Noyes–Whitney equation shows that dissolution in a flask may be influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. The dissolution of drug in the body, particularly in the gastrointestinal tract, is considered to be dissolving in an aqueous environment. Permeation of drug across the gut wall (a model lipid membrane) is affected by the ability of the drug to diffuse ($D$) and to partition between the lipid membranes. A favorable partition coefficient ($K_{oil/water}$) will facilitate drug absorption (see Chapter 13).

In addition to these factors, the temperature of the medium and the agitation rate also affect the rate of drug dissolution. In vivo, body temperature is maintained at a constant 37°C, and the agitation (primarily peristaltic movements in the gastrointestinal tract) is reasonably constant. In contrast, in vitro studies of dissolution kinetics require maintenance of constant temperature and agitation. Temperature is generally kept at 37°C, and the agitation or stirring rate is held to a specified agitation rate such as 75 rpm (revolutions per minute). An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant, $D$. Moreover, an increase in agitation of the solvent medium will reduce the thickness, $h$, of the stagnant layer, allowing for more rapid drug dissolution.

Factors that affect drug dissolution of a solid oral dosage form include (1) the physical and chemical nature of the active drug substance, (2) the nature of the excipients, (3) the method of manufacture, and (4) the dissolution test conditions.

**Frequently Asked Questions**

- What is meant by the rate-limiting step in drug bioavailability from a solid oral drug product?
- What is the usual rate-limiting step for a poorly soluble and highly permeable drug (BCS2)?
- How could the manufacturing process affect drug product performance?
**PHYSICOCHEMICAL NATURE OF THE DRUG**

In addition to their effect on dissolution kinetics, the physical and chemical properties of the drug substance as well as the excipients are important considerations in the design of a drug product (Table 14-1). For example, intravenous solutions are difficult to prepare with drugs that have poor aqueous solubility. Drugs that are physically or chemically unstable may require special excipients, coatings, or manufacturing processes to protect the drug from degradation. The potent pharmacodynamic activity of drugs, such as estrogens and other hormones, penicillin antibiotics, cancer chemotherapeutic agents, and others, may cause adverse reactions to personnel who are exposed to these drugs during manufacture and also presents a problem.

**Solubility, pH, and Drug Absorption**

The solubility–pH profile is a plot of the solubility of the drug at various physiologic pH values. In designing oral dosage forms, the formulator must consider that the natural pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the small intestine. A basic drug is more soluble in an acidic medium, forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH. The solubility–pH profile gives a rough estimation of the completeness of dissolution for a dose of a drug in the stomach or in the small intestine. Solubility may be improved with the addition of an acidic or basic excipient. Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer. In the formulation of controlled-release drugs, buffering agents may be added to slow or modify the release rate of a fast-dissolving drug. To be effective, however, the controlled-release drug product must be a nondisintegrating dosage form. The buffering agent is released slowly rather than rapidly, so that the drug does not dissolve immediately in the surrounding gastrointestinal fluid.

**Stability, pH, and Drug Absorption**

The stability–pH profile is a plot of the reaction rate constant for drug degradation versus pH. If drug decomposition occurs by acid or base catalysis, some prediction of degradation of the drug in the

<table>
<thead>
<tr>
<th>TABLE 14-1 Physicochemical Properties for Consideration in Drug Product Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ and pH profile</td>
</tr>
<tr>
<td>Particle size</td>
</tr>
<tr>
<td>Polymorphism</td>
</tr>
<tr>
<td>Hygroscopicity</td>
</tr>
<tr>
<td>Partition coefficient</td>
</tr>
<tr>
<td>Excipient interaction</td>
</tr>
<tr>
<td>pH stability profile</td>
</tr>
<tr>
<td>Impurity profile</td>
</tr>
<tr>
<td>Chirality</td>
</tr>
</tbody>
</table>
gastrointestinal tract may be made. For example, erythromycin has a pH-dependent stability profile. In an acidic medium, as in the stomach, erythromycin decomposition occurs rapidly, whereas in neutral or alkaline pH, the drug is relatively stable. Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach. This information also led subsequently to the preparation of a less water-soluble erythromycin salt that is more stable in the stomach. The dissolution rate of erythromycin powder varied from 100% dissolved in 1 hour to less than 40% dissolved in 1 hour. The slow-dissolving raw drug material (active pharmaceutical ingredient) also resulted in slow-dissolving drug products. Therefore, the dissolution of powdered raw drug material is a very useful in vitro method for predicting bioavailability problems of the erythromycin product in the body.

**Particle Size and Drug Absorption**

The effective surface area of a drug is increased enormously by a reduction in the particle size. Because dissolution takes place at the surface of the solute (drug), the greater the surface area, the more rapid the rate of drug dissolution. The geometric shape of the particle also affects the surface area, and, during dissolution, the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Many drugs are very active intravenously but are not very effective when given orally, because of poor oral absorption. Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size by milling to a micronized form has improved the oral absorption of these drugs. Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rate. For poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles. The addition of surface-active agents may increase wetting as well as solubility of these drugs.

**Polymorphism, Solvates, and Drug Absorption**

Polymorphism refers to the arrangement of a drug substance in various crystal forms or polymorphs. In recent years the term polymorph has been used frequently to describe polymorphs, solvates, amorphous forms, and desolvated solvates. Amorphous forms are noncrystalline forms, solvates are forms that contain a solvent (solvate) or water (hydrate), and desolvated solvates are forms that are made by removing the solvent from the solvate. Many drugs exist in an anhydrous state (no water of hydration) or in a hydrous state.

Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics. Some polymorphic crystals have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed. Chloramphenicol, for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be dependent on the percent of β-polymorph in the suspension. The β form is more soluble and better absorbed (Fig. 14-4). In general, the crystal form that has the lowest free energy is the most stable polymorph. A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more...
drug, stabilize the drug against degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc. Some of the excipients used in the manufacture of solid and liquid drug products are listed in Tables 14.2 and 14.3.

Excipients in the drug product may also affect the dissolution kinetics of the drug, either by altering the medium in which the drug is dissolving or by reacting with the drug itself. Some of the more common manufacturing problems that affect dissolution are listed in Table 14-4. Other excipients include suspending agents that increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions. Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities. Coatings,

structurally rigid crystalline form. Some polymorphs are metastable and may convert to a more stable form over time. A change in crystal form may cause problems in manufacturing the product. For example, a change in the crystal structure of the drug may cause cracking in a tablet or even prevent a granulation from being compressed into a tablet. Re-formulation of a product may be necessary if a new crystal form of a drug is used. Some drugs interact with solvent during preparation to form a crystal called a solvate. Water may form special crystals with drugs called hydrates; for example, erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug (Fig. 14-5). Ampicillin trihydrate, on the other hand, was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter.

**FORMULATION FACTORS AFFECTING DRUG PRODUCT PERFORMANCE**

Excipients are added to a formulation to provide certain functional properties to the drug and dosage form; excipients also affect drug product performance, in vivo (Amidon et al, 2007; Chapter 16). Some of these functional properties of the excipients are used to improve the compressibility of the active

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**TABLE 14-2 Common Excipients Used in Solid Drug Products**

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Property in Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Diluent</td>
</tr>
<tr>
<td>Dibasic calcium phosphate</td>
<td>Diluent</td>
</tr>
<tr>
<td>Starch</td>
<td>Disintegrant, diluent</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Disintegrant, diluent</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Hydrogenated vegetable oil</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Talc</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Sucrose (solution)</td>
<td>Granulating agent</td>
</tr>
<tr>
<td>Polyvinyl pyrrolidone (solution)</td>
<td>Granulating agent</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose</td>
<td>Tablet-coating agent</td>
</tr>
<tr>
<td>Titinium dioxide</td>
<td>Combined with dye as colored coating</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>Coating or granulating agent</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>Enteric-coating agent</td>
</tr>
</tbody>
</table>
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

369

to form micelles with the drug and thus decrease the dissolution rate. Large drug particles have a smaller surface area and dissolve more slowly than smaller particles. Poor disintegration of a compressed tablet may be due to high compression of tablets without sufficient disintegrant.

Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance. Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves. The term for this process is dissolution in a reactive medium. The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. However, as the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. These small particles have enormous collective surface area, dispersing and redissolving readily for more rapid absorption upon contact with the mucosal surface.

Excipients in a formulation may interact directly with the drug to form a water-soluble or water-insoluble complex. For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Excipients may be added intentionally to the formulation to enhance the rate and extent of drug absorption or to delay or slow the rate of drug absorption particularly shellac, will crosslink upon aging and decrease the dissolution rate. However, surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactants concentrations tend

### TABLE 14-3 Common Excipients Used in Oral Liquid Drug Products

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Property in Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium carboxymethyl cellulose</td>
<td>Suspending agent</td>
</tr>
<tr>
<td>Tragacanth</td>
<td>Suspending agent</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Suspending agent</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Thixotropic suspending agent</td>
</tr>
<tr>
<td>Veegum</td>
<td>Thixotropic suspending agent</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Sweetener</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Solubilizing agent, preservative</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Solubilizing agent</td>
</tr>
<tr>
<td>Methyl, propylparaben</td>
<td>Preservative</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Sweetener</td>
</tr>
<tr>
<td>Polysorbates</td>
<td>Surfactant</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>For emulsion vehicle</td>
</tr>
<tr>
<td>Corn oil</td>
<td>For emulsion vehicle</td>
</tr>
</tbody>
</table>

### TABLE 14-4 Effect of Excipients on the Pharmacokinetic Parameters of Oral Drug Products

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Example</th>
<th>$k_a$</th>
<th>$t_{\text{max}}$</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disintegrants</td>
<td>Avicel, Explotab</td>
<td>↑</td>
<td>↓</td>
<td>↑/-</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Talc, hydrogenated vegetable oil</td>
<td>↓</td>
<td>↑</td>
<td>↓/-</td>
</tr>
<tr>
<td>Coating agent</td>
<td>Hydroxypropylmethyl cellulose</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Enteric coat</td>
<td>Cellulose acetate phthalate</td>
<td>↓</td>
<td>↑</td>
<td>↓/-</td>
</tr>
<tr>
<td>Sustained-release agents</td>
<td>Methylcellulose, ethylcellulose</td>
<td>↓</td>
<td>↑</td>
<td>↓/-</td>
</tr>
<tr>
<td>Sustained-release agents (waxy agents)</td>
<td>Castorwax, Carbowax</td>
<td>↓</td>
<td>↑</td>
<td>↓/-</td>
</tr>
<tr>
<td>Sustained-release agents (gum/viscous)</td>
<td>Veegum, Keltrol</td>
<td>↓</td>
<td>↑</td>
<td>↓/-</td>
</tr>
</tbody>
</table>

*This may be concentration and drug dependent. ↑ = increase, ↓ = decrease, = no effect, $k_a$ = absorption rate constant, $t_{\text{max}}$ = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration–time curve.
(see Table 14-4). For example, excipients that increase the aqueous solubility of the drug generally increase the rate of dissolution and drug absorption. Excipients may increase the retention time of the drug in the gastrointestinal tract and therefore increase the total amount of drug absorbed. Excipients may act as carriers to increase drug diffusion across the intestinal wall. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.

Common excipients found in oral drug products are listed in Tables 14.2 and 14.3. Excipients should be pharmacodynamically inert. However, excipients may change the functionality (performance) of the drug substance and the bioavailability of the drug from the dosage form. For solid oral dosage forms such as compressed tablets, excipients may include (1) a diluent (eg, lactose), (2) a disintegrant (eg, starch), (3) a lubricant (eg, magnesium stearate), and (4) other components such as binding and stabilizing agents. If used improperly in a formulation, the rate and extent of drug absorption may be affected. For example, Fig. 14-6 shows that an excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption. The total amount of drug absorbed may also be reduced (Fig. 14-7). To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution. However, with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted. The influence of some common ingredients on drug absorption parameters is summarized in Table 14-4. These are general trends for typical preparations.

**DRUG PRODUCT PERFORMANCE, IN VITRO: DISSOLUTION AND DRUG RELEASE TESTING**

Dissolution and drug release tests are *in vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions. *In vitro* dissolution testing provides useful information throughout the drug development process (Table 14-5).

The dissolution test is an important quality control procedure used to confirm batch-to-batch reproducibility and to show typical variability in composition and manufacturing parameters. Dissolution and drug release tests are used as a measure of drug product performance, *in vitro* when linked to product performance *in vivo*. The dissolution test should reflect relevant changes in the drug product formulation or
changes in the manufacturing process that might affect drug product performance in vivo. Ideally, the dissolution method used for a particular drug product in vitro relates to the bioavailability of the drug in vivo (see in vitro–in vivo correlation, IVIVC later in this chapter).

In vitro drug dissolution studies are often used for monitoring drug product stability and manufacturing process control. In this case, the dissolution test provides evidence that the product will perform consistently throughout its use period or shelflife.

The dissolution test is a valuable tool in formulation development. A variety of dissolution tests using various media and different pH conditions are used during formulation development. A suitable dissolution method may uncover a formulation problem with the drug product that could result in a bioavailability problem. Each dissolution method is specific for the drug product and its formulation. The dissolution test should be able to distinguish between acceptable and unacceptable drug formulations as observed by different drug dissolution rates under the same experimental conditions. A suitable dissolution test should be able to reflect changes in the formulation, manufacturing process, and physical and chemical characteristics of the drug, such as particle size, polymorphs, and surface area (Gray et al, 2001). The dissolution test is a major requirement for scale-up and postapproval changes, SUPAC (see Chapter 16). After a change is made in a formulation, the manufacturer should assess the potential effect of the change on bioequivalence, which usually includes multipoint and/or multimedia dissolution profiling. If necessary, an in vivo bioequivalence study is performed to validate the dissolution test (see Chapter 15).

Discriminating Dissolution Test
The dissolution test procedure should be discriminating, capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. If the dissolution test is too discriminating, the dissolution test procedure may show differences between batches when no significant bioavailability difference is observed in vivo. If the test has insufficient discrimination, then significant changes in formulation composition and/or manufacturing process that might affect in vivo performance will not be observed. The dissolution test needs careful evaluation as to whether the procedure is too sensitive or is appropriately discriminating.

Development and Validation of Dissolution and Drug Release Tests
The USP dissolution test is an in vitro performance test applicable to many dosage forms such as tablets, capsules, transdermals, suppositories, suspensions, etc. The development and validation of dissolution tests is discussed in a USP general information chapter. The dissolution procedure requires a dissolution apparatus, dissolution medium, and test conditions that provide a method that is discriminating yet sufficiently rugged and reproducible for day-to-day operation and capable of being transferred between laboratories.

The choice of apparatus and dissolution medium are based on the physico-chemical characteristics of the active drug (including solubility, stability) and the type of dosage form (such as immediate release, enteric coated, extended release, orally dissolving tablet, etc).

The development of an appropriate dissolution test requires the investigator to try different agitation rates, different media (including volume and pH of medium), and different kinds of dissolution apparatus (Table 14-6). For solid oral dosage forms, USP Apparatus 1 and Apparatus 2 are used most frequently. The dissolution test conditions should be
day-to-day operation and capable of being transferred between laboratories. The current USP-NF lists officially recognized dissolution apparatus (Table 14-7). Once a suitable dissolution test is obtained, acceptable dissolution criteria (specifications) are developed for the drug product, its formulation, and manufacturing process. Dissolution specifications (eg, percent of drug dissolved in 30 minutes) are used to investigate formulation problems that might affect drug product performance, \textit{in vivo}. For example, Philip and Daly (1983) devised a method using pH 6.6 phosphate buffer as the dissolution medium instead of 0.1 N HCL to avoid instability of the antibiotic drug erythromycin. Using the USP paddle method at 50 rpm and a temperature of 22°C, the dissolution of the various erythromycin tablets was shown to vary with the source of the bulk active drug (Table 14-8 and Fig. 14-8).

Visual observations of the dissolution and disintegration behavior of the drug product are important and should be recorded. Dissolution and disintegration patterns can indicate manufacturing variables. These observations are particularly useful during dissolution method development and formulation optimization.

The size and shape of the dissolution vessel may affect the rate and extent of dissolution. For

<table>
<thead>
<tr>
<th>TABLE 14-6</th>
<th>Conditions That May Affect Drug Dissolution and Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug substance</td>
<td>Particle size</td>
</tr>
<tr>
<td>Formulation of drug product</td>
<td>Surface area</td>
</tr>
<tr>
<td>Medium</td>
<td>Volume</td>
</tr>
<tr>
<td>Medium</td>
<td>Molarity</td>
</tr>
<tr>
<td>Temperature of medium</td>
<td>Apparatus</td>
</tr>
<tr>
<td>Apparatus</td>
<td>Agitation rate</td>
</tr>
<tr>
<td>Apparatus</td>
<td>Placement of tablet in vessel</td>
</tr>
</tbody>
</table>

TABLE 14-7 USP-NF and Non-USP-NF Dissolution Apparatus

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Name</th>
<th>Agitation Method</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus 1</td>
<td>Rotating basket</td>
<td>Rotating stirrer</td>
<td>Tablets, capsules</td>
</tr>
<tr>
<td>Apparatus 2</td>
<td>Paddle</td>
<td>Rotating stirrer</td>
<td>Tablets, capsules, modified drug products, suspensions</td>
</tr>
<tr>
<td>Apparatus 3</td>
<td>Reciprocating cylinder</td>
<td>Reciprocation</td>
<td>Extended-release drug products</td>
</tr>
<tr>
<td>Apparatus 4</td>
<td>Flow cell</td>
<td>Fluid movement</td>
<td>Drug products containing low-water-soluble drugs</td>
</tr>
<tr>
<td>Apparatus 5</td>
<td>Paddle over disk</td>
<td>Rotating stirrer</td>
<td>Transdermal drug products</td>
</tr>
<tr>
<td>Apparatus 6</td>
<td>Cylinder</td>
<td>Rotating stirrer</td>
<td>Transdermal drug products</td>
</tr>
<tr>
<td>Apparatus 7</td>
<td>Reciprocating disk</td>
<td>Reciprocation</td>
<td>Extended-release drug products</td>
</tr>
<tr>
<td>Rotating bottle (Non-USP-NF)</td>
<td></td>
<td>Rotating stirrer</td>
<td>Transdermal drug products</td>
</tr>
<tr>
<td>Diffusion cell (Franz) (Non-USP-NF)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aUSP-NF dissolution apparatus and Non-USP-NF dissolution apparatus.*
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

373
dissolution. In some cases, 1% sodium lauryl sulfate (SLS) may be used as the dissolution medium for water-insoluble drugs. Sink conditions is a term referring to an excess volume of medium that allows the solid drug to dissolve continuously. If the drug solution becomes saturated, no further net drug dissolution will take place. According to the USP-NF, “the quantity of medium used should not be less than 3 times that required to form a saturated solution of the drug substance.”

The amount of agitation and the nature of the stirrer affect hydrodynamics of the system, thereby affecting the dissolution rate. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50–75 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. However, a higher dissolution rate may be needed for some special formulations in order to obtain reproducible dissolution rates. Suspensions that contain viscous or thickening agents may settle into a diffusion-controlled “cone-shape” region in the flask when stirring rate is too slow. The temperature of the dissolution medium must be controlled, and variations in temperature must be avoided. Most dissolution tests are performed at 37°C. However, for transdermal drug products, the recommended temperature is 32°C.

The nature of the dissolution medium will also affect the dissolution test. The solubility of the drug must be considered, as well as the total amount of drug in the dosage form. The dissolution medium should not be saturated by the drug (ie, sink conditions are maintained). Usually, a volume of medium larger than the amount of solvent needed to completely dissolve the drug is used in the dissolution test. Which medium is best is a matter of considerable controversy. The dissolution medium in many USP dissolution tests is deaerated water or, if substantiated by the solubility characteristics of the drug or formulation, a buffered aqueous solution (typically pH 4–8) or dilute HCl may be used. The significance of deaeration of the medium should be determined. Various investigators have used 0.1 N HCl, phosphate buffer, simulated gastric juice, water, and simulated intestinal juice, depending on the nature of the drug product and the location in the gastrointestinal tract where the drug is expected to dissolve.

### TABLE 14-8 Dissolution of Erythromycin Stearate Bulk Drug and Corresponding Tablets

<table>
<thead>
<tr>
<th>Curve No.</th>
<th>Bulk Drug</th>
<th>500-mg Tablet</th>
<th>250-mg Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>49</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>78</td>
<td>–</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>92</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

From Philip and Daly (1983), with permission.

![Figure 14-8](example-image.png)

**FIGURE 14-8** Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M, pH 6.6 phosphate buffer). (From Philip and Daly, 1983, with permission.)
The design of the dissolution apparatus, along with the factors described, has a marked effect on the outcome of the dissolution test. No single apparatus and test can be used for all drug products. Each drug product must be tested individually with the dissolution test that best correlates to in vivo bioavailability.

Usually, the dissolution test will state that a certain percentage of the labeled amount of drug product must dissolve within a specified period of time. In practice, the absolute amount of drug in the drug product may vary from tablet to tablet. Therefore, a prescribed number of tablets from each lot are usually tested to get a representative dissolution rate for the product.

**Frequently Asked Questions**

- Drug absorption involves at least three distinct steps: dissolution, permeation, and disposition during transit in GI (an additional step of drug disposition in the body is involved as well for bioavailability). How are these processes validated in vitro when the in vivo requirement for drug bioavailability is waived?
- What are the risk mitigating steps taken above if some manufacturing processes cannot be validated in vitro?

**COMPELLID METHODS OF DISSOLUTION**

The USP-NF describes the official dissolution apparatus and includes information for performing dissolution tests on a variety of drug products including tablets, capsules, and other special products such as transdermal preparations. The selection of a particular dissolution method for a drug may be specified in the USP-NF monograph for a particular drug product or may be recommended by the FDA. The USP-NF sets standards for dissolution and drug release tests of most drug products listed in USP monographs. Alternative dissolution methods, particularly the use of comparative dissolution rate profiles under various conditions are often used during drug development to better understand the relationship of the formulation components and manufacturing process on drug release.

The USP dissolution apparatus and the type of drug products that is often used with the apparatus are listed in Table 14-7. For USP Apparatus 1 (basket) and 2 (paddle), low rotational speeds affect the reproducibility of the hydrodynamics, whereas at high rotational speeds, turbulence may occur. Dissolution profiles that show the drug dissolving too slowly or too rapidly may justify increasing or decreasing the rotational speed (Gray et al, 2001). The choice of apparatus for solid oral dosage forms is often Apparatus 1 (rotating basket) or Apparatus 2 (paddle) due to the ease of use, availability of the apparatus, and availability of automated methods.

**Apparatus 1: Rotating Basket**

The rotating basket apparatus (Apparatus 1) consists of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant-temperature bath set at 37°C. Agitation is provided by rotating the basket. The rotating speed and the position of the basket must meet specific requirements set forth in the current USP. The most common operating speeds for Apparatus 1 are 50 to 100 rpm. A disadvantage of the rotating basket is that the formulation may clog to 40-mesh screen.

**Apparatus 2: Paddle Method**

The paddle apparatus (Apparatus 2) consists of a special, coated paddle that minimizes turbulence due to stirring (Fig. 14-9). The paddle is attached vertically to a variable-speed motor that rotates at a controlled speed. The tablet or capsule is placed into the round-bottom dissolution flask, which minimizes turbulence of the dissolution medium. The apparatus is housed in a constant-temperature water bath maintained at 37°C, similar to the rotating-basket method. The position and alignment of the paddle are specified in the USP. The paddle method is very sensitive to tilting. Improper alignment may drastically affect the dissolution results with some drug products. The most common operating speeds for Apparatus 2 are 50 rpm for

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solid oral dosage forms. Apparatus 2 is generally preferred for tablets. A *sinker*, such as a few turns of platinum wire, may be used to prevent a capsule or tablet from floating. A sinker may also be used for film-coated tablets that stick to the vessel walls or to help position the tablet or capsule under the paddle (Gray et al, 2001). The sinker should not alter the dissolution characteristics of the dosage form.

**Apparatus 3: Reciprocating Cylinder**

The reciprocating cylinder apparatus (Apparatus 3) consists of a set of cylindrical, flat-bottomed glass vessels equipped with reciprocating cylinders for dissolution testing of extended-release products, particularly bead-type modified-release dosage forms. Reciprocating agitation moves the dosage form up and down in the media. The agitation rate is generally 5 to 30 dpm (dips per minute). The reciprocating cylinder can be programmed for dissolution in various media for various times. The media can be changed easily. This apparatus may be used during drug product development to attempt to mirror pH changes and transit times in the GI tract such as starting at pH 1 and then pH 4.5 and then at pH 6.8.
Chapter 14

Apparatus 4: Flow-through-Cell
The flow-through-cell apparatus (Apparatus 4) consists of a reservoir for the dissolution medium and a pump that forces dissolution medium through the cell holding the test sample. The media may be a non-recirculating, continuous flow solution, or a recirculating solution. The flow rate is critical. Flow rate ranges from 4 to 32 mL/min. Apparatus 4 may be used for modified-release dosage forms that contain active ingredients having very limited solubility. The high volume provides “infinite” sink conditions.

There are many variations of this method. Essentially, the sample is held in a fixed position while the dissolution medium is pumped through the sample holder, thus dissolving the drug. Laminar flow of the medium is achieved by using a pulseless pump. Peristaltic or centrifugal pumps are not recommended. The flow rate is usually maintained between 10 and 100 mL/min. The dissolution medium may be fresh or recirculated. In the case of fresh medium, the dissolution rate at any moment may be obtained, whereas in the official paddle or basket method, cumulative dissolution rates are monitored. A major advantage of the flow-through method is the easy maintenance of a sink condition for dissolution. A large volume of dissolution medium may also be used, and the mode of operation is easily adapted to automated equipment.

Apparatus 5: Paddle-over-Disk
The USP-NF also lists a paddle-over-disk method for testing the release of drugs from transdermal products. The apparatus (Apparatus 5) uses the paddle and vessel assembly from Apparatus 2 with the addition of a stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel. The entire preparation is placed in a dissolution flask filled with specified medium maintained at 32°C. The paddle is placed directly over the disk assembly. Samples are drawn midway between the surface of the dissolution medium and the top of the paddle blade at specified times. Matrix transdermal patches can be cut to size of the disk assembly.

Apparatus 6: Cylinder
The cylinder method (Apparatus 6) for testing transdermal preparation is modified from the basket method (Apparatus 1). In place of the basket, a stainless steel cylinder is used to hold the sample. The sample is mounted onto cuprophan (an inert porous cellulosic material) and the entire system adheres to the cylinder. Testing is maintained at 32°C. Apparatus 6 may be used for reservoir transdermal patches that cannot be cut smaller. Samples are drawn midway between the surface of the dissolution medium and the top of the rotating cylinder for analysis.

Apparatus 7: Reciprocating Disk
The reciprocating disk method for testing transdermal products uses a motor drive assembly (Apparatus 7) that reciprocates vertically. The samples are placed on disk-shaped holders using cuprophan supports. The test is also carried out at 32°C, and reciprocating frequency is about 30 cycles per minute.

ALTERNATIVE METHODS OF DISSOLUTION TESTING

Rotating Bottle Method
The rotating bottle method was suggested in NF-XIII (National Formulary) but has become less popular since. The rotating bottle method was used mainly for controlled-release beads. For this purpose the dissolution medium may be easily changed, such as from artificial gastric juice to artificial intestinal juice. The equipment consists of a rotating rack that holds the sample drug products in bottles. The bottles are capped tightly and rotated in a 37°C temperature bath. At various times, the samples are removed from the bottle, decanted through a 40-mesh screen, and the residues are assayed. An equal volume of fresh medium is added to the remaining drug residues within the bottles and the dissolution test is continued. A dissolution test with pH 1.2 medium for 1 hour, pH 2.5 medium for the next 1 hour, followed by pH 4.5 medium for 1.5 hours, pH 7.0 medium for 1.5 hours, and pH 7.5 medium for 2 hours was recommended to simulate condition of the gastrointestinal tract. The main disadvantage is that this procedure is manual and tedious. Moreover, it is not known if the rotating bottle procedure results in a better in vitro–in vivo correlation (see later) for drugs.
Intrinsic Dissolution Method

Most methods for dissolution deal with a finished drug product. Sometimes a new drug or substance may be tested for dissolution without the effect of excipients or the fabrication effect of processing. The dissolution of a drug powder by maintaining a constant surface area is called intrinsic dissolution. Intrinsic dissolution is usually expressed as mg/cm²/min. In one method, the basket method is adapted to test dissolution of powder by placing the powder in a disk attached with a clipper to the bottom of the basket.

Peristalsis Method

The peristalsis method attempts to simulate the hydrodynamic conditions of the gastrointestinal tract in an in vitro dissolution device. The apparatus consists of a rigid plastic cylindrical tubing fitted with a septum and rubber stoppers at both ends. The dissolution chamber consists of a space between the septum and the lower stopper. The apparatus is placed in a beaker containing the dissolution medium. The dissolution medium is pumped with peristaltic action through the dosage form.

Diffusion Cells

Static and flow-through diffusion cells are commercially available to characterize in vitro drug release and drug permeation kinetics from a topical drug product (eg, ointment, cream) or transdermal drug product. The Franz diffusion cell is a static diffusion system that is used for characterizing drug permeation through a skin model (Fig. 14-10). The source of skin may be human cadaver skin or animal skin (eg, hairless mouse skin). Anatomically, each skin site (eg, abdomen, arm) has different drug permeation qualities. The skin is mounted on the Franz diffusion cell system. The drug product (eg, ointment) is placed on the skin surface and the drug permeates across the skin into a receptor fluid compartment that may be sampled at various times. The Franz diffusion cell system is useful for comparing in vitro drug release profiles and skin permeation characteristics to aid in selecting an appropriate formulation that has optimum drug delivery.

Dissolution Testing of Enteric-Coated Products

USP-NF lists two methods (Method A and Method B) for testing enteric-coated products. The latest revision of the USP-NF should be consulted for complete details of the methods.

Both methods require that the dissolution test be performed in the apparatus specified in the drug monograph (usually Apparatus 2 or Apparatus 1). The product is first tested with 0.1 N HCl for 2 hours and then the medium is changed to pH 6.8 buffer medium. The buffer stage generally runs for 45 minutes or for the time specified in the monograph. The objective is that no significant dissolution occurs in the acid phase (less than 10% for any sample unit), and a specified percentage of drug must be released in the buffer phase. Specifications are set in the individual drug monographs.

Dissolution Approaches for Novel/Special Dosage Forms

New dosage forms are being developed for improving patient compliance, to enhance therapeutic response and for marketing exclusivity. These products include oral suspensions, orally disintegrating tablets, medicated chewing gums, soft gelatin capsules containing drug dissolved in oil, nanoparticle and liposomal drug products, drug eluting stents, and others. Drug release test for some of these products can use conventional dissolution apparatus. Drug release tests for some of these drug products such as medicated chewing gum
and extended-release parenteral products need a specialized dissolution apparatus or a modified dissolution apparatus (Siewart et al, 2003).

**USP Performance Verification Test, and Mechanical Calibration**

Dissolution is a complex system that is mainly comprised of three components: (1) the analyst, (2) the dissolution apparatus, and (3) the analytical procedure/instrument. In order for the dissolution test to be performed properly, and give meaningful results, these three components must interact together optimally or the results can be misleading. The USP performance verification test (PVT) qualifies the instrument and analyst to perform dissolution testing. PVT requires chemical calibration with calibrator tablets that may be obtained from USP-NF. The calibration tablets, either prednisone tablets for dissolution tests requiring disintegrating tablets or salicylic acid as a standard for nondisintegrating tablets, are used to qualify USP dissolution Apparatus 1 and Apparatus 2. PVT is also useful to compare performance of different dissolution apparatus used in different laboratories.

Mechanical calibration is a critical component of the qualification of the dissolution apparatus. The FDA has introduced a mechanical calibration approach that considers mechanical specifications of the instrument design and its manufacture (FDA Guidance, January 2010). Instead of using a calibrator tablet, a pharmaceutical manufacturer can use an appropriately rigorous method of mechanical calibration for dissolution Apparatus 1 and 2.

**Frequently Asked Questions**

- Which dissolution apparatus are most often used for tablets and capsules?
- What is meant by “sink” conditions?
- Can a dissolution test be too discriminating?

**MEETING DISSOLUTION REQUIREMENTS**

Dissolution test times and specifications are usually established on the basis of an evaluation of dissolution profile data. The dissolution test time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve. USP-NF sets dissolution requirements for many products (Table 14-9). The requirements apply to both the basket and the paddle methods. The amount of drug dissolved within a given time period ($Q$) is expressed as a percentage of label content.

<p>| TABLE 14-9 Theophylline Extended-Release Capsules, USP |</p>
<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test 1</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Between 10% and 30%</td>
</tr>
<tr>
<td>2</td>
<td>Between 30% and 55%</td>
</tr>
<tr>
<td>4</td>
<td>Between 55% and 80%</td>
</tr>
<tr>
<td>8</td>
<td>Not less than 80%</td>
</tr>
<tr>
<td><strong>Test 2</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Between 3% and 15%</td>
</tr>
<tr>
<td>2</td>
<td>Between 20% and 40%</td>
</tr>
<tr>
<td>4</td>
<td>Between 50% and 75%</td>
</tr>
<tr>
<td>6</td>
<td>Between 65% and 100%</td>
</tr>
<tr>
<td>8</td>
<td>Not less than 80%</td>
</tr>
</tbody>
</table>

Both of these theophylline ER capsule products are for products labeled for dosing every 12 h. These products are bioequivalent in vivo and are approved by FDA as therapeutic equivalents.

For many products the passing value for $Q$ is set at 75% in 45 minutes. Some products require a $Q$ of 85% in 30 minutes, others 75% in 60 minutes. For a new drug product, setting the dissolution specification requires a thorough consideration of the physical and chemical properties of the drug. In addition to the consideration that the dissolution test must...
clog up the basket screen and create a local nonsink condition for dissolution. Furthermore, dissolved gas in the medium may form air bubbles on the surface of the dosage form unit and can affect dissolution in both the basket and paddle methods.

The interpretation of dissolution data is probably the most difficult job for the pharmacist. In the absence of in vivo data, it is generally impossible to make valid conclusions about bioavailability from the dissolution data alone. The use of various testing methods makes it even more difficult to interpret dissolution results, because there is no simple correlation among dissolution results obtained with various methods. For many drug products, the dissolution rates are higher with the paddle method. Dissolution results at 50 rpm with the paddle method may be equivalent to dissolution at 100 rpm with the basket method. In a study of sustained-release theophylline tablets compressed at various degrees of hardness, Cameron et al (1983) found that, at 50 rpm, dissolution with the paddle method was faster than that of the basket method for tablets of 4.0-kg hardness. However, with tablets of 6.8-kg hardness, similar dissolution profiles were obtained at 125 rpm for the basket and paddle methods over a period of 6 hours. With both methods, increased dissolution rates were observed as the rates were increased. Apparently, the composition of the formulation as well as the process variables in manufacturing may both be important. No simple correlation can be made for dissolution results obtained with different methods.

In a comparison of the paddle and basket methods in evaluating a sustained-release pseudoephedrine–guaifenesin preparation, Masih et al (1983) found that the paddle method was more discriminating in demonstrating dissolution differences among drug products. At 100 rpm, the basket method failed to pick up formulation differences detected by the paddle method. In the absence of in vivo data, the selection of the dissolution method is based on the type of drug product to be tested. For example, a low-density preparation may be poorly wetted in the basket method. A gummy preparation may clog the basket screen; therefore the paddle method is preferred. A floating dosage form (eg, suppository) may be placed in a stainless steel coil (sinker) so that the dosage form remains at the bottom of the dissolution

<table>
<thead>
<tr>
<th>TABLE 14-10 Dissolution Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>$S_1$</td>
</tr>
<tr>
<td>$S_2$</td>
</tr>
<tr>
<td>$S_3$</td>
</tr>
</tbody>
</table>

Adapted with permission from United States Pharmacopeia.
flask. For many drugs, a satisfactory dissolution test may be obtained with more than one method by optimizing the testing conditions.

**PERFORMANCE OF DRUG PRODUCTS: IN VITRO–IN VIVO CORRELATION**

An important goal during the development of a new drug product is to find a relationship between an in vitro characteristic of the dosage form and its in vivo performance. An in vitro–in vivo correlation (IVIVC) establishes a relationship between a biological property of the drug (such as pharmacodynamic effect or plasma drug concentration) and a physicochemical property of the drug product containing the drug substance, such as dissolution rate (Leeson, 2002, USP Chapter <1088>). To establish IVIVC, some property of the drug release from the drug product in vitro, under specified conditions, must relate to in vivo drug performance. The ability to predict, accurately and precisely, the expected bioavailability characteristics of a drug from a drug product using a dissolution profile characteristics is highly desirable and would eliminate the need to perform additional clinical testing.

The biological properties most commonly used are one or more pharmacokinetic parameters obtained following the administration of the dosage form are the plasma drug concentration profile, AUC, or $C_{\text{max}}$. The physicochemical property most commonly used to estimate drug product performance is its in vitro dissolution behavior expressed as the percent of drug released under a given set of conditions. The relationship between the two properties, biological and physicochemical, is then expressed quantitatively.

A successful IVIVC can assist in the selection of appropriate dissolution acceptance criteria and reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

**Categories of In Vitro–In Vivo Correlations**

**Level A Correlation**

Level A correlation is the highest level of correlation and represents a point-to-point (1:1) relationship between an in vitro dissolution and the in vivo input rate of the drug from the dosage form. Level A correlation compares the percent (%) drug released versus percent (%) drug absorbed. Generally, the percentage of drug absorbed may be calculated by the Wagner–Nelson or Loo–Riegelman procedures (see Chapter 7) or by direct mathematical deconvolution, a process of mathematical resolution of blood level into an input (absorption) and an output (disposition) component (Fig. 14-11). The IVIVC relationship should be demonstrated with two or more formulations with different release rates to result in corresponding differences in absorption profiles. Although an IVIVC can be defined with a minimum of two formulations with different release rates, three or more formulations with different release rates are recommended.

The major advantage of a Level A correlation is that a point-to-point correlation is developed. All in vitro dissolution data and all in vivo plasma drug concentration–time profile data are used. Once a Level A correlation is established, an in vitro dissolution curve can serve as a surrogate for in vivo performance. A change in manufacturing site, method of manufacture, raw material supplies, minor formulation modification, and even product strength using the same formulation can be justified without the need for additional human studies. Level A correlation provides a meaningful in vitro quality control procedure which can predict in vivo drug product performance.

**Level B Correlation**

Level B correlation utilizes the principle of statistical moment (see Chapter 22) in which the mean in vitro characteristic is compared to either the mean residence time (MRT)$^3$ or the mean in vivo dissolution time (MDT). Level B correlation uses all of the in vitro and in vivo data, but is not a point-to-point correlation. Different profiles can give the same parameter values. The Level B correlation alone cannot justify formulation modification, manufacturing site change, excipient source change, batch-to-batch quality, etc.

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$^3$MRT is the mean (average) time that the drug molecules stay in the body, whereas the MDT is the mean time for drug dissolution.
The absorption time refers to the time for a constant amount of drug to be absorbed. In one study involving three sustained-release aspirin products (Levy et al, 1965), the dissolution times for the preparations were linearly correlated to the absorption times (Fig. 14-12). The results from this study demonstrated that aspirin was rapidly absorbed and was very much dependent on the dissolution rate for absorption.

**Level C Correlation**

A level C correlation is not a statistical correlation. Level C correlation establishes a single-point relationship between a dissolution parameter, such as percent dissolved in a given time and a pharmacokinetic parameter such as AUC and $C_{\text{max}}$. Level C correlation is useful in formulation selection and development but not for regulatory purposes. *Multiple Level C correlation* relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile. Several examples of Level C correlation are given below.

**Dissolution rate versus absorption rate.** If dissolution of the drug is rate limiting, a faster dissolution rate may result in a faster rate of appearance of the drug in the plasma. It may be possible to establish a correlation between rate of dissolution and rate of absorption of the drug.

The absorption rate is usually more difficult to determine than peak absorption time. Therefore, the absorption time may be used in correlating dissolution data to absorption data. In the analysis of *in vitro—in vivo* drug correlation, rapid drug dissolution may be distinguished from the slower drug absorption by observation of the absorption time for the preparation.
Percent of drug dissolved versus percent of drug absorbed. If a drug is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percentage of drug absorbed to the percentage of drug dissolved. In choosing the dissolution method, one must consider the appropriate dissolution medium and use a slow dissolution stirring rate so that \textit{in vivo} dissolution is approximated.

Aspirin is absorbed rapidly, and a slight change in formulation may be reflected in a change in the amount and rate of drug absorption during the period of observation (see Figs. 14-12 and 14-13). If the drug is absorbed slowly, which occurs when absorption is the rate-limiting step, a difference in dissolution rate of the product may not be observed. In this case, the drug would be absorbed very slowly independent of the dissolution rate.

Maximum plasma concentrations versus percent of drug dissolved \textit{in vitro}. When different drug formulations are tested for dissolution, a poorly formulated drug may not be completely dissolved and released, resulting in lower plasma drug concentrations. The percentage of drug released at any time interval will be greater for the more bioavailable drug product. When such drug products are tested \textit{in vivo}, the peak drug serum concentration will be higher for the drug product that shows the highest percent of drug dissolved. An example of \textit{in vitro–in vivo} correlation for 100-mg phenytoin sodium capsules is shown in Fig. 14-14. Several products were tested (Shah et al, 1983). A linear correlation was observed between the maximum drug concentration in the body and the percent of drug dissolved \textit{in vitro}.

The dissolution study on the phenytoin sodium products (Shah et al, 1983) showed that the fastest dissolution rate was product C, for which about 100% of the labeled contents dissolved in the test (Fig. 14-15). Interestingly, these products also show the shortest time to reach peak concentration ($t_{\text{max}}$). The $t_{\text{max}}$ is dependent on the absorption rate constant. In this case, the fastest absorption would also result in the shortest $t_{\text{max}}$ (see Chapter 9).
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

383

The Biopharmaceutic Drug Classification system, BCS, discussed more fully in Chapter 15, is a predictive approach to relate certain physicochemical characteristics of a drug substance and drug product to in vivo bioavailability. The BCS is not a direct in vitro–in vivo correlation. For example, the drug substance from an immediate-release oral drug product would tend to be rapidly and mostly absorbed if the drug substance and drug product meet the criteria for BCS Class I drugs. A BCS Class I drug product contains a highly soluble drug substance that is highly permeable and from which the drug rapidly dissolves from the drug product (FDA Guidance for Industry August, 2000). Since predictability is a major function of IVIVC, any system that predicts in vivo performance from in vitro data may be considered an IVIVC (Leeson, 2002).

Dissolution and Clinical Performance

Various clinical studies are performed during new drug development to determine safety and efficacy of the new drug product. Several different batches of the drug product are often developed for use in multiple

FIGURE 14-15 In vitro–in vivo correlation between $t_{\text{max}}$ and percent drug dissolved in 30 minutes by basket method. Letters on graph indicate different products. (From Shah et al, 1983, with permission.)

Serum drug concentration versus percent of drug dissolved. In a study on aspirin absorption, the serum concentration of aspirin was correlated to the percent of drug dissolved using an in vitro dissolution method (Wood, 1966). The dissolution medium was simulated gastric juice. Because aspirin is rapidly absorbed from the stomach, the dissolution of the drug is the rate-limiting step, and various formulations with different dissolution rates will cause differences in the serum concentration of aspirin by minutes (Fig. 14-16).

In Vitro–In Vivo Relationship, IVIVCR

Various other in vitro–in vivo relationships known as IVIVR have been reviewed. Polli et al (1997) applied a nonlinear, deconvolution-based model to the in vitro–in vivo relationships of metoprolol, piroxicam, and ranitidine. Their model was based on both a dissolution rate and permeation rate relationship as shown in the following scheme:

Solid dosage form → Dissolution → Solution in GI tract → Permeation → Drug in plasma

These investigators assumed a first-order rate for dissolution and first-order rate for permeation and that permeation rate obtained in vitro using CaCo-2 cells reflects the fraction of drug absorbed in vivo.

FIGURE 14-16 Example of in vivo–in vitro two-point correlation between 10-min serum level and percent dissolved at 1.2 min (○) and the 20-min serum level and percent dissolved at 4.2 min (•). (From Wood, 1966, with permission.)

Biopharmaceutic Drug Classification System

The Biopharmaceutic Drug Classification system, BCS, discussed more fully in Chapter 15, is a predictive approach to relate certain physicochemical characteristics of a drug substance and drug product to in vivo bioavailability. The BCS is not a direct in vitro–in vivo correlation. For example, the drug substance from an immediate-release oral drug product would tend to be rapidly and mostly absorbed if the drug substance and drug product meet the criteria for BCS Class I drugs. A BCS Class I drug product contains a highly soluble drug substance that is highly permeable and from which the drug rapidly dissolves from the drug product (FDA Guidance for Industry August, 2000). Since predictability is a major function of IVIVC, any system that predicts in vivo performance from in vitro data may be considered an IVIVC (Leeson, 2002).
clinical trials. Using quality-by-design, QbD (see Chapter 16), the manufacturer of the new drug product should explore the relationship between “desired” clinical outcome and in vitro dissolution/release characteristics in the presence of uncertainty from multiple sources such as physical–chemical characteristics of the drug, the formulation of the drug product, and the manufacturing process. By establishing a link relating product attributes to clinical performance, the dissolution tests provide continued assurance of clinical performance (Selen, 2008).

**Discriminating Dissolution Test**

Dissolution tests should discriminate formulation factors that may affect bioavailability of the drug (see Chapter 15). The dissolution test procedure should be capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. If the dissolution test is too discriminating, the dissolution test procedure may show differences between batches when no significant bioavailability difference are observed in vivo. If the test has insufficient discrimination, then significant changes in formulation composition and/or manufacturing process that might affect in vivo performance will not be observed. The dissolution test needs careful evaluation as to whether the procedure is too sensitive or is appropriately discriminating. In some cases, dissolution tests for immediate-release solid oral drug products may be over-discriminating and a clinically acceptable product might perform poorly in the dissolution test.

**Failure of Correlation of In Vitro Dissolution to In Vivo Absorption**

When a proper dissolution method is chosen, the rate of dissolution of the product may be correlated to the rate of absorption of the drug into the body. Well-defined in vitro–in vivo correlations have been reported for modified-release drug products (see Chapter 17) but have been more difficult to predict for immediate-release drug products. Immediate release and rapidly dissolving drug products often have rapid absorption (Table 14-11). Only a few plasma drug concentration values can be obtained prior to $t_{\text{max}}$ (eg, $t_{\text{max}} < 1$ hour) and only one or two dissolution samples (eg, >85% label contents are dissolved in 45 minutes) may be obtained.

An IVIVC should be evaluated to demonstrate that predictability of in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. The in vitro dissolution characteristics are dependent on the physical properties of the active pharmaceutical ingredient (API), the drug formulation, the hydrodynamics of the dissolution apparatus, and the dissolution medium. IVIVC may be useful for establishing upper and lower dissolution specifications for a solid oral dosage form. IVIVC tends to be drug and product formulation specific. An IVIVC may not be established for multisource, generic drug products that have different formulations or different drug release mechanisms. The USP-NF may list multiple dissolution tests for multisource drug products (brand and interchangeable generic drug products) containing the same active drug, a separate dissolution test for each product. The USP-NF includes 10 separate dissolution tests for theophylline extended-release capsules that are labeled “for dosing every 12 hours.” USP-NF has separate and distinct dissolution test requirements for two different phenytoin

<table>
<thead>
<tr>
<th>TABLE 14-11 Failure of In Vitro–In Vivo Correlation (IVIVC)</th>
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<tr>
<td><strong>Biorelevant dissolution method needed</strong></td>
</tr>
<tr>
<td>Immediate-release drug product containing a rapidly dissolving and rapidly absorbed drug (BCS1)</td>
</tr>
<tr>
<td>Dissolution media may not reflect physiological conditions in the GI tract</td>
</tr>
<tr>
<td>GI transit time</td>
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<tr>
<td>pH in different regions of GI tract</td>
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<tr>
<td>Contents of GI tract</td>
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<tr>
<td>Fed or fasted state</td>
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<tr>
<td>Normal digestive enzymes</td>
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<tr>
<td>Flora of GI tract</td>
</tr>
<tr>
<td>Other factors affecting systemic drug absorption</td>
</tr>
<tr>
<td>In vitro dissolution is a closed system, whereas in vivo drug absorption is an open system</td>
</tr>
<tr>
<td>Pre-systemic drug elimination (first-pass effects)</td>
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<td>Enterohepatic circulation</td>
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sodium capsules. For extended-release phenytoin sodium capsules, USP-NF states that “not more than 35%, between 30% and 70%, and not less than 85% of the labeled amount of \( \text{C}_{15}\text{H}_{11}\text{N}_{2}\text{NaO}_2 \) in the extended capsules dissolves in 30 minutes, 60 minutes, and 120 minutes, respectively, under the specified dissolution conditions.” In contrast, about tolerances for “prompt phenytoin sodium capsules,” USP states “not less than 85% of the labeled amount of \( \text{C}_{15}\text{H}_{11}\text{N}_{2}\text{NaO}_2 \) in the prompt capsules dissolves in 30 minutes.”

It is important to note that multisource, pharmaceutically equivalent drug products may not be bioequivalent even if these drug products meet the same USP-NF monograph specifications (see Chapters 15 and 16). In the United States, only FDA-approved generic, bioequivalent drug products that meet the requirements for therapeutic equivalence may be interchanged. These generic drug products are listed in the FDA publication, Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book (www.fda.gov/cder/ob/default.htm). Bioequivalent drug products are discussed in Chapter 15.

Although there are many published examples of drugs with dissolution data that correlate well with drug absorption in the body, there are also many examples indicating poor correlation of dissolution to drug absorption. There are also instances where a drug has failed the dissolution test and yet is well absorbed. The problem of no correlation between bioavailability and dissolution may be due to the complexity of drug absorption and the weakness of the dissolution design. For example, a product that involves fatty components may be subjected to longer retention in the gastrointestinal tract. The effect of digestive enzymes may also play an important role in the dissolution of the drug in vivo. These factors may not be adequately simulated with a simple dissolution medium. An excellent example of the importance of dissolution design is shown in Fig. 14-17. Dissolution tests using four different dissolution media were performed for two quinidine gluconate sustained-release tablets (Prasad et al, 1983). Brand BE was

**FIGURE 14-17** Dissolution profile of two quinidine gluconate sustained-release products in different dissolution media. Each data point is the mean of 12 tablets. (• = product BE, o = product BO-1.) (Data from Prasad et al, 1983.)
known to be bioavailable, whereas product BO-1 was known to be incompletely absorbed. It is interesting to see that using acid medium as well as acid followed by pH 7.4 buffer did not distinguish the two products well, whereas using water or pH 5.4 buffer as dissolution medium clearly distinguished the “good” product from the one that was not completely available. In this case, the use of an acid medium is consistent with the physiologic condition in the stomach, but this procedure would be misleading as a quality control tool. It is important that any new dissolution test be carefully researched before being adopted as a method for predicting drug absorption.

**DISSOLUTION PROFILE COMPARISONS**

Dissolution profiles may be considered similar by virtue of overall profile similarity at each dissolution sample time point. A model independent approach uses a difference factor \( f_1 \) and a similarity factor \( f_2 \) to compare dissolution profiles. The difference factor \( f_1 \) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves.

\[
\left( 1 + \frac{(1/n) \sum (R_i - T_i)^2}{\left( \sum R_i \right)^2} \right)^{-0.5} \times 100
\]

where \( n \) is the number of time points, \( R \) is the dissolution value of the reference batch at time \( t \), and \( T \) is the dissolution value of the test batch at time \( t \).

The similarity factor \( f_2 \) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

\[
f_2 = 50 \times \log \left( 1 + \frac{(1/n) \sum (R_i - T_i)^2}{\left( \sum R_i \right)^2} \right)^{-0.5} \times 100
\]

where \( n \) is the number of time points, \( R \) is the dissolution value of the reference (prechange) batch at time \( t \) and \( T \) is the dissolution value of the test (postchange) batch at time \( t \).

The similarity factor \( f_2 \) is determined by comparing the dissolution profile of 6 to 12 units each of the test and reference products (Fig. 14-18). Using the mean dissolution values from both curves at each time interval, the similarity factor \( f_2 \) is calculated. For this calculation, three to four or more dissolution time points should be available. The dissolution measurements of the test and reference batches should be performed under exactly the same conditions. The dissolution time points for both profiles should be the same (eg, 15, 30, 45, 60 minutes). \( f_2 \) values greater than 50 (50–100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and reference (pre-change) products.”

**DRUG PRODUCT STABILITY**

The demonstration of stability is a key component of drug product quality. Stability is usually determined by the dissolution profile and a stability-indicating assay. Quality tests may include drug potency, specified, unspecified, total impurities, and content uniformity, etc. The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. The term “shelf-life” is used interchangeably...
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

**CONSIDERATIONS IN THE DESIGN OF A DRUG PRODUCT**

**Biopharmaceutic Considerations**

Some of the major biopharmaceutic considerations in the design of a drug product are given in Table 14-12. The prime considerations in the design of a drug product are therapeutic objective, safety, and efficacy. The drug product must effectively deliver the active drug at an appropriate rate and amount to the target receptor site so that the intended therapeutic effect is achieved. The finished dosage form should not produce any additional side effects or discomfort due to the drug and/or excipients. Ideally, all excipients in the drug product should be pharmacologically inactive ingredients alone or in combination in the final dosage form.

The finished drug product is a compromise of various factors, including therapeutic objectives, pharmacokinetics, physical and chemical properties, manufacturing, cost, and patient acceptance. Most important, the finished drug product should meet the therapeutic objective by delivering the drug with maximum bioavailability and minimum adverse effects.

**Pharmacodynamic Considerations**

Therapeutic considerations include the desired pharmacodynamic and pharmacologic properties of the drug, including the desired therapeutic response and the type and frequency of adverse reactions to the drug. The therapeutic objective influences the design of the drug product, route of drug administration, dose, dosage regimen, and the manufacturing process. An oral drug used to treat an acute illness is generally formulated to release the drug rapidly, allowing for quick absorption and rapid onset. If more rapid drug absorption is desired, then an injectable drug formulation might be formulated. In the case of nitroglycerin, which is highly metabolized if swallowed, a sublingual tablet formulation allows for rapid absorption of the drug from the buccal area of the mouth for the treatment of angina pectoris. For the treatment of certain chronic diseases, such as asthma, hypertension, chronic pain, etc, an extended- or controlled-release dosage form is preferred. The extended-release dosage form releases the drug slowly, thereby controlling the rate of drug absorption and allowing for more constant plasma drug concentrations. In some cases, an immediate-drug-release component is included in the extended-release dosage form to allow for both rapid onset followed by a slower sustained release of the drug, eg, zolpidem tartrate extended-release tablets (Ambien® CR tablets). Controlled-release and modified-release dosage forms are discussed in Chapter 17.

**Drugs Considerations**

The physicochemical properties of the drug (see Table 14-1) are major factors that are controlled or modified by the formulator. Important physicochemical properties include solubility, stability, chirality,
an alternative route of drug administration, as in the case of nitroglycerin. Drugs that are only partially absorbed after oral administration usually leave residual drug in the gastrointestinal tract, which may cause local bowel irritation or alter the normal gastrointestinal flora. Incompletely absorbed drugs and drugs with highly variable bioavailability have a risk that under unusual conditions (e.g., change in diet or disease condition, drug–drug interaction), excessive drug bioavailability can occur leading to more intense pharmacodynamic activity and possible adverse events. If the drug is not absorbed after the oral route or a higher dose causes toxicity, then the drug must be given by an alternative route of administration, and a different dosage form such as a parenteral drug product might be needed.

Pharmacokinetics of the Drug
Bioavailability and pharmacokinetic profile studies relate the pharmacokinetics to the desired pharmacodynamic activity, also with an aim of undesirable adverse events. The data obtained from these studies allow the development of a dose(s) and dosage regimen including an appropriate drug release rate that will maintain a desired drug level in the body. The effect of food on drug bioavailability is also an important consideration. The therapeutic window determines the desired or target plasma drug concentration that will be effective with minimal adverse effects. Drug concentrations higher than the minimum toxic concentration may cause more intense pharmacodynamic and/or adverse events. Drug concentrations below the minimum effective concentration may be subtherapeutic.

Bioavailability of the Drug
The stability of the drug in the gastrointestinal tract, including the stomach and intestine, is another consideration. Some drugs, such as penicillin G, are unstable in the acidic medium of the stomach. The addition of buffering in the formulation or the use of an enteric coating on the dosage form will protect the drug from degradation at a low pH. Some drugs have poor bioavailability because of first-pass effects (pre-systemic elimination). If oral drug bioavailability is poor due to metabolism by enzymes in the gastrointestinal tract or in the liver, then a higher dose may be needed, as in the case of propranolol, or
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

Older patients may have more difficulties in swallowing large tablets and capsules. Most of these swallowing difficulties may be overcome by taking the product with a large amount of fluid.

Dosing Frequency

Both the amount of each dose and the dosing frequency including the total daily dose should be considered when developing a therapeutic dosage regimen for a patient (see Chapter 20). The dosing frequency is related to the clearance of the drug and the target plasma drug concentration. If the pharmacokinetics show that the drug has a short duration of action due to a short elimination half-life or rapid clearance from the body, the drug must be given more frequently or given in an extended-release drug product. To minimize fluctuating plasma drug concentrations and improve patient compliance, an extended-release drug product may be preferred. An extended-release product contains two or more doses of the drug that are released over a prolonged period (see Chapter 17).

Patient Considerations

The drug product and therapeutic regimen must be acceptable to the patient. Poor patient compliance may result from poor product attributes, such as difficulty in swallowing, disagreeable odor, bitter medicine taste, or two frequent and/or unusual dosage requirements. In recent years, creative packaging has allowed the patient to remove one tablet each day from a specially designed package so that the daily doses are not missed. Orally disintegrating tablets and chewable tablets allow the patient to take the medication without water. These innovations improve compliance. Of course, pharmacodynamic factors, such as side effects of the drug or an allergic reaction, also influence patient compliance.

Route of Drug Administration

The route of drug administration (see Chapter 13) affects the bioavailability of the drug, thereby affecting the onset and duration of the pharmacologic effect. In the design of a drug dosage form, the pharmaceutical manufacturer must consider (1) the intended route of administration; (2) the size of the dose; (3) the anatomic and physiologic characteristics of the administration site, such as membrane permeability and blood flow; (4) the physicochemical properties of the site, such as pH, osmotic pressure, and presence of physiologic fluids; and (5) the interaction of the drug and dosage form at the administration site, including alteration of the administration site due to the drug and/or dosage form.

Although the pharmacodynamic activity of the drug at the receptor site is similar with different routes of administration, severe differences in the intensity of the pharmacodynamic response and the occurrence of adverse events may be observed. For example, isoproterenol has a thousand fold difference in activity when given orally or by IV injection. Figure 14-19 shows the change in heart rate due to isoproterenol with different routes of administration. (From Gillette JR, Mitchell JR: Routes of drug administration and response. In Brodie B, et al: Concepts in Biochemical Pharmacology. Berlin, Springer-Verlag, 1975, chap 64, with permission.)


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to invasive drug delivery such as intramuscular, intravenous, and subcutaneous (Mathias and Hussain, 2010). Although the oral route of drug administration is preferred and is the most popular route of drug administration, alternate noninvasive systemic drug delivery is being considered for biotechnology-derived drugs (proteins), ease of self-administration (orally disintegrating tablets), or prolonged drug delivery (transdermal patch). The discussion below briefly describes some of the more popular drug products.

**Oral Drug Products**

Oral drug products are the most common route of drug administration. The major advantages of oral drug products are the convenience of administration, safety, and the elimination of discomforts involved with injections. The hazard of rapid intravenous administration causing toxic high concentration of drug in the blood is avoided. The main disadvantages of oral drug products are the potential problems of reduced, erratic, or incomplete bioavailability. Unabsorbed drug may also alter the contents and microbiologic flora of the gastrointestinal tract. Some orally administered drugs may irritate the gastrointestinal linings causing nausea or gastrointestinal discomfort. Bioavailability may be altered by drug and food interactions and any pathology of the GI tract such as ulcerative colitis (see Chapter 13).

Highly ionized drug molecules are not absorbed easily. The ganglion-blocking drugs hexamethonium, pentolinium, and bretylium are ionized at intestinal pH. Therefore, they are not sufficiently absorbed orally to be effective systemically. Neomycin, gentamicin, and cefamandole are not well absorbed orally. Drugs with large molecular weights may not be well absorbed when given orally. The antibiotics, neomycin and vancomycin are not absorbed after oral administration and are used for local antibacterial effect in the gastrointestinal tract. There is some evidence that large drug molecules may be absorbed through the lymphatic system when formulated with a “carrier.” The mechanism is not known. Some large molecules are absorbed when administered in solution with a surface-active agent. For example, cyclosporine has been given orally with good absorption when formulated with a surfactant in oil. A possible role of the oil is to stimulate the flow of lymph as well as to delay retention of the drug. Oily vehicles have been used to lengthen the gastrointestinal transit time of oral preparations.

**Oral Delivery of Insulin**

Insulin is a small peptide (protein) hormone consisting of 51 amino acids synthesized and stored within the pancreas and is involved in the metabolism of glucose. Diabetes mellitus is the disease resulting from a deficiency in insulin production. Currently, insulin is given to patients by subcutaneous injection since oral insulin is degraded in the stomach and intestine. Pharmaceutical scientists have been very interested in developing an insulin drug product that may be taken orally (Dhawan et al, 2009). Scientists have been able to protect the insulin delivery systems from acidic environment of the stomach and target it to the intestine using a variety of approaches including microspheres, liposomes, microemulsions, and other approaches. However, currently these approaches have not yet led to an oral insulin product that has reliable and consistent bioavailability.

**Absorption of Lipid-Soluble Drugs**

Most hydrophobic drugs are poorly soluble in water and generally are not well absorbed orally because of failure of the drug to dissolve in the fluids of the gastrointestinal tract. These lipophilic drugs are more soluble in lipids or oily vehicles. Lipid-soluble drugs given with fatty excipients mix with digested fatty acids, which are emulsified by bile in the small intestine. The emulsified drug is then absorbed through the GI mucosa or through the lymphatic system. A normal digestive function of the small intestine is the digestion and absorption of fats such as triglycerides. These fats are first hydrolyzed into monoglycerides and fatty acids by pancreatic lipase. The fatty acids then react with carrier lipoproteins to form chylomicrons, which are absorbed through the lymph. The chylomicrons eventually release the fatty acids, and any lipophilic drugs incorporated in the oil phase. Fat substances trigger receptors in the stomach to
delay stomach emptying and reduce GI transit rates. Prolonged transit time allows more contact time for increased drug absorption.

When griseofulvin or phenytoin was given orally in corn oil suspensions, an increase in drug absorption was demonstrated (Bates and Equeira, 1975). The increase in absorption was attributed to the formation of mixed micelles with bile secretions, which aid drug dissolution.

Many hydrophobic drugs such as griseofulvin and metaxalone have greater bioavailability when given with a high-fat meal. A meal high in lipids will delay stomach emptying depending on the volume and nature of the oil. Long-chain fatty acids (above C-10) are more effective than short-chain acids in delaying stomach emptying. Unsaturated fatty acids are more effective than saturated straight-chain fatty acids; triglycerides are not as effective as fatty acids. Oleic acid, arachis oil, and myristic acid also delay stomach emptying. For example, the bioavailability of a water-insoluble antimalarial drug was increased in dogs when oleic acid was incorporated as part of a vehicle into a soft gelatin capsule (Stella et al, 1978). The integrity of certain modified-release drug products, both delayed (enteric coated) and extended-release drug products, may be affected by food resulting in significant differences in drug bioavailability under fasting or fed conditions.

Calcium carbonate, a source of calcium for the body, was only about 30% available in a solid dosage form, but was almost 60% bioavailable when dispersed in a special vehicle as a soft gelatin capsule (Fordtran et al, 1986). Bleomycin, an anticancer drug (MW 1500), is poorly absorbed orally and therefore was formulated for absorption through the lymphatic system. The lymphotropic carrier was dextran sulfate. Bleomycin was linked by ionic bonds to the carrier to form a complex. The carrier dextran (MW 500,000) was too large to be absorbed through the membrane and pass into the lymphatic vessels (Yoshikawa et al, 1989).

Gastrointestinal Side Effects
Many orally administered drugs such as aspirin are irritating to the stomach. These drugs may cause nausea or stomach pain due to local irritation when taken on an empty stomach. In some cases, food or antacids may be given together with the drug to reduce stomach irritation. Alternatively, the drug may be enteric coated to reduce gastric irritation. Buffered aspirin tablets, enteric-coated aspirin tablets, and rapidly dissolving effervescent tablets and granules are available to minimize local gastric irritation. However, enteric coating may sometimes delay or reduce the amount of drug absorbed. Furthermore, enteric coating may not abolish gastric irritation completely, because the drug may occasionally be regurgitated back to the stomach after the coating dissolves in the intestine. Enteric-coated tablets may be greatly affected by the presence of food in the stomach. The drug may not be released from the stomach for several hours when stomach emptying is delayed by food.

Buffering material or antacid ingredients have also been used with aspirin to reduce stomach irritation. When a large amount of antacid or buffering material is included in the formulation, dissolution of aspirin may occur quickly, leading to reduced irritation to the stomach. However, many buffered aspirin formulations do not contain sufficient buffering material to make a difference in dissolution in the stomach.

Certain drugs have been formulated into soft gelatin capsules to improve drug bioavailability and reduce gastrointestinal side effects. If the drug is formulated in the soft gelatin capsule as a solution, the drug may disperse and dissolve more rapidly, leaving less residual drug in the gut and causing less irritation. This approach may be useful for a drug that causes local irritation but will be ineffective if the drug is inherently ulcerogenic. Indomethacin, for example, may cause ulceration in animals even when administered parenterally.

There are many options available to the formulator to improve the tolerance of the drug and minimize gastric irritation. The nature of excipients and the physical state of the drugs are important and must be carefully assessed before a drug product is formulated. Some excipients may improve the solubility of the drug and facilitate absorption, whereas others may physically adsorb the drug to reduce irritation. Often, a great number of formulations must be tested before an acceptable one is chosen.
Immediate-Release and Modified-Release Drug Products

The USP differentiates between an immediate-release (IR) drug product and a modified-release (MR) drug product. For the IR drug product, no deliberate effort has been made to modify the drug release rate. In the case of IR capsules and tablets, the inclusion or exclusion of a disintegrating agent is not interpreted as a modification. For MR drug products, the pattern of drug release from the dosage form has been deliberately changed from that of a conventional (immediate-release) form of the drug. Types of MR drug products include delayed release (eg, enteric coated), extended release (ER), and orally disintegrating tablet (ODT). Chapter 17 discusses MR drug products in more detail.

Buccal and Sublingual Tablets

A drug that diffuses and penetrates rapidly across mucosal membranes may be placed under the tongue and be rapidly absorbed. A tablet designed for release under the tongue is called a sublingual tablet. Nitroglycerin, isoproterenol, erythritol tetranitrate, and isosorbide dinitrate are common examples.

A tablet designed for release and absorption of the drug in the buccal (cheek) pouch is called a buccal tablet. The buccal cavity is the space between the mandibular arch and the oral mucosa, an area well supplied with blood vessels for efficient drug absorption. A buccal tablet may release drug rapidly or may be designed to release drug slowly for a prolonged effect. For example, Sorbitrate sublingual tablet, Sorbitrate chewable tablet, and Sorbitrate oral tablet (Zeneca) are three different dosage forms of isosorbide dinitrate for the relief and prevention of angina pectoris. The sublingual tablet is a lactose formulation that dissolves rapidly under the tongue and is then absorbed. The chewable tablet is chewed, and some drug is absorbed in the buccal cavity; the oral tablet is simply a conventional product for GI absorption. The chewable tablet contains flavor, confectioner’s sugar, and mannitol, which are absent in both the oral and sublingual tablets. The sublingual tablet contains lactose and starch for rapid dissolution. The onset of sublingual nitroglycerin is rapid, much faster than when nitroglycerin is taken orally or absorbed through the skin. The duration of action, however, is shorter than with the other two routes. Drug absorbed through the buccal mucosa will not pass through the liver before general distribution. Consequently, for a drug with significant first-pass effect, buccal absorption may provide better bioavailability than oral administration. Some peptide drugs have been reported to be absorbed by the buccal route, which provides a route of administration without the drug being destroyed by enzymes in the GI tract.

A newer approach to drug absorption from the oral cavity has been the development of a translingual nitroglycerin spray (Nitrolinqual Pumpspray). The spray, containing 0.4 mg per metered dose, is given by spraying one or two metered doses onto the oral mucosa at the onset of an acute angina attack.

Fentanyl citrate is a potent, lipid-soluble opioid agonist that crosses mucosal membranes rapidly. Fentanyl has been formulated as a transdermal drug product (Durapress®) and as an oral lozenge on a handle (Actiq®) containing fentanyl citrate for oral transmucosal delivery. According to the manufacturer, fentanyl bioavailability from Actiq® is about 50%, representing a combination of rapid absorption across the oral mucosa and slower absorption through swallowing and transport across the gastrointestinal mucosa.

Colonic Drug Delivery

Oral drug products for colonic drug delivery have been studied not only for the delivery of drugs for the treatment of local diseases associated with the lower bowel and colon (eg, Crohn’s disease) but also for their potential for the delivery of proteins and therapeutic peptides (eg, insulin) for systemic absorption (Chourasia and Jain, 2003). Crohn’s disease or chronic inflammatory colitis may be more effectively treated by direct drug delivery to the colon. For example, mesalamine (5-aminosalicylic acid, Asacol®) is available in a delayed-release tablet coated with an acrylic-based resin that delays the release of the drug until it reaches the distal ileum and beyond. Other approaches include prodrugs (sulfasalazine and balsalazine) to deliver 5-aminosalicylic acid (5-ASA) for localized chemotherapy

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of inflammatory bowel disease (IBD). Drugs containing an azo bond (balsalazide) and azo cross-linked polymers used as a coating are degraded by anaerobic microbes in the lower bowel.

Protein drugs are generally unstable in the acidic environment of the stomach and are also degraded by proteolytic enzymes present in the stomach and small intestine. Researchers are investigating the oral delivery of protein and peptide drugs by protecting them against enzymatic degradation for later release in the colon.

Over 500 different bacterial species inhabit the colon, although five frequent species dominate the microflora. Within the cecum and colon, anaerobic species dominate and bacterial counts of $10^{12}$/mL have been reported. Drugs such as the beta-blockers, oxprenolol and metoprolol, and isosorbide-5-mononitrate are well absorbed in the colon, similar to absorption in the small intestine. Thus, these drugs are suitable candidates for colonic delivery. The nonsteroidal anti-inflammatory drug naproxen has been formed into a prodrug naproxen–dextran that survives intestinal enzyme and intestinal absorption. The prodrug reaches the colon, where it is enzymatically decomposed into naproxen and dextran (Harboe et al, 1989).

Rectal and Vaginal Drug Delivery

Products for rectal or vaginal drug delivery may be administered in either solid or liquid dosage forms. Rectal drug administration can be used for either local or systemic drug delivery. Rectal drug delivery for systemic absorption is preferred for drugs that cannot be tolerated orally (eg, when a drug causes nausea) or in situations where the drug cannot be given orally. A sustained-release preparation may be prepared for rectal administration. The rate of release of the drug from this preparation is dependent on the nature of the base composition and on the solubility of the drug involved. Rectal drug absorption may partially bypass the first-pass effects due to enzymes in the liver. Drug absorbed in the lower rectal region does not pass through the liver, whereas drug absorbed in the upper rectal region passes through the hepatic portal vein. Release of drug from a suppository depends on the composition of the suppository base. A water-soluble base, such as polyethylene glycol and glycerin, generally dissolves and releases the drug; on the other hand, an oleaginous base with a low melting point may melt at body temperature and release the drug. Some suppositories contain an emulsifying agent that keeps the fatty oil emulsified and the drug dissolved in it.

Vaginal drug delivery is generally for local drug delivery, but some systemic drug absorption can occur. Progesterone vaginal suppositories have been evaluated for the treatment of premenstrual symptoms of anxiety and irritability. Antifungal agents are often formulated into suppositories for treating vaginal infections. Fluconazole, a triazole antifungal agent, has been formulated to treat vulvovaginal candidiasis. The result of oral doses is comparable to that of a clotrimazole vaginal suppository. Many vaginal preparations are used for the delivery of antifungal agents.

Parenteral Drug Products

In general, intravenous (IV) bolus administration of a drug provides the most rapid onset of drug action. After IV bolus injection, the drug is distributed via the circulation to all parts of the body within a few minutes. After intramuscular (IM) injection, drug is absorbed from the injection site into the bloodstream (Fig. 14-20). Plasma drug input after oral and IM administration involves an absorption phase in which the drug concentration rises slowly to a peak and then declines according to the elimination half-life of the drug. (Note that the systemic elimination of all products is essentially similar; only the rate and extent of absorption may be modified by formulation.) The plasma drug level peaks instantaneously after an IV bolus injection, so a peak is usually not visible. After 3 hours, however, the plasma level of the drug after intravenous administration has declined to a lower level than after the oral and intramuscular administration. In this example (see Fig. 14-20), the areas under the plasma curves are all approximately equal, indicating that the oral and intramuscular preparations are both well formulated and are 100% available. Frequently, because of incomplete absorption or metabolism, oral preparations may have a lower area under the curve.
Modified-release parenteral dosage forms have been developed in which the drug is entrapped or encapsulated into inert polymeric or lipophilic matrices that slowly release the drug in vivo over a week or up to several years (Patil and Burgess, 2010). The polymers or lipophilic carriers used to deliver the drugs in MR parenterals are either biodegradable in vivo or are nonbiodegradable. Nonerodible, nonbiodegradable systems are removed at the end of therapy. Drugs, including peptides and proteins, have also been formulated as emulsions, suspensions, liposomes, and nanoparticles for parenteral injection. A change in a parenteral drug product from a solution to an emulsion, liposome, etc will alter the drug’s distribution and pharmacokinetic profile.

**CLINICAL EXAMPLE**

Haloperidol® (Haldol) is a butyrophenone antipsychotic agent with pharmacologic effects similar to the piperazine phenothiazines. Haloperidol is available for oral and IM administration. Two IM preparations of haloperidol are available, including haloperidol lactate in an aqueous vehicle and haloperidol deconate in a nonaqueous sesame oil vehicle.

Haloperidol lactate is given in an aqueous solution and after intramuscular injection has a time for peak drug concentration of 20 minutes and an elimination half-life of 21 hours (longer after chronic administration). In contrast, haloperidol deconate, the deconate ester of the butyrophenone, is lipid soluble and is formulated in sesame oil. Due to the slow drug release from the oil after IM administration, the time for peak drug concentration is 4 to 11 days and the elimination half-life is about 3 weeks. Thus, the suggested dosage interval between IM injections for haloperidol deconate is 4 weeks.

A major advantage of intramuscular injections compared to intravenous bolus injections is the flexibility of formulation. A drug that is not water soluble cannot be easily administered by the intravenous route. A nonaqueous injection for intravenous administration must be given very slowly to avoid any drug precipitation in the vein. Propylene glycol and PEG 400 in combination with other solvents have been used in intravenous preparations.

Drug absorption after an intramuscular injection may be faster or slower than after oral drug administration. Intramuscular preparations are generally injected into a muscle mass such as in the buttocks (gluteus muscle) or in the deltoid muscle. Drug absorption occurs as the drug diffuses from the muscle into the surrounding tissue fluid and then into the blood. Different muscle tissues have different blood flow. For example, blood flow to the deltoid muscle is higher than blood flow to the gluteus muscle. Intramuscular injections may be formulated to have a faster or slower drug release by changing the vehicle of the injection preparation. Aqueous solutions release drug more rapidly, and the drug is more rapidly absorbed from the injection site, whereas a viscous, oily, or suspension vehicle may result in a slow drug release and consequently slow and sustained drug absorption. Viscous vehicles generally slow drug diffusion and distribution. A drug in an oily vehicle must partition into an aqueous phase before systemic absorption. A drug that is very soluble in oil and relatively insoluble in water may have a relatively long and sustained release from the absorption site because of slow partitioning.

**FIGURE 14-20** Plasma concentration of a drug after the same dose is administered by three different routes.

Modified-release parenteral dosage forms have been developed in which the drug is entrapped or encapsulated into inert polymeric or lipophilic matrices that slowly release the drug in vivo over a week or up to several years (Patil and Burgess, 2010). The polymers or lipophilic carriers used to deliver the drugs in MR parenterals are either biodegradable in vivo or are nonbiodegradable. Nonerodible, nonbiodegradable systems are removed at the end of therapy. Drugs, including peptides and proteins, have also been formulated as emulsions, suspensions, liposomes, and nanoparticles for parenteral injection. A change in a parenteral drug product from a solution to an emulsion, liposome, etc will alter the drug’s distribution and pharmacokinetic profile.
Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

Parenteral dosage forms for IV administration containing suspensions, liposomes, or nanoparticles have been developed for the administration of antineoplastic drugs. In this case, the dosage form may alter the distribution of the drug, because small particles are engulfed by macrophages of the reticuloendothelial system, resulting in drug concentration in the liver and spleen.

Nasal Drug Products

Nasal drug products are formulated as sprays applied to the nasal cavity for local and/or systemic effects. Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (eg, preservatives, viscosity modifiers, emulsifiers, buffering agents) in nonpressurized dispensers that deliver a spray. The dose can be metered by the spray pump or could have been premetered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance (FDA Guidance, 2002; Bell et al, 2010).

The nasal mucosa are highly vascularized and easily accessible. The vehicle used for nasal administration must be nonirritating and well tolerated. The most common drug products for local activity are the nasal vasoconstrictors phenylephrine and naphazoline. An example of a new nasal delivery for both local and systemic effect is ipratropium bromide, a drug used for rhinitis and the common cold. In patients with perennial rhinitis, about 10% of the drug was absorbed intranasally (Wood et al, 1995).

Triamcinolone acetonide (Nasacort AQ) nasal spray used for allergic rhinitis delivers about 50 μg of the drug in each puff. The action is partially systemic and local. Levocabastine (Livostin) is a histamine H1-receptor antagonist developed as a nasal spray. Peak plasma concentrations (C_{max}) occur within 1 to 2 hours, with systemic availability ranging from 60% to 80% (Heykants et al, 1995). Benefits of levocabastine are predominantly mediated through local antihistaminic effects, with some systemic contribution. Butorphanol tartrate (Stadol NS) nasal spray is an opioid analgesic available as a nasal spray for the treatment of pain as a preoperative or preanesthetic medication and for pain relief. The nasal route offers an alternative to injection.

Some biological products such as peptides and proteins have been suggested for nasal delivery, because they are then not digested by enzymes as they are in the GI tract. The luteinizing hormone-releasing hormone agonist buserelin acetate (Suprefact® nasal spray—Aventis Pharma) has been formulated with oleic acid for systemic nasal delivery in an experimental formulation. Therapeutic proteins, such as recombinant interferon-alpha/D, have also been investigated for nasal delivery. Detectable levels of interferon-alpha in serum were achieved via the nasal route and in the lung. Drug bioavailability was 6.8% from the lung in the rat, and 2.9% from the nasal cavity in the rabbit (Bayley et al, 1995).

Examples of nasal delivery of drug products for systemic drug absorption are Nicotrol for the delivery of nicotine to aid smokers in quitting smoking, and Miacalcin for the delivery of calcitonin salmon, a parathyroid agent for the treatment of postmenopausal osteoporosis.

An in vitro human nasal model was developed as a tool to study the local tolerability of nasal powder forms using excised nasal mucosa in a diffusion chamber (De Fraissinette et al, 1995). The suitability of this model was tested using Sandostatin, an octapeptide analog of somatostatin. The drug is also used for ocular treatment of allergic rhinoconjunctivitis as eye drops; it was about 30% to 60% available systemically by that route.

Recently, a live influenza virus vaccine, FluMist® (influenza virus vaccine live, intra-nasal—Wyeth), has been marketed for intranasal delivery. FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses.

Inhalation Drug Products

Drugs administered into the respiratory system, such as bronchodilators and corticosteroids, may be formulated as aerosols or inhalation solutions. Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer. The advantages of drugs given by inhalation include (1) rapid absorption and rapid onset of activity (eg, bronchodilators), (2) avoidance of
Chapter 14

Propellants for aerosols were chlorinated fluorocarbons (CFCs, such as Freons, DuPont). However, these compounds deplete the ozone layer of the stratosphere, and propellants older were replaced. The new propellants include classes of hydrofluorokanes (HFAs), which do not contain chlorines. HFA-227 and HFA-134a show promise as new propellants for medical inhalers because they are nonflammable, not chemically reactive, and do not have ozone-depleting potential. Some examples of inhalation and intranasal products are shown in Table 14-13. Insulin \textsuperscript{®} administration by inhalation (Exubera) was available in the US market but was withdrawn in 2007.

### Transdermal Drug Products

Transdermal drug products, sometimes referred to as transdermal delivery systems or “patches,” \footnote{Several “patches” are available for local activity on the skin. Examples include lidocaine patch for local anesthetic activity due to pain from shingles and diclofenac sodium patch, a topical nonsteroidal anti-inflammatory drug (NSAID).} are placed on the skin to deliver drug into the patient’s systemic circulation for systemic activity. Scopolamine\textsuperscript{®} (Transderm Scop) delivers drug through the skin of

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Generic Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation</strong></td>
<td>Proventil</td>
<td>Albuterol</td>
</tr>
<tr>
<td>Beconase</td>
<td>Beclomethasone dipropionate</td>
<td>Anti-inflammatory steroid</td>
</tr>
<tr>
<td>Foradil Aerolizer</td>
<td>Formoterol fumarate inhalation powder</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Pulmicort Turbuhaler</td>
<td>Budesonide inhalation powder</td>
<td>Anti-inflammatory steroid</td>
</tr>
<tr>
<td>Virazole</td>
<td>Ribavirin for inhalation solution</td>
<td>Antiviral nucleoside</td>
</tr>
<tr>
<td><strong>Intranasal</strong></td>
<td>Mucomyst</td>
<td>Acetylcysteine</td>
</tr>
<tr>
<td>Flonase</td>
<td>Fluticasone propionate</td>
<td>Anti-inflammatory steroid</td>
</tr>
<tr>
<td>FluMist</td>
<td>Influenza virus intranasal vaccine</td>
<td>Live (attenuated) influenza virus</td>
</tr>
<tr>
<td>Nasalcrom</td>
<td>Cromolyn sodium</td>
<td>Mast cell stabilizer</td>
</tr>
<tr>
<td>Nasalcort</td>
<td>Triamcinolone actonide</td>
<td>Anti-inflammatory steroid</td>
</tr>
</tbody>
</table>
such as acrylate or silicone; performing the dual functions of release control and adhesion, this product is known as “drug in adhesive.” In other products, the drug dose may be placed in a separate insoluble matrix layer, which helps control the release rate. This is generally known as a “matrix patch,” and provides a little more control of the release rate as compared to the simple “reservoir” type of patch. Multilayers of drugs may be involved in other transdermal products using a “laminate” design. In many cases, drug permeation through the skin is the slowest step in the transdermal delivery of drug into the body. See Chapter 17 for a discussion of modified-release drug products.

Absorption Enhancers

A variety of excipients known as absorption enhancers or permeation enhancers have been incorporated into the drug product to promote systemic drug absorption from the application site. For oral drug products that contain poorly absorbed hydrophobic drugs, surfactants have been added to the formulation to help solubilize the drug by making the drug more miscible in water. The stratum corneum is the major barrier to systemic drug absorption from transdermal drug products. The addition of excipients or the use of physical approaches have been used to enhance drug permeation from transdermal products. For example, Estraderm®, a estradiol transdermal system, contains ethanol which promotes drug delivery through the stratum corneum of the skin. The use of ultrasound (phonophoresis or sonophoresis) has been used by physical therapists to enhance percutaneous absorption of hydrocortisone ointments and creams from intact skin. Iontophoresis is a technique using a small electric charge to deliver drug containing an ionic charge through the stratum corneum. Most of these absorption enhancement approaches attempt to disrupt the cellular barriers to drug transport and allow the drug to permeate better.

Scale-Up and Postapproval Changes (SUPAC)

Any changes in a drug product after it has been approved for marketing by the FDA is known as a postapproval change (see Chapter 16). Postapproval changes may include analytical, manufacturing, and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>Vivelle</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>Opiate agonist</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Habitrol Tran</td>
<td>Smoking control</td>
</tr>
<tr>
<td></td>
<td>Nicoderm</td>
<td>Smoking control</td>
</tr>
<tr>
<td></td>
<td>Nicotrol</td>
<td>Smoking control</td>
</tr>
<tr>
<td></td>
<td>Prostep patch</td>
<td>Smoking control</td>
</tr>
<tr>
<td>Naftine HCl</td>
<td>Naftin</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Adalat</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitrodisc</td>
<td>Antiangina</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catopress</td>
<td>Antiangina</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>Evra</td>
<td>Contraception</td>
</tr>
<tr>
<td>and norelgestromin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Frequently Asked Questions

- What physical or chemical properties of a drug substance are important in designing a drug for (a) oral administration or (b) parenteral administration?
- For a lipid-soluble drug that has very poor aqueous solubility, what strategies could be used to make this drug more bioavailable after oral administration?
- For a weak ester drug that is unstable in highly acid or alkaline solutions, what strategies could be used to make this drug more bioavailable after oral administration?
LEARNING QUESTIONS

1. What are the two rate-limiting steps possible in the oral absorption of a solid drug product? Which one would apply to a soluble drug? Which one could be altered by the pharmacist? Give examples.

2. What is the physiologic transport mechanism for the absorption of most drugs from the gastrointestinal tract? What area of the gastrointestinal tract is most favorable for the absorption of drugs? Why?

3. Explain why the absorption rate of a soluble drug tends to be greater than the elimination rate of the drug.

4. What type of oral dosage form generally yields the greatest amount of systemically available drug in the least amount of time? (Assume that the drug can be prepared in any form.) Why?

5. What effect does the oral administration of an anticholinergic drug, such as atropine sulfate, have on the bioavailability of aspirin from an enteric-coated tablet? (Hint: Atropine sulfate decreases gastrointestinal absorption.)

6. Drug formulations of erythromycin, including its esters and salts, have significant differences in bioavailability. Erythromycin is unstable in an acidic medium. Suggest a method for preventing a potential bioavailability problem for this drug.

7. Why can two generic drug products have different dissolution profiles in vitro and still be bioequivalent in vivo?

REFERENCES


FDA Guidance for Industry: Changes to an Approved NDA or ANDA, November 1999.


FDA recommends that manufacturers should control sources of significant variability in dissolution testing including dissolved gases, vibration, and vessel dimensions.


Selen A: Dissolution and QbD: Ensuring Product Quality (Patient Benefit), USP Annual Scientific Meeting, September 25, 2008.


USP Chapter <1088> In vitro and in vivo evaluation of dosage forms.


BIBLIOGRAPHY


Chapter Objectives

- Define bioavailability, bioequivalence, and drug product performance.
- Explain why certain drugs and drug products have low bioavailability.
- Explain why first-pass effect as well as chemical instability of a drug can result in low relative bioavailability.
- Distinguish between bioavailability and bioequivalence.
- Explain why relative bioavailability may have values greater than 100%.
- Explain why bioequivalence may be considered as a measure of drug product performance.
- Describe various methods for measuring bioavailability and the advantages and disadvantages of each.
- Describe the statistical criteria for bioequivalence and 90% confidence intervals.

DRUG PRODUCT PERFORMANCE

Drug product performance,\(^1\) *in vivo*, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance. The assessment of drug product performance is important since bioavailability is related to the pharmacodynamic response and related adverse events. Thus, performance tests relate the quality of a drug product to clinical safety and efficacy. 

Bioavailability studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, and the manufacture process of the drug product (dosage form). Bioavailability is one aspect of drug product quality that links the *in vivo* performance of a new drug product to the original formulation that was used in clinical safety and efficacy studies. Bioequivalence studies are drug product performance tests that compare the bioavailability of the same active pharmaceutical ingredient from one drug product (test) to a second drug product (reference). Bioavailability and bioequivalence can be considered as measures of the drug product performance *in vivo*.

Drug product performance studies are used in the development of new and generic drug products. The initial safety and efficacy clinical studies during new drug development may use a simple formulation such as a hard gelatin capsule containing only the active ingredient diluted with lactose. If the new drug demonstrates appropriate human efficacy and safety, a to-be-marketed drug product (eg, compressed tablet) may be developed. Since the initial safety and efficacy studies were performed using a different formulation (ie, hard gelatin capsule), the pharmaceutical manufacturer must demonstrate that the to-be-marketed drug product demonstrates equivalent drug product performance to the original formulation (Fig. 15-1). Equivalent drug product performance is generally demonstrated by an *in vivo* bioequivalence study in normal healthy volunteers. Under certain conditions, equivalent drug product performance may be demonstrated *in vitro* using comparative dissolution profiles (see Chapter 14).

\(^1\)A glossary of important terms appears at the end of this chapter.
Explain the conditions under which a generic drug product manufacturer may request a waiver (biowaiver) for performing an \textit{in vivo} bioequivalence study.

Define therapeutic equivalence and explain why bioequivalence is only one component of the regulatory requirements for therapeutic equivalence.

As stated above, the marketed drug product that is approved by the FDA may not be the same formulation that was used in the original safety and efficacy clinical studies. After the drug product is approved by the FDA and marketed, the manufacturer may perform changes to the formulation. These changes to the marketed drug product are known as postapproval changes (see also Chapter 16). These postapproval changes, often termed SUPAC (scale-up and postapproval change), could include a change in the supplier of the active ingredient, a change in the formulation, a change in the manufacturing process and/or a change in the manufacturing site. In each case, the manufacturer must demonstrate that drug product performance did not change and is the same for the drug product manufactured before and after the SUPAC change. As shown in Fig. 15-1, drug product performance may be determined \textit{in vivo} by bioequivalence studies or \textit{in vitro} by comparative drug/dissolution studies. BA = bioavailability.

Comparative drug product performance studies are important in the development of generic drug products (Fig. 15-2). A generic drug product is a \textit{multisource drug product}\(^2\) that has been approved by the FDA as a therapeutic equivalent to the reference listed drug product (usually the brand or innovator drug product) and has proven equivalent drug product performance. Clinical safety and efficacy studies are not generally performed on generic drug products. Since the formulation and method of manufacture of a drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is pharmaceutically equivalent, bioequivalent, and therapeutically equivalent.

\(^2\)\textit{Multisource drug products} are drug products that contains the same active drug substance in the same dosage form and are marketed by more than one pharmaceutical manufacturer.
In vitro and/or in vivo bioequivalence studies must be performed on a drug formulation proposed for marketing as a generic drug product. The essential pharmacokinetics of the active drug ingredient or therapeutic moiety must be characterized. Essential pharmacokinetic parameters, including the rate and extent of systemic absorption (ie, bioavailability), elimination half-life, and rates of excretion and metabolism, should be established after single-dose and possibly multiple-dose administration. Data from these in vivo bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

In vitro bioavailability studies are also performed for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and to characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation.

In summary, clinical studies are used to determine the safety and efficacy of drug products. Bioavailability studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, and manufacture process of the drug product (dosage form). Bioequivalence studies are used to compare the bioavailability of the same drug (same salt or ester) from various drug products.

A manufacturer may design a new formulation such as an extended release drug product that contains an active drug previously approved as a different dosage form (eg, immediate release drug product)

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3SUPAC changes are discussed in Chapter 16.

---
Bioavailability and bioequivalence can be considered as performance measures of the drug product in vivo. If the drug products are pharmaceutically equivalent, bioequivalent, and therapeutically equivalent (as defined above), then the clinical efficacy and the safety profile of these drug products are assumed to be similar and may be substituted for each other.

**Frequently Asked Questions**

- Why are bioequivalence studies considered as drug product performance studies?
- What are the differences between a safety/efficacy study and an in vivo bioequivalence study? How do the study objectives differ?
- What's the difference between drug product performance and bioequivalence?

**RELATIVE AND ABSOLUTE AVAILABILITY**

The area under the drug concentration–time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation. The AUC is dependent on the total quantity of available drug, $FD_0$, divided by the elimination rate constant, $k$, and the apparent volume of distribution, $V_D$. $F$ is the fraction of the dose absorbed. After IV administration, $F$ is equal to unity (1.0 or 100%), because the entire dose enters the systemic circulation. The drug is considered to be completely available after IV administration. After oral or other extravascular route of administration of a drug, $F$ may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption).

**Relative Availability**

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard. The fraction of dose systemically available from an oral drug product is difficult to ascertain. The availability of drug in the formulation is compared to the availability of drug in a standard dosage formulation, usually a solution of the pure drug evaluated in a crossover study. The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained using the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A}{[\text{AUC}]_B} \tag{15.1}$$

where drug product $B$ is the recognized reference standard. This fraction may be multiplied by 100 to give percent relative availability.

When different doses are administered, a correction for the size of the dose is made, as in the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A / \text{dose}_A}{[\text{AUC}]_B / \text{dose}_B} \tag{15.2}$$

Urinary drug excretion data may also be used to measure relative availability, as long as the total amount of intact drug excreted in the urine is collected. The percent relative availability using urinary excretion data can be determined as follows:

$$\text{Percent relative availability} = \frac{[D_u]_A}{[D_u]_B} \times 100 \tag{15.3}$$

where $[D_u]$ is the total amount of drug excreted in the urine.

Relative bioavailability may exceed the value of 1 or 100% as compared to the reference drug product.

**Absolute Availability**

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing. The absolute availability of a drug is generally measured by comparing the respective AUCs after extravascular and IV administration. This measurement may be performed as long as $V_D$ and $k$ are independent of the route of administration. Absolute availability after oral drug administration using plasma data can be determined as follows:

$$\text{Absolute availability} = F = \frac{[\text{AUC}]_{PO}/\text{dose}_O}{[\text{AUC}]_{IV}/\text{dose}_IV} \tag{15.4}$$

Absolute availability, $F$, may be expressed as a fraction or as a percent by multiplying $F \times 100$. 
Absolute availability using urinary drug excretion data can be determined by the following:

\[
\text{Absolute availability} = \frac{[D]_{\text{oral}}/\text{dose}_{\text{oral}}}{[D]_{\text{IV}}/\text{dose}_{\text{IV}}} 
\]  

(15.5)

The absolute bioavailability is also equal to \( F \), the fraction of the dose that is bioavailable. Absolute availability is sometimes expressed as a percent, ie, \( F = 1 \), or 100%. For drugs given intravascularly, such as by IV bolus injection, \( F = 1 \) because all of the drug is completely absorbed. For all extravascular routes of administration, such as the oral route (PO), the absolute bioavailability, \( F \) may not exceed 100% \( (F > 1) \). \( F \) is usually determined by Equation 15.4 or 15.5, where PO is the oral route or any other extravascular route of drug administration.

**PRACTICE PROBLEM**

The bioavailability of a new investigational drug was studied in 12 volunteers. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. Plasma samples were obtained periodically up to 48 hours after the dose and assayed for drug concentration. The average AUC values (0–48 hours) are given in the table below. From these data, calculate (a) the relative bioavailability of the drug from the tablet compared to the oral solution and (b) the absolute bioavailability of the drug from the tablet.

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Dose (mg)</th>
<th>AUC (μg h/mL)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tablet</td>
<td>200</td>
<td>89.5</td>
<td>19.7</td>
</tr>
<tr>
<td>Oral solution</td>
<td>200</td>
<td>86.1</td>
<td>18.1</td>
</tr>
<tr>
<td>IV bolus injection</td>
<td>50</td>
<td>37.8</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**Solution**

The relative bioavailability of the drug from the tablet is estimated using Equation 15.1. No adjustment for dose is necessary.

Relative bioavailability = \( \frac{89.5}{86.1} = 1.04 \) or 104%

The absolute bioavailability of the drug from the tablet is 1.04, or 104%, compared to the solution. In this study, the difference in drug bioavailability between tablet and solution was not statistically significant. It is possible for the relative bioavailability to be greater than 100%.

The absolute drug bioavailability from the tablet is calculated using Equation 15.4 and adjusting for the dose.

\[
F = \frac{\text{absolute bioavailability}}{\text{dose}} = \frac{89.5/200}{37.5/50} = 0.592 \text{ or } 59.2%
\]

Because \( F \), the fraction of dose absorbed from the tablet, is less than 1, the drug is not completely absorbed systemically, as a result of either poor absorption or metabolism by first-pass effect. The relative bioavailability of the drug from the tablet is approximately 100% when compared to the oral solution.

Results from bioequivalence studies may show that the relative bioavailability of the test oral product is greater than, equal to, or less than 100% compared to the reference oral drug product. However, the results from these bioequivalence studies should not be misinterpreted to imply that the absolute bioavailability of the drug from the oral drug products is also 100% unless the oral formulation was compared to an intravenous injection of the drug.

**METHODS FOR ASSESSING BIOAVAILABILITY**

Direct and indirect methods may be used to assess drug bioavailability. The in vivo bioavailability of a drug product is demonstrated by the rate and extent of drug absorption, as determined by comparison of measured parameters, eg, concentration of the active drug ingredient in the blood, cumulative urinary excretion rates, or pharmacological effects. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent
to which the active ingredient or active moiety becomes available at the site of action. The design of the bioavailability study depends on the objectives of the study, the ability to analyze the drug (and metabolites) in biological fluids, the pharmacodynamics of the drug substance, the route of drug administration, and the nature of the drug product. Pharmacokinetic and/or pharmacodynamic parameters as well as clinical observations and in vitro studies may be used to determine drug bioavailability from a drug product (Table 15-1).

**Frequently Asked Questions**

- **What are the study protocol considerations for conducting a bioequivalence study?**
- **What is the reference listed drug, RLD, and how is the RLD selected?**
- **How is a bioavailability study of a new molecular entity conducted?**
- **Why does the value for relative bioavailability sometimes exceed 1.0, whereas the value for absolute bioavailability cannot exceed 1.0?**

**TABLE 15-1 Methods for Assessing Bioavailability and Bioequivalence**

<table>
<thead>
<tr>
<th>Plasma drug concentration</th>
<th>Time for peak plasma (blood) concentration (t_max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak plasma drug concentration (C_max)</td>
</tr>
<tr>
<td></td>
<td>Area under the plasma drug concentration–time curve (AUC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary drug excretion</th>
<th>Cumulative amount of drug excreted in the urine (D_u)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of drug excretion in the urine (dD_u/dt)</td>
</tr>
<tr>
<td></td>
<td>Time for maximum urinary excretion (t)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute pharmacodynamic effect</th>
<th>Maximum pharmacodynamic effect (E_max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time for maximum pharmacodynamic effect</td>
</tr>
<tr>
<td></td>
<td>Area under the pharmacodynamic effect—time curve</td>
</tr>
<tr>
<td></td>
<td>Onset time for pharmacodynamic effect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical observations</th>
<th>Well-controlled clinical trials</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Invitro studies</th>
<th>Drug dissolution</th>
</tr>
</thead>
</table>

**Plasma Drug Concentration**

Measurement of drug concentrations in blood, plasma, or serum after drug administration is the most direct and objective way to determine systemic drug bioavailability. By appropriate blood sampling, an accurate description of the plasma drug concentration–time profile of the therapeutically active drug substance(s) can be obtained using a validated drug assay.

**t_max:** The time of peak plasma concentration, t_max, corresponds to the time required to reach maximum drug concentration after drug administration. At t_max, peak drug absorption occurs and the rate of drug absorption exactly equals the rate of drug elimination (Fig. 15-3). Drug absorption still continues after t_max is reached, but at a slower rate. When comparing drug products, t_max can be used as an approximate indication of drug absorption rate. The value for t_max will become smaller (indicating less time required to reach peak plasma concentration) as the absorption rate for the drug becomes more rapid. Units for t_max are units of time (eg, hours, minutes).

**C_max:** The peak plasma drug concentration, C_max, represents the maximum plasma drug concentration obtained after oral administration of drug. For many drugs, a relationship is found between the pharmacodynamic drug effect and the plasma drug concentration. C_max provides indications that the drug is sufficiently systemically absorbed to provide a therapeutic response. In addition, C_max provides warning of possibly toxic levels of drug. The units of C_max are concentration units (eg, mg/mL, ng/mL). Although not a unit for rate, C_max is often used in bioequivalence studies as a surrogate measure for the rate of drug bioavailability.

**AUC:** The area under the plasma level–time curve, AUC, is a measurement of the extent of drug bioavailability (see Fig. 15-3). The AUC reflects the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma level–time curve from t = 0 to t = ∞, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.
Drug Product Performance, *In Vivo*: Bioavailability and Bioequivalence

409

an enzyme-dependent process. For drugs such as salicylate and phenytoin, continued increase of the dose causes saturation of one of the enzyme pathways for drug metabolism and consequent prolongation of the elimination half-life. The 

\[ \text{AUC} = \int_0^\infty C_d \, dt \]  

(15.6)

\[ [\text{AUC}]_0^\infty = \frac{FD_0}{\text{clearance}} = \frac{FD_0}{kV_D} \]  

(15.7)

where \( F \) = fraction of dose absorbed, \( D_0 \) = dose, \( k \) = elimination rate constant, and \( V_D \) = volume of distribution. The AUC is independent of the route of administration and processes of drug elimination as long as the elimination processes do not change. The AUC can be determined by a numerical integration procedure, such as the trapezoidal rule method. The units for AUC are concentration × time (eg, \( \mu g \, h/mL \)).

For many drugs, the AUC is directly proportional to dose. For example, if a single dose of a drug is increased from 250 to 1000 mg, the AUC will also show a fourfold increase (Figs. 15-4 and 15-5).

In some cases, the AUC is not directly proportional to the administered dose for all dosage levels. For example, as the dosage of drug is increased, one of the pathways for drug elimination may become saturated (Fig. 15-6).

Drug elimination includes the processes of metabolism and excretion. Drug metabolism is
difficult to evaluate because drug kinetics may be dose dependent. Conversely, absorption may also become saturated resulting in lower-than-expected changes in AUC.

**Urinary Drug Excretion Data**

Urinary drug excretion data is an indirect method for estimating bioavailability. The drug must be excreted in significant quantities as unchanged drug in the urine. In addition, timely urine samples must be collected and the total amount of urinary drug excretion must be obtained (see Chapter 3).

\( D_u^\infty \): The cumulative amount of drug excreted in the urine, \( D_u^\infty \), is related directly to the total amount of drug absorbed. Experimentally, urine samples are collected periodically after administration of a drug product. Each urine specimen is analyzed for free drug using a specific assay. A graph is constructed that relates the cumulative drug excreted to the collection-time interval (Fig. 15-7).

The relationship between the cumulative amount of drug excreted in the urine and the plasma level–time curve is shown in Fig. 15-6. When the drug is almost completely eliminated (point \( C \)), the plasma concentration approaches zero and the maximum amount of drug excreted in the urine, \( D_u^\infty \), is obtained. 

\( dD_u/dt \): The rate of drug excretion. Because most drugs are eliminated by a first-order rate process, the rate of drug excretion is dependent on the first-order elimination rate constant, \( k \) and the concentration of drug in the plasma, \( C_p \). In Fig. 15-8, the maximum rate of drug excretion, \( (dD_u/dt)_{\text{max}} \), is at point \( B \), whereas the minimum rate of drug excretion is at points \( A \) and \( C \). Thus, a graph comparing the rate of drug excretion with respect to time should be similar in shape to the plasma level–time curve for that drug (Fig. 15-9).

\( t^\infty \): The total time for the drug to be excreted. In Figs. 15-8 and 15-9, the slope of the curve segment \( A-B \) is related to the rate of drug absorption, whereas point \( C \) is related to the total time required after drug administration for the drug to be absorbed and completely excreted, \( t = \infty \). The \( t^\infty \) is a useful parameter in bioequivalence studies that compare several drug products.
Acute Pharmacodynamic Effect

In some cases, the quantitative measurement of a drug in plasma or urine lacks an assay with sufficient accuracy and/or reproducibility. For locally acting, nonsystemically absorbed drug products, such as topical corticosteroids, plasma drug concentrations may not reflect the bioavailability of the drug at the site of action. An acute pharmacodynamic effect, such as an effect on forced expiratory volume, FEV$_1$ (inhaled bronchodilators), or skin blanching (topical corticosteroids) can be used as an index of drug bioavailability. In this case, the acute pharmacodynamic effect is measured over a period of time after administration of the drug product. Measurements of the pharmacodynamic effect should be made with sufficient frequency to permit a reasonable estimate for a time period at least three times the half-life of the drug (Gardner, 1977). This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

The use of an acute pharmacodynamic effect to determine bioavailability generally requires demonstration of a dose–response curve (Fig. 15-10 and Chapter 19). Bioavailability is determined by...
The clinical trials approach is the least accurate, least sensitive to bioavailability differences, and most variable. The highly variable clinical responses require the use of a large patient population which increases the study costs and requires a longer time to complete compared to the other approaches for determination of bioequivalence. The FDA considers this approach only when analytical methods and pharmacodynamic methods are not available to permit use of one of the approaches described above. Comparative clinical studies have been used to establish bioequivalence for topical antifungal drug products (e.g., ketoconazole) and for topical acne preparations. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the other approaches.

**In Vitro Studies**

Comparative drug release/dissolution studies under certain conditions may give an indication of drug bioavailability and bioequivalence. Ideally, the *in vitro* drug dissolution rate should correlate with *in vivo* drug bioavailability (see Chapters 7 and 14 on *in vivo–in vitro* correlation, IVIVC). Comparative dissolution studies are often performed on several test formulations of the same drug during drug development. For drugs whose dissolution rate is related to the rate of systemic absorption, the test formulation that demonstrates the most rapid rate of drug dissolution *in vitro* will generally have the most rapid rate of drug bioavailability *in vivo*. Under certain conditions, comparative dissolution profiles of higher and lower dose strengths of a solid oral drug product such as an immediate-release tablet, are used to obtain a waiver (bio waiver) from performing an *in vivo* bioequivalence study on the lower-dose strength drug product.\(^6\)

The FDA may also use *in vitro* approaches other than comparative dissolution for establishing bioequivalence. The use of the *Biopharmaceutics Classification System* (Biopharm) is a method to predict the rate and extent of drug absorption from *in vitro* dissolution data.

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5. A pharmacodynamic endpoint is an acute pharmacologic effect that is directly related to the drug’s activity that can be measured quantitatively. An example is changes in FEV\(_1\) (forced expiratory volume) that can be measured after the administration of a bronchodilator such as albuterol inhalation.

Drug Product Performance, In Vivo: Bioavailability and Bioequivalence

413

the presence of food or even a change in the metabolic clearance of the drug. Feldman and associates (1982) reported that patients on a high-carbohydrate diet have a much longer elimination half-life of theophylline, due to the reduced metabolic clearance of the drug ($t_{1/2} = 18.1$ hours), compared to patients on normal diets ($t_{1/2} = 6.76$ hours). Previous studies demonstrated that the theophylline drug product was completely bioavailable. The higher plasma drug concentration resulting from a carbohydrate diet may subject the patient to a higher risk of drug intoxication with theophylline. The effect of food on the availability of theophylline has been reported by the FDA concerning the risk of higher theophylline plasma concentrations from a 24-hour sustained-release drug product taken with food. Although most bioavailability drug studies use fasted volunteers, the diet of patients actually using the drug product may increase, decrease, or have no effect on the bioavailability of the drug (Hendles et al, 1984).

BIOEQUIVALENCE STUDIES

Differences in the predicted clinical response or an adverse event may be due to differences in the pharmacokinetic and/or pharmacodynamic behavior of the drug among individuals or to differences in the bioavailability of the drug from the drug product. Bioequivalent drug products that have the same systemic drug bioavailability will have the same predictable drug response. However, variable clinical responses among individuals that are unrelated to bioavailability may also be due to differences in the pharmacodynamics of the drug. Differences in pharmacodynamics, ie, the relationship between the drug and the receptor site, may be due to differences in receptor sensitivity to the drug. Various factors affecting pharmacodynamic drug behavior may include age, drug tolerance, drug interactions, and unknown pathophysiologic factors.

The bioavailability of a drug may be more reproducible among fasted individuals in controlled studies who take the drug on an empty stomach. When the drug is used on a daily basis, however, the nature of an individual’s diet and lifestyle may affect the plasma drug levels because of variable absorption in the presence of food or even a change in the metabolic clearance of the drug. Feldman and associates (1982) reported that patients on a high-carbohydrate diet have a much longer elimination half-life of theophylline, due to the reduced metabolic clearance of the drug ($t_{1/2} = 18.1$ hours), compared to patients on normal diets ($t_{1/2} = 6.76$ hours). Previous studies demonstrated that the theophylline drug product was completely bioavailable. The higher plasma drug concentration resulting from a carbohydrate diet may subject the patient to a higher risk of drug intoxication with theophylline. The effect of food on the availability of theophylline has been reported by the FDA concerning the risk of higher theophylline plasma concentrations from a 24-hour sustained-release drug product taken with food. Although most bioavailability drug studies use fasted volunteers, the diet of patients actually using the drug product may increase, decrease, or have no effect on the bioavailability of the drug (Hendles et al, 1984).

Bases for Determining Bioequivalence

Bioequivalence is established if the in vivo bioavailability of a test drug product (usually the generic product) does not differ significantly (ie, statistically insignificant) from that of the reference listed drug (usually the brand-name product) in the product’s rate and extent of drug absorption. Bioequivalence is determined by comparison of measured parameters (eg, concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacodynamic effects), when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.

In a few cases, a drug product that differs from the reference listed drug in its rate of absorption, but not in its extent of absorption, may be considered bioequivalent if the difference in the rate of absorption is intentional and appropriately reflected in the labeling and/or the rate of absorption is not detrimental to the safety and effectiveness of the drug product.

Drug Products with Possible Bioavailability and Bioequivalence Problems

Lack of bioequivalence may be suspected when evidence from well-controlled clinical trials or controlled
observations in patients of various marketed drug products do not give comparable therapeutic effects. These drug products need to be evaluated either in vitro (eg, drug dissolution/release test) or in vivo (eg, bioequivalence study) to determine if the drug product has a bioavailability problem (see also US Code of Federal Regulations, 21 CFR 320.33).

In addition, during the development of a drug product, certain biopharmaceutical properties of the active drug substance or the formulation of the drug product may indicate that the drug may have variable bioavailability and/or a bioequivalence problem. Some of these biopharmaceutic indicators include:

- The active drug ingredient has low solubility in water (eg, less than 5 mg/mL).
- The dissolution rate of one or more such products is slow (eg, <50% in 30 minutes when tested with a general method specified by the FDA).
- The particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability.
- Certain structural forms of the active drug ingredient (eg, polymorphic forms, solvates, complexes, and crystal modifications) dissolve poorly, thus affecting absorption.
- Drug products that have a high ratio of excipients to active ingredients (eg, >5:1).
- Specific inactive ingredients (eg, hydrophilic or hydrophobic excipients and lubricants) either may be required for absorption of the active drug or may interfere with such absorption.
- The active drug ingredient, or its precursor is absorbed mostly in a particular segment of the GI tract or is absorbed from a localized site.
- The degree of absorption of the therapeutic moiety or its precursor is poor (eg, <50%, ordinarily in comparison to an intravenous dose), even when it is administered in pure form (eg, in solution).
- There is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the absorption process (first-pass metabolism), so that the rate of absorption is unusually important in the therapeutic effect and/or toxicity of the drug product.
- The therapeutic moiety is rapidly metabolized or excreted, so that rapid dissolution and absorption are required for effectiveness.
- The active drug ingredient or therapeutic moiety is unstable in specific portions of the GI tract and requires special coatings or formulations (eg, buffers, enteric coatings, etc) to ensure adequate absorption.
- The drug product is subject to dose-dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important in establishing bioequivalence.

**DESIGN AND EVALUATION OF BIOEQUIVALENCE STUDIES**

**Objective**
All scientific studies should have clearly stated objectives. The main objective for a bioequivalence study is that the drug bioavailability from test and reference products are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.

**Study Considerations**
The basic design for a bioequivalence study is determined by (1) the scientific questions and objectives to be answered, (2) the nature of the reference material and the dosage form to be tested, (3) the availability of analytical methods, (4) the pharmacokinetics and pharmacodynamics of the drug substance, (5) the route of drug administration, and (6) benefit–risk and ethical considerations with regard to testing in humans.

Since bioequivalence studies are performed to compare the bioavailability of the generic drug product to the brand-name product, the statistical techniques should be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability. Once bioequivalence is established, it is likely that both the generic and brand-name dosage forms will produce the same therapeutic effect. The FDA publishes guidances for bioequivalence studies (www.fda.gov/cder/guidance; see also 21 CFR 320.25). Sponsors may also request a meeting with the FDA to review the study design.
for a specific drug product. Pharmacokinetic parameters, pharmacodynamic parameters, clinical observations and/or in vitro studies may be used to determine drug bioavailability from a drug product.

The design and evaluation of well-controlled bioequivalence studies require cooperative input from pharmacokineticists, statisticians, clinicians, bioanalytical chemists, and others. For some generic drugs, the FDA offers general guidelines for conducting these studies. For example, Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design is available from the FDA; the publication addresses three specific aspects, including (1) logarithmic transformation of pharmacokinetic data, (2) sequence effect, and (3) outlier consideration. However, even with the availability of such guidelines, the principal investigator should prepare a detailed protocol for the study. Some of the elements of a protocol for an in vivo bioavailability study are listed in Table 15-2. Bioavailability studies for controlled-release dosage forms are discussed in Chapter 17.

For bioequivalence studies, the test and reference drug formulations must contain the pharmaceutically equivalent drug in the same dose strength and in similar dosage forms (eg, immediate release or controlled release), and it must be given by the same route of administration. Both a single-dose and/or a multiple-dose (steady-state) study may be required. Before beginning the study, the Institutional Review Board (IRB) of the clinical facility in which the study is to be performed must approve the study. The IRB is composed of both professional and lay persons with diverse backgrounds who have clinical experience and expertise as well as sensitivity to ethical issues and community attitudes. The IRB is responsible for all ethical issues including safeguarding the rights and welfare of human subjects.

The basic guiding principle in performing studies is do not do unnecessary human research. Generally, the study is performed in normal, healthy male and female volunteers who have given informed consent to be in the study. Critically ill patients are not included in an in vivo bioavailability study unless the attending physician determines that there is a potential benefit to the patient. The number of subjects in the study will depend on the expected intersubject and intrasubject variability. Patient selection is made according to certain established criteria for inclusion in, or exclusion from, the study. For example, the study might exclude any volunteers who have known

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**TABLE 15-2 Elements of a Bioavailability Study Protocol**

<table>
<thead>
<tr>
<th>I. Title</th>
<th>B. Project/protocol number and date</th>
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<tbody>
<tr>
<td>A. Principal investigator (study director)</td>
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<td>II. Study objective</td>
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<td>III. Study design</td>
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<tr>
<td>A. Design</td>
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<td>B. Drug products</td>
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<td>1. Test product(s)</td>
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<td>2. Reference product</td>
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<td>C. Dosage regimen</td>
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<td>D. Sample collection schedule</td>
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<td>E. Housing/confine ment</td>
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<td>F. Fasting/meals schedule</td>
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<td>G. Analytical methods</td>
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<td>IV. Study population</td>
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<td>A. Subjects</td>
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<td>B. Subject selection</td>
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<td>1. Medical history</td>
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<td>2. Physical examination</td>
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<td>3. Laboratory tests</td>
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<tr>
<td>C. Inclusion/exclusion criteria</td>
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<tr>
<td>1. Inclusion criteria</td>
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<td>2. Exclusion criteria</td>
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<td>D. Restrictions/prohibitions</td>
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<td>V. Clinical procedures</td>
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<tr>
<td>A. Dosage and drug administration</td>
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<td>B. Biological sampling schedule and handling procedures</td>
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<td>C. Activity of subjects</td>
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<td>VI. Ethical considerations</td>
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<td>A. Basic principles</td>
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<td>B. Institutional review board</td>
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<td>C. Informed consent</td>
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<td>D. Indications for subject withdrawal</td>
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<td>E. Adverse reactions and emergency procedures</td>
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<td>VII. Facilities</td>
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<td>VIII. Data analysis</td>
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<td>A. Analytical validation procedure</td>
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<td>B. Statistical treatment of data</td>
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<td>IX. Drug accountability</td>
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<td>X. Appendix</td>
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allergies to the drug, are overweight, or have taken any medication within a specified period (often 1 week) prior to the study. Moderate smokers may be included in these studies. The subjects generally fast for 10 to 12 hours (overnight) prior to drug administration and may continue to fast for a 2- to 4-hour period after dosing.

Reference Listed Drug, RLD

For bioequivalence studies, one formulation of the drug is chosen as a reference standard against which all other formulations of the drug are compared. The FDA designates a single reference listed drug\(^7\) as the standard drug product to which all generic versions must be shown to be bioequivalent. The FDA hopes to avoid possible significant variations among generic drugs and their brand-name counterparts. Such variations could result if generic drugs were compared to different reference listed drugs.

The reference drug product should be administered by the same route as the comparison formulations unless an alternative route or additional route is needed to answer specific pharmacokinetic questions. For example, if an active drug is poorly bioavailable after oral administration, the drug may be compared to an oral solution or an intravenous injection. For bioequivalence studies on a proposed generic drug product the reference standard is the reference listed drug (RLD), which is listed in Approved Drug Products with Therapeutic Equivalence Evaluations—the Orange Book (www.fda.gov/cder/ob/default.htm), and the proposed generic drug product is often referred to as the “test” drug product. The RLD is generally a formulation currently marketed with a fully approved NDA for which there are valid scientific safety and efficacy data. The RLD is usually the innovator’s or original manufacturer’s brand-name product and is administered according to the dosage recommendations in the labeling.

Before beginning an in vivo bioequivalence study, the total content of the active drug substance in the test product (generally the generic product) must be within 5% of that of the reference product. Moreover, in vitro comparative dissolution or drug-release studies under various specified conditions are usually performed for both test and reference products before performing the in vivo bioequivalence study.

Modified-Release Formulations

The purpose of an in vivo bioavailability study involving an extended-release drug product is to determine if (1) the drug product meets the controlled-release claims made for it, (2) the bioavailability profile established for the drug product rules out the occurrence of any dose-dumping, (3) the drug product’s steady-state performance is equivalent to that of a currently marketed non-extended-release formulation, and (4) the drug product’s formulation provides consistent pharmacokinetic performance between individual dosage units. A comparison bioavailability study is used for the development of a new extended-release drug product in which the reference drug product may be either a solution or suspension of the active ingredient or a currently marketed non-controlled-release drug product such as a tablet or capsule. For example, the bioavailability of a non-controlled-release (immediate-release) drug product given at a dose of 25 mg every 8 hours is compared to an extended-release product containing 75 mg of the same drug given once daily.

For a bioequivalence study of a new generic extended-release drug product, the reference drug product is the currently marketed-extended release drug product listed as the RLD in the Orange Book and is administered according to the dosage recommendations in the approved labeling.

Combination Drug Products

Generally, the purpose of an in vivo bioavailability study involving a combination drug product containing more than one active drug substance is to determine if the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations. The reference

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\(^7\)The reference listed drug, RLD, is listed in the Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations. www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
Drug Product Performance, In Vivo: Bioavailability and Bioequivalence

and in vivo bioequivalence studies. Generally, two bioequivalence studies are required for solid oral dosage forms, including (1) a fasting study and (2) a food intervention study. For extended-release capsules containing beads (pellets) that might be poured on a semi-solid food such as applesauce, an additional “sprinkle” bioequivalence study is required. Other study designs such as a multiple-dose (steady-state) bioequivalence study have been proposed by the FDA. Proper study design and statistical evolution are important considerations for the determination of bioequivalence. Some of the designs listed above are summarized here.

### Fasting Study

Bioequivalence studies are usually evaluated by a single-dose, two-period, two-treatment, two-sequence, open-label, randomized crossover design comparing equal doses of the test and reference products in fasted, adult, healthy subjects. This study is required for all immediate-release and modified-release oral dosage forms. Both male and female subjects may be used in the study. Blood sampling is performed just before (zero time) the dose and at appropriate intervals after the dose to obtain an adequate description of the plasma drug concentration–time profile. The subjects should be in the fasting state (overnight fast of at least 10 hours) before drug administration and should continue to fast for up to 4 hours after dosing. No other medication is normally given to the subject for at least 1 week prior to the study. In some cases, a parallel design may be more appropriate for certain drug products, containing a drug with a very long elimination half-life. A replicate design may be used for a drug product containing a drug that has high intrasubject variability.

### Food Intervention Study

Co-administration of food with an oral drug product may affect the bioavailability of the drug. Food intervention or food effect studies are generally conducted using meal...
CROSSOVER STUDY DESIGNS

Subjects who meet the inclusion and exclusion study criteria and have given informed consent are selected at random. A complete crossover design is usually employed, in which each subject receives the test drug product and the reference product. Examples of Latin-square crossover designs for a bioequivalence study in human volunteers, comparing three different drug formulations (A, B, C) or four different drug formulations (A, B, C, D), are described in Tables 10.3 and 10.4. The Latin-square design plans the clinical trial so that each subject receives each drug product only once, with adequate time between medications for the elimination of the drug from the body (see Table 15-3). In this design, each subject is his own control, and subject-to-subject variation is reduced. Moreover, variation due to sequence, period, and treatment (formulation) are reduced, so that all patients do not receive the same drug product on the same day and in the same order. Possible carryover effects from any particular drug product are minimized by changing the sequence or order in which the drug products are given to the subject. Thus, drug product B may be followed by drug product A, D, or C (see Table 15-4). After each subject receives a drug product, blood samples are collected at appropriate time intervals so that a valid blood drug level–time curve is obtained. The time intervals should be spaced so that the peak blood concentration, the total area under the curve, and the absorption conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability.

Meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. The test meal is a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. A typical test meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz of brown potatoes, and 8 oz of milk. This test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (www.fda.gov/cder/guidance/4613dft.pdf).

For bioequivalence studies, drug bioavailability from both the test and reference products should be affected similarly by food. The study design uses a single-dose, randomized, two-treatment, two-period, crossover study comparing equal doses of the test and reference products. Following an overnight fast of at least 10 hours, subjects are given the recommended meal 30 minutes before dosing. The meal is consumed over 30 minutes, with administration of the drug product immediately after the meal. The drug product is given with 240 mL (8 fluid oz) of water. No food is allowed for at least 4 hours post-dose. This study is required for all modified-release dosage forms and may be required for immediate-release dosage forms if the bioavailability of the active drug ingredient is known to be affected by food (e.g., ibuprofen, naproxen). For certain extended-release capsules that contain coated beads, the capsule contents are sprinkled over soft foods such as applesauce, which is taken by the fasted subject and the bioavailability of the drug is then measured. Bioavailability studies might also examine the effects of other foods and special vehicles such as apple juice.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Study Period 1</th>
<th>Study Period 2</th>
<th>Study Period 3</th>
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<tr>
<td>1</td>
<td>A</td>
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<td>6</td>
<td>B</td>
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Table 15-4 shows a design for three different drug treatment groups given in a three-period study with six different sequences. The order in which the drug treatments are given should not stay the same in order to prevent any bias in the data due to a residual effect from the previous treatment.

### Replicated Crossover Study Designs

The standard bioequivalence criteria using the standard crossover design and a reasonable number of study subjects (<80 subjects) is difficult to achieve with highly variable drugs and drug products (%CV greater than 30). Drugs with high within-subject variability generally have a wide therapeutic window and despite high variability, these products have been demonstrated to be both safe and effective. Replicate designs for highly variable drugs/products require a smaller number of subjects and therefore, do not unnecessarily expose a large number of healthy subjects to a drug when this large number of subjects is not needed for assurance of bioequivalence (Haidar et al, 2008).

Replicated crossover designs are used for the determination of individual bioequivalence, to estimate within-subject variance for both the test and reference drug products, and to provide an estimate of the subject-by-formulation interaction variance. A four-period, two-sequence, two-formulation design is shown below:

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence 1</td>
<td>T</td>
<td>R</td>
<td>T</td>
</tr>
<tr>
<td>Sequence 2</td>
<td>R</td>
<td>T</td>
<td>R</td>
</tr>
</tbody>
</table>

where R = reference and T = treatment.

### Scaled Average Bioequivalence

Recently a three-sequence, three-period, two-treatment partially replicated crossover design for bioequivalence studies of highly variable drugs has been
Chapter 15

plasma drug levels. The multiple-dose study is designed as a steady-state, randomized, two-treatment, two-way, crossover study comparing equal doses of the test and reference products in healthy adult subjects. Each subject receives either the test or reference product separated by a “washout” period, which is the time needed for the drug to be completely eliminated from the body.

To ascertain that the subjects are at steady state, three consecutive trough concentrations \(C_{\text{min}}\) are determined. The last morning dose is given to the subject after an overnight fast, with continual fasting for at least 2 hours following dose administration. Blood sampling is then performed similar to the single-dose study.

Pharmacokinetic analyses for multiple-dose studies include calculation of the following parameters for each subject:

- \(AUC_{0-t}\) — Area under the curve during a dosing interval
- \(t_{\text{max}}\) — Time to \(C_{\text{max}}\) during a dosing interval
- \(C_{\text{max}}\) — Maximum drug concentration during dosing interval
- \(C_{\text{min}}\) — Drug concentration at the end of a dosing interval
- \(C_{\text{av}}\) — The average drug concentration during a dosing interval

Degree of Fluctuation = \(\frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{max}}}\)

Swing = \(\frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{min}}}\)

The data are analyzed statistically using analysis of variance (ANOVA) on the log-transformed \(AUC\) and \(C_{\text{max}}\). To establish bioequivalence, both \(AUC\) and \(C_{\text{max}}\) for the test (generic) product should be within 80% to 125% of the reference product using a 90% confidence interval. Estimation of the absorption rate constant during multiple dosing is difficult, because the residual drug from the previous dose superimposes on the dose that follows. However, the data obtained in multiple doses are useful in calculating a steady-state plasma level.

The extent of bioavailability, measured by assuming the \([AUC]_0\) is dependent on clearance:

\[ [AUC]_0 = \frac{FD_s}{Cl_T} \]

### Table

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence 1</td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Sequence 2</td>
<td>R</td>
<td>T</td>
</tr>
<tr>
<td>Sequence 3</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

Under this design, if the test product has lower variability than the reference product, the study will need a smaller number of subjects to pass the bioequivalence criteria. Scaled average bioequivalence is evaluated for both \(AUC\) and \(C_{\text{max}}\).

### Nonreplicate, Parallel Study Designs

A nonreplicate, parallel design is used for drug products that contain drugs that have a long elimination half-life or drug products such as depot injections in which the drug is slowly released over weeks or months. In this design, two separate groups of volunteers are used. One group will be given the test product and the other group will be given the reference product. It is important to balance the demographics of both groups of volunteers. Blood sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. \(C_{\text{max}}\) and a suitably truncated \(AUC\), generally to 72 hours after dose administration, can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, an \(AUC\) truncated at 72 hours (\(AUC_{72}\)) can be used in place of \(AUC_{0\rightarrow\infty}\) or \(AUC_{0\rightarrow\infty}\). This design is not recommended for drugs that have high intrasubject variability in distribution and clearance.

### Multiple-Dose (Steady-State) Study Design

A bioequivalence study may be performed using a multiple-dose study design. Multiple doses of the same drug are given consecutively to reach steady-state plasma drug levels. The multiple-dose study is designed as a steady-state, randomized, two-treatment, two-way, crossover study comparing equal doses of the test and reference products in healthy adult subjects. Each subject receives either the test or reference product separated by a “washout” period, which is the time needed for the drug to be completely eliminated from the body.

To ascertain that the subjects are at steady state, three consecutive trough concentrations \(C_{\text{min}}\) are determined. The last morning dose is given to the subject after an overnight fast, with continual fasting for at least 2 hours following dose administration. Blood sampling is then performed similar to the single-dose study.

Pharmacokinetic analyses for multiple-dose studies include calculation of the following parameters for each subject:

- \(AUC_{0-t}\) — Area under the curve during a dosing interval
- \(t_{\text{max}}\) — Time to \(C_{\text{max}}\) during a dosing interval
- \(C_{\text{max}}\) — Maximum drug concentration during dosing interval
- \(C_{\text{min}}\) — Drug concentration at the end of a dosing interval
- \(C_{\text{av}}\) — The average drug concentration during a dosing interval

Degree of Fluctuation = \(\frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{max}}}\)

Swing = \(\frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{min}}}\)

The data are analyzed statistically using analysis of variance (ANOVA) on the log-transformed \(AUC\) and \(C_{\text{max}}\). To establish bioequivalence, both \(AUC\) and \(C_{\text{max}}\) for the test (generic) product should be within 80% to 125% of the reference product using a 90% confidence interval. Estimation of the absorption rate constant during multiple dosing is difficult, because the residual drug from the previous dose superimposes on the dose that follows. However, the data obtained in multiple doses are useful in calculating a steady-state plasma level.

The extent of bioavailability, measured by assuming the \([AUC]_0\) is dependent on clearance:

\[ [AUC]_0 = \frac{FD_s}{Cl_T} \]
Drug Product Performance, In Vivo: Bioavailability and Bioequivalence

Determination of bioequivalence using multiple doses reveals changes that are normally not detected in a single-dose study. For example, nonlinear pharmacokinetics may occur after multiple drug doses due to the higher plasma drug concentrations saturating an enzyme system involved in absorption or elimination of the drug. Nonlinear pharmacokinetics after multiple-dose studies may be observed by rising $C_{\text{min}}$ drug concentrations after each dosing interval. With some drugs, a drug-induced malabsorption syndrome can also alter the percentage of drug absorbed. In this case, drug bioavailability may decrease after repeated doses if the fraction of the dose absorbed ($F$) decreases or if the total body clearance ($kV_D$) increases.

There are several disadvantages of using the multiple-dose crossover method for the determination of bioequivalence. (1) The study takes more time to perform, because steady-state conditions must be reached. A longer time for completion of a study leads to greater clinical costs and the possibility of a subject dropping out and not completing the study. (2) More plasma samples must be obtained from the patient to ascertain that steady state has been reached and to describe the plasma level–time curve accurately. (3) Because $C_\text{av}$ depends primarily on the dose of the drug and the time interval between doses, the extent of drug systematically available is more important than the rate of drug availability. Small differences in the rate of drug absorption may not be observed with steady-state study comparisons. If there is wide variation in the rate of a drug’s availability, then it is possible that initial high blood levels may lead to toxicity.

**Clinical Endpoint Bioequivalence Study**

Study design for a clinical endpoint study generally consists of a randomized, double-blind, placebo-controlled, parallel-designed study comparing test product, reference product, and placebo product in patients. In some cases, the use of a placebo may not be included for safety reasons. The primary analysis for bioequivalence is determined by evaluating the difference between the proportion of patients in the test and reference treatment groups who are considered a “therapeutic cure” at the end of study. The superiority of the test and reference products against the placebo is also tested using the same dichotomous endpoint of “therapeutic cure.”

**Determination of Bioequivalence of Drug Products in Patients Maintained on a Therapeutic Drug Regimen**

A bioequivalence study may be performed in patients already maintained on the reference (brand-name) drug. Due to safety concerns, certain drugs such as clozapine, a dibenzodiazepine derivative with potent antipsychotic properties should not be given to normal healthy subjects. Instead, bioequivalence studies on clozapine should be performed in patients who have been stabilized on the highest strength (eg, 100 mg) using a multiple-dose bioequivalence study design. Patients on these or other drugs such as hormone replacement therapy and cancer chemotherapeutic drugs would be at risk if a washout period is used between drug treatments. Therefore, the patient is maintained on his or her own medication, and blood sampling is performed during a dosage interval (Fig. 15-12, reference product A). Once blood sampling is accomplished, the patient takes equal oral doses of the test drug product and the reference drug product is discontinued. Drug dosing with the test drug product continues until attainment of steady state. When steady state is reached, the plasma level–time curve for a dosage interval with the second drug product is described (Fig. 15-12, drug product B). Using the same plasma measures as before, the bioequivalence or lack of bioequivalence may be determined. The patient then continues with his or her therapy with the original drug product.

If the blood level–time curve of the second drug product is comparable to that of the reference drug product, the second product is considered to be bioequivalent. If the second drug has less bioavailability (assuming that only the extent of drug absorption is less than that of the reference drug), the resulting $C_\text{av}$ will be smaller than that obtained with the first drug. Usually the drug manufacturer will perform dissolution and content uniformity tests before performing a bioequivalence study. These in vitro dissolution tests will help ensure that the $C_\text{av}$ obtained from each drug product in vivo will not be
iodothyronine (T3), the major metabolite of T4, and thyrotropin (TSH).

a. Why were hypothyroid patients used in this study?
b. Why were the subjects dosed for 50 days with each thyroid product?
c. Why were blood samples obtained on days 48, 49, and 50?
d. Why was T3 measured?
e. Why was TSH measured?

Solution

a. Normal healthy euthyroid subjects would be at risk if they were to take levothyroxine sodium for an extended period of time.
b. The long (50-day) daily dosing for each product was required to obtain steady-state drug levels because of the long elimination half-life of levothyroxine.
c. Serum from blood samples was taken on days 48, 49, and 50 to obtain three consecutive $C_{\text{min}}^{\text{av}}$ drug levels.
d. T3 is the active metabolite of T4.
The serum TSH concentration is inversely proportional to the free serum T4 concentrations and gives an indication of the pharmacodynamic activity of the active drug.

**CLINICAL EXAMPLE**

**Mercaptopurine (Purinethol) Oral Tablets**

Mercaptopurine (Purinethol) is a cytotoxic drug used to treat cancer and is available in a 50-mg oral tablet. The FDA recommends bioequivalence steady-state studies in patients receiving therapeutic oral doses (usually 100–200 mg/d in the average adult) or maintenance daily doses (usually 50–100 mg/d in the average adult).

Patients should be on a stable regimen using the same dosage unit (multiples of the same 50-mg strength). Plasma drug concentration–time profiles are obtained in these patients at steady state with the brand product. The proposed generic drug product is then given to these patients at the same dosage regimen until steady state is reached. Plasma drug concentration–time profiles are obtained for the generic drug product, then the patients return to the original brand medication.

**Frequently Asked Questions**

- What do sequence, washout period, and period mean in a crossover bioavailability study?
- Why does the FDA require a food intervention (food effect) study for generic drug products before granting approval?
- What type of bioequivalence studies are required for drugs that are not systemically absorbed or for those drugs in which the 
  \( C_{\text{max}} \) and 
  \( \text{AUC} \) cannot be measured in the plasma?
- How do inter- and intrasubject variability affect the statistical demonstration of bioequivalence for a drug product?

**EVALUATION OF THE DATA**

**Pharmacokinetic Evaluation of the Data**

For single-dose studies, including a fasting study or a food intervention study, the pharmacokinetic analyses include calculation for each subject of the area under the curve to the last quantifiable concentration (\( \text{AUC}_{0}^{t} \)) and to infinity (\( \text{AUC}_{0}^{\infty} \)), \( t_{\text{max}} \), and \( C_{\text{max}} \). Additionally, the elimination rate constant, \( k \), the elimination half-life, \( t_{1/2} \), and other parameters may be estimated. For multiple-dose studies, pharmacokinetic analysis includes calculation for each subject of the steady-state area under the curve, \( (\text{AUC}_{\infty}^{t}) \), \( t_{\text{max}} \), \( C_{\text{min}} \), \( C_{\text{max}} \), and the percent fluctuation \( [100 \times (C_{\text{max}} - C_{\text{min}})/C_{\text{min}}] \). Proper statistical evaluation should be performed on the estimated pharmacokinetic parameters.

**Statistical Evaluation of the Data**

Bioequivalence is generally determined using a comparison of population averages of a bioequivalence metric, such as \( \text{AUC} \) and \( C_{\text{max}} \). This approach, termed **average bioequivalence**, involves the calculation of a 90% confidence interval for the ratio of averages (population geometric means) of the bioequivalence metrics for the test and reference drug products (Schuirmann, 1987; FDA Guidance, 2001).

Many statistical approaches (parametric tests) assume that the data are distributed according to a normal distribution or “bell-shaped curve” (see Appendix A). The pharmacokinetic parameters such as \( C_{\text{max}} \) and \( \text{AUC} \) may not be normally distributed and the true distribution is difficult to ascertain because of the small number of subjects used in a bioequivalence study. The distribution of data that have been transformed to log values resembles more closely a normal distribution compared to the distribution of non-log-transformed data.

**Two One-Sided Tests Procedure**

The two one-sided tests procedure is also referred to as the **confidence interval approach** (Schuirmann, 1987). This statistical method is used to demonstrate if the bioavailability of the drug from the test formulation is too low or high in comparison to that of the reference product. The objective of the approach is to determine if there are large differences (ie, greater than 20%) between the mean parameters.

The 90% confidence limits are estimated for the sample means. The interval estimate is based on Student’s \( t \) distribution of the data. In this test, presently required by the FDA, a 90% confidence interval about the ratio of means of the two drug products...
Chapter 15

average bioequivalence estimates are used to establish bioequivalence of generic drug products.

**Analysis of Variance**

An analysis of variance (see ANOVA) is a statistical procedure (see Appendix A) used to test the data for differences within and between treatment and control groups. A bioequivalent product should produce no significant difference in all pharmacokinetic parameters tested. The parameters tested statistically usually include $AUC_{0}^{t}$, $AUC_{0}^{\infty}$, and $C_{\text{max}}$ obtained for each treatment or dosage form. Other metrics of bioavailability have also been used to compare the bioequivalence of two or more formulations. The ANOVA may evaluate variability in subjects, treatment groups, study period, formulation, and other variables, depending on the study design. If the variability in the data is large, the difference in means for each pharmacokinetic parameter, such as $AUC$, may be masked, and the investigator might erroneously conclude that the two drug products are bioequivalent.

A statistical difference between the pharmacokinetic parameters obtained from two or more drug products is considered statistically significant if there is a probability of less than 1 in 20 times or 0.05 probability ($p \leq 0.05$) that these results would have happened on the basis of chance alone. The probability, $p$, is used to indicate the level of statistical significance. If $p < 0.05$, the differences between the two drug products are not considered statistically significant.

To reduce the possibility of failing to detect small differences between the test products, a power test is performed to calculate the probability that the conclusion of the ANOVA is valid. The power of the test will depend on the sample size, variability of the data, and desired level of significance. Usually the power is set at 0.80 with a $\beta = 0.2$ and a level of significance of 0.05. The higher the power, the more sensitive the test and the greater the probability that the conclusion of the ANOVA is valid.

**BIOEQUIVALENCE EXAMPLE**

A simulated example of the results for a single-dose, fasting study is shown in Table 15-6 and in

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Table 15-5  **Statistical Analysis for Average Bioequivalence**

- Based on log-transformed data
- Point estimates of the mean ratios
  - Test/reference for $AUC$ and $C_{\text{max}}$ are between 80% to 125%
  - $AUC$ and $C_{\text{max}}$
    - 90% confidence intervals (CI) must fit between 80% and 125%
- Bioequivalence criteria
  - Two one-sided tests procedure
    - Test ($T$) is not significantly less than reference
    - Reference ($R$) is not significantly less than test
    - Significant difference is 20% ($\alpha = 0.05$ significance level)
    - $T/R = 80/100 = 80$
    - $R/T = 80$ (all data expressed as $T/R$ so this becomes 100/80 = 125%)
- The statistical model typically includes factors accounting for the following sources of variation: sequence, subjects nested in sequences, period, and treatment

*From FDA Guidance for Industry (2001).*
based on log transformation of the data. The power test for the AUC measures were above 99%, showing good precision of the data. The power test for the $C_{\text{max}}$ values was 87.9%, showing that this parameter was more variable.

Table 15-7 shows the results for a hypothetical bioavailability study in which three different tablet
formulations were compared to a solution of the drug given in the same dose. As shown in the table, the bioavailability from all three tablet formulations was greater than 80% of that of the solution. According to the ANOVA, the mean AUC values were not statistically different from one another nor different from that of the solution. However, the 90% confidence interval for the AUC showed that for tablet A, the bioavailability was less than 80% (ie, 74%), compared to the solution at the low-range estimate and would not be considered bioequivalent based on the AUC.

For illustrative purposes, consider a drug that has been prepared at the same dosage level in three formulations, A, B, and C. These formulations are given to a group of volunteers using a three-way, randomized crossover design. In this experimental design, all subjects receive each formulation once. From each subject, plasma drug level and urinary drug excretion data are obtained. With these data we can observe the relationship between plasma and urinary excretion parameters and drug bioavailability (Fig. 15-14). The rate of drug absorption from formulation C is the same as that from formulation A, but the extent of drug available is less. The $C_{\text{max}}$ for formulation C is less than that for formulation A. The decrease in $C_{\text{max}}$ for formulation C is proportional to the decrease in AUC in comparison to the drug plasma level data for formulation A. The corresponding urinary excretion data confirm these observations. These relationships are

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>$C_{\text{max}}$ (μg/mL)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>AUC$_{0-24}$ (μg h/mL)</th>
<th>$F^b$</th>
<th>90% Confidence Interval for AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution</td>
<td>16.1 ± 2.5</td>
<td>1.5 ± 0.85</td>
<td>1835 ± 235</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablet A</td>
<td>10.5 ± 3.2</td>
<td>2.5 ± 1.0</td>
<td>1523 ± 381</td>
<td>81</td>
<td>74%–90%</td>
</tr>
<tr>
<td>Tablet B</td>
<td>13.7 ± 4.1</td>
<td>2.1 ± 0.98</td>
<td>1707 ± 317</td>
<td>93</td>
<td>88%–98%</td>
</tr>
<tr>
<td>Tablet C</td>
<td>14.8 ± 3.6</td>
<td>1.8 ± 0.95</td>
<td>1762 ± 295</td>
<td>96</td>
<td>91%–103%</td>
</tr>
</tbody>
</table>

*The bioavailability of a drug from four different formulations was studied in 24 healthy, adult male subjects using a four-way Latin-square crossover design. The results represent the mean ± standard deviation.

*Oral bioavailability relative to the solution.

$p \leq .05$. 

---

**FIGURE 15-14** Corresponding plots relating plasma concentration and urinary excretion data.
The results are analyzed both statistically and pharmacokinetically. These results, along with case reports and various data supporting the validity of the analytical method, are included in the submission. The FDA reviews the study in detail according to the outline presented in Table 15-11. If necessary, an FDA investigator may inspect both the clinical and analytical facilities summarized in Table 15-8. The table illustrates how bioavailability parameters for plasma and urine change when only the extent and rate of bioavailability are changed, respectively. Formulation changes in a drug product may affect both the rate and extent of drug bioavailability.

### STUDY SUBMISSION AND DRUG REVIEW PROCESS

The contents of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) are similar in terms of the quality of manufacture (Table 15-9). The submission for an NDA must contain safety and efficacy studies as provided by animal toxicology studies, clinical efficacy studies, and pharmacokinetic/bioavailability studies. For the generic drug manufacturer, the bioequivalence study is the pivotal study in the ANDA that replaces the animal, clinical, and pharmacokinetic studies.

An outline for the submission of a completed bioavailability to the FDA is shown in Table 15-10. The investigator should be sure that the study has been properly designed, the objectives are clearly defined, and the method of analysis has been validated (ie, shown to measure precisely and accurately

### TABLE 15-8 Relationship of Plasma Level and Urinary Excretion Parameters to Drug Bioavailability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Extent of Drug Bioavailability Decreases</th>
<th>Rate of Drug Bioavailability Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\text{max}} )</td>
<td>Same</td>
<td>( t_{\text{max}} )</td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>Decrease</td>
<td>( C_{\text{max}} )</td>
</tr>
<tr>
<td>AUC</td>
<td>Decrease</td>
<td>AUC</td>
</tr>
<tr>
<td><strong>Urine data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\infty} )</td>
<td>Same</td>
<td>( t_{\infty} )</td>
</tr>
<tr>
<td>([dD_u/dt]_{\text{max*}} )</td>
<td>Decrease</td>
<td>([dD_u/dt]_{\text{max*}} )</td>
</tr>
<tr>
<td>( D_u )</td>
<td>Decrease</td>
<td>( D_u )</td>
</tr>
</tbody>
</table>

*Maximum rate of urinary drug excretion.*

### TABLE 15-9 NDA versus ANDA Review Process

<table>
<thead>
<tr>
<th>Brand-Name Drug NDA Requirements</th>
<th>Generic Drug ANDA Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemistry</td>
<td>1. Chemistry</td>
</tr>
<tr>
<td>3. Controls</td>
<td>3. Controls</td>
</tr>
<tr>
<td>4. Labeling</td>
<td>4. Labeling</td>
</tr>
<tr>
<td>5. Testing</td>
<td>5. Testing</td>
</tr>
<tr>
<td>7. Clinical studies</td>
<td></td>
</tr>
<tr>
<td>8. Bioavailability</td>
<td></td>
</tr>
</tbody>
</table>

Source: Center for Drug Evaluation & Research, US Food & Drug Administration.
### TABLE 15-10  Proposed Format and Contents of an *In Vivo* Bioequivalence Study Submission and Accompanying *In Vitro* Data

<table>
<thead>
<tr>
<th><strong>Title page</strong></th>
<th><strong>V. Pharmacokinetic Parameters and Tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study title</td>
<td>Definition and calculations</td>
</tr>
<tr>
<td>Name of sponsor</td>
<td>Statistical tests</td>
</tr>
<tr>
<td>Name and address of clinical laboratory</td>
<td>Drug levels at each sampling time and pharmacokinetic parameters</td>
</tr>
<tr>
<td>Name of principal investigator(s)</td>
<td>Figure of mean plasma concentration–time profile</td>
</tr>
<tr>
<td>Name of clinical investigator</td>
<td>Figures of individual subject plasma concentration–time profiles</td>
</tr>
<tr>
<td>Name of analytical laboratory</td>
<td>Figure of mean cumulative urinary excretion</td>
</tr>
<tr>
<td>Dates of clinical study (start, completion)</td>
<td>Figures of individual subject cumulative urinary excretion</td>
</tr>
<tr>
<td>Signature of principal investigator (and date)</td>
<td>Figure of mean urinary excretion rates</td>
</tr>
<tr>
<td>Signature of clinical investigator (and date)</td>
<td>Figures of individual subject urinary excretion rates</td>
</tr>
<tr>
<td>Table of contents</td>
<td>Tables of individual subject data arranged by drug, drug/period, drug/sequence</td>
</tr>
<tr>
<td>I. Study Résumé</td>
<td></td>
</tr>
<tr>
<td>Product information</td>
<td></td>
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<tr>
<td>Summary of bioequivalence study</td>
<td></td>
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<tr>
<td>Summary of bioequivalence data</td>
<td></td>
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<tr>
<td>Plasma</td>
<td></td>
</tr>
<tr>
<td>Urinary excretion</td>
<td></td>
</tr>
<tr>
<td>Figure of mean plasma concentration–time profile</td>
<td></td>
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<tr>
<td>Figure of mean cumulative urinary excretion</td>
<td></td>
</tr>
<tr>
<td>Figure of mean urinary excretion rates</td>
<td></td>
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<tr>
<td>II. Protocol and Approvals</td>
<td></td>
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<tr>
<td>Protocol</td>
<td></td>
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<tr>
<td>Letter of acceptance of protocol from FDA</td>
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<tr>
<td>Informed consent form</td>
<td></td>
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<tr>
<td>Letter of approval of Institutional Review Board</td>
<td></td>
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<tr>
<td>List of members of Institutional Review Board</td>
<td></td>
</tr>
<tr>
<td>III. Clinical Study</td>
<td></td>
</tr>
<tr>
<td>Summary of the study</td>
<td></td>
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<tr>
<td>Details of the study</td>
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<tr>
<td>Demographic characteristics of the subjects</td>
<td></td>
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<tr>
<td>Subject assignment in the study</td>
<td></td>
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<tr>
<td>Mean physical characteristics of subjects arranged by sequence</td>
<td></td>
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<tr>
<td>Details of clinical activity</td>
<td></td>
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<tr>
<td>Deviations from protocol</td>
<td></td>
</tr>
<tr>
<td>Vital signs of subjects</td>
<td></td>
</tr>
<tr>
<td>Adverse reactions report</td>
<td></td>
</tr>
<tr>
<td>IV. Assay Methodology and Validation</td>
<td></td>
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<tr>
<td>Assay method description</td>
<td></td>
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<tr>
<td>Validation procedure</td>
<td></td>
</tr>
<tr>
<td>Summary of validation</td>
<td></td>
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<tr>
<td>Data on linearity of standard samples</td>
<td></td>
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<tr>
<td>Data on interday precision and accuracy</td>
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<td>Data on intraday precision and accuracy</td>
<td></td>
</tr>
<tr>
<td>Figure for standard curve(s) for low/high ranges</td>
<td></td>
</tr>
<tr>
<td>Chromatograms of standard and quality control samples</td>
<td></td>
</tr>
<tr>
<td>Sample calculation</td>
<td></td>
</tr>
<tr>
<td><strong>V. Pharmacokinetic Parameters and Tests</strong></td>
<td></td>
</tr>
<tr>
<td>Definition and calculations</td>
<td></td>
</tr>
<tr>
<td>Statistical tests</td>
<td></td>
</tr>
<tr>
<td>Drug levels at each sampling time and pharmacokinetic parameters</td>
<td></td>
</tr>
<tr>
<td>Figure of mean plasma concentration–time profile</td>
<td></td>
</tr>
<tr>
<td>Figures of individual subject plasma concentration–time profiles</td>
<td></td>
</tr>
<tr>
<td>Figure of mean cumulative urinary excretion</td>
<td></td>
</tr>
<tr>
<td>Figures of individual subject cumulative urinary excretion</td>
<td></td>
</tr>
<tr>
<td>Figure of mean urinary excretion rates</td>
<td></td>
</tr>
<tr>
<td>Figures of individual subject urinary excretion rates</td>
<td></td>
</tr>
<tr>
<td>Tables of individual subject data arranged by drug, drug/period, drug/sequence</td>
<td></td>
</tr>
<tr>
<td><strong>VI. Statistical Analyses</strong></td>
<td></td>
</tr>
<tr>
<td>Statistical considerations</td>
<td></td>
</tr>
<tr>
<td>Summary of statistical significance</td>
<td></td>
</tr>
<tr>
<td>Summary of statistical parameters</td>
<td></td>
</tr>
<tr>
<td>Analysis of variance, least squares estimates and least-squares means</td>
<td></td>
</tr>
<tr>
<td>Assessment of sequence, period, and treatment effects</td>
<td></td>
</tr>
<tr>
<td>90% confidence intervals for the difference between test and reference products for the log-normal-transformed parameters of $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ should be within 80% and 125%</td>
<td></td>
</tr>
<tr>
<td><strong>VII. Appendices</strong></td>
<td></td>
</tr>
<tr>
<td>Randomization schedule</td>
<td></td>
</tr>
<tr>
<td>Sample identification codes</td>
<td></td>
</tr>
<tr>
<td>Analytical raw data</td>
<td></td>
</tr>
<tr>
<td>Chromatograms of at least 20% of subjects</td>
<td></td>
</tr>
<tr>
<td>Medical record and clinical reports</td>
<td></td>
</tr>
<tr>
<td>Clinical facilities description</td>
<td></td>
</tr>
<tr>
<td>Analytical facilities description</td>
<td></td>
</tr>
<tr>
<td><em>Curriculum vitae</em> of the investigators</td>
<td></td>
</tr>
<tr>
<td><strong>VIII. In Vitro Testing</strong></td>
<td></td>
</tr>
<tr>
<td>Dissolution testing</td>
<td></td>
</tr>
<tr>
<td>Dissolution assay methodology</td>
<td></td>
</tr>
<tr>
<td>Content uniformity testing</td>
<td></td>
</tr>
<tr>
<td>Potency determination</td>
<td></td>
</tr>
<tr>
<td><strong>IX. Batch Size and Formulation</strong></td>
<td></td>
</tr>
<tr>
<td>Batch record</td>
<td></td>
</tr>
<tr>
<td>Quantitative formulation</td>
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</tbody>
</table>

Modified from Dighe and Adams (1991), with permission.
used in the study and audit the raw data used in support of the bioavailability study. For ANDA applications, the FDA Office of Generic Drugs reviews the entire ANDA as shown in Fig. 15-15. If the application is incomplete, the FDA will not review the submission and the sponsor will receive a Refusal to File letter.

**Waivers of In Vivo Bioequivalence Studies (Biowaivers)**

In some cases, *in vitro* dissolution testing may be used in lieu of *in vivo* bioequivalence studies. When the drug product is in the same dosage form but in different strengths and is proportionally similar in active and inactive ingredients, an *in vivo* bioequivalence study of one or more of the lower strengths can be waived based on the dissolution tests and an
in vivo bioequivalence study on the highest strength. Ideally, if there is a strong correlation between dissolution of the drug and the bioavailability of the drug, then the comparative dissolution tests comparing the test product to the reference product should be sufficient to demonstrate bioequivalence. For most drug products, especially immediate-release tablets and capsules, no strong correlation exists, and the FDA requires an in vivo bioequivalence study. For oral solid dosage forms, an in vivo bioequivalence study may be required to support at least one dose strength of the product. Usually, an in vivo bioequivalence study is required for the highest dose strength. If the lower-dose-strength test product is substantially similar in active and inactive ingredients, then only a comparative in vitro dissolution between the test and brand-name formulations may be used.

For example, an immediate-release tablet is available in 200-mg, 100-mg, and 50-mg strengths. The 100- and 50-mg-strength tablets are made the same way as the highest-strength tablet. A human bioequivalence study is performed on the highest or 200-mg strength. Comparative in vitro dissolution studies are performed on the 100-mg and 50-mg dose strengths. If these drug products have no known bioavailability problems, are well absorbed systemically, are well correlated with in vitro dissolution, and have a large margin of safety, then arguments for not performing an in vivo bioavailability study may be valid. Methods for correlation of in vitro dissolution of the drug with in vivo drug bioavailability are discussed in Chapters 14 and 17. The manufacturer does not need to perform additional in vivo bioequivalence studies on the lower-strength products if the products meet all in vitro criteria.

**Dissolution Profile Comparison**

Comparative dissolution profiles are used as (1) the basis for formulation development of bioequivalent drug products and proceeding to the pivotal in vivo bioequivalence study; (2) comparative dissolution profiles are used for demonstrating the equivalence of a change in the formulation of a drug product after the drug product has been approved for marketing (see SUPAC in Chapter 16); and (3) the basis of a biowaiver of a lower-strength drug product that is dose proportional in active and inactive ingredients to the higher-strength drug product.

A model-independent mathematical method was developed by Moore and Flanner (1996) to compare dissolution profiles using two factors, $f_1$ and $f_2$. The factor $f_2$, known as the similarity factor, measures the closeness between the two profiles:

$$f_2 = 50 \times \log \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{-0.5} \times 100$$

where $n$ is the number of time points, $R_i$ is the dissolution value of the reference product at time $t$, and $T_i$ is the dissolution value of the test product batch at time $t$.

The reference may be the original drug product before a formulation change (prechange) and the test may be the drug product after the formulation was changed (postchange). Alternatively, the reference may be the higher-strength drug product and the test may be the lower-strength drug product. The $f_2$ comparison is the focus of several FDA guidances and is of regulatory interest in knowing the similarity of the two dissolution curves. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time points results in an $f_2$ value of 50 (Shah et al, 1998). The FDA has set a public standard for $f_2$ value between 50 and 100 to indicate similarity between two dissolution profiles.

In some cases, two generic drug products may have dissimilar dissolution profiles and still be bioequivalent in vivo. For example, Polli et al (1997) have shown that slow-, medium-, and fast-dissolving formulations of metoprolol tartrate tablets were bioequivalent. Furthermore, bioequivalent modified-release drug products may have different drug release mechanisms and therefore different dissolution profiles. For example, for theophylline extended-release capsules, the United States Pharmacopeia (USP) lists 10 individual drug release tests for products labeled for dosing every 12 hours. However, only generic drug products that are FDA approved as bioequivalent drug products and listed in the current edition of the Orange Book may be substituted for each other.
and/or intestinal transport. Using this approach, Amidon et al (1995) studied the solubility and permeability characteristics of various representative drugs and obtained a biopharmaceutic drug classification (Table 15-12) for predicting the in vitro drug dissolution of immediate-release solid oral drug products with in vivo absorption.

The FDA may waive the requirement for performing an in vivo bioavailability or bioequivalence study for certain immediate-release solid oral drug products that meet very specific criteria, namely, the permeability, solubility, and dissolution of the drug. These characteristics include the in vitro dissolution, of the drug product in various media, drug permeability information, and assuming ideal behavior of the drug product, drug dissolution, and absorption in the GI tract. For regulatory purposes, drugs are classified according to the Biopharmaceutics Classification System (BCS) in accordance the solubility, permeability, and dissolution characteristics of the drug (FDA Guidance for Industry, 2000; Amidon et al, 1995).

**Solubility**

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate physiologic conditions. For this purpose, determination of pH–solubility profiles over a pH range of 1 to 8 is suggested. The solubility class is determined by calculating what volume of an aqueous medium is sufficient to dissolve the highest

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>High</td>
<td>High</td>
<td>Drug dissolves rapidly and is well absorbed. Bioavailability problem is not expected for immediate-release drug products.</td>
</tr>
<tr>
<td>Class 2</td>
<td>Low</td>
<td>High</td>
<td>Drug is dissolution limited and well absorbed. Bioavailability is controlled by the dosage form and rate of release of the drug substance.</td>
</tr>
<tr>
<td>Class 3</td>
<td>High</td>
<td>Low</td>
<td>Drug is permeability limited. Bioavailability may be incomplete if drug is not released and dissolved within absorption window.</td>
</tr>
<tr>
<td>Class 4</td>
<td>Low</td>
<td>Low</td>
<td>Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed.</td>
</tr>
</tbody>
</table>

anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous medium over the pH range 1 to 8. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 oz) of water.

**Permeability**

Studied of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption ≥90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical–chemical properties (e.g., octanol: water partition coefficient).

Some methods to determine the permeability of a drug from the gastrointestinal tract include: (1) *in vivo* intestinal perfusion studies in humans; (2) *in vivo* or *in situ* intestinal perfusion studies in animals; (3) *in vitro* permeation experiments using excised human or animal intestinal tissues; and (4) *in vitro* permeation experiments across a monolayer of cultured human intestinal cells. When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.

After oral drug administration, *in vivo* permeability can be affected by the effects of efflux and absorptive transporters in the gastrointestinal tract, by food, and possibly by the various excipients present in the formulation.

**Dissolution**

The dissolution class is based on the *in vitro* dissolution rate of an immediate-release drug product under specified test conditions and is intended to indicate rapid *in vivo* dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate-release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 minutes using USP Apparatus I (see Chapter 14) at 100 rpm or Apparatus II at 50 rpm in a volume of 900 mL or less in each of the following media: (1) acidic media such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

**Biopharmaceutics Drug Disposition Classification System**

The major aspects of BCS are the consideration of solubility and permeation. According to BCS, permeability *in vivo* is considered high when the active drug is systemically absorbed ≥90%. Wu and Benet (2005) and Benet et al (2008) have proposed modification of the BCS system known as the Biopharmaceutics Drug Disposition Classification System (BDDCS) which takes into account drug metabolism (hepatic clearance) and transporters in the gastrointestinal tract for drugs that are orally administered. For BCS 1 drugs (i.e., high solubility and high permeability), transporter effects will be minimal. However, BCS 2 drugs (low solubility and high permeability), transporter effects are more important. These investigators suggest that the BCS should be modified on the basis of the extent of drug metabolism, overall drug disposition, including routes of drug elimination and the effects of efflux, and absorptive transporters on oral drug absorption.

**Drug Products for Which Bioavailability or Bioequivalence May Be Self-Evident**

The best measure of a drug product’s performance is to determine the *in vivo* bioavailability of the drug. For some well-characterized drug products and for certain drug products in which bioavailability is self-evident (e.g., sterile solutions for injection), *in vivo* bioavailability studies may be unnecessary or unimportant to the achievement of the product’s intended purposes. The FDA will waive the requirement for submission of *in vivo* evidence demonstrating the bioavailability of the drug product if the product meets one of the following criteria (US Code of Federal Regulations, 21 CFR 320.22). However, there may be specific requirements for certain drug products, and the appropriate FDA division should be consulted.
1. The drug product (a) is a solution intended solely for intravenous administration and (b) contains an active drug ingredient or therapeutic moiety combined with the same solvent and in the same concentration as in an intravenous solution that is the subject of an approved, full NDA.

2. The drug product is a topically applied preparation (e.g., a cream, ointment, or gel intended for local therapeutic effect). The FDA has released guidances for the performance of bioequivalence studies on topical corticosteroids and antifungal agents. The FDA is also considering performing dermatopharmacokinetic (DPK) studies on other topical drug products. In addition, in vitro drug release and diffusion studies may be required.

3. The drug product is in an oral dosage form that is not intended to be absorbed (e.g., an antacid or a radiopaque medium). Specific in vitro bioequivalence studies may be required by the FDA. For example, the bioequivalence of cholestyramine resin is demonstrated in vitro by the binding of bile acids to the resin.

4. The drug product meets both of the following conditions:
   a. It is administered by inhalation as a gas or vapor (e.g., as a medicinal or as an inhalation anesthetic).
   b. It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved, full NDA.

5. The drug product meets all of the following conditions:
   a. It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.
   b. It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved, full NDA.
   c. It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

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**GENERIC BIOLOGICS (BIOSIMILAR DRUG PRODUCTS)**

*Biosimilars,* or biotechnology-derived drugs, in contrast to drugs that are chemically synthesized, are derived from living sources such as humans, animals, or microorganisms. Many biologics are complex mixtures that are not easily identified or characterized and are manufactured using biotechnology or are purified from natural sources. Other biological drugs, such as insulin and growth hormone, are proteins derived by biotechnology and have been well characterized.

Presently, there is no FDA regulatory pathway to establish the bioequivalence of a biotechnology-derived drug product, sometimes referred to as generic biologics or biosimilar drug products. Scientifically, there are advocates for and against the feasibility for the manufacture of generic biotechnology-derived drug products (generic biologics) that are bioequivalent to the innovator or brand-drug product.

Those opposed to the development of generic biologics have claimed that generic manufacturers do not have the ability to fully characterize the active ingredient(s), that immunogenicity-related impurities may be present in the product, and that the manufacture of a biologic drug product is process dependent.

**Biosimilarity versus Interchangeability**

The “Drug Price Competition and Patent Term Restoration Act of 1984,” also known as “The Hatch-Waxman Act,” established an abbreviated regulatory process for generic drug products. Under the Hatch-Waxman Act, applicants for an Abbreviated New Drug Application (ANDA) must show the bioequivalence of a generic drug, but do not need to conduct a full panel of clinical trials to demonstrate safety and efficacy of the drug. Generic drugs are not evaluated or differentiated based on their class or type and, once approved, can be substituted for brand name drugs automatically. In 2010, the U.S. Congress passed landmark healthcare reform legislation, known as the “Patient Protection and Affordable Care Act,” which reshaped the biopharmaceutical industry. This legislation contains provisions that establish, for the first time ever, an abbreviated regulatory approval pathway for generic versions of biological medicines.
The manufacture of generic drug products derived from biotechnology-derived drugs should be possible. For example, a biologic manufacturer institutes a change in its manufacturing process before FDA approval of its product but after completion of a pivotal clinical study. The FDA may not require the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. Such manufacturing process changes, implemented before or after product approval, have included changes implemented during expansion from pilot-scale to full-scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the manufacturing process such as fermentation, purification, and formulation. The manufacturer may be able to demonstrate product comparability between a biologic product made after a manufacturing change (“new” product) and a product made before implementation of the change (“old” product) through different types of analytical and functional testing, with or without preclinical animal testing. The FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency (FDA Guidance, 1996). The FDA currently requires that manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the preexisting product. Determinations of product comparability may be based on chemical, physical, and biologic assays and, in some cases, other nonclinical data.

It is important to note that the FDA uses such terms as comparable and similar for approval of manufacturing changes of biologic drug products (FDA Guidance, 1996). In contrast, the FDA uses the term bioequivalence for approval of manufacturing changes of drug products that contain chemically derived active ingredients. Advocates for the manufacturer of generic biologics feel that the science and technology for the manufacture of certain bioequivalent biologic drug products are already available. Moreover, if the innovator manufacturer of a marketed biologic drug product can perform a manufacturing change and demonstrate the comparability of the “new” to the “old” marketed biologic drug product, then a generic manufacturer should be able to use...

**FDA Guidance Documents**

The legislation makes clear that the FDA will play a central role in defining the specific criteria needed to demonstrate biosimilarity for a given class of biological. In deference to the FDA’s expertise in this area, the legislation specifically states that the FDA can issue guidance documents with respect to the approval of a biosimilar product. The guidance can be general or specific in nature, and the public must be provided with an opportunity to comment.

Advocates for the manufacture of generic biologics argue that bioequivalent biotechnology-derived drug products can be made on a case-by-case basis. Currently, manufacturers of marketed biotechnology drugs may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. These manufacturers have developed improvements in production methods, process and control test methods, and test methods for product characterization. Currently, there are several manufacturers of recombinant human growth hormone (somatotropin), but none of these products has been considered as a generic alternative or therapeutic equivalent.
Theoretically possible that the excipients in one of the dosage forms tested may pose a problem in a patient who uses the generic dosage form.

**Clinical Significance of Bioequivalence Studies**

Bioequivalence of different formulations of the same drug substance involves equivalence with respect to rate and extent of systemic drug absorption. Clinical interpretation is important in evaluating the results of a bioequivalence study. A small difference between drug products, even if statistically significant, may produce very little difference in therapeutic response. Generally, two formulations whose rate and extent of absorption differ by 20% or less are considered bioequivalent. The Report by the Bioequivalence Task Force (1988) considered that differences of less than 20% in AUC and $C_{\text{max}}$ between drug products are “unlikely to be clinically significant in patients.” The Task Force further stated that “clinical studies of effectiveness have difficulty detecting differences in doses of even 50% to 100%.” Therefore, normal variation is observed in medical practice and plasma drug levels may vary among individuals greater than 20%.

According to Westlake (1972), a small, statistically significant difference in drug bioavailability from two or more dosage forms may be detected if the study is well controlled and the number of subjects is sufficiently large. When the therapeutic objectives of the drug are considered, an equivalent clinical response should be obtained from the comparison dosage forms if the plasma drug concentrations remain above the minimum effective concentration (MEC) for an appropriate interval and do not reach the minimum toxic concentration (MTC). Therefore, the investigator must consider whether any statistical difference in bioavailability would alter clinical efficiency.

Special populations, such as the elderly or patients on drug therapy, are generally not used for bioequivalence studies. Normal, healthy volunteers are preferred for bioequivalence studies, because these subjects are less at risk and may more easily endure the discomforts of the study, such as blood sampling. Furthermore, the objective of these studies is to evaluate the bioavailability of the drug from the dosage form, and use of healthy subjects should minimize both inter- and intra-subject variability. It is theoretically possible that the excipients in one of the dosage forms tested may pose a problem in a patient who uses the generic dosage form.

For the manufacture of a dosage form, specifications are set to provide uniformity of dosage forms. With proper specifications, quality control procedures should minimize product-to-product variability by different manufacturers and lot-to-lot variability with a single manufacturer (see Chapter 16).

**Example**

**Impact of Efflux Transporters on Bioequivalence Study**

Digoxin is a drug that may be absorbed differently in individuals that expressed the efflux gene MDR1.

Questions

- What would be the impact of such an individual recruited into a bioavailability study?
- Would a protocol with the usual crossover design be able to adequately evaluate the bioequivalence of a generic digoxin product with a reference? Explain why or why not.

Solution

Bioequivalence studies for generic drug products compare the bioavailability of the drug from the test (generic) product to the bioavailability of the drug from the reference (brand) product. The study design is a two-way, crossover design in which each subject takes each drug product. The study design usually includes males and females with different ethnic backgrounds. In addition, some studies include both smokers and nonsmokers. Although there may be large intersubject variability due to gender, enviromental, and genetic factors, the crossover design minimizes intrasubject variability by comparing the bioavailability of test and reference products in the same individual. Thus each individual subject should have similar drug absorption characteristics after taking the test or reference drug products.

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For a few drug products, a high intrasubject variability (>30% CV) may be observed for which the bioavailability response changes for the same drug product each time the drug is dosed in the same subject.
For drugs with very long elimination half-lives or a complex elimination phase, a complete plasma drug concentration–time curve (ie, three elimination half-lives or an AUC representing 90% of the total AUC) may be difficult to obtain for a bioequivalence study using a crossover design. For these drugs, a truncated (shortened) plasma drug concentration–time curve (0–72 hours) may be more practical. The use of a truncated plasma drug concentration–time curve allows for the measurement of peak absorption and decreases the time and cost for performing the bioequivalence study.

Many drugs are stereoisomers, and each isomer may give a different pharmacodynamic response and may have a different rate of biotransformation. The bioavailability of the individual isomers may be difficult to measure because of problems in analysis. Some drugs have active metabolites, which should be quantitated as well as the parent drug. Drugs such as thioridazine and selegilene have two active metabolites. The question for such drugs is whether bioequivalence should be proven by matching the bioavailability of both metabolites and the parent drug. Assuming both biotransformation pathways follow first-order reaction kinetics, then the metabolites

**TABLE 15-13  Problems in Bioavailability and Bioequivalence**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Drugs with high intrasubject variability</td>
<td>Inhalation</td>
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<tr>
<td>Drugs with long elimination half-life</td>
<td>Ophthalmic</td>
</tr>
<tr>
<td>Biotransformation of drugs</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Stereoselective drug metabolism</td>
<td>Bioavailable drugs that should not produce peak drug levels</td>
</tr>
<tr>
<td>Drugs with active metabolites</td>
<td>Potassium supplements</td>
</tr>
<tr>
<td>Drugs with polymorphic metabolism</td>
<td></td>
</tr>
<tr>
<td>Nonbioavailable drugs (drugs intended for local effect)</td>
<td>Endogeneous drug levels</td>
</tr>
<tr>
<td>Antacids</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Biotechnology-derived drugs</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>Erythropoietin interferon</td>
</tr>
<tr>
<td>Anti-inflammatory steroids</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Dosage forms for nonoral administration</td>
<td>Complex drug substances</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Conjugated estrogens</td>
</tr>
</tbody>
</table>
transdermal delivery system is applied. Thus, the determination of bioequivalence among different manufacturers of transdermal delivery systems for the same active drug is difficult. Dermatokinetics are pharmacokinetic studies that investigate drug uptake into skin layers after topical drug administration. The drug is applied topically, the skin is peeled at various time periods after the dose, using transparent tape, and the drug concentrations in the skin are measured.

Drugs such as potassium supplements are given orally and may not produce the usual bioavailability parameters of AUC, $C_{\text{max}}$, and $t_{\text{max}}$. For these drugs, more indirect methods must be used to ascertain bioequivalence. For example, urinary potassium excretion parameters are more appropriate for the measurement of bioavailability of potassium supplements. However, for certain hormonal replacement drugs (eg, levothyroxine), the steady-state hormone concentration in hypothyroid individuals, the thyroid-stimulating hormone level, and pharmacodynamic endpoints may also be appropriate to measure.

### GENERIC SUBSTITUTION

Drug product selection and generic drug product substitution are major responsibilities for physicians, pharmacists, and others who prescribe, dispense, or purchase drugs. To facilitate such decisions, the FDA publishes annually, in print and on the Internet, *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book (www.fda.gov/cder/ob/default.htm). The Orange Book identifies drug products approved on
the basis of safety and effectiveness by the FDA and contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of healthcare costs.

To contain drug costs, most states have adopted generic substitution laws to allow pharmacists to dispense a generic drug product for a brand-name drug product that has been prescribed. Some states have adopted a positive formulary, which lists therapeutically equivalent or interchangeable drug products that pharmacists may dispense. Other states use a negative formulary, which lists drug products that are not therapeutically equivalent, and/or the interchange of which is prohibited. If the drug is not in the negative formulary, the unlisted generic drug products are assumed to be therapeutically equivalent and may be interchanged.

**Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)**

The *Orange Book* contains therapeutic equivalence evaluations for approved drug products made by various manufacturers. These marketed drug products are evaluated according to specific criteria. The evaluation codes used for these drugs are listed in Table 15-15. The drug products are divided into two major categories:

<table>
<thead>
<tr>
<th><strong>TABLE 15-15 Therapeutic Equivalence Evaluation Codes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Codes</strong></td>
</tr>
<tr>
<td>Drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products</td>
</tr>
<tr>
<td>AA</td>
</tr>
<tr>
<td>AB</td>
</tr>
<tr>
<td>AN</td>
</tr>
<tr>
<td>AO</td>
</tr>
<tr>
<td>AP</td>
</tr>
<tr>
<td>AT</td>
</tr>
<tr>
<td><strong>B Codes</strong></td>
</tr>
<tr>
<td>Drug products that the FDA does not consider to be therapeutically equivalent to other pharmaceutically equivalent products</td>
</tr>
<tr>
<td>B*</td>
</tr>
<tr>
<td>BC</td>
</tr>
<tr>
<td>BD</td>
</tr>
<tr>
<td>BE</td>
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<tr>
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<td>BX</td>
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</tbody>
</table>

Drug Product Performance, In Vivo: Bioavailability and Bioequivalence

“A” codes apply to drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products, and “B” codes apply to drug products that the FDA at this time does not consider to be therapeutically equivalent to other pharmaceutically equivalent products. A list of therapeutic-equivalence-related terms and their definitions is also given in the monograph. According to the FDA, evaluations do not mandate that drugs be purchased, prescribed, or dispensed, but provide public information and advice. The FDA evaluation of the drug products should be used as a guide only, with the practitioner exercising professional care and judgment.

The concept of therapeutic equivalence as used to develop the Orange Book applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride versus pentazocine hydrochloride for the treatment of pain). Any drug product in the Orange Book that is repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder’s drug product even if the application holder’s drug product is single source or coded as nonequivalent (e.g., BN). Also, distributors or repackagers of an application holder’s drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications. With this limitation, however, the FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product (www.fda.gov/cder/ob/default.htm).

Professional care and judgment should be exercised in using the Orange Book. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by the FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of the FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician’s specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

EXAMPLE

INTERPRETATION OF THERAPEUTIC EVALUATION CODE FOR NIFEDIPINE EXTENDED-RELEASE TABLETS

The FDA has approved a few drug products containing the same active drug from different pharmaceutical manufacturers, each of which has provided a separate new drug application (NDA) for its own product. Since no information is available to demonstrate whether the two NDA-approved drug products are bioequivalent, each branded drug product becomes a separate reference listed drug (Table 15-16). Generic drug manufacturers must demonstrate to which RLD product is bioequivalent.
However, an AB1 product cannot be substituted for an AB2 product. The BX product should not be used.

In Table 15-16, AB1 products are bioequivalent to each other and can be substituted. AB2 products are bioequivalent to each other and can be substituted. However, an AB1 product cannot be substituted for an AB2 product. The BX product should not be used.

### Glossary

**Bioavailability**: Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

**Bioequivalence requirement**: A requirement imposed by the FDA for *in vitro* and/or *in vivo* testing of specified drug products, which must be satisfied as a condition for marketing.

**Bioequivalent drug products**: This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. For systemically absorbed drugs, the test (generic) and reference listed drug (brand name) shall be considered bioequivalent if: (1) the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses or (2) the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

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When the above methods are not applicable (eg, for drug products that are not intended to be absorbed into the bloodstream), other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate. Bioequivalence may sometimes be demonstrated using an in vitro bioequivalence standard, especially when such an in vitro test has been correlated with human in vivo bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Bioequivalent drug products may contain different inactive ingredients, provided the manufacturer identifies the differences and provides information that the differences do not affect the safety or efficacy of the product.

**Brand name**: The trade name of the drug. This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor’s products (eg, Tylenol, McNeil Laboratories).

**Chemical name**: The name used by organic chemists to indicate the chemical structure of the drug (eg, N-acetyl-p-aminophenol).

**Abbreviated New Drug Application (ANDA)**: Drug manufacturers must file an ANDA for approval to market a generic drug product. The generic manufacturer is not required to perform clinical efficacy studies or nonclinical toxicology studies for the ANDA.

**Drug product**: The finished dosage form (eg, tablet, capsule, or solution) that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

**Drug product selection**: The process of choosing or selecting the drug product in a specified dosage form.

**Drug substance**: A drug substance is the active pharmaceutical ingredient (API) or component in the drug product that furnishes the pharmacodynamic activity.

**Equivalence**: Relationship in terms of bioavailability, therapeutic response, or a set of established standards of one drug product to another.

**Generic name**: The established, nonproprietary, or common name of the active drug in a drug product (eg, acetaminophen).

**Generic substitution**: The process of dispensing a different brand or an unbranded drug product in place of the prescribed drug product. The substituted drug product contains the same active ingredient or therapeutic moiety as the same salt or ester in the same dosage form but is made by a different manufacturer. For example, a prescription for Motrin brand of ibuprofen might be dispensed by the pharmacist as Advil brand of ibuprofen or as a nonbranded generic ibuprofen if generic substitution is permitted and desired by the physician.

**Pharmaceutical alternatives**: Drug products that contain the same therapeutic moiety but as different salts, esters, or complexes. For example, tetracycline phosphate or tetracycline hydrochloride equivalent to 250-mg tetracycline base are considered pharmaceutical alternatives. Different dosage forms and strengths within a product line by a single manufacturer are pharmaceutical alternatives (eg, an extended-release dosage form and a standard immediate-release dosage form of the same active ingredient). The FDA currently considers a tablet and capsule containing the same active ingredient in the same dosage strength as pharmaceutical alternatives.

**Pharmaceutical equivalents**: Drug products in identical dosage forms that contain the same active ingredient(s), ie, the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration (eg, chlordiazepoxide hydrochloride, 5-mg capsules). Pharmacologically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (ie, strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling. When applicable, pharmaceutical equivalents must meet the same content uniformity, disintegration times, and/or dissolution rates. Modified-release dosage forms that require a reservoir or overage or certain dosage forms such as prefilled syringes in which residual volume may vary must deliver identical amounts of active drug ingredient over an identical dosing period.
Pharmaceutical substitution: The process of dispensing a pharmaceutical alternative for the prescribed drug product. For example, ampicillin suspension is dispensed in place of ampicillin capsules, or tetracycline hydrochloride is dispensed in place of tetracycline phosphate. Pharmaceutical substitution generally requires the physician’s approval.

Reference listed drug: The reference listed drug (RLD) is identified by the FDA as the drug product on which an applicant relies when seeking approval of an Abbreviated New Drug Application (ANDA). The RLD is generally the brand-name drug that has a full New Drug Application (NDA). The FDA designates a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent. The FDA hopes to avoid possible significant variations among generic drugs and their brand-name counterparts. Such variations could result if generic drugs were compared to different reference listed drugs.

Drug Product Performance: Drug product performance, in vivo, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance and leading to a pharmacodynamic response. Bioequivalence studies are drug product performance tests.

Therapeutic alternatives: Drug products containing different active ingredients that are indicated for the same therapeutic or clinical objectives. Active ingredients in therapeutic alternatives are from the same pharmacologic class and are expected to have the same therapeutic effect when administered to patients for such condition of use. For example, ibuprofen is given instead of aspirin; cimetidine may be given instead of ranitidine.

Therapeutic equivalents: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. The FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. The FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Therapeutic substitution: The process of dispensing a therapeutic alternative in place of the prescribed drug product. For example, amoxicillin is dispensed instead of ampicillin or ibuprofen is dispensed instead of naproxen. Therapeutic substitution can also occur when one NDA-approved drug is substituted for the same drug which has been approved by a different NDA, eg, the substitution of Nicoderm (nicotine transdermal system) for Nicotrol (nicotine transdermal system).

Frequently Asked Questions

- Can pharmaceutical equivalent drug products that are not bioequivalent have similar clinical efficacy?
- What is the difference between generic substitution and therapeutic substitution?
CHAPTER SUMMARY

Drug product performance may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance. Bioequivalence is a measure of comparative drug product performance and relates the quality of a drug product to clinical safety and efficacy. The absolute availability of drug is the systemic availability of a drug after extravascular administration (e.g., oral, rectal, transdermal, subcutaneous) compared to IV dosing, whereas relative bioavailability compares the bioavailability of a drug from two or more drug products. The most direct method to assess drug bioavailability is to determine the rate and extent of systemic drug absorption by measurement of the active drug concentrations in plasma. The main pharmacokinetic parameters, \( C_{\text{max}} \) and AUC are used to determine bioequivalence. However, other pharmacokinetic parameters such as \( t_{\text{max}} \) and elimination \( t_{1/2} \) should also be assessed. The most common statistical design for bioequivalence studies is the two-way, crossover design in normal healthy volunteers. Bioequivalence is generally determined if the 90% confidence intervals for \( C_{\text{max}} \) and AUC fall within 80% to 125% of the reference listed drug based on log transformation of the data. Food intervention or food effect studies are generally conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. The Biopharmaceutics Classification System (BCS) is based on the solubility, permeability, and dissolution characteristics of the drug. However, systemic drug bioavailability may also be affected by transporters in the GI tract, hepatic clearance, GI transit and motility, and the contents of the GI tract.

Drug product selection and generic substitution are important responsibilities of the pharmacist. A listing of approved drug products of generic drug products that may be safely substituted is available in Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

LEARNING QUESTIONS

1. An antibiotic was formulated into two different oral dosage forms, A and B. Biopharmaceutic studies revealed different antibiotic blood level curves for each drug product (Fig. 15-16). Each drug product was given in the same dose as the other. Explain how the various possible formulation factors could have caused the differences in blood levels. Give examples where possible. How would the corresponding urinary drug excretion curves relate to the plasma level–time curves?

2. Assume that you have just made a new formulation of acetaminophen. Design a protocol to compare your drug product against the acetaminophen drug products on the market. What criteria would you use for proof of bioequivalence for your new formulation? How would you determine if the acetaminophen was completely (100%) systemically absorbed?

3. The data in Table 15-17 represent the average findings in antibiotic plasma samples taken from 10 humans (average weight 70 kg), tabulated in a four-way crossover design.
   a. Which of the four drug products in Table 15-17 would be preferred as a reference standard for the determination of relative bioavailability? Why?
   b. From which oral drug product is the drug absorbed more rapidly?
   c. What is the absolute bioavailability of the drug from the oral solution?
   d. What is the relative bioavailability of the drug from the oral tablet compared to the reference standard?
From the data above, graph the cumulative urinary excretion curves that would correspond to the plasma concentration–time curves.

4. Aphrodisia is a new drug manufactured by the Venus Drug Company. When tested in humans, the pharmacokinetics of the drug assumes a one-compartment open model with first-order absorption and first-order elimination:

![Diagram of blood level curves for two different oral dosage forms of a hypothetical antibiotic.](image)

**FIGURE 15-16** Blood level curves for two different oral dosage forms of a hypothetical antibiotic.

(iii) First-order elimination rate constant \( k \)

(iv) Total body clearance

f. From the data above, graph the cumulative urinary excretion curves that would correspond to the plasma concentration–time curves.

The drug was given in a single oral dose of 250 mg to a group of college students 21 to 29 years of age. Mean body weight was 60 kg. Samples of blood were obtained at various time intervals after the administration of the drug, and the plasma fractions were analyzed for active drug. The data are summarized in Table 15-18.

### TABLE 15-17 Comparison of Plasma Concentrations of Antibiotic, as Related to Dosage Form and Time

<table>
<thead>
<tr>
<th>Time after Dose (h)</th>
<th>IV Solution (2 mg/kg)</th>
<th>Oral Solution (10 mg/kg)</th>
<th>Oral Tablet (10 mg/kg)</th>
<th>Oral Capsule (10 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>5.94</td>
<td>23.4</td>
<td>13.2</td>
<td>18.7</td>
</tr>
<tr>
<td>1.0</td>
<td>5.30</td>
<td>26.6</td>
<td>18.0</td>
<td>21.3</td>
</tr>
<tr>
<td>1.5</td>
<td>4.72</td>
<td>25.2</td>
<td>19.0</td>
<td>20.1</td>
</tr>
<tr>
<td>2.0</td>
<td>4.21</td>
<td>22.8</td>
<td>18.3</td>
<td>18.2</td>
</tr>
<tr>
<td>3.0</td>
<td>3.34</td>
<td>18.2</td>
<td>15.4</td>
<td>14.6</td>
</tr>
<tr>
<td>4.0</td>
<td>2.66</td>
<td>14.5</td>
<td>12.5</td>
<td>11.6</td>
</tr>
<tr>
<td>6.0</td>
<td>1.68</td>
<td>9.14</td>
<td>7.92</td>
<td>7.31</td>
</tr>
<tr>
<td>8.0</td>
<td>1.06</td>
<td>5.77</td>
<td>5.00</td>
<td>4.61</td>
</tr>
<tr>
<td>10.0</td>
<td>0.67</td>
<td>3.64</td>
<td>3.16</td>
<td>2.91</td>
</tr>
<tr>
<td>12.0</td>
<td>0.42</td>
<td>2.30</td>
<td>1.99</td>
<td>1.83</td>
</tr>
<tr>
<td>AUC (( \mu g/\mu L \times h ))</td>
<td>29.0</td>
<td>145.0</td>
<td>116.0</td>
<td>116.0</td>
</tr>
</tbody>
</table>
TABLE 15-18  Data Summary of Active Drug Concentration in Plasma Fractions

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$C_p$ (µg/mL)</th>
<th>Time (h)</th>
<th>$C_p$ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>12</td>
<td>3.02</td>
</tr>
<tr>
<td>1</td>
<td>1.88</td>
<td>18</td>
<td>1.86</td>
</tr>
<tr>
<td>2</td>
<td>3.05</td>
<td>24</td>
<td>1.12</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
<td>36</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>4.21</td>
<td>48</td>
<td>0.14</td>
</tr>
<tr>
<td>7</td>
<td>4.08</td>
<td>60</td>
<td>0.05</td>
</tr>
<tr>
<td>9</td>
<td>3.70</td>
<td>72</td>
<td>0.02</td>
</tr>
</tbody>
</table>

6. Four different drug products containing the same antibiotic were given to 12 volunteer adult males (age 19–28 years, average weight 73 kg) in a four-way crossover design. The volunteers fasted for 12 hours prior to taking the drug product. Urine samples were collected up to 72 hours after the administration of the drug to obtain the maximum urinary drug excretion, $D_u^\infty$. The data are presented in Table 15-19.

   a. What is the absolute bioavailability of the drug from the tablet?
   b. What is the relative bioavailability of the capsule compared to the oral solution?

7. According to the prescribing information for cimetidine (Tagamet), following IV or IM administration, 75% of the drug is recovered from the urine after 24 hours as the parent compound. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. From this information, determine what fraction of the drug is absorbed systemically from an oral dose after 24 hours.

8. Define bioequivalence requirement. Why does the FDA require a bioequivalence requirement for the manufacture of a generic drug product?

9. Why can we use the time for peak drug concentration ($t_{max}$) in a bioequivalence study for an estimate of the rate of drug absorption, rather than calculating the $k_a$?

10. Ten male volunteers (18–26 years of age) weighing an average of 73 kg were given either four tablets each containing 250 mg of drug

TABLE 15-19  Urinary Drug Excretion Data Summary

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Dose (mg/kg)</th>
<th>Cumulative Urinary Drug Excretion ($D_u^\infty$), 0–72 h (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV solution</td>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td>Oral solution</td>
<td>4</td>
<td>380</td>
</tr>
<tr>
<td>Oral tablet</td>
<td>4</td>
<td>340</td>
</tr>
<tr>
<td>Oral capsule</td>
<td>4</td>
<td>360</td>
</tr>
</tbody>
</table>
Chapter 15

11. After performing a bioequivalence test comparing a generic drug product to a brand-name drug product, it was observed that the generic drug product had greater bioavailability than the brand-name drug product.

12. The following study is from Welling and associates (1982):

**Tolazamide Formulations**: Four tolazamide tablet formulations were selected for this study.

### TABLE 15-20 Blood Level Data Summary for Two Drug Products

<table>
<thead>
<tr>
<th>Kinetic Variable</th>
<th>Unit</th>
<th>Drug Product</th>
<th>A 4 × 250-mg Tablet</th>
<th>B 1000-mg Tablet</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for peak drug concentration (range)</td>
<td>h</td>
<td></td>
<td>1.3 (0.7–1.5)</td>
<td>1.8 (1.5–2.2)</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Peak concentration (range)</td>
<td>μg/mL</td>
<td></td>
<td>53 (46–58)</td>
<td>47 (42–51)</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>AUC (range)</td>
<td>μg h/mL</td>
<td></td>
<td>118</td>
<td>103</td>
<td>NS</td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>h</td>
<td></td>
<td>3.2 (2.5–3.8)</td>
<td>3.8 (2.9–4.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### TABLE 15-21 Disintegration Times and Dissolution Rates of Tolazamide Tablets

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Mean Disintegration Timea min (Range)</th>
<th>Percent Dissolved in 30 minb (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.8 (3.0–4.0)</td>
<td>103.9 (100.5–106.3)</td>
</tr>
<tr>
<td>B</td>
<td>2.2 (1.8–2.5)</td>
<td>10.9 (9.3–13.5)</td>
</tr>
<tr>
<td>C</td>
<td>2.3 (2.0–2.5)</td>
<td>31.6 (26.4–37.2)</td>
</tr>
<tr>
<td>D</td>
<td>26.5 (22.5–30.5)</td>
<td>29.7 (20.8–38.4)</td>
</tr>
</tbody>
</table>

---

a N = 6.
b By the method of USP-23.
c Dissolution rates in pH 7.6 buffer.

From Welling et al (1982), with permission.
The tablet formulations were labeled A, B, C, and D. Disintegration and dissolution tests were performed by standard USP-23 procedures.

**Subjects**: Twenty healthy adult male volunteers between the ages of 18 and 38 (mean, 26 years) and weighing between 61.4 and 95.5 kg (mean, 74.5 kg) were selected for the study. The subjects were randomly assigned to four groups of five each. The four treatments were administered according to a $4 \times 4$ Latin-square design. Each treatment was separated by 1-week intervals. All subjects fasted overnight before receiving the tolazamide tablet the following morning. The tablet was given with 180 mL of water. Food intake was allowed at 5 hours post-dose. Blood samples (10 mL) were taken just before the dose and periodically after dosing. The serum fraction was separated from the blood and analyzed for tolazamide by high-pressure liquid chromatography.

**Data Analysis**: Serum data were analyzed by a digital computer program using a regression analysis and by the percent of drug unab-

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Treatment (μg/mL)</th>
<th>Mean Tolazamide Concentrations$^a$ in Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>0</td>
<td>10.8 ± 7.4</td>
<td>1.3 ± 1.4</td>
</tr>
<tr>
<td>1</td>
<td>20.5 ± 7.3</td>
<td>2.8 ± 2.8</td>
</tr>
<tr>
<td>3</td>
<td>23.9 ± 5.3</td>
<td>4.4 ± 4.3</td>
</tr>
<tr>
<td>4</td>
<td>25.4 ± 5.2</td>
<td>5.7 ± 4.1</td>
</tr>
<tr>
<td>5</td>
<td>24.1 ± 6.3</td>
<td>6.6 ± 4.0</td>
</tr>
<tr>
<td>6</td>
<td>19.9 ± 5.9</td>
<td>6.8 ± 3.4</td>
</tr>
<tr>
<td>8</td>
<td>15.2 ± 5.5</td>
<td>6.6 ± 3.2</td>
</tr>
<tr>
<td>12</td>
<td>8.8 ± 4.8</td>
<td>5.5 ± 3.2</td>
</tr>
<tr>
<td>16</td>
<td>5.6 ± 3.8</td>
<td>4.6 ± 3.3</td>
</tr>
<tr>
<td>24</td>
<td>2.7 ± 2.4</td>
<td>3.1 ± 2.6</td>
</tr>
<tr>
<td>$C_{max}$ μg/mL$^c$</td>
<td>27.8 ± 5.3</td>
<td>7.7 ± 4.1</td>
</tr>
<tr>
<td>$t_{max}$ h$^d$</td>
<td>3.3 ± 0.9</td>
<td>7.0 ± 2.2</td>
</tr>
<tr>
<td>AUC$_{0-24}$ μg h/mL$^e$</td>
<td>260 ± 81</td>
<td>112 ± 63</td>
</tr>
</tbody>
</table>

$^a$Concentrations ± 1 SD, n = 20.
$^b$For explanation see text.
$^c$Maximum concentration of tolazamide in serum.
$^d$Time of maximum concentration.
$^e$Area under the 0–24-h serum tolazamide concentration curve calculated by trapezoidal rule.

From Welling et al (1982), with permission.
correlated with the bioavailability of the drug in vivo, why should the pharmaceutical manufacturer continue to perform in vitro release studies for each production batch of the solid dosage form?

14. Is it possible for two pharmaceutically equivalent solid dosage forms containing different inactive ingredients (ie, excipients) to demonstrate bioequivalence in vivo even though these drug products demonstrate differences in drug dissolution tests in vitro?

15. For bioequivalence studies, $t_{\text{max}}$, $C_{\text{max}}$, and AUC, along with an appropriate statistical analysis, are the parameters generally used to demonstrate the bioequivalence of two similar drug products containing the same active drug.

a. Why are the parameters $t_{\text{max}}$, $C_{\text{max}}$, and AUC acceptable for proving that two drug products are bioequivalent?

b. Are pharmacokinetic models needed in the evaluation of bioequivalence?

c. Is it necessary to use a pharmacokinetic model to completely describe the plasma drug concentration–time curve for the determination of $t_{\text{max}}$, $C_{\text{max}}$, and AUC?

d. Why are log-transformed data used for the statistical evaluation of bioequivalence?

e. What is an add-on study?

13. If in vitro drug dissolution and/or release studies for an oral solid dosage form (eg, tablet) does not correlate with the bioavailability of the drug in vivo, why should the pharmaceutical manufacturer continue to perform in vitro release studies for each production batch of the solid dosage form?

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FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996.


66485457-66485438 www.ketabpezeshki.com


### BIBLIOGRAPHY


Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy

Chapter Objectives

► Describe the types of safety and efficacy risks that may occur after taking a drug product and various means for preventing these risks.

► Differentiate between drug product quality and drug product performance.

► Explain how quality-by-design ensures the development and manufacture of a drug product that will deliver consistent performance.

► Define critical quality attributes and how these attributes relate to clinical safety and efficacy.

► Differentiate between quality control and quality assurance.

► Explain how postapproval changes in a drug product may affect drug quality and performance.

► List the major reasons that a drug product might be recalled due to quality defects.

RISKS FROM MEDICINES

Side effects from the use of drugs are the major cause of drug-related injuries, adverse events, and deaths. The FDA (FDA, CDER, 2005, 2007) has summarized various types of safety and efficacy risks from medicines (Fig. 16-1). Side effects are observed in clinical trials or postmarketing surveillance and result in listing of adverse events in the drug's labeling.

Some side effects are avoidable, and others are unavoidable. Avoidable side effects may include known drug–drug or drug–food interactions, contraindications, improper compliance, etc. In many cases, drug therapy requires an individualized drug treatment plan and careful patient monitoring. Some known side effects occur with the best medical practice and even when the drug is used appropriately. Examples include nausea from antibiotics or bone marrow suppression from chemotherapy. Medication errors include wrong drug, wrong dose, or incorrect drug administration. Some side effects are unavoidable. These uncertainties include unexpected adverse events, side effects due to long-term therapy, and unstudied uses and populations. For example, a rare adverse event occurring in fewer than 1 in 10,000 persons would not be identified in normal premarket testing. Chapters 12, 19, and 20 discuss how pharmacogenetics, pharmacokinetics, pharmacodynamics, and clinical considerations may improve drug efficacy and safety in many instances. Drug product quality is another important consideration. Quality is recognized and defined in ICH (International Conference on Harmonisation, which provides for international standards of new drug product quality; see below) as the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. Drug product quality defects are an important source of risk that affects drug product performance and can affect patient safety and therapeutic efficacy. Product quality includes strength and purity of the drug substance, the manufacturing process of the drug product and the
monitoring of the manufacturing operations. This chapter will focus on drug product quality and risks of product quality defects that affect drug product performance. To minimize product quality defects, regulatory agencies such as the FDA must consider risk-based regulatory decisions supporting the drug approval process. These decisions depend on the scientific understanding of how formulation and manufacturing process factors affect product quality and performance and are the underlying basis for the development, manufacture, and quality assurance of the drug product throughout its lifecycle.

**DRUG PRODUCT QUALITY AND DRUG PRODUCT PERFORMANCE**

*Drug product quality* relates to the biopharmaceutic and physiochemical properties of the drug substance and the drug product to the *in vivo* performance of the drug. The performance of each drug product must be consistent and predictable to assure both clinical efficacy and safety. Drug product attributes and performance are critical factors that influence product quality (Table 16-1). Each component of the drug product and the method of manufacture contribute to quality. Quality must be built into the product during research, development, and production. Quality is maintained by implementing systems and procedures that are followed during the development and manufacture of the drug product.

**Frequently Asked Questions**

**TABLE 16-1 Drug Product Quality and Performance Attributes**

| Product quality attributes
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry, manufacturing and controls (CMC)</td>
</tr>
<tr>
<td>Microbiology</td>
</tr>
<tr>
<td>Information that pertains to the identity, strength, quality, purity and potency of the drug product</td>
</tr>
<tr>
<td>Validation of manufacturing process and identification of critical quality attributes</td>
</tr>
</tbody>
</table>

| Product performance attributes
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vivo</em></td>
</tr>
<tr>
<td>Bioavailability and bioequivalence</td>
</tr>
<tr>
<td><em>In vitro</em></td>
</tr>
<tr>
<td>Drug release/dissolution</td>
</tr>
</tbody>
</table>

For convenience, drug product quality is listed in Table 16-2 separately from drug product performance. However, drug product quality must be maintained since drug product quality impacts directly on drug product performance.

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1 Pharmaceutical manufacturers are required to follow current Good Manufacturing Practices (cGMP) to ensure that the drug products are made consistently with high quality.

2 A glossary of terms appears at the end of the chapter.
PHARMACEUTICAL DEVELOPMENT

Prior to FDA approval and marketing, the drug product and manufacturing method must be designed and developed with quality and the desired final product in mind (QbD, quality by design). This manufacturing process is carefully designed using scientific principles throughout and integrating assurance of product quality into the design of the manufacturing process (quality assurance). Every step that affects drug manufacture must also be tested to demonstrate that the desired physical and functional outcomes are achieved (process validation). Once the manufacturing process has been validated, every single lot produced by this method must meet the desired specifications (quality control). A quality drug product should be designed with an appropriate manufacturing process that produces consistent drug product performance and achieves the desired therapeutic objective. Information gained from pharmaceutical development studies and from the manufacturing process provides scientific understanding to support the establishment of the design space (see below), specifications, and manufacturing controls that ensures that each batch of the drug product will be produced with the same quality and performance. The information from pharmaceutical development studies is also the basis for quality risk management. Changes in formulation and manufacturing processes during development and lifecycle management after market approval provide additional knowledge and further support the manufacture of the drug product.

Quality (by) Design (QbD)

A major principle that drives manufacturing process development is quality-by-design. Quality-by-design is a systematic, scientific, risk-based, holistic, and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes the understanding of product and processes and process control. Product and process performance characteristics are scientifically designed to meet specific objectives (Yu, 2009). To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development. Quality cannot be tested in drug products. Quality should be built in the design and confirmed by testing. With a greater understanding of the drug product and its manufacturing process, regulatory agencies are working with pharmaceutical manufacturers to use systematic approaches to drug product development that will achieve product quality and the desired drug product performance (FDA, 2009). The elements of QbD are listed in Table 16-2.

Critical Manufacturing Attributes (CMA) and Critical Process Parameters (CPP)

In process development, the most important processes and component properties should be identified in the manufacturing process. A critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure

<table>
<thead>
<tr>
<th>TABLE 16-2 Elements of Quality (by) Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Define target product quality profile.</td>
</tr>
<tr>
<td>• Design and develop formulations and manufacturing processes to ensure predefined product quality.</td>
</tr>
<tr>
<td>• Identify critical quality attributes, process parameters, and sources of variability that are critical to quality from the perspective of patients, then translate them into the attributes that the drug product should possess.</td>
</tr>
<tr>
<td>• Identify a design space for critical processing variables and formulation variables that impact in vivo product performance.</td>
</tr>
<tr>
<td>• Establish how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.</td>
</tr>
<tr>
<td>• Establish the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters); identify desired product characteristics and sources of variability.</td>
</tr>
<tr>
<td>• Implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time.</td>
</tr>
<tr>
<td>• Develop process analytical technology, PAT, to integrate systems during drug product manufacture that provides continuous real time quality assurance.</td>
</tr>
<tr>
<td>• Control manufacturing processes to produce consistent quality over time.</td>
</tr>
</tbody>
</table>
product quality. The pharmaceutical manufacturer should identify critical manufacturing attributes (CMA), critical process parameters (CPP), and sources of variability that ensure the quality of the finished dosage form. The critical quality attributes should be based on clinical relevance. Thus, the manufacturer of the drug product designs and develops the formulations and manufacturing processes to ensure a predefined quality.

**Design space**

The interaction between critical processes and materials should also be studied to optimize manufacturing processes. A design space is defined for critical processing variables and formulation variables that impact in vivo product performance. There may be several variables that affect the product variability in vitro. It is important to identify which of these variables are actually relevant to drug product performance in vivo. ICH defines design space in Q8 as follows:

- The multidimensional combination and interaction of input variables (eg, material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Design space is the geometrical region suitable for quality manufacturing when two or more process/material variables are plotted in a two-dimensional or higher-dimensional space to show the combined effects of the relevant processing variables during manufacturing. Some of these processing variables may or may not be critical to drug product performance. Thus, the manufacturer knows which process variable is critical and must have stricter control. As part of the quality system, the concept of Quality Target Product Profile (QTPP) was introduced in QbD. QTPP summarizes all the important product attributes that is targeted and designed by the manufacturer during design and manufacturing (see Table 16-2).

**Process Analytical Technology (PAT)**

Like design space, process analytical technology, PAT, also uses critical processes and materials to improve the quality of the product but in PAT the emphasis is on monitoring these variables in a timely manner. PAT is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance (FDA Guidance, 2004). Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on samples collected during the manufacturing process and after the drug product is made (finished dosage form). These laboratory tests are used to evaluate quality of the drug product (see quality control and quality assurance below). Newer methods based on science and engineering principles now exist for improving pharmaceutical development, manufacturing, and quality assurance starting earlier in the development timeline through innovation in product and process development, analysis, and control.

PAT uses an integrated systems approach to regulating pharmaceutical product quality. PAT assesses mitigating risks related to poor product and process quality, then monitors and controls them. PAT is characterized by the following:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes.
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance.
- Continuous real time quality assurance.
- Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge.
- Risk-based regulatory approaches recognize:
  - The scientific understanding of how formulation and manufacturing process factors affect product quality and performance.
  - The capability of process control strategies to prevent or mitigate the risk of producing a poor quality product.

PAT enhances manufacturing efficiencies by improving the manufacturing process, through scientific innovation and with better communication
between manufacturers and the regulatory agencies. PAT may be considered a part of the overall QbD such that quality is built into the product during manufacture. An increased emphasis on building quality into drug products allows more focus to be placed on relevant multi-factorial relationships among material, manufacturing process, environmental variables, and their effects on quality. This enhanced focus provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (eg, product specifications, process controls, training). The data and information to help understand these relationships can be leveraged through preformulation programs, development and scale-up studies, as well as from improved analysis of manufacturing data collected over the life of a product.

**Integrating Quality (by) Design and Biopharmaceutics**

Risk assessment and risk control are important in maintaining the quality of drug products. By the use of an integrated approach to quality-by-design using biopharmaceutic principles, drug products can be manufactured with the assurance that product quality and performance will be maintained throughout its life cycle. Figure 16-2 shows how QbD is supported by biopharmaceutic tools and related studies.

![Figure 16-2 Integrating quality (by) design and biopharmaceutics. (From Selen, 2009, with permission.)](image_url)

**EXCIPIENT AFFECT ON DRUG PRODUCT PERFORMANCE**

Drug products are finished dosage forms that contain the active pharmaceutical ingredient along with suitable diluents and/or excipients. Excipients are generally considered inert in that they have no pharmacodynamic activity of their own. However, excipients have different functional purposes and influence the performance of the drug product (Amidon et al, 2007, Shargel, 2010). Compressed tablets may consist of the active ingredient, a diluent (filler), a binder, buffering agents, disintegrating agent, and one or more lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. These excipients provide various functional purposes such as improving compression, improving powder flow, stability of the active ingredient, and other properties (Table 16-3). For example, diluents such as lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose are added where the quantity of active ingredient is small and/or difficult to compress.

The physical and chemical properties of the excipients, the physical and chemical properties of the active pharmaceutical ingredient, and the manufacturing process all play a role in performance of the finished dosage form. Each excipient
**Chapter 16**

Magnesium stearates, a vegetative source may be used to avoid the BSE/TSE concern.

**Gelatin Capsules Stability**

Soft and hard gelatin capsules show a decrease in the dissolution rate as they age in simulated gastric fluid (SGF) with and without pepsin or in simulated intestinal fluid (SIF) without pancreatin. This has been attributed to pellicle formation. When the dissolution of aged or slower-releasing capsules was carried out in the presence of an enzyme (pepsin in SGF or pancreatin in SIF), a significant increase in dissolution was observed. In this setting, multiple dissolution media may be necessary to assess product quality adequately.

**Excipient Effects**

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved immediate-release solid oral dosage forms within a suitable range will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving immediate-release product.

Excessive use of lubricant should be avoided. When new excipients or atypically large amounts of magnesium stearates, a vegetative source may be used to avoid the BSE/TSE concern.

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**PRACTICAL FOCUS**

**BSE in Gelatin**

Gelatin and other excipients may be produced from ruminant sources such bones and hides obtained from cattle. In the early 1990s, the FDA became concerned about transmissible spongiform encephalopathies (TSEs) in animals and Creutzfeldt-Jakob disease in humans. In 1993, the FDA recommended against the use of materials from cattle that had resided in, or originated from, countries in which bovine spongiform encephalopathy (BSE, or “mad cow disease”) had occurred. The FDA organized a Transmissible Spongiform Encephalopathies Advisory Committee to help assess the safety of imported and domestic gelatin and gelatin by-products in FDA-regulated products with regard to the risk posed by BSE. The FDA published a guidance to industry concerning the sourcing and processing of gelatin used in pharmaceutical products to ensure the safety of gelatin as it relates to the potential risk posed by BSE (www.fda.gov/opacom/morechoices/industry/guidance/gelguide.htm). In some cases, such as the

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<table>
<thead>
<tr>
<th>Excipient</th>
<th>Function in Compressed Tablet</th>
<th>Possible Effect on Drug Product Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose, lactose, calcium carbonate</td>
<td>Diluent</td>
<td>Very low dose drug (e.g., 5 mg) may have high ratio of excipients to active drug leading to a problem of homogeneous blending and possible interaction of drug with excipients.</td>
</tr>
<tr>
<td>Copovidone, starch, methylcellulose</td>
<td>Binder</td>
<td>Binders give adhesiveness to the powder blend and can affect tablet hardness. Harder tablets tend to disintegrate more slowly.</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>Lubricants are hydrophobic; over lubrication can slow dissolution of API.</td>
</tr>
<tr>
<td>Starch</td>
<td>Disintegrant</td>
<td>Disintegrant allows for more rapid fragmentation of tablet in vivo, reducing disintegration time and allowing for more rapid dissolution.</td>
</tr>
<tr>
<td>FD&amp;C colors and lakes</td>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Various</td>
<td>Coating</td>
<td>Coatings may have very little effect (film coat) or have rate controlling effect on drug release and dissolution (e.g., enteric coat).</td>
</tr>
</tbody>
</table>
commonly used excipients are included in an immediate release solid dosage form, additional information documenting the absence of an impact on bioavailability of the drug may be requested by the FDA. Such information can be provided with a relative bioavailability solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic.

**QUALITY CONTROL AND QUALITY ASSURANCE**

An independent quality assurance (QA) unit is a vital part of drug development and manufacture. QA is responsible for ensuring that all the appropriate procedures have been followed and documented. QA provides a high probability that each dose or package of a drug product will have predictable characteristics and perform according to its labeled use. The quality control (QC) unit is responsible for the in-process tests beginning from receipt of raw materials, throughout production, finished product, packaging, and distribution.

Principles of quality assurance include: (1) quality, safety, and effectiveness must be designed and built into the product; (2) quality cannot be inspected or tested into the finished product; and (3) each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.

QA/QC has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated. QA/QC is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

**PRACTICAL FOCUS**

Tablet compression may affect drug product performance of either immediate-release or extended-release drug products even between products containing the same active drug. Metoprolol is a beta 1-selective (cardioselective) adrenoreceptor blocking agent that is available as an immediate-release tablet (metoprolol tartrate tablets, USP—Lopressor®) and an extended-release tablet (metoprolol succinate extended-release tablets—Toprol-XL®). Metoprolol is a highly soluble and highly permeable drug that meets the Biopharmaceutics Classification System, BCS 1 (Chapter 15). Metoprolol is rapidly and completely absorbed from the immediate-release tablet.

Compression makes the powder blend more compact and affects tablet hardness, especially when inadequate amount of binder is added. Excessive compression may cause the tablet to disintegrate more slowly, resulting in a slower rate of dissolution and systemic drug absorption. Adequate use of binder and lubricant during product design obviates the need to use excessive force during compression/compaction.

The metoprolol succinate extended-release tablet (Toprol-XL®) is a multiple-unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval (Toprol-XL approved label). The controlled-release pellets are mixed with excipients and compressed into tablets. If the tablet is compressed too strongly, the high compression will not only increase tablet hardness, but can also deform the controlled-release pellets. The deformed pellets lose their controlled release characteristics and the active drug, metoprolol dissolves more quickly resulting in a faster than desired rate of systemic drug absorption. Inadequate amount of
lubricant or glidant can also aggravate or damage
pellets during compression.

**Good Manufacturing Practices**

*Good Manufacturing Practices* (GMPs) are FDA reg-
ulations that describe the methods, equipment, facili-
ties, and controls required for producing human and
veterinary products. GMPs define a quality system that
manufacturers use to build quality into their products.
For example, approved drug products developed and
produced according to GMPs are considered safe,
properly identified, of the correct strength, pure, and of
high quality. The US regulations are called *current*
Good Manufacturing Practices (cGMPs), to empha-
size that the expectations are dynamic. These regula-
tions are minimum requirements that may be exceeded
by the manufacturer. GMPs help prevent inadvertent
use or release of unacceptable drug products into
manufacturing and distribution. GMP requirements
include well-trained personnel and management, build-
ings and facilities, and written and approved Standard
Operating Procedures (SOPs), as listed in Table 16-4.

<table>
<thead>
<tr>
<th>Table 16-4</th>
<th>Current Good Manufacturing Practice for Finished Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subpart A</strong>—General Provisions</td>
<td></td>
</tr>
<tr>
<td>Scope, definitions</td>
<td></td>
</tr>
<tr>
<td><strong>Subpart B</strong>—Organization and Personnel</td>
<td></td>
</tr>
<tr>
<td>Responsibilities of quality control unit, personnel qualifications,</td>
<td></td>
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<tr>
<td>Personnel responsibilities, consultants</td>
<td></td>
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<tr>
<td><strong>Subpart C</strong>—Buildings and Facilities</td>
<td></td>
</tr>
<tr>
<td>Design and construction features, lighting, ventilation, air filtration, air heating and cooling, plumbing, sewage and refuse,</td>
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<tr>
<td>washing and toilet facilities, sanitation, maintenance</td>
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<tr>
<td><strong>Subpart D</strong>—Equipment</td>
<td></td>
</tr>
<tr>
<td>Equipment design, size, and location, equipment construction, equipment cleaning and maintenance, automatic, mechanical,</td>
<td></td>
</tr>
<tr>
<td>and electronic equipment, filters</td>
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</tr>
<tr>
<td><strong>Subpart E</strong>—Control of Components and Drug Product Containers and Closures</td>
<td></td>
</tr>
<tr>
<td>General requirements, receipt and storage of untested components, drug product containers and closures; testing and</td>
<td></td>
</tr>
<tr>
<td>approval or rejection of components, drug product containers, and closures; use of approved components, drug product</td>
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</tr>
<tr>
<td>containers and closures; retesting of approved components, drug product containers and closures, rejected components, drug</td>
<td></td>
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<tr>
<td>product containers and closures, drug product containers and closures</td>
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<tr>
<td><strong>Subpart F</strong>—Production and Process Controls</td>
<td></td>
</tr>
<tr>
<td>Written procedures; deviations, change in of components, calculation of yield, equipment identification, sampling and testing</td>
<td></td>
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<tr>
<td>of in-process materials and drug products, time limitations on production, control of microbiological contamination,</td>
<td></td>
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<tr>
<td>reprocessing</td>
<td></td>
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<tr>
<td><strong>Subpart G</strong>—Packaging and Labeling Controls</td>
<td></td>
</tr>
<tr>
<td>Materials examination and usage criteria, labeling issuance, packaging and labeling operations, tamper-resistant packaging</td>
<td></td>
</tr>
<tr>
<td>requirements for over-the-counter human drug products, drug product inspection, expiration dating</td>
<td></td>
</tr>
<tr>
<td><strong>Subpart H</strong>—Holding and Distribution</td>
<td></td>
</tr>
<tr>
<td>Warehousing procedures, distribution procedures</td>
<td></td>
</tr>
<tr>
<td><strong>Subpart I</strong>—Laboratory Controls</td>
<td></td>
</tr>
<tr>
<td>General requirements, testing and release for distribution, stability testing, special testing requirements, reserve samples,</td>
<td></td>
</tr>
<tr>
<td>laboratory animals, penicillin contamination</td>
<td></td>
</tr>
<tr>
<td><strong>Subpart J</strong>—Records and Reports</td>
<td></td>
</tr>
<tr>
<td>General requirements; equipment cleaning and use log; component, drug product, container, closure, and labeling records;</td>
<td></td>
</tr>
<tr>
<td>master production and control records, batch production and control records, production record review, laboratory records,</td>
<td></td>
</tr>
<tr>
<td>distribution, complaint files</td>
<td></td>
</tr>
<tr>
<td><strong>Subpart K</strong>—Returned and Salvaged Drug Products</td>
<td></td>
</tr>
<tr>
<td>Returned drug products, drug product salvaging</td>
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</tr>
</tbody>
</table>

Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy

Guidances for Industry
The FDA publishes guidances for the industry to provide recommendations to pharmaceutical manufacturers for the development and manufacture of drug substances and drug products (www.fda.gov/cedt/guidance/index.htm). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is composed of the regulatory authorities of Europe, Japan, and the United States, and experts from the pharmaceutical industry. The ICH is interested in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health (www.ifpma.org).

Quality Standards
Public standards are necessary to ensure that drug substances and drug products have consistent and reproducible quality. The United States Pharmacopeia National Formulary, USP-NF (www.usp.org), is legally recognized by the US Food, Drug and Cosmetic Act and sets public standards for drug products and drug substances. The USP-NF contains monographs for drug substances and drug products that include standards for strength, quality, and purity. In addition, the USP-NF contains general chapters that describe specific procedures that support the monographs. The tests in the monographs may provide acceptance criteria, i.e., numerical limits, ranges, or other criteria for the test for the drug substance or drug product. An impurity is defined as any component of the drug substance that is not the entity defined as the drug substance. Drugs with a USP or NF designation that do not conform to the USP monograph may be considered adulterated. Specifications are the standards a drug product must meet to ensure conformance to predetermined criteria for consistent and reproducible quality and performance.

International Conference on Harmonization (ICH) has published several guidances to regulate drug substance and drug product manufacturing. The main approach is to promote “better understanding of manufacturing processes with quality (by) design.” QbD improves the quality of the product and makes it easier for regulatory agencies to evaluate post-approval changes of a drug product. ICH guideline Q8 describes Pharmaceutical Development and ICH guidance Q10 discusses Pharmaceutical Quality Systems. Earlier guidances such as ICH Q6A provide more specific details on setting acceptance criteria and test specification for new drug substances and new drug products. The ICH guidance Q6A has been recommended for adoption in the United States, the European Union, and Japan. These regulations will be applied to new drug substances and drug products.

RISK MANAGEMENT

Regulatory and Scientific Considerations
The FDA develops rational, science-based regulatory requirements for drug substances and finished drug products. The FDA establishes quality standards and acceptance criteria for each component used in the manufacture of a drug product. Each component must meet an appropriate quality and performance objective.

Drug Manufacturing Requirements
Assurance of product quality is derived from careful attention to a number of factors, including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end-product testing. Because of the complexity of today’s medical products, routine end-product testing alone is not sufficient to ensure product quality. The Chemistry, Manufacturing Controls (CMC) section of a Drug Application describes the composition, manufacture, and specifications of the drug substance and drug product (Table 16-5).

Process Validation
Process validation is the process for establishing documented evidence to provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation is a key element in ensuring that these quality assurance goals are met. Proof of validation is obtained through collection and evaluation of data, preferably beginning at the process development phase and continuing through the production phase.
Through careful design and validation of both the process and process controls, a manufacturer can establish with a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence on intensive in-process and finished product testing. In most cases, end-product testing plays a major role in ensuring that quality assurance goals are met; ie, validation and end-product testing are not mutually exclusive.

**Drug Recalls and Withdrawals**

The FDA coordinates drug recall information and prepares health hazard evaluations to determine the risk to public health from products being recalled. The FDA classifies recall actions in accordance to the level of risk. The FDA and the manufacturer develop recall strategies based on the potential health hazard and other factors, including distribution patterns and market availability. The FDA also determines the need for public warnings and assists the recalling firm with public notification. Table 16-6 lists some of the major reasons for drug recalls.

**TABLE 16-5 Guidelines for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application**

<table>
<thead>
<tr>
<th>I. Drug Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Description, including physical and chemical characteristics and stability</td>
</tr>
<tr>
<td>1. Name(s)</td>
</tr>
<tr>
<td>2. Structural formula</td>
</tr>
<tr>
<td>3. Physical and chemical characteristics</td>
</tr>
<tr>
<td>4. Elucidation of structure</td>
</tr>
<tr>
<td>5. Stability</td>
</tr>
<tr>
<td>B. Manufacturer(s)</td>
</tr>
<tr>
<td>C. Method(s) of manufacturer and packaging</td>
</tr>
<tr>
<td>1. Process controls</td>
</tr>
<tr>
<td>2. Container-closure system</td>
</tr>
<tr>
<td>D. Specifications and analytical methods for the drug substance</td>
</tr>
<tr>
<td>E. Solid-state drug substance forms and their relationship to bioavailability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Components</td>
</tr>
<tr>
<td>B. Specifications and analytical methods for inactive components</td>
</tr>
<tr>
<td>C. Manufacturer(s)</td>
</tr>
<tr>
<td>D. Method(s) of manufacture and packaging</td>
</tr>
<tr>
<td>1. Process controls</td>
</tr>
<tr>
<td>2. Container closure system</td>
</tr>
</tbody>
</table>

| III. Methods validation package |

| IV. Environmental assessment |

**TABLE 16-6 Major Reasons for Drug Recalls**

- Failed USP dissolution test requirements
- Microbial contamination of nonsterile products
- Lack of efficacy
- Impurities/degradation products
- Lack of assurance of sterility
- Lack of product stability—Stability data failing to support expiration date
- Cross-contamination with other products
- Deviations from good manufacturing practices
- Failure or inability to validate manufacturing processes
- Failure or inability to validate drug analysis methods
- Subpotency or superpotency
- Labeling mix-ups including
  - Labeling: Label error on declared strength
  - Labeling: Correctly labeled product in incorrect carton or package
- Misbranded: Promotional literature with unapproved therapeutic claims
- Marketed without a new or generic approval

Adapted from Center for Drug Evaluation and Research, CDER 2007 Update and other sources.

The product’s end use should be a determining factor in the development of product (and component) characteristics and specifications. All pertinent aspects of the product that may affect safety and effectiveness should be considered. These aspects include performance, reliability, and stability. Acceptable ranges or limits should be established for each characteristic to set up allowable variations. **Specifications** are the quality standards (ie, tests, analytical procedures, and acceptance criteria) that confirm the quality of drug substances, drug products, intermediates, raw material reagents, components, in-process material, container closure systems, and other materials used in the production of the drug substance or drug product. The standards or specifications which are critical to product quality are considered CMAs or CPPs.
**SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)**

A postapproval change is any change in a drug product after it has been approved for marketing by the FDA. Postapproval manufacturing changes may adversely impact drug product quality. Since safety and efficacy are established using clinical batches, the same level of quality must be ensured in the finished drug product released to the public. A change to a marketed drug product can be initiated for a number of reasons, including a revised market forecast, change in an active pharmaceutical ingredient source, change in excipients, optimization of the manufacturing process, and upgrade of the packaging system. A change within a given parameter can have varied effect depending on the type of product. For example, a change in the container closure/system of a solid oral dosage form may have little impact on an oral tablet dosage form unless the primary packaging component is critical to the shelf life of the finished product.

If a pharmaceutical manufacturer makes any change in the drug formulation, scales up the formulation to a larger batch size, or changes the process, equipment, or manufacturing site, the manufacturer should consider whether any of these changes will affect the identity, strength, purity, quality, safety, and efficacy of the approved drug product. Moreover, any changes in the raw material (ie, active pharmaceutical ingredient), excipients (including a change in grade or supplier), or packaging (including container closure system) should also be shown not to affect the quality of the drug product. The manufacturer should assess the effect of the change on the identity, strength (eg, assay, content uniformity), quality (eg, physical, chemical, and biological properties), purity (eg, impurities and degradation products), or potency (eg, biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

The FDA has published several SUPAC guidances, including *Changes to an Approved NDA or ANDA* (www.fda.gov/cder/guidance/index.htm) for the pharmaceutical industry. These guidances address the following issues:

- Components and composition of the drug product
- Manufacturing site change
- Scale-up of drug product
- Manufacturing equipment
- Manufacturing process
- Packaging
- Active pharmaceutical ingredient

These documents describe (1) the level of change, (2) recommended chemistry, manufacturing and controls tests for each level of change, (3) *in vitro* dissolution tests and/or bioequivalence tests for each level of change, and (4) documentation that should support the change. The level of change is classified as to the likelihood that a change in the drug product as listed above might affect the quality of the drug product. The levels of change as described by the FDA are listed in Table 16-7.

As noted in Table 16-7, a Level 1 change, which could be a small change in the excipient amount (eg, starch, lactose), would be unlikely to alter the quality or performance of the drug product, whereas a Level 3 change, which may be a qualitative or quantitative change in the excipients beyond an allowable range, particularly for drug products containing a narrow therapeutic window might require an *in vivo* bioequivalence study to demonstrate that drug quality and performance were not altered by the change.

**TABLE 16-7  FDA Definitions of Level of Changes That May Affect the Quality of an Approved Drug Product**

<table>
<thead>
<tr>
<th>Change Level</th>
<th>Definition of Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Changes that are unlikely to have any detectable impact on the formulation quality and performance.</td>
</tr>
<tr>
<td>Level 2</td>
<td>Changes that could have a significant impact on formulation quality and performance.</td>
</tr>
<tr>
<td>Level 3</td>
<td>Changes that are likely to have a significant impact on formulation quality and performance.</td>
</tr>
</tbody>
</table>
Assessment of the Effects of the Change

Assessment of the effect of a change should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria. Additional testing may be needed to confirm that the material affected by manufacturing changes continues to meet its specification. The assessment may include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment may involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing depends on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. Examples of additional tests include:

- Evaluation of changes in the impurity or degradant profile
- Toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level
- Evaluation of the hardness or friability of a tablet
- Assessment of the effect of a change on bioequivalence (may include multipoint and/or multimedia dissolution profiles and/or an in vivo bioequivalence study)
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system

Equivalence

The manufacturer usually assesses the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product by comparing test results from pre- and postchange material and then determining if the test results are equivalent. The drug product after any changes should be equivalent to the product made before the change. An exception to this general approach is that when bioequivalence should be redocumented for certain Abbreviated New Drug Application (ANDA) postapproval changes, the comparator should be the reference listed drug. Equivalence does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

Critical Manufacturing Variables

Critical manufacturing variables, CMVs, (sometimes referred to as critical manufacturing attributes, CMAs), include items in the formulation, process, equipment, materials, and methods for the drug product that can significantly affect in vitro dissolution. If possible, the manufacturer should determine whether there is a relationship between CMV, in vitro dissolution, and in vivo bioavailability. The goal is to develop product specifications that will ensure bioequivalence of future batches prepared within limits of acceptable dissolution specifications. One approach to obtaining this relationship is to compare the bioavailability of test products with slowest and fastest dissolution characteristics to the bioavailability of the marketed drug product. Dissolution specifications for the drug product are then established so that future production batches do not fall outside the bioequivalence of the marketed drug product.

Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. For example, a type of process change could cause a new degradant to be formed that requires qualification and/or quantification. The manufacturer must show that the new degradant will not affect the safety or efficacy of the product. Changes in the qualitative or quantitative

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3In vitro dissolution/drug release studies that relate to the in vivo drug bioavailability may be considered a drug product performance test.
formulation, including inactive ingredients, are considered major changes and are likely to have a significant impact on formulation quality and performance. However, the deletion or reduction of an ingredient intended to affect only the color of a product is considered to be a minor change that is unlikely to affect the safety of the drug product.

**Bulk Actives Postapproval Changes (BACPACs)**

Manufacturing changes of the *active pharmaceutical ingredient* (API)—also known as the drug substance or bulk active—may change its quality attributes. These quality attributes include chemical purity, solid-state properties, and residual solvents. Chemical purity is dependent on the synthetic pathway and purification process. Solid-state properties include particle size, polymorphism, hydrate/solvate, and solubility. Small amounts of residual solvents such as dichloromethane may remain in the API after extraction and/or purification. Changes in the solid-state properties of the API may affect the manufacture of the dosage form or product performance. For example, a change in particle size may affect API bulk density and tablet hardness, whereas different polymorphs may affect API solubility and stability. Changes in particle size and/or polymorph may affect the drug’s bioavailability *in vivo*. Moreover, the excipient(s) and vehicle functionality and possible pharmacologic properties may affect product quality and performance.

### Frequently Asked Question

**Does a change in the manufacturing process require FDA approval?**

PRACTICAL FOCUS

**Quantitative Change in Excipients**

A manufacturer would like to increase the amount of starch by 2% (w/w) in an immediate-release drug product.

- Would you consider this change in an excipient to be a Level 1, 2, or 3 change? Why?

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Percent Excipient (W/W) of Total Target Dosage Form Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
<td>±5</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>±3</td>
</tr>
<tr>
<td>Starch</td>
<td>±1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Binder</td>
<td>±0.5</td>
</tr>
<tr>
<td>Lubricant</td>
<td>±0.25</td>
</tr>
<tr>
<td>Calcium stearate</td>
<td>±0.25</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>±1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Glidant</td>
<td>±1</td>
</tr>
<tr>
<td>Talc</td>
<td>±0.1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Film coat</td>
<td>±1</td>
</tr>
</tbody>
</table>

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. Source: FDA Guidance, 1995.

The FDA has determined that small changes in certain excipients for immediate-release drug products may be considered Level 1 changes (see Table 16-7). Table 16-8 lists the changes in excipients, expressed as percentage (w/w) of the total formulation, less than or equal to the following percent ranges that are considered Level 1 changes. According to this table, a 2% increase in starch would be considered a Level 1 change.

The total additive effect of all excipient changes should not be more than 5%. For example, a drug product containing the active ingredient lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (eg, lactose increases 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the Level 1 range. The examples are for illustrations only and the latest official guidance should be consulted for current views.

It should be noted that a small change in the amount of excipients is less likely to affect the bioavailability of a highly soluble, highly permeable drug in an immediate-release drug product compared to a drug that has low solubility and low permeability.
Changes in Batch Size (Scale-Up/Scale-Down)

For commercial reasons, a manufacturer may increase the batch size of a drug product from 100,000 units to 5 million units. Even though similar equipment is used and the same Standard Operating Procedures (SOPs) are used, there may be problems in manufacturing a very large batch. This problem is similar to a chef’s problem of cooking the main entrée for two persons versus cooking the same entrée for a banquet of 200 persons using the same recipe. The FDA has generally considered that a change in batch size greater than 10-fold is a Level 2 change and requires the manufacturer to notify the FDA and provide documentation for all testing before marketing this product.

PRODUCT QUALITY PROBLEMS

The FDA and industry are working together to establish a set of quality attributes and acceptance criteria for certain approved drug substances and drug products that would indicate less manufacturing risk. Table 16-9 summarizes some of the quality attributes for these products. However, all approved drug products must be manufactured under current Good Manufacturing Practices.

Drug substances and drug products that have more quality risk are generally those products that are more complex to synthesize or manufacture (Fig. 16-3). For example, biotechnology-derived drugs (e.g., proteins) made by fermentation may have more quality risk than chemically synthesized small molecules. Extended-release and delayed-release drug products may also present a greater quality risk than an immediate-release drug product. Drug products that have a very small ratio of active drug substance to excipients are more difficult to blend uniformly and thus may have a greater quality risk. Good Manufacturing Practices and control of the critical manufacturing operations help maintain the quality of the finished product. Complex operations can have consistent outcome quality as long as the manufacturer maintains control of the process and builds in quality during manufacturing operations.

<table>
<thead>
<tr>
<th>TABLE 16-9</th>
<th>Quality Attributes and Criteria for Certain Approved Drug Substances and Drug Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Substances</strong></td>
<td><strong>Drug Products</strong></td>
</tr>
<tr>
<td>Attribute</td>
<td>Criteria</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>Well characterized</td>
</tr>
<tr>
<td>Synthetic process</td>
<td>Simple process</td>
</tr>
<tr>
<td>Quality</td>
<td>No toxic impurities; adequate specifications</td>
</tr>
<tr>
<td>Physical properties</td>
<td>Polymorphic forms, particle size are well controlled</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable drug substance</td>
</tr>
<tr>
<td>Manufacturing history</td>
<td>TBD</td>
</tr>
<tr>
<td>Others</td>
<td>TBD</td>
</tr>
</tbody>
</table>

TBD, to be defined.

Adapted from Chui (2000), with permission.
POSTMARKETING SURVEILLANCE

Pharmaceutical manufacturers are required to file periodic Post-Market Reports for an approved ANDA to the FDA through its Postmarketing Surveillance Program. The main component of the requirement is the reporting of adverse drug experiences. This is accomplished by reassessing drug risks based on data learned after the drug is marketed. In addition, labeling changes may occur after market approval. For example, a new adverse reaction discussed by postmarketing surveillance is required for both branded and generic drug products.

GLOSSARY

Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Design Space: The multidimensional combination and interaction of input variables (eg, material attributes) and process parameters that have been demonstrated to provide quality assurance. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Formal Experimental Design: A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “Design of Experiments.”

Lifecycle: All phases in the life of a product from the initial development through marketing until the product’s discontinuation.

Process Analytical Technology (PAT): A system for designing, analyzing, and controlling manufacturing through timely measurements (ie, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Robustness: Ability of a process to tolerate variability of materials and changes in the process and equipment without negative impact on quality.

Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances).

Specified Impurity: An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to ensure the quality of the new drug substance or new drug product.

Unidentified Impurity: An impurity which is defined solely by qualitative analytical properties (eg, chromatographic retention time).

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CHAPTER SUMMARY

Drug product quality and drug product performance are important for patient safety and therapeutic efficacy. Drug product quality and drug product performance relate to the biopharmaceutic and physicochemical properties of the drug substance and the drug product and to the manufacturing process. The development of a drug product requires a systematic, scientific, risk-based, holistic, and proactive approach that begins with predefined objectives and emphasizes product and processes understanding and process control (quality-by-design, QbD). Quality cannot be tested into drug products. Quality should be built in the design and confirmed by testing. Quality control, QC, and quality assurance, QA, help ensure that drug products are manufactured with quality and have consistent performance throughout their lifecycle. Manufacturers must demonstrate that any changes in the formulation after FDA approval (SUPAC) does not alter drug product quality and performance compared to the initial formulation. Excipients that have no inherent pharmacodynamic activity may affect drug product performance. Drug products may be recalled due to deficiencies in drug product quality. Product quality defects are controlled through good manufacturing practices, monitoring, and surveillance.

LEARNING QUESTIONS

1. Three batches of ibuprofen tablets, 200 mg, are manufactured by the same manufacturer using the same equipment. Each batch meets the same specifications. Does meeting specifications mean that each batch of drug product contains the identical amount of ibuprofen?

2. What should a manufacturer of a modified-release tablet consider when making a qualitative or quantitative change in an excipient?

3. Explain how a change in drug product quality may affect drug product performance. Provide at least three examples.

4. For solid oral drug products, a change in the concentration of which of the following excipients is more likely to influence the bioavailability of a drug? Why?
   - Starch
   - Magnesium stearate
   - Microcrystalline cellulose
   - Talc
   - Lactose

5. How does the polymorphic form of the active drug substance influence the bioavailability of a drug? Can two different polymorphs of the same active drug substance have the same bioavailability?

REFERENCES


Chiu, Yuan-yuan: Risk-based CMC review, Advisory Committee for Pharmaceutical Sciences, FDA, October 21, 2002.


FDA, CDER 2007 Update.

FDA Guidance for Industry: Changes to an Approved NDA or ANDA, April 2004 (www.fda.gov/cder/guidance/index.htm)

Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy

Risk-Based CMC Review; Advisory Committee for Pharmaceutical Sciences, FDA, Oct 21, 2002.

Chapter Objectives

- Define modified-release drug products.
- Differentiate between conventional, immediate-release, extended-release, delayed-release, and targeted drug products.
- Explain the advantages and disadvantages of extended-release drug products.
- Describe the kinetics of extended-release drug products compared to immediate-release drug products.
- Explain when an extended-release drug product should contain an immediate-release drug dose.
- Explain why extended-release beads in capsule formulation may have a different bioavailability profile compared to an extended release tablet formulation of the same drug.
- Describe several approaches for the formulation of an oral extended-release drug product.
- Explain why a transdermal drug product (patch) may be considered an extended-release drug product.

CONVENTIONAL (IMMEDIATE-RELEASE) AND MODIFIED-RELEASE DRUG PRODUCTS

Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. In the formulation of conventional drug products, no deliberate effort is made to modify the drug release rate. Immediate-release products generally result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. In the case of conventional oral products containing prodrugs, the pharmacodynamic activity may be slow due to conversion to the active drug by hepatic or intestinal metabolism or by chemical hydrolysis. Alternatively, conventional oral products containing poorly soluble (lipophilic drugs), drug absorption may be gradual due to slow dissolution in or selective absorption across the GI tract, also resulting in a delayed onset time.

The pattern of drug release from modified-release (MR) dosage forms is deliberately changed from that of a conventional (immediate-release) dosage formulation to achieve a desired therapeutic objective or better patient compliance. Types of MR drug products include delayed release (eg, enteric coated), extended release (ER), and orally disintegrating tablets (ODT).

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is a formulation in which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Several types of modified-release oral drug products are recognized:

1. Extended-release drug products. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.
Describe the components of a transdermal drug delivery system.

Explain why an extended-release formulation of a drug may have a different efficacy profile compared to the same dose of drug given in as a conventional, immediate-release, oral dosage form in multiple doses.

List the studies that might be required for the development of an extended-release drug product.

2. *Delayed-release drug products.* A dosage form that releases a discrete portion or portions of drug at a time other than promptly after administration. An initial portion may be released promptly after administration. Enteric-coated dosage forms are common delayed-release products (e.g., enteric-coated aspirin and other NSAID products).

3. *Targeted-release drug products.* A dosage form that releases drug at or near the intended physiologic site of action (see Chapter 18). Targeted-release dosage forms may have either immediate- or extended-release characteristics.

4. *Orally disintegrating tablets* (ODT). ODT have been developed to disintegrate rapidly in the saliva after oral administration. ODT may be used without the addition of water. The drug is dispersed in saliva and swallowed with little or no water.

The term *controlled-release drug product* was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Other terms, such as ER, SR, XL, XR, and CD, are also used to indicate an extended-release drug product. Retarded release is an older term for a slow release drug product. Many of these terms for modified-release drug products were introduced by drug companies to reflect either a special design for an extended-release drug product or for use in marketing.

Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacodynamic, and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form (Table 17-1). Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

**Examples of Modified-Release Oral Dosage Forms**

The pharmaceutical industry uses various terms to describe modified-release drug products. New and novel drug delivery systems are being developed by the pharmaceutical industry to alter the drug release profile, which in turn, results in a unique plasma drug concentration versus time profile and pharmacodynamic effect. In many cases, the industry will patent the novel drug delivery system, the resulting drug release profile and the plasma drug concentration versus time profile. Due to the proliferation of these modified-release dosage forms, the following terms are general descriptions and should not be considered definitive.

An *enteric-coated* tablet is an example of a delayed-release type of modified-release dosage form designed to release drug
<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Drug Product</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral drug products</td>
<td>Extended release</td>
<td>Diltiazem HCl extended release</td>
<td>Once-a-day dosing.</td>
</tr>
<tr>
<td></td>
<td>Delayed release</td>
<td>Diclofenac sodium delayed-release</td>
<td>Enteric-coated tablet for drug delivery into small intestine.</td>
</tr>
<tr>
<td></td>
<td>Oral mucosal drug delivery</td>
<td>Oral transmucosal fentanyl citrate</td>
<td>Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth.</td>
</tr>
<tr>
<td></td>
<td>Oral soluble film</td>
<td>Ondansetron</td>
<td>The film is placed top of the tongue. Film will dissolve in 4 to 20 seconds.</td>
</tr>
<tr>
<td></td>
<td>Orally disintegrating tablets (ODT)</td>
<td>Aripiprazole</td>
<td>ODT is placed on the tongue. Tablet disintegration occurs rapidly in saliva.</td>
</tr>
<tr>
<td>Transdermal drug delivery systems</td>
<td>Transdermal therapeutic system (TTS)</td>
<td>Clonidine transdermal therapeutic system</td>
<td>Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest. Small electric current moves charged molecules across the skin.</td>
</tr>
<tr>
<td></td>
<td>Iontophoretic drug delivery</td>
<td>Clonidine transdermal therapeutic system</td>
<td>Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest. Small electric current moves charged molecules across the skin.</td>
</tr>
<tr>
<td>Ophthalmic drug delivery</td>
<td>Insert</td>
<td>Controlled-release pilocarpine</td>
<td>Elliptically shaped insert designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye.</td>
</tr>
<tr>
<td>Intravaginal drug delivery</td>
<td>Insert</td>
<td>Dinoprostone vaginal insert</td>
<td>Hydrogel pouch containing prostaglandin within a polyester retrieval system.</td>
</tr>
<tr>
<td>Parenteral drug delivery</td>
<td>Intramuscular drug products</td>
<td>Depot injections</td>
<td>Lyophilized microspheres containing leuprolide acetate for depot suspension.</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous drug products</td>
<td>Water-immiscible injections (eg, oil) Controlled-release insulin</td>
<td>Medroxyprogesterone acetate (Depo-Provera). Baselin is a controlled-release, recombinant human insulin delivered by nanoparticulate technology.</td>
</tr>
<tr>
<td>Targeted delivery systems</td>
<td>IV injection</td>
<td>Daunorubicin citrate liposome injection</td>
<td>Liposomal preparation to maximize the selectivity of daunorubicin for solid tumors in situ.</td>
</tr>
<tr>
<td>Implants</td>
<td>Brain tumor</td>
<td>Polifeprosan 20 with carmustine implant (Gliadel wafer)</td>
<td>Implant designed to deliver carmustine directly into the surgical cavity when a brain tumor is resected.</td>
</tr>
<tr>
<td></td>
<td>Intravitreal implant</td>
<td>Fluocinolone acetonide intravitreal implant</td>
<td>Sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye.</td>
</tr>
</tbody>
</table>
in the small intestine. For example, aspirin irritates the gastric mucosal cells of the stomach. An enteric coating on the aspirin tablet prevents the tablet from dissolving and releasing its contents at the low pH in the stomach. The coating and the tablet later dissolve and release the drug in the higher pH of the duodenum, where the drug is rapidly absorbed with less irritation to the mucosal cells. Mesalamine (5-aminosalicylic acid) tablets (Asacol, Proctor & Gamble) is a delayed-release tablet coated with an acrylic-based resin that delays the release of mesalamine until it reaches the terminal ileum and colon. Mesalamine tablets could also be considered a targetted-release dosage form.

A repeat-action tablet is a type of modified-release drug product that is designed to release one dose of drug initially, followed by a second dose of drug at a later time. A prolonged-action drug product is designed to release the drug slowly and to provide a continuous supply of drug over an extended period. The prolonged-action drug product prevents very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration. Most prolonged-release products extend the duration of action but do not release drug at a constant rate. A prolonged-action tablet is similar to a first-order-release product except that the peak is delayed differentially. A prolonged-action tablet typically results in peak and trough drug levels in the body. The product releases drug without matching the rate of drug elimination, resulting in uneven plasma drug levels in the body.

A sustained-release drug product can be designed to deliver an initial therapeutic dose of the drug (loading dose), followed by a slower and constant release of drug. The purpose of a loading dose is to provide immediate or fast drug release to quickly provide therapeutic drug concentrations in the plasma. The rate of release of the maintenance dose is designed so that the amount of drug loss from the body by elimination is constantly replaced. With the sustained-release product, a constant plasma drug concentration is maintained with minimal fluctuations. Figure 17-1 shows the dissolution rate of three sustained-release products without loading dose. The plasma concentrations resulting from the sustained-release products are shown in Fig. 17-2.

Various terms for extended-release drug products often imply that drug release is at a constant or zero-order drug release rate. However, many of these drug products release the drug at a first-order rate. Some modified-release drug products are formulated with materials that are more soluble at a specific pH, and the product may release the drug depending on the pH of a particular region of the gastrointestinal (GI) tract. Ideally, an extended-release drug product
**Frequently Asked Questions**

- What is the difference between extended release, delayed release, sustained release, modified release, and controlled release?
- Why does the drug bioavailability from some conventional, immediate-release drug products resemble an extended-release drug product?

**BIOPHARMACEUTIC FACTORS**

Modified-release drug product should produce a pharmacokinetic profile that provides the desired therapeutic efficacy and minimizes adverse events. In the case of delayed-release drug products, the enteric coating minimizes gastric irritation of the drug in the stomach. The major objective of extended-release drug products is to achieve a prolonged therapeutic effect while minimizing unwanted side effects due to fluctuating plasma drug concentrations.

Ideally, the extended-release (ER) drug product should release the drug at a constant rate, independent of the pH, the ionic content and other contents within the entire segment of the gastrointestinal tract.

An extended-release dosage form with zero- or first-order drug absorption is compared to drug absorption from a conventional dosage form given in multiple doses in Figs. 17-3 and 17-4, respectively. Drug absorption from conventional (immediate-release) dosage forms generally follows first-order drug absorption.

FIGURE 17-3  Plasma level of a drug from a conventional tablet containing 50 mg of drug given at 0, 4, and 8 hours (A) compared to a single 150-mg drug dose given in an extended-release dosage form (B). The drug absorption rate constant from each drug product is first order. The drug is 100% bioavailable and the elimination half-life is constant.

FIGURE 17-4  Bioavailability of a drug from an immediate-release tablet containing 50 mg of drug given at 0, 4, and 8 hours compared to a single 150-mg drug dose given in an extended-release dosage form. The drug absorption rate constant from the immediate-release drug product is first order, whereas the drug absorption rate constant from the extended-release drug product is zero order. The drug is 100% bioavailable and the elimination half-life is constant.
of the extended-release drug product within the GI tract and may affect the drug release rate from the product. In some cases, there may be a specific absorption site or location within the GI tract in which the extended-release drug product should release the drug. This specific drug absorption site or location within the GI tract is referred to as an absorption window. The absorption window is the optimum site for drug absorption. If drug is not released and available for absorption within the absorption window, the extended release tablet moves further distally in the GI tract and incomplete drug absorption may occur.

**Stomach**

The stomach is a “mixing and secreting” organ, where food is mixed with digestive juices and emptied periodically into the small intestine. However, the movement of food or drug product in the stomach and small intestine is very different depending on the physiologic state. In the presence of food, the stomach is in the digestive phase; in the absence of food, the stomach is in the interdigestive phase (Chapter 13). During the digestive phase, food particles or solids larger than 2 mm are retained in the stomach, whereas smaller particles are emptied through the pyloric sphincter at a first-order rate depending on the content and size of the meals. During the interdigestive phase, the stomach rests for a period of up to 30 to 40 minutes, coordinated with an equal resting period in the small intestine. Peristaltic contractions then occur, which end with strong housekeeper contractions that move everything in the stomach through to the small intestine. Similarly, large particles in the small intestine are moved along only in the housekeeper contraction period.

A drug may remain for several hours in the stomach if it is administered during the digestive phase. Fatty material, nutrients, and osmolality may further extend the time the drug stays in the stomach. When the drug is administered during the interdigestive phase, the drug may be swept along rapidly into the small intestine. Dissolution of drugs in the stomach may also be affected by the presence or absence of food. When food is present, HCl is secreted and the pH is about 1 to 2. Although some food and nutrients can neutralize the acid and raise stomach pH, the fasting pH of the stomach is about 3 to 5. The drug release rates from some extended-release drug products are affected by food. For example, an older extended-release drug product, Theo-24 (theophylline, anhydrous) extended-release capsule, releases drug at a higher rate in the presence of food compared to fasting conditions (Chapter 13). This more rapid drug release rate appeared to be related to food in the GI tract, a change in pH, the stomach-emptying rate, or a food interaction affecting the extended-release formulation. After the introduction of Theo-24, food effect studies were initiated on all new drug products. A longer time of retention in the stomach may expose the drug to stronger agitation in the acid environment. The stomach has been described as having “jet mixing” action, which sends mixture at up to 50 mm Hg pressure toward the pyloric sphincter, causing it to open and periodically release chyme to the small intestine.

**Small Intestine and Transit Time**

The small intestine is about 10 to 14 ft in length. The duodenum is sterile, while the terminal part of the small intestine that connects the cecum contains some bacteria. The proximal part of the small intestine has a pH of about 6, because of neutralization of acid by bicarbonates secreted into the lumen by the duodenal mucosa and the pancreas. The small intestine provides an enormous surface area for drug absorption because of the presence of microvilli. The small-intestine transit time of a solid preparation has been concluded to be about 3 hours or less in 95% of the population (Hofmann et al, 1983). Transit time for meals from mouth to cecum (beginning of large intestine) has been reviewed by Shareef et al (2003). Various investigators have used the lactulose hydrogen test, which measures the appearance of hydrogen in a patient’s breath, to estimate transit time. Lactulose is metabolized rapidly by bacteria in the large intestine, yielding hydrogen that is exhaled. Hydrogen is normally absent in a person’s breath. These results and the use of gamma-scintigraphy studies confirm a relatively short GI transit time from mouth to cecum of 4 to 6 hours.

This transit time interval was concluded to be too short for extended-release dosage forms that last
The properties of the drug and required dosage are important in formulating an extended-release product. The transit time for pellets has been studied in both disintegrating and nondisintegrating forms using both insoluble and soluble radioopaque
dyes. Most of the insoluble pellets were released from the capsule within 15 minutes. Scattering of pellets was seen in the stomach and along the entire length of the small intestine at 3 hours. At 12 hours most of the pellets were in the ascending colon, and at 24 hours the pellets were all in the descending colon, ready to enter the rectum. With the disintegrating pellets, there was more scattering of the pellets along the GI tract. The pellets also varied widely in their rate of disintegration in vivo (Galeone et al, 1981).

Large Intestine
The large intestine is about 4 to 5 ft long. It consists of the cecum, the ascending and descending colons, and eventually ends at the rectum. Little fluid is in the colon, and drug transit is slow. Not much is known about drug absorption in this area, although unabsorbed drug that reaches this region may be metabolized by bacteria. Incompletely absorbed antibiotics may affect the normal flora of the bacteria. The rectum has a pH of about 6.8 to 7.0 and contains more fluid compared to the colon. Drugs are absorbed rapidly when administered as rectal preparations. However, the transit rate through the rectum is affected by the rate of defecation. Presumably, drugs formulated for 24 hours’ duration must remain in this region to be absorbed.

Several extended-release and delayed-release drug products, such as mesalamine delayed-release tablets (Asacol), are formulated to take advantage of the physiologic conditions of the GI tract (Shareef et al, 2003). Enteric-coated beads have been found to release drug over 8 hours when taken with food, because of the gradual emptying of the beads into the small intestine. Specially formulated “floating tablets” that remain in the top of the stomach have been used to extend the residence time of the product in the stomach. None of these methods, however, is consistent enough to perform reliably for potent medications. More experimental research is needed in this area.

**DOSE FORM SELECTION**

The properties of the drug and required dosage are important in formulating an extended-release product. For example, a drug with low aqueous solubility generally should not be formulated into a nondisintegrating tablet, because the risk of incomplete drug dissolution is high. Instead, a drug with low solubility at neutral pH should be formulated, so that most of the drug is released before it reaches the colon, since the lack of fluid in the colon may make complete dissolution difficult. Erosion tablets are more reliable for these drugs because the entire tablet eventually dissolves.

A drug that is highly water soluble in the acid pH in the stomach but very insoluble at intestinal pH may be very difficult to formulate into an ER drug product. An ER drug product with too much coating protection may result in low drug bioavailability, while too little coating protection may result in rapid drug release or dose dumping in the stomach. A moderate extension of duration with enteric-coated beads may be possible. However, the risk of erratic performance is higher than with a conventional dosage form. The osmotic type of controlled drug release system may be more suitable for this type of drug.

With most single-unit dosage forms, there is a risk of erratic performance due to variable stomach emptying and GI transit time. Selection of a pellet or bead dosage form may minimize the risk of erratic stomach emptying, because pellets are usually scattered soon after ingestion. Disintegrating tablets have the same advantages because they break up into small particles soon after ingestion.

**ADVANTAGES AND DISADVANTAGES OF EXTENDED-RELEASE PRODUCTS**

ER drug products offer several important advantages over immediate-release dosage forms of the same drug. Extended release allows for sustained therapeutic blood levels of the drug; sustained blood levels provide for a prolonged and consistent clinical
response in the patient. Moreover, if the drug input rate is constant, the blood levels should not fluctuate between a maximum and minimum compared to a multiple-dose regimen with an immediate-release drug product (Chapter 8). Highly fluctuating blood concentrations of drug may produce unwanted side effects in the patient if the drug level is too high, or may fail to exert the proper therapeutic effect if the drug level is too low. Another advantage of extended release is patient convenience, which leads to better patient compliance. For example, if the patient needs to take the medication only once daily, he or she will not have to remember to take additional doses at specified times during the day. Furthermore, because the dosage interval is longer, the patient’s sleep may not be interrupted to take another drug dose. With longer therapeutic drug concentrations, the patient awakes without having subtherapeutic drug levels. The patient may also derive an economic benefit in using an extended-release drug product. A single dose of an extended-release product may cost less than an equivalent drug dose given several times a day in rapid-release tablets. For patients under nursing care, the cost of nursing time required to administer medication is decreased if only one drug dose is given to the patient each day.

For some drugs with long elimination half-lives, such as chlorpheniramine, the inherent duration of pharmacologic activity is long. Minimal fluctuations in blood concentrations of these drugs are observed after multiple doses are administered. Therefore, there is no rationale for extended-release formulations of these drugs. However, such drug products are marketed with the justification that extended-release products minimize toxicity, decrease adverse reactions, and provide patients with more convenience and, thus, better compliance. In contrast, drugs with very short half-lives need to be given at frequent dosing intervals to maintain therapeutic efficacy. For drugs with very short elimination half-lives, an extended-release drug product maintains the efficacy over a longer duration.

There are also a number of disadvantages in using extended-release medication. If the patient suffers from an adverse drug reaction or accidentally becomes intoxicated, the removal of drug from the system is more difficult with an extended-release drug product. Orally administered extended-release drug products may yield erratic or variable drug absorption as a result of various drug interactions with the contents of the GI tract and changes in GI motility. The formulation of extended-release drug products may not be practical for drugs that are usually given in large doses (eg, 500 mg) in conventional dosage forms. Because the extended-release drug product may contain two or more times the dose given at more frequent intervals, the size of the extended-release drug product may have to be quite large, too large for the patient to swallow easily.

The extended-release dosage form contains the equivalent of two or more drug doses given in a conventional dosage form. Therefore, failure of the extended-release dosage form may lead to dose dumping. Dose dumping is defined either as the release of more than the intended fraction of drug or as the release of drug at a greater rate than the customary amount of drug per dosage interval, such that potentially adverse plasma levels may be reached (Dighe and Adams, 1988; Skelly and Barr, 1987). With delayed release or enteric drug products, two possible problems may occur if the enteric coating is poorly formulated. First, the enteric coating may become degraded in the stomach, allowing for early release of the drug, possibly causing irritation to the gastric mucosal lining. Second, the enteric coating may fail to dissolve at the proper site, and therefore the tablet may be lost prior to drug release, resulting in incomplete absorption.

In recent years, pharmaceutical manufacturers have made new extended-release drug products of branded drugs that are losing patent protection. Although these extended-release drug products may have some of the advantages stated above, the cost of the medication may be much higher than that of the generic drug in a conventional drug product given several times a day.

**KINETICS OF EXTENDED-RELEASE DOSAGE FORMS**

The amount of drug required in an extended-release dosage form to provide a sustained drug level in the body is determined by the pharmacokinetics of
For many sustained-release drug products, there is no built-in loading dose (i.e., \(D_I = 0\)). The dose needed to maintain a therapeutic concentration for \(\tau\) hours is

\[
D_0 = C_p \tau Cl_T
\]  
(17.7)

where \(\tau\) is the dosing interval.

**Example**

What dose is needed to maintain a therapeutic concentration of 10 \(\mu\)g/mL for 12 hours in a sustained-release product? (a) Assume that \(t_{1/2}\) for the drug is 3.46 hours and \(V_D\) is 10 L. (b) Assume that \(t_{1/2}\) of the drug is 1.73 hours and \(V_D\) is 5 L.

\[
\begin{align*}
\text{a. } k &= \frac{0.693}{3.46} = 0.2/\text{h} \\
Cl_T &= kV_D = 0.2 \times 10 = 2\text{L/h}
\end{align*}
\]

From Equation 17.7,

\[
D_0 = (10 \text{ } \mu\text{g/mL})(1000 \text{ mL/L})(12 \text{ hr})(2 \text{ L/hr})
= 240,000 \mu\text{g} \text{ or } 240 \text{ mg}
\]

\[
\begin{align*}
\text{b. } k &= \frac{0.693}{1.73} = 0.4/\text{h} \\
Cl_T &= 0.4 \times 5 = 2\text{L/h}
\end{align*}
\]

From Equation 17.8,

\[
D_0 = 10 \times 2 \times 1000 \times 12 \times 240,000 \mu\text{g} \text{ or } 240 \text{ mg}
\]

In this example, the amount of drug needed in a sustained-release product to maintain therapeutic drug concentration is dependent on both \(V_D\) and the elimination half-life. In part b of the example, although the elimination half-life is shorter, the volume of distribution is also smaller. If the volume of distribution is constant, then the amount of drug needed to maintain \(C_p\) is dependent simply on the elimination half-life.
Table 17-2 shows the influence of $t_{1/2}$ on the amount of drug needed for an extended-release drug product. Table 17-2 was constructed by assuming that the drug has a desired serum concentration of 5 $\mu$g/mL and an apparent volume of distribution of 20,000 mL. The release rate needed to achieve the desired concentration, $R$, decreases as the elimination half-life increases. Because elimination is slower for a drug with a long half-life, the input rate should be slower. The total amount of drug needed in the extended-release drug product is dependent on both the release rate $R$ and the desired duration of activity for the drug. For a drug with an elimination half-life of 4 hours and a release rate of 17.3 mg/h, the extended-release product must contain 207.6 mg to provide a duration of activity of 12 hours. The bulk weight of the extended-release product will be greater than this amount, due to the presence of excipients needed in the formulation. The values in Table 17-2 show that, in order to achieve a long duration of activity (≥12 hours) for a drug with a very short half-life (1–2 hours), the extended-release drug product becomes quite large and impractical for most patients to swallow.

**PHARMACOKINETIC SIMULATION OF EXTENDED-RELEASE PRODUCTS**

The plasma drug concentration profiles of many extended-release products fit an oral one-compartment model assuming first-order absorption and elimination. Compared to an immediate-release product, the extended-release product typically shows a smaller absorption rate constant, because of the slower absorption of the extended-release product. The time for peak concentration ($t_{max}$) is usually longer (Fig. 17-5), and the peak drug concentration ($C_{max}$) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same.

**TABLE 17-2**  Release Rates for Extended-Release Drug Products as a Function of Elimination Half-Life*

<table>
<thead>
<tr>
<th>$t_{1/2}$ (h)</th>
<th>$k$ (h⁻¹)</th>
<th>$R$ (mg/h)</th>
<th>6 h</th>
<th>8 h</th>
<th>12 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.693</td>
<td>69.3</td>
<td>415.8</td>
<td>554.4</td>
<td>831.6</td>
<td>1663</td>
</tr>
<tr>
<td>2</td>
<td>0.347</td>
<td>34.7</td>
<td>208.2</td>
<td>277.6</td>
<td>416.4</td>
<td>832.8</td>
</tr>
<tr>
<td>4</td>
<td>0.173</td>
<td>17.3</td>
<td>103.8</td>
<td>138.4</td>
<td>207.6</td>
<td>415.2</td>
</tr>
<tr>
<td>6</td>
<td>0.116</td>
<td>11.6</td>
<td>69.6</td>
<td>92.8</td>
<td>139.2</td>
<td>278.4</td>
</tr>
<tr>
<td>8</td>
<td>0.0866</td>
<td>8.66</td>
<td>52.0</td>
<td>69.3</td>
<td>103.9</td>
<td>207.8</td>
</tr>
<tr>
<td>10</td>
<td>0.0693</td>
<td>6.93</td>
<td>41.6</td>
<td>55.4</td>
<td>83.2</td>
<td>166.3</td>
</tr>
<tr>
<td>12</td>
<td>0.0577</td>
<td>5.77</td>
<td>34.6</td>
<td>46.2</td>
<td>69.2</td>
<td>138.5</td>
</tr>
</tbody>
</table>

*Assume $C_{desired}$ is 5 $\mu$g/mL and the $V_D$ is 20,000 mL; $R = kV_DC_p$: no immediate-release dose.

**FIGURE 17-5** Plasma drug concentration of a sustained-release and a regular-release product. Note the difference of peak time and peak concentration of the two products.
Parameters such as $C_{\text{max}}$, $t_{\text{max}}$, and area under the curve (AUC) conveniently show how successfully the extended-release product performs in vivo. For example, a product with a $t_{\text{max}}$ of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, an excessively high $C_{\text{max}}$ is a sign of dose dumping due to inadequate formulation. The pharmacokinetic analysis of single- and multiple-dose plasma data has been used by regulatory agencies to evaluate many sustained-release products. The analysis is practical because many products can be fitted to this model even though the drug is not released in a first-order manner. The limitation of this type of analysis is that the absorption rate constant may not relate to the rate of drug dissolution in vivo. If the drug strictly follows zero-order release and absorption, the model may not fit the data.

Various other models have been used to simulate plasma drug levels of extended-release products (Welling, 1983). The plasma drug levels from a zero-order, extended-release drug product may be simulated with Equation 17.8.

$$C_p = \frac{R}{kV_D} (1 - e^{-kt}) \quad (17.8)$$

where $R$ = rate of drug release (mg/min), $C_p$ = plasma drug concentration, $k$ = overall elimination constant, and $V_D$ = volume of distribution. In the absence of a loading dose, the drug level in the body rises slowly to a plateau with minimum fluctuations (Fig. 17-6). This simulation assumes that (1) rapid drug release occurs without delay, (2) perfect zero-order release and absorption of the drug takes place, and (3) the drug is given exactly every 12 hours. In practice, the above assumptions are not precise, and fluctuations in drug level do occur.

When a sustained-release drug product with a loading dose (rapid release) and a zero-order maintenance dose is given, the resulting plasma drug concentrations are described by

$$C_p = \frac{D_i k}{V_D (k_a - k)} (e^{-kt} - e^{-k't}) + \frac{D_s}{V_D k} (1 - e^{-kt}) \quad (17.9)$$

where $D_i$ = immediate-release (loading dose) dose and $D_s$ = maintenance dose (zero-order). This expression is the sum of the oral absorption equation (first part) and the intravenous infusion equation (second part).

Extended-Release Drug Product with Immediate-Release Component

Extended-release drug products may be formulated with or without an immediate release loading dose. Extended-release drug products that are given to patients in daily multiple doses to maintain steady state therapeutic drug concentrations do not need a built-in loading dose when given subsequent doses. Pharmacokinetic models have been proposed for extended-release drug products that have a rapid first-order drug release component and a slow zero-order release maintenance dose component. This model assumes a long elimination $t_{1/2}$ in which drug accumulation occurs until steady-state is attained. The model predicts spiking peaks due to the loading dose component when the extended-release drug product is given continuously in multiple doses. In this model, a rapid-release loading dose along with the extended-release drug dose given in a daily multiple dose regimen introduces more drug into the body than is necessary. This is observed by a “topping” effect.

When a loading dose is necessary, a rapid- or immediate-release drug product may be given separately as a loading dose to initially bring the patient’s plasma drug level to the desired therapeutic level. In certain clinical situations, an extended-release drug product with an immediate-release component along with a controlled-release core can provide a specific pharmacokinetic profile that provides rapid onset

**FIGURE 17-6** Simulated plasma drug level of an extended-release product administered every 12 hours. The plasma level shows a smooth rise to steady-state level with no fluctuations.
and prolonged plasma drug concentrations that relates to the time course for the desired pharmacodynamic activity. For these extended-release drug products with initial immediate-release components, the active drug must have a relatively short elimination $t_{1/2}$ so that the drug does not accumulate between dosing.

**CLINICAL EXAMPLES**

**Methylphenidate HCl Extended-Release Tablets (Concerta®)**

Methylphenidate HCl is a CNS (central nervous system) stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) and is often used in children 6 years of age and older. Methylphenidate is readily absorbed after oral administration and has an elimination $t_{1/2}$ of about 3.5 hours. Methylphenidate HCl extended-release tablets (Concerta) have an osmotically active controlled release core with an immediate-release drug overcoat. After oral administration of Concerta, the plasma methylphenidate concentration increases rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins. Mean $t_{max}$ occurs between 6 to 10 hours. When the patient takes this product in the morning, the patient receives an initial loading dose followed by a maintenance dose that is eliminated by the evening when the patient wants to go to sleep. Due to the short elimination $t_{1/2}$, the drug does not accumulate.

**Zolpidem Tartrate Extended-Release Tablets (Ambien CR)**

Zolpidem tartrate extended-release tablets are indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Zolpidem has a mean elimination $t_{1/2}$ of 2.5 hours. Zolpidem tartrate extended-release tablets exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond 3 hours after administration.\(^1\) Patients who use this product have a more rapid onset of sleep due to the initial dose and are able to maintain sleep due to the maintenance dose. Due to the short elimination $t_{1/2}$, the drug does not accumulate.

**TYPES OF EXTENDED-RELEASE PRODUCTS**

The pharmaceutical industry has been developing newer modified-release drug products at a very rapid pace. Many of these modified-release drug products have patented drug delivery systems. This chapter provides an overview of some of the more widely used methods for the manufacture of modified drug products.

The extended-release drug product is designed to contain a drug dose which will release drug at a desired rate over a specified period of time. As discussed previously, the extended-release drug product may also contain an immediate-release component. The general approaches to manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended or dissolved, the use of a rate-controlling membrane through which the drug diffuses, or a combination of both. None of the extended-release drug products works by a single drug-release mechanism. Most extended-release products release drug by a combination of processes involving drug dissolution, permeation, erosion, and diffusion. The single most important factor is water permeation into the drug product, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves in the gastrointestinal tract. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate. Table 17-3 describes some common extended-release product examples and the mechanisms for controlling drug release. Table 17-4 lists the composition for some drugs.

**Drug Release from Matrix**

A matrix is an inert solid vehicle in which a drug is uniformly suspended. A matrix may be formed by

\(^1\)Approved label for Ambien CR, April 2010.
some matrix materials may swell slowly in water. Drug release using a matrix dosage form may be achieved using tablets or small beads, depending on the formulation composition and therapeutic objective. Figure 17-7 shows three common approaches by which matrix

<table>
<thead>
<tr>
<th>Type</th>
<th>Trade Name</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended-Release Drug Products</td>
<td>Constant-T</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Tenuate Dospan</td>
<td>Diethylpropion HCl dispersed in hydrophilic matrix</td>
</tr>
<tr>
<td></td>
<td>Tedral SA</td>
<td>Combination product with a slow-erosion component (theophylline, ephedrine HCl) and an initial-release component (theophylline, ephedrine HCl, phenobarbital)</td>
</tr>
<tr>
<td>Waxy matrix tablet</td>
<td>Kaon CI</td>
<td>Slow release of potassium chloride to reduce GI irritation</td>
</tr>
<tr>
<td>Coated pellets in capsule</td>
<td>Ornade spansule</td>
<td>Combination phenylpropanolamine HCl and chlorpheniramine with initial-and extended-release component</td>
</tr>
<tr>
<td>Pellets in tablet Leaching</td>
<td>Theo-Dur Ferro-Gradumet (Abbott)</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Desoxyn gradumet tablet (Abbott)</td>
<td>Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation</td>
</tr>
<tr>
<td>Coated ion exchange</td>
<td>Tussionex</td>
<td>Cation ion-exchange resin complex of hydrocodone and phenyltoloxamine</td>
</tr>
<tr>
<td>Flotation–diffusion Osmotic delivery</td>
<td>Valrelease</td>
<td>Diazapam</td>
</tr>
<tr>
<td></td>
<td>Acurtrim</td>
<td>Phenylpropanolamine HCl (Oros delivery system)</td>
</tr>
<tr>
<td></td>
<td>Procardia-XL</td>
<td>GITS—Gastrointestinal therapeutic system with NaCl-driven (osmotic pressure) delivery system for nifedipine</td>
</tr>
<tr>
<td>Microencapsulation</td>
<td>Bayer timed-release</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Nitrosan</td>
<td>Microencapsulated nitroglycerin</td>
</tr>
<tr>
<td></td>
<td>Micro-K Extencaps</td>
<td>Potassium chloride microencapsulated particles</td>
</tr>
<tr>
<td>Delayed-release drug products</td>
<td>diclofenac sodium enteric-coated tablets mesalamine) delayed-release tablets</td>
<td>Enteric coating dissolves at pH &gt;5 for release of drug in duodenum</td>
</tr>
<tr>
<td></td>
<td>Delayed-release tablets are coated with acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon</td>
<td></td>
</tr>
<tr>
<td>Orally disintegrating tables</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 17-4 Composition and Examples of Some Modified-Release Products

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Composition/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-Tab (Abbott)</td>
<td>750 mg or 10 mEq of potassium chloride in a film-coated matrix tablet. The matrix may be excreted intact, but the active ingredient is released slowly without upsetting the GI tract. Inert ingredients: Cellulosic polymers, castor oil, colloidal silicon dioxide, polyvinyl acetate, paraffin. The product is listed as a waxy/polymer matrix tablet for release over 8–10 h.</td>
</tr>
<tr>
<td>Toprol-XL tablets (Astra)</td>
<td>Contains metoprolol succinate for sustained release in pellets, providing stable beta-blockade over 24 h with one daily dose. Exercise tachycardia was less pronounced compared to immediate-release preparation. Each pellet separately releases the intended amount of medication. Inert ingredients: Paraffin, PEG, povidone, acetyltributyl citrate, starch, silicon dioxide, and magnesium stearate.</td>
</tr>
<tr>
<td>Quinglute Dura tablets (Berlex)</td>
<td>Contains 320 mg quinidine gluconate in a prolonged-action matrix tablet lasting 8–12 h and provides PVC protection. Inert ingredients: Starch, confectioner’s sugar and magnesium stearate.</td>
</tr>
<tr>
<td>Slow Fe tablets (Ciba)</td>
<td>Phendimetrazine tartrate 105 mg sustained pellet in capsule. Slow-release iron preparation (OTC medication) with 160 mg ferrous sulfate for iron deficiency. Inert ingredients: PEG, starch, PVP, alginate, talc, gum tragacanth, and mineral oil.</td>
</tr>
<tr>
<td>Sinemed CR tablets (Dupont pharma)</td>
<td>Contains a combination of carbidopa and levodopa for sustained-release delivery. This is a special erosion polymeric tablet for Parkinson’s disease treatment.</td>
</tr>
<tr>
<td>Pentasa capsules (Hoechst Marion/Roussel)</td>
<td>Contains mesalamine for ulcerative colitis in a sustained-release mesalamine coated with ethylcellulose. For local effect mostly, about 20% absorbed versus 80% otherwise.</td>
</tr>
<tr>
<td>Isoptin SR (Knoll)</td>
<td>Verapamil HCl sustained-release tablet. Inert ingredients: PEG, starch, PVP, alginate, talc, HPMC, methylcellulose, and microcrystalline cellulose.</td>
</tr>
<tr>
<td>Cotazym-S (Organon)</td>
<td>Enteric-coated microspheres of pancrelipase.</td>
</tr>
<tr>
<td>Eryc (erythromycin delayed-release capsules) (Warner-Chilcott)</td>
<td>Erythromycin enteric-coated tablet that protects the drug from instability and irritation.</td>
</tr>
<tr>
<td>Dilantin Kapseals (Parke-Davis)</td>
<td>Extended-release phenytoin capsule which contains beads of sodium phenytoin, gelatin, sodium lauryl sulfate, glyceryl monooleate, PEG 200, silicon dioxide, and talc.</td>
</tr>
<tr>
<td>Micro-K Extencaps (Robbins)</td>
<td>Ethylcellulose forms semipermeable film surrounding granules by microencapsulation for release over 8–10 h without local irritation. Inert ingredients: Gelatin, and sodium lauryl sulfate.</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 17-4  Composition and Examples of Some Modified-Release Products (Continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidex Extentabs (Robbins)</td>
<td>300-mg dose, 100-mg release immediately in the stomach and is absorbed in the small intestine. The rest is absorbed later over 10–12 h in a slow-dissolving core as it moves down the GI tract. Inert ingredients: White wax, carnauba wax, acacia, acetylated monoglyceride, guar gum, edible ink, calcium sulfate, corn derivative, and shellac.</td>
</tr>
<tr>
<td>Compazine Spansules (GSK)</td>
<td>Initial dose of prochlorperazine release first, then release slowly over several hours. Inert ingredients: Glycerylmonostearate, wax, gelatin, sodium lauryl sulfate.</td>
</tr>
<tr>
<td>Slo-bid Gyrocaps (Rhone-Poulenc Rorer)</td>
<td>A controlled-release 12–24-h theophylline product.</td>
</tr>
<tr>
<td>Sorbitrate SA (Zeneca)</td>
<td>The tablet contains isosorbide dinitrate 10 mg in the outer coat and 30 mg in the inner coat. Inert ingredients: Carbomer 934P, ethylcellulose, lactose magnesium stearate, and Yellow No. 10.</td>
</tr>
</tbody>
</table>

mechanisms are employed. In Fig. 17-7A, the drug is coated with a soluble coating, so drug release relies solely on the regulation of drug release by the matrix material. If the matrix is porous, water penetration will be rapid and the drug will diffuse out rapidly. A less porous matrix may give a longer duration of release. Unfortunately, drug release from a simple matrix tablet is not zero order. The Higuchi equation describes the release rate of a matrix tablet:

\[
Q = DS \left[ \frac{P}{\lambda} \right] (A - 0.5SP)^{1/2} \sqrt{t} \quad (17.10)
\]

where \(Q\) = amount of drug release per cm\(^2\) of surface at time \(t\), \(S\) = solubility of drug in g/cm\(^3\) in the dissolution medium, \(A\) = content of drug in insoluble matrix, \(P\) = porosity of matrix, \(D\) = diffusion coefficient of drug, and \(\lambda\) = tortuosity factor.

Figure 17-7B represents a matrix enclosed by an insoluble membrane, so the drug release rate is regulated by the permeability of the membrane as well as the matrix. Fig. 17-7C represents a matrix tablet enclosed with a combined film. The film becomes porous after dissolution of the soluble part of the film. An example of this is the combined film formed by ethylcellulose and methylcellulose. Close to zero-order release has been obtained with this type of release mechanism.

Gum-Type Matrix Tablets

Some excipients have a remarkable ability to swell in the presence of water and form a substance with a gel-like consistency. When this happens, the gel provides a natural barrier to drug diffusion from the tablet. Because the gel-like material is quite viscous
and may not disperse for hours, this approach provides a means for maintaining the drug for hours until all the drug has been completely dissolved and diffused into the intestinal fluid. Gelatin is a common gelling material. However, gelatin dissolves rapidly after the gel is formed. Drug excipients such as methylcellulose, gum tragacanth, Veegum, and alginic acid form a viscous mass and provide a useful matrix for controlling drug release and dissolution. Drug formulations with these excipients provide extended drug release for hours.

**Polymeric Matrix Tablets**

Various polymeric materials have been used to prolong the rate of drug release. The most important characteristic of this type of preparation is that the prolonged release may last for days or weeks rather than for a shorter duration (as with other techniques). An early example of an oral polymeric matrix tablet was Gradumet (Abbott Laboratories), which was marketed as an iron preparation. The non-biodegradable plastic matrix provides a rigid geometric surface for drug diffusion, so that a relatively constant rate of drug release is obtained. In the case of the iron preparation, the matrix reduces the exposure of the irritating drug to the GI mucosal tissues. The matrix is usually expelled unchanged in the feces after all the drug has leached out.

Polymeric matrix tablets for oral use are generally quite safe. However, for certain patients with reduced GI motility caused by disease, polymeric matrix tablets should be avoided, because accumulation or obstruction of the GI tract by matrix tablets has been reported. As an oral sustained-release product, the matrix tablet has not been popular. In contrast, the use of the matrix tablet in implantation has been more popular.

The use of biodegradable polymeric material for extended release has been the focus of more recent research. One such example is polylactic acid copolymer, which degrades to lactic acid and eliminates the problem of retrieval after implantation.

Other polymers for drug formulations include polyacrylate, methacrylate, polyester, ethylene—vinyl acetate copolymer (EVA), polyglycolide, polylactide, and silicone. Of these, the hydrophilic polymers, such as polylactic acid and polyglycolic acid, erode in water and release the drug gradually over time. A hydrophobic polymer such as EVA releases the drug over a longer duration time of weeks or months. The rate of release may be controlled by blending two polymers and increasing the proportion of the more hydrophilic polymer, thus increasing the rate of drug release. The addition of a low-molecular-weight polylactide to a polylactide polymer formulation increased the release rate of the drug and enabled the preparation of an extended-release system (Bodmeier et al, 1989). The type of plasticizer and the degree of cross-linking provide additional means for modifying the release rate of the drug. Many drugs are incorporated into the polymer as the polymer is formed chemically from its monomer. Light, heat, and other agents may affect the polymer chain length, degree of cross-linking, and other properties. This may provide a way to modify the release rate of the polymer matrices prepared. Drugs incorporated into polymers may have release rates that last over days, weeks, or even months. These vehicles have been often recommended for protein and peptide drug administration. For example, EVA is biocompatible and was shown to prolong insulin release in rats.

Hydrophobic polymers with water-labile linkages are prepared so that partial breakdown of the polymers allows for desired drug release without deforming the matrix during erosion. For oral drug delivery, the problem of incomplete drug release from the matrix is a major hurdle that must be overcome with the polymeric matrix dosage form. Another problem is that drug release rates may be affected by the amount of drug loaded. For implantation and other uses, the environment is more stable compared to oral routes, so a stable drug release from the polymer matrix may be attained for days or weeks.

**Slow-Release Pellets, Beads or Granules**

Pellets or beads are small spherical particles that can be formulated to provide a variety of modified drug release properties. The size of these beads can be very small (microencapsulation) for injections or larger for oral drug delivery. Several approaches have been used to manufacture beaded formulations including pan coating, spray drying, fluid bed drying, and extrusion-spheronization.
An early approach to the manufacture of ER drug products was the use of encapsulated drugs in a beaded or pellet formulation. In general, the beads are prepared by coating the powdered drug onto preformed cores known as nonpareil seeds. The nonpareil seeds are made from a slurry of starch, sucrose, and lactose. The drug-coated beads are then coated by a variety of materials that act as a barrier to drug release. The beads may have a blend of different thicknesses to provide the desired drug release. The beads may be placed in a capsule (eg, amphetamine ER capsules, Adderal XR) or with the addition of other excipients compressed into tablets (eg, metoprolol succinate extended-release tablets, Toprol XL).

Pan coating is a modified method adopted from candy manufacturing. Cores or nonpareil seeds of a given mesh size are slowly added to known amount of fine drug powder and coating solution and rounded for hours to become coated drug beads. The drug-coated beads are then coated with a polymeric layer which regulates drug release rate by changing either the thickness of the film or the composition of the polymeric material. Coatings may be aqueous or nonaqueous. Aqueous coatings are generally preferred. Nonaqueous coatings may leave residual solvents in the product, and the removal of solvents during manufacture presents danger to workers and the environment. Cores are coated by either sprayed pan coating or by air-suspension coating. Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug. Spray dry coating or fluid-bed coating is a more recent approach and has several advantages over pan coating. Drug may be dissolved in a solution that is sprayed or dispersed in small droplets in a chamber. A stream of hot air vaporates the solvent and the drug becomes a dry powder. The powdered material which is aerated may be coated with a variety of excipients to achieve the desired drug release. Several experimental process variables for fluid-bed coating include inlet air temperature, spray rate (g/min), atomizing air pressure, solid content, and curing time. Pelletization may also be obtained by extrusion-spheronization in which the powdered drug and excipients are mixed in a mixer/granulator. The moist mixture is then fed through an extruder at a specified rate and becomes spheronized on exit though small diameter dies. A wide range of extrusion screen sizes and configurations are available for optimization of pellet diameter.

The use of various amounts of coating solution can provide beads with various coating protection. A careful blending of beads is used to achieve a desired drug release profile. The finished drug product (eg, beads in capsule or beads in tablet) may contain a blend of beads coated with materials of different solubility rates to provide a means of controlling drug release and dissolution.

Some products take advantage of bead blending to provide two doses of drug in one formulation. For example, a blend of rapid-release beads with some pH-sensitive enteric-coated material may provide a second dose of drug release when the drug reaches the intestine.

The pellet dosage form can be prepared as a capsule or tablet. When pellets are prepared as tablets, the beads must be compressed lightly so that they do not break. Usually, a disintegrant is included in the tablet, causing the beads to be released rapidly after administration. Formulation of a drug into pellet form may reduce gastric irritation, because the drug is released slowly over a period of time, therefore avoiding high drug concentration in the stomach. Dextroamphetamine sulfate formulated as timed-release pellets in capsules (Dexedrine Spansule) is an early example of a beaded dosage form. Another older product is a pellet-type extended-release product of theophylline (Gyrocap). Table 17-5 shows the frequency of adverse reactions after theophylline is administered as a solution or as pellets. If theophylline is administered as a solution, a high drug concentration is reached in the body due to rapid drug absorption. Some side effects may be attributed to the high concentration of theophylline. Pellet dosage forms allows drug to be absorbed gradually, therefore reducing the incidence of side effects by preventing a high $C_{\text{max}}$.

Bitolterol mesylate (Tornalate) is a $\beta_2$-adrenergic receptor agonist used as a bronchodilator in asthma. A study in dogs indicated that the incidence of tachycardia was reduced using an extended-release bead preparation, whereas the bronchodilation effect was not reduced. Administering the drug as extended-release pellets apparently reduced excessively high drug
Chapter 17

the drug dissolves slowly over a period of several hours. The solubility of a drug is dependent on the salt form used. An examination of the solubility of the various salt forms of the drug is performed in early drug development. In general, the nonionized base or acid form of the drug is usually much less soluble than the corresponding salt. For example, sodium phenobarbital is more water soluble than phenobarbital, the acid form of the drug. Diphenhydramine hydrochloride is more soluble than the base form, diphenhydramine.

In cases where it is inconvenient to prepare a less soluble form of the drug, the drug may be granulated with an excipient to slow dissolution of the drug. Often, fatty or waxy lipophilic materials are employed in formulations. Stearic acid, castor wax, high-molecular-weight polyethylene glycol (Carbowax), glyceryl monostearate, white wax, and spermaceti oil are useful ingredients in providing an oily barrier to slow water penetration and the dissolution of the tablet. Many of the lubricants used in tableting may also be used as lipophilic agents to slow dissolution. For example, magnesium stearate and hydrogenated vegetable oil (Sterotex) are actually used in high percentages to cause sustained drug release in a preparation. The major disadvantage of this type of preparation is the difficulty in maintaining a reproducible drug release from patient to patient, because oily materials may be subjected to digestion, temperature, and mechanical stress, which may affect the release rate of the drug.

**Ion-Exchange Products**

Ion-exchange preparations usually involve an insoluble resin capable of reacting with either an anionic or cationic drug. An anionic resin is negatively charged so that a positively charged cationic drug may react with the resin to form an insoluble nonabsorbable resin–drug complex. Upon exposure in the GI tract, cations in the gut, such as potassium and sodium, may displace the drug from the resin, releasing the drug, which is absorbed freely. The main disadvantage of ion-exchange preparations is that the amount of cation–anion in the GI tract is not easily controllable and varies among individuals, making it difficult to provide a consistent mechanism or

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Volunteers Showing Side Effects</th>
<th>Using Solution</th>
<th>Using Sustained-Release Pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*After 5-day dosing at 600 mg theophylline/24 h, adverse reaction points on fifth day: solution, 135; pellets, 18.*

From Breimer and Dauhof (1980), with permission.
rate of drug release. A further disadvantage is that resins may provide a potential means of interaction with nutrients and other drugs.

Ion exchange may be used in extended-release liquid preparations. An added advantage is that the technique provides some protection for very bitter or irritating drugs. Ion exchange has been combined with a coating to obtain a more effective sustained-release product. Examples include dextromethorphan polistirex (Delsyn®), an oral suspension formulated as an ion-exchange complex to mask the bitter taste and to prolong the duration of drug action, and Tussionex Pennkinetic®, an oral suspension containing chlorpheniramine polistirex and hydrocodone polistirex.

A general mechanism for the formulation of cationic drugs is

\[
\text{H}^+ + \text{resin} - \text{SO}_3^- \text{drug} \rightleftharpoons \text{resin} - \text{SO}_3^- \text{H}^+ \text{+ drug}^+
\]

Insoluble drug complex Soluble drug

For anionic drugs, the corresponding mechanism is

\[
\text{Cl}^- + \text{resin} - \text{N}(\text{CH}_3)_3 \text{drug}^- \rightleftharpoons \text{resin} - \text{N}(\text{CH}_3)_3 \text{Cl}^- \text{+ drug}^-
\]

Insoluble drug complex Soluble drug

The insoluble drug complex containing the resin and drug dissociates in the GI tract in the presence of the appropriate counter ions. The released drug dissolves in the fluids of the GI tract and is rapidly absorbed.

**Core Tablets**

A core tablet is a tablet within a tablet. The inner core is usually used for the slow-drug-release component, and the outside shell contains a rapid-release dose of drug. Formulation of a core tablet requires two granulations. The core granulation is usually compressed lightly to form a loose core and then transferred to a second die cavity, where a second granulation containing additional ingredients is compressed further to form the final tablet.

The core material may be surrounded by hydrophobic excipients so that the drug leaches out over a prolonged period of time. This type of preparation is sometimes called a *slow-erosion core tablet*, because the core generally contains either no disintegrant or insufficient disintegrant to fragment the tablet. The composition of the core may range from wax to gum or polymeric material. Numerous slow-erosion tablets have been patented and are sold commercially under various trade names.

The success of core tablets depends very much on the nature of the drug and the excipients used. As a general rule, this preparation is very much hardness dependent in its release rate. Critical control of hardness and processing variables are important in producing a tablet with a consistent release rate.

Core tablets are occasionally used to avoid incompatibility in preparations containing two physically incompatible ingredients. For example, buffered aspirin has been formulated into a core and shell to avoid a yellowing discoloration of the two ingredients upon aging.

**Microencapsulation**

Microencapsulation is a process of encapsulating microscopic drug particles with a special coating material, therefore making the drug particles more desirable in terms of physical and chemical characteristics. A common drug that has been encapsulated is aspirin. Aspirin has been microencapsulated with ethylcellulose, making the drug superior in its flow characteristics; when compressed into a tablet, the drug releases more gradually compared to a simple compressed tablet.

Many techniques are used in microencapsulating a drug. One process used in microencapsulating acetaminophen involves suspending the drug in an aqueous solution while stirring. The coating material, ethylcellulose, is dissolved in cyclohexane, and the two liquids are added together with stirring and heating. As the cyclohexane is evaporated by heat, the ethylcellulose coats the microparticles of the acetaminophen. The microencapsulated particles have a slower dissolution rate because the ethylcellulose is not water soluble and provides a barrier for diffusion of drug. The amount of coating material deposited on the acetaminophen determines the rate of drug dissolution. The coating also serves as a
means of reducing the bitter taste of the drug. In practice, microencapsulation is not consistent enough to produce a reproducible batch of product, and it may be necessary to blend the microencapsulated material in order to obtain a desired release rate.

**Osmotic Drug Delivery Systems**

Osmotic drug delivery systems have been developed for both oral extended-release products known as gastrointestinal therapeutic systems (GITS) and for parenteral drug delivery as an implantable drug delivery (eg, osmotic minipump). Drug delivery is controlled by the use of an osmotically controlled device in which a constant amount of water flows into the system causing the dissolving and releasing of a constant amount of drug per unit time. Drug is released via a single laser-drilled hole in the tablet.

Figure 17-8 describes an osmotic drug delivery system in the form of a tablet which contains an outside semipermeable membrane and an inner core filled with a mixture of drug and osmotic agent (salt solution). When the tablet is placed in water, osmotic pressure is generated by the osmotic agent within the core. Water moves into the device, forcing the dissolved drug to exit the tablet through an orifice. The rate of drug delivery is relatively constant and unaffected by the pH of the environment.

Newer osmotic drug delivery systems are considered “push-pull” systems. Nifedine (Procardia XL) extended-release tablets have the appearance of a conventional tablet. Procardia XL ER tablets have a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers: an “active” layer containing the drug, and a “push” layer containing pharmaceutically inert (but osmotically active) components. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and “pushes” against the drug layer, releasing drug through a laser-drilled tablet orifice in the active layer. Drug delivery is essentially constant (zero order) as long as the osmotic gradient remains constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

Methylphenidate HCl (Concerta®) extended-release tablets uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. A laser-drilled orifice on the drug-layer end of the tablet allows for exit of the drug. This product is similar to the GITS discussed earlier. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as an insoluble tablet shell.

The frequency of side effects experienced by patients using GITS was considerably less than that with conventional tablets. When the therapeutic system was compared to the regular 250-mg tablet given twice daily, ocular pressure was effectively controlled by the osmotic system. The blood level of acetazolamide using GITS, however, was considerably below that from the tablet. In fact, the therapeutic index of the drug was measurably increased by using the therapeutic system. The use of extended-release drug products, which release drug consistently, may provide promise for administering many drugs that previously had frequent adverse side effects because of the drug’s narrow therapeutic index. The osmotic drug delivery system has become a popular drug vehicle for many products that require
an extended period of drug delivery for 12 to 24 hours (Table 17-6).

A newer osmotic delivery system is the L-Oros Softcap (Alza), which claims to enhance bioavailability of poorly soluble drug by formulating the drug in a soft gelatin core and then providing extended drug delivery through an orifice drilled into an osmotic driven shell (Fig. 17-9). The soft gelatin capsule is surrounded by the barrier layer, the expanding osmotic layer, and the release-rate-controlling membrane. A delivery orifice is formed through the three outer layers but not through the gelatin shell. When the system is administered, water permeates through the rate-controlling membrane and activates the osmotic engine. As the engine expands, hydrostatic pressure inside the system builds up, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice and be pumped out of the system. At the end of the operation, liquid drug fill is squeezed out, and the gelatin capsule shell becomes flattened. The osmotic layer, located between the inner layer and the rate-controlling membrane, is the driving force for pumping the liquid formulation out of the system. This layer can gel when it hydrates. In addition, the high osmotic pressure can be sustained to achieve a constant release. This layer should comprise, therefore, a high-molecular-weight hydrophilic polymer and an osmotic agent. It is a challenge to develop a coating solution for a high-molecular-weight hydrophilic polymer. A mixed solvent of water and ethanol was used for this coating composition.

**Gastroretentive System**

The extended-release drug product should release the drug completely within the region in the GI tract.
in which the drug is optimally absorbed. Due to GI transit, the extended-release drug product continuously moves distally down the GI tract. In some cases, the extended-release drug product containing residual drug may exit from the body. Pharmaceutical formulation developers have used various approaches to retain the dosage form in the desired area of the gastrointestinal tract. One such approach is a gastroretentive system that can remain in the gastric region for several hours and prolong the gastric residence time of drugs (Arora et al, 2005). These gastroretentive systems are sometimes referred to as floating drug delivery systems. For example, diazepam (Valium) was been formulated using methylcellulose to provide sustained release (Valrelease). The manufacturer of Valrelease claimed that the hydrocolloid (gel) floated in the stomach to give sustained release diazepam. In other studies, however, materials of various densities were emptied from the stomach without any difference as to whether the drug product was floating on top or sitting at the bottom of the stomach.

The most important consideration in this type of formulation appears to be the gelling strength of the gum material and the concentration of gummy material. Modification of the release rates of the product may further be achieved with various amounts of talc or other lipophilic lubricant.

**Transdermal Drug Delivery Systems**

A transdermal drug delivery system (patch) is a dosage form intended for delivering drug across the skin for systemic drug absorption (see Chapters 7, 13). Transdermal drug absorption also avoids presystemic metabolism or “first-pass” effects. The transdermal drug delivery systems deliver the drug through the skin in a controlled rate over an extended period of time (Chapter 14, Table 14-12). Examples of transdermal drug delivery systems are listed in Tables 17-7 and 17-8. Transdermal delivery drug products vary in patch design (Fig. 17-10). Generally, the transdermal patch consists of (1) a backing or support layer that protects the patch, (2) a drug layer that might be in the form of a solid gel reservoir or in a matrix, (3) a pressure-sensitive adhesive layer, and (4) a release liner or protective strip that is removed before placing the patch on the skin. In some cases, the adhesive layer may also contain the active drug (Gonzalez and Cleary, 2010).

Drug diffusion may be controlled by a semipermeable membrane next to the reservoir layer. In other cases, drug diffusion is controlled by passage through the epidermis layer of the skin. The transdermal delivery system generally contains large drug concentrations to produce the ideal drug delivery with a zero-order rate. The patch may contain residual drug when the patch is removed from the application site.
area and provides up to 12 hours of angina protection. In a study comparing these three dosage forms in patients, no substantial difference was observed among the three preparations. In all cases, the skin was found to be the rate-limiting step in nitroglycerin absorption. There were fewer variations among products than of the same product among different patients.

Nitroglycerin is commonly administered by transdermal delivery (eg, Nitro-Dur, Transderm-Nitro®). Transdermal delivery systems of nitroglycerin may provide hours of protection against angina, whereas the duration of nitroglycerin given in a sublingual tablet (Nitrostat®) or sublingual spray (Nitrolingual) may be only a few minutes. The nitroglycerin patch is placed over the chest.

### TABLE 17-7  Examples of Transdermal Delivery Systems

<table>
<thead>
<tr>
<th>Type</th>
<th>Trade Name</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane-controlled system</td>
<td>Transderm-Nitro (Novartis)</td>
<td>Drug in reservoir, drug release through a rate-controlling polymeric membrane</td>
</tr>
<tr>
<td>Adhesive diffusion-controlled system</td>
<td>Deponit system (PharmaSchwartz)</td>
<td>Drug dispersed in an adhesive polymer and in a reservoir</td>
</tr>
<tr>
<td>Matrix-dispersion system</td>
<td>Nitro-Dur (Key)</td>
<td>Drug dispersed into a rate-controlling hydrophilic or hydrophobic matrix molded into a transdermal system</td>
</tr>
<tr>
<td>Microreservoir system</td>
<td>Nitro-Disc (Searle)</td>
<td>Combination reservoir and matrix-dispersion system</td>
</tr>
</tbody>
</table>

### TABLE 17-8  Transdermal Delivery Systems

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Generic Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catapres-TTS</td>
<td>Boehringer Ingelheim</td>
<td>Clonidine</td>
<td>Once-weekly product for the treatment of hypertension</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Janssen Pharmaceutical</td>
<td>Fentanyl</td>
<td>Management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means</td>
</tr>
<tr>
<td>Estraderm</td>
<td>Ciba-Geigy</td>
<td>Estradiol</td>
<td>Twice-weekly product for treating certain postmenopausal symptoms and preventing osteoporosis</td>
</tr>
<tr>
<td>Nicoderm CQ</td>
<td>Hoechst Marion</td>
<td>Nicotine</td>
<td>An aid to smoking cessation for the relief of nicotine-withdrawal symptoms</td>
</tr>
<tr>
<td>Testoderm</td>
<td>Alza</td>
<td>Testosterone</td>
<td>Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone</td>
</tr>
<tr>
<td>Transderm-Nitro</td>
<td>Novartis</td>
<td>Nitroglycerin</td>
<td>Once-daily product for the prevention of angina pectoris due to coronary artery disease; contains nitroglycerin in a proprietary, transdermal therapeutic system</td>
</tr>
<tr>
<td>Transderm Scop</td>
<td></td>
<td>Scopolamine</td>
<td>Prevention of nausea and vomiting associated with motion sickness</td>
</tr>
</tbody>
</table>
Transderm Nitro consists of several layers: (1) an aluminized plastic backing that protects nitroglycerin from loss through vaporization; (2) a drug reservoir containing nitroglycerin adsorbed onto lactose, colloidal silicon dioxide, and silicone medical fluid; (3) a diffusion-controlling membrane consisting of ethylene–vinyl acetate copolymer; (4) a layer of silicone adhesive; and (5) a protective strip.

Other transdermal delivery manufacturers have made transdermal systems in which the adhesive functions both as a pressure-sensitive adhesive and as a controlling matrix. Dermaflex (Elan) is a uniquely passive transdermal patch system that employs a hydrogel matrix into which the drug is incorporated. Dermaflex regulates both the availability and absorption of the drug in a manner that allows for controlled and efficient systemic delivery of many drugs.

An important limitation of transdermal preparation is the amount of drug that is needed in the transdermal patch to be absorbed systemically to provide the optimum therapeutic response. The amount of drug absorbed transdermally is related to the amount of drug in the patch, the size of the patch, and the method of manufacture. A dose–response relationship is obtained by applying a proportionally larger transdermal patch that differs only in surface area. For example, a 5-cm\(^2\) transdermal patch will generally provide twice as much drug absorbed systemically as a 2.5-cm\(^2\) transdermal patch.

In general, drugs given at a dose of over 100 mg would require too large a patch to be used practically. However, new advances in pharmaceutical solvents may provide a mechanism for an increased amount of drug to be absorbed transdermally. Azone, a permeation enhancer, is a solvent that increases the absorption of many drugs through the skin. This solvent is relatively nontoxic.

The skin is a natural barrier to prevent the influx of foreign chemicals (including water) into the body and the loss of water from the body (Guy, 1996). To be a suitable candidate for transdermal drug delivery, the drug must possess the right combination of physicochemical and pharmacodynamic properties. The drug must be highly potent so that only a small systemic drug dose is needed and the size of the patch (dose is also related to surface area) need not be exceptionally large, not greater than 50 cm\(^2\) (Guy, 1996). Physicochemical properties of the drug include a small molecular weight (<500 Da), and high lipid solubility. The elimination half-life should not be too short, to avoid having to apply the patch more frequently than once a day.

After the application of a transdermal patch, there is generally a lag time before the onset of the drug action, because of the drug’s slow diffusion into the dermal layers of the skin. When the patch is removed, diffusion of the drug from the dermal layer to the systemic circulation may continue for some time until the drug is depleted from the site of application. The solubility of drug in the skin rather than the concentration of drug in the patch layer is the most important factor controlling the rate of drug absorption through the skin. Humidity, temperature, and other factors have been shown to affect the rate of drug absorption through the skin. With most drugs, transdermal delivery provides a more stable blood level of the drug than oral dosing. However, with nitroglycerin, the sustained blood level of the drug provided by transdermal delivery is not desirable, due to induced tolerance to the drug not seen with sublingual tablets.

Transdermal Therapeutic Systems (TTS) consist of a thin, flexible composite of membranes, resembling a small adhesive bandage, which is applied to the skin and delivers drug through intact skin into the bloodstream. Other examples of products delivered using this system are shown in Table 17-8. Transderm Nitro consists of several layers: (1) an aluminized plastic backing that protects nitroglycerin from loss through vaporization; (2) a drug reservoir containing nitroglycerin adsorbed onto lactose, colloidal silicon dioxide, and silicone medical fluid; (3) a diffusion-controlling membrane consisting of ethylene–vinyl acetate copolymer; (4) a layer of silicone adhesive; and (5) a protective strip.

Other transdermal delivery manufacturers have made transdermal systems in which the adhesive functions both as a pressure-sensitive adhesive and as a controlling matrix. Dermaflex (Elan) is a uniquely passive transdermal patch system that employs a hydrogel matrix into which the drug is incorporated. Dermaflex regulates both the availability and absorption of the drug in a manner that allows for controlled and efficient systemic delivery of many drugs.

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For ionic drugs, absorption may be enhanced transdermally by **iontophoresis**, a method in which an electric field is maintained across the epidermal layer with special miniature electrodes. Some drugs, such as lidocaine, verapamil, insulin, and peptides, have been absorbed through the skin by iontophoresis. A process in which transdermal drug delivery is aided by high-frequency sound is called **sonophoresis**. Sonophoresis has been used with hydrocortisone cream applied to the skin to enhance penetration for treating “tennis elbow” and other mild inflammatory muscular problems. Many such novel systems are being developed by drug delivery companies.

**Panoderm XL patch technology** (Elan) is a new system that delivers a drug through a concealed miniature probe which penetrates the stratum corneum. Panoderm XL is fully disposable and may be programmed to deliver drugs as a preset bolus, in continuous or pulsed regimen. The complexity of the device is hidden from the patient and is simple to use. Panoderm (Elan) is an electrotransdermal drug delivery system that overcomes the skin diffusion barriers through the use of low-level electric current to transport the drug through the skin. Several transdermal products, such as fentanyl, hydromorphone, calcitonin, and LHRH (luteinizing hormone–releasing hormone), are in clinical trials. More improvements in transdermal delivery of larger molecules and the use of absorption enhancers will be available in future transdermal delivery systems.

Several additional studies that are unique to the development of a transdermal drug delivery system include: (1) wear and adhesiveness of the patch, (2) skin irritation, (3) skin sensitization, and (4) residual drug in the patch after removal. The FDA is asking drug companies to consider minimizing the amount of residual drug left in transdermal patches. Marketed products that use transdermal and transmucosal drug delivery systems can contain between 10 percent and 95 percent of the initial active drug even after use, according to the FDA’s draft guidance published in the Federal Register, August 3, 2010. Adverse events have been reported after patients have failed to remove a patch, resulting in increased or prolonged effects of the drug (eg, fentanyl patch).

### Combination Products

Combination products are defined in 21 CFR 3.2(e). The term combination product includes:

1. A product comprised of two or more regulated components, ie, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, eg, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Examples of combination products where the components are physically, chemically, or otherwise combined:

- Monoclonal antibody combined with a therapeutic drug
- Device coated or impregnated with a drug or biologic
  - Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide
- Skin substitutes with cellular components; orthopedic implant with growth factors

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2[http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm](http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm).
Chapter 17

- Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches
- Drug or biological product packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs
- Photosensitizing drug and activating laser/light source
- Iontophoretic drug delivery patch and controller

In summary, combination products consist of the drug in combination with a device that is physically, chemically, or otherwise combined or mixed and produced as a single entity. The device and/or biologic is intended for use with the approved drug and influences the route of administration and pharmacokinetics of the drug.

**Modified-Release Parenteral Dosage Forms**

Modified-release parenteral dosage forms are parenteral dosage forms that maintain plasma drug concentrations through rate-controlled drug release from the formulation over a prolonged period of time (Patil and Burgess, 2010; Martinez, 2008). Some examples of modified-release parenteral dosage forms include microspheres, liposomes, drug implants, inserts, drug-eluting stents, and nanoparticles. These formulations are designed by entrapment or microencapsulation of the drug into inert polymeric or lipophilic matrices that slowly release the drug, in vivo, for the duration of several days or up to several years. Modified-release parenteral dosage forms may be biodegradable or nonbiodegradable. Nonbiodegradable implants need to be surgically removed at the end of therapy.

**Implants and Inserts**

Polymeric drug implants can deliver and sustain drug levels in the body for an extended period of time. Both biodegradable and nonbiodegradable polymers can be impregnated with drugs in a controlled drug delivery system. For example, levo-norgestrel implants (Norplant system, Wyeth-Ayerst) is a set of six flexible closed capsules made of silastic (dimethylsiloxane/methylvinylsiloxane copolymer), each containing 36 μg of the progestin levonorgestrel. The capsules are sealed with silastic adhesive and sterilized. The Norplant system is available in an insertion kit to facilitate subdermal insertion of all six capsules in the midportion of the upper arm. The dose of levonorgestrel is about 85 μg/day, followed by a decline to about 50 μg/day by 9 months and to about 35 μg/day by 18 months, declining further to about 30 μg/day (Facts and Comparisons, 1997). The levonorgestrel implants are effective for up to 5 years for contraception and then must be replaced. An intrauterine progesterone contraceptive system (Progestasert, Alza) is a T-shaped unit that contains a reservoir of 38 μg of progesterone. Contraceptive effectiveness for Progestasert is enhanced by continuous release of progesterone into the uterine cavity at an average rate of 65 μg/day for 1 year.

A dental insert available for the treatment of periodontitis is the doxycycline hyclate delivery system (Atrigel®). This is a subgingival controlled-release product consisting of two syringe mixing systems that, when combined, form a bioabsorbable, flowable polymeric formulation. After administration under the gum, the liquid solidifies and then allows for controlled release of doxycycline for a period of 7 days.

**Nanotechnology Derived Drugs**

*Nanotechnology* is the manufacture of materials in the nanometer size range. Nanotechnology has been applied to drug development, food, electronics, biomaterials, and other applications. Nanoscale materials often have chemical, physical, or biological properties that are different from those of their larger counterparts. Such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Nanotechnology, FDA 2007). Because of these properties, nanoscale materials have great potential for use in a variety of therapeutic agents. Because of some of their special properties, nanoscale materials may pose different safety and efficacy issues compared to their larger or smaller (ie, molecular) counterparts.

In addition to the large surface area of nanoparticles, surface area modification of the nanoparticles such as binding different chemical groups to the surface with surfactants or biocompatible polymers (eg, polyethylene glycol, PEG) changes the pharmacoki-
Conclusions in the Evaluation of Modified-Release Products

The two important requirements in the development of extended-release products are (1) demonstration of safety and efficacy and (2) demonstration of controlled drug release.

Safety and efficacy data are available for many drugs given in a conventional or immediate release dosage form. Bioavailability data of the drug from the extended-release drug product should demonstrate sustained plasma drug concentrations and bioavailability equivalent to giving the conventional dosage in the same total daily dose in two or more multiple doses. The bioavailability data requirements are specified in the Code of Federal Regulations, 21 CFR 320.25(f). The important points are as follows.

1. The product should demonstrate sustained release, as claimed, without dose dumping (abrupt release of a large amount of the drug in an uncontrolled manner).
2. The drug should show steady-state levels comparable to those reached using a conventional dosage form given in multiple doses, and which was demonstrated to be effective.
3. The drug product should show consistent pharmacokinetic performance between individual dosage units.
4. The product should allow for the maximum amount of drug to be absorbed while maintaining minimum patient-to-patient variation.
5. The demonstration of steady-state drug levels after the recommended doses are given should be within the effective plasma drug levels for the drug.
6. An in vitro method and data that demonstrate the reproducible extended-release nature of the product should be developed. The in vitro method usually consists of a suitable dissolution procedure that provides a meaningful in vitro—in vivo correlation.
Chapter 17

7. *In vivo* pharmacokinetic data consist of single and multiple dosing comparing the extended-release product to a reference standard (usually an approved nonsustained-release or a solution product).

The pharmacokinetic data usually consist of plasma drug data and/or drug excreted into the urine. Pharmacokinetic analyses are performed to determine such parameters as $t_{1/2}$, $V_D$, $t_{max}$, AUC, and $k$.

Pharmacodynamic and Safety Considerations
Pharmacokinetic and safety issues must be considered in the development and evaluation of a modified-release dosage form. The most critical issue is to consider whether the modified-release dosage form truly offers an advantage over the same drug in an immediate-release (conventional) form. This advantage may be related to better efficacy, reduced toxicity, or better patient compliance. However, because the cost of manufacture of a modified-release dosage form is generally higher than the cost for a conventional dosage form, economy or cost savings for patients also may be an important consideration.

Ideally, the extended-release dosage form should provide a more prolonged pharmacodynamic effect compared to the same drug given in the immediate-release form. However, an extended-release dosage form of a drug may have a different pharmacodynamic activity profile compared to the same drug given in an acute, intermittent, rapid-release dosage form. For example, transdermal patches of nitroglycerin, which produce prolonged delivery of the drug, may produce functional tolerance to vasodilation that is not observed when nitroglycerin is given sublingually for acute angina attacks. Certain bactericidal antibiotics such as penicillin may be more effective when given in intermittent (pulsed) doses compared to continuous dosing. The continuous blood level of a hormone such as a corticosteroid might suppress adrenocorticotropic hormone (ACTH) release from the pituitary gland, resulting in atrophy of the adrenal gland. Furthermore, drugs that act indirectly or cause irreversible toxicity may be less efficacious when given in an extended-release rather than in conventional dosage form.

Because the modified-release dosage form may be in contact with the body for a prolonged period, the recurrence of sensitivity reactions or local tissue reactions due to the drug or constituents of the dosage form are possible. For oral modified-release dosage forms, prolonged residence time in the GI tract may lead to a variety of interactions with GI tract contents, and the efficiency of absorption may be compromised as the drug moves distally from the duodenum to the large intestine.

Moreover, dosage form failure due to either dose dumping or to the lack of drug release may have important clinical implications. Another possible unforeseen problem with modified-release dosage forms is an alteration in the metabolic fate of the drug, such as nonlinear biotransformation or site-specific disposition.

Design and selection of extended-release products are often aided by dissolution tests carried out at different pH units for various time periods to simulate the condition of the GI tract. Topographical plots of the dissolution data may be used to graph the percent of drug dissolved versus two variables (time, pH) that may affect dissolution simultaneously. For example, Skelly and Barr (1987) have shown that extended-release preparations of theophylline, such as Theo-24, have a more rapid dissolution rate at a higher pH of 8.4 (Fig. 17-11), whereas Theo-Dur is less affected by pH (Fig. 17-12). These dissolution

**FIGURE 17-11** Topographical dissolution characterization of theophylline controlled release. Topographical dissolution characterization (as a function of time and pH) of Theo-24, a theophylline controlled-release preparation, which has been shown to have a greater rate and extent of bioavailability when dosed after a high-fat meal than when dosed under fasted conditions. (From Skelly and Barr, 1987, with permission.)
Modified-Release Drug Products

EVALUATION OF MODIFIED-RELEASE PRODUCTS

Dissolution Studies

Dissolution requirements for each of the three types of modified-release dosage form are published in the USP-NF. Some of the key elements for the in vitro dissolution/drug release studies are listed in Table 17-9. Dissolution studies may be used together with bioavailability studies to predict in vitro–in vivo correlation of the drug release rate of the dosage forms.

In Vitro–In Vivo Correlations

A general discussion of correlating in vitro drug product performance (e.g., dissolution rate) to an in vivo biologic response (e.g., blood-level versus time profile) is discussed in Chapter 14. Ideally, the in vitro drug release of the extended-release drug product should relate to the bioavailability of the drug in vivo, so that changes in drug dissolution rates will correlate directly to changes in drug bioavailability.

Pharmacokinetic Studies

In many cases, the active drug is first formulated in an immediate-release drug product. After market experience with the immediate-release drug product, a manufacturer may design a modified or an extended-release drug product based on the pharmacokinetic profile of the immediate-release drug product as discussed earlier in this chapter. Various types of pharmacokinetic studies may be required by the Food and Drug Administration (FDA) for marketing approval of the modified-release drug product, depending on knowledge of the drug, its clinical pharmacokinetics and pharmacodynamics, and its biopharmaceutic properties (Skelly et al, 1990).

**TABLE 17-9**  Suggested Dissolution/Drug Release Studies for Modified-Release Dosage Forms

<table>
<thead>
<tr>
<th>Dissolution studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reproducibility of the method.</td>
</tr>
<tr>
<td>2. Proper choice of medium.</td>
</tr>
<tr>
<td>3. Maintenance of sink conditions.</td>
</tr>
<tr>
<td>4. Control of solution hydrodynamics.</td>
</tr>
<tr>
<td>5. Dissolution rate as a function of pH, ranging from pH 1 to pH 8 and including several intermediate values.</td>
</tr>
<tr>
<td>6. Selection of the most discriminating variables (medium, pH, rotation speed, etc) as the basis for the dissolution test and specification.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolution procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of dose dumping, as indicated by a narrow limit on the 1-h dissolution specification.</td>
</tr>
<tr>
<td>2. Controlled-release characteristics obtained by employing additional sampling windows over time. Narrow limits with an appropriate Q value system will control the degree of first-order release.</td>
</tr>
<tr>
<td>3. Complete drug release of the drug from the dosage form. A minimum of 75%–80% of the drug should be released from the dosage form at the last sampling interval.</td>
</tr>
<tr>
<td>4. The pH dependence/independence of the dosage form as indicated by percent dissolution in water, appropriate buffer, simulated gastric juice, or simulated intestinal fluid.</td>
</tr>
</tbody>
</table>

Data from Skelly and Barr (1987).
Moreover, the extended-release dosage form should be available in several dosage strengths to allow flexibility for the clinician to adjust the dose for the individual patient.

Single dose ranging studies and multiple-dose steady-state crossover studies using the highest strength of the dosage form may be performed. In addition, a food intervention bioavailability study is also performed. The reference dosage form may be a solution of the drug or the full NDA-approved conventional, immediate-release dosage form given in an equal daily dose as the extended-release dosage form. If the dosage strengths differ from each other only in the amount of the drug–excipient blend, but the concentration of the drug–excipient blend is the same in each dosage form, then the FDA may approve the NDA or ANDA on the basis of single- and multiple-dose studies of the highest dosage strength, whereas the other lower-strength dosage forms may be approved on the basis of comparative in vitro dissolution studies (Chapter 14). The latest FDA Guidance for Industry should be consulted for regulatory requirements (www.fda.gov/cder/guidance/index.htm). Skelly et al (1990, 1993) have described several types of such pharmacokinetic studies.

**Clinical Considerations of Modified-Release Drug Products**

Clinical efficacy and safety may be altered when drug therapy is changed from a conventional, immediate-release drug product given several times a day to a modified, extended-release drug product given once or twice a day. Usually, the original marketed drug is a conventional, immediate-release (IR) drug product. After experience with the IR drug product, a pharmaceutical manufacturer (sponsor) may develop an extended-release product containing the same drug. In this case, the sponsor needs to demonstrate that the pharmacokinetic profile of the extended-release drug product has sustained plasma drug concentrations compared to the conventional drug product. In addition, the sponsor may perform a clinical safety and efficacy study comparing both drug products.

Bupropion hydrochloride (Wellbutrin), an antidepressant drug, is available as an immediate release (IR) drug product given three times a day, a sustained release (SR) drug product given twice a day, and an extended-release (XL) drug product given once a day. Jefferson et al (2005) reviewed the pharmacokinetics of these three products. These investigators reported that although the pharmacokinetic profiles are different for each drug product, the clinical efficacy for each drug product is similar if bupropion hydrochloride is given in equal daily doses. According to the approved label information for Wellbutrin XL, patients who are currently being treated with Wellbutrin tablets at 300 mg/day (for example, 100 mg three times a day) may be switched to Wellbutrin XL 300 mg once daily. Patients who are currently being treated with Wellbutrin SR sustained-release tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to Wellbutrin XL 300 mg once daily. Thus, for bupropion HCl, the fluctuations in plasma drug concentration versus time profiles do not affect clinical efficacy as long as the patient is given the same daily dose of drug.

**Generic Substitution of Modified-Release Drug Products**

Generic extended-release drug products may have different drug release mechanisms compared to the brand-drug product. The different drug release mechanisms may lead to slightly different pharmacokinetic profiles. Generic extended-release drug products are approved by FDA and are bioequivalent based on AUC and Cmax criteria and therapeutic equivalence to the brand name equivalent (Chapter 16). For some drugs, several different modified-release products containing exactly the same active ingredient are commercially available. These modified release drug products have different pharmacokinetic profiles and may have different clinical efficacy compared to the conventional form of the drug given in the same daily dose and compared to other extended-release products containing the same active drug. Since the pharmacokinetic profiles may differ, the practitioner needs to consult the FDA publication, Approved

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3 A sustained release drug product may also be called an extended release drug product.
Drug Products with Therapeutic Equivalence Evaluations (Orange Book), to determine which of these drug products may be substituted.

**EXAMPLE**

**Methylphenidate Drug Products**
Methylphenidate hydrochloride is a central nervous system (CNS) stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD). Numerous conventional and modified-release drug products containing methylphenidate hydrochloride are available (Table 17-10). Although each of these methylphenidate hydrochloride drug products have the same indication, the prescriber needs to understand which product would be most appropriate for the patient.

**EVALUATION OF IN VIVO BIOAVAILABILITY DATA**

The data from a properly designed in vivo bioavailability study are evaluated using both pharmacokinetic and statistical analysis methods. The evaluation may include a pharmacokinetic profile, steady-state plasma drug concentrations, rate of drug absorption, occupancy time, and statistical evaluation of the computed pharmacokinetic parameters.

**Pharmacokinetic Profile**
The plasma drug concentration–time curve should adequately define the bioavailability of the drug from the dosage form. The bioavailability data should include a profile of the fraction of drug absorbed (Wagner–Nelson) and should rule out dose dumping or lack of a significant food effect. The bioavailability data should also demonstrate the extended-release characteristics of the dosage form compared to the reference or immediate-release drug product.


### Steady-State Plasma Drug Concentration

The fluctuation between the $C_{\text{max}}$ (peak) and $C_{\text{min}}$ (trough) concentrations should be calculated:

$$\text{Fluctuation} = \frac{C_{\text{max}} - C_{\text{min}}}{C_{av}}$$

where $C_{av}$ is equal to $[\text{AUC}]/\tau$

An ideal extended-release dosage form should have minimum fluctuation between $C_{\text{max}}$ and $C_{\text{min}}$. A true zero-order release will have no fluctuation. In practice, the fluctuation in plasma drug levels after the extended-release dosage form should be less than the fluctuation after the same drug given in an immediate-release dosage form.

### Rate of Drug Absorption

For the extended-release drug product to claim zero-order absorption, an appropriately calculated input function such as used in the Wagner–Nelson approach should substantiate this claim. The difference between first-order and zero-order absorption of a drug is shown in Fig. 17-13. The rate of drug absorption from the conventional or immediate-release dosage form is generally first order, as shown by Fig. 17-13A. Drug absorption after an extended-release dosage form may be zero order (Fig. 17-13B), first order (see Fig. 17-13A), or an indeterminate order (Fig. 17-13C). For many extended-release dosage forms, the rate of drug absorption is first order, with an absorption rate constant $k_a$ smaller than the elimination rate constant $k$.

The pharmacokinetic model when $k_a > k$ is termed flip-flop pharmacokinetics and is discussed in Chapter 7.

### Occupancy Time

Drugs for which the therapeutic window is known, the plasma drug concentrations should be maintained above the minimum effective drug concentration (MEC) and below the minimum toxic drug concentration (MTC). The time required to obtain plasma drug levels within the therapeutic window is known as occupancy time (Fig. 17-14).

### Bioequivalence Studies

Bioequivalence studies for extended-release drug products are discussed in detail in Chapter 15.
Bioequivalence studies may include (1) a fasting study, (2) a food-intervention study, and (3) a multiple dose study. The FDA’s Center for Drug Evaluation and Research (CDER) maintains a website (www.fda.gov/cder) that lists regulatory guidances to provide the public with the FDA’s latest submission requirements for NDAs and ANDAs.

### Table 17-10 Various Methylphenidate Hydrochloride Drug Products

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Formulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>Immediate release</td>
<td>Conventional drug product</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Extended release</td>
<td>ER drug product with no initial dose</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>Extended release with an initial IR dose</td>
<td>Produces a bi-modal plasma concentration-time profile when given orally; not interchangeable with Concerta</td>
</tr>
<tr>
<td>Concerta</td>
<td>Extended release with an initial IR dose</td>
<td>Not interchangeable for Ritalin LA</td>
</tr>
<tr>
<td>Daytrana</td>
<td>Film, extended release; transdermal</td>
<td>Provides extended release via transdermal drug absorption</td>
</tr>
<tr>
<td>Methylin</td>
<td>Solution; oral</td>
<td>Immediate release drug product</td>
</tr>
<tr>
<td>Methylin</td>
<td>Tablet, chewable; oral</td>
<td>Immediate release drug product</td>
</tr>
</tbody>
</table>

### Statistical Evaluation

Variables subject to statistical analysis generally include plasma drug concentrations at each collection time, AUC (from zero to last sampling time), AUC (from zero to time infinity), $C_{max}$, $t_{max}$, and elimination half-life $t_{1/2}$. Statistical testing may include an analysis of variance (ANOVA), computation of 90% and 95% confidence intervals on the difference in formulation means, and the power of ANOVA to detect a 20% difference from the reference mean.

#### Frequently Asked Questions

- **Are extended-release drug products always more efficacious than immediate-release drug products containing the same drug?**

- **Why do some extended-release formulations of a drug have a different efficacy profile compared to a conventional dosage form, given in multiple doses?**

- **What are the advantages and disadvantages of a zero-order rate design for drug absorption?**

### Figures

#### Figure 17-13

The fraction of drug absorbed using the Wagner–Nelson method may be used to distinguish between the first-order drug absorption rate of a conventional (immediate-release) dosage form (A) and an extended-release dosage form (C). Curve B represents an extended-release dosage form with zero-order absorption rate.

#### Figure 17-14

Occupancy time.
CHAPTER SUMMARY

The modified-release drug product refers to a class of drug products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is a formulation designed with release characteristics, time course, and/or location that are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. The major objective of extended-release (ER) drug products is to achieve a prolonged therapeutic effect while minimizing unwanted side effects due to fluctuating plasma drug concentrations. Ideally, the ER drug product should release the drug at a constant or zero-order rate. For BCS 1 drugs, as the drug is released from the drug product, the drug is rapidly absorbed, and drug absorption rate should follow zero-order kinetics similar to an intravenous drug infusion. The drug product is designed so that the rate of systemic drug absorption is limited by the rate of drug release from the drug delivery system. Oral modified-release drug products are easily affected by the anatomy and physiology of the gastrointestinal tract, gastrointestinal transit, pH, and its contents compared to conventional oral drug products. Modified-release drug products may also have a different pharmacodynamic and safety profile compared to immediate release drug products containing the same drug. Various approaches have been used to manufacture modified- and extended-release drug products including matrix tablets, coated beads, osmotic release, ion-exchange, etc. Transdermal drug delivery systems may also be considered as extended release drug products. There may be several different modified-release drug products for the same active drug, each product with different pharmacokinetic profiles. For products containing the drug in combination with a device, the device influences the route of administration and pharmacokinetics of the drug. MR products may have different clinical efficacy compared to other extended-release products containing the same active drug. The practitioner needs to consult the FDA publication Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) to determine which of these drug products may be substituted.

LEARNING QUESTIONS

1. The design for most extended-release or sustained-release oral drug products allows for the slow release of the drug from the dosage form and subsequent slow absorption of the drug from the gastrointestinal tract.
   a. Why does the slow release of a drug from an extended-release drug product produce a longer-acting pharmacodynamic response compared to the same drug prepared in a conventional, oral, immediate-release drug product?
   b. Why do manufacturers of sustained-release drug products attempt to design this dosage form to have a zero-order rate of systemic drug absorption?

2. The dissolution profiles of three drug products are illustrated in Fig. 17-15.

FIGURE 17-15 Dissolution profile of three different drug products. Drug dissolved (percent).
a. Which of the drug products in Fig. 17-15 releases drug at a zero-order rate of about 8.3% every hour?
b. Which of the drug products does not release drug at a zero-order rate?
c. Which of the drug products has an almost zero rate of drug release during certain hours of the dissolution process?
d. Suggest a common cause of slowing drug dissolution rate of many rapid-release drug products toward the end of dissolution.
e. Suggest a common cause of slowing drug dissolution of a sustained-release product toward the end of a dissolution test.

3. A drug is normally given at 10 mg four times a day. Suggest an approach for designing a 12-hour, zero-order release product.

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Modified-Release Drug Products

503

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Chapter Objectives

- Describe various methods for targeted drug delivery.
- Compare and contrast biological and small molecule drugs in terms of their synthesis, mechanism of action, design, and development hurdles.
- Discuss why biological drugs may require specialized delivery and/or targeting systems.
- Describe the main methods used to deliver and target biologic drugs and give examples.
- Explain the difference between active and passive targeting.
- State whether or not generic biologics can be developed.
- Explain the pharmacokinetic differences between small molecule and biologic drugs and why these differences exist.
- Discuss the scientific issues in the development of interchangeable biosimilars or follow-on biologics.

Many diseases occur as a result of defects or errors in the genes involved in producing essential enzymes or proteins in the body. The genes are coded in deoxyribonucleic acid (DNA), helical double-stranded molecules folded into chromosomes in the nucleus of cells. The Human Genome Project was created several years ago to sequence the human genome. This national effort has generated information on the role of genetics in congenital defects, cancer, disorders involving the immune system, and other diseases that have a genetic link.

The emerging genetic basis of disease is providing novel opportunities for the development of biotechnology-derived pharmaceuticals (biopharmaceuticals) to treat specific disorders. The use of recombinant DNA (rDNA) technology and its application to new drug development has revolutionized the biopharmaceutical industry.

Presently, most drugs that are used to treat disease are small-molecular-weight, well-characterized molecules that are generally manufactured by chemical synthesis. In contrast, biotechnology-derived drugs are very large-molecular-weight drugs (eg, proteins) that have complex chemical structures. In some cases, there is limited ability to characterize the identity and structure of the biopharmaceutical and to measure the activity of the clinically active component(s) such as the specific active moiety. These biopharmaceuticals are often manufactured by fermentation, using recombinant DNA or other biosynthetic approaches in which the manufacturing process, original cell lines, and purification process can have an impact on quality, safety and efficacy of the drug.

These large biopharmaceuticals have enormous potential to treat disease in novel ways previously unavailable to small drug molecules. As a result, biotechnology, or the use of biological materials to create specific biopharmaceuticals, has become an important sector of the pharmaceutical industry and accounts for the fastest-growing class of new drugs in the market. Nucleic acid, protein and peptide drugs, and diagnostics are the main drug products emerging from the biopharmaceutical industry.
The human genome produces thousands of gene products that prevent disease and maintain health. Many of these gene products may have therapeutic applications if supplemented to normal or supraphysiologic levels in the body. Most of the biologic molecules listed in Table 18-1 are normally present in the body in small concentrations but are used for certain therapeutic indications. For example, some diseases such as insulin-dependent diabetes result from insufficient production of a natural product, in this case insulin. For these patients, the treatment is to supplement the patient’s own insulin production with recombinant human insulin (eg, Humulin). Similarly, human recombinant growth hormone (Protropin, Nutropin) and glucocerebrosidase (Ceredase, Cerezyme) are used to treat growth hormone deficiency and Gaucher’s disease, respectively.

In contrast, interferons are proteins produced by the immune system in response to viral infection and other biologic inducers. When infection or cancer surpasses the capacity of the body’s immune system, recombinant interferons (Roferon-A, Intron A, Alferon N, Actimmune, Infergen, Rebif) or other immune-enhancing molecules can be used to boost immunity. Recombinant interferons and interleukins (Proleukin, Neumega) are therefore used to strengthen the immune system during infection, immunosuppression, cancer, and multiple sclerosis. Erythropoetin and derivatives (Epogen, Procrit, Aranesp) and growth factors (Prokine, Leukine, Neupogen, Becaplermin) are also used to stimulate red and white cell production for anemia or immune suppression following chemotherapy. These molecules were originally available only by purification from human or animal sources. Biotechnology, bioengineering, and the use of cell banks have enabled the large-scale and reproducible production of these naturally occurring biologically derived drugs (see Table 18-1).

The size and complexity of protein and nucleic acid drugs require extensive design and engineering of the manufacturing and control processes to produce the drug in large quantities with consistent quality. The size of a protein or peptide drug can range from a few hundred to several hundred thousand daltons. The three-dimensional structure of a protein or peptide drug is important for its pharmacodynamic activity, so the corresponding specific primary amino acid, secondary (alpha helix or beta sheet), tertiary (special relationship of secondary structures), or even quaternary orientation of subunits must be considered. A biotechnology-derived drug (also referred to as a biologic drug or biopharmaceutical) must be designed such that the structure is stable, reproducible, and accurate during manufacture, storage, and administration. The manufacturing process and product are intricately linked. Small changes in the manufacturing process may affect the sequence of the resulting protein, but are more likely to affect the structure, yield, or activity of the protein or drug product. Therefore, pharmaceutical controls and testing must be carefully designed, controlled, and monitored, and must also be able to distinguish minor chemical or structural changes that could affect the safety or efficacy in the product during each of these stages.

Drug delivery of biologics can be a problem for therapeutic use because the protein drug must reach the site of action physically and structurally intact. Biologic drugs are notoriously unstable in plasma and the gastrointestinal tract, so modifications to improve drug delivery or stability are often required. Currently, most biologic drugs are generally too unstable for oral delivery and must usually be administered by parenteral routes. However, other nonparenteral routes of administration, such as intranasal and inhalation, are being investigated for biologic drug delivery. The first recombinant drug for inhalation, insulin (Exubera®) was approved in 2006, only to be withdrawn from the market 2 years later because of poor patient and physician acceptance due to route-related side effects. Fortunately, because many of these recombinant protein drugs are designed to act extracellularly, transmembrane delivery may not be required once the drug reaches the plasma.

**Monoclonal Antibodies**

Another class of protein drugs is monoclonal antibodies (mAbs). Antibodies are produced by the body’s immune system for specific recognition and removal of foreign bodies. The power of mAbs lies
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Pharmacokinetics</th>
<th>Year Introduced, Company (Trade Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldesleukin; interleukin-2</td>
<td>Renal cell carcinoma</td>
<td>Half-life = 85 min; ( CI = 268 \text{ mL/min} )</td>
<td>1992 Chiron (Proleukin)</td>
</tr>
<tr>
<td>Alteplase</td>
<td>Acute myocardial infarction</td>
<td>Half-life &lt; 5 min; ( CI = 380–570 \text{ mL/min} ); ( V_d = \text{plasma volume} )</td>
<td>1987 Genentech (Activase) 1990 Genentech (Activase)</td>
</tr>
<tr>
<td>Antihemophilic factor</td>
<td>Hemophilia B</td>
<td>Half-life = 13 h</td>
<td>1992 Armour (Mononine)</td>
</tr>
<tr>
<td>Antihemophilic factor</td>
<td>Hemophilia A</td>
<td>Half-life = 5–8 h; ( Cl = 380–570 \text{ mL/min} ); ( V_d = \text{plasma volume} )</td>
<td>1992 Genetics Institute, Baxter Healthcare, Bayer (ReFacto, Recombinate, Kogenate, Helixate FS)</td>
</tr>
<tr>
<td>Agalsidase-beta; ( \alpha )-galactosidase A</td>
<td>Fabry’s disease</td>
<td>Half-life = 45–102 min; nonlinear kinetics</td>
<td>2003 Genzyme (Fabrazyme)</td>
</tr>
<tr>
<td>Anakinara; IL-1 receptor antagonist</td>
<td>Rheumatoid arthritis</td>
<td>Half-life = 4–6 h</td>
<td>2001 Amgen (Kinerase)</td>
</tr>
<tr>
<td>( \beta )-Glucocerebrosidase</td>
<td>Type I Gaucher’s disease</td>
<td></td>
<td>1991 Genzyme (Ceredase)</td>
</tr>
<tr>
<td>CMV immune globulin</td>
<td>CMV prevention in kidney transplant</td>
<td></td>
<td>1990 Medimmune (CytoGam)</td>
</tr>
<tr>
<td>DNase</td>
<td>Cystic fibrosis</td>
<td></td>
<td>1993 Genentech (Pulmozyme)</td>
</tr>
<tr>
<td>Drotrecogin-( \alpha ); activated protein C</td>
<td>Severe sepsis</td>
<td>( Cl = 40 \text{ L/h} )</td>
<td>2001 Lilly (Xigris)</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Anemia associated with chronic renal failure</td>
<td>Half-life = 4–13 h</td>
<td>1989 Amgen; Johnson &amp; Johnson; Kirin (Epogen); 1990 Ortho Biotech (Procrit) 1993 Amgen; Ortho Biotech (Procrit) 1994 Amgen (Neupogen)</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Hemophilia A</td>
<td></td>
<td>1993 Genentech; Miles (Kogenate)</td>
</tr>
<tr>
<td>Filgrastim; G-CSF</td>
<td>Chemotherapy-induced neutropenia Bone marrow transplant</td>
<td>Half-life = 3.5 h; ( V_d = 150 \text{ mL/kg} ); ( Cl = 0.5–0.7 \text{ mL/kg/min} )</td>
<td>1991 Amgen (Neupogen) 1994 Amgen (Neupogen)</td>
</tr>
<tr>
<td>Human insulin</td>
<td>Diabetes</td>
<td></td>
<td>1982 Eli Lilly, Genentech (Humulin)</td>
</tr>
<tr>
<td>Interferon-( \alpha )-2a</td>
<td>Hairy cell leukemia; AIDS-related Kaposi’s sarcoma</td>
<td>Half-life = 5.1 hr; ( V_d = 0.4 \text{ L/kg} ); ( Cl = 2.9 \text{ mL/min/kg} )</td>
<td>1986 Hoffmann-La Roche (Roferon-A)</td>
</tr>
<tr>
<td>Interferon-( \alpha )-2b</td>
<td>Hairy cell leukemia; AIDS-related Kaposi’s sarcoma</td>
<td>Half-life = 2–3 h</td>
<td>1986 Schering-Plough; Biogen (Intron A)</td>
</tr>
<tr>
<td>Interferon-( \alpha )-n3</td>
<td>Genital warts</td>
<td></td>
<td>1989 Interferon Sciences (Alferon N injection)</td>
</tr>
</tbody>
</table>

(Continued)
in their highly specific binding of only one antigenic determinant. As a result, mAb drugs, targeting agents, and diagnostics are creating new ways to treat and diagnose previously untreatable diseases and to detect extraordinarily low concentrations of protein or other molecules (Table 18-2).

Theoretically, an almost infinite amount and number of antibodies can be produced by the body to respond immunologically to foreign substances containing antigenic sites. These antigenic sites are usually on protein molecules, but nonprotein material or haptens may be conjugated to a protein to form an
TABLE 18-2  Applications of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Application</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer treatment</td>
<td>mAbs against leukemia and lymphomas have been used in treatment with variable results. Regression of tumor is produced in about 25%, although mostly transient.</td>
</tr>
<tr>
<td>Imaging diagnosis</td>
<td>mAbs may be used together with radioactive markers to locate and visualize the location and extent of the tumors.</td>
</tr>
<tr>
<td>Target-specific delivery</td>
<td>mAbs may be conjugated to drugs or other delivery systems such as liposomes to allow specific delivery to target sites. For example, urokinase was conjugated to an antifibrin mAb to dissolve fibrin clots. The carrier system would seek fibrin sites and activate the conversion of plasminogen to plasmin to cause fibrin to degrade.</td>
</tr>
<tr>
<td>Transplant rejection suppression</td>
<td>In kidney transplants, an mAb against CD3, a membrane protein of cytotoxic T cells that causes a rejection reaction, was very useful in suppressing rejection and allowing the transplant to function. The drug was called OKT3. mAbs are also used for kidney and bone marrow transplants.</td>
</tr>
</tbody>
</table>

Monoclonal antibodies may be used therapeutically to neutralize unwanted cells or molecules. Several mAbs with proven indications are listed in Tables 18-1, 18-2, and 18-3. Monoclonal antibodies are used as antivenoms (CroFab), for overdose of digoxin (DigiFab), or to neutralize endotoxin (Nebacumab, investigative) or viral antigen (Nabi-HB). Nebacumab is a human IgM mAb (HA-1A) with specificity for the lipid designed for septic shock treatment. Monoclonal antibodies (mAb) are named by a source identifier preceding “-mab,” e.g., -umab (human), -omab (mouse), -zumab (humanized), and -ximab (chimeric). Other common indications for mAb drugs include imaging (ProstaScint, Myocint, Verluma), cancer (Campath, Ontak, Zevalin, Rituxan, Herceptin), rheumatoid arthritis (Humira, Remicade), and transplant immunosuppression (Simulect, Thymoglobulin). Monoclonal antibodies are also used for more novel indications. For example, Abciximab (c7E3 Fab, ReoPro) is a chimeric mAb Fab (humanized) fragment specific for platelet glycoprotein IIb-IIIa receptors. This drug is extremely effective in reducing fatalities (50%) in subjects with unstable angina after angioplasty treatment.
FIGURE 18-1  Monoclonal antibody production. A. A mouse is immunized with an antigen bearing three antigenic determinants (distinct sites that can be recognized by an antibody). Antibodies to each determinant are produced in the spleen. One spleen cell produces a single type of antibody. A spleen cell has a finite lifetime and cannot be cultured indefinitely in vitro. B. In the mouse, the antibody-producing cells from the spleen secrete into the blood. The liquid portion of the blood (serum) therefore contains a mixture of antibodies reacting with all three sites on the antigen (antiserum). A'. A mutant cell derived from a mouse myeloma tumor of an antibody-producing cell that has stopped secreting antibody and is selected for sensitivity to the drug aminopterin (present in HAT medium). This mutant tumor cell can grow indefinitely in vitro but is killed by HAT medium. B'. The mutant myeloma cell is fused by chemical means with spleen cells from an immunized mouse. The resulting hybrid cells can grow indefinitely in vitro due to properties of the myeloma cell parent and can grow in HAT medium because of an enzyme provided by the spleen cell parent. The unfused myeloma cells die because of their sensitivity to HAT, and unfused spleen cells cannot grow indefinitely in vitro. The hybrid cells are cloned so that individual cultures are grown from a single hybrid cell. These individual cells produce a single type of antibody because they derive from a single spleen cell. The monoclonal antibody isolated from these cultures is specific for only one antigenic determinant on the original antigen. (From Milstein, 1980, and Brodsky, 1988, with permission.)
TABLE 18-3  Approved Monoclonal Antibody Drugs and In Vivo Diagnostics

<table>
<thead>
<tr>
<th>mAb Product (Trade Name)</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab (ReoPro)</td>
<td>Platelet surface glycoprotein</td>
<td>Half-life &lt; 10 min</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>Tumor necrosis factor</td>
<td>$V_d = 4$–6 L; $CI = 12$ mL/h; half-life = 2 wk</td>
</tr>
<tr>
<td>Alefacept (Amevive)</td>
<td>CD2 (LFA) on lymphocytes</td>
<td>Half-life = 270 h; $CI = 0.25$ mL/kg/h; $V_d = 94$ mL/kg</td>
</tr>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>CD52 on blood cells</td>
<td>Half-life = 12 d</td>
</tr>
<tr>
<td>Antithymocyte globulin (rabbit) thymoglobulin</td>
<td>T-lymphocyte antigens</td>
<td>Half-life = 2–3 d</td>
</tr>
<tr>
<td>Basiliximab (Simulect)</td>
<td>Interleukin-2</td>
<td>Half-life = 7.2 d; $V_d = 8.6$ L; $CI = 41$ mL/h</td>
</tr>
<tr>
<td>Capromab pendetide (ProstaScint)</td>
<td>Prostate glycoprotein</td>
<td>Half-life = 67 h; $CI = 42$ mL/h; $V_d = 4$ L</td>
</tr>
<tr>
<td>Daclizumab (Zenapax)</td>
<td>Interleukin-2 receptor</td>
<td>Half-life = 20 d; $CI = 15$ mL/h; $V_d = 6$ L</td>
</tr>
<tr>
<td>Denileukin diftitox (Ontak)</td>
<td>Interleukin-2 mAb conjugate to dipheria toxin</td>
<td>Half-life = 70–80 min; $CI = 1.5$–2 mL/min/kg; $V_d = 0.06$–0.08 L/kg</td>
</tr>
<tr>
<td>Digoxin Immune Fab—Ovine (DigiFab)</td>
<td>Digoxin</td>
<td>Half-life = 15–20 h; $V_d = 0.3$–0.4 L/kg</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Tumor necrosis factor receptor</td>
<td>Half-life = 115 h; $CI = 89$ mL/h</td>
</tr>
<tr>
<td>Hepatitis B immune globulin—human (Nabi-HB)</td>
<td>Hepatitis B</td>
<td>Half-life = 25 d; $CI = 0.4$ L/d; $V_d = 15$ L</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin)</td>
<td>CD28 on B cells</td>
<td>Half-life = 30 h</td>
</tr>
<tr>
<td>Imciromab pentetate (Myoscint)</td>
<td>Myosin</td>
<td>Half-life = 20 h</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Tumor necrosis factor</td>
<td>Half-life = 9.5 d; $V_d = 3$ L</td>
</tr>
<tr>
<td>Nofetumomab (Verluma)</td>
<td>Carcinoma-associated antigen, Tc$^{99m}$ labeled</td>
<td>Half-life = 10.5 h</td>
</tr>
<tr>
<td>Muromonab-CD3 (Orthoclone OKT3)</td>
<td>CD3 on T cells</td>
<td></td>
</tr>
<tr>
<td>Palivizumab (Synagis)</td>
<td>RSV antigens</td>
<td>Half-life = 197 h; $CI = 0.33$ mL/h/kg; $V_d = 90$ mL/kg</td>
</tr>
</tbody>
</table>

(Continued)
regions such as the promoter, the actual rDNA (recombinant DNA) to be delivered to target cell nuclei can easily be 10 to 20 kilobases (kb) in size.

Two main approaches have been used for in vivo delivery of rDNA. The first is a virus-based approach that involves replacing viral replicative genes with the transgene, then packaging the rDNA into the viral particle. The recombinant virus can then infect target cells, and the transgene is expressed, though the virus is not capable of replicating. Both retroviruses, RNA viruses that have the ability to permanently insert their genes into the chromosomes of the host cells, and DNA viruses (which remain outside host chromosomes) have been used successfully in viral gene delivery. Most of the gene therapy trials worldwide involve the use of such viral delivery systems.

In addition to viral delivery systems (vectors), nonviral approaches have been used with some success for in vivo gene delivery. The transgene is engineered into a plasmid vector, which contains gene-expression control regions. These naked DNA molecules may enter cells and express product in some cell types, such as muscle cells. This naked DNA delivery technique is being tested as possible DNA vaccines, in which the muscle cells produce small amounts of antigen that stimulate immunity to the antigen. However, usually either a cationic or a fusogenic liposome delivery system (see below) is required in most other cell types to produce measurable levels of transgene expression. Both types of lipid vesicles or particles result in intracellular delivery of DNA to cells. Nanoparticles are also increasingly used as a delivery method for gene therapy and other nucleic acid therapies.

An alternative to direct in vivo delivery is a cell-based approach that involves the administration of transgenes to cells that have been removed from a patient. For example, cells (usually bone

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**TABLE 18-3 Approved Monoclonal Antibody Drugs and In Vivo Diagnostics (Continued)**

<table>
<thead>
<tr>
<th>mAb Product (Trade Name)</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan)</td>
<td>CD20 on B cells</td>
<td>Half-life = 60 h</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Human epidermal growth factor receptor</td>
<td>Half-life = 1.7–12 d; $V_d = 44$ mL/kg</td>
</tr>
</tbody>
</table>

Monoclonal antibodies can also target and deliver toxins specifically to cancer cells and destroy them while sparing normal cells (see below), and they are important detectors used in laboratory diagnostics.

**Gene Therapy**

*Gene therapy* refers to a pharmaceutical product that delivers a recombinant gene to somatic cells in vivo (Ledley, 1996). In turn, the gene within the patient’s cell produces a protein that has therapeutic benefit to the patient. The therapeutic approach in gene therapy is often the restoration of defective biologic function within cells or enhancing existing functions such as immunity, as is frequently seen in inherited disorders and cancer.

Gene therapy has been applied to the inherited disorder cystic fibrosis, in which patients have a defective chloride ion channel gene, resulting in chloride ion channel abnormalities. Although improved therapy has transformed cystic fibrosis from a disease characterized by death in early childhood to a chronic illness, there is still no cure for the disease and most patients eventually succumb to infections of the airways and lung failure. The aim of gene therapy for these patients is to deliver a “normal” chloride ion channel gene to the cells of cystic fibrosis patients and restore chloride transport in cells. More information on gene therapy of cystic fibrosis has been published by the National Institutes of Health (www.niddk.nih.gov/health/endo/pubs/cystic/cystic.htm).

Gene therapy faces several challenges despite over two decades of research and development. These challenges include gene delivery, sufficient extent and duration of stable gene expression, and safety. Because of the gene coding the therapeutic protein (transgene) must also contain gene control
 marrow cells) are removed from the patient, genes encoding a therapeutic product are then introduced into these cells \textit{ex vivo} using a viral or nonviral delivery system, and then the cells are returned into the patient. The advantage of \textit{ex vivo} approaches is that systemic toxicity of viral or nonviral delivery systems is avoided.

Effective gene therapy depends on several conditions. The vector must be able to enter the target cells efficiently and deliver the corrective gene without damaging the target cell. The corrective gene should be stably expressed in the cells, to allow continuous production of the functional protein. Neither the vector nor the functional protein produced from it should cause an immune reaction in the patient. It is also difficult to control the amount of functional protein produced after gene therapy, and excess production of the protein could cause side effects, although insufficient production is more typically observed. Additional problems in gene therapy include the physical and chemical properties of DNA and RNA molecules, such as size, shape, charge, surface characteristics, and the chemical stability of these molecules and delivery systems. \textit{In vivo} problems may include bioavailability, distribution, and uptake of these macromolecules into cells. Moreover, naked DNA molecules are rapidly degraded in the body (Ledley, 1996).

**Oligonucleotide Drugs**

\textit{Antisense oligonucleotide} drugs are drugs that seek to block DNA transcription or RNA translation in order to moderate many disease processes. Antisense drugs consist of nucleotides linked together in short DNA or RNA sequences known as \textit{oligonucleotides}. Antisense oligonucleotides are based on the sequence of target DNA/RNA (e.g., messenger RNA) and designed to block transcription or translation of that targeted protein. An oligonucleotide that binds complementary (“sense”) mRNA sequences and blocks translation is referred to as \textit{antisense}. Oligonucleotides can also be selected for their nonsequence-specific, high affinity binding to proteins (“aptamers”). To further stabilize the drug, many chemical modifications have been made to the oligonucleotide structure. The most common modification used involves substitution of a nonbridging oxygen in the phosphate backbone with sulfur, resulting in a phosphorothioate-derived antisense oligonucleotide. Some of these drugs have been designed to target viral disease and cancer cells in the body. Fomivirsen sodium (Vitravene) intravitreal injectable is an oligonucleotide targeted to cytomegalovirus. Fomivirsen sodium was the first antisense oligonucleotide drug approved by the FDA. Pegaptanib sodium (Macugen), an aptamer oligonucleotide, was introduced in 2005 for the treatment of age-related macular degeneration. Both oligonucleotide drugs act locally (in the eye) and are available as sterile ophthalmic products. Biotechnologic products could be more costly than conventional products due to generally higher cost of development.

For this approach to be useful, the etiology and genetics of the disease must be known. For example, in the case of viral infection, known sequences belonging to viral genes can be targeted and inhibited by antisense drugs. Many antisense sequences are usually tested to find the best candidate, since intra- and intermolecular interactions can affect oligonucleotide activity and delivery. Though oligonucleotides are relatively well internalized compared to rDNA molecules, cellular uptake is often low enough to require delivery systems, such as liposomes. Oligonucleotide and gene therapy approaches have also been combined using viral vectors to deliver the desired antisense sequence. In this case, the transgene is transcribed into an mRNA molecule that is antisense and therefore binds to the target mRNA. The resulting RNA:RNA interaction is high affinity and results in inhibition of translation of that mRNA molecule.

**miRNAs**

miRNA, or microRNA, is a semisynthetic class of compounds related to oligonucleotides. These single-stranded RNA molecules are regulated under the class of regulatory RNA molecules in cells involved in gene regulation. Similar to miRNAs are double-stranded siRNA (small, interfering RNAs), also known as RNAi, or RNA interference. RNAi are naturally occurring molecules in cells involved in sequence-specific gene inhibition mediated by RNAi
molecules complementary to the target mRNA to be inhibited. Both miRNA and siRNA involve target, complementary RNA strand degradation via a molecular complex called RISC (RNA-induced silencing complex). siRNA requires high homology in target base-pairing but miRNA activity can occur even with some mismatches. miRNAs mutations may be involved in disease pathogenesis. RNAi mechanisms are now commonly used in research and in new drug development as an effective way to inhibit expression of specific gene sequences. Enzymatic RNA molecules called ribozymes are also naturally occurring RNA molecules involved in regulation of gene expression. Chemical modification and delivery technologies are also applied to miRNA and siRNA drugs because of stability and transport issues. Ribozyme, miRNA, and siRNA drugs are currently in clinical testing for diseases involving cancer, viral infection, and cardiovascular disease.

### Frequently Asked Questions

- **What is the most frequent route of administration of biologic compounds? Why?**
- **What is the effect of glycosylation on the activity of a biologic compound? Give an example.**
- **What kind of biological drugs are available and how are they used? Is this similar or different from small molecule drugs?**

### DRUG CARRIERS AND TARGETING

#### Formulation and Delivery of Protein Drugs

Advances in biotechnology have resulted in the commercial production of naturally produced active drug substances for drug therapy (see Table 18-1). These substances hold great potential for more specific drug action with fewer side effects. However, many naturally produced substances are complex molecules, such as large-molecular-weight proteins and peptides. Conventional delivery of protein and peptide drugs is generally limited to injectables and implantable dosage forms. Insulin pumps for implantation and an inhaled insulin product have been developed for precise control of glucose levels in diabetes. Other novel delivery methods such as transdermal devices and orally administered products are being investigated for the delivery of biopharmaceuticals.

Formulating protein drugs for systemic use by oral, or any extravascular, route of administration is extremely difficult due to drug degradation and absorption from the site of administration. There are several requirements for effective oral drug delivery of protein and peptide drugs: (1) protection of the drug from degradation while in the harsh environment of the digestive tract, (2) consistent absorption of the drug in a manner that meets bioavailability requirements, (3) consistent release of the drug so that it enters the bloodstream in a reproducible manner, (4) nontoxicity, and (5) delivery of the drug through the GI tract and maintenance of pharmacologic effect similar to IV injection.

Designing, evaluating, and improving protein and peptide drug stability is considerably more complex than for small conventional drug molecules. A change in quaternary structure, such as aggregation or deaggregation of the protein, may result in loss of activity. Changes in primary structure of proteins frequently occur and include deamidation of the amino acid chains, oxidation of chains with sulfhydryl groups, and cleavage by proteolytic enzymes present throughout the body and that may be present due to incomplete purification. Because of the complex structures of protein drugs, impurities are much harder to detect and quantify. In addition, proteins may be recognized as foreign substances in the body and become actively phagocytized by the reticuloendothelial system (RES), resulting in the inability of these proteins to reach the intended target. Proteins may also have a high allergic or immunogenic potential, particularly when nonhuman genes or production cells are used.

Because of the many stability and delivery problems associated with protein and nucleic acid drugs, new delivery systems are being tested to improve their in vivo properties. Carriers can be used to protect the drug from degradation, improve transport or delivery to cells, decrease clearance, or a combination of the above. In this chapter, carriers...
used for both small traditional drug and biopharmaceutical drug delivery are reviewed. Carriers may be covalently bound to the drug, where drug release is usually required for pharmacologic activity. Noncovalent drug carriers such as liposomes typically require uncoating of the drug for biologic activity to occur.

**Polymeric Delivery Systems**

Polymers can be designed to include a wide range of physical and chemical properties and are popularly used in drug formulations because of their versatility. Polymers were used initially to prolong drug release in controlled-release dosage forms. The development of site-specific polymer or macromolecular carrier systems is a more recent extension of earlier research. The basic components of site-specific polymer carriers are (1) the polymeric backbone (Fig. 18-2), (2) a site-specific component (homing device) for recognizing the target, (3) the drug covalently or electrostatically attached to the polymer chain, and (4) functional chains to enhance the physical characteristics of the carrier system. Improved physical characteristics may include improved aqueous solubility. In the case of polymeric prodrugs, a spacer group may be present, bridging the drug and the carrier. The spacer chain may influence the rate at which the drug will hydrolyze from the prodrug system. At present, most site-specific polymeric drug carriers are limited to parenteral administration and primarily utilize soluble polymers.

Positively charged polymers such as polyethylenediamine (PEI), polylysine, and chitosan (Fig. 18-3) are used in noncovalent complexes for macromolecular drugs, such as gene or oligonucleotide therapy. For example, polymer:DNA complexes improve DNA delivery to cells in part by providing some protection from nuclease degradation in vivo. An added advantage of complexed cationic polymers is that targeting agents such as receptor ligands can be covalently attached to the polymer rather than the drug to provide cell-specific targeting. Cationic polymer use is limited because of toxicity of the polymer and dissociation of the complex in vivo.

Polymers may also be covalently conjugated to drugs to improve their solubility or pharmacokinetic properties. Polymers with molecular weights greater than 30 to 50 kDa bypass glomerular filtration, thereby extending the duration of drug circulation in the body. Polyethylene glycol (PEG) is used to improve the clearance of some drugs, such as adenosine deaminase (PEG-ADA), filgrastim (Neulasta), pegaptanib (Macugen), interferon (PEG-Intron and PEGASYS), and asparaginase (Oncospar). Daunomycin has been linked to dextran, resulting in improved drug activity in animal studies (Levishaffer et al, 1982). Dextrans are large polysaccharide molecules (MW 2000 to 1 million Da) with good water solubility, stability, and low toxicity. Drugs with a free amino or hydroxyl group may be linked chemically to hydroxyl groups in dextran by activation of the dextran with periodate, azide, or other agents.

The molecular weight of the polymer carrier is an important consideration in designing these dosage forms. Generally, large-molecular-weight polymers have longer residence times and diffuse more slowly. However, large polymers are also more prone to capture by the reticuloendothelial system. To gain specificity, a monoclonal antibody, a recognized sugar moiety, or a small cell-specific ligand may be incorporated as a targeting agent into the delivery system. For example, exposed galactose residues are recognized by hepatocytes, whereas mannose or l-fructose is recognized by surface receptors in macrophages. HMPA [N-(2-hydroxypropyl)methacrylamide] is commonly used in drug conjugates because the polymer can be modified with monosaccharides that act as targeting...
agents for cells expressing the appropriate receptor (Joshi, 1988; Seymour, 1994).

In addition to use as regular carriers, polymers may also be formulated into microparticles and nanoparticles. In such delivery systems, the therapeutic agent is encapsulated within a biodegradable polymeric colloidal particle that is in the micrometer or nanometer size range, respectively. Micro- and nanosphere formulations are useful for solubilizing poorly soluble drugs, improving oral bioavailability, protecting against degradation, or providing sustained drug delivery. The small size of nanospheres generally allows good tissue penetration while providing protection or sustained release.

The size of the microsphere and nanosphere has a profound impact on the \textit{in vivo} properties and disposition of an encapsulated drug. At over 12 \(\mu\text{m}\), particles are lodged in the capillary bed at the site of the injection. From 2 to 12 \(\mu\text{m}\), particles are retained at the lung, spleen, or liver. Particles less than 0.5 \(\mu\text{m}\) (500 nm) deposit into the spleen and bone marrow. In gene therapy, particles smaller than 100 nm demonstrate higher gene expression \textit{in vitro} compared to larger particles (Panyam and Labhasetwar, 2003). More recently, nanoparticles are believed to accumulate in cancer tissue because of hyperpermeability of the permeating vascular endothelia due to fenestrations in the \(\mu\text{m}\) range, also known as the enhanced permeation and retention (EPR) effect. Delivery systems may be used to differentially target certain cancer cell types or stage of disease based on such permeabilities (see Ferrari, 2010). Though some peptides and nucleic acids have been successfully formulated into nanospheres, protein denaturation and degradation can be significant during encapsulation.

\textbf{Cyclodextrins} (CDs) are also used to improve stability, delivery, and water solubility of drugs. The lipophilic cavity of CDs typically contains the therapeutic agent, while the exterior of the CD molecule is hydrophilic and allows solubilization of the complex. Many folded proteins and nucleic acids are too large to be completely included into the CD cavity and can result in protein denaturation. However, CDs have been used to solubilize and stabilize several proteins and peptides (Irie and Uekama, 1999).

\textbf{Albumin}

Albumin is a large protein (MW 69,000 Da) that is distributed in the plasma and extracellular water. Albumin has been experimentally conjugated with many drugs to improve site-specific drug delivery or as a coating in microspheres for controlled release or oral delivery. Many anticancer drugs such as methotrexate, cytosine arabinoside, and 6-fluorodeoxyuridine have each been conjugated with albumin. Paclitaxel has been formulated into an albumin-bound nanoparticle (Abraxane) to allow increased drug accumulation into breast cancer tissue without the use of Cremophor, a surfactant frequently associated with adverse reactions such as hypersensitivity and demyelination, and possibly increased drug penetration.

\textbf{Lipoproteins}

Lipoproteins are lipid protein complexes in the blood involved in the circulation and distribution of lipids in the body. The lipid components are polar phospholipids and cholesterol. Because of their various sizes, lipoproteins have been classified according to molecular weight based on centrifugation: (1) high-density lipoprotein (HDL, MW 300,000–600,000 Da), (2) low-density lipoprotein (LDL, MW \(2.3 \times 10^6\) Da), (3) very-low-density lipoprotein (VLDL, MW \(10^6\) Da), and (4) chylomicrons (MW \(10^9\) Da). Low-density lipoproteins enter the cell by a receptor-mediated pathway through the process of endocytosis. Endocytosis is a potential means of transporting drugs into the cell in which the lipoprotein–drug complex is hydrolyzed by intracellular lysosomal enzymes, releasing the active drug within the vesicle.

More research is needed on the use of lipoproteins for drug targeting. For example, lipophilic drugs may be dissolved within the core of the lipoprotein. After oral administration, fatty substances incorporated into the chylomicron formed in the gastrointestinal tract may be absorbed into the lymphatic system.

\textbf{Liposomes}

Liposomes have an aqueous, drug- or imaging agent-containing interior surrounded by an exterior lipid bilayer though more complex structures can also be used, and typically range in size from 0.5 to 100 \(\mu\text{m}\). Liposomes have been used successfully to reduce side effects of antitumor drugs and antibiotics. For example, doxorubicin liposomes have reduced cardiotoxicity and emetic side effects. Amphotericin B may have reduced nephrotoxicity side effects when formulated with liposomes. An innovative liposome-related product (Abelcet) consists of amphotericin B complexed with two phospholipids, 1,2-dimyristoyl-phosphatidylcholine and
Common anionic lipid materials are phosphatidylcholine and cholesterol. The phosphatidyl group is amphiphilic, with the choline being the polar group. This structure allows each molecule to attach to others through hydrophobic and hydrophilic interactions. Thermodynamically, liposomes are in equilibrium between different membrane conformations or structures (lipid polymorphism). Thus, some seemingly stable liposome systems exhibit leakage and generally do not have long shelf lives.

Liposomes can be engineered to be site specific. Generally, site specificity is conferred by the type of lipid or by inclusion of a targeting agent, such as a monoclonal antibody or a tumor-specific antigen, into the liposome bilayer (see Targeted Drug Delivery) or just above a protective polymer layer, such as PEG. Magneto-, light- and thermosensitive liposomes have also been developed to enable site-specific drug release.

Liposomes may be used to improve intracellular delivery, in which case the liposome must also be designed to fuse with the plasma or endosome membrane. Lipids or fusogenic peptides that facilitate membrane fusion, such as phosphatidyl ethanolamine or GALA and KALA peptides, respectively, have been used to improve liposome intracellular delivery. Peptides such as TAT or octa-arginine have also been used for intracellular targeting and increased uptake of genes. Cationic lipids, such as N-[1-(2, 3 dioleyloxy)propyl]-N, N, N-trimethylammonium chloride (DOTMA) or oleoyl-phosphatidylethanolamine (DOPE), are also commonly used for in vitro delivery of DNA. When cationic lipids are mixed with DNA, a particle forms from DNA:lipid charge interactions. The cationic lipid is believed to destabilize biological membranes resulting in improved intracellular DNA delivery. The in vivo use of cationic lipids is limited by systemic toxicity due to the positive charge of the lipid. Combinations of modifications to liposomes may also be employed to increase residence time in the body including PEG to make the liposome invisible to macrophages combined with a targeting antibody and/or cationic lipids. However, PEG coatings may prevent recognition of targeting agents when placed simultaneously on nanoparticle delivery systems (see Ferrari, 2010).
Site-specific drug delivery has also been characterized as passive or active targeting (Takakura and Hashida, 1996). Passive targeting refers to the exploitation of the natural (passive) disposition profiles of a drug carrier, which are passively determined by its physicochemical properties relative to the anatomic and physiologic characteristics of the body. Active targeting refers to alterations of the natural disposition of a drug carrier, directing it to specific cells, tissues, or organs. One approach to active targeting is the use of ligands or monoclonal antibodies which can target specific cells. Monoclonal antibodies were discussed more fully earlier in this chapter. Active targeting employing receptor-mediated endocytosis is a saturable, nonlinear process that depends on the drug–carrier concentration, whereas passive targeting is most often a linear process over a large range of doses.

**General Considerations in Targeted Drug Delivery**

Considerations in the development of site-specific or targeted drug delivery systems include: (1) the anatomic and physiologic characteristics of the target site, including capillary permeability to macromolecules and cellular uptake of the drug (Molema et al, 1997); (2) the physicochemical characteristics of the therapeutically active drug; (3) the physical and chemical characteristics of the carrier; (4) the selectivity of the drug–carrier complex; and (5) any impurities introduced during the conjugation reaction linking the drug and the carrier that may be immunogenic, toxic, or produce other adverse reactions.

**Target Site**

The accessibility of the drug–carrier complex to the target site may present bioavailability and pharmacokinetic problems, which also include anatomic and/or physiologic considerations. For example, targeting a drug into a brain tumor requires a different route of drug administration (intrathecal injection) than targeting a drug into the liver or spleen. Moreover, the permeability of the blood vessels or biologic membranes to macromolecules or drug carrier complex may be a barrier preventing delivery and intracellular uptake of these drugs (Molema et al, 1997).
Targeting Agents

Properly applied, drug targeting can improve the therapeutic index of many toxic drugs. However, monoclonal antibodies (see discussion above) are not the “magic bullet” for drug targeting that many people had hoped. One difficulty encountered is that the large molecule reduces the total amount of active drug that can be easily dosed (ie, the ratio of drug to carrier). In contrast, conventional carriers or targeting agents that are not specific are often many orders of magnitude smaller in size, and a larger effective drug dose may be given more efficiently. Transferrin is an example of a smaller targeting agent that is frequently used to deliver conjugates across the capillary endothelial cells in the brain or to cancer. Single chain polypeptides that include the antibody binding domain, effector, and hinge regions called SMIPs (small modular immunopharmaceutical proteins) have been developed as smaller alternatives to therapeutic mAbs (trueemergent.com).

In addition to employing monoclonal antibodies in liposomes and other delivery systems as described above, mAbs may be conjugated directly to drugs. The resulting conjugate can theoretically deliver the drug directly to a cell that expresses a unique or an abundance of a surface marker. For example, a tumor cell may overexpress the interleukin-2 receptor. In this case, a cytotoxic molecule such as recombinant diphtheria toxin is coupled to an mAb specific for the interleukin-2 receptor (Ontak). The conjugate delivers the toxin preferentially to these tumor cells. An overall tumor response rate for Ontak is 38%, with side effects including acute hypersensitivity reaction (69%) and vascular leak syndrome (27%). Zolimomab arixon (Orthozyrne-CD5, Xoma/Ortho Biotech) is an investigational immunoconjugate of monoclonal anti-CD5 murine IgG and the ricin A-chain toxin. This conjugate is used in the treatment of steroid-resistant graft-versus-host disease after allogeneic bone marrow transplants for hematopoietic neoplasms, such as acute myelogenous leukemia. Myoscin is an 111In-labeled mAb targeted to myosin that is used to image myocardial injury in patients with suspected myocardial infarction. An immune response to mAb drugs may develop, since mAbs are produced in mouse cells. “Humanized” mAbs are genetically engineered to produce molecules that are less immunogenic.

Site-Specific Carrier

To target a drug to an active site, one must consider whether there is a unique property of the active site that makes the target site different from other organs or tissue systems in the body. The next consideration is to take advantage of this unique difference so that the drug goes specifically to the site of action and not to other tissues in which adverse toxicity may occur. In many cases the drug is complexed with a carrier that targets the drug to the site of action. For example, one of the first approved drugs developed using pharmacogenomic principles is Herceptin® (trastuzumab), a monoclonal antibody designed to bind to the human epidermal growth factor receptor. This receptor is overexpressed on HER-2 positive breast cancer cells. Therefore, the drug will preferentially bind HER-2 positive breast cancer cells, though other noncancerous cells may also express the receptor. Trastuzumab is also in clinical trials as a drug conjugate, where the antibody is linked to anticancer/antimicrotubule agents that may, for example, be released in the lysosome after internalization. Similarly, trastuzumab has also been used as a targeting agent for anticancer drug-encapsulated nanoparticles. The successful application of these delivery systems requires the drug–carrier complex to have both affinity for the target site and favorable pharmacokinetics for delivery to the organ, cells, and subcellular target sites. An additional problem, particularly in the use of protein carriers, is the occurrence of adverse immunological reactions—an occurrence that is partially overcome by designing less immunoreactive proteins (Takakura and Hashida, 1996).

Drugs

Most of the drugs used for targeted drug delivery are highly reactive drugs that have potent pharmacodynamic activities with a narrow therapeutic range. These drugs are often used in cancer chemotherapy. Many of these drugs may be derived from biologic sources, made by a semisynthetic process using a biologic source as a precursor, or produced by recombinant DNA techniques. The drugs may also be large macromolecules, such as proteins, and are prone to instability and inactivation problems during processing, chemical manipulation, and storage.
Oral Immunization

Antigens or fragmented antigenic protein may be delivered orally and stimulate gut-associated lymphoid tissue (GALT) in the gastrointestinal tract. This represents a promising approach for protecting many secretory surfaces against a variety of infectious pathogens. Immunization against salmonella and *Escherichia coli* in chickens was investigated for agricultural purposes. Particulate antigen delivery systems, including several types of microspheres, have been shown to be effective in orally inducing various types of immune response. Encapsulation of antigens with mucosal adjuvants can protect both the antigen and the adjuvant against gastric degradation and increase the likelihood that they will reach the site of absorption. For example, Vivotif(R) is an enteric-coated capsule containing a live attenuated typhoid vaccine for oral administration only.

PHARMACOKINETICS OF BIOPHARMACEUTICALS

The unusual nature of biopharmaceuticals compared to traditional drugs presents development challenges for scientists in the biotechnology industry. Because of the size and complexity of biopharmaceuticals, stability and delivery are major developmental issues with these new drugs. The prerequisite of the maintenance of higher-order structure adds a new dimension to formulation, drug delivery, and stability testing of biologic drugs. Pharmacokinetic studies are often complicated by bioanalytic challenges, since preservation of primary structure or an isotope label alone does not necessarily coincide with biologic activity, and effective drug concentrations are often much lower compared to conventional low-molecular-weight drugs.

Once in the body, protein and nucleic acid drugs are subject to rapid degradation by endogenous proteases and nucleases that are present in the serum, tissues, and cells. Unmodified phosphodiester DNA and RNA are extremely labile in the body, with half-lives of the order of a few minutes. Houk et al (2001) report that naked DNA clearance in rats is rapid and depends on the conformation of the plasmid: supercoiled, open circular, versus linear. Many of the early recombinant protein drugs, such as Alteplase (Activase) and interleukin-2 (Proleukin) (see Table 18-1), also have half-lives of the order of a few minutes. However, if immediate stability or immunogenicity concerns can be remedied by chemical modification or bioengineering, the biopharmaceutical may be large enough to escape glomerular filtration and enjoy a prolonged circulation in the body (see Table 18-1). In addition, since biologics are typically eliminated from the body by noncytochrome-mediated mechanisms, drug–drug interactions with small molecule drugs are less likely to occur.

The size and generally hydrophilic nature of the nucleic acid and protein molecules also often preclude the use of diffusional and paracellular transport pathways available to small drug molecules. The capillary wall in most organs and tissues limits passage of macromolecules such as albumin. A typical vector is 20 to 150 nm, and monoclonal antibodies are composed of four polypeptide chains (over 1200 amino acids total). Such compounds would be expected to have limited diffusional access to most tissues, except the liver, spleen, bone marrow, and tumor tissues, which have higher vascular permeability. As a result, the volume of drug distribution is often smaller for the larger protein and nucleic acid drugs because of vascular confinement or binding to specific tissues. Indeed, the volume of distribution for some of these drugs approximates plasma volume: the apparent volume of distribution at steady state of the mAb Nebacumab is 0.11 ± 0.03 L/kg (Romano et al, 1993), and of Simulect is approximately 7.5 L.

Because of the stability and distribution limitations of large biologic drugs, delivery systems such as conjugates, nanoparticles, liposomes, and viral vectors as described above have been used to improve activity and delivery. The pharmacokinetics of recombinant viral gene delivery systems has been difficult to measure because of the relatively low doses given and often inefficient transgene expression. As a result, gene expression and transgene persistence in tissues are used to determine pharmacokinetic profiles (NIH Report, 2002). Nonviral and naked DNA delivery systems are relatively well characterized in comparison to viral delivery systems. Hengge et al (2001), using polymerase chain reaction (PCR), demonstrate that intramuscular or cutaneous injection of a DNA vaccine resulted in
gene expression primarily in surrounding tissues unless extremely high doses were administered. Nomura et al (1998) similarly showed that intratumoral injection of plasmid complexed with cationic lipid resulted in primarily local expression.

Liposome delivery systems are fairly well characterized in terms of their pharmacokinetic properties. Liposome encapsulation may reduce the $V_D$ (Minchin et al, 2001), and may (Houk et al, 2001) or may not (Minchin et al, 2001) improve upon DNA half-life by several hours. However, lipid delivery systems are also rapidly cleared by the mononuclear phagocyte system (spleen and liver) unless injected intratumorally (Nomura et al, 1997). In addition, liposomes may enhance an immune response to the drug and complement activation, also resulting in rapid clearance.

Alternatively, liposomes can be designed to evade phagocyte detection and improve circulation time by coating with polyethylene glycol (PEG), which minimizes opsonin-dependent clearance. In vivo, the PEG provides a “bulky” headgroup that serves as a barrier to prevent interaction with the plasma opsonins. The hydrated groups sterically inhibit hydrophobic and electrostatic interaction of a variety of blood components at the liposome surface, thereby evading recognition by the reticuloendothelial system. An example of this concept is the Stealth liposome, which led to the marketing of the PEGylated liposomal doxorubicin Doxil in the United States. Liposomal PEGylation can reduce the volume of distribution and extend the half-life of a drug such as doxorubicin (Gabizon et al, 2003). Optimal formulation of a PEGylated liposome can improve liposome stability from 1% to 31% of dose remaining in the body at 24 hours postinjection (Allen et al, 2002).

The pharmacokinetics of a liposomal formulation can be different from those of a nonliposomal product given by the same route of administration. For new liposome products, the FDA (draft document, see www.fda.gov/cder/guidance/2191dft.pdf) recommends a comparative mass balance study be performed to assess the differences in systemic exposure and pharmacokinetics between liposome and nonliposome drug products when (1) the two products have the same active moiety, (2) the two products are given by the same route of administration, and (3) one of the products is already approved for marketing. If satisfactory mass balance information is already available for the approved drug product, a limited mass balance study can be undertaken for the new drug product. Comparison of the absorption, distribution, metabolism, and excretion (ADME) of the liposome and nonliposome drug product forms should be made, using a crossover or a parallel noncrossover study design that employs an appropriate number of subjects.

### BIOEQUIVALENCE AND COMPARABILITY OF BIOTECHNOLOGY-DERIVED DRUG PRODUCTS

The dosage form or formulation of a drug product may change during the course of drug development and after drug approval (see also Chapter 16). For biotechnology-derived drugs, the drug product quality (including number and type of contaminants) and product microheterogeneities (eg, degree of glycosylation, post-translational modifications, genetic variants, etc) are a function of the manufacturing process and therefore, the manufacturing process must be highly controlled. Moreover, purification and the removal of impurities that might be antigenic can be problematic. The protein or nucleic acid drug itself will continue to evolve prior to approval of the biologics license agreement (BLA). The initial drug formulation used in early clinical studies (eg, Phase I/II) may not be the same formulation as the drug formulation used in later clinical trials (Phase III) or the marketed formulation. In addition, changes in the manufacturing process, equipment, or facilities could result in changes in the biological product itself and sometimes required additional clinical studies to demonstrate the product’s safety, identity, purity, and potency (FDA Guidance, 1996). It is recognized that even genetically “identical” recombinant drugs will

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1Biological products are approved for marketing via a Biologic License Application (BLA) under the provisions of the Public Health Service (PHS) Act. A biologics license application is a submission similar to a New Drug Application (NDA) and contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and the medical effects of the biologic product.
differ because of differences in variables such as cell, cell clone, manufacturing, purification and storage, formulation, expression system, and raw chemicals. Such variations may result in profound differences in bioavailability, immunogenicity, adverse reactions, and efficacy. Therefore, manufacturers of biopharmaceuticals need to perform comparability testing for manufacturing changes made prior to product approval and after product approval, from these tests, which may include a small clinical study, the manufacturer must demonstrate that drug product is the same before and after the manufacturing change.

**Biosimilars or Follow on Biologics**

After both patent expiration and any exclusivity period, manufacturers of small-molecular-weight drugs may make a generic drug product that is bioequivalent to the innovator or brand-drug product (see Chapter 15). In the past, the regulatory pathway for generic drug products in the FDA is only for small-molecular weight, well-characterized drugs. The scientific community and regulatory agencies are not in agreement as to the requirements for a generic biological drug product (Mordenti et al., 1997). Several interchangeable biologic drug products have been approved by the FDA (eg, somatropin recombinant, enoxaparin sodium). These products have been termed biosimilars or follow-on biologics. On March 21, 2010, the “Patient Protection and Affordable Care Act” was passed that allows generic biosimilars qualified to be approved based on interchangeability.

**CHAPTER SUMMARY**

Biologics (biotechnology-derived drugs or biopharmaceuticals) are larger and more complex molecules than conventional small-molecular-weight drug products. Since biopharmaceuticals are generally proteins, the formulation of the drug product must be properly designed and formulated to protect the stability of the biopharmaceuticals from degradation at the site of administration. Most biopharmaceuticals are given by injection. In addition, the biopharmaceuticals may be affected by the immune system, for example, attacked by antibodies or cells from the reticuloendothelial system. Special polymeric carriers or systems with targeting properties may be used to deliver the drug to desired sites in the body.

Targeted delivery systems may be more efficient and avoid unintended side effects if properly formulated. mAbs is a type of targeted drug delivery that has less potential for drug–drug interaction (DDI). However, some mAb-modified systems may have increased immunogenic potential. The indicated route of administration should be strictly followed to avoid unintended side effects. Due to the complexity of biotechnology-derived drugs and the importance of controlling the manufacturing and purification process, the development of interchangeable biosimilars or follow-on biologics is more difficult compared to small-molecular-weight drug products.
LEARNING QUESTIONS

1. Explain why most drugs produced by biotechnology cannot be given orally. What routes of drug administration would you recommend for these drugs? Why?

2. What is meant by site-specific drug delivery? Describe several approaches that have been used to target a drug to a specific organ.

3. Doxorubicin (Adriamycin) is available as a conventional solution and as a liposomal preparation. What effect would the liposomal preparation have on the distribution of doxorubicin compared to an injection of the conventional doxorubicin injection?

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Chapter Objectives

- Quantitatively describe the relationship between drug, receptor, and the pharmacologic response.
- Explain why the intensity of the pharmacologic response increases with drug concentrations and/or dose up to a maximum response.
- Explain the difference between an agonist, a partial agonist, and an antagonist.
- Describe the difference between a reversible and a non-reversible pharmacologic response.
- Define the term biomarker and explain how biomarkers may be used in the clinical development of drugs.
- Show how the \( E_{\text{max}} \) and sigmoidal \( E_{\text{max}} \) model describe the relationship of the pharmacodynamic response to drug concentration.
- Define the term pharmacokinetic–pharmacodynamic model and provide an equation that quantitatively simulates the time course of drug action.
- Explain the effect compartment in the pharmacodynamic model and name the underlying assumptions.

**PHARMACODYNAMICS AND PHARMACOKINETICS**

In the previous chapters, pharmacokinetics was used to develop dosing regimens for achieving therapeutic drug concentrations for optimal safety and efficacy. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events, resulting in a pharmacodynamic or pharmacologic response. The term pharmacodynamics refers to the relationship between drug concentrations at the site of action (receptor) and pharmacologic response. Pharmacodynamics includes the biochemical and physiologic effects that result from the interaction of the drug with the receptor. Early pharmacologic research demonstrates that the pharmacodynamic response produced by the drug depends on the chemical structure of the drug molecule and the affinity of the drug at the receptor site. The drug affinity for the receptor site and the resultant pharmacodynamic response is referred to as the intrinsic activity of the drug. Drug receptors interact only with drugs of specific chemical structure, and the receptors are classified according to the type of pharmacodynamic response induced. Drugs may be considered a full agonist, partial agonist, or antagonist, depending upon the type of drug interaction with the receptor and the resulting pharmacodynamic response (see discussion below).

**Drug Receptor and Occupancy Concept**

Drugs may react with receptors to form covalent or noncovalent bonds. Drugs that form covalent bonds with the receptor produce a nonreversible pharmacodynamic response. Most pharmacologic responses are due to weak, noncovalent bonds (eg, hydrogen bonding, ionic electrostatic bonds, van der Waals forces) between the drug and the receptor. These interactions between drug and receptor are assumed to be reversible and to conform to the law of mass action. One or more drug molecules may interact simultaneously with the receptor to produce a pharmacologic response. Typically, a single drug molecule interacts with a receptor with a
Describe the effect of changing drug dose and/or drug elimination half-life on the duration of drug response.

Describe how observed drug tolerance or unusual hysteresis-type drug response may be explained using PD models based on simple drug receptor theory.

Define the term drug exposure and explain how it is used to improve drug therapy and safety.

Describe the relationship between therapeutic response and systemic exposure for an anticancer drug.

single binding site to produce a pharmacologic response, as illustrated below.

\[
[\text{Drug}] + [\text{receptor}] \Leftrightarrow [\text{drug–receptor complex}] \rightarrow \text{response}
\]

where the brackets [ ] denote molar concentrations.

This scheme illustrates the occupation theory for the interaction of a drug molecule with a receptor molecule. More recent schemes consider a drug that binds to macromolecules as a ligand. Thus, the reversible interaction of a ligand (drug) with a receptor may be written as (Neubig et al, 2003).

\[
L + R \xrightleftharpoons[k_{-1}]{k_{1}} LR \xrightarrow{k_{2}} LR^{*}
\]

where \( L \) is generally referred to as ligand concentration (since many drugs are small molecules) and \( LR \) is analogous to the [drug–receptor complex]. \( LR^{*} \) is the activated form which results in the effect.

The last step is written to accommodate different modes of how \( LR \) leads to a drug effect. For example, the interaction of a subsequent ligand with the receptor may involve a conformation change of the receptor or simply lead to an additional effect. In this chapter, effect and response are used interchangeably.

This model makes the following assumptions:

1. The drug molecule combines with the receptor molecule as a bimolecular association, and the resulting drug–receptor complex disassociates as a unimolecular entity.
2. The binding of drug with the receptor is fully reversible.
3. The basic model assumes a single type of receptor binding site, with one binding site per receptor molecule. It is also assumed that a receptor with multiple sites may be modeled after this (Taylor and Insel, 1990).
4. The occupancy of the drug molecule at one receptor site does not change the affinity of more drug molecules to complex at additional receptor sites.

Each receptor has equal affinity for the drug molecule. The model is not suitable for drugs with allosteric binding to receptors, in which the binding of one drug molecule to the receptor affects the binding of subsequent drug molecules, as in the case of oxygen molecules binding to iron in hemoglobin. As more receptors are occupied by drug molecules, a greater pharmacodynamic response is obtained until a maximum response is reached.

The receptor occupancy concept was extended to show how drugs elicit a pharmacologic response as an agonist, or block the pharmacologic response as an antagonist through drug–receptor interactions. Basically, three types of related responses may occur.
at the receptor: (1) a drug molecule that interacts with the receptor and elicits a maximal pharmacologic response is referred to as an agonist; (2) a drug that elicits a partial (below maximal) response is termed a partial agonist; and (3) an agent that elicits no response from the receptor, but inhibits the receptor interaction of a second agent, is termed an antagonist. An antagonist may prevent the action of an agonist by competitive (reversible) or noncompetitive (irreversible) inhibition. A few drugs (eg, pento- zocine) have mixed agonist-antagonist activity in that the initial drug binding to a receptor produces a pharmacologic effect followed by blocking the receptor from eliciting additional pharmacologic activity.

Spare, unoccupied receptors are assumed to be present at the site of action, because a maximal pharmacologic response may be obtained when only a small fraction of the receptors are occupied by drug molecules. Equimolar concentrations of different drug molecules that normally bind to the same receptor may give different degrees of pharmacologic response. The term intrinsic activity is used to distinguish the relative extent of pharmacologic response between different drug molecules that bind to the same receptor. The potency of a drug is the concentration of drug needed to obtain a specific pharmacologic effect, such as the EC<sub>50</sub> (see <em>E<sub>max</sub></em> model, below).

The receptor occupation theory, however, was not consistent with all kinetic observations. An alternative theory, known as the rate theory, essentially states that the pharmacologic response is not dependent on drug–receptor complex concentration but rather depends on the rate of association of the drug and the receptor. Each time a drug molecule combines with a receptor, a response is produced, similar to a ball bouncing back and forth, to and from the receptor site. The rate theory predicts that an agonist will associate rapidly to form a receptor complex, which dissociates rapidly to produce a response. An antagonist associates rapidly to form a receptor–drug complex and dissociates slowly to maintain the antagonist response.

Both theories are consistent with the observed saturation (sigmoidal) drug–dose response relationships, but neither theory is sufficiently advanced to give a detailed description of the “lock-and-key” or the more recent “induced-fit” type of drug interactions with enzymatic receptors. Newer theories of drug action are based on in vitro studies on isolated tissue receptors and on observation of the conformational and binding changes with different drug substrates. These in vitro studies show that other types of interactions between the drug molecule and the receptor are possible. However, the results from the in vitro studies are difficult to extrapolate to in vivo conditions. The pharmacologic response in drug therapy is often a product of physiologic adaptation to a drug response. Many drugs trigger the pharmacologic response through a cascade of enzymatic events highly regulated by the body.

Unlike pharmacokinetic modeling, pharmacodynamic modeling can be more complex because the clinical measure (change in blood pressure or clotting time) is often a surrogate for the drug’s actual pharmacologic action. For example, after the drug is systemically absorbed, it is then transported to site of action where the pharmacologic receptor resides. Drug-receptor binding may then cause a secondary response, such as signal transduction, which then produces the desired effect. Clinical measurement of drug response may only occur after many such biologic events, such as transport or signal transduction (an indirect effect), so pharmacodynamic modeling must account for biologic processes involved in eliciting drug-induced responses.

The complexity of the molecular events triggering a pharmacologic response is less difficult to describe using a pharmacokinetic approach. Pharmacokinetic models allow very complex processes to be simplified. The process of pharmacokinetic modeling continues until a model is found that describes the real process quantitatively. The understanding of drug response is greatly enhanced when pharmacokinetic modeling techniques are combined with clinical pharmacology, resulting in the development of pharmacokinetic–pharmacodynamic models. Pharmacokinetic–pharmacodynamic models use data derived from the plasma drug concentration-versus-time profile and from the time course of the pharmacologic effect to predict the pharmacodynamics of the drug. Pharmacokinetic–pharmacodynamic models have been reported for antipsychotic medications, anticoagulants, neuromuscular blockers, anti hypertensives, anesthetics, and many antiarrhythmic drugs (the pharmacologic
responses of these drugs are well studied because of easy monitoring).

**Drug Receptors**

The best-characterized drug receptors are regulatory proteins, which mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones. Other protein receptors are endogenous enzymes, which may be inhibited or activated by binding to a drug. For example, the enzyme dihydrofolate reductase is the receptor for the antineoplastic drug methotrexate. The transport protein could also be a class of receptor (e.g., Na+/K+ ATPase, the membrane receptor for cardioactive digitalis glycosides).

Various types of drug receptors and pharmacologic responses are described by Katzung et al (2009, Goodman & Gilman, 2006) and quantitative models for many are reviewed by Neubig et al (2003). A simple pharmacologic response measured may be perceived as the result of many receptors and biological processes working together. The whole series of events may be the interplay of (1) pharmacologic response due to drug–receptor interaction, (2) physiologic or compensatory action or adjustment by the body, (3) pharmacogenetics that modify the drug response, and (4) alteration in biological responses due to an intervention by a pathogenic process. A comprehensive model incorporating all aspects is ideally best but may be too complicated to measure and validate in practice. An alternative approach is the monitoring of a biologic marker(s) in which the events in the biological processes may be observed directly or indirectly. The general approach for applying markers or biomarkers in pharmacodynamics is deeply rooted in pharmacology and pharmacokinetics and is illustrated by the modeling of various drugs shown in this chapter. Biomarkers broadly include markers that characterize the disease and the physical/biological changes associated with its progress in or drug treatment response in the body. During drug development, biomarkers developed with appropriate PD models can greatly increase understanding of drug therapy as well as the underlying disease.

Unlike pharmacokinetic modeling, pharmacodynamic modeling has a greater advantage in that the clinical response (e.g., change in blood pressure or clotting time) is affected by disposition of the drug as well as many events at the receptor site that may modulate actual pharmacologic action. In a simple case, drug that is systemically absorbed is transported to the site of action (receptor site) in which the pharmacologic receptor resides. Drug–receptor binding may occur, causing a response directly or through signal transduction that leads to the response. Observation of a drug response may involve several biologic steps as listed above and therefore, pharmacodynamic modeling must quantitatively account for all the processes involved to be useful.

**Pharmacodynamic (PD) models** involve complex mechanisms that may not be easily simplified. Earlier PD models in this chapter are empirical models since the pharmacodynamic mechanisms were not well understood. Empirical models may help eliminate an unlikely pharmacokinetic mechanism. Generally, PK–PD models should be mechanism based whenever possible for simulations to be predictive. The understanding of drug response is greatly enhanced when pharmacokinetic modeling techniques are combined with clinical pharmacology, resulting in the development of mechanism-based pharmacokinetic–pharmacodynamic models. Pharmacokinetic–pharmacodynamic models use data derived from the plasma drug concentration-versus-time profile and from the time course of the pharmacologic effect to predict the pharmacodynamics of the drug. Pharmacokinetic–pharmacodynamic models have been reported for virtually every category of drugs. Examples in this chapter include antipsychotics, anticoagulants, neuromuscular blockers, antihypertensives, antiinfectives, and sedatives.

The relationship between drug response and pharmacokinetics of many drugs may be explained in simple models. The computer model–simulated response based on assumptions should be distinguished from those models that are based on results obtained from clinical trials. These models are far more sophisticated and objective. Clinical effects in drug development are usually well defined, multicentered, and may be performed with special patient inclusion/exclusion criteria, subject size, controls, and other considerations as described in the clinical study protocols. The FDA publishes regulatory
guidances that describe various aspects of e-study design and data analysis. Pharmacodynamics is indispensable for understanding drug receptors and disease state variables. Disease progress and drug therapy are both intimately related to pharmacokinetics (Chapter 12).

**Biomarkers (BM), Pharmacodynamics (PD), and Clinical Endpoints (CE)**

Biomarkers have been used to monitor biologic or genetic changes associated with the progress of a disease or a pharmacologic action.¹ Biomarkers may include gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others. For pharmacodynamic modeling of a drug, the biomarker (BM) selected should ideally indicate the biological/pathological process(es) and/or pharmacological response(s) modified due to the therapeutic intervention.

A biomarker is measured objectively and specifically evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. A biomarker can also define a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function. Data from genomic and proteomics differentiating healthy versus disease states can therefore lead to the discovery of new biomarkers. Rational use of BMs can accelerate drug development and decision making and can provide a bridge between mechanistic preclinical studies and empiric clinical testing. The development of BM science including its definition has evolved during the last two decades (Lesko and Atkinson, 2001; Rolan et al 2003; Colburn and Lee, 2003). The use of BMs may be defined and developed by different disciplines to address special needs (FDA draft guidance, 2011).

During drug development, clinical data and special markers also may be developed to demonstrate safety and efficacy. Clinical endpoints (CE) measure how patients feel, function, or survive. Since clinical endpoint data may be somewhat subjective, the CE (eg, pain) is often categorized (eg, using a 0–5 scale) to reflect the intensity of the feeling for quantitation. These clinical observations or treatment results may be partly or totally related to a BM. The surrogate markers (SM) or surrogate endpoints may be more objective and are designed to replace CE for efficacy and/or toxicity under a set of well-defined criteria. Clinically, few biomarkers are developed as surrogate endpoints due to the complexity of the disease. For example, the surrogate endpoints blood pressure and serum cholesterol concentrations may be used in evaluation of cardiovascular drugs (Temple, 1999). For example, the most widely used surrogate biomarkers are plasma concentrations of drugs that reflect systemic exposure to drug including bioavailability, bioequivalence, and pharmacokinetic guide for dosage regimens in clinical practice (eg, therapeutic drug monitoring).

Biomarkers may reduce uncertainty in drug development and evaluation by providing quantitative predictions about drug performance, and with PK–PD modeling simulation, can play a critical role in the drug development process. Biomarkers are broadly used to follow disease or drug treatment effects over time and thus are important for understanding drug mechanism (Lesko and Atkinson 2001; Rolan et al, 2003). However, because the range of biologic measurements that can be considered biomarkers is now so broad, some classification and stratification are needed to provide an understanding of what types of biologic measurements are used for which purposes. The following mechanistic classification of BMs was cited by the International committee on BM (Rolan et al, 2003) (Table 19-1).

**Clinical Considerations in the Use of Biomarkers**

Most biomarkers are endogenous macromolecules, which are measured *in vivo* in biological fluids. However, not all biomarkers reflect *in vivo* processes (Stern et al, 2003). To be most informative in drug development, a biomarker assay or assays should measure *in vivo* drug effects, *not* drug concentrations. Stern et al (2003) cited an example involving phosphate and...
the clotting time and activated partial thromboplastin time measured for ecarin. These coagulation tests that seemingly meet the definition of a biomarker by prolongation of the coagulation times closely correlated with blood concentrations of the oral thrombin inhibitor. However, these tests reflect enzyme inhibition assays as a function of drug concentration. Changes in coagulation test results demonstrate only that \textit{ex vivo} clot formation has been altered but do not indicate that an \textit{in vivo} process has been affected. Reliable and selective assays could be validated under a GLP-like environment for quantitative methods (Colburn and Lee, 2003).

In early-phase clinical drug development, biomarkers may be used to guide dose selection and escalation. For a few drugs, well-characterized pharmacokinetic–pharmacodynamic (PK–PD) relationships can support, without further clinical data, therapeutic potential in a new target population, or justification for a different formulation or dosing regimen. Several considerations are important for BM selection to improve drug development based on Colburn and Lee (2003): (1) mechanism-based biomarker selection and correlation to clinical endpoints; (2) quantification of drug and/or metabolites in biological fluids under good laboratory practices (GLP); (3) GLP-like biomarker method validation and measurements; and (4) mechanism-based PK/PD modeling and validation.

Changes in biomarkers following drug treatment may predict or identify safety problems related to a drug candidate or reveal a pharmacological activity expected to predict an eventual benefit from treatment. These measurements may be related to the mechanism of response to treatments or may be useful to evaluate the therapeutic response or clinical benefit endpoints. According to some scientists (Temple, 1999; Lesko and Atkinson, 2001), biomarkers:

- May be valid surrogates for clinical benefit (eg, blood pressure, cholesterol, viral load)
- May reflect the pathologic process and be at least candidate surrogates (eg, brain appearance in Alzheimer’s disease, brain infarct size, various radiographic/isotopic function tests)
- Reflect drug action but are of uncertain relation to clinical outcome (eg, inhibition of ADP-dependent platelet aggregation, ACE inhibition)

A pharmacodynamic biomarker may be described as a dynamic assessment that shows that a biological response has occurred in a patient after receiving a drug for treatment. A pharmacodynamic biomarker may be treatment-specific or more broadly informative of disease response. Examples include blood pressure, cholesterol, HbA1C, intraocular pressure, radiographic measures, and C-reactive protein. However, even if carefully chosen, BMs may fail to become surrogate endpoints.

### Pharmacogenomic Biomarkers in Drug Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels (FDA 2011) may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

### Drug Receptors and the Development of Pharmacokinetic–Pharmacodynamic (PK–PD) Models

The description of drug receptors was historically based on observations of drug response using known
drug agonists and antagonists. From both these drug response observations and from pharmacokinetic data, PK–PD models were developed to describe quantitative relationships. Advances in molecular biology now allow the molecular structures of many drug receptors to be characterized and their locations elucidated (Katzung et al, 2009). Receptors are generally protein or macromolecules located inside or outside cell membranes. A tabulation of various receptors is listed in Table 19-2.

Receptors are responsible for selectivity of drug action. The nature of the receptors determines the quantitative relationship between the drug dose or drug concentration and the pharmacologic effect. This relationship is an important basis for PD. The receptor’s affinity for drug binding and the total number of receptors available determine the concentration of drug required to exert a PD response and the number of drug–receptor complexes which may limit the attainment of a maximal effect. This relationship forms the basis of the $E_{\text{max}}$ model discussed in later sections of this chapter.

The molecular size, shape, and electrical charge of a drug determine whether a drug will bind to a particular receptor among the vast number of chemically and structurally different binding sites in a cell, tissue, or patient. The drug may be referred to as a ligand when the drug binds a macromolecule or as a substrate when the receptor is an enzyme. An adverse drug reaction can occur when a drug interacts with different, unintended receptors, thus affecting therapeutic efficacy and toxic effects. The drug’s relationship to drug receptor binding explains drug classes such as agonists, partial agonists, and antagonists. Elucidating this relationship also greatly helps the development of new drug therapies. Drugs may be designed to mimic or reproduce natural ligands, such as hormones and neurotransmitters.

### Table 19-2  Selected Examples of Drug Receptors

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channels</td>
<td>Located on cell surface or transmembrane; governs ion flux</td>
<td>Acetylcholine (nicotinic)</td>
</tr>
</tbody>
</table>
| G-protein coupled receptor| Located on cell surface or transmembrane; GTP involved in receptor action | Acetylcholine (muscarinic)  
|                           |                                                  | $\alpha$- and $\beta$-Adrenergic receptor Proteins  
|                           |                                                  | Eicosanoids                                   |
| Transcription factors     | Within cell in cytoplasm, activate or suppress DNA transcription | Steroid hormones  
|                           |                                                  | Thyroid hormone                               |


Pharmacokinetic–Pharmacodynamic (PK–PD) Models

As discussed, PK–PD models relate the pharmacological effect of a drug to the log concentration of the drug in the plasma or in other body fluids close to the receptor site. The model equations created predict the time course of drug action and help to more accurately estimate a therapeutic dosage regimen for the patient. Similarly, the PK–PD model may relate drug concentrations to side effects or adverse events, such as the reduction of QT interval or slowing of repolarization of the heart due to side effects of some drugs such as torsades de pointes. The association between torsades and a prolonged
QT interval has long been known. Common drugs such as erythromycin, clarithromycin, terfenadine, and some antihistamines may cause prolongation of the QT interval without necessarily causing overt clinical problems. PK–PD models can provide a much better understanding of how the mechanism of the drug acts and improves safety of these drugs. For either new or newly approved drugs, clinical information may be limited until adequate Phase 4 studies are completed. Phase 4 post marketing studies provide more information on the incidence of side effects and drug efficacy in various subpopulations. Mechanistic studies of a drug often reveal that there are biological changes as measured using biomarkers in the body associated with drug use.

During PK–PD modeling, it is important to describe the following prospectively:

1. **Statement of the Problem**
   The objectives of modeling, the study design, and the available PK and PD data

2. **Statement of Assumptions**
   The assumptions of the model regarding dose-response, PK, PD, and/or one or more of the following:
   - The mechanism of the drug actions for efficacy and adverse effects
   - Immediate or cumulative clinical effects
   - Development or absence of tolerance
   - Drug-induced inhibition or induction of PK processes
   - Disease state progression
   - Response in a placebo group

### RELATIONSHIP OF DOSE TO PHARMACOLOGIC EFFECT

The onset, intensity, and duration of the pharmacologic effect depend on the dose and the pharmacokinetics of the drug. As the dose increases, the drug concentration at the receptor site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum effect at the plateau (Fig. 19-1). The same data may be compressed and plotted on a log–linear scale and results in a sigmoid curve (Fig. 19-2).

For many drugs, the graph of the log dose–response curve shows a linear relationship at a dose range between 20% and 80% of the maximum response, which typically includes the therapeutic dose range for many drugs. For a drug that follows one-compartment pharmacokinetics, the volume of distribution is constant; therefore, the pharmacologic response is also proportional to the log plasma drug concentration within a therapeutic range, as shown in Fig. 19-3.

Mathematically, the relationship in Fig. 19-3 may be expressed by the following equation, where \( m \) is the slope, \( e \) is an extrapolated intercept, and \( E \) is the drug effect at drug concentration \( C \):

\[
\text{Drug dose} \quad \frac{\text{Pharmacologic response}}{A \text{ small increase in response occurs by a given dose change in this region}}
\]

\[
\text{Max response}
\]

**FIGURE 19-1** Plot of pharmacologic response versus dose on a linear scale.

**FIGURE 19-2** Typical log dose versus pharmacologic response curve.
Relationship Between Pharmacokinetics and Pharmacodynamics

\[ E = m \log C + e \]  
(19.1)

Solving for \( \log C \) yields

\[ \log C = \frac{E - e}{m} \]  
(19.2)

However, after an intravenous dose, the concentration of a drug in the body in a one-compartment open model is described as follows:

\[ \log C = \log C_0 - \frac{kt}{2.3} \]  
(19.3)

By substituting Equation 19.2 into Equation 19.3, we get Equation 19.4, where \( E_0 = \) effect at concentration \( C_0 \):

\[ \frac{E - e}{m} = \frac{E_0 - e - kt}{m} \]  
(19.4)

\[ E = E_0 - \frac{kmt}{2.3} \]

The theoretical pharmacologic response at any time after an intravenous dose of a drug may be calculated using Equation 19.4. Equation 19.4 predicts that the pharmacologic effect will decline linearly with time for a drug that follows a one-compartment model, with a linear log dose–pharmacologic response. From this equation, the pharmacologic effect declines with a slope of \( km/2.3 \). The decrease in pharmacologic effect is affected by both the elimination constant \( k \) and the slope \( m \). For a drug with a large \( m \), the pharmacologic response declines rapidly and multiple doses must be given at short intervals to maintain the pharmacologic effect.

The relationship between pharmacokinetics and pharmacologic response can be demonstrated by observing the percent depression of muscular activity after an IV dose of \( \pm \) tubocurarine. The decline of pharmacologic effect is linear as a function of time (Fig. 19-4). For each dose and resulting pharmacologic response, the slope of each curve is the same. Because the values for each slope, which include \( km \) (Equation 19.4), are the same, the sensitivity of the receptors for \( \pm \) tubocurarine is assumed to be the same at each site of action. Note that a plot of the log concentration of drug versus time yields a straight line.

A second example of the pharmacologic effect declining linearly with time was observed with lysergic acid diethylamide, or LSD (Fig. 19-5). After an IV dose of the drug, log concentrations of drug decreased linearly with time except for a brief distribution period. Furthermore, the pharmacologic effect, as measured by the performance score of each subject, also declined linearly with time. Because the slope is governed in part by the elimination rate constant, the pharmacologic effect declines much more
rapidly when the elimination rate constant is increased as a result of increased metabolism or renal excretion. Conversely, a longer pharmacologic response is experienced in patients when the drug has a longer half-life.

**RELATIONSHIP BETWEEN DOSE AND DURATION OF ACTIVITY (t_{eff}), SINGLE IV BOLUS INJECTION**

The relationship between the duration of the pharmacologic effect and the dose can be inferred from Equation 19.3. After an intravenous dose, assuming a one-compartment model, the time needed for any drug to decline to a concentration C is given by the following equation, assuming the drug takes effect immediately:

\[ t = \frac{2.3 (\log C_0 - \log C)}{k} \]  \hspace{1cm} (19.5)

Using \( C_{eff} \) to represent the minimum effective drug concentration, the duration of drug action can be obtained as follows:

\[ t_{eff} = \frac{2.3 [\log (D/V_D) - \log C_{eff}]}{k} \]  \hspace{1cm} (19.6)

Some practical applications are suggested by this equation. For example, a doubling of the dose will not result in a doubling of the effective duration of pharmacologic action. On the other hand, a doubling of \( t_{1/2} \) or a corresponding decrease in \( k \) will result in a proportional increase in duration of action. A clinical situation is often encountered in the treatment of infections in which \( C_{eff} \) is the bacteriocidal concentration of the drug, and, in order to double the duration of the antibiotic, a considerably greater increase than simply doubling the dose is necessary.

**PRACTICE PROBLEM**

The minimum effective concentration (MEC or Ceff) in plasma for a certain antibiotic is 0.1 \( \mu \)g/mL. The drug follows a one-compartment open model and has an apparent volume of distribution, \( V_D \), of 10 L and a first-order elimination rate constant of 1.0 h^{-1}.

a. What is the \( t_{eff} \) for a single 100-mg IV dose of this antibiotic?

b. What is the new \( t_{eff} \) or \( t'_{eff} \) for this drug if the dose were increased 10-fold, to 1000 mg?

**Solution**

a. The \( t_{eff} \) for a 100-mg dose is calculated as follows. Because \( V_D = 10,000 \) mL,

\[ C_0 = \frac{100 \text{ mg}}{10,000 \text{ mL}} = 0.01 \mu \text{g/mL} \]
For a one-compartment-model IV dose, $C = C_0 e^{-kt}$. Then,

$$0.1 = 10 e^{-1.0\text{t}_{\text{eff}}}$$

$$t_{\text{eff}} = 4.61 \text{h}$$

b. The $t'_{\text{eff}}$ for a 1000-mg dose is calculated as follows (prime refers to a new dose). Because $V_D = 10,000 \text{mL}$,

$$C'_0 = \frac{1000 \text{mg}}{10,000 \text{mL}} = 100 \mu\text{g/mL}$$

and

$$C'_{\text{eff}} = C'_0 e^{-k't_{\text{eff}}}$$

$$0.1 = 100 e^{-1.00't'_{\text{eff}}}$$

$$t'_{\text{eff}} = 6.91 \text{h}$$

The percent increase in $t_{\text{eff}}$ is therefore found as

$$\text{Percent increase in } t_{\text{eff}} = \frac{t'_{\text{eff}} - t_{\text{eff}}}{t_{\text{eff}}} \times 100$$

Percent increase in $t_{\text{eff}} = \frac{6.91 - 4.61}{4.61} \times 100$

Percent increase in $t_{\text{eff}} = 50\%$

This example shows that a 10-fold increase in the dose increases the duration of action of a drug ($t_{\text{eff}}$) by only 50%.

**EFFECT OF BOTH DOSE AND ELIMINATION HALF-LIFE ON THE DURATION OF ACTIVITY**

A single equation can be derived to describe the relationship of dose ($D_0$) and the elimination half-life ($t_{1/2}$) on the effective time for therapeutic activity ($t_{\text{eff}}$). This expression is derived below.

$$\ln C_{\text{eff}} = \ln \left( \frac{D_0}{V_D} \right) - kt_{\text{eff}}$$

$$kt_{\text{eff}} = \ln \left( \frac{D_0}{V_D} \right) - \ln C_{\text{eff}} \quad (19.7)$$

$$t_{\text{eff}} = \frac{1}{k} \ln \left( \frac{D_0}{V_D C_{\text{eff}}} \right) \quad (19.8)$$

Substituting $0.693/t_{1/2}$ for $k$,

$$t_{\text{eff}} = 1.44 t_{1/2} \ln \left( \frac{D_0}{V_D C_{\text{eff}}} \right)$$

From Equation 19.8, an increase in $t_{1/2}$ will increase the $t_{\text{eff}}$ in direct proportion. However, an increase in the dose, $D_0$, does not increase the $t_{\text{eff}}$ in direct proportion. The effect of an increase in $V_D$ or $C_{\text{eff}}$ can be seen by using generated data. Only the positive solutions for Equation 19.8 are valid, although mathematically a negative $t_{\text{eff}}$ can be obtained by increasing $C_{\text{eff}}$ or $V_D$. The effect of changing dose on $t_{\text{eff}}$ is shown in Fig. 19-6 using data generated with Equation 19.8. A nonlinear increase in $t_{\text{eff}}$ is observed as dose increases.

**EFFECT OF ELIMINATION HALF-LIFE ON DURATION OF ACTIVITY**

Because elimination of drugs is due to the processes of excretion and metabolism, an alteration of any of these elimination processes will affect the $t_{1/2}$ of the drug. In
certain disease states, pathophysiologic changes in hepatic or renal function will decrease the elimination of a drug, as observed by a prolonged \( t_{1/2} \). This prolonged \( t_{1/2} \) will lead to retention of the drug in the body, thereby increasing the duration of activity of the drug (\( t_{eff} \)) as well as increasing the possibility of drug toxicity.

To improve antibiotic therapy with the penicillin and cephalosporin antibiotics, clinicians have intentionally prolonged the elimination of these drugs by giving a second drug, probenecid, which competitively inhibits renal excretion of the antibiotic. This approach to prolonging the duration of activity of antibiotics that are rapidly excreted through the kidney has been used successfully for a number of years. Similarly, Augmentin is a combination of amoxicillin and clavulanic acid; the latter is an inhibitor of \( \beta \)-lactamase. This \( \beta \)-lactamase is a bacterial enzyme that degrades penicillin-like drugs. The data in Table 19-3 illustrate how a change in the elimination \( t_{1/2} \) will affect the \( t_{eff} \) for a drug. For all doses, a 100% increase in the \( t_{1/2} \) will result in a 100% increase in the \( t_{eff} \). For example, for a drug whose \( t_{1/2} \) is 0.75 hour and that is given at a dose of 2 mg/kg, the \( t_{eff} \) is 3.24 hours. If the \( t_{1/2} \) is increased to 1.5 hours, the \( t_{eff} \) is increased to 6.48 hours, an increase of 100%. However, the effect of doubling the dose from 2 to 4 mg/kg (no change in elimination processes) will only increase the \( t_{eff} \) to 3.98 hours, an increase of 22.8%. The effect of prolonging the elimination half-life has an extremely important effect on the treatment of infections, particularly in patients with high metabolism, or clearance, of the antibiotic. Therefore, antibiotics must be dosed with full consideration of the effect of alteration of the \( t_{1/2} \) on the \( t_{eff} \). Consequently, a simple proportional increase in dose will leave the patient’s blood concentration below the effective antibiotic level most of the time during drug therapy. The effect of a prolonged \( t_{eff} \) is shown in lines \( a \) and \( c \) in Fig. 19-7.

### Table 19-3  Relationship between Elimination Half-Life and Duration of Activity

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>( t_{1/2} = 0.75 \text{ h} )</th>
<th>( t_{eff} ) (h)</th>
<th>( t_{1/2} = 1.5 \text{ h} )</th>
<th>( t_{eff} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>3.24</td>
<td>6.48</td>
<td>4.22</td>
<td>8.45</td>
</tr>
<tr>
<td>3.0</td>
<td>3.67</td>
<td>7.35</td>
<td>4.42</td>
<td>8.84</td>
</tr>
<tr>
<td>4.0</td>
<td>3.98</td>
<td>7.97</td>
<td>4.59</td>
<td>9.18</td>
</tr>
<tr>
<td>5.0</td>
<td>4.22</td>
<td>8.45</td>
<td>4.73</td>
<td>9.47</td>
</tr>
<tr>
<td>6.0</td>
<td>4.42</td>
<td>8.84</td>
<td>4.86</td>
<td>9.72</td>
</tr>
<tr>
<td>7.0</td>
<td>4.59</td>
<td>9.18</td>
<td>4.97</td>
<td>9.95</td>
</tr>
<tr>
<td>8.0</td>
<td>4.73</td>
<td>9.47</td>
<td>5.08</td>
<td>10.2</td>
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<tr>
<td>9.0</td>
<td>4.86</td>
<td>9.72</td>
<td>5.17</td>
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<tr>
<td>10</td>
<td>4.97</td>
<td>9.95</td>
<td>5.26</td>
<td>10.5</td>
</tr>
<tr>
<td>11</td>
<td>5.08</td>
<td>10.2</td>
<td>5.34</td>
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<td>10.5</td>
<td>5.48</td>
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<td>10.7</td>
<td>5.55</td>
<td>11.1</td>
</tr>
<tr>
<td>15</td>
<td>5.41</td>
<td>10.8</td>
<td>5.61</td>
<td>11.2</td>
</tr>
<tr>
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<td>5.67</td>
<td>11.3</td>
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<td></td>
</tr>
<tr>
<td>20</td>
<td>5.72</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 19-7**  Plasma level–time curves describing the relationship of both dose and elimination half-life on duration of drug action. \( C_{eff} \) = effective concentration. Curve \( a \) = single 100-mg IV injection of drug; \( k = 1.0 \text{ h}^{-1} \). Curve \( b \) = single 1000-mg IV injection; \( k = 1.0 \text{ h}^{-1} \). Curve \( c \) = single 100-mg IV injection; \( k = 0.5 \text{ h}^{-1} \). \( V_d \) is 10 L.
and the disproportionate increase in $t_{\text{eff}}$ as the dose is increased 10-fold is shown in lines $a$ and $b$.

**CLINICAL EXAMPLES**

**Pharmacokinetic/Pharmacodynamic Relationships and Efficacy of Antibiotics**

In the previous section, the time above the effective concentration, $t_{\text{eff}}$, was shown to be important in optimizing the therapeutic response of many drugs. This concept has been applied to antibiotic drugs (Drusano, 1988; Craig, 1995; Craig and Andes, 1996; Scaglione, 1997). For example, Craig and Andes (1996) discussed the antibacterial treatment of otitis media. Using the minimum inhibitory antibiotic concentration (MIC) for the microorganism in serum, the percent time for the antibiotic drug concentration to be above the MIC was calculated for several antibacterial classes, including cephalosporins, macrolides, and trimethoprim-sulfamethoxazole (TMP/SMX) combination (Table 19-4). Although the drug concentration in the middle ear fluid (MEF) is important, once the ratio (MEF/serum) is known, the serum drug level may be used to project MEF drug levels. The percent time above MIC of the dosing interval during therapy correlated well to the percent of bacteriologic cure (Fig. 19-8). An almost 100% cure was attained by maintaining the drug concentration above the MIC for 60%–70% of the dosing interval; an 80%–85% cure was achieved with 40%–50% of the dosing interval above MIC. When the percent of time above MIC falls below a critical value, bacteria will regrow, thereby prolonging the time for eradication of the infection. The pharmacokinetic model was further supported by experiments from a mouse infection model in which an infection in the thigh due to *Pseudomonas aeruginosa* was treated with ticarcillin and tobramycin.

In another study, Craig (1995) compared the AUC/MIC, the time above MIC, and drug peak concentration over MIC and found that the best fit was obtained when colony-forming units (CFUs) were plotted versus time above MIC for cefotaxime in a mouse infection model (Fig. 19-9).

Both Drusano (1988) and Craig (1995) reviewed the relationship of pharmacokinetics and pharmacodynamics in the therapeutic efficacy of antibiotics. For some antibiotics, such as the aminoglycosides and fluoroquinolones, both the drug concentration and the dosing interval have an influence on the antibacterial effect. For some antibiotics, such as the $\beta$-lactams, vancomycin, and the macrolides, the duration of exposure (time-dependent killing) or the time the drug levels are maintained above the MIC ($t_{\text{eff}}$) is most important for efficacy. For many antibiotics (eg, fluoroquinolones), there is a defined period of

---

**TABLE 19-4** Middle Ear Fluid-to-Serum Ratios for Common Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Middle Ear Fluid (MEF)/Serum Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.18–0.28</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Macrolide antibiotic</strong></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Sulfa drug</strong></td>
<td></td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Reproduced with permission from Craig and Andes (1996).
bacterial growth suppression after short exposures to the antibiotic. This phenomenon is known as the postantibiotic effect (PAE). Other influences on antibiotic activity include the presence of active metabolite(s), plasma drug protein binding, and the penetration of the antibiotic into the tissues. In addition, the MIC for the antibiotic depends on the infectious microorganism and the resistance of the microorganism to the antibiotic. In the case of ciprofloxacin, a quinolone, the percent of cure of infection at various doses was better related to AUIC, which is the product of area under the curve and the reciprocal of minimum inhibition concentration, MIC (Forrest et al, 1993). Interestingly, quinolones inhibit bacterial DNA gyrase, quite different from the β-lactam antibiotics, which involve damage to bacterial cell walls.

**Relationship Between Systemic Exposure and Response—Anticancer Drugs**

Plasma drug concentrations for drugs that have highly variable drug clearance in patients fluctuate widely even after intravenous infusion (Rodman and Evans, 1991). For highly variable drugs, there is no apparent relationship between the therapeutic response and the drug dose. For example, the anticancer drug teniposide at three different doses give highly variable steady-state drug concentrations and therapeutic response (Fig. 19-10). In some patients, single-point drug concentrations were variable and even higher with lower doses. Careful pharmacokinetic–pharmacodynamic analysis showed that a graded response curve may be obtained when responses are plotted versus systemic exposure as measured by “concentration × time” which is an integration of area under the concentration curve. For example, the response of quinolones is often related to AUC/MIC. Figure 19-11 demonstrates another example showing that anticancer response may be better correlated to total area under the drug concentration curve (AUC), even when no apparent dose–response relationship is observed. Undoubtedly,
the cytotoxic effect of the drug involves killing cancer cells with multiple-resistance thresholds that require different time exposures to the drug. The objective of applying pharmacokinetic–pharmacodynamic principles is to achieve therapeutic efficacy without triggering drug toxicity. This relationship is illustrated by the sigmoid curves for response and toxicity (see Fig. 19-11), each of which is close to the other and intensify as drug concentration increases.

**Equilibration Pharmacodynamic Half-Life**

For some drugs, the half-time for drug equilibration has been estimated by observing the onset of response. A list of drug half-times reported by Lalonde (1992) is shown in Table 19-5. The factors that affect this parameter include perfusion of the effect compartment, blood–tissue partitioning, drug diffusion from capillaries to the effect partitioning, protein binding, and elimination of the drug from the effect compartment.

**Substance Abuse Potential**

The rate of drug absorption has been associated with the potential for substance abuse. Drugs taken by the oral route have the lowest abuse potential. For example, cocoa leaves containing cocaine alkaloid have been chewed by South American Indians for centuries (Johanson and Fischman, 1989). Cocaine abuse has become a problem as a result of the availability of cocaine alkaloid (“crack” cocaine) and because of the use of other routes of drug administration (intravenous, intranasal, or smoking) that allow a very rapid rate of drug absorption and onset of action (Cone, 1995). Studies on diazepam (deWit et al, 1993) and nicotine (Henningfield and Keenan, 1993) have shown that the rate of drug delivery correlates with the abuse liability of such drugs. Thus, the rate of drug absorption influences the abuse potential of these drugs, and the route of drug administration that provides faster absorption and more rapid onset leads to greater abuse.
Chapter 19

DRUG TOLERANCE AND PHYSICAL DEPENDENCY

The study of drug tolerance and physical dependency is of particular interest in understanding the actions of abused drug substances, such as opiates and cocaine. Drug tolerance is a quantitative change in the sensitivity of the drug of the receptor site and is demonstrated by a decrease in pharmacodynamic effect after repeated exposure to the same drug. The degree of tolerance may vary greatly (Cox, 1990). Drug tolerance has been well described for organic nitrates, opioids, and other drugs. For example, the nitrates relax vascular smooth muscle and have been used for both acute angina (eg, nitroglycerin sublingual spray or transmucosal tablet) or angina prophylaxis (eg, nitroglycerin transdermal, oral controlled-release isosorbide dinitrate). Well-controlled clinical studies have shown that tolerance to the vascular and antianginal effects of nitrates may develop. For nitrate therapy, the use of a low nitrate or nitrate-free periods has been advocated as part of the therapeutic approach. The magnitude of drug tolerance is a function of both the dosage and the frequency of drug administration. Cross tolerance can occur for similar drugs that act on the same receptors. Tolerance does not develop uniformly to all the pharmacologic or toxic actions of the drug. For example, patients who show tolerance to the depressant activity of high doses of opiates will still exhibit “pinpoint” pupils and constipation.

The mechanism of drug tolerance may be due to (1) disposition or pharmacokinetic tolerance or (2) pharmacodynamic tolerance. Pharmacokinetic tolerance is often due to enzyme induction (discussed in earlier chapters), in which the hepatic drug clearance increases with repeated drug exposure. Pharmacodynamic tolerance is due to a cellular or receptor alteration in which the drug response is less than what is predicted in the patient

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equilibration $t_{1/2}$ (min)</th>
<th>Pharmacologic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-Tubocurarine</td>
<td>4</td>
<td>Muscle paralysis</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>2</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Quinidine</td>
<td>8</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Digoxin</td>
<td>214</td>
<td>LVET shortening</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>7.5</td>
<td>FEV$_1$</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>11.5</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Theophylline</td>
<td>11</td>
<td>FEV$_1$</td>
</tr>
<tr>
<td>Verapamil</td>
<td>2</td>
<td>PR prolongation</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>83</td>
<td>Gastric pH</td>
</tr>
<tr>
<td>Thiopental</td>
<td>1.2</td>
<td>Spectral edge</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6.4</td>
<td>Spectral edge</td>
</tr>
<tr>
<td>Alimentil</td>
<td>1.1</td>
<td>Spectral edge</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>595</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>4</td>
<td>Muscle paralysis</td>
</tr>
<tr>
<td>N-Acetylprocainamide</td>
<td>6.4</td>
<td>QT prolongation</td>
</tr>
</tbody>
</table>

From Lalonde (1992), with permission.
given subsequent drug doses. Measurement of serum drug concentrations may differentiate between pharmacokinetic tolerance and pharmacodynamic tolerance. Acute tolerance, or tachyphylaxis, which is the rapid development of tolerance, may occur due to a change in the sensitivity of the receptor or depletion of a cofactor after only a single or a few doses of the drug. Drugs that work indirectly by releasing norepinephrine may show tachyphylaxis. Drug tolerance should be differentiated from genetic factors which account for normal variability in the drug response.

Physical dependency is demonstrated by the appearance of withdrawal symptoms after cessation of the drug. Workers exposed to volatile organic nitrates in the workplace may initially develop headaches and dizziness followed by tolerance with continuous exposure. However, after leaving the workplace for a few days, the workers may demonstrate nitrate withdrawal symptoms. Factors that may affect drug dependency may include the dose or amount of drug used (intensity of drug effect), the duration of drug use (months, years, and peak use), and the total dose (amount of drug × duration). The appearance of withdrawal symptoms may be abruptly precipitated in opiate-dependent subjects by the administration of naloxone (Narcan), an opioid antagonist that has no agonist properties.

Allergic reactions can occur at extremely low drug concentrations. Some urticaria episodes in patients have been traced to penicillin contamination in food or to penicillin contamination during dispensing or manufacturing of other drugs. A patient’s allergic reactions are important data that must be recorded in the patient’s profile along with other adverse reactions. Penicillin allergic reaction in the population is often detected by skin test with benzylpenicilloyl polylysine (PPL). The incidence of penicillin allergic reaction occurs in about 1%–10% of patients. The majority of these reactions are minor cutaneous reactions such as urticaria, angioedema, and pruritus. Serious allergic reactions such as anaphylaxis are rare, with an incidence of 0.021%–0.106% for penicillins (Lin, 1992). For cephalosporins, the incidence of anaphylactic reaction is less than 0.02%. Anaphylactic reaction for cefaclor was reported to be 0.001% in a postmarketing survey. There are emerging trends showing that there may be a difference between the original and the new generations of cephalosporins (Reisman and Reisman, 1995). Cross-sensitivity to similar chemical classes of drugs can occur.

Allergic reactions may be immediate or delayed and have been related to IgE mechanisms. In β-lactam (penicillin) drug allergy, immediate reactions occur in about 30 to 60 minutes, but either a delayed reaction or accelerated reaction may occur from 1 to 72 hours after administration. Anaphylactic reaction may occur in both groups. Although some early evidence of cross-hypersensitivity between penicillin and cephalosporin was observed, the incidence in patients sensitive to penicillin shows only a two-fold increase in sensitivity to cephalosporin compared with that of the general population. The report rationalized that it is safe to administer cephalosporin to penicillin-sensitive patients and that the penicillin skin test is not useful in identifying patients who are allergic to cephalosporin, because of the low incidence of cross-reactivity (Reisman and Reisman, 1995). In practice, the clinician should evaluate the risk of drug allergy against the choice of alternative medication. Some earlier reports showed that cross-sensitivity between penicillin and cephalosporin was due to the presence of trace penicillin present in cephalosporin products.
After systemic absorption, the drug is carried throughout the body by the general circulation. Most of the drug dose will reach unintended target tissues, in which the drug may be passively stored, produce an adverse effect, or be eliminated. A fraction of the dose will reach the target site and combine with the receptor, which is generally located in the tissue. The receptor site is unknown most of the time, but, kinetically, it is known as the *effect compartment*. The time course of drug delivery to the effect compartment will determine whether the onset of pharmacologic response is immediate or delayed. The delivery of drug to the effect compartment is affected by the rate of blood flow, diffusion, and partition properties of the drug and the receptor molecules.

At the receptor site, the onset, duration, and intensity of the pharmacologic response are controlled by receptor concentration and the concentration of the drug and/or its active metabolites. The ultimate pharmacologic response (effect) may depend largely on the stereospecific nature of the interaction of the drug with the receptor and the rates of association and dissociation of the drug–receptor complex. Depending on their location and topography, not all receptor molecules are occupied by drug molecules when a maximum pharmacologic response is produced. Other variables, such as age, sex, genetics, nutrition, and tolerance, may also modify the pharmacologic response, making it difficult to relate the pharmacologic response to plasma drug concentration. To control data fluctuation and simplify pharmacodynamic fitting, the pharmacologic response is often expressed as a percent of response above a baseline or percent of maximum response. By combining pharmacokinetics and pharmacodynamics, some drugs with relatively complex pharmacologic responses have been described by pharmacodynamic models that account for their onset, intensity, and duration of action.

After the pharmacodynamics of a drug are characterized, the time course of pharmacologic response may be predicted after drug administration. Also, from these data, it is possible to determine from the pharmacokinetic parameters whether an observed change in pharmacologic response is due to pharmacodynamic factors, such as tachyphylaxis or tolerance, or due to pharmacokinetic factors, such as a change in drug absorption, elimination, or distribution.

### Drug–Receptor Theory Relating Pharmacologic Effect and Dose

The relationship between pharmacologic effect and dose was advanced by Wagner (1968), who derived a kinetic expression that relates drug concentration to pharmacologic effect. This theoretical development transformed the semi-empirical dose–effect relationship (the hyperbolic or log sigmoid profile) into a theoretical equation that relates pharmacologic effect to pharmacokinetics (ie, a pharmacokinetics/pharmacodynamic, PK/PD model). Because the equation was developed for a drug receptor with either single or multiple drug binding, many drugs with a sigmoid concentration effect profile may be described by this model. The slope of the profile also provides some insight into the drug–receptor interaction.

The basic equation mimics somewhat the kinetic equation for protein drug binding (Chapter 10). One or more drug molecules may interact with a receptor to form a complex that in turn elicits a pharmacodynamic response, as illustrated in Fig. 19-12. The rate of change in the number of drug–receptor complexes is expressed as \(\frac{db}{dt}\). From Fig. 19-12, a differential equation is obtained as shown:

\[
\frac{db}{dt} = k_1c(a - b) - bk_2
\]

where \(k_1c(a - b)\) is rate of receptor complex formation and \(bk_2\) = rate of dissociation of the receptor complex.

At steady state, \(db/dt = 0\) and Equation 19.9 reduces to
Relationship Between Pharmacokinetics and Pharmacodynamics

For many drugs, the pharmacologic response \( R \) is proportional to the number of receptors occupied:

\[
R \propto \frac{b}{a}
\]  

(19.11)

The pharmacologic response \( R \) is related to the maximum pharmacologic response \( R_{\text{max}} \), concentration of drug, and rate of change in the number of drug receptor complexes occupied:

\[
R = \frac{R_{\text{max}}}{1 + (k_d / k_c')}
\]  

(19.12)

A graph of Equation 19.12 constructed from the percent pharmacologic response \( (R/R_{\text{max}}) \times 100 \), versus the concentration of drug gives the response–concentration curve (Fig. 19-13). This type of theoretical development explains that the pharmacologic response–dose curve is not completely linear over the entire dosage range, as is frequently observed.

The total pharmacologic response elicited by a drug is difficult to quantitate in terms of the intensity and the duration of the drug response. The integrated pharmacologic response is a measure of the total pharmacologic response and is expressed mathematically as the product of these two factors (ie, duration and intensity of drug action) summed up over a period of time. Using Equation 19.12, an integrated pharmacologic response is generated if the drug plasma concentration–time curve can be adequately described by a pharmacokinetic model.

Table 19-6 is based on a hypothetical drug that follows a one-compartment open model. The drug is given intravenously in divided doses. With this drug, the total integrated response increases considerably when the total dose is given in a greater number of divided doses. By giving the drug in a single dose, two doses, four doses, and eight doses, an integrated response was obtained that ranged from 100% to 138.9%, using the single-dose response as a 100% reference. It should be noted that when the bolus dose is broken into a smaller number of doses, the largest percent increase in the integrated response occurs when the bolus dose is divided into two doses. Further division will cause less of an increase, proportionally. The actual percent increase in integrated response depends on the \( t_{1/2} \) of the drug as well as the dosing interval.

The values in Table 19-6 were generated from theory. However, these data illustrate that the pharmacologic response depends on the dosing schedule. A large total dose given in divided doses may produce a pharmacologic response quite different from that obtained by administering the drug in a single dose.

Correlation of pharmacologic response to pharmacokinetics is not always possible with all drugs. Sometimes intermediate steps are involved in the mechanism of drug action that are more complex than is assumed in the model. For example, warfarin (an anticoagulant) produces a delayed response, and there is no direct correlation of the anticoagulant activity to the plasma drug concentration. The plasma warfarin level is correlated with the inhibition of the prothrombin complex production rate. However, many correlations between pharmacologic effect and plasma drug concentration are performed by proposing models that may be discarded after more data are collected. The process of pharmacokinetic modeling can greatly enhance our understanding of the way drugs act in a quantitative manner.

**PHARMACODYNAMIC MODELS**

No unified general pharmacodynamic model based on detailed drug–receptor theory that relates pharmacologic response to pharmacokinetics is available.
Most of the drug–receptor-based models are descriptive and lack quantitative details. Successful modeling of pharmacologic response has been achieved with semi-empirically based assumptions and usually with some oversimplification of the real process. Many of the classic pharmacodynamic models were developed without detailed knowledge of the drug–receptor interaction. The successful modeling of the degree of muscle paralysis of $\alpha$-tubocurarine to plasma concentrations is an interesting example in which the exact mechanism of the drug–receptor interaction was not considered. One of the few pharmacodynamic models that takes into account the interaction between the receptor and the drug molecule leading to a pharmacologic effect was described by Boudinot et al (1986) using the drug prednisolone as an example. Prednisolone is a corticosteroid that binds to cytosolic receptors within the cell (Fig. 19-14). The bound steroid receptor complex is activated and translocated into the nucleus of the cell. Within the cell, the drug–receptor complex associates with specific DNA sequences and modulates the transcription of RNA, which ultimately initiates protein synthesis (Boudinot et al, 1986). Tyrosine aminotransferase (TAT) is an enzyme protein that is increased (induced) by the action of prednisolone. In the liver cell, the prednisolone concentration, drug–receptor concentration, and TAT enzyme were measured with respect to time.

The pharmacodynamic model accounted for the delayed response of prednisolone, a characteristic of corticosteroid response. In this model, prednisolone is first bound to plasma protein, and free drug must leave the plasma compartment and enter the cell to form a drug–receptor complex; creation of this complex then triggers the pharmacologic events leading to an increase in intracellular TAT concentration. A decrease in free receptor or an increase in bound receptor complexes after drug administration was observed. Plasma prednisolone concentrations were described by a triexponential equation, and a time lag was built into the model to account for the delay between TAT increase and the drug–receptor–DNA complex formation (Figs. 19-15 and 19-16). A review of PK–PD modelling has been published by Meibohm and Derendorf (1997).

### Equations Used in Pharmacodynamic Models

Historically, pharmacologists have noted that pharmacodynamic effects increase with increasing drug concentration and then reach a plateau or maximum

---

**TABLE 19-6 Hypothetical Drug Given Intravenously in Single and Divided Doses**

<table>
<thead>
<tr>
<th>Dose Number</th>
<th>Single Dose</th>
<th>Dose Given Initially and at 12th h</th>
<th>Dose Given at 0, 6, 12, 18 h</th>
<th>Dose Given at 0, 3, 6, 9, 12, 15, 18, 21 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>422</td>
<td>272</td>
<td>139.4</td>
<td>62.53</td>
</tr>
<tr>
<td>2</td>
<td>276</td>
<td></td>
<td>148.2</td>
<td>71.46</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>148.5</td>
<td>74.41</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>149.0</td>
<td>75.61</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>76.27</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>76.44</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>76.71</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>76.81</td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>422</td>
<td>548</td>
<td>585.1</td>
<td>590.2</td>
</tr>
<tr>
<td>Percent response</td>
<td>100</td>
<td>130</td>
<td>138.7</td>
<td>138.9</td>
</tr>
</tbody>
</table>

*The drug follows a one-compartment open model. Each value represents a unit of integrated pharmacologic response. Adapted with permission from Wagner (1968).*

FIGURE 19-15  A. Prednisolone levels in plasma (●) and liver (△) fall exponentially after 50 mg/kg of drug IV during the first 10 hours, as described by a pharmacokinetic model. B. Free cytosolic glucocorticoid receptor (CGR) concentration fell from control level (●) after 5- (○) and 50-mg/kg (□) IV doses of prednisolone. Free CGR fell as prednisolone interacted with receptor to form receptor complex. The free CGR returned to baseline level after about 10 hours. (From Boudinot et al, 1986, with permission.)
Chapter 19

pharmacologic effect. With application in many fields, the Hill equation was developed in 1910 (Goutelle et al, 2008; Weiss, 1997), later used to describe nonlinear and saturable mechanisms, such as the binding of oxygen to hemoglobin. The Hill equation has been used as an empirical equation to describe the relationship between drug concentration and pharmacologic response (Equation 19.12b).

The better known sigmoid curve (or S-curve) is the logistic function, Equation 19.12a. The two equations are mathematically related as shown below. The logistic function is defined by the equation where \( x \) is the independent variable and \( a \) and \( b \) are constants:

\[
y = \frac{1}{1 + e^{-(ax + b)}} \tag{19.12a}
\]

If \( a \) is redefined as \( \ln(K^0) \), and \( x \) as \( \ln(z) \), then the Hill equation is obtained, which looks more similar to equation 19.14a that is used in \( E_{\text{max}} \) models.

\[
y = \frac{z^b}{K^b + z^b} \tag{19.12b}
\]

Maximum Effect (\( E_{\text{max}} \)) Model

The maximum effect model (\( E_{\text{max}} \)) is an empirical model that relates pharmacologic response to drug concentrations. This model incorporates the observation known as the law of diminishing return, which shows that an increase in drug concentration near the maximum pharmacologic response produces a disproportionately smaller increase in the pharmacologic response (Fig. 19-17). The \( E_{\text{max}} \) model describes drug action in terms of maximum effect (\( E_{\text{max}} \)) and \( EC_{50} \), the drug concentration that produces 50% maximum pharmacologic effect.

\[
E = \frac{E_{\text{max}} C}{EC_{50} + C} \tag{19.13}
\]

where \( C \) is the plasma drug concentration and \( E \) is the pharmacologic effect.

Equation 19.13 is a saturable process resembling Michaelis–Menten enzyme kinetics. As the plasma drug concentration \( C \) increases, the pharmacologic effect \( E \) approaches \( E_{\text{max}} \) asymptotically. A double-reciprocal plot of Equation 19.13 may be used to linearize the relationship, similar to a Lineweaver–Burke equation.

\( E_{\text{max}} \) is the maximum pharmacologic effect that may be obtained by the drug. \( EC_{50} \) is the drug concentration that produces one-half (50%) of the maximum pharmacologic response. In this model, both \( E_{\text{max}} \) and \( EC_{50} \) can be measured. For example, the bronchodilator activity of theophylline may be monitored by measuring \( FEV_1 \) (forced expiratory volume) at various plasma drug concentrations (Fig. 19-18). For theophylline, a small gradual increase in \( FEV_1 \) is obtained as the plasma drug concentrations are increased higher than 10 mg/L. Only a 17% increase in \( FEV_1 \) is observed when the plasma theophylline concentration is doubled from 10 to 20 mg/L. The \( EC_{50} \) for theophylline is 10 mg/L. The \( E_{\text{max}} \) is equivalent to 63% of normal \( FEV_1 \). A further increase in the plasma theophylline concentration will not yield
an improvement in the FEV\textsubscript{1} beyond \(E_{\text{max}}\). Either drug saturation of the receptors or other limiting factors prevent further improvement in the pharmacologic response.

The \(E_{\text{max}}\) model describes two key features of the pharmacologic response: (1) the model mimics the hyperbolic shape of the pharmacologic response–drug concentration curve, and (2) a maximum pharmacologic response (\(E_{\text{max}}\)) may be induced by a certain drug concentration, beyond which no further increase in pharmacologic response is obtained (see Fig. 19-17). The drug concentration that produces a 50% maximum pharmacologic response (\(EC_{50}\)) is useful as a guide for achieving drug concentration that lies within the therapeutic range.

In many cases, the measured pharmacologic effect has some baseline value when drug is absent (e.g., blood pressure, heart rate, respiration rate). \(E_0\) is the measured pharmacologic effect (baseline activity) at zero drug concentration in the body. The measurement for \(E_0\) may be variable due to intra- and intersubject differences. Using \(E_0\) as a baseline constant-effect term, Equation 19.13 may be modified as follows:

\[
E = E_0 + \frac{E_{\text{max}} C}{EC_{50} + C} \quad (19.14)
\]

The effect may be expressed as a fraction or a percentage of maximum effect \(E_{\text{max}}\), and so Equation 19.14 becomes 19.14a:

\[
\frac{E}{E_{\text{max}}} = E_0' + \frac{C^n}{EC_{50} + C^n} \quad (19.14a)
\]

where, \(E_0' = E_0/E_{\text{max}}\).

**Sigmoid \(E_{\text{max}}\) Model**

The sigmoid \(E_{\text{max}}\) model describes the pharmacologic response–drug concentration curve for many drugs that appear to be S shaped (i.e., sigmoidal) rather than hyperbolic as described by the simpler \(E_{\text{max}}\) model. The model was first used by Hill (1910) to describe the association of oxygen with hemoglobin, in which the association with one oxygen molecule influences the association of the hemoglobin with the next oxygen molecule. The equation for the sigmoid \(E_{\text{max}}\) model is an extension of the \(E_{\text{max}}\) model:

\[
E = \frac{E_{\text{max}} C^n}{EC_{50} + C^n} \quad (19.15)
\]

where \(n\) is an exponent describing the number of drug molecules that combine with each receptor molecule. When \(n\) is equal to unity (\(n = 1\)), the sigmoidal \(E_{\text{max}}\) model reduces to the \(E_{\text{max}}\) model. A value of \(n > 1\) influences the slope of the curve and the model fit.

The sigmoidal \(E_{\text{max}}\) model has been used to describe the effect of tocainamide on the suppression of ventricular extrasystoles (Winkle et al, 1976). As shown in Fig. 19-19, the very steep slope of the tocainamide concentration–response curve required that \(n = 20\) in order to fit the model. Although this model was developed empirically, the mathematical equation describing the model is similar to the one elaborated by Wagner (1968) and discussed earlier in this chapter.

In the sigmoid \(E_{\text{max}}\) model, the slope is influenced by the number of drug molecules bound to the receptor. Moreover, a very large \(n\) value may indicate allosteric or cooperative effects in the interaction of the drug molecules with the receptor.
Pharmacokinetic Pharmacodynamic Models with an Effect Compartment

Many pharmacokinetic models describe the time course for drug and metabolite concentrations in the body. Using either the sigmoid E\textsubscript{max} or one of the other pharmacodynamic models described earlier, the pharmacologic response may be obtained and modeled at various time periods. This simple approach has worked for some neuromuscular blockers and anesthetic agents, whose activities are related to plasma drug concentrations.

For some drugs, the time course for the pharmacologic response may not directly parallel the time course of the plasma drug concentration. The maximum pharmacologic response produced by the drug may be observed before or after the plasma drug concentration has peaked. Moreover, other drugs may produce a delayed pharmacologic response unrelated to the plasma drug concentration.

A pharmacokinetic/pharmacodynamic model with an effect compartment is used to describe the pharmacokinetics of the drug in the plasma and the time course of a pharmacologic effect of a drug in the site of action. To account for the pharmacodynamics of an indirect or delayed drug response, a hypothetical effect compartment has been postulated (Fig. 19-20). This effect compartment is not part of the pharmacokinetic model but is a hypothetical pharmacodynamic compartment that links to the plasma compartment containing drug. Drug transfers from the plasma compartment to the effect compartment, but no significant amount of drug moves from the effect compartment to the plasma compartment. Only free drug will diffuse into the effect compartment, and the transfer rate constants are usually first order. The pharmacologic response is determined from the rate constant, k\textsubscript{e0}, and the drug concentration in the effect compartment (see Fig. 19-20).

The amount of drug in the hypothetical effect compartment after a bolus IV dose may be obtained by writing a differential equation describing the rate of change in drug amounts in each compartment:

\[
\frac{dD_e}{dt} = k_{1e}D_1 - k_{e0}D_e
\]  

(19.16)

where D\textsubscript{e} is the amount of drug in the effect compartment, D\textsubscript{1} is the amount of drug in the central compartment, k\textsubscript{1e} is the transfer rate constant for drug movement from the central compartment into the effect compartment, and k\textsubscript{e0} is the transfer rate constant out of the effect compartment.

Integrating Equation 19.16 yields the amount of drug in the effect compartment D\textsubscript{e}:

\[
D_e = \frac{D_0k_{1e}}{k_{e0} - k} \left( e^{-kt} - e^{-k_{e0}t} \right)
\]  

(19.17)

Dividing Equation 19.17 by V\textsubscript{e}, the volume of the effect compartment, yields the concentration C\textsubscript{e} of the effect compartment:

\[
C_e = \frac{D_0k_{1e}}{V_e(k_{e0} - k)} \left( e^{-kt} - e^{-k_{e0}t} \right)
\]  

(19.18)

where D\textsubscript{0} is the dose, V\textsubscript{e} is the volume of the effect compartment, and k is the elimination rate constant.
from the central compartment. Equation 19.18 is not very useful because the parameters \( V_e \) and \( k_{ie} \) are both unknown and cannot be obtained from plasma drug concentration data. Several assumptions were made to simplify this equation.

The pharmacodynamic model assumes that even though an effect compartment is present in addition to the plasma compartment, this hypothetical effect compartment takes up only a negligible amount of the drug dose, so that plasma drug level still follows a one-compartment equation. After an IV bolus dose, the rate of drug entering and leaving the effect compartment is controlled by the incoming rate constant \( k_{1e} \) and the elimination rate constant \( k_{e0} \). (There is no diffusion of drug from the effect compartment into the plasma compartment.) At steady state, both the input and output rates from the effect compartment are equal,

\[
k_{ie} D_i = D_e k_{e0}
\]

Rearranging,

\[
D_i = \frac{k_{e0} D_e}{k_{ie}}
\]

Dividing by \( V_D \) yields the steady-state plasma drug concentration \( C_1 \):

\[
C_1 = \frac{k_{eo} D_e}{k_{ie} V_D}
\]

Substituting for \( D_e \) into Equation 19.21 yields

\[
C_1 = -\frac{k_{eo} D_o k_{le}}{k_{ie} V_D (k_{eo} - k)} (e^{-k_{ie}t} - e^{-k_{e0}t})
\]

Cancelling the common term \( k_{le} \),

\[
C_1 = \frac{k_{eo} D_o}{V_D (k_{eo} - k)} (e^{-k_{e0}t} - e^{-k_{eo}t})
\]

At steady state, \( C_1 \) is unaffected by \( k_{le} \) and is controlled only by the elimination constant \( k \) and \( k_{e0} \). \( C_1 \) is called \( C_{pss} \), or steady-state drug concentration, and has been used successfully to relate the pharmacodynamics of many drugs, including some with delayed equilibration between the plasma and the effect compartment. Thus, \( k \) and \( k_{e0} \) jointly determine the pharmacodynamic profile of a drug. In fitting the pharmacokinetic–pharmacodynamic model, the IV bolus equation is fitted to the plasma drug concentration–time data to obtain \( k \) and \( V_D \), while \( C_{pss} \), or \( C_1 \) from Equation 19.24, is used to substitute into the concentration in Equation 19.15 to fit the pharmacologic response.

Many drug examples have been described by this type of pharmacokinetic–pharmacodynamic model. The key feature of this model is its dynamic flexibility and adaptability to pharmacokinetic models that account for drug distribution and pharmacologic response. The aggregate effects of drug elimination, binding, partitioning, and distribution in the body are accommodated by the model. The basic assumptions are practical and pragmatic, although some critics of the model (Colburn, 1987) believe the hypothetical effect compartment may oversimplify more complex drug–receptor events. On the positive side, the model represents elegantly an \textit{in vivo} pharmacologic event relating to the plasma drug concentrations that a clinician can monitor and adjust.

Until more information is known about the effect compartment, a pharmacokinetic–pharmacodynamic model is proposed to describe these kinetic processes combining some of the variables. A good fit of the data to the model is useful but does not necessarily describe the actual pharmacodynamic process. The process of model development evolves until a better model replaces an inadequate one. Several examples of drugs incorporating the effect compartment concept cited in the next section support the versatility of this model. The model accommodates some difficult drug response–concentration profiles, such as the puzzling hysteresis profile of some drug responses (eg, responses to cocaine and ajmaline).

**Pharmacodynamic Models Using an Effect Compartment**

The antiarrhythmic drug ajmaline slows the heart rate by delaying the depolarization of the heart muscle in the atrium and the ventricle. The pharmacologic effect of the drug is observed in the ECG by
measuring the prolongation of the PQ and QRS interval after an IV infusion of ajmaline. A two-compartment model with binding described the pharmacokinetics of the drug and a pharmacodynamic model with an effect compartment was linked to the central compartment in which free drug may diffuse into the effect compartment. The effect compartment was necessary because the plasma ajmaline concentration did not correlate well with changes in recorded ECG events. When the effect-compartment drug concentration was used instead, drug activity was well described by the model (Figs. 19-21 and 19-22).

**Hysteresis of Pharmacologic Response**

Many pharmacologic responses are complex and do not show a direct relationship between pharmacologic effect and plasma drug concentration. Some drugs have a plasma drug concentration–pharmacologic response that resembles a hysteresis loop (Fig. 19-23). For these drugs, an identical plasma concentration can result in significantly different pharmacologic responses, depending on whether the plasma drug concentration is on the ascending or descending phase of the loop. The time-dependent nature of a pharmacologic response may be due to tolerance, induced metabolite deactivation, reducedresponse, or translocation of receptors at the site of action. This type of time-dependent pharmacologic response is characterized by a clockwise profile when pharmacologic response is plotted versus plasma drug concentrations over time (see Fig. 19-23).

For example, fentanyl (a lipid-soluble, opioid anesthetic) and alfentanil (a closely related drug) display *clockwise* hysteresis, apparently due to rapid lipid partition. β-Adrenoreceptors, such as isoproterenol, apparently have no direct relationship between response and plasma drug concentration and show hysteresis features. The diminished pharmacologic response was speculated to be a result of cellular response and physiologic adaptation to intense stimulation of the drug. A decrease in the number of receptors as well as translocation of receptors was proposed as the explanation for the observation. The euphoria produced by cocaine also displayed a clockwise profile when responses were plotted versus plasma cocaine concentration (Fig. 19-24).

A second type of pharmacologic response shows a *counterclockwise* hysteresis profile (Fig. 19-25). The pharmacologic response increases with time as the pharmacologic response is plotted ver-
sus plasma drug concentrations. An example of a counterclockwise hysteresis loop is the antiarrhythmic drug ajmaline. When the QRS interval changes in dogs were plotted versus plasma ajmaline concentration in each dog, an interesting counterclockwise hysteresis loop was seen (see Fig. 19-21). Yasuhara and co-workers (1987) developed a pharmacodynamic model to analyze the molecular events between drug concentration and change in ECG parameters such as QRS. A relationship was established between pharmacologic response and drug concentration in the effect-compartment drug level (see Fig. 19-22). The hysteresis profile (see Fig. 19-21) is the result of the drug being highly bound to the plasma protein ($\alpha_1$-acid glycoprotein), and of a slow initial diffusion of drug into the effect compartment.

Counterclockwise hysteresis curves may also result when the measured pharmacodynamic response is not the primary effect of the drug, ie, there is an indirect effect. For example, warfarin inhibits hepatic synthesis of clotting factors II, VII, IX, and X, but prothrombin time is measured as a surrogate for warfarin activity and clotting factor concentration.

![FIGURE 19-23](image-url)  
Response of the EEG spectral edge to changing fentanyl (A) and alfentanil (B) serum concentrations. Plots are data from single patients after rapid drug infusion. Time is indicated by arrows. The clockwise hysteresis indicates a significant time lag between blood and effect site. (From Scott and Stanitski, 1985, with permission.)

![FIGURE 19-24](image-url)  
Clockwise hysteresis loop typical of tolerance is seen after intranasal administration of cocaine when related to degree of euphoria experienced in volunteers. (Reproduced with permission from van Dyke et al, 1978.)

![FIGURE 19-25](image-url)  
Counterclockwise hysteresis loop indicating equilibration delay between plasma concentration and the effect site producing the effect. (Holford NH, Sheiner LB. Pharmacokinetics and pharmacodynamic modeling in vivo, Crit Rev Bioeng 5(4):273-322, 1981, with permission.)
To predict the time course of drug response using a pharmacodynamic model, a mathematical expression is developed to describe the drug concentration–time profile of the drug at the receptor site. This equation is then used to relate drug concentrations to the time course and intensity of the pharmacologic response. Most pharmacodynamic models assume that pharmacologic action is due to a drug–receptor interaction, and the magnitude of the response is related quantitatively to the drug concentration in the receptor compartment. In the simplest case, the drug receptor lies in the plasma compartment and pharmacologic response is established through a one-compartment model with drug response proportional to log drug concentration (Equation 19.1). A more complicated model involving a receptor compartment that lies outside the central compartment was proposed by Sheiner and associates (1979). This model locates the receptor in an effect compartment in which a drug equilibrates from the central compartment by a first-order rate constant \( k_{1e} \). There is no back diffusion of drug away from the effect compartment, thereby simplifying the complexity of the equations. This model was applied successfully to monitor the pharmacologic effects of the drug trimazosin (Meredith et al, 1983).

The pharmacokinetics of trimazosin are described as a two-compartment open model with conversion to a metabolite by a first-order rate constant \( k_{1m} \). The pharmacokinetics of the metabolite are described by a one-compartment model with a first-order elimination constant \( k_{m0} \). The drug effect may be described by two pharmacodynamic models, either model A or B. Model A assumes that the drug effect in the effect compartment is produced by the drug only. Model B assumes that both the drug and a metabolite produce drug effect (Fig. 19-26).

The following equation describes the pharmacokinetics and pharmacodynamics of the drug:

\[
C_p = A e^{-at} - B e^{-bt} \tag{19.25}
\]

where \( C_p \) is the concentration of the drug in the central compartment.

\[
C_m = \frac{V_k k_{im}}{V_m} \left[ \frac{A}{(k_{m0} - a)} (e^{-at} - e^{-k_{ae}t}) \right. \\
\left. + \frac{B}{(k_{m0} - b)} (e^{-bt} - e^{-k_{af}t}) \right] \tag{19.26}
\]

where \( C_m \) is the concentration of the metabolite in the body, \( V_k \) is the volume of distribution of the metabolite, \( V_m \) is the volume of the central compartment of the body, \( k_{im} \) is the first-order constant for converting drug to metabolite, \( k_{m0} \) is the elimination rate con-

![FIGURE 19-26 Two proposed pharmacodynamic models for describing the hypotensive effect of trimazosin. A assumes an effect compartment (left of dashed line) for the drug. B assumes an effect compartment for the drug as well as the metabolite. (From Meredith et al, 1983, with permission.)](image-url)
stant of the metabolite, $A$ and $B$ are two-compartment model coefficients for the drug (see Chapter 4), and $k_{01}$ is the elimination rate constant of the drug.

The drug concentration in the effect compartment is calculated by assuming that at equilibrium the concentration of the drug in the effect compartment and the central compartment are equal,

$$k_{t}V_t = k_{eq}V_e$$  \hspace{1cm} (19.27)

where $V_t$ is volume of the effect compartment and $k_{eq}$ is the elimination rate constant of the drug from the effect compartment. Therefore, the drug concentration in the effect compartment $C(e, d)$ is calculated as

$$C(e, d) = \frac{AK_{eq}}{(k_{eq} - a)}(e^{-at} - e^{-k_{eq}t}) + \frac{Bk_{eq}}{(k_{eq} - b)}(e^{-bt} - e^{-k_{eq}t})$$  \hspace{1cm} (19.28)

The effect due to drug is assumed to be linear,

$$E = M_d C(e, d) + i$$  \hspace{1cm} (19.29)

where $M_d$ is the sensitivity slope to the drug (ie, the effect per unit of drug concentration in the effect compartment). The parameters $M_d$, $i$, and $k_{eq}$ are determined by least-squares fitting of the data. For the metabolite, the concentration of metabolite in the effect compartment $C(e, m)$ is calculated as

$$C(e, m) = \frac{AV_{m}k_{eq}k_{em}}{V_{m}}$$  \hspace{1cm} (19.30)

$$C(e, m) = \left[ \frac{e^{-at}}{(a-k_{0m})(a-k_{eq}m)} + \frac{e^{-k_{0m}t}}{(a-k_{0m})(k_{eq}m-k_{0m})} \right]$$

$$- \frac{e^{-k_{eq}m}}{(a-k_{eq}m)(k_{eq}m-k_{0m})}$$

$$+ \frac{BV_{m}k_{em}}{V_{m}} \frac{e^{-bt}}{(b-k_{0m})(b-k_{eq}m)}$$

The concentration of the metabolite in the effect compartment is then related to drug effect as for the parent drug. The total effect produced is

$$E = M_d C(e, d) + M_m C(e, m) + i$$  \hspace{1cm} (19.31)

The five parameters $M_d$, $M_m$, $i$, $k_{eq}$, $k_{0m}$ may be estimated from Equation 19.31 by fitting the data to an appropriate model. Figure 19-27 shows the observed decline in systolic blood pressure compared with the theoretical decline in blood pressure predicted by the model. An excellent fit of the data was obtained by assuming that both drug and metabolite are active. This example illustrates that, for a dose of a drug, the drug concentration in the effect compartment and others may be described by a mathematical model. These equations were further developed to describe the time course of a

![Figure 19-27](https://www.ketabpezeshki.com)
pharmacologic event. In this case, Meredith and associates (1983) demonstrated that both the drug and the metabolite formed in the body may affect the time course of the pharmacologic action of the drug in the body.

**Simulation of In Vitro Pharmacodynamic Effect Involving Hysteresis**

An in vitro model simulation of the sum of pharmacologic effect contributed by a drug and its active metabolite may explain the observation of the hysteresis response curve in vivo. Gupta et al (1993) discussed the factors that affect the shape of the response curve. In the simplest case, pharmacokinetic equations are developed to calculate $C_p$, the drug concentration, and $C_m$, the metabolite concentration. To estimate the pharmacologic effect due to both the drug and active metabolite, the potency of the drug is defined as $P$, the potency of the metabolite is $P_m$, and the sum of the pharmacologic effect is as shown below. (In their first simulation, Gupta et al assumed that the effect is linearly related to drug and metabolite concentrations.)

$$E = PC_p + P_mC_m$$  \hspace{1cm} (19.32)

The shape of hysteresis simulated is very dependent on $P_m$ and $k_{m0}$, the rate constant of metabolite elimination. If $k_{m0}$ is given a high, medium, or low value, the effect on the shape of the hysteresis loop is changed dramatically, as shown in Fig. 19-28. A temporal effect causes a counterclockwise loop. In the case of a metabolite that acts as an antagonist, the hysteresis loop is clockwise. The more elaborate features of an $E_{max}$ model were simulated by Gupta et al (1993) in their paper.

**CLINICAL EXAMPLE**

**Lorazepam Pharmacodynamics—Example of an In Vivo Hysteresis Loop**

Many drugs that act on the central nervous systems (CNS) have a lag time before the tissues and the plasma are equilibrated with drug. The pharmacokinetics of lorazepam after oral absorption were fitted to a two-compartment model with lag time. Lorazepam was studied because the drug accounts for all the activity, such that the counterclockwise response profile may be attributed to equilibration rather than to metabolism (Gupta et al, 1990).

The description of the plasma drug concentrations, $C_p$, is obtained by conventional pharmacokinetic equations, whereas the pharmacodynamic effect, $E$, is described by a sigmoid $E_{max}$ model similar to Equation 19.15, except that the baseline effect is also included. Gupta et al (1990) monitored three pharmacodynamic effects due to lorazepam. The monitored
pharmacodynamic effects were mental impairment processes evaluated by the cognitive and psychomotor performance of the subjects, including (A) subcritical tracking, (B) sway open (a measurement of gross body movements), and (C) digital symbol substitution. When the time course of each effect was plotted versus plasma drug concentration, a counterclockwise loop was observed (Fig. 19-29). When the same pharmacodynamic responses were plotted versus lorazepam concentration in the effect compartment accounting for the equilibration lag, a classical sigmoid relation was observed (Fig. 19-30). The observations showed that the temporal response of many drugs may be the result of pharmacodynamic and distributional factors interacting with each other.

Thus, a model with an effect compartment can more fully help understand the time course of the drug response.

**Simulation of Antiplatelet Effect of a Mechanism-Based Pharmacodynamic Model for Aspirin**

Low-dose aspirin, ASA (50–325 mg), has been shown to reduce the risk of myocardial infarction and stroke and is indicated for its cardioprotective effect. ASA acts by irreversibly acetylating a serine residue at position 529 in platelet cyclo-oxygenase-1 (COX-1), resulting in reduced production of proaggregatory thromboxane A2 (TXA2). Once COX-1 has been
acetylated by aspirin, the access of substrate arachidonic acid to the catalytic site is impeded for the remainder of the platelet lifespan (8–10 days). Although ASA has an effect on COX-2, the cardio-protective effect is adequately explained by its inhibition of platelet COX-1 by low doses and is sufficient to explain the cardio-protective effect of aspirin observed in clinical trials (Altman et al, 2004).

Hong et al (2008) developed a mechanism-based pharmacodynamic model that characterizes the antiplatelet effects of aspirin and ibuprofen alone and in combination (see Fig. 19-31). Ten healthy volunteers were enrolled in a single-blinded, randomized, three-way crossover study. Treatments consisted of single doses of either oral aspirin (325 mg) or ibuprofen (400 mg) and concomitant administration of aspirin (325 mg) and ibuprofen (400 mg). Ex vivo whole blood platelet aggregation induced by collagen (1 µg/mL) or arachidonic acid (0.5 mmol/L) was measured by impedance aggregometry. Development and population parameter estimation were performed using nonlinear mixed-effects modeling implemented in NONMEM. The PK–PD model shows inhibition of platelet aggregation was achieved following aspirin treatment (~77% inhibition within 2 hours), and return to baseline values occurred within 72 to 96 hours after dosing. In contrast, treatment with ibuprofen produced transient inhibition of platelet aggregation, with complete recovery observed in 6 to 8 hours. The PK–PD simulation predicts a significant inhibition of aspirin antiplatelet effects in the presence of a typical ibuprofen dosing regimen.

**FIGURE 19-31** Model of cyclo-oxygenase-1 (COX-1 enzyme) inhibition by aspirin (ASA) and ibuprofen. $C_{asa}$ = aspirin plasma concentration; $C_{ibu}$ = ibuprofen plasma concentration; $E$ = COX-1 free enzyme; $EI$ = enzyme plus ibuprofen complex; $K$ = second-order rate constant of irreversible enzyme inactivation by aspirin; $K_0$ = zero-order production rate constant; $k_{in}$ = second-order association rate constant; $k_{off}$ = first-order dissociation rate constant; $k_{out}$ = first-order elimination.

**DRUG EXPOSURE-PHARMACOLOGIC RESPONSE RELATIONSHIPS**

Model simulations are used to predict the relationship between drug exposure and pharmacologic response in situations where real experimental data are sparse or absent. There are many different types of models for the analysis of exposure-response data: (1) descriptive PD models (Emax model for exposure-response relationships), (2) empirical models that link a PK model (dose-concentration relationship), and (3) PD model (concentration-response relationship).

*Descriptive or empirical model-based analysis does not necessarily establish causality or provide a mechanistic understanding of a drug’s effect. Surrogate endpoints are a subset of biomarkers. A surrogate endpoint is a laboratory measurement or physical sign used in therapeutic trials as a substitute for a clinically meaningful endpoint that is
expected to predict the effect of the therapy (Temple, 1999). Adequate and well-controlled clinical studies that investigate several fixed doses and/or measure systemic exposure levels, when analyzed using scientifically reasonable causal models, can predict exposure-response relationships for safety and/or efficacy and provide plausible hypotheses about the effects of alternative doses and dosage regimens not actually tested (FDA guidance: Exposure-Response Relationships 2003). The broad term exposure refers to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (eg, \( C_{\text{max}} \), \( C_{\text{min}} \), \( C_{\text{ss}} \), AUC). Response refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (eg, receptor occupancy) to a presumed mechanistic effect (eg, ACE inhibition), to a potential or accepted surrogate (eg, effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety.

### Frequently Asked Questions

- Explain why doubling the dose of a drug does not double the pharmacodynamic effect of the drug.
- What is meant by a hysteresis loop? Why do some drugs follow a clockwise hysteresis loop and other drugs follow a counterclockwise hysteresis loop?
- What is meant by an effect compartment? How does the effect compartment differ from pharmacokinetic compartments, such as the central compartment and the tissue compartment?
- Why are in vitro or ex vivo biomarkers not useful for monitoring the clinical progress of drug treatment? What are the main considerations for using biomarkers to monitor drug treatment or disease progression?

### CHAPTER SUMMARY

Both agonist and antagonist drug effect can be quantitatively simulated by PK–PD models. The most common models are \( E_{\text{max}} \) models mechanistically based on drug receptor theory. Although most drug responses are complex, pharmacologic response versus log dose type of plots have been shown to follow sigmoid type of curve (S-curve) with maximum response peaking when all receptors become saturated. In vitro screening preparations are useful to study \( EC_{50} \), potency, and mechanism of a drug. However, pharmacologic response in a patient is generally far more complicated. Physiologically based PD models must consider how the drug is delivered to the active site and the effect of various drug disposition processes, as well as plasma and tissue drug binding. In addition, pharmacogenomics of the drug and disease processes must be considered in the model. Appropriately developed PK–PD models may be applied to predict onset, intensity, and duration of action of a drug. Toxicokinetics may also be applied to explain the side effects or drug-drug interactions.

The progress of a disease or its response to a therapeutic agent is often accompanied by biologic changes (markers or biomarkers) that are observable and/or measurable. Biomarkers (BM) may be selected and validated to monitor the course of drug response in the body. BMs should be mechanistically based and fulfill a number of clinically relevant criteria in order to be useful as potential clinical endpoints. BM together with PK–PD could be a very useful tool in expediting drug development, and many reviews and discussions are available about this application.
LEARNING QUESTIONS

1. On the basis of the graph in Fig. 19-32, answer “true” or “false” to statements (a) through (e) and state the reason for each answer.
   a. The plasma drug concentration is more related to the pharmacodynamic effect of the drug compared to the dose of the drug.
   b. The pharmacologic response is directly proportional to the log plasma drug concentration.
   c. The volume of distribution is not changed by uremia.
   d. The drug is exclusively eliminated by hepatic biotransformation.
   e. The receptor sensitivity is unchanged in the uremic patient.

2. What do clavulanate, sulbactam, and tazobactam have in common? Why are they used together with antibiotics?

3. Explain why subsequent equal doses of a drug do not produce the same pharmacodynamic effect as the first dose of a drug.
   a. Provide an explanation based on pharmacokinetic considerations.
   b. Provide an explanation based on pharmacodynamic considerations.

4. How are the parameters AUC and $t_{\text{eff}}$ used in pharmacodynamic models?

5. What class of drug tends to have a lag time between the plasma and the effect compartment?

6. Name an example of a pharmacodynamic response that does not follow a drug dose–response profile?

7. When an antibiotic concentration falls below the MIC, there is a short time period in which bacteria fail to regrow because of postantibiotic effect (PAE). This time period is referred to as PAT. What is PAT?

8. What is AUIC with regard to an antibiotic?

9. What is the difference between IC$_{50}$ and EC$_{50}$? Are the values reproducible from one lab to another? In functional studies, the antagonist IC$_{50}$ is most useful if the concentration of the agonist is below maximal. Higher concentrations of the agonist will increase the IC$_{50}$ of the competitive antagonist well above its equilibrium dissociation constant. Even with low agonist concentrations, the IC$_{50}$ from functional studies, like an agonist EC$_{50}$ or maximal response, is dependent on the conditions of the experiment (tissue, receptor expression, type of measurement, etc). True or false?

10. $K_i$ refers to the equilibrium dissociation constant of a ligand determined in inhibition studies. The $K_i$ for a given ligand is typically determined in a competitive radioligand binding study by measuring the inhibition of the binding of a reference radioligand by the inhibiting ligand of under equilibrium conditions. Why?

11. What is the dissociation constant $K$ in the following interaction between a drug Ligand $L$

$$L + R \overset{k_{-1}}{\underset{k_{11}}{\rightleftharpoons}} LR$$

and a drug receptor $R$

$$P_{LR} = \frac{|L|}{|L| + K}$$

where $K$ is expressed as $k_{-1}/k_{11}$ and $P_{LR}$ is the proportion of receptor occupied by $L$.

How many binding sites are assumed in the above model?

12. According to Katzung et al, 2009, propranolol is an example of a competitive

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**FIGURE 19-32** Graph of pharmacologic response $E$ as a function of time for the same drug in patients with normal (A) and uremic (B) kidney function, respectively.
antagonist (ie, β-adrenocceptor antagonist). The degree of inhibition produced depends on its concentration in the body. Some patients receiving a fixed dose of propranolol exhibit differences in inhibitory effects on physiologic responses to norepinephrine and epinephrine (endogenous adrenergic receptor agonists, based on drug receptor theory), and the dose of propranolol must be adjusted accordingly. Based on your understanding of drug receptor theory and propranolol PK (refer to Appendix E), which of the following may contribute to propranolol response differences?

(a) Clearance, (b) protein binding, and (c) bioavailability of the drug

\[ y = \frac{z^b}{K_s + z^b} \]  
\[ \text{Equation 19-12b} \]

Applying Equation 19.12b above, for a one-binding site reaction, substituting \( b = 1 \), and the variable \( z \) in the above equation may be seen to be essentially \( [L] \), it can be seen that the Hill equation is applicable to this simple case of \([L]\) binding to a receptor having one binding site.

13. Which one of the following would you select as a biomarker for a Type II diabetic patient? State the reasons that support your selection.

a) Blood sugar level  
b) Blood insulin level  
c) HbA1C

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Chapter Objectives

- Define Medication Therapy Management (MTM) and explain how MTM can improve the success of drug therapy.
- Explain what are “critical-dose drugs” and name an example.
- Define therapeutic drug monitoring and explain which drugs should be monitored through a therapeutic drug monitoring service.
- Calculate a drug dosage regimen in an individual patient for optimal drug therapy for a drug that has complete pharmacokinetic information and for a drug that has incomplete pharmacokinetic information.
- Explain the relationship of changing the dose and/or the dosing interval on the $C_{\text{max}}$, $C_{\text{min}}$, and $C_{\text{avg}}$.
- Define drug–drug interactions, the mechanisms of drug–drug interactions, and provide examples.
- Provide instructions to a patient who has missed a dose and discuss the therapeutic implications.

The success of drug therapy is highly dependent on the choice of the drug, the drug product, and the design of the dosage regimen. The choice of the drug is generally made by the physician after careful patient diagnosis and physical assessment. The choice of the drug product (eg, immediate release vs modified release) and dosage regimen are based on the patient’s individual characteristics and known pharmacokinetics of the drug as discussed in earlier chapters. Ideally, the dosage regimen is designed to achieve a desired drug concentration at a receptor site to produce an optimal therapeutic response with minimum adverse effects. Individual variation in pharmacokinetics and pharmacodynamics makes the design of dosage regimens difficult. Therefore, the application of pharmacokinetics to dosage regimen design must be coordinated with proper clinical evaluation of the patient. For certain critical-dose drugs, monitoring both the patient and drug regimen is important for proper efficacy.

MEDICATION THERAPY MANAGEMENT

Medication Therapy Management (MTM) was officially recognized by the US Congress in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.¹ The objective of this act is to improve the quality, effectiveness, and efficiency of healthcare delivery including prescription drugs. An MTM program is developed in cooperation with pharmacists and physicians to optimize therapeutic outcomes through improved medication use. MTM provides consultative, educational, and monitoring services to patients to obtain better therapeutic outcomes from medications by the enhanced understanding of medication therapy, improved compliance, control of costs, and prevention of adverse events and drug interactions. MTM programs have been developed for specific practice areas such as elderly care, diabetes, and asthma (Barnett et al, 2009).

¹www.cms.gov/PrescriptionDrugCovContra/082_MTMon.asp.
INDIVIDUALIZATION OF DRUG DOSAGE REGIMENS

Not all drugs require rigid individualization of the dosage regimen. Many drugs have a large margin of safety (i.e., exhibit a wide therapeutic window), and strict individualization of the dose is unnecessary. For a number of drugs generally recognized as safe and effective (GRAS), the US Food and Drug Administration (FDA) has approved an over-the-counter (OTC) classification for drugs that the public may buy without prescription. In addition, many prescription drugs, such as ibuprofen, loratidine, omeprazole, naproxen, nicotine patches, and others, that were originally prescription drugs, have been approved by the FDA for OTC status. These OTC drugs and certain prescription drugs, when taken as directed, are generally safe and effective for the labeled indications without medical supervision. For drugs that are relatively safe and have a broad safety-dose range, such as the penicillins, cephalosporins, and tetracyclines, the antibiotic dosage is not dose titrated precisely but is based rather on the clinical judgment of the physician to maintain an effective plasma antibiotic concentration above a minimum inhibitory concentration. Individualization of the dosage regimen is very important for drugs with a narrow therapeutic window (also known as critical dose drugs and narrow therapeutic index, NTI drugs), such as digoxin, aminoglycosides, antiarrhythmics, anticoagulants, anticonvulsants, and some antiasthmatics, such as theophylline. Critical-dose drugs are defined as those drugs where comparatively small differences in dose or concentration lead to dose and concentration dependent, serious therapeutic failures and/or serious adverse drug reactions. These adverse reactions may be persistent, irreversible, slowly reversible, or life threatening, or could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious (Guidance for Industry, 2006).

The objective of the dosage regimen design is to produce a safe plasma drug concentration that does not exceed the minimum toxic concentration or fall below a critical minimum drug concentration below which the drug is not effective. For this reason, the dose of these drugs is carefully individualized to avoid plasma drug concentration fluctuations due to intersubject variation in drug absorption, distribution, or elimination processes. For drugs such as phenytoin, a critical-dose drug that follows nonlinear pharmacokinetics at therapeutic plasma drug concentrations, a small change in the dose may cause a huge increase in the therapeutic response and possible adverse effects.
THERAPEUTIC DRUG MONITORING

Many drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and calcium channel blocking agents, such as nifedipine, have a wide therapeutic range and do not need therapeutic drug monitoring. In addition, over-the-counter drugs such as various cough and cold remedies, analgesics, and other products are also generally safe when used as directed. Therapeutic monitoring of plasma drug concentrations is valuable only if a relationship exists between the plasma drug concentration and the desired clinical effect or between the plasma drug concentration and an adverse effect. For those drugs in which plasma drug concentration and clinical effect are not directly related, other pharmacodynamic or “surrogate” parameters may be monitored. For example, clotting time may be measured directly in patients on warfarin anticoagulant therapy. Glucose concentrations are often monitored in diabetic patients using insulin products. Asthmatic patients may use the bronchodilator, albuterol taken by inhalation via a metered-dose inhaler. For these patients, FEV₁ (forced expiratory volume) may be used as a measure of drug efficacy. In cancer chemotherapy, dose adjustment for individual patients may depend more on the severity of side effects and the patient’s ability to tolerate the drug. For some drugs that have large inter- and intra-subject variability, clinical judgment and experience with the drug are needed to dose the patient properly.

The therapeutic range for a drug is an approximation of the average plasma drug concentrations that are safe and efficacious in most patients. When using published therapeutic drug concentration ranges, such as those in Table 20-1, the clinician must realize that the therapeutic range is essentially a probability concept and should never be considered as absolute values (Evans et al, 1992; Schumacher, 1995). For example, the accepted therapeutic range for theophylline is 10 to 20 μg/mL. Some patients may exhibit signs of theophylline intoxication such as central nervous system excitation and insomnia at serum drug concentrations below 20 μg/mL (Fig. 20-1), whereas other patients may show drug efficacy at serum drug concentrations below 10 μg/mL.

In administering potent drugs to patients, the physician must maintain the plasma drug level

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>20–30 μg/mL</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4–12 μg/mL</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1–2 ng/mL</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5–10 μg/mL</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1–5 μg/mL</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.6–1.2 mEq/L</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10–20 μg/mL</td>
</tr>
<tr>
<td>Procainamide</td>
<td>4–10 μg/mL</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1–4 μg/mL</td>
</tr>
<tr>
<td>Theophylline</td>
<td>10–20 μg/mL</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>5–10 μg/mL</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>50–100 μg/mL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>20–40 μg/mL</td>
</tr>
</tbody>
</table>

From Schumacher (1995), with permission.

FIGURE 20-1  Correlation between the frequency and severity of adverse effects and plasma concentration of theophylline (mean ± SD) in 50 adult patients. Mild symptoms of toxicity included nausea, vomiting, headache, and insomnia. A potentially serious effect was sinus tachycardia, and severe toxicity was defined as the occurrence of life-threatening cardiac arrhythmias and seizures. (Adapted from Hendeles and Weinberger, 1980, with permission.)
within a narrow range of therapeutic concentrations (see Table 20-1). Various pharmacokinetic methods may be used to calculate the initial dose or dosage regimen. Usually, the initial dosage regimen is calculated based on body weight or body surface after a careful consideration of the known pharmacokinetics of the drug, the pathophysiologic condition of the patient, and the patient’s drug history including nonprescription drugs and nutraceuticals.

Because of interpatient variability in drug absorption, distribution, and elimination as well as changing pathophysiologic conditions in the patient, therapeutic drug monitoring (TDM) or clinical pharmacokinetic (laboratory) services (CPKS) have been established in many hospitals to evaluate the response of the patient to the recommended dosage regimen. The improvement in the clinical effectiveness of the drug by therapeutic drug monitoring may decrease the cost of medical care by preventing untoward adverse drug effects. The functions of a TDM service are listed below.

- Select drug.
- Design dosage regimen.
- Evaluate patient response.
- Determine need for measuring serum drug concentrations.
- Assay for drug concentration in biological fluids.
- Perform pharmacokinetic evaluation of drug concentrations.
- Readjust dosage regimen, if necessary.
- Monitor serum drug concentrations.
- Recommend special requirements.

**Drug Selection**

The choice of drug and drug therapy is usually made by the physician. However, many practitioners consult with the clinical pharmacist in drug product selection and dosage regimen design. Increasingly, clinical pharmacists in hospitals and nursing care facilities are closely involved in prescribing, monitoring, and substitution of medications as part of a total medication therapy management (MTM) program. The choice of drug and the drug product is made not only on the basis of therapeutic consideration, but also based on cost and therapeutic equivalency.

### Table 20-2 Factors Producing Variability in Drug Response

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Drug Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Bioavailability and biopharmaceutics</td>
</tr>
<tr>
<td>Weight</td>
<td>Pharmacokinetics (including absorption, distribution, and elimination)</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Drug interactions</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Receptor sensitivity</td>
</tr>
<tr>
<td>Genetic variability</td>
<td>Rapid or slow metabolism</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
</tbody>
</table>

Hospitals and various prescription reimbursement plans have a drug formulary. Pharmacokinetics and pharmacodynamics are part of the overall considerations in the selection of a drug for inclusion in the drug formulary. An Institutional Pharmacy and Therapeutic Committee (IPTC) periodically reviews clinical efficacy data on new drug products for inclusion in the formulary and on older products for removal from the formulary. Drugs with similar therapeutic indications may differ in dose and pharmacokinetics. The pharmacist may choose one drug over another based on cost, therapeutic, and pharmacokinetic considerations. Other factors include patient-specific information such as medical history, pathophysiologic states, concurrent drug therapy, known allergies, drug sensitivities, and drug interactions; all are important considerations in drug selection (Table 20-2). As discussed in Chapter 12, the use of pharmacogenetic data may become another tool in assisting in drug selection for the patient.

### Dosage Regimen Design

The main objective of designing an appropriate dosage regimen for the patient is to provide a drug dose and dosage regimen that achieve a target drug

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2A drug formulary contains a list of prescription drug products that will be reimbursed fully or partially by the prescription plan provider. Drug products not listed in the formulary may be reimbursed if specially requested by the physician.
concentration at the receptor site. Once the proper drug is selected for the patient, a number of factors must be considered when designing a therapeutic dosage regimen. Usually, the manufacturer’s dosing recommendations in the package insert will provide guidance on the initial starting dose and dosage regimen in the typical patient population. These recommendations are based upon clinical trials performed during and after drug development. The package insert containing the FDA-approved label suggests an average dose and dosage regimen for the “average” patient who was enrolled in these studies. Genetic variation, drug interactions, or physiologic conditions such as disease or pregnancy may change the pharmacokinetics and/or pharmacodynamics of a drug, therefore requiring dosing regimen individualization. First, the known pharmacokinetics of the drug, including its absorption, distribution, and elimination profile, are considered in the patient who is to be treated. Some patients may have unusual first-pass metabolism (eg, fast or slow metabolizers) that will affect bioavailability after oral administration and the elimination half-life after systemic drug absorption. Second, the physiology of the patient, age, weight, gender, and nutritional status will affect the disposition of the drug and should be considered. Third, any pathophysiologic conditions, such as renal dysfunction, hepatic disease, or congestive heart failure, may change the normal pharmacokinetic profile of the drug, and the dose must be carefully adjusted. Fourth, the effect of long-term exposure to the medication in the patient must be considered including the possibility of drug abuse by the patient. In addition, personal lifestyle factors, such as cigarette smoking, alcohol abuse, and obesity, are other issues that are known to alter the pharmacokinetics of drugs. Lastly, lack of patient compliance (ie, patient noncompliance) in taking the medication can also be a problem in achieving effective therapeutic outcomes.

An optimal dosing design can greatly improve the safety and efficacy of the drug, including reduced side effects and a decrease in frequency of therapeutic drug monitoring and its associated costs. For some drugs, TDM will be necessary because of the unpredictable nature of their pharmacodynamics and pharmacokinetics. Changes in drug or drug dose may be required after careful assessment by the pharmacist of the patient, including changes in the drug’s pharmacokinetics, drug tolerance, cross-sensitivity, or history of unusual reactions to related drugs. The pharmacist must develop competency and experience in clinical pharmacology and therapeutics in addition to the necessary pharmacokinetic skills. Several mathematical approaches to dosage regimen design are given in later sections of this chapter and in Chapter 21.

Dosage regimen guidelines obtained from the literature and from approved product labeling are often based upon average patient response. However, substantial individual variation to drug response can occur. The design of the dosage regimen must be based upon clinical assessment of the patient. Labeling for recently approved drugs provide information for dosing in patients with renal and/or hepatic disease. Frequently, drug dose adjustment of another co-administered drug may be necessary due to drug–drug interactions. For example, an elderly patient who is on haloperidol (Haldol®) may require a reduction of his usual morphine dose. With many new drugs, pharmacogenetic information is also available and should be considered for dosing individual patients. For example, the role of multidrug resistances MDRs and resistance are important considerations during dosage regimen design in cancer chemotherapy.

**Pharmacokinetics of the Drug**

Various popular drug references list pharmacokinetic parameters such as clearance, bioavailability, and elimination half-life. The values for these pharmacokinetic parameters are often obtained from small clinical studies. Therefore, it is difficult to determine whether these reported pharmacokinetic parameters are reflected in the general population or in a specific patient group. Differences in study design, patient population, and data analysis may lead to conflicting values for the same pharmacokinetic parameters. For example, values for the apparent volume of distribution and clearance can be estimated by different methods, as discussed in previous chapters.

Ideally, the effective target drug concentration and the therapeutic window for the drug should be
obtained. When using the target drug concentration in the development of a dosage regimen, the clinical pharmacist should know whether the reported target drug concentration represents an average steady-state drug concentration, a peak drug concentration, or a trough concentration.

**Drug Dosage Form (Drug Product)**

The dosage form of the drug will affect drug bioavailability and the rate of absorption and thus the subsequent pharmacodynamics of the drug in the patient (see also Chapter 14). The choice of drug dosage form may be based on the desired route of drug administration, the desired onset and duration of the clinical response, cost, and patient compliance. For example, an extended-release drug product instead of an immediate-release drug product may provide a longer duration of action and better patient compliance. An orally disintegrating tablet (ODT) may be easier for the patient who has difficulty in swallowing a conventional tablet. Some patients may prefer the use of a transdermal delivery system rather than an oral drug product. Available dosage forms and strengths are usually listed under the *How Supplied section* in the package insert.

**Patient Compliance**

Factors that may affect patient compliance include the cost of the medication, complicated instructions, multiple daily doses, difficulty in swallowing, type of dosage form, and adverse drug reactions. The patient who is in an institution may have different issues compared to an ambulatory patient. Institutionalized patients may have very little choice as to the prescribed drug and drug dosage form. Patient compliance in institutions is maintained by the medical personnel who provides the medication. Ambulatory patients must remember to take the medication as prescribed to obtain the optimum clinical effect of the drug. It is very important that the prescriber or clinical pharmacist consider the patient’s lifestyle and personal needs when developing a drug dosage regimen. The FDA-approved labeling in the package insert contains *Patient Counseling Information* to improve patient compliance. There are also sections on *Information for Patients* and *Medication Guide*.

**Evaluation of Patient’s Response**

After the drug and drug products are chosen and the patient receives the initial dosage regimen, the practitioner should evaluate the patient’s clinical response. If the patient is not responding to drug therapy as expected, then the drug and dosage regimen should be reviewed. The dosage regimen should be reviewed for adequacy, accuracy, and patient compliance with the drug therapy. In many situations, sound clinical judgment may preclude the need for measuring serum drug concentrations.

**Measurement of Drug Concentrations**

Before blood samples are taken from the patient, the practitioner needs to determine whether serum drug concentrations in the patient need to be measured. In some cases, adverse events that may not be related to the serum drug concentration may preclude the patient from using the prescribed drug. For example, allergy or mild nausea may not be dose related. (See examples in Chapter 9.)

Plasma, serum, saliva, urine, and occasionally tissue drug concentrations may be measured for (1) clinical drug monitoring to improve drug therapy, (2) drug abuse screening, and (3) toxicology evaluation such as poisoning and drug overdose. Examples of common drugs that may be measured are listed in Table 20-3. In addition, many prescription medications (e.g., opiates, benzodiazepines, NSAIDs) and nonprescription drugs (e.g., dextromethorphan, NSAIDs) are also abused. Analyses have been used for measurement of the presence of abused drugs in blood, urine, saliva, hair, and breath (alcohol).

A major assumption made by the practitioner is that serum drug concentrations relate to the therapeutic and/or toxic effects of the drug. For many drugs, clinical studies have demonstrated a therapeutically effective range of serum concentrations. Knowledge of the serum drug concentration may clarify why a patient is not responding to the drug therapy or why the drug is having an adverse effect. In some cases, the practitioner may want to verify the accuracy of the dosage regimen.

The timing of the blood sample and the number of blood samples to be taken from the patient must be considered. In many cases, a single blood sample
gives insufficient information. Several blood samples are often needed to clarify the adequacy of the dosage regimen. When ordering serum drug concentrations to be measured, a single serum drug concentration may not yield useful information unless other factors are considered. For example, the dosage regimen of the drug should be known, including the size of the dose and the dosage interval, the route of drug administration, the time of sampling (peak, trough, or steady state), and the type of drug product (eg, immediate-release or extended-release drug product).

In practice, trough serum concentrations are easier to obtain than peak or $C_{av}$ samples under a multiple-dose regimen. In addition, there are limitations in terms of the number of blood samples that may be taken, total volume of blood needed for the assay, and time to perform the drug analysis may exist. Schumacher (1985) has suggested that blood sampling times for therapeutic drug monitoring should be taken during the postdistributive phase for loading and maintenance doses, but at steady state for maintenance doses. After distribution equilibrium has been achieved, the plasma drug concentration during the postdistributive phase is better correlated with the tissue concentration and, presumably, the drug concentration at the site of action. In some cases, the clinical pharmacist may want an early-time sample that approximates the peak drug level, whereas a blood sample taken at three or four elimination half-lives during multiple dosing will approximate the steady-state drug concentration. The practitioner who orders the measurement of serum concentrations should also consider the cost of the assays, the risks and discomfort for the patient, and the utility of the information gained.

### Assay for Drug

Drug analyses are usually performed either by a clinical chemistry laboratory or a clinical pharmacokinetics laboratory. A variety of analytic techniques are available for drug measurement, such as high-pressure liquid chromatography coupled with mass spectrometry (LCMS), immunoassay, and other methods. The methods used by the analytic

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**Table 20-3 Drugs Commonly Measured in Serum, Plasma, or Other Tissues**

<table>
<thead>
<tr>
<th>Therapeutic Drug Monitoring</th>
<th>Drug Abuse Screen</th>
<th>Drug Overdose or Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>Alcohol</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin,</td>
<td>Cytosine</td>
<td>Ethyl alcohol, methanol</td>
</tr>
<tr>
<td>valproic acid, primidone</td>
<td></td>
<td>Opiates</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Anabolic steroids</td>
<td>Heroin, morphine, codeine derivatives, methadone, buprenorphine</td>
</tr>
<tr>
<td>Aminoglycosides (gentamicin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular agents</strong></td>
<td>Opiates</td>
<td></td>
</tr>
<tr>
<td>Digoxin, lidocaine, procainamide, quinidine</td>
<td>Heroin, morphine, codeine derivatives, methadone, buprenorphine</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td>Stimulants</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus, sirolimus</td>
<td>Cocaine, amphetamine, methamphetamine</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Cannabinoids</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Marijuana, hashish</td>
<td></td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td>Other drugs</td>
<td></td>
</tr>
<tr>
<td>Lithium, theophylline</td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal drugs</strong></td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>TSH, thyroxin, estrogens</td>
<td>Alcohol</td>
<td></td>
</tr>
</tbody>
</table>
| **Nicotine from tobacco is often included in some drug abuse literature, but is not usually part of a drug abuse screen.**

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laboratory may depend on such factors as the physicochemical characteristics of the drug, target drug concentration, amount (volume) and nature of the biologic specimen (serum, urine, saliva), available instrumentation, cost for each assay, and analytical skills of the laboratory personnel. The laboratory should have a standard operating procedure (SOP) for each drug analysis method and follow good laboratory practices (GLP). Moreover, analytic methods used for the assay of drugs in serum or plasma should be validated with respect to specificity, linearity, sensitivity, precision, accuracy, stability, and ruggedness. The time to perform the assays and receive the results are important factors that should be considered if the clinician needs this information to make a quick therapeutic decision.

**Specificity**

Chromatographic evidence is generally required to demonstrate that the analytic method is specific for detection of the drug and other analytes, such as an active metabolite. The method should demonstrate that there is no interference between the drug and its metabolites and endogenous or exogenous substances such as other drugs that the patient may have taken. In addition, the internal standard should be resolved completely and also demonstrate no interference with other compounds. Immunoassays depend on an antibody and antigen (usually the drug to be measured) reaction. The antibody should be specific for the drug analyte, but may instead also cross-react with drugs that have similar structures, including related compounds (endogenous or exogenous chemicals) and metabolites of the drug. Colorimetric and spectrophotometric assays are usually less specific. Interference from other materials may inflate the results.

**Sensitivity**

Sensitivity is the minimum detectable level or concentration of drug in serum that may be approximated as the lowest drug concentration that is two to three times the background noise. A minimum quantifiable level (MQL) or minimum detectable limit (MDL) is a statistical method for the determination of the precision of the lower level.

**Linearity and Dynamic Range**

Dynamic range refers to the relationship between the drug concentration and the instrument response (or signal) used to measure the drug. Many assays show a linear drug concentration–instrument response relationship. Immunoassays generally have a nonlinear dynamic range. High serum drug concentrations, above the dynamic range of the instrument response, must be diluted before assay. The dynamic range is determined by using serum samples that have known (standard) drug concentrations (including a blank serum sample or zero drug concentration). Extrapolation of the assay results above or below the measured standard drug concentrations may be inaccurate if the relationship between instrument response and extrapolated drug concentration is unknown.

**Precision**

Precision is a measurement of the variability or reproducibility of the data. Precision measurements are obtained by replication of various drug concentrations and by replication of standard concentration curves prepared separately on different days. A suitable statistical measurement of the dispersion of the data, such as standard deviation or coefficient of variation, is then performed.

**Accuracy**

Accuracy refers to the difference between the average assay values and the true or known drug concentrations. Control (known) drug serum concentrations should be prepared by an independent technician using such techniques to minimize any error in their preparation. These samples, including a “zero” drug concentration, are assayed by the technician assigned to the study along with a suitable standard drug concentration curve.

**Stability**

Standard drug concentrations should be maintained under the same storage conditions as the unknown serum samples and assayed periodically. The stability study should continue for at least the same length of time as the patient samples are to be stored. Freeze–thaw stability studies are performed to
determine the effect of thawing and refreezing on the stability of the drug in the sample. On occasion, a previously frozen biologic sample must be thawed and reassayed if the first assay result is uncertain.

Plasma samples obtained from subjects on a drug study are usually assayed along with a minimum of three standard processed serum samples containing known standard drug concentrations and a minimum of three control plasma samples whose concentrations are unknown to the analyst. These control plasma samples are randomly distributed in each day’s run. Control samples are replicated in duplicate to evaluate both within-day and between-day precision. The concentration of drug in each plasma sample is based on each day’s processed standard curve.

**Ruggedness**

Ruggedness is the degree of reproducibility of the test results obtained by the analysis of the same samples by different analytical laboratories or by different instruments. The determination of ruggedness measures the reproducibility of the results under normal operational conditions from laboratory to laboratory, instrument to instrument, and from analyst to analyst.

Because each method for drug assay may have differences in sensitivity, precision, and specificity, the clinical pharmacokineticist should be aware of which drug assay method the laboratory used.

**Pharmacokinetic Evaluation**

After the serum or plasma drug concentrations are measured, the clinical pharmacokineticist must evaluate the data. Many laboratories report total drug (free plus bound drug) concentrations in the serum. The pharmacokineticist should be aware of the usual therapeutic range of serum drug concentrations from the literature. However, the literature may not indicate whether the reported values were trough, peak serum, or average drug levels. Moreover, the methodology for the drug assay used in the analytical laboratory may be different in terms of accuracy, specificity, and precision.

The assay results from the analytical laboratory may show that the patient’s serum drug levels are higher, lower, or similar to the expected serum levels.

The pharmacokineticist should evaluate these results while considering the patient and the patient’s pathophysiologic condition. Table 20-4 lists a number of factors the pharmacokineticist should consider when interpreting serum drug concentration. Often, the concentration of drug in each plasma sample is based on each day’s processed standard curve.

**TABLE 20-4 Pharmacokinetic Evaluation of Serum Drug Concentrations**

<table>
<thead>
<tr>
<th>Serum Concentrations Lower Than Anticipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient compliance</td>
</tr>
<tr>
<td>Error in dosage regimen</td>
</tr>
<tr>
<td>Wrong drug product (controlled release instead of immediate release)</td>
</tr>
<tr>
<td>Poor bioavailability</td>
</tr>
<tr>
<td>Rapid elimination (efficient metabolizer)</td>
</tr>
<tr>
<td>Reduced plasma–protein binding</td>
</tr>
<tr>
<td>Enlarged apparent volume of distribution</td>
</tr>
<tr>
<td>Steady state not reached</td>
</tr>
<tr>
<td>Timing of blood sample</td>
</tr>
<tr>
<td>Improving renal/hepatic function</td>
</tr>
<tr>
<td>Drug interaction due to stimulation of elimination enzyme autoinduction</td>
</tr>
<tr>
<td>Changing hepatic blood flow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Concentrations Higher Than Anticipated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient compliance</td>
</tr>
<tr>
<td>Error in dosage regimen</td>
</tr>
<tr>
<td>Wrong drug product (immediate release instead of controlled release)</td>
</tr>
<tr>
<td>Rapid bioavailability</td>
</tr>
<tr>
<td>Smaller-than-anticipated apparent volume of distribution</td>
</tr>
<tr>
<td>Slow elimination (poor metabolizer)</td>
</tr>
<tr>
<td>Increased plasma–protein binding</td>
</tr>
<tr>
<td>Deteriorating renal/hepatic function</td>
</tr>
<tr>
<td>Drug interaction due to inhibition of elimination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Concentration Correct but Patient Does Not Respond to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered receptor sensitivity (eg, tolerance)</td>
</tr>
<tr>
<td>Drug interaction at receptor site</td>
</tr>
<tr>
<td>Changing hepatic blood flow</td>
</tr>
</tbody>
</table>
additional data, such as a high serum creatinine and high blood urea nitrogen (BUN), may help verify that an observed high serum drug concentration in a patient is due to lower renal drug clearance because of compromised kidney function. In another case, a complaint by the patient of overstimulation and insomnia might collaborate the laboratory’s finding of higher-than-anticipated serum concentrations of theophylline. Therefore, the clinician or pharmacokineticist should evaluate the data using sound medical judgment and observation. The therapeutic decision should not be based solely on serum drug concentrations.

Dosage Adjustment
From the serum drug concentration data and patient observations, the clinician or pharmacokineticist may recommend an adjustment in the dosage regimen. Ideally, the new dosage regimen should be calculated using the pharmacokinetic parameters derived from the patient’s serum drug concentrations. Although there may not be enough data for a complete pharmacokinetic profile, the pharmacokineticist should still be able to derive a new dosage regimen based on the available data and the pharmacokinetic parameters in the literature that are based on average population data.

Monitoring Serum Drug Concentrations
In many cases, the patient’s pathophysiology may be unstable, either improving or deteriorating further. For example, proper therapy for congestive heart failure will improve cardiac output and renal perfusion, thereby increasing renal drug clearance. Therefore, continuous monitoring of serum drug concentrations is necessary to ensure proper drug therapy for the patient. For some drugs, an acute pharmacologic response can be monitored in lieu of actual serum drug concentration. For example, prothrombin clotting time might be useful for monitoring anticoagulant therapy and blood pressure monitoring for hypotensive agents.

Special Recommendations
At times, the patient may not be responding to drug therapy because of other factors. For example, the patient may not be following instructions for taking the medication (patient noncompliance). The patient may be taking the drug after a meal instead of before or may not be adhering to a special diet (e.g., low-salt diet). Therefore, the patient may need special instructions that are simple and easy to follow. It may be necessary to discontinue the drug and prescribe another drug from the same therapeutic class.

CLINICAL EXAMPLE
Dosage and Administration of Lanoxin (Digoxin) Tablets, USP
In the new package insert, dosing information is available under Dosage and Administration. In addition, the section under Clinical Pharmacology provides valuable information for therapeutic considerations such as:

• Mechanism of action
• Pharmacodynamics
• Pharmacokinetics

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides indicated for the treatment of congestive heart failure and atrial fibrillation. According to the approved label for Lanoxin, the recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications. In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (i.e., ideal) body weight.

Lanoxin (digoxin) tablets, USP, NDA 20405/S-004, GlaxoSmithKline, August 2009.
2. The patient’s renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient’s age: Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (ie, below 1.5 mg/dL).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin.

**Serum Digoxin Concentrations**

In general, the dose of digoxin used should be determined based on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL (lower serum trough concentrations of 0.5 to 1 ng/mL) may be appropriate in some adult patients. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/mL. Since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/mL, values below 2.0 ng/mL do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/mL. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug (trough level). If this is not possible, sampling should be done at least 6 to 8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10%–25% lower when sampled at 24 versus 8 hours, depending upon the patient’s renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

1. Analytical problems in the assay procedure.
2. Inappropriate serum sampling time.
3. Administration of a digitalis glycoside other than digoxin.
4. Conditions causing an alteration in the sensitivity of the patient to digoxin.
5. Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

An important statement in the approved label for Lanoxin® is the following which is in bold lettering for emphasis: “*It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.*”

**Adverse Events and Therapeutic Monitoring**

An *adverse drug reaction*, also called a *side effect* or *adverse event* (AE), is any undesirable experience associated with the use of a medicine in a patient. Adverse events can range from mild to severe. Serious adverse events are those that can cause disability, are life threatening, result in hospitalization or death, or cause birth defects. Some AEs are expected and are documented in the literature and in the approved labeling for the drug. Other AEs may be unexpected. The severity of these AEs should be

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*4FDA Consumer Health Information, April 11, 2008. (http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm107976.pdf).*
considered and whether the AE is related or unrelated to the patient’s drug therapy. FDA maintains safety information and an adverse event reporting program (MedWatch) that provides important and timely medical product information to healthcare professionals, including information on prescription and over-the-counter drugs, biologics, medical devices, and special nutritional products.

It is sometimes difficult to determine whether the AE in the patient is related to the drug, due to progression of the disease or other pathology, or due to some unknown source. There are several approaches to determining whether the observed AE is due to the drug:

1. Check that the correct drug product and dose was ordered and given to the patient.
2. Verify that the onset of the AE was after the drug was taken and not before.
3. Determine the time interval between the beginning of drug treatment and the onset of the event.
4. Discontinue the drug and monitor the patient’s status, looking for improvement.
5. Rechallenge or restart the drug, if appropriate, and monitor for recurrence of the AE.

For some drugs, there may be an AE due to the initial exposure to the drug. However, the patient may become desensitized to the AE after longer drug treatment or drug dose titration. The clinician should be familiar with the drug and relevant literature concerning AEs. Generally, the manufacturer of the drug can also be a resource to consult.

**DESIGN OF DOSAGE REGIMENS**

Several methods may be used to design a dosage regimen. Generally, the initial dosage of the drug is estimated using average population pharmacokinetic parameters obtained from the literature and modified according to the patient’s known diagnosis, pathophysiology, demographics, allergy, and any other known factor that might affect the patient’s response to the dosage regimen.

After initiation of drug therapy, the patient is then monitored for the therapeutic response by patient consultation and clinical and physical assessment. After evaluation of the patient, adjustment of the dosage regimen may be needed. If necessary, measurement of plasma drug concentrations may be used to obtain the patient’s individual pharmacokinetic parameters from which the data are used to modify the dosage regimen. Further therapeutic drug monitoring in the patient may be needed.

Various clinical pharmacokinetic software are available for dosage regimen calculations. The dosing strategies are based generally on pharmacokinetic calculations that were previously performed manually. Computer automation and pharmacokinetic software packages improve the accuracy of the calculation, make the calculations “easier,” and have an added advantage of maintaining proper documentation (see Appendix B). However, the use of these software programs should not replace good clinical judgment.

- The package insert (PI) is a useful source for dose regimen. The section Use in Specific Populations, provides information that may apply to individual patients.
  - Pregnancy
  - Labor and delivery
  - Nursing mothers
  - Pediatric use
  - Geriatric use
  - Hepatic impairment
  - Renal impairment
  - Gender effect

**Individualized Dosage Regimens**

The most accurate approach to dosage regimen design is to calculate the dose based on the pharmacokinetics of the drug in the individual patient. This approach is not feasible for calculation of the initial dose. However, once the patient has been medicated, the readjustment of the dose may be calculated using
pharmacokinetic parameters derived from measurement of the serum drug levels from the patient after the initial dose. Most dosing programs record the patient’s age and weight and calculate the individual dose based on creatinine clearance and lean body weight.

**Dosage Regimens Based on Population Averages**

The method most often used to calculate a dosage regimen is based on average pharmacokinetic parameters obtained from clinical studies published in the drug literature. This method may be based on a fixed or an adaptive model (Greenblatt, 1979; Mawer, 1976).

The **fixed model** assumes that population average pharmacokinetic parameters may be used directly to calculate a dosage regimen for the patient, without any alteration. Usually, pharmacokinetic parameters such as absorption rate constant \( k_a \), bioavailability factor \( F \), apparent volume of distribution \( V_d \), and elimination rate constant \( k \), are assumed to remain constant. Most often the drug is assumed to follow the pharmacokinetics of a one-compartment model. When a multiple-dose regimen is designed, multiple-dosage equations based on the principle of superposition (see Chapter 8) are used to evaluate the dose. The practitioner may use the usual dosage suggested by the literature and then make a small adjustment of the dosage based on the patient’s weight and/or age.

The **adaptive model** for dosage regimen calculation uses patient variables such as weight, age, sex, body surface area, and known patient pathophysiology, such as renal disease, as well as the known population average pharmacokinetic parameters of the drug. In this case, calculation of the dosage regimen takes into consideration any changing pathophysiology of the patient and attempts to adapt or modify the dosage regimen according to the needs of the patient. In some cases, pharmacogenetic data may be helpful in determining dosing. For example, clopidogrel (Plavix) has a black box warning cautioning use in patients who have slow CYP2D6 metabolism and who will therefore have slower activation of the prodrug to the active metabolite. However, an appropriate dose regimen has not been established for these patients. The adaptive model generally assumes that pharmacokinetic parameters such as drug clearance do not change from one dose to the next. However, some adaptive models allow for continuously adaptive change with time in order to simulate more closely the changing process of drug disposition in the patient, especially during a disease state (Whiting et al, 1991).

**Dosage Regimens Based on Partial Pharmacokinetic Parameters**

For many drugs, the entire pharmacokinetic profile of the drug is unknown or unavailable. Therefore, the pharmacokineticist needs to make some assumptions in order to calculate the dosage regimen in the absence of pharmacokinetic data in animals or humans. For example, a common assumption is to let the bioavailability factor \( F \) equal 1 or 100%. Thus, if the drug is less than fully absorbed systemically, the patient will be undermedicated rather than overmedicated. Some of these assumptions will depend on the safety, efficacy, and therapeutic range of the drug. The use of population pharmacokinetics (discussed later in this chapter) employs average patient population characteristics and only a few serum drug concentrations from the patient. Population pharmacokinetic approaches to therapeutic drug monitoring have increased with the increased availability of computerized databases and the development of statistical tools for the analysis of observational data (Schumacher, 1985).

**Nomograms and Tabulations in Dosage Regimen Designs**

For ease of calculation of dosage regimens, many clinicians rely on nomograms to calculate the proper dosage regimen for their patients. The use of a nomogram may give a quick dosage regimen adjustment for patients with characteristics requiring adjustments, such as age, body weight, and physiologic state. In general, the nomogram of a drug is based on population pharmacokinetic data collected and analyzed using a specific pharmacokinetic model. In order to keep the dosage regimen calculation simple, complicated equations are often solved and the results displayed diagrammatically on special scaled axes or as a table to produce a simple
dose recommendation based on patient information. Some nomograms make use of certain physiologic parameters, such as serum creatinine concentration, to help modify the dosage regimen according to renal function (see Chapter 21).

Pharmaceutical manufacturers provide dosage recommendations in the approved label for many marketed drugs in the form of a table or as a nomogram. These are general guidelines to aid the clinician in establishing an initial dosage regimen for patients. The tables may include loading and maintenance doses that are modified for the demographics of the patient (eg, age, weight) and for certain diseases states (eg, renal clearance).

For drugs with a narrow therapeutic range, such as theophylline, a guide for monitoring serum drug concentrations is given. Another example is the aminoglycoside antibiotic, tobramycin sulfate USP (Nebcin, Eli Lilly), which is eliminated primarily by renal clearance. Thus, the dosage of tobramycin sulfate should be reduced in direct proportion to a reduction in creatinine clearance (see Chapter 21). The manufacturer provides a nomogram for estimating the percent of the normal dose of tobramycin sulfate assuming the serum creatinine level (mg/100 mL) has been obtained.

**Empirical Dosage Regimens**

In many cases, the physician selects a dosage regimen for the patient without using any pharmacokinetic variables. In such a situation, the physician makes the decision based on empirical clinical data, personal experience, and clinical observations. The physician characterizes the patient as representative of a similar well-studied clinical population that has used the drug successfully.

**CONVERSION FROM INTRAVENOUS INFUSION TO ORAL DOSING**

After the patient’s dosing is controlled by intravenous infusion, it is often desirable to continue to medicate the patient with the same drug using the oral route of administration. When intravenous infusion is stopped, the serum drug concentration decreases according to first-order elimination kinetics (see Chapter 5). For most oral drug products, the time to reach steady state depends on the first-order elimination rate constant for the drug. Therefore, if the patient starts the dosage regimen with the oral drug product at the same time as the intravenous infusion is stopped, then the exponential decline of serum levels from the intravenous infusion should be matched by the exponential increase in serum drug levels from the oral drug product.

The conversion from intravenous infusion to a controlled-release oral medication given once or twice daily has become more common with the availability of more extended-release drug products, such as theophylline (Stein et al, 1982) and quinidine. Computer simulation for the conversion of intravenous theophylline (aminophylline) therapy to oral controlled-release theophylline demonstrated that oral therapy should be started at the same time as intravenous infusion is stopped (Iafrate et al, 1982). With this method, minimal fluctuations are observed between the peak and trough serum theophylline levels. Moreover, giving the first oral dose when IV infusion is stopped may make it easier for the nursing staff or patient to comply with the dosage regimen.

Either of these methods may be used to calculate an appropriate oral dosage regimen for a patient whose condition has been stabilized by an intravenous drug infusion. Both methods assume that the patient’s plasma drug concentration is at steady state.

**Method 1**

Method 1 assumes that the steady-state plasma drug concentration, $C_{SS}^\infty$, after IV infusion is identical to the desired $C_{av}^\infty$ after multiple oral doses of the drug. Therefore, the following equation may be used:

$$ C_{av}^\infty = \frac{SF D_0}{k V_D \tau} \quad (20.1) $$

$$ \frac{D_0}{\tau} = \frac{C_{av}^\infty k V_D}{SF} \quad (20.2) $$

where $S$ is the salt form of the drug and $D_0/\tau$ is the dosing rate.
DETERMINATION OF DOSE

Method 2

Method 2 assumes that the rate of intravenous infusion (mg/h) is the same desired rate of oral dosage.

EXAMPLE

An adult male asthmatic patient (age 55, 78 kg) has been maintained on an intravenous infusion of aminophylline at a rate of 34 mg/h. The steady-state theophylline drug concentration was 12 μg/mL and total body clearance was calculated as 3.0 L/h. Calculate an appropriate oral dosage regimen of theophylline for this patient.

Solution

Aminophylline is a soluble salt of theophylline and contains 85% theophylline (S = 0.85). Theophylline is 100% bioavailable (F = 1) after an oral dose. Because total body clearance, CL = kVD, Equation 20.2 may be expressed as

\[ \frac{D_0}{\tau} = \frac{C_{av} CL}{SF} \]  

(20.3)

The dose rate, \(D_0/\tau\) (34 mg/h), was calculated on the basis of aminophylline dosing. The patient, however, will be given theophylline orally. To convert to oral theophylline, S and F should be considered.

Theophylline dose rate = \(\frac{SF D_0}{\tau}\)  

= \(\frac{(0.85)(1)(34)}{1}\) = 28.9 mg/h

The theophylline dose rate of 28.9 mg/h must be converted to a reasonable schedule for the patient with a consideration of the various commercially available theophylline drug products. Therefore, the total daily dose is 28.9 mg/h × 24 h or 693.6 mg/d. Possible theophylline dosage schedules might be 700 mg/d, 350 mg every 12 hours, or 175 mg every 6 hours. Each of these dosage regimens would achieve the same \(C_{av}\) but different \(C_{max}\) and \(C_{min}\), which should be calculated. The dose of 350 mg every 12 hours could be given in sustained-release form to avoid any excessive high drug concentration in the body.

Determination of DOSE

The calculation of the starting dose of a drug and dosage regimen is based on the objective of delivering a desirable (target) therapeutic level of the drug in the body. For many drugs, the desirable therapeutic drug levels and pharmacokinetic parameters are available in the clinical literature. However, the literature in some cases may not yield complete drug information, or some of the information available may be equivocal. Therefore, the pharmacokineticist must make certain necessary assumptions in accordance with the best pharmacokinetic information available.

For a drug that is given in multiple doses for an extended period of time, the dosage regimen is usually calculated to maintain the average steady-state blood level within the therapeutic range. The dose can be calculated with Equation 20.4, which expresses the \(C_{av}\) in terms of dose (\(D_0\)), dosing interval (\(\tau\)), volume of distribution (\(V_D\)), and the elimination half-life of the drug. \(F\) is the fraction of drug absorbed and is equal to 1 for drugs administered intravenously.

\[ C_{av} = \frac{1.44 D_0 t_{1/2} F}{V_D \tau} \]  

(20.4)
PRACTICE PROBLEMS

1. Pharmacokinetic data for clindamycin were reported by DeHaan et al (1972) as follows:

\[ k = 0.247 \text{ h}^{-1} \]
\[ t_{1/2} = 2.81 \text{ h} \]
\[ V_D = 43.9 \text{ L/1.73 m}^2 \]

What is the steady-state concentration of the drug after 150 mg of the drug is given orally every 6 hours for a week? (Assume the drug is 100% absorbed.)

Solution

\[ C_{av} = \frac{1.44D_0t_{1/2}F}{V_D\tau} \]
\[ = \frac{1.44 \times 150,000 \times 2.81 \times 1}{43,900 \times 6} \mu\text{g/mL} \]
\[ = 2.3 \mu\text{g/mL} \]

2. According to Regamey et al (1973), the elimination half-life of tobramycin was reported to be 2.15 hours and the volume of distribution was reported to be 33.5% of body weight.

a. What is the dose for an 80-kg individual if a steady-state level of 2.5 \( \mu\text{g/mL} \) is desired? Assume that the drug is given by intravenous bolus injection every 8 hours.

Solution

Assuming the drug is 100% bioavailable as a result of IV injection

\[ C_{av} = \frac{1.44D_0t_{1/2}F}{V_D\tau} \]
\[ 2.5 = \frac{1.44 \times 2.15 \times 1 \times D_0}{80 \times 0.335 \times 1000 \times 8} \]
\[ D_0 = \frac{2.5 \times 80 \times 0.335 \times 1000 \times 8}{1.44 \times 2.15} \mu\text{g} \]
\[ D_0 = 173 \text{ mg} \]

The dose should be 173 mg every 8 hours.

b. The manufacturer has suggested that in normal cases, tobramycin should be given at a rate of 1 mg/kg every 8 hours. With this dosage regimen, what would be the average steady-state level?

Solution

\[ C_{av} = \frac{1.44 \times 1 \times 1000 \times 2.15}{0.335 \times 1000 \times 8} \]
\[ = 1.16 \mu\text{g/mL} \]

Because the bacteriocidal concentration of an antibiotic varies with the organism involved in the infection, the prescribed dose may change. The average plasma drug concentration is used to indicate whether optimum drug levels have been reached. With certain antibiotics, the steady-state peak and trough levels are sometimes used as therapeutic indicators. (See Chapter 19 for discussion of time above minimum effective concentration [MIC]). For example, the effective concentration of tobramycin was reported to be around 4 to 5 \( \mu\text{g/mL} \) for peak levels and around 2 \( \mu\text{g/mL} \) for trough levels when given intramuscularly every 12 hours (see Table 20-1). Although peak and trough levels are frequently reported in clinical journals, these drug levels are only transitory in the body. Peak and trough drug levels are less useful pharmacokinetically, because peak and trough levels fluctuate more and are usually reported less accurately than average plasma drug concentrations. When the average plasma drug concentration is used as a therapeutic indicator, an optimum dosing interval must be chosen. The dosing interval is usually set at approximately one to two elimination half-lives of the drug, unless the drug has a very narrow therapeutic index. In this case the drug must be given in small doses more frequently or by IV infusion.

EFFECT OF CHANGING DOSE AND DOSING INTERVAL ON \( C_{av}^{\infty} \), \( C_{av}^{\min} \) AND \( C_{av}^{\max} \)

During intravenous infusion, \( C_{SS} \) may be used to monitor the steady-state serum concentrations. In contrast, when considering therapeutic drug monitoring of serum concentrations after the initiation of
As the size of the dose or dosage intervals change proportionately, the $C_{\text{av}}^\infty$ may be the same but the steady-state peak, $C_{\text{max}}^\infty$, and trough, $C_{\text{min}}^\infty$, drug levels will change. $C_{\text{max}}^\infty$ is influenced by the size of the dose and the dosage interval. An increase in the size of the dose given at a longer dosage interval will cause an increase in $C_{\text{max}}^\infty$, and a decrease in $C_{\text{min}}^\infty$. In this case $C_{\text{max}}^\infty$ may be very close or above the minimum toxic drug concentration (MTC). However, the $C_{\text{min}}^\infty$ may be lower than the minimum effective drug concentration (MEC). In this latter case the low $C_{\text{min}}^\infty$ may be subtherapeutic and dangerous for the patient, depending on the nature of the drug.

**DETERMINATION OF FREQUENCY OF DRUG ADMINISTRATION**

The size of a drug dose is often related to the frequency of drug administration. The more frequently a drug is administered, the smaller the dose is needed to obtain the same $C_{\text{av}}^\infty$. Thus, a dose of 250 mg every 3 hours can be changed to 500 mg every 6 hours without affecting the average steady-state plasma concentration of the drug. However, as the dosing intervals get longer, the size of the dose required to maintain the average plasma drug concentration gets correspondingly larger. When an excessively long dosing interval is chosen, the larger dose may result in peak plasma levels that are above toxic drug concentration and trough plasma concentrations that are below the minimum effective concentration, even though $C_{\text{av}}^\infty$ will remain the same (see Chapter 8).

In general, the dosing interval for most drugs is determined by the elimination half-life. Drugs such as the penicillins, which have relatively low toxicity, may be given at intervals much longer than their elimination half-lives without any toxicity problems. Drugs having a narrow therapeutic range, such as digoxin and phenytoin, must be given relatively frequently to minimize excessive “peak-and-trough” fluctuations in blood levels. For example, the common maintenance schedule for digoxin is 0.25 mg/d and the elimination half-life of digoxin is 1.7 days. In contrast, penicillin G is given at 250 mg every
6 hours, while the elimination half-life of penicillin G is 0.75 hour. Penicillin is given at a dosage interval equal to 8 times its elimination half-life, whereas digoxin is given at a dosing interval only 0.59 times its elimination half-life. The toxic plasma concentration of penicillin G is over 100 times greater than its effective concentration, whereas digoxin has an effective concentration of 1 to 2 ng/mL and a toxicity level of 3 ng/mL. The toxic concentration of digoxin is only 1.5 times effective concentration. Therefore, a drug with a large therapeutic index (ie, a large margin of safety) can be given in large doses and at relatively long dosing intervals.

**DETERMINATION OF BOTH DOSE AND DOSAGE INTERVAL**

Both the dose and the dosage interval should be considered in the dosage regimen calculations. Ideally, the calculated dosage regimen should maintain the serum drug concentrations between $C_{\text{max}}$ and $C_{\text{min}}$. For intravenous multiple-dosage regimens the ratio of $C_{\text{max}} / C_{\text{min}}$ may be expressed by

$$\frac{C_{\text{max}}}{C_{\text{min}}} = \frac{C_0 e^{k\tau}(1-e^{-k\tau})}{C_0 e^{-k\tau}(1-e^{-k\tau})}$$  \hspace{1cm} (20.5)

which can be simplified to

$$\frac{C_{\text{max}}}{C_{\text{min}}} = \frac{1}{e^{-k\tau}}$$  \hspace{1cm} (20.6)

From Equation 20.6, a maximum dosage interval, $\tau$, may be calculated that will maintain the serum concentration between $C_{\text{min}}$ and $C_{\text{max}}$. After the dosage interval is calculated, then a dose may be calculated.

**PRACTICE PROBLEM**

The elimination half-life of an antibiotic is 3 hours with an apparent volume of distribution equivalent to 20% of body weight. The usual therapeutic range for this antibiotic is between 5 and 15 $\mu$g/mL. Adverse toxicity for this drug is often observed at serum concentrations greater than 20 $\mu$g/mL. Calculate a dosage regimen (multiple IV doses) that will just maintain the serum drug concentration between 5 and 15 $\mu$g/mL.

**Solution**

From Equation 20.6, determine the maximum possible dosage interval $\tau$.

$$\frac{15}{5} = \frac{1}{e^{-(0.693/3)\tau}}$$

$$e^{0.231\tau} = 0.333$$

Take the natural logarithm (ln) on both sides of the equation.

$$-0.231\tau = -1.10$$

$$\tau = 4.76 \text{ h}$$

Then determine the dose required to produce $C_{\text{max}}$ from Equation 20.7 after substitution of $C_p = D_0/V_D$:

$$C_{\text{max}} = \frac{D_0/V_D}{1-e^{-k\tau}}$$  \hspace{1cm} (20.7)

Solve for dose $D_0$, letting $V_D = 200 \text{ mL/kg}$ (20% body weight).

$$15 = \frac{D_0/200}{1-e^{-(0.231)(4.76)}}$$

$$D_0 = 2 \text{ mg/kg}$$

To check this dose for therapeutic effectiveness, calculate $C_{\text{min}}$ and $C_{\text{av}}$.

$$C_{\text{min}} = \frac{(D_0/V_D)e^{-k\tau}}{1-e^{-k\tau}} = \frac{(2000/200)e^{-(0.231)(4.76)}}{1-e^{-(0.231)(4.76)}}$$

$$C_{\text{min}} = 4.99 \mu\text{g/mL}$$

As a further check on the dosage regimen, calculate $C_{\text{av}}$.

$$C_{\text{av}} = \frac{D_0}{V_Dk\tau} = \frac{2000}{(200)(0.231)(4.76)}$$

$$C_{\text{av}} = 9.09 \mu\text{g/mL}$$
By calculation, the dose of this antibiotic should be 2 mg/kg every 4.76 hours to maintain the serum drug concentration between 5 and 15 \( \mu g/mL \).

In practice, rather than a dosage interval of 4.76 hours, the dosage regimen and the dosage interval should be made as convenient as possible for the patient, and the size of the dose should take into account the commercially available drug formulation. Therefore, the dosage regimen should be recalculated to have a convenient value (below the maximum possible dosage interval) and the size of the dose adjusted accordingly.

**DETERMINATION OF ROUTE OF ADMINISTRATION**

Selection of the proper route of administration is an important consideration in drug therapy. The rate of drug absorption and the duration of action are influenced by the route of drug administration. However, the use of certain routes of administration is precluded by physiologic and safety considerations. For example, intra-arterial and intrathecal drug injections are less safe than other routes of drug administration and are used only when absolutely necessary. Drugs that are unstable in the gastrointestinal tract such as proteins or drugs that undergo extensive first-pass effect are not suitable for oral administration. For example, insulin is a protein that is degraded in the gastrointestinal tract by proteolytic enzymes. Drugs such as xylocaine and nitroglycerin are not suitable for oral administration because of high first-pass effect. These drugs, therefore, must be given by an alternative route of administration.

Intravenous administration is the fastest and most reliable way of delivering a drug into the circulatory system. Drugs administered by intravenous bolus are delivered to the plasma immediately and the entire dose is immediately subject to elimination. Consequently, more frequent drug administration is required. Drugs administered extravascularly must be absorbed into the bloodstream, and the total absorbed dose is eliminated more slowly. The frequency of administration can be lessened by using routes of administration that give a sustained rate of drug absorption. Intramuscular injection generally provides more rapid systemic absorption than oral administration of drugs that are not very soluble.

Certain drugs are not suitable for administration intramuscularly because of erratic drug release, pain, or local irritation. Even though the drug is injected into the muscle mass, the drug must reach the circulatory system or other body fluid to become bioavailable. The anatomic site of drug deposition following intramuscular injection will affect the rate of drug absorption. A drug injected into the deltoid muscle is more rapidly absorbed than a drug injected similarly into the gluteus maximus, because there is better blood flow in the former. In general, the method of drug administration that provides the most consistent and greatest bioavailability should be used to ensure maximum therapeutic effect. The various routes of drug administration can be classified as either extravascular or intravascular and are listed in Table 20-5 (see also Chapter 13).

Precipitation of an insoluble drug at the injection site may result in slower absorption and a delayed response. For example, a dose of 50 mg of chlordiazepoxide (Librium) is more quickly absorbed after oral administration than after intramuscular injection. Some drugs, such as haloperidol decanoate, are very oil-soluble products that release very slowly after intramuscular injection (see Chapter 14).

**TABLE 20-5 Common Routes of Drug Administration**

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Extravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Enteral</td>
</tr>
<tr>
<td>Intravenous injection (IV bolus)</td>
<td>Buccal</td>
</tr>
<tr>
<td>Intravenous infusion (IV drip)</td>
<td>Sublingual</td>
</tr>
<tr>
<td>Intra-arterial injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>Rectal</td>
</tr>
<tr>
<td>Intradermal injection</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td>Transdermal</td>
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<td>Intrathecal injection</td>
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</tbody>
</table>
Infants and children have different dosing requirements than adults (Bartelink et al., 2006; FDA Guidance for Industry, 2000; Leeder et al., 2010). Information for pediatric dosings were generally lacking in the past. In December 1994, the FDA required drug manufacturers to determine whether existing data were sufficient to support information on pediatric use for drug labeling purposes and implemented a plan to encourage the voluntary collection of pediatric data. The FDA Modernization (FDAMA) authorized an additional 6 months of patent protection for manufacturers that conducted pediatric clinical trials. As a consequence of various legislative initiatives later, the results of pediatric studies conducted on 322 drugs and biological products are available to help dosing in children. The studies reveal important new information regarding dosing and pharmacokinetic differences between children and adults (Leeder et al., 2010). Dosing of drugs in this population requires a thorough consideration of the differences in the pharmacokinetics and pharmacology of a specific drug in the preterm newborn infant, newborn infant (birth–28 days), infant (28 days–23 months), young child (2–5 years), older child (6–11 years), adolescent (12–18 years), and the adult. Unfortunately, the pharmacokinetics and pharmacodynamics of most drugs are still not well known in children under 12 years of age. The variation in body composition and the maturity of liver, kidney, and other organ functions are potential sources of differences in pharmacokinetics with respect to age. For convenience, “infants” are here arbitrarily defined as children of 0 to 2 years of age. However, within this group, special consideration is necessary for infants less than 4 weeks (1 month) old, because their ability to handle drugs often differs from that of more mature infants.

In addition to different dosing requirements for the pediatric population, there is a need to select pediatric dosage forms that permit more accurate dosing and patient compliance. For example, liquid pediatric drug products may have a calibrated dropper or a premeasured teaspoon (5 mL) for more accurate dosing and also have a cherry flavor for pediatric patient compliance. Pediatric drug formulations may also contain different drug concentrations compared to the adult drug formulation and must be considered in order to prevent dosage errors. Because of the small muscle mass in an infant, alternative drug delivery such as an intramuscular antibiotic drug injection into the gluteus medius may be considered for a pediatric patient, as opposed to the deltoid muscle for an adult patient. However, body composition is different in infants compared to adults.

In general, complete hepatic function is not attained until the third week of life. Oxidative processes are fairly well developed in infants, but there is a deficiency of conjugative enzymes, in particular, glucuronidation. For example, kernicterus is a form of jaundice in the newborn characterized by very high levels of unconjugated bilirubin in the blood. Since the tissues protecting the brain (the blood–brain barrier) are not well formed in newborns, unconjugated bilirubin may enter the brain and cause brain damage. In addition to reduced liver function in infants, altered drug distribution may occur due to reduction in drug binding to plasma albumin and to different body composition, especially water and fat content.

Newborns show only 30% to 50% of the renal activity of adults on the basis of activity per unit of body weight (Table 20-6). Drugs that are heavily dependent on renal excretion will have a sharply decreased elimination half-life. For example, the penicillins are excreted for the most part through the kidney. The elimination half-lives of such drugs are much reduced in infants, as shown in Table 20-7.

When dosage guidelines are not available for a drug, empirical dose adjustment methods are often used. These empirical dose adjustment methods are based on body surface area or body weight. Dosage based on the child’s age and body weight and normalized to drug dosages in humans was used in the past.
However, pharmacokinetic parameters may vary as a function of age. Dosage based on body surface area has the advantage of avoiding some bias due to obesity or unusual body weight, because the height and weight of the patient are both considered. The body surface area method gives only a rough estimation of the proper dose, because the pharmacokinetic differences between patients of the same body surface area are not considered. Dosage regimens for the newborn, infant, and child must consider the changing physiologic development of the patient and the pharmacokinetics of the specific drug for that age group. In the package insert of new drugs, under the section on Use in Specific Populations, pediatric use information should be consulted for drug-specific information.

### PRACTICE PROBLEM

The elimination half-life of penicillin G is 0.5 hour in adults and 3.2 hours in neonates (0–7 days old). Assuming that the normal adult dose of penicillin G is 4 mg/kg every 4 hours, calculate the dose of penicillin G for an 11-lb infant.

#### Solution

\[
\frac{\tau_2}{\tau_1} = \frac{(t_{1/2})_1}{(t_{1/2})_2}
\]

\[
t_{1/2} = 0.5 \text{ h}
\]

\[
\frac{\tau_2}{\tau_1} = \frac{4 \times 3.2}{0.5} = 25.6 \text{ h}
\]

Therefore, this infant may be given the following dose:

\[
\text{Dose} = 4 \text{ mg/kg} = \frac{11 \text{ lb}}{2.2 \text{ lb/kg}} = 20 \text{ mg every 24 h}
\]

Alternatively, 10 mg every 12 hours would achieve the same \( C_{av} \).

### DOSING OF DRUGS IN THE ELDERLY

Defining “elderly” is difficult. The geriatric population is often arbitrarily defined as patients who are older than 65 years, and many of these people live active and healthy lives. In addition, there is an increasing number of people who are living more than 85 years, who are often considered the “older elderly” population. The aging process is more
often associated with physiologic changes during aging rather than purely chronological age. Chronologically, the elderly have been classified as the young old (ages 65–75 years), the old (ages 75–85 years), and the old old (age > 85 years) (Abernethy, 2001).

Performance capacity and the loss of homeostatic reserve decrease with advanced age but occurs to a different degree in each organ and in each patient. Physiologic and cognitive functions tend to change with the aging process and can affect compliance and the therapeutic safety and efficacy of a prescribed drug. The elderly also tend to be on multiple drug therapy due to concomitant illness. Decreased cognitive function in some geriatric patients, complicated drug dosage schedules, and/or the high cost of drug therapy may result in poor drug compliance, resulting in lack of drug efficacy, possible drug interactions, and/or drug intoxication.

Several vital physiologic functions related to age as measured by markers show that renal plasma flow, glomerular filtration, cardiac output, and breathing capacity can drop from 10% to 30% in elderly subjects compared to those at age 30. The physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly. For some drugs, an age-dependent increase in adverse drug reactions or toxicity may be observed. This apparent increased drug sensitivity in the elderly may be due to pharmacodynamic and/or pharmacokinetic changes (Mayersohn, 1994; Schmueker, 1985a).

The pharmacodynamic hypothesis assumes that age causes alterations in the quantity and quality of target drug receptors, leading to enhanced drug response. Quantitatively, the number of drug receptors may decline with age, whereas qualitatively, a change in the affinity for the drug may occur. Alternatively, the pharmacokinetic hypothesis assumes that age-dependent increases in adverse drug reactions are due to physiologic changes in drug absorption, distribution, and elimination, including renal excretion and hepatic clearance.

In the elderly, age-dependent alterations in drug absorption may include a decline in the splanchnic blood flow, altered gastrointestinal motility, increase in gastric pH, and alteration in the gastrointestinal absorptive surface. The incidence of achlorhydria in the elderly may have an effect on the dissolution of certain drugs such as weak bases and certain dosage forms that require an acid environment for disintegration and release (Mayersohn, 1994). From a distribution consideration, drug–protein binding in the plasma may decrease as a result of decrease in the albumin concentration, and the apparent volume of distribution may change due to a decrease in muscle mass and an increase in body fat. Renal drug excretion generally declines with age as a result of decrease in the glomerular filtration rate and/or active tubular secretion. Moreover, the activity of the enzymes responsible for drug biotransformation may decrease with age, leading to a decline in hepatic drug clearance.

Elderly patients may have several different pathophysiologic conditions that require multiple drug therapy that increases the likelihood for a drug interaction. Moreover, increased adverse drug reactions and toxicity may result from poor patient compliance. Both penicillin and kanamycin show prolonged \( t_{1/2} \) in the aged patient, as a consequence of an age-related gradual reduction in the kidney size and function. The Gault–Cockroft rule for calculating creatinine clearance clearly quantitates a reduction in clearance with increased age (see Chapter 21). Age-related changes in plasma albumin and \( \alpha_1 \)-acid glycoprotein may also be a factor in the binding of drugs in the body.

**PRACTICE PROBLEMS**

1. An aminoglycoside has a normal elimination half-life of 107 minutes in young adults. In patients 70 to 90 years old, the elimination half-life of the aminoglycoside is 282 minutes. The normal dose of the aminoglycoside is 15 mg/kg per day divided into two doses. What is the dose for a 75-year-old patient, assuming that the volume of distribution per body weight is not changed by the patient’s age?

**Solution**

The longer elimination half-life of the aminoglycoside in elderly patients is due to a decrease in renal function. A good inverse correlation has been obtained of elimination half-life to the aminoglycoside and creatinine.
clearance. To maintain the same average concentration of the aminoglycoside in the elderly as in young adults, the dose may be reduced.

\[
C_{av} = \frac{1.44D_N(t_{1/2})_N}{\tau_N V_N} = \frac{1.44D_0(t_{1/2})_0}{\tau_0 V_0}
\]

\[
\frac{D_N(t_{1/2})_N}{\tau_N} = \frac{D_0(t_{1/2})_0}{\tau_0}
\]

Keeping the dose constant,

\[
D_N = D_0
\]

where \(D_N\) is the new dose and \(D_0\) is the old dose.

\[
\tau_N = \frac{(t_{1/2})_0}{(t_{1/2})_N}
\]

\[
\tau_0 = 12 \times \frac{282}{107} = 31.6 \text{ h}
\]

Therefore, the same dose of the aminoglycoside may be administered every 32 hours without affecting the average steady-state level of the aminoglycoside.

2. The clearance of lithium was determined to be 41.5 mL/min in a group of patients with an average age of 25 years. In a group of elderly patients with an average age of 63 years, the clearance of lithium was 7.7 mL/min. What percentage of the normal dose of lithium should be given to a 65-year-old patient?

**Solution**

The dose should be proportional to clearance; therefore,

\[
\text{Dose reductions (\%)} = \frac{7.7 \times 100}{41.5} = 18.5\%
\]

The dose of lithium may be reduced to about 20% of the regular dose in the 65-year-old patient without affecting the steady-state blood level.

**CLINICAL EXAMPLE**

Hypertension is common in elderly patients. The pharmacokinetics of felodipine (Plendil), a calcium channel antagonist for hypertension, was studied in young and elderly subjects. After a dose of 5 mg oral felodipine, the AUC and \(C_{max}\) in the elderly patients (67–79 years of age, mean weight 71 kg) were three times that of the young subjects (20–34 years of age, mean weight 75 kg), as shown in Fig. 20-2. Side effects of felodipine in the elderly patients, such as flushing, were reported in 9 of 11 subjects, and palpitation was reported in 3 of 11 subjects, whereas only 1 of 12 of the young subjects reported side effects. Systemic clearance in the elderly was 248 ± 108 L/h compared to 619 ± 214 L/h in the young subjects. The bioavailability of felodipine was reported to be about 15.5% in the elderly and 15.3% in the young subjects. (Concomitant medications included a diuretic and a beta-blocker.)

a. What is the main cause for the difference in the observed AUC between the elderly and young subjects?

b. What would be the steady-state level of felodipine in the elderly if dose and dosing interval are unchanged?

c. Can felodipine be given safely to elderly patients?

**Solution**

a. The higher AUC in the elderly compared to young adults is due to the decreased drug clearance in the older subjects.
b. The elderly have more side effects with felodipine compared to young adults. Factors that may have increased side effects in the elderly could be (1) reduced hepatic blood flow, (2) potassium depletion in the body, (3) increased bioavailability, or (4) reduced clearance.

c. \[ C_{av} = \frac{FD_0}{Cl} \quad (20.8) \]

If \( D_0 \), \( F \), and \( \tau \) are the same, the steady-state drug concentration, \( C_{av} \), will be inversely proportional to clearance:

\[
\frac{C_{av \ \text{elderly}}}{C_{av \ \text{young}}} = \frac{Cl_{young}}{Cl_{elderly}}
\]

\[
\frac{C_{av \ \text{elderly}}}{C_{av \ \text{young}}} = \frac{619}{248} = 2.5
\]

(Note: \( Cl \) is in the denominator in Equation 20.8 and is inversely related to concentration.) The steady concentration of felodipine will be 250% or 2.5 times that in the young subjects.

**Examples**

1. An elderly 85-year-old adult patient with congestive heart failure has a serum creatinine of 1.0 mg/dL. The 24-hour urinary creatinine excretion was 0.7 g. Based on the serum creatinine only, this patient has normal renal function, whereas based on both serum creatinine concentration and total 24-hour urinary creatinine excretion, the patient has a GFR of less than 50 mL/min. In practice, serum creatinine clearance is often estimated from serum creatinine concentration alone for dose adjustment. In elderly subjects, the clinician should carefully assess the patient, since substantial deviation from the true clearance may occur in some elderly subjects.

2. Diflunisal pharmacokinetics was studied in healthy young and old subjects. After a single dose of diflunisal, the terminal plasma half-life, mean residence time, and apparent volume of distribution were higher in elderly subjects than in young adults (Erikson et al, 1989). This study shows that renal function in elderly subjects is generally reduced somewhat compared to younger patients because of a diminished rate of glomerular filtration.

**Changes in Renal Function with Age**

Many studies have shown a general decline in glomerular filtration rate (GFR) with age. Lindeman (1992) reported that the GFR as measured by creatinine clearance (see Chapter 21) decreases at a mean rate of 1% per year after 40 years of age. However, there is considerable variation in this rate of decline in normal healthy aging adults. In a previous study by Lindeman et al (1985), approximately two-thirds of the subjects (162 of 254) had declining creatinine clearances, whereas about one-third of the subjects (92 of 254) had no decrease in creatinine clearance. Since muscle mass and urinary creatinine excretion decrease at nearly the same rate in the elderly, mean serum concentrations may stay relatively constant. Creatinine clearance measured by serum creatinine concentrations only (see Chapter 21) may yield inaccurate GFR function if urinary creatinine excretion is not measured.

**Dosing of Drugs in the Obese Patient**

Obesity is a major problem in the United States and is also becoming a problem in other countries. Obesity has been associated with increased mortality resulting from increases in the incidence of hypertension, atherosclerosis, coronary artery disease, diabetes, and other conditions compared to nonobese patients (Blouin and Warren, 1999; National Institutes of Health, 2003).

A patient is considered obese if actual body weight exceeds ideal or desirable body weight by 20%, according to Metropolitan Life Insurance Company data (latest published tables). Ideal or
desirable body weights are based on average body weights and heights for males and for females considering age. Athletes who have a greater body weight due to greater muscle mass are not considered obese. Obesity often is defined by body mass index (BMI), a value that normalizes body weight based on height. BMI is expressed as body weight (kg) divided by the square of the person’s height (meters) or kg/m². BMI is calculated according to the following two equations:

\[
\text{BMI} = \left( \frac{\text{weight (lb)}}{\text{height (in)}} \right)^2 \times 703
\]

\[
\text{BMI} = \left( \frac{\text{weight (kg)}}{\text{height (cm)}} \right)^2 \times 10,000
\]

An extensive study on obesity has been published by the National Institutes of Health, National Heart, Lung and Blood Institute (2003), giving five weight classifications based on body mass index, BMI:

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight:</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal body weight:</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight:</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obese:</td>
<td>30–39.9</td>
</tr>
<tr>
<td>Extreme obesity:</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

BMI correlates strongly with total body fat in nonelderly adults; it is commonly used as a surrogate for total body fat. Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers. The obese patient (BMI > 30) has a greater accumulation of fat tissue than is necessary for normal body functions. Adipose (fat) tissue has a smaller proportion of water compared to muscle tissue. Thus, the obese patient has a smaller proportion of total body water to total body weight compared to the patient of ideal body weight, which could affect the apparent volume of distribution of the drug. For example, Abernethy and Greenblatt (1982) showed a significant difference in the apparent volume of distribution of antipyrine in obese patients (0.46 L/kg) compared to ideal-body-weight patients (0.62 L/kg) based on actual total body weight. Ideal body weight (IBW) refers to the appropriate or normal weight for a male or female based on age, height, weight, and frame size; ideal body weights are generally obtained from the latest table of desirable weights for men and women compiled by the Metropolitan Life Insurance Company.

BMI is not a very accurate measure of adiposity in certain individual patients, particularly in people with elevated lean body mass, such as athletes, and in children. Other approaches have been used to predict the relationship of obesity to cardiovascular risk, such as waist circumference, waist-to-hip ratio, and the waist-to-hip-to-height index (Green and Duffull, 2004).

In addition to differences in total body water per kilogram body weight in the obese patient, the greatest proportion of body fat in these patients could lead to distributional changes in the drug’s pharmacokinetics due to partitioning of the drug between lipid and aqueous environments (Blouin and Warren, 1999). Drugs such as digoxin and gentamicin are very polar and tend to distribute into water rather than into fat tissue. Although lipophilic drugs are associated with larger volumes of distribution in obese patients compared to hydrophilic drugs, there are exceptions and the effect of obesity on specific drugs must be considered for accurate dosing strategy.

Other pharmacokinetic parameters may be altered in the obese patient as a result of physiologic alterations, such as fatty infiltration of the liver affecting biotransformation and cardiovascular changes that may affect renal blood flow and renal excretion (Abermthethy and Greenblatt, 1982).

Dosing by actual body weight may result in overdosing of drugs such as aminoglycosides (eg, gentamicin), which are very polar and are distributed in extracellular fluids. Dosing of these drugs is based on ideal body weight. Lean body weight (LBW) has been estimated by several empirical equations based on the patient’s height and actual (total) body weight. The following equations have been used for estimat-
ing lean body weight, particularly for adjustment of dosage in renally impaired patients:

\[
\text{LBW (males)} = 50 \text{ kg} + 2.3 \text{ kg} \\
\text{for each inch over 5 ft} \\
\text{(20.9)}
\]

\[
\text{LBW (females)} = 45.5 \text{ kg} + 2.3 \text{ kg} \\
\text{for each inch over 5 ft} \\
\text{(20.10)}
\]

where LBW is lean body weight.

**EXAMPLE**

Calculate the lean body weight for an adult male patient who is 5 ft 9 in (175.3 cm) tall and weighs 264 lb (120 kg).

**Solution**

Using Equation 20.9,

\[
\text{LBW} = 50 + (2.3 \times 9) = 70.7 \text{ kg}
\]

**PHARMACOKINETICS OF DRUG INTERACTIONS**

A *drug interaction* generally refers to a modification of the expected drug response in the patient as a result of exposure of the patient to another drug or substance. Some unintentional drug interactions produce adverse reactions in the patient, whereas some drug interactions may be intentional, to provide an improved therapeutic response or to decrease adverse drug effects. Drug interactions may include drug–drug interactions, food–drug interactions, or chemical–drug interactions, such as the interaction of a drug with alcohol or tobacco. A listing of food interactions is given in Chapter 13. A drug–laboratory test interaction pertains to an alteration in a diagnostic clinical laboratory test result because of the drug.

Drug interactions may cause an alteration in the pharmacokinetics of the drug due to an interaction in drug absorption, distribution, or elimination (Tables 20-8 and 20-9). Drug interactions can also

**TABLE 20-8 Sources of Drug Interactions**

<table>
<thead>
<tr>
<th>Type of Drug Interaction</th>
<th>Source</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic</td>
<td>Absorption</td>
<td>Drug interactions can affect the rate and the extent of systemic drug absorption (bioavailability) from the absorption site, resulting in increased or decreased drug bioavailability.</td>
</tr>
<tr>
<td></td>
<td>Distribution</td>
<td>Drug distribution may be altered by displacement of the drug from plasma protein or other binding sites due to competition for the same binding site.</td>
</tr>
<tr>
<td></td>
<td>Hepatic elimination</td>
<td>Drugs that share the same drug-metabolizing enzymes have a potential for a drug interaction.</td>
</tr>
<tr>
<td></td>
<td>Renal clearance</td>
<td>Drugs that compete for active renal secretion may decrease renal clearance of the first drug. Probenecid blocks the active renal secretion of penicillin drugs.</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td>Drug receptor site</td>
<td>Pharmacodynamic drug interactions at the receptor site in which the competing drug potentiates or antagonizes the action of the first drug.</td>
</tr>
<tr>
<td>Pharmaceutical compounding</td>
<td>Pharmaceutical interactions are caused by a chemical or physical incompatibility when two or more drugs are mixed together</td>
<td>An IV solution of aminophylline has an alkaline pH and should not be mixed with such drugs as epinephrine which decompose in an alkaline pH.</td>
</tr>
</tbody>
</table>
**TABLE 20-9 Pharmacokinetic Drug Interactions**

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Examples (Precipitant Drugs)</th>
<th>Effect (Object Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complexation/chelation</td>
<td>Calcium, magnesium, or aluminum and iron salts</td>
<td>Tetracycline complexes with divalent cations, causing a decreased bioavailability</td>
</tr>
<tr>
<td>Adsorption binding/ionic interaction</td>
<td>Cholestyramine resin (anion-exchange resin binding)</td>
<td>Decreased bioavailability of thyroxine, and digoxin; binds anionic drugs and reduces absorption. Some antacid may cause HCl salt to precipitate out in stomach.</td>
</tr>
<tr>
<td>Adsorption</td>
<td>Antacids (adsorption) Charcoal, antidiarrheals</td>
<td>Decreased bioavailability of antibiotics Decreased bioavailability of many drugs</td>
</tr>
<tr>
<td>Increased GI motility</td>
<td>Laxatives, cathartics</td>
<td>Increases GI motility, decreases bioavailability for drugs which are absorbed slowly; may also affect the bioavailability of drugs from controlled-release products</td>
</tr>
<tr>
<td>Decreased GI motility</td>
<td>Anticholinergic agents</td>
<td>Propantheline decreases the gastric emptying of acetaminophen (APAP), delaying APAP absorption from the small intestine</td>
</tr>
<tr>
<td>Alteration of gastric pH</td>
<td>H-2 blockers, antacids</td>
<td>Both H-2 blockers and antacids increase gastric pH; the dissolution of ketoconazole is reduced, causing decreased drug absorption</td>
</tr>
<tr>
<td>Alteration of intestinal flora</td>
<td>Antibiotics (eg, tetracyclines, penicillin)</td>
<td>Digoxin has better bioavailability after erythromycin; erythromycin administration reduces bacterial inactivation of digoxin</td>
</tr>
<tr>
<td>Inhibition of drug metabolism in intestinal cells</td>
<td>Monoamine oxidase inhibitors (MAO-I) (eg, tranylcypromine, phenelzine)</td>
<td>Hypertensive crisis may occur in patients treated with MAO-I and foods containing tyramine</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein binding</td>
<td>Warfarin–phenylbutazone Phenytoin–valproic acid</td>
<td>Displacement of warfarin from binding Displacement of phenytoin from binding</td>
</tr>
<tr>
<td><strong>Hepatic Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzyme induction</td>
<td>Smoking (polycyclic aromatic hydrocarbons) Barbiturates</td>
<td>Smoking increases theophylline clearance Phenobarbital increases the metabolism of warfarin</td>
</tr>
<tr>
<td>Enzyme inhibition</td>
<td>Cimetidine</td>
<td>Decreased theophylline, diazepam metabolism</td>
</tr>
<tr>
<td>Mixed-function oxidase</td>
<td>Fluvoxamine</td>
<td>Diazepam $t_{1/2}$ longer</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Decreased nifedipine metabolism</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Increased levels of phenytoin, warfarin</td>
</tr>
<tr>
<td>Other enzymes</td>
<td>Monoamine oxidase inhibitors, MAO-I (eg, pargyline, tranylcypromine)</td>
<td>Serious hypertensive crisis may occur following ingestion of foods with a high content of tyramine or other pressor substances (eg, cheddar cheese, red wines)</td>
</tr>
<tr>
<td>Inhibition of biliary secretion</td>
<td>Verapamil</td>
<td>Decreased biliary secretion of digoxin causing increased digoxin levels</td>
</tr>
</tbody>
</table>

*(Continued)*
Chapter 20

The risk of a drug interaction increases with multiple drug therapy, multiple prescribers, poor patient compliance, and patient risk factors, such as predisposing illness (diabetes, hypertension, etc) or advancing age. Multiple drug therapy has become routine in most acute and chronic care settings. Elderly patients and patients with various predisposing illnesses tend to be a population using multiple drug therapy. A recent student survey found an aver-

TABLE 20-9  Pharmacokinetic Drug Interactions (Continued)

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Examples (Precipitant Drugs)</th>
<th>Effect (Object Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (GFR) and renal blood flow</td>
<td>Methylxanthines (eg, caffeine, theobromine)</td>
<td>Increased renal blood flow and GFR will decrease time for reabsorption of various drugs, leading to more rapid urinary drug excretion</td>
</tr>
<tr>
<td>Active tubular secretion</td>
<td>Probencid</td>
<td>Probencid blocks the active tubular secretion of penicillin and some cephalosporin antibiotics</td>
</tr>
<tr>
<td>Tubular reabsorption and urine pH</td>
<td>Antacids, sodium bicarbonate</td>
<td>Alkalization of the urine increases the reabsorption of amphetamine and decreases its clearance Alkalization of urine pH increases the ionization of salicylates, decreases reabsorption, and increases its clearance</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charcoal hamburgers</td>
<td>Theophylline, Terfenadine, cyclosporin</td>
<td>Increased elimination half-life of theophylline decreases due to increased metabolism Blood levels of terfenadine and cyclosporine increase due to decreased metabolism</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Lovastatin, simvastatin, nifedipine</td>
<td>Grapefruit juice is a moderate CYP3A inhibitor and increases plasma drug concentrations</td>
</tr>
<tr>
<td>Alcohol (ethanol)</td>
<td>Acetaminophen</td>
<td>Possible hepatotoxicity</td>
</tr>
<tr>
<td>Alcohol (ethanol)</td>
<td></td>
<td>May increase or decrease absorption of many drugs</td>
</tr>
<tr>
<td>Environmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Theophylline</td>
<td>Cigarette smoke contains aromatic hydrocarbons that induce cytochrome isozymes involved in metabolism of theophylline, thereby, shortening the elimination $t_{1/2}$</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (ethanol)</td>
<td>Antihistamines, opioids</td>
<td>Increased drowsiness</td>
</tr>
<tr>
<td>Virus Drug Interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reye's syndrome</td>
<td>Aspirin</td>
<td>Aspirin in children exposed to certain viral infections such as influenza B virus leads to Reye's syndrome</td>
</tr>
</tbody>
</table>

be pharmacodynamic interactions at the receptor site in which the competing drug potentiates or antagonizes the action of the first drug. Pharmaceutical drug interaction occurs when physical and/or chemical incompatibilities arise during extemporaneous pharmaceutical compounding. Pharmaceutical drug interactions, such as drug-excipient interactions, are considered during the development and manufacture of new and generic drug products.
alanine aminotransferase (ALT), aspartate aminotransferase (AST), or other markers of hepatic metabolism (see Chapter 21), should be undertaken. In general, if the therapeutic response is predictable from serum drug concentration, dosing at regular intervals may be based on a steady-state concentration equation such as Equation 20.1. When the elimination half-life is lengthened by drug interaction, the dosing interval may be extended or the dose reduced according to Equation 20.4. Some examples of pharmacokinetic drug interactions are listed in Table 20-9. A more complete discussion of pharmacologic and therapeutic drug interactions of drugs is available in standard textbooks on clinical pharmacology.

Many drugs affect the cytochrome P-450 (CYP) family of hemoprotein enzymes that catalyze drug biotransformation (see also Chapters 11 and 12). Dr. David A. Flockhart, Indiana University School of Medicine, has compiled an excellent website that lists various drugs that may be substrates or inhibitors of cytochrome P-450 isozymes (http://medicine.iupui.edu/flockhart). Some examples of substrates of CYPs are:

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Amitriptyline, fluvoxamine</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Ibuprofen, fluoxetine, tolbutamide, amitriptyline</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole, 5-methynitro, amitriptyline</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Propanol, amitriptyline, fluoxetine, paroxetine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Halothane</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Erythromycin, clarithromycin, midazolam, diazepam</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Clarithromycin, simvastatin, indinavir</td>
</tr>
<tr>
<td>CYP3A6</td>
<td>Erythromycin, clarithromycin, diltiazam</td>
</tr>
</tbody>
</table>

Many calcium channel blockers, macrolides, and protease inhibitors are substrates of CYP3A4, CYP3A5, or CYP3A6. An enzyme substrate may competitively interfere with other substrates’ metabolism if co-administered. Drug inducers of CYPs may also result in drug interactions by accelerating the rate of drug metabolism. When an unusually high plasma level is observed as a result of co-administration...
of a second drug, pharmacists should check whether the two drugs share a common CYP substrate. New substrates are still being discovered. For example, many proton inhibitors share the common CYP2C19 substrate, and many calcium channel blockers are CYP3A4 substrates. It is important to assess the clinical significance with the clinician before alarming the patient. It is also important to suggest an alternative drug therapy to the clinician if a clinically significant drug interaction is likely to be occurring.

Some examples of pharmacokinetic drug interactions are discussed in more detail below and in Chapters 11 and 12. Many side effects occur as a result of impaired or induced (stimulated) drug metabolism. Changes in pharmacokinetics due to impaired drug metabolism should be evaluated quantitatively. For example, acetaminophen is an OTC drug that has been used safely for decades, but incidences of severe hepatic toxicity leading to coma have occurred in some subjects with impaired liver function because of chronic alcohol use. Drugs that have reactive intermediates, active metabolites, and/or metabolites with a longer half-life than the parent drug need to be considered carefully if there is a potential for a drug interaction. A polar metabolite may also distribute to a smaller fluid volume, leading to high concentration in some tissues. Drug interactions involving metabolism may be temporal, observed as a delayed effect. Temporal drug interactions are more difficult to detect in a clinical situation.

**INHIBITION OF DRUG METABOLISM**

Numerous clinical instances of severe adverse reactions as a result of drug interaction involving a change in the rate of drug metabolism have been reported. Knowledge of pharmacokinetics allows the clinical pharmacist to evaluate the clinical significance of the drug interaction. Pharmacokinetic models help determine the need for dose reduction or discontinuing a drug. In assessing the situation, the pathophysiology of the patient and the effect of chronic therapy on drug disposition in the patient must be considered. A severe drug reaction in a patient with liver impairment has resulted in near-fatal reaction in subjects taking otherwise safe doses of acetaminophen. In some patients with injury or severe cardiovascular disease, blood flow may be impaired, resulting in delayed drug absorption and distribution. Many incidents of serious toxicity or accidents are caused by premature administration of a “booster dose” when the expected response is not immediately observed. Potent drugs such as morphine, midazolam, lidocaine, pentothal, and fentanyl can result in serious adverse reactions if the kinetics of multiple dosing are not carefully assessed.

**EXAMPLES**

1. **Fluvoxamine doubles the half-life of diazepam:**
   The effect of fluvoxamine on the pharmacokinetics of diazepam was investigated in healthy volunteers (Perucca et al, 1994). Concurrent fluvoxamine intake increased mean peak plasma diazepam concentrations from 108 to 143 ng/mL, and oral diazepam clearance was reduced from 0.40 to 0.14 mL/min/kg. The half-life of diazepam increased from 51 to 118 hours. The area under the plasma concentration–time curve for the diazepam metabolite N-desmethyldiazepam was also significantly increased during fluvoxamine treatment. These data suggest that fluvoxamine inhibits the biotransformation of diazepam and its active N-demethylated metabolite.

   In this example, the dosing interval, $\tau$, may be increased twofold to account for the doubling of elimination half-life to keep average steady-state concentration unchanged based on Equation 20.4. The rationale for this recommendation may be demonstrated by sketching a diagram showing how the steady-state plasma drug level of diazepam differs after taking 10 mg orally twice a day with or without taking fluvoxamine for a week.

   $$C_{av} = \frac{1.44D_{av}V_F}{V_F\tau}$$
2. Quinidine inhibits the metabolism of nifedipine and other calcium channel-blocking agents: Quinidine co-administration significantly inhibited the aromatization of nifedipine to its major first-pass pyridine metabolite and prolonged the elimination half-life by about 40% (Schellens et al, 1991). The interaction between quinidine and nifedipine supports the involvement of a common cytochrome P-450 (P450 3A4) in the metabolism of the two drugs. Other calcium channel antagonists may also be affected by a similar interaction. What could be a potential problem if two drugs metabolized by the same isozyme are co-administered?

3. Theophylline clearance is decreased by cimetidine: Controlled studies have shown that cimetidine can decrease theophylline plasma clearance by 20% to 40% (apparently by inhibiting demethylation) (Loi et al, 1997). Prolongation of half-life by as much as 70% was found in some patients. Elevated theophylline plasma concentrations with toxicity may lead to nausea, vomiting, cardiovascular instability, and even seizure. What could happen to an asthmatic patient whose meals are high in protein and low in carbohydrate, and who takes Tagamet 400 mg BID? (Hint: Check the effect of food on theophylline, below.)

4. Interferon-β reduces metabolism of theophylline: Theophylline pharmacokinetics was also examined before and after interferon treatment (Okuno et al, 1993). Interferon-β treatment reduced the activities of both O-dealkylases by 47%. The total body clearance of theophylline was also decreased (from 0.76 to 0.56 mL/kg/min) and its elimination half-life was increased (from 8.4 to 11.7 hours; p < 0.05). This study provided the first direct evidence that interferon-β can depress the activity of drug-metabolizing enzymes in the human liver. What percent of steady-state theophylline plasma concentration would be changed by the interaction? (Use Equation 20.8.)

5. Torsades de pointes interaction: A life-threatening ventricular arrhythmia associated with prolongation of the QT interval, known as torsades de pointes, caused the removal of the antihistamine terfenadine (Seldane) from the market because of drug interactions with cisapride, astemizole, and ketoconazole. Clinical symptoms of torsades de pointes include dizziness, syncope, irregular heartbeat, and sudden death. The active metabolite of terfenadine is not cardiac toxic and is now marked as fexofenadine (Allegra), a non-sedative antihistamine.

6. Cimetidine and diazepam interaction: The administration of 800 mg of cimetidine daily for 1 week increased the steady-state plasma diazepam and nordiazepam concentrations due to a cimetidine-induced impairment in microsomal oxidation of diazepam and nordiazepam. The concurrent administration of cimetidine caused a decrease in total metabolic clearance of diazepam and its metabolite, nordiazepam (Lima et al, 1991). How would the following pharmacokinetic parameters of diazepam be affected by the co-administration of cimetidine?
   a. Area under the curve in the dose interval (AUC$_{0-24h}$)
   b. Maximum plasma concentration ($C_{max}$)
   c. Time to peak concentration ($t_{max}$)
   d. Elimination rate constant ($k$)
   e. Total body clearance ($Cl_T$)
   f. Inhibition of monoamine oxidase (MAO)

---

**INHIBITION OF MONOAMINE OXIDASE (MAO)**

Nonhepatic enzymes can be involved in drug interactions. For example, drug interactions have been reported for patients taking the antibacterial drug linezolid (Zyvox) who are concurrently taking certain psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Linezolid is a reversible monoamine oxidase inhibitor (MAOI). Serotonergic psychiatric medications may include antidepressant drugs such as citalopram, paroxetine, fluoxetine, sertraline, and other drugs that affect the serotonergic pathway in
the brain. MAOIs, such as phenelzine and isocarboxazid, are also contraindicated. Although the exact mechanism of this drug interaction is unknown, linezolid inhibits the action of monoamine oxidase A—an enzyme responsible for breaking down serotonin in the brain. It is believed that when linezolid is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as serotonin syndrome. Its signs and symptoms include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever. A complete list is posted on the FDA website, http://www.fda.gov/Drugs/DrugSafety/ucm265305.htm (accessed 8/26/2011).

**INDUCTION OF DRUG METABOLISM**

Cytochrome P-450 isozymes are often involved in the metabolic oxidation of many drugs (see Chapter 11). Many drugs can stimulate the production of hepatic enzymes. Therapeutic doses of phenobarbital and other barbiturates accelerate the metabolism of coumarin anticoagulants such as warfarin and substantially reduce the hypoprothrombinemic effect. Fatal hemorrhagic episodes can result when phenobarbital is withdrawn and warfarin dosage maintained at its previous level. Other drugs known to stimulate drug metabolism include carbamazepine, rifampin, valproic acid, and phenytoin. Enzymatic stimulation can shorten the elimination half-life of the affected drug. For example, phenobarbital can result in lower levels of dexamethasone in asthmatic patients taking both drugs. St. John’s wort, an herbal supplement, also induces cytochrome P-450 isozymes and is known to reduce plasma drug concentrations of digoxin, indinavir, and other drugs.

**INHIBITION OF DRUG ABSORPTION**

Various drugs and dietary supplements can decrease the absorption of drugs from the gastrointestinal tract. Antacids containing magnesium and aluminum hydroxide often interfere with absorption of many drugs. Co-administration of magnesium and aluminum hydroxide caused a decrease of plasma levels of perfloxacin. The drug interaction is caused by the formation of chelate complexes and is possibly also due to adsorption of the quinolone to aluminum hydroxide gel. Perflloxacin should be given at least 2 hours before the antacid to ensure sufficient therapeutic efficacy of the quinolone.

Sucralfate is an aluminum glycopyranoside complex that is not absorbed but retards the oral absorption of ciprofloxacin. Sucralfate is used in the local treatment of ulcers. Cholestyramine is an anion-exchange resin that binds bile acid and many drugs in the gastrointestinal tract. Cholestyramine can bind digitoxin in the GI tract and shorten the elimination half-life of digitoxin by approximately 30% to 40%. Absorption of thyroxine may be reduced by 50% when it is administered closely with cholestyramine.

**INHIBITION OF BILIARY EXCRETION**

The interaction between digoxin and verapamil (Hedman et al, 1991) was studied in six patients (mean age 61 ± 5 years) with chronic atrial fibrillation. The effects of adding verapamil (240 mg/d) on steady-state plasma concentrations of digoxin were studied. Verapamil induced a 44% increase in steady-state plasma concentrations of digoxin. The biliary clearance of digoxin was determined by a duodenal perfusion technique. The biliary clearance of digoxin decreased by 43%, from 187 ± 89 to 101 ± 55 mL/min, whereas the renal clearance was not significantly different (153 ± 31 vs 173 ± 51 mL/min).

**ALTERED RENAL REABSORPTION DUE TO CHANGING URINARY pH**

The normal adult urinary pH ranges from 4.8 to 7.5 but can increase due to chronic antacid use. This change in urinary pH affects the ionization and reabsorption of weak electrolyte drugs (see Chapter 6). An increased ionization of salicylate due to an increase in urine pH reduces salicylate reabsorption in the renal tubule, resulting in increased renal excretion. Magnesium aluminum hydroxide gel (Maalox),
120 mL/d for 6 days, decreased serum salicylate levels from 19.8 to 15.8 mg/dL in six subjects who had achieved a control serum salicylate level of 0.10 mg/dL with the equivalent of 3.76 g/d aspirin (Hansten et al, 1980). Single doses of magnesium aluminum hydroxide gel did not alter urine pH significantly. Five milliliters of Titalac (calcium carbonate with glycine) 4 times a day or magnesium hydroxide for 7 days also increased urinary pH. In general, drugs with pKₐ values within the urinary pH range are affected the most. Basic drugs tend to have longer half-lives when urinary pH is increased, especially near its pKₐ.

**PRACTICAL FOCUS**

Some drugs can change urinary pH and thereby, affect the rate of excretion of weak electrolyte drugs in the urine. Which of the following treatments would be most likely to decrease the elimination $t_{1/2}$ of aspirin? Explain the rationale for your answer.

1. Calcium carbonate PO
2. Sodium carbonate PO
3. IV sodium bicarbonate

**EFFECT OF FOOD ON DRUG DISPOSITION**

**Diet–Theophylline Interaction**

Theophylline disposition is influenced by diet. A protein-rich diet will increase theophylline clearance. Average theophylline half-lives in subjects on a low-carbohydrate, high-protein diet increased from 5.2 to 7.6 hours when subjects were changed to a high-carbohydrate, low-protein diet. A diet of charcoal-broiled beef, which contains polycyclic aromatic hydrocarbons from the charcoal, resulted in a decrease in theophylline half-life of up to 42% when compared to a control non-charcoal-broiled-beef diet. Irregular intake of vitamin K may modify the anticoagulant effect of warfarin. Many foods, especially green, leafy vegetables such as broccoli and spinach, contain high concentrations of vitamin K. In one study, warfarin therapy was interfered with inpatients receiving vitamin K, broccoli, or spinach daily for 1 week (Pedersen et al, 1991).

**Grapefruit–Drug Interactions**

The ingredients in a common food product, grapefruit juice, taken in usual dietary quantities, can significantly inhibit the metabolism by gut-wall cytochrome P-450 3A4 (CYP3A4) (Spence, 1997). For example, grapefruit juice increases average felodipine levels about threefold, increases cyclosporine levels, and increases the levels of terfenadine, a common antihistamine. In the case of terfenadine, Spence (1997) reported the death of a 29-year-old man who had been taking terfenadine and drinking grapefruit juice 2 to 3 times per week. Death was attributed to terfenadine toxicity. Grapefruit juice can also affect P-gp-mediated efflux of some drugs.

**ADVERSE VIRAL DRUG INTERACTIONS**

Recent findings have suggested that some interactions of viruses and drugs may predispose individuals to specific disease outcomes (Haverkos et al, 1991). For example, Reye’s syndrome has been observed in children who had been taking aspirin and were concurrently exposed to certain viruses, including influenza B virus and varicella zoster virus. The mechanism by which salicylates and certain viruses interact is not clear. However, the publication of this interaction has led to the prevention of morbidity and mortality due to this complex interaction (Haverkos et al, 1991).

**POPULATION PHARMACOKINETICS**

Population pharmacokinetics (PopPK) is the study of variability in plasma drug concentrations between and within patient populations receiving therapeutic doses of a drug. Traditional pharmacokinetic studies are usually performed on healthy volunteers or highly selected patients, and the average behavior of a group (ie, the mean plasma concentration–time profile) is the main focus of interest. PopPK examines the relationship of the demographic, genetic, pathophysiological, environmental, and other drug-related factors that contribute to the variability observed in safety and efficacy of
the drug. The PopPK approach encompasses some of the following features (FDA Guidance, 1999):

- The collection of relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug.
- The identification and measurement of variability during drug development and evaluation.
- The explanation of variability by identifying factors of demographic, pathophysiological, environmental, or concomitant drug-related origin that may influence the pharmacokinetic behavior of a drug.
- The quantitative estimation of the magnitude of the unexplained variability in the patient population.

The resolution of the issues causing variability in patients allows for the development of an optimum dosing strategy for a population, subgroup, or individual patient. The importance of developing optimum dosing strategies has led to an increase in the use of PopPK approaches in new drug development.

**Introduction to Bayesian Theory**

Bayesian theory was originally developed to improve forecast accuracy by combining subjective prediction with improvement from newly collected data. In the diagnosis of disease, the physician may make a preliminary diagnosis based on symptoms and physical examination. Later, the results of laboratory tests are received. The clinician then makes a new diagnostic forecast based on both sets of information. Bayesian theory provides a method to weigh the prior information (eg, physical diagnosis) and new information (eg, results from laboratory tests) to estimate a new probability for predicting the disease.

In developing a drug dosage regimen, we assess the patient’s medical history and then use average or population pharmacokinetic parameters appropriate for the patient’s condition to calculate the initial dose. After the initial dose, plasma or serum drug concentrations are obtained from the patient that provide new information to assess the adequacy of the dosage. The dosing approach of combining old information with new involves a “feedback” process and is, to some degree, inherent in many dosing methods involving some parameter readjustment when new serum drug concentrations become known. The advantage of the Bayesian approach is the improvement in estimating the patient’s pharmacokinetic parameters based on Bayesian probability versus an ordinary least-squares-based program. An example comparing the Bayesian method with an alternative method for parameter estimation from some simulated theophylline data will be shown in the next section. The method is particularly useful when only a few blood samples are available.

Because of inter- and intrasubject variability, the pharmacokinetic parameters of an individual patient must be estimated from limited data in the presence of unknown random error (assays, etc), known covariates and variables such as clearance, weight, and disease factor, etc, and possible structural (kinetic model) error. From knowledge of mean population pharmacokinetic parameters and their variability, Bayesian methods often employ a special weighted least-squares (WLS) approach and allow improved estimation of patient pharmacokinetic parameters when there is a lot of variation in data. The methodology is discussed in more detail under the Bayes estimator in the next section and also under pharmacokinetic analysis.

**EXAMPLE**

After diagnosing a patient, the physician gave the patient a probability of 0.4 of having a disease. The physician then ordered a clinical laboratory test. A positive laboratory test value had a probability of 0.8 of positively identifying the disease in patients with the disease (true positive) and a probability of 0.1 of positive identification of the disease in subjects without the disease (false positive). From the prior information (physician’s diagnosis) and current patient-specific data (laboratory test), what is the posterior probability of the patient having the disease using the Bayesian method?

**Solution**

Prior probability of having the disease (positive) = 0.4

Prior probability of not having the disease (negative) = 1 – 0.4 = 0.6
Ratio of disease positive/disease negative = 0.4/0.6 = 2/3, or the physician’s evaluation shows a 2/3 chance for the presence of the disease.

The probability of the patient actually having the disease can be better evaluated by including the laboratory findings. For this same patient, the probability of a positive laboratory test of 0.8 for the detection of disease in positive patients (with disease) and the probability of 0.1 in negative patients (without disease) are equal to a ratio of 0.8/0.1 or 8/1. This ratio is known as the likelihood ratio. Combining with the prior probability of 2/3, the posterior probability ratio is

\[
\text{Posterior probability ratio} = (2/3) (8/1) = 16/3
\]

\[
\text{Posterior probability} = 16/(16 + 3) = 84.2\%
\]

Thus, the laboratory test that estimates the likelihood ratio and the preliminary diagnostic evaluation are both used in determining the posterior probability. The results of this calculation show that with a positive diagnosis by the physician and a positive value for the laboratory test, the probability that the patient actually has the disease is 84.2%.

Bayesian probability theory when applied to dosing of a drug involves a given pharmacokinetic parameter \(P\) and plasma or serum drug concentration \(C\), as shown in Equation (20.11). The probability of a patient with a given pharmacokinetic parameter \(P\), taking into account the measured concentration, is \(\text{Prob}(P/C)\):

\[
\text{Prob}(P/C) = \frac{\text{Prob}(P) \cdot \text{Prob}(C/P)}{\text{Prob}(C)} \quad \text{(20.11)}
\]

where \(\text{Prob}(P)\) = the probability of the patient’s parameter within the assumed population distribution, \(\text{Prob}(C/P)\) = the probability of measured concentration within the population, and \(\text{Prob}(C)\) = the unconditional probability of the observed concentration.

Theophylline has a therapeutic window of 10 to 20 µg/mL. Serum theophylline concentrations above 20 µg/mL produce mild side effects, such as nausea and insomnia; more serious side effects, such as sinus tachycardia, may occur at drug concentrations above 40 µg/mL; at serum concentrations above 45 µg/mL, cardiac arrhythmia and seizure may occur (see Fig. 20-1). However, the probability of some side effect occurring is by no means certain. Side effects are not determined solely by plasma concentration, as other known or unknown variables (called covariates) may affect the side effect outcome. Some patients have initial side effects of nausea and restlessness (even at very low drug concentrations) that later disappear when therapy is continued. The clinician should therefore assess the probability of side effects in the patient, order a blood sample for serum theophylline determination, and then estimate a combined (or posterior) probability for side effects in the patient.

The decision process is illustrated graphically in Fig. 20-3. The probability of initial (prior) estimation of side effects is plotted on the x axis, and the final (posterior) probability of side effects is plotted on the y axis for various serum theophylline concentrations. For example, a patient was placed on theophylline and the physician estimated the chance of side effects to be 40%, but therapeutic drug monitoring showed a theophylline level of 27 µg/mL. A vertical line of prior probability at .4 intersects curve \(a\) at about 0.78 or 78%. Hence, the Bayesian probability of having side effects is 78% taking both the laboratory and physician assessments into consideration. The curves (a–e in Fig. 20-3) for various theophylline concentrations are called conditional probability curves. Bayesian theory does not replace clinical judgment, but it provides a quantitative tool for incorporating subjective judgment (human) with objective (laboratory assay) in making risk decisions. When complex decisions involving several variables are involved, this objective tool can be very useful.
Adaptive Method or Dosing with Feedback

In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on mean population pharmacokinetic parameters. After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable. This type of approach has been referred to as adaptive, or Bayesian adaptive method with feedback when a spacial extended least-squares algorithm is used. Many ordinary least-squares computer software packages are available to clinical practice for parameter and dosage calculation (see Appendix B). Some software packages record medical history and provide adjustments for weight, age, and in some cases, disease factors. A common approach is to estimate the clearance and volume of distribution from intermittent infusion (see Chapter 5).

Abbottbase Pharmacokinetic Systems (1986 and 1992) is an example of patient-oriented software that records patient information and dosing history based on 24-hour clock time. An adaptive-type algorithm is used to estimate pharmacokinetic parameters. The average population clearance and volume of distribution of drugs are used for initial estimates and the program computes patient-specific $Cl$ and $V_D$ as serum drug concentrations are entered. The program accounts for renal dysfunction based on creatinine clearance, which is estimated from serum creatinine concentration using the Cockroft–Gault equation (see Chapter 21). The software package allows specific parameter estimation for digoxin, theophylline, and aminoglycosides, although other drugs can also be analyzed manually.

Many least-squares (LS) and weighted least-squares (WLS) algorithms are available for estimating patient pharmacokinetic parameters. Their common objective involves estimating the parameters with minimum bias and good prediction, often as evaluated by mean predictive error. The advantage of the Bayesian method is the ability to input known information into the program, so that the search for the real pharmacokinetic parameter is more efficient and, perhaps, more precise. For example, a drug is administered by intravenous infusion at a rate, $R$, to a patient. The drug is infused...
over \( t \) hours (\( t \) may be 0.5–2 hours for a typical infusion). The patient’s clearance, \( CL_p \), may be estimated from plasma drug concentration taken at a known time according to a one-compartment model equation. Sheiner and Beal (1982) simulated a set of theophylline data and estimated parameters from the data using one- and two-serum concentrations, assuming different variabilities. These investigators tested the method with a Bayesian approach and with an ordinary least-squares method, OBJ_{OLS}:

\[
C_i = f(P, t) + \varepsilon_i
\]  

(20.12)

\[
OBJ_{OLS} = \sum_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2}
\]  

(20.13)

**The Bayes Estimator**

When the pharmacokinetic parameter, \( P \), is estimated from a set of plasma drug concentration data (\( C_i \)) having several potential sources of error with different variance, the ordinary least-squares (OLS) method for parameter estimation is no longer adequate (it yields trivial estimates). The intersubject variation, intrasubject variance, and random error must be minimized properly to allow efficient parameter estimation. The weighted least-squares function in Equation 20.14 was suggested by Sheiner and Beal (1982). The equation represents the least-squares estimation of the concentration by minimizing deviation squares (first summation term of Equation 20.14), and deviation of population parameter squares (second summation term). Equation 20.14 is called the Bayes estimator. This approach is frequently referred to as extended least-squares (ELS).

Intrasubject \( C_i = f(P, X_i) + \varepsilon_i \)

Intersubject \( P_k = \hat{P}_k + \eta_k \)  

(20.14)

\[
OBJ_{BAYES} = \sum_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2} + \sum_{k=1}^{K} \frac{(P_k - \hat{P}_k)^2}{\omega_k^2}
\]

For \( n \) number of drug plasma concentration data, \( i \) is an index to refer to each data item, \( C_i \) is the \( i \)th concentration, \( \hat{C}_i \) is the \( i \)th model-estimated concentration, and \( \sigma_i^2 \) is the variance of random error, \( \varepsilon_i \) (assay errors, random intrasubject variation, etc). There is a series of population parameters in the model for the \( k \)th population parameter, \( P_k \). \( \hat{P}_k \) is the estimated population parameter and \( \eta_k \) is the \( k \)th parameter random error with variance of \( \omega_k^2 \).

To compare the performance of the Bayesian method to other methods in drug dosing, Sheiner and Beal (1982) generated some theophylline plasma drug concentrations based on known clearance. They added various error levels to the data and divided the patients into groups with one and two plasma drug samples. The two pharmacokinetic parameters used were based on population pharmacokinetics for theophylline derived from the literature: (1) for \( P_1 \), a \( V_D \) of 0.5 L/kg and coefficient of variation of 32%; and (2) for \( P_2 \), clearance of 0.052 L/kg/h and coefficient of variation of 44%.

The data were then analyzed using the Bayesian method and a second (alternative) approach in determining the pharmacokinetic parameter (\( CL_t \)). In the presence of various levels of error, the Bayesian approach was robust and resulted in better estimation of clearance in both the one- and two-sample groups (Fig. 20-4 and Table 20-10). The success of the Bayesian approach is due to the ability of the algorithm to minimize the total mean square terms of errors. A more precise clearance estimation will lead to more accurate dose estimation in the patient.

The implementation of the Bayesian (ELS) approach uses the NONMEM computer software, facilitated by response criteria defined through a first-order (FO) Taylor series expansion. Among other computer software packages available, the NPME2 (USC*PACK) is a nonparametric maximum expectation maximization method that makes no parametric assumptions about the mean and standard deviation of the distribution. The program can also discover unrecognized subpopulations. NONMEM also features FOEM, a first-order expectation maximization method. Generally, finding a set of best parameter estimates to describe the data involves minimizing the error terms; alternatively, another paradigm that maximizes the probability of the parameter estimates in the distribution serves the same purpose equally well or better. Thus, the first-order expectation maximization (FOEM) paradigm is also available in NONMEM and in other programs, such as P-PHARM (Mentre and Gomeni, 1995).
Chapter 20

were compared by Hurley and McNeil (1988). The Bayes method compared favorably with other methods (Tables 20-11 and 20-12). The steady-state method was also useful, but none of the methods was

**Comparison of Bayes, Least-Squares, Steady-State, and Chiou Methods**

For theophylline dosing, the Bayes method and others, including the conventional steady-state method, were compared by Hurley and McNeil (1988). The Bayes method compared favorably with other methods (Tables 20-11 and 20-12). The steady-state method was also useful, but none of the methods was

**TABLE 20-10 Performance of Clearance Estimation Methods**

<table>
<thead>
<tr>
<th>Method</th>
<th>$\frac{\omega_{y,s}}{\sigma}$</th>
<th>$\frac{\omega_{y,s}}{\sigma}$</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>—</td>
<td>—</td>
<td>−5.77(5.8)</td>
<td>−2.82(3.3)</td>
<td>37.1(4.5)</td>
<td>26.4(2.1)</td>
</tr>
<tr>
<td>Bayesian</td>
<td>1</td>
<td>1</td>
<td>−1.02(3.0)</td>
<td>−1.08(3.1)</td>
<td>22.2(2.0)$^a$</td>
<td>21.7(2.2)$^a$</td>
</tr>
<tr>
<td></td>
<td>3/2</td>
<td>1</td>
<td>−4.94(3.4)</td>
<td>−3.77(3.0)</td>
<td>25.6(2.3)$^a$</td>
<td>23.1(2.1)$^a$</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
<td>1</td>
<td>5.02(3.2)</td>
<td>2.52(3.4)</td>
<td>23.7(2.2)$^a$</td>
<td>23.5(2.4)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3/2</td>
<td>0.44(3.0)</td>
<td>−0.26(3.1)</td>
<td>22.5(2.1)$^a$</td>
<td>21.4(2.2)$^a$</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2/3</td>
<td>−0.76(3.0)</td>
<td>−1.56(3.1)</td>
<td>22.5(1.9)$^a$</td>
<td>21.7(2.2)</td>
</tr>
</tbody>
</table>

$^a$Ratio of standard deviation of clearance (or $V_d$) to $\sigma$ used in the Bayesian method. All ratios are divided by the correct ratio so that a value of unity signifies that the correct ratio itself was used.

$^b$Mean absolute error of Bayesian method less than that of alternative ($p < 0.05$).

From Sheiner and Beal (1982), with permission.
Application of Pharmacokinetics to Clinical Situations

Pharmacokinetic estimation methods was given by D’Argenio and Schumitzky (1979). Some common pharmacokinetic algorithms for parameter estimation are: (1) Newton–Raphson with first and second derivative, (2) Gauss–Newton method, (3) Levenberg–Marquardt method, and (4) Nelder–Mead simplex method. The Gauss–Newton method was used in the early versions of NONLIN. As discussed in relation to the mixed-effect models in later sections, assuming a relationship such as $Cl_{R}$ proportional to $Cl_{R}^*$ (technically called linearization) reduces the minimum number of data necessary for parameter estimation.

Analysis of Population Pharmacokinetic Data

Traditional pharmacokinetic studies involve taking multiple blood samples periodically over time in a sufficiently accurate, probably due to other variables, such as saturation kinetics or use of an inappropriate compartment model.

Model fitting in pharmacokinetics often involves the search for a set of parameters that fits the data, a situation analogous to finding a point within a large geometric space. The ordinary least-squares (OLS) approach of iteratively minimizing the error terms may not be adequate when data are sparse, but are fine when sufficient data and good initial estimates are available. The Bayesian approach uses prior information, and, in essence, guides the search pointer to a proximity in the geometric space where the estimates are more likely to be found (reducing variability but increasing subjectivity). Many algorithms use some form of gradient- or derivative-based method; other algorithms use a variable sequential simplex method. A discussion of the pharmacokinetic estimation methods was given by D’Argenio and Schumitzky (1979). Some common pharmacokinetic algorithms for parameter estimation are: (1) Newton–Raphson with first and second derivative, (2) Gauss–Newton method, (3) Levenberg–Marquardt method, and (4) Nelder–Mead simplex method. The Gauss–Newton method was used in the early versions of NONLIN. As discussed in relation to the mixed-effect models in later sections, assuming a relationship such as $Cl_{R}$ proportional to $Cl_{R}^*$ (technically called linearization) reduces the minimum number of data necessary for parameter estimation.

### Table 20-11 Pharmacokinetic Parameter Estimates (Mean ± SD)

<table>
<thead>
<tr>
<th>Method</th>
<th>$CP$ (L/h/kg IBW)</th>
<th>$k^a$ (h⁻¹)</th>
<th>$V_D$ (L/kg IBW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-squares</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.0383 ± 0.0129</td>
<td>0.105 ± 0.014</td>
<td>0.519 ± 0.291</td>
</tr>
<tr>
<td>Final</td>
<td>0.0391 ± 0.0117</td>
<td>0.095 ± 0.064</td>
<td>0.511 ± 0.239</td>
</tr>
<tr>
<td>Chiou</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.0399 ± 0.0306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.0437 ± 0.0193</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.0438 ± 0.0212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-state clearance</td>
<td>0.0408 ± 0.0174</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayesian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.0421 ± 0.0143</td>
<td>0.081 ± 0.030</td>
<td>0.534 ± 0.0745</td>
</tr>
<tr>
<td>2</td>
<td>0.0424 ± 0.0158</td>
<td>0.082 ± 0.035</td>
<td>0.532 ± 0.0802</td>
</tr>
<tr>
<td>3</td>
<td>0.0408 ± 0.0182</td>
<td>0.078 ± 0.037</td>
<td>0.531 ± 0.0820</td>
</tr>
<tr>
<td>4</td>
<td>0.0403 ± 0.0147</td>
<td>0.077 ± 0.027</td>
<td>0.530 ± 0.0787</td>
</tr>
<tr>
<td>Final</td>
<td>0.0372 ± 0.0113</td>
<td>0.070 ± 0.026</td>
<td>0.536 ± 0.0741</td>
</tr>
</tbody>
</table>

$Cl =$ total body clearance, $k =$ elimination rate constant, $V_D =$ volume of distribution, IBW = ideal body weight.

*Calculated from least-squares estimates.

*Calculated by Bayesian estimates.

From Hurley and McNeil (1988), with permission.
few individual patients, and characterizing basic pharmacokinetic parameters such as $k$, $V_D$, and $Cl$; because the studies are generally well designed, there are fewer parameters than data points (ie, that provide sufficient degree of freedom to reflect lack of fit of the model), and the parameters are efficiently estimated from the model with most least-squares programs. Traditional pharmacokinetic parameter estimation is very accurate, provided that enough samples can be taken for the individual patient. The disadvantage is that only a few relatively homogeneous healthy subjects are included in pharmacokinetic studies, from which dosing in different patients must be projected.

In the clinical setting, patients are usually not very homogeneous; patients vary in sex, age, body weight; they may have concomitant disease and may be receiving multiple drug treatments. Even the diet, lifestyle, ethnicity, and geographic location can differ from a selected group of “normal” subjects. Further, it is often not possible to take multiple samples from the same subject, and, therefore, no data are available to reflect intrasubject difference, so that iterative procedures for finding the maximum likelihood estimate can be complex and unpredictable due to incomplete or missing data. However, the vital information needed about the pharmacokinetics of drugs in patients at different stages of their disease with various therapies can only be obtained from the same population, or from a collection of pooled blood samples. The advantages of population pharmacokinetic analysis using pooled data were reviewed by Sheiner and Ludden (1992) and included a summary of population pharmacokinetics for dozens of drugs. Pharmacokinetic analysis of pooled data of plasma drug concentration from a large group of subjects may reveal much information about the disposition of a drug in a population. Unlike data from an individual subject collected over time, inter- and intrasubject variations must be considered. Both pharmacokinetic and nonpharmacokinetic factors, such as age, weight, sex, and creatinine concentration, should be examined in the model to determine the relevance to the estimation of pharmacokinetic parameters.

The nonlinear mixed-effect model (or NONMEM) is so called because the model uses both fixed and random factors to describe data. Fixed factors such as patient weight, age, gender, and creatinine concentration are assumed to have no error, whereas random factors include inter- and intrasubject differences. NONMEM is a statistical program written in Fortran (see Appendix B) that allows Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the first-order (FO) method. The parameters may now be estimated also with a first-order conditional estimate (FOCE) algorithm. In addition, to pharmacokinetic parameters, many examples of population plasma data have been analyzed to determine population factors. Multiplicative coefficients or parameters for patient factors may also be estimated.

NONMEM fits plasma drug concentration data for all subjects in the groups simultaneously and estimates the population parameter and its variance. The parameter may be clearance and/or $V_D$. The model may also test for other fixed effects on the drug due to factors such as age, weight, and creatinine concentration.

### TABLE 20-12 Predictive Accuracy at the End of Infusion 1a

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean Prediction Error (mg/L)</th>
<th>Mean Percent Absolute Prediction Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-squares</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>−0.06 (−1.1, 0.95)</td>
<td>17.6 (13.4, 21.7)</td>
</tr>
<tr>
<td>Chiou</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.96 (−1.7, 3.60)</td>
<td>36.8 (27.3, 46.3)</td>
</tr>
<tr>
<td>2</td>
<td>−1.7 (−3.3, −0.08)</td>
<td>20.8 (14.1, 27.5)</td>
</tr>
<tr>
<td>3</td>
<td>−1.5 (−3.7, 0.80)</td>
<td>27.7 (17.8, 37.5)</td>
</tr>
<tr>
<td>Bayesian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−0.61 (−1.7, 0.50)</td>
<td>18.8 (14.1, 23.6)</td>
</tr>
<tr>
<td>2</td>
<td>−0.65 (−2.0, 0.69)</td>
<td>22.7 (16.3, 29.2)</td>
</tr>
<tr>
<td>3</td>
<td>0.16 (−1.1, 1.40)</td>
<td>21.7 (16.1, 27.2)</td>
</tr>
<tr>
<td>4</td>
<td>−0.15 (−1.2, 0.96)</td>
<td>19.8 (15.6, 24.1)</td>
</tr>
</tbody>
</table>

*Figures in parentheses are 95% confidence intervals.
From Hurley and McNeil (1988), with permission.
The model describes the observed plasma drug concentration \( C_i \) in terms of a model with:

1. \( P_k \) = fixed effect parameters, which include pharmacokinetic parameters or patient factor parameters. For example, \( P_1 \) is \( Cl \), \( P_2 \) is the multiplicative coefficient including creatinine factor, and \( P_3 \) is the multiplicative coefficient for weight.

2. Random effect parameters, including (a) the variance of the structural (kinetic) parameter, \( P_k \) or intersubject variability within the population, \( \omega_k^2 \); and (b) the residual intrasubject variance or variance due to measurement errors, fluctuations in individual parameter values, and all other errors not accounted for by the other parameters.

There are generally two reliable and practical approaches to population pharmacokinetic data analysis. One approach is the standard two-stage (STS) method, which estimates parameters from the plasma drug concentration data for an individual subject during the first stage. The estimates from all subjects are then combined to obtain an estimate of the parameters for the population. The method is useful because unknown factors that affect the response in one patient will not carry over and bias parameter estimates of the others. The method works well when sufficient drug concentration–time data are available.

A second approach, the first-order (FO) method, is also used but is perhaps less well understood. The estimation procedure is based on minimization of an extended least-squares criterion, which was defined through a first-order Taylor series expansion of the response vector about the fixed effects and which utilized a Newton–Raphson-like algorithm (Beal and Sheiner, 1980). This method attempts to fit the data and partition the unpredictable differences between theoretical and observed values into random error terms. When this model includes concomitant effects, it is called a mixed-effect statistical model (Beal and Sheiner, 1985).

The advantage of the first-order model is that it is applicable even when the amount of time–concentration data obtained from each individual is small, provided that the total number of individuals is sufficiently large. For example, in the example cited by Beal and Sheiner (1985), 116 plasma concentrations were collected from 39 patients with various weight, age, gender, serum creatinine, and congestive heart failure conditions. The two-stage method was not suitable, but the FO method was useful for analyzing this set of data. With a large number of factors and only limited data, and with hidden factors possibly affecting the pharmacokinetics of the drug, the analysis may sometimes be misleading. Beal and Sheiner (1985) suggested that the main concomitant factor should be measured whenever possible. Several examples of population pharmacokinetic data analysis using clinical data are listed below. Typically, a computer method is used in the data analysis based on a statistical model using either the weighted least-squares (WLS) or the extended least-squares (ELS) method in estimating the parameters. In the last few years, NONMEM has been regularly updated and improved. Many drugs have been analyzed with population pharmacokinetics to yield the information not obtainable using the traditional two-stage method (Sheiner and Ludden, 1992). An added feature is the development of a population model involving both pharmacokinetics and pharmacodynamics, the so-called population PK/PD models.

One example involving analysis of population plasma concentration data involved the drug procainamide. The drug clearance of an individual in a group may be assumed to be affected by several factors (Whiting et al, 1986). These factors include body weight, creatinine clearance, and a clearance factor \( P_1 \) described in the following equation:

\[
Cl_{drug} = P_1 + P_2 (Cl_{creatinine}) + P_3 (weight) + \eta_{Clj}
\]  

(20.15)

where \( \eta_{Clj} \) is the intersubject error of clearance and its variance is \( \omega_{Clj}^2 \).

In another mixed-effect model involving the analysis of lidocaine and mexiletine, Vozeh and associates (1984) tested age, sex, time on drug therapy, and congestive heart failure (CHF) for effects on drug clearance. The effects of CHF and weight on \( V_D \) were also examined. The test statistic, DELS, or difference extended least-squares, was significant for CHF and moderately significant for weight on lidocaine clearance.
**CLINICAL EXAMPLE**

**Fitting Warfarin Population Data**

Population pharmacokinetics may be analyzed from various clinical sites. The population pharmacokinetics of racemic warfarin was evaluated using 613 measured warfarin plasma concentrations from 32 adult hospitalized patients and 131 adult outpatients (Mungall et al, 1985). Warfarin concentrations were measured in duplicate using a high-performance liquid chromatographic procedure. The pharmacokinetic model used was a one-compartment open model with first-order absorption and first-order elimination. The extent of availability was assumed to be 100%. A linear regression model was used to evaluate the influence of various disease and demographic factors (Table 20-13) on warfarin drug clearance. Age appeared to be an important determinant of warfarin clearance in this adult population. There was about a 1% per year decrease in oral clearance over the age range 20 to 70 years. Smoking appeared to result in a 10% increase in warfarin clearance, while co-administration of the inducer phenytoin or phenobarbital yielded about a 30% increase in clearance. Other factors such as race, gender, and hospital site did not significantly affect $Cl_T$ based on this model. This study yielded a predictive model that, when combined with appropriate pharmacologic response data, may be useful in the design and adjustment of warfarin regimens.

$$SIZEVD = \frac{TBW}{70}$$

$$VD = SIZEVD \times P1$$

$$SIZECL = \left(\frac{TBW}{70}\right) \times P2$$

$$Cl = SIZECL \times \left(P3 + P4 \times CHF + P5 \times VAH + P6 \times AGE + P7 \times GEN + P8 \times SKG + P9 \times ANG + P10 \times BLK + P11 \times INH + P12 \times IND + P13 \times DIS\right)$$

The patient variables are the following: 1 = present; 0 = absent; CHF = congestive heart failure; VAH = VA hospital site; AGE = age in years; GEN = 1 for male and 0 for female; SKG = smoker; ANG = 1 if Caucasian; BLK = 1 if Black; INH = 1 if taking an inhibitor drug; IND = 1 if taking an inducer drug; DIS = 1 if taking a displacer (protein-binding) drug.

**TABLE 20-13  Population Pharmacokinetics of Warfarin Regression**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Value</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>7.85 L/70 kg</td>
<td>Factor relating TBW to $V_d$</td>
</tr>
<tr>
<td>P2</td>
<td>0.460</td>
<td>exponential factor relating TBW to SIZECL</td>
</tr>
<tr>
<td>P3</td>
<td>3.31 L/d</td>
<td>Factor relating SIZECL to $Cl$</td>
</tr>
<tr>
<td>P4</td>
<td>0</td>
<td>Factors relating CHF to $Cl$</td>
</tr>
<tr>
<td>P5</td>
<td>0</td>
<td>Factor relating VAH site to $Cl$</td>
</tr>
<tr>
<td>P6</td>
<td>-0.0214 L/d/year of age</td>
<td>Factor relating age to $Cl$</td>
</tr>
<tr>
<td>P7</td>
<td>0</td>
<td>Factor relating gender to $Cl$</td>
</tr>
<tr>
<td>P8</td>
<td>0.367 L/d</td>
<td>Factor relating smoking to $Cl$</td>
</tr>
<tr>
<td>P9</td>
<td>0</td>
<td>Factor relating Caucasian vs Latin difference to $Cl$</td>
</tr>
<tr>
<td>P10</td>
<td>0</td>
<td>Factor relating Black vs Latin difference to $Cl$</td>
</tr>
<tr>
<td>P11</td>
<td>0</td>
<td>Factor relating drug inhibitor to $Cl$</td>
</tr>
<tr>
<td>P12</td>
<td>1.16 L/d</td>
<td>Factor relating drug inducer to $Cl$</td>
</tr>
<tr>
<td>P13</td>
<td>0</td>
<td>Factor relating drug displacer to $Cl$</td>
</tr>
</tbody>
</table>

generally well estimated. Other pharmacokinetic parameters are more sensitive to model choice, particularly the apparent elimination rate constant. Prediction of concentrations is generally more precise when the correct model is chosen.

### Decision Analysis Involving Diagnostic Tests

Diagnostic tests may be performed to determine the presence or absence of a disease. A scheme for the predictability of a disease by a diagnostic test is shown in Table 20-14. A true positive, represented by $a$, indicates that the laboratory test correctly predicted the disease, whereas a false positive, represented by $b$, shows that the laboratory test incorrectly predicted that the patient had the disease when, in fact, the patient did not have the disease. In contrast, a true negative, represented by $d$, correctly gave a negative test in patients without the disease, whereas a false negative, represented by $c$, incorrectly gave a negative test when, in fact, the patient did have the disease.

### Model Selection Criteria

Data analysis in pharmacokinetics frequently selects either a monoexponential or polyexponential that will better describe the concentration–time relationship. The selection criteria for the better model is determined by the goodness-of-fit, taking into account the number of parameters involved. Three common model selection criteria are (1) the Akaike Information Criterion (AIC), (2) the Schwarz Criterion (SC), and (3) the $F$ test ($\alpha = 0.05$). The performance characteristics of these criteria were examined by Ludden et al (1994) using Monte Carlo (random or stochastic) simulations. The precision and bias of the estimated parameters were considered. The Akaike Information Criterion and the Schwarz Criterion lead to selection of the correct model more often than does the $F$ test, which tends to choose the simpler model even when the more complex model is correct. The $F$ test is also more sensitive to deficient sampling designs. Clearance was quite robust among the different methods and generally well estimated.

### CLINICAL EXAMPLE

A new diagnostic test for HIV+/AIDS was developed and tested in 5772 intravenous drug users. The results of this study are tabulated in Table 20-15. From the results in Table 20-15, a total of 2863 subjects had a positive diagnostic test for HIV+/AIDS and 2909 subjects had a negative diagnostic test for HIV+/AIDS. Further tests on these subjects showed that 2967 subjects actually had HIV+/AIDS, although 211 of these subjects had negative diagnostic test
Chapter 20

5. The **specificity** of the test is the likelihood that a test result will be negative in a patient without the disease and is estimated as

\[
\text{Specificity} = \frac{d}{b+d} = \frac{2698}{2909} = 0.962 \quad (96.2\%)
\]

Analysis of the results in Table 20-15 shows that a positive result from the new test for HIV+ /AIDS will only predict the disease correctly 94.5% of the time. Therefore, the clinician must use other measures to predict whether the patient has the disease. These other measures may include physical diagnosis of the patient, other laboratory tests, normal incidence of the disease in the patient population (in this case, intravenous drug users), and the experience of the clinician. Each test has different predictive values.

### REGIONAL PHARMACOKINETICS

Pharmacokinetics is the study of the time course of drug concentrations in the body. Pharmacokinetics is based generally on the time course of drug concentrations in systemic blood sampled from either a vein or an artery. This general approach is useful as long as the drug concentrations in the tissues of the body are well reflected by drug concentrations in the blood. Clinically, the blood drug concentration may not be proportional to the drug concentration in tissues. For example, after IV bolus administration, the distributive phase is attributed to temporally different changes in mixing and redistribution of drug in organs such as the lung, heart, and kidney (Upton, 1990). The time course for the pharmacodynamics of the drug may have no relationship to the time course for the drug concentrations in the blood. The pharmacodynamics of the drug may be
related to local tissue drug levels and the status of homeostatic physiologic functions. After an IV bolus dose, Upton (1990) reported that lignocaine (lidocaine) rapidly accumulates in the spleen and kidney but is slowly sequestered into fat. More than 30 minutes were needed before the target-site (heart and brain) drug levels established equilibrium with drug concentrations in the blood. These regional equilibrium factors are often masked in conventional pharmacokinetic models that assume rapid drug equilibrium.

Regional pharmacokinetics is the study of pharmacokinetics within a given tissue region. The tissue region is defined as an anatomic area of the body between specified afferent and efferent blood vessels. For example, the myocardium includes the region perfused by the coronary arterial (afferent) and the coronary sinus (efferent) blood vessels. The selection of a region bounded by its network of blood vessel is based on the movement of drug between the blood vessels and the interstitial and intracellular spaces of the region. The conventional pharmacokinetic approach for calculating systemic clearance and volume of distribution tends to average various drug distributions together, such that the local perturbations are neglected. Regional pharmacokinetics (see Mather, 2001, Chapter 10) supplement systemic pharmacokinetics when inadequate information is provided by conventional pharmacokinetics.

Various homeostatic physiologic functions may be responsible for the nonequilibrium of drug concentrations between local tissue regions and the blood. For example, most cells have an electrochemical difference across the cell membrane consisting of a membrane potential of negative 70 mV inside the membrane relative to the outside. Moreover, regional differences in pH normally exist within a cell. For example, the pH within the lysosome is between 4 and 5, which could allow a basic drug to accumulate within the lysosome with a concentration gradient of 400-fold to 160,000-fold over the blood. Other explanations for regional drug concentration differences have been reviewed by Upton (1990), who also considers that dynamic processes may be more important than equilibrium processes in affecting dynamic response. Thus, regional pharmacokinetics is another approach in applying pharmacokinetics to pharmacodynamics and clinical effect.

CHAPTER SUMMARY

Successful drug therapy involves the selection of the drug, the drug product, and the development of a dosage regimen that meets the needs of the patient. Often, drug dosage regimens are based on average population pharmacokinetics. Ideally, the dosage regimen can be developed for the individual patient by taking into consideration the patient’s demographics, genetics, pathophysiology, environmental issues, possible drug–drug interactions, known variability in drug response, and other drug-related issues. The development of Medication Therapy Management (MTM) and therapeutic drug monitoring services can improve patient compliance and the success of drug therapy. Drug dosage regimens may be calculated in an individual patient based on complete or incomplete pharmacokinetic information. Changes in the dose and/or in the dosing interval can affect the $C_{\text{max}}$, $C_{\text{min}}$, and $C_{\text{av}}$.

Pharmacokinetics of a drug may be altered in special populations, such as the elderly, infants, obese patients, and in patients with renal or hepatic disease. Elderly patients may have several different pathophys-
iologic conditions that require multiple drug therapy that increases the likelihood for a drug interaction. Infants and children have different dosing requirements than adults. Dosing of drugs in this population requires a thorough consideration of the differences in the pharmacokinetics and pharmacology of a specific drug in the preterm newborn infant, newborn infant, young child, older child, adolescent, and the adult. Unfortunately, the pharmacokinetics and pharmacodynamics of most drugs are not well known in children under 12 years of age. Obesity often is defined by body mass index (BMI). For some drugs, dosing is based on ideal body weight. A drug interaction generally refers to a modification of the expected drug response in the patient as a result of exposure of the patient to another drug or substance. Drug–drug interactions may cause an alteration in the pharmacokinetics of the drug due to an interaction in drug absorption, distribution, or elimination. Bayesian theory can help determine the probability of a diagnostic test to give accurate results. Population pharmacokinetics (PopPK) is the study of variability in plasma drug concentrations between and within patient populations receiving therapeutic doses of a drug and enables the estimate of pharmacokinetic parameters from relatively sparse data obtained from study subjects.

**LEARNING QUESTIONS**

1. Why is it harder to titrate patients with a drug whose elimination half-life is 36 hours compared to a drug whose elimination is 6 hours?

2. Penicillin G has a volume of distribution of 42 L/1.73 m² and an elimination rate constant of 1.034 h⁻¹. Calculate the maximum peak concentration that would be produced if the drug was given intravenously at a rate of 250 mg every 6 hours for a week.

3. Dicloxacillin has an elimination half-life of 42 minutes and a volume of distribution of 20 L. Dicloxacillin is 97% protein bound. What would be the steady-state free concentration of dicloxacillin if the drug was given intravenously at a rate of 250 mg every 6 hours?

4. The normal elimination half-life of cefamandole is 1.49 hours and the apparent volume of distribution (\(V_p\)) is 39.2% of body weight. The elimination half-life for a patient with a creatinine clearance of 15 mL/min was reported by Czerwinski and Pederson (1979) to be 6.03 hours, and cefamandole’s \(V_p\) is 23.75% of body weight. What doses of cefamandole should be given to the normal and the uremic patient (respectively) if the drug is administered intravenously every 6 hours and the desired objective is to maintain an average steady concentration of 2 μg/mL?

5. The maintenance dose of digoxin was reported to be 0.5 mg/d for a 60-kg patient with normal renal function. The half-life of digoxin is 0.95 days and the volume of distribution is 306 L. The bioavailability of the digoxin tablet is 0.56.
   a. Calculate the steady-state concentration of digoxin.
   b. Determine whether the patient is adequately dosed (effective serum digoxin concentration is 1–2 ng/mL).
   c. What is the steady-state concentration if the patient is dosed with the elixir instead of the tablet? (Assume the elixir to be 100% bioavailable.)

6. An antibiotic has an elimination half-life of 2 hours and an apparent volume of distribution of 200 mL/kg. The minimum effective serum concentration is 2 μg/mL and the minimum toxic serum concentration is 16 μg/mL. A physician ordered a dosage regimen of this antibiotic to be given at 250 mg every 8 hours by repetitive intravenous bolus injections.
   a. Comment on the appropriateness of this dosage regimen for an adult male patient (23 years, 80 kg) whose creatinine clearance is 122 mL/min.
1.5 g every 4 hours. The drug is 85% bound to serum proteins. The elimination half-life of this drug is 6 hours and the apparent volume of distribution is 1.3 L/kg. Sulfisoxazole is 100% bioavailable.

a. Calculate the steady-state plasma concentration of sulfisoxazole in this patient.

b. Calculate an appropriate loading dose of sulfisoxazole for this patient.

c. Gantrisin (sulfisoxazole) is supplied in tablets containing 0.5 g of drug. How many tablets would you recommend for the loading dose?

d. If no loading dose was given, how long would it take to achieve 95% to 99% of steady state?

12. The desired plasma level for an antiarrhythmic agent is 5 μg/mL. The drug has an apparent volume of distribution of 173 mL/kg and an elimination half-life of 2 hours. The kinetics of the drug follow the kinetics of a one-compartment open model.

a. An adult male patient (75 kg, 56 years of age) is to be given an IV injection of this drug. What loading dose (D_L) and infusion rate (R) would you suggest?

b. The patient did not respond very well to drug therapy. Plasma levels of drug were measured and found to be 2 μg/mL. How would you readjust the infusion rate to increase the plasma drug level to the desired 5 μg/mL?

c. How long would it take to achieve 95% of steady-state plasma drug levels in this patient assuming no loading dose was given and the apparent V_D was unaltered?

13. An antibiotic is to be given to an adult male patient (75 kg, 58 years of age) by intravenous infusion. The elimination half-life for this drug is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 30-mL ampules at a concentration of 15 mg/mL. The desired steady-state serum concentrations for this drug range from 0.001 to 0.002 μg/mL.

a. What infusion rate (R) would you suggest for this patient?

b. What loading dose would you suggest for this patient?
c. If the manufacturer suggests a starting infusion rate of 0.2 mL/h/kg of body weight, what is the expected steady-state serum concentration in this patient?
d. You would like to verify that this patient received the proper infusion rate. At what time after the start of the IV infusion would you take a blood sample to monitor the serum antibiotic concentration? Why?
e. Assume that the serum antibiotic concentration was measured and found to be higher than anticipated. What reasons, based on sound pharmacokinetic principles, would account for this situation?

14. Nomograms are frequently used in lieu of pharmacokinetic calculations to determine an appropriate drug dosage regimen for a patient. Discuss the advantages and disadvantages for using nomograms to calculate a drug dosage regimen.

15. Based on the following pharmacokinetic data for drugs A, B, and C: (a) Which drug takes the longest time to reach steady state? (b) Which drug would achieve the highest steady-state drug concentration? (c) Which drug has the largest apparent volume of distribution?

<table>
<thead>
<tr>
<th>Rate of infusion (mg/h)</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of infusion (mg/h)</td>
<td>10</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>k (h⁻¹)</td>
<td>0.5</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Ci (L/h)</td>
<td>5</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

16. The effect of repetitive administration of phenytoin (PHT) on the single-dose pharmacokinetics of primidone (PRM) was investigated by Sato et al (1992) in three healthy male subjects. The peak concentration of unchanged PRM was achieved at 12 and 8 hours after the administration of PRM in the absence and the presence of PHT, respectively. The elimination half-life of PRM was decreased from 19.4 ± 2.2 (mean ± SE) to 10.2 ± 5.1 hours (p < 0.05) and the total body clearance was increased from 24.6 ± 3.1 to 45.1 ± 5.1 mL/h/kg (p < 0.01) in the presence of PHT. No significant change was observed for the apparent volume of distribution between the two treatments. Based on pharmacokinetics of the two drugs, what are the possible reasons for phenytoin to reduce primidone elimination half-life and increase its renal clearance?

17. Traconazole (Sporanox, Janssen) is a lipophilic drug with extensive lipid distribution. The drug levels in fatty tissue and organs contain 2 to 20 times the drug levels in the plasma. Little or no drug was found in the saliva and in the cerebrospinal fluid and the half-life is 64 ± 32 hours. The drug is 99.8% bound. How does (a) plasma drug–protein binding, (b) tissue drug distribution, and (c) lipid tissue partitioning contribute to the long elimination half-life for traconazole?

18. JL (29-year-old man, 180 kg) received oral ofloxacin 400 mg twice a day for presumed bronchitis due to *Streptococcus pneumoniae*. His other medications were the following: 400 mg cimetidine, orally, three times a day; 400 mg metronidazole, as directed. JL was still having a fever of 100.1°C a day after taking the quinolone antibiotic. Comment on any appropriate action.

19. CK (70-year-old man, 177 lb). Scr = 0.9 mg/dL. Allergy: PCN. Claudication, rhinitis: URI infection. His medication includes: Ilosone, 250 QID × 1 week; Trental, 200 mg TID; Colace, 100 mg BID; Seldane, 1 TID PRN. Which of the following should the pharmacist conclude from this information?

a. There is an interaction between colace and seldane.
b. The dose of Trental is too high for this patient based on his renal function.
c. Seldane should be substituted with a therapeutic alternative because of an interaction.
REFERENCES


BIBLIOGRAPHY


Chapter Objectives

- List the common causes of chronic kidney disease (CKD) and describe how CKD affects drug elimination.
- Compare the advantages and disadvantages of the use of drugs or endogenous substances as markers for the measurement of renal function.
- Describe the relationship between creatinine clearance, serum creatinine concentration, and glomerular filtration rate.
- Explain and contrast the methods of Cockcroft–Gault and modification of diet in renal disease (MDRD) for the calculation of creatinine clearance.
- List the causes for fluctuating serum creatinine concentration in the body.
- Calculate the dose for a drug in a patient with renal disease.
- Describe quantitatively using equations how renal or hepatic disease can alter the disposition of a drug.
- Describe hemoperfusion and the limitations for its use.

RENNAL IMPAIRMENT

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy (Levey et al, 2009). The kidney is an important organ in regulating body fluids, electrolyte balance, removal of metabolic waste, and drug excretion from the body. Impairment or degeneration of kidney function affects the pharmacokinetics of drugs. Some of the more common causes of kidney failure include disease, injury, and drug intoxication. Table 21-1 lists some of the conditions that may lead to chronic or acute renal failure. Acute diseases or trauma to the kidney can cause uremia, in which glomerular filtration is impaired or reduced, leading to accumulation of excessive fluid and blood nitrogenous products in the body. Uremia generally reduces glomerular filtration and/or active secretion, which leads to a decrease in renal drug excretion resulting in a longer elimination half-life of the administered drug.

In addition to changing renal elimination directly, uremia can affect drug pharmacokinetics in unexpected ways. For example, declining renal function leads to disturbances in electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug. Pharmacokinetic processes such as drug distribution (including both the volume of distribution and protein binding) and elimination (including both biotransformation and renal excretion) may also be altered by renal impairment. Both therapeutic and toxic responses may be altered as a result of changes in drug sensitivity at the receptor site. Overall, uremic patients have special dosing considerations to account for such pharmacokinetic and pharmacodynamic alterations.

PHARMACOKINETIC CONSIDERATIONS

Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution, and clearance. The oral bioavailability of a drug in severe uremia may be decreased as a result of...
disease-related changes in gastrointestinal motility and pH caused by nausea, vomiting, and diarrhea. Mesenteric blood flow may also be altered. However, the oral bioavailability of a drug such as propranolol (which has a high first-pass effect) may be increased in patients with renal impairment as a result of the decrease in first-pass hepatic metabolism (Bianchetti et al, 1978).

The apparent volume of distribution depends largely on drug–protein binding in plasma or tissues and total body water. Renal impairment may alter the distribution of the drug as a result of changes in fluid balance, drug–protein binding, or other factors that may cause changes in the apparent volume of distribution (see Chapter 10). The plasma protein binding of weak acidic drugs in uremic patients is decreased, whereas the protein binding of weak basic drugs is less affected. A decrease in drug–protein binding results in a larger fraction of free drug and an increase in the volume of distribution. However, the net elimination half-life is generally increased as a result of the dominant effect of reduced glomerular filtration. Protein binding of the drug may be further compromised due to the accumulation of metabolites of the drug and various biochemical metabolites, such as free fatty acids and urea, which may compete for the protein-binding sites for the active drug.

Total body clearance of drugs in uremic patients is also reduced by either a decrease in the glomerular filtration rate and possibly active tubular secretion or reduced hepatic clearance resulting from a decrease in intrinsic hepatic clearance.

In clinical practice, estimation of the appropriate drug dosage regimen in patients with impaired renal function is based on an estimate of the remaining renal function of the patient and a prediction of the total body clearance. A complete pharmacokinetic analysis of the drug in the uremic patient may not be possible. Moreover, the patient’s uremic condition may not be stable and may be changing too rapidly for pharmacokinetic analysis. Each of the approaches for the calculation of a dosage regimen has certain assumptions and limitations that must be carefully assessed by the clinician before any approach is taken. Dosing guidelines for individual drugs in patients with renal impairment may be found in various reference books, such as the Physicians’ Desk Reference, and in the medical literature (Bennett 1988, 1990; St Peter et al, 1992). Most newly approved drugs now contain dosing instructions for CKD patients.

**GENERAL APPROACHES FOR DOSE ADJUSTMENT IN RENAL DISEASE**

Several approaches are available for estimating the appropriate dosage regimen for a patient with renal impairment. Each of these approaches has similar assumptions, as listed in Table 21-2. Most of these methods assume that the required therapeutic plasma drug
concentration in uremic patients is similar to that required in patients with normal renal function. Uremic patients are maintained on the same $C_{av}$ after multiple oral doses or multiple IV bolus injections. For IV infusions, the same $C_{av}$ is maintained. ($C_{SS}$ is the same as $C_{av}$ after the plasma drug concentration reaches steady state.)

The design of dosage regimens for uremic patients is based on the pharmacokinetic changes that have occurred as a result of the uremic condition. Generally, drugs in patients with uremia or kidney impairment have prolonged elimination half-lives and a change in the apparent volume of distribution. In less severe uremic conditions there may be neither edema nor a significant change in the apparent volume of distribution. Consequently, the methods for dose adjustment in uremic patients are based on an accurate estimation of the drug clearance in these patients.

Several specific clinical approaches for the calculation of drug clearance based on monitoring kidney function are presented later in this chapter. Two general pharmacokinetic approaches for dose adjustment include methods based on drug clearance and methods based on the elimination half-life.

### TABLE 21-1  Common Causes of Kidney Failure

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>Inflammation and deterioration of the pyelonephrons due to infection, antigens, or other idiopathic causes.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Chronic overloading of the kidney with fluid and electrolytes may lead to kidney insufficiency.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>The disturbance of sugar metabolism and acid–base balance may lead to or predispose a patient to degenerative renal disease.</td>
</tr>
<tr>
<td>Nephrotoxic drugs/metals</td>
<td>Certain drugs taken chronically may cause irreversible kidney damage—eg, the aminoglycosides, phenacetin, and heavy metals, such as mercury and lead.</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Any condition that causes a reduction in renal blood flow will eventually lead to renal ischemia and damage.</td>
</tr>
<tr>
<td>Neophroallergens</td>
<td>Certain compounds may produce an immune type of sensitivity reaction with nephritic syndrome—eg, quartan malaria nephrotoxic serum.</td>
</tr>
</tbody>
</table>

### TABLE 21-2  Common Assumptions in Dosing Renal-Impaired Patients

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance accurately measures the degree of renal impairment</td>
<td>Creatinine clearance estimates may be biased. Renal impairment should also be verified by physical diagnosis and other clinical tests.</td>
</tr>
<tr>
<td>Drug follows dose-independent pharmacokinetics</td>
<td>Pharmacokinetics should not be dose dependent (nonlinear).</td>
</tr>
<tr>
<td>Nonrenal drug elimination remains constant</td>
<td>Renal disease may also affect the liver and cause a change in nonrenal drug elimination (drug metabolism).</td>
</tr>
<tr>
<td>Drug absorption remains constant</td>
<td>Unchanged drug absorption from gastrointestinal tract.</td>
</tr>
<tr>
<td>Drug clearance, $Cl_d$, declines linearly with creatinine clearance, $Cl_C$</td>
<td>Normal drug clearance may include active secretion and passive filtration and may not decline linearly.</td>
</tr>
<tr>
<td>Unaltered drug–protein binding</td>
<td>Drug–protein binding may be altered due to accumulation of urea, nitrogenous wastes, and drug metabolites.</td>
</tr>
<tr>
<td>Target drug concentration remains constant</td>
<td>Changes in electrolyte composition such as potassium may affect response to the effect of digoxin. Accumulation of active metabolites may cause more intense pharmacodynamic response compared to parent drug alone.</td>
</tr>
</tbody>
</table>
Dose Adjustment Based on Drug Clearance

Methods based on drug clearance try to maintain the desired $C_{av}$ after multiple oral doses or multiple IV bolus injections as total body clearance, $Cl_T$, changes. The calculation for $C_{av}$ is

$$C_{av} = \frac{FD_0}{Cl_T \tau} \quad (21.1)$$

For patients with uremic condition or renal impairment, total body clearance will change to a new value, $Cl_{Tu}$. Therefore, to maintain the same desired $C_{av}$, the dose must be changed to a uremic dose, $D_0^u$, or the dosage interval must be changed to $\tau^u$, as shown in the following equation:

$$C_{av} = \frac{D_0^u}{Cl_{Tu} \tau^u} = \frac{D_0}{Cl_T \tau} \quad (21.2)$$

(normal) (uremic)

where the superscripts N and u represent normal and uremic conditions, respectively.

Rearranging Equation 21.2 and solving for $D_0^u$

$$D_0^u = \frac{D_0^u Cl_{Tu} \tau^u}{Cl_T \tau} \quad (21.3)$$

If the dosage interval $\tau$ is kept constant, then the uremic dose $D_0^u$ is equal to a fraction $(k_u/k_N)$ of the normal dose, as shown in the equation

$$D_0^u = \frac{D_0^u Cl_{Tu}}{Cl_T} \quad (21.4)$$

For IV infusions the same desired $C_{SS}$ is maintained both for patients with normal renal function and for patients with renal impairment. Therefore, the rate of infusion, $R$, must be changed to a new value, $R^u$, for the uremic patient, as described by the equation

$$C_{SS} = \frac{R}{Cl_T} = \frac{R^u}{Cl_{Tu}} \quad (21.5)$$

(normal) (uremic)

Dose Adjustment Based on Changes in the Elimination Rate Constant

The overall elimination rate constant for many drugs is reduced in the uremic patient. A dosage regimen may be designed for the uremic patient either by reducing the normal dose of the drug and keeping the frequency of dosing (dosage interval) constant, or by decreasing the frequency of dosing (prolonging the dosage interval) and keeping the dose constant. Doses of drugs with a narrow therapeutic range should be reduced—particularly if the drug has accumulated in the patient prior to deterioration of kidney function.

The usual approach to estimating a multiple-dosage regimen in the normal patient is to maintain a desired $C_{av}$, as shown in Equation 21.1. Assuming the $V_D$ is the same in both normal and uremic patients and $\tau$ is constant, then the uremic dose $C_{0u}$ is a fraction $(k_u/k_N)$ of the normal dose:

$$D_0^u = \frac{D_0^N k_u}{k_N} \quad (21.6)$$

When the elimination rate constant for a drug in the uremic patient cannot be determined directly, indirect methods are available to calculate the predicted elimination rate constant based on the renal function of the patient. The assumptions on which these dosage regimens are calculated include the following.

1. The renal elimination rate constant $(k_R)$ decreases proportionately as renal function decreases. (Note that $k_R$ is the same as $k_e$ as used in previous chapters).

2. The nonrenal routes of elimination (primarily, the rate constant for metabolism) remain unchanged.

3. Changes in the renal clearance of the drug are reflected by changes in the creatinine clearance.

The overall elimination rate constant is the sum total of all the routes of elimination in the body, including the renal rate and the nonrenal rate constants:

$$k^u = k_{in} + k_R^u \quad (21.7)$$

where $k_{in}$ is the nonrenal elimination rate constant and $k_R^u$ is the renal excretion rate constant.
Renal clearance is the product of the apparent volume of distribution and the rate constant for renal excretion:

$$Cl_R = k_R^a V_D$$

(21.8)

Rearrangement of Equation 21.8 gives

$$k_R^a = Cl_R \frac{1}{V_D}$$

(21.9)

Assuming that the apparent volume of distribution and nonrenal routes of elimination do not change in uremia, then $k_R^a = k_N^a$ and $V_D = V_N^a$.

Substitution of Equation 21.9 into Equation 21.7 yields

$$k^a = k_{ur}^a + \frac{1}{V_D} Cl_R^a$$

(21.10)

From Equation 21.10, a change in the renal clearance, $Cl_R^a$, due to renal impairment will be reflected in a change in the overall elimination rate constant $k_a$. However, a small amount of creatinine may be secreted by the renal tubules, and the values of GFR obtained by the creatinine clearance tend to be higher than GFR measured by inulin clearance. Therefore, the rate at which these drug markers are filtered from the blood into the urine per unit of time reflects the GFR of the kidney. Changes in GFR reflect changes in kidney function that may be diminished in uremic conditions.

Inulin, a fructose polysaccharide, fulfills most of the criteria listed above and is therefore used as a standard reference for the measurement of GFR. In practice, however, the use of inulin involves a time-consuming procedure in which inulin is given by intravenous infusion until a constant steady-state plasma level is obtained. Clearance of inulin may then be measured by the rate of infusion divided by the steady-state plasma inulin concentration. Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice.

The clearance of creatinine is used most extensively as a measurement of GFR. Creatinine is an endogenous substance formed from creatine phosphate during muscle metabolism. Creatinine production varies with the age, weight, and gender of the individual. In humans, creatinine is filtered mainly at the glomerulus, with no tubular reabsorption. However, a small amount of creatinine may be actively secreted by the renal tubules, and the values of GFR obtained by the creatinine clearance tend to be higher than GFR measured by inulin clearance. Creatinine clearance tends to decrease in the elderly patient. As mentioned in Chapter 20, the physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly.

**Frequently Asked Questions**

- **What are the main causes of uremia?**
- **How does renal impairment affect the pharmacokinetics of a drug that is primarily eliminated by hepatic clearance?**
- **What are the main factors that influence drug dosing in renal disease?**
- **Name and contrast the two methods for adjusting drug dose in renal disease.**

**MEASUREMENT OF GLOMERULAR FILTRATION RATE**

Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus. Several criteria are necessary to use a drug as a marker to measure GFR:

1. The drug must be freely filtered at the glomerulus.
2. The drug must neither be reabsorbed nor actively secreted by the renal tubules.
3. The drug should not be metabolized.
4. The drug should not bind significantly to plasma proteins.
5. The drug should neither have an effect on the filtration rate nor alter renal function.
6. The drug should be nontoxic.
7. The drug may be infused in a sufficient dose to permit simple and accurate quantitation in plasma and in urine.

Therefore, the drug chosen to measure GFR should meet the following criteria:

1. The drug should be freely filtered at the glomerulus.
2. The drug should neither be reabsorbed nor actively secreted.
3. The drug should not be metabolized.
4. The drug should not bind significantly to plasma proteins.
5. The drug should neither have an effect on filtration rate nor alter renal function.
6. The drug should be nontoxic.
7. The drug may be infused in a sufficient dose to permit simple and accurate quantitation in plasma and in urine.

Thus, the change in the overall elimination rate constant due to renal impairment will be reflected in a change in the renal clearance, which in turn is estimated by changes in the patient’s creatinine clearance.
Measurement of blood urea nitrogen (BUN) is a commonly used clinical diagnostic laboratory test for renal disease. Urea is the end product of protein catabolism and is excreted through the kidney. Normal BUN levels range from 10 to 20 mg/dL. Higher BUN levels generally indicate the presence of renal disease. However, other factors, such as excessive protein intake, reduced renal blood flow, hemorrhagic shock, or gastric bleeding, may affect increased BUN levels. The renal clearance of urea is by glomerular filtration and partial reabsorption in the renal tubules. Therefore, the renal clearance of urea is less than creatinine or inulin clearance and does not give a quantitative measure of kidney function.

SERUM CREATININE CONCENTRATION AND CREATININE CLEARANCE

Under normal circumstances, creatinine production is roughly equal to creatinine excretion, so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum creatinine will accumulate in accordance with the degree of loss of glomerular filtration in the kidney. The serum creatinine concentration alone is frequently used to determine creatinine clearance, \( C_l_{cr} \). Creatinine clearance from the serum creatinine concentration is a rapid and convenient way to monitor kidney function.

Creatinine clearance may be defined as the volume of plasma cleared of creatinine per unit time. Creatinine clearance can be calculated directly by dividing the rate of urinary excretion of creatinine by the patient’s serum creatinine concentration. The approach is similar to that used in the determination of drug clearance. In practice, the serum creatinine concentration is determined at the midpoint of the urinary collection period and the rate of urinary excretion of creatinine is measured for the entire day (24 hours) to obtain a reliable excretion rate. Creatinine clearance is expressed in mL/min and serum creatinine concentration in mg/dL or mg%. Other \( C_l_{cr} \) methods based solely on serum creatinine are generally compared to the creatinine clearance obtained from the 24-hour urinary creatinine excretion.

The following equation is used to calculate creatinine clearance in mL/min when the serum creatinine concentration is known:

\[
C_l_{cr} = \frac{\text{rate of urinary excretion of creatinine}}{\text{serum concentration of creatinine}}
\]

\[
C_l_{cr} = \frac{C_u V \times 100}{C_{cr} \times 1440}
\]  

(21.11)

where \( C_u = \) creatinine concentration (mg/dL) of the serum taken at the 12th hour or at the midpoint of the urine-collection period, \( V = \) volume of urine excreted (mL) in 24 hours, \( C_{cr} = \) concentration of creatinine in urine (mg/mL), and \( C_l_{cr} = \) creatinine clearance in mL/min.

Creatinine is eliminated primarily by glomerular filtration. A small fraction of creatinine also is eliminated by active secretion and some nonrenal elimination. Therefore, \( C_l_{cr} \) values obtained from creatinine measurements overestimate the actual glomerular filtration rate.

Creatinine clearance has been normalized both to body surface area, using 1.73 m\(^2\) as the average, and to body weight for a 70-kg adult male. Creatinine distributes into total body water, and when clearance is normalized to a standard \( V_{TBW} \), similar drug half-lives in adults and children correspond to identical clearances.

Creatinine clearance values must be considered carefully in special populations such as elderly, obese, and emaciated patients. In elderly and emaciated patients, muscle mass may have declined, thus lowering the production of creatinine. However, serum creatinine concentration values may appear to be in the normal range, because of lower renal creatinine excretion. Thus, the calculation of creatinine clearance from serum creatinine may give an inaccurate estimation of the renal function. For obese patients, generally defined as patients more than 20% over ideal body weight (IBW), creatinine clearance should be based on ideal body weight. Estimation of creatinine clearance based on total body weight (TBW) would exaggerate the \( C_l_{cr} \) values in the obese patient. Women with normal kidney function have smaller creatinine clearance values than men, approximately 80%–85% of that in men with normal kidney function.

Several empirical equations have been used to estimate lean body weight (LBW) based on the
patient’s height and actual (total) body weight (see Chapter 20). The following equations have been used to estimate LBW in renally impaired patients:

\[
\text{LBW (males)} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft} \\
\text{LBW (females)} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft}
\]

For the purpose of dose adjustment in renal patients, normal creatinine clearance is generally assumed to be between 100 and 125 mL/min per 1.73 m² for a subject of ideal body weight: for an adult female, \( Cl_{cr} = 108.8 \pm 13.5 \text{ mL/1.73 m}^2 \), and for an average adult male, \( Cl_{cr} = 124.5 \pm 9.7 \text{ mL/1.73 m}^2 \) (Scientific Table, 1973). Creatinine clearance is affected by diet and salt intake. As a convenient approximation, the normal clearance has often been assumed by many clinicians to be approximately 100 mL/min.

**Frequently Asked Questions**

- Why is creatinine clearance difficult to predict?
- Why is creatinine clearance used in renal disease?
- What patient-specific factors influence the accuracy of \( Cl_{cr} \) estimates?
- How is \( Cl_{cr} \) determined?

**Calculation of Creatinine Clearance from Serum Creatinine Concentration**

The problems of obtaining a complete 24-hour urine collection from a patient, the time necessary for urine collection, and the analysis time preclude a direct estimation of creatinine clearance. *Serum creatinine concentration*, \( C_{cr} \), is related to creatinine clearance and is measured routinely in the clinical laboratory. Therefore, creatinine clearance, \( Cl_{cr} \), is most often estimated from the patient’s \( C_{cr} \). Several methods are available for the calculation of creatinine clearance from the serum creatinine concentration. The more accurate methods are based on the patient’s age, height, weight, and gender. These methods should be used only for patients with intact liver function and no abnormal muscle disease, such as hypertrophy or dystrophy. Moreover, most of the methods assume a stable creatinine clearance. The units for \( Cl_{cr} \) are mL/min.

**Adults**

The method of Cockcroft and Gault (1976) shown in Equation 21.12 is used to estimate creatinine clearance from serum creatinine concentration. This method considers both the age and the weight of the patient. For males

\[
Cl_{cr} = \frac{\left[140 - \text{age (year)} \times \text{body weight (kg)}\right]}{72(C_{cr})}
\]

(21.12)

For females, use 90% of the \( Cl_{cr} \) value obtained in males. In some hospitals, 85% is used for female subjects (Stevens et al, 2006)

The nomogram method of Siersback-Nielsen et al (1971) estimates creatinine clearance on the basis of age, weight, and serum creatinine concentration, as shown in Fig. 21-1. Cockcroft and Gault (1976)
compared their method with the nomogram method in adult males of various ages. Creatinine clearance estimated by both methods were comparable. Both methods also demonstrated an age-related linear decline in creatinine excretion, which may be due to the decrease in muscle mass with age.

**Children**

There are a number of methods for calculation of creatinine clearance in children, based on body length and serum creatinine concentration. Equation 21.13 is a method developed by Schwartz and associates (1976):

$$CL_{cr} = \frac{0.55 \text{body length (cm)}}{C_{cr}}$$  \hspace{1cm} (21.13)

where $CL_{cr}$ is given in mL/min/1.73 m$^2$. The value 0.55 represents a factor used for children ages 1 to 12 years.

Another method of calculating creatinine clearance in children uses the nomogram of Traub and Johnson (1980), shown in Fig. 21-2. This nomogram is based on observations of 81 children aged 6 to 12 years and requires the patient’s height and serum creatinine concentration.

**PRACTICE PROBLEMS**

1. What is the creatinine clearance for a 25-year-old male patient with $C_{cr}$ of 1 mg/dL and a body weight of 80 kg?

   **Solution**

   Using the nomogram (see Fig. 21-1), join the points at 25 years (male) and 80 kg with a ruler—let the line intersect line $R$. Connect the intersection point at line $R$ with the creatinine concentration point of 1 mg/dL, and extend the line to intersect the “clearance line.” The extended line will intersect the clearance line at 110 mL/min, giving the creatinine clearance for the patient.

2. What is the creatinine clearance for a 25-year-old male patient with a $C_{cr}$ of 1 mg/dL? The patient is 5 ft, 4 in in height and weighs 103 kg.

   **Solution**

   The patient is obese and the $CL_{cr}$ calculation should be based on ideal body weight.

   $$LBW \text{ (males)} = \frac{50 \text{kg} + [2.3 \times 4]}{59.2 \text{kg}}$$

   Using the Cockcroft–Gault method (Equation 21.12), the $CL_{cr}$ can be calculated.

   $$CL_{cr} = \frac{(140 - 25)(59.2 \text{kg})}{72(1)} = 94.6 \text{ mL/min}$$
The serum creatinine methods for the estimation of the creatinine clearance assume stabilized kidney function and a steady-state serum creatinine concentration. In acute renal failure and in other situations in which kidney function is changing, the serum creatinine may not represent steady-state conditions. If $C_{cr}$ is measured daily and the $C_{cr}$ value is constant, then the serum creatinine concentration is probably at steady state. If the $C_{cr}$ values are changing daily, then kidney function is changing.

Although the Cockcroft–Gault method for estimating $C_{cr}$ has some biases, this method has gained general acceptance for the determination of renal impairment (Schneider et al, 2003; Hailmeskel et al, 1999; Spinler et al, 1998). A suggested representation of patients with various degrees of renal impairment based on creatinine clearance is shown in Table 21-3.

The practice problems show that, depending on the formula used, the calculated $C_{cr}$ can vary considerably. Consequently, unless a clinically significant change in the creatinine clearance occurs, dosage adjustment may not be needed. According to St Peter et al (1992), dose adjustment of many antibiotic drugs is necessary only when the glomerular filtration rate as measured by $C_{cr}$ is less than 50 mL/min. For the aminoglycoside antibiotics and vancomycin, dose adjustment is individualized according to the wide range of $C_{cr}$. Therefore, dose adjustment for all drugs on the basis of these $C_{cr}$ methods alone is not justified.

### TABLE 21-3 Classification of Renal Function Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance ($C_{cr}$)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR(^c) (mL/min/1.73m(^2))</th>
<th>$C_{cr}$(^d) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal GFR</td>
<td>$\geq 90$</td>
<td>$\geq 90$</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in GFR</td>
<td>60–89</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>End-stage renal disease (ESRD)</td>
<td>$&lt;15$ Not on dialysis Requiring dialysis</td>
<td>$&lt;15$ Not on dialysis Requiring dialysis</td>
</tr>
</tbody>
</table>

\(^a\)In some situations, collection of 24-hour urine samples for measurement of creatinine clearance, or measurement of clearance of an exogenous filtration marker, may provide better estimates of GFR than the prediction equations. The situations include determination of GFR for patients in the following scenarios: undergoing kidney replacement therapy; acute renal failure; extremes of age, body size, or muscle mass; conditions of severe malnutrition or obesity; disease of skeletal muscle; or on a vegetarian diet.

\(^b\)Stages of renal impairment are based on K/DOQI Clinical Practice Guidelines for chronic kidney disease (CKD) from the National Kidney Foundation in 2002; GFR: glomerular filtration rate.

\(^c\)eGFR: estimate of GFR based on an MDRD equation.

\(^d\)Cl\(_{cr}\): estimated creatinine clearance based on the Cockcroft–Gault equation.

Estimated GFR (eGFR) Using Modification of Diet in Renal Disease (MDRD) Formula or Using the Chronic Kidney Disease–Epidemiology Collaboration (CKD–EPI) Equations

Various approaches for the estimation of glomerular filtration rate from serum creatinine have been published (Levey et al, 1999, 2009; FDA Guidance, 2010). Several versions of the MDRD and the CKD–EPI equations have been published. For example,\(^1\)

\(^1\)FDA Guidance 2010.
eGFR (mL/min/1.73 m²) = 175 × (Scr, std) − 1.154 × (age) − 0.203 × (0.742 if female) × (1.212 if African American)

where eGFR is estimated GFR using the MDRD equation.

Each equation for the calculation of GFR from serum creatinine concentrations gives somewhat different results. The Cockcroft–Gault method for estimating $Cl_{cr}$ has been used most frequently and tends to be the preferred approach at this time. The FDA Guidance, 2010 on impaired renal function includes a classification of renal function based on creatinine clearance (see Table 21-3). Although the two methods, estimated GFR (eGFR) using the MDRD equation and calculated GFR using the Cockcroft–Gault method, do not give the same values, the classification in Table 21-3 brackets the values for diminishing renal function.

**Comparison of Methods for the Measurement of Glomerular Filtration Rate**

The estimate of glomerular filtration rate (GFR) based on serum creatinine concentration is widely used, even though serum creatinine concentrations are known to fluctuate with disease state and patient conditions such as age, gender, and endogenous factors that affect creatinine synthesis and elimination. Various factors that affect serum creatinine concentration are listed in Table 21-4. These methods for the measurement of GFR use equations referred to as creatinine-based in the clinical literature (Stevens et al, 2006; Levey et al, 2009). Two creatinine-based methods that have been extensively studied and widely applied are the Cockcroft–Gault and the Modification of Diet in Renal Disease (MDRD) study equations. The Cockcroft–Gault has a longer history of use but the original equation was based on fewer subjects. The MDRD method is a more recent method based on more subjects with application better defined for certain groups of patients. For example, in patients with diabetic nephropathy the relationship of serum creatinine concentration and GFR may be different than in normal subjects without real renal disease. Some reports indicated that the MDRD method is less biased for obese and diabetic patients whereas other studies do not find a difference between the two methods.

The Cockcroft–Gault formula was developed initially with the data from 249 men with creatinine clearance ($Cl_{cr}$) from 30 to 130 mL/min

$$Cl_{cr} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{Scr}} \times 0.85 \text{ (if the subject is female)} \quad (21.12)$$

The Cockcroft–Gault formula systematically overestimates GFR because of the tubular secretion of creatinine. The values are not adjusted for body surface area; a comparison with normal values for creatinine clearance requires measurement of height, computation of body surface area, and adjustment to

| TABLE 21-4  Factors Affecting Creatinine Generation |
|----------------|----------------|
| Factor                  | Effect on Serum Creatinine |
| Aging                | Decreased                           |
| Female Sex                 | Decreased                           |
| Race or ethnic group            |                                     |
| Black                    | Increased                           |
| Hispanic                 | Decreased                           |
| Asian                    | Decreased                           |
| Body habitus             |                                     |
| Muscular                 | Increased                           |
| Amputation               | Decreased                           |
| Obesity                  | No Change                           |
| Chronic illness          |                                     |
| Malnutrition, inflammation, deconditioning (eg, cancer, severe cardiovascular disease, hospitalized patients) | Decreased |
| Neuromuscular diseases    | Decreased                           |
| Diet                     |                                     |
| Vegetarian diet           | Decreased                           |
| Ingestion of cooked meat  | Increased                           |

1.73 m². The MDRD study equation was developed in 1999 with the use of data from 1628 patients with chronic kidney disease. It estimates GFR adjusted for body-surface area. The estimating equation is

\[ GFR = 186 \times (C_{cr})^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if the subject is female) or } \times 1.212 \text{ (if the subject is black)} \]

This equation was reexpressed in 2005 for use with a standardized serum creatinine assay that yields serum creatinine values that are 5% lower.

\[ GFR = 175 \times (\text{standardized } C_{cr})^{-1.154} \times \text{age}^{-0.203} \]

(GFR is expressed in milliliters per minute per 1.73 m²)

In the MDRD study population, 91% of the GFR estimates were within 30% of the measured values, and this approach was more accurate than the use of the Cockcroft–Gault equation. The Cockcroft–Gault equation was reported to be less accurate than the MDRD study equation in older and obese people. Both methods are less accurate in healthy subjects. The MDRD method will provide more accurate renal function of the patient for the physician. However, drug clearance is not entirely governed by GFR. Reabsorption and nonrenal elimination are also important for many drugs. Therefore, the MDRD method should be compared with previous methods and see how accurately it adjusts drug doses for different drugs in different uremic patients. For many new drugs, drug dosing information for renal-impaired patients is now available and should be consulted in the package insert. In patients with chronic kidney disease, the following recommendations are good practices that physicians and pharmacists should be aware of (Munar and Singh, 2007).

1. OTC and herbal medicine use should be assessed to ensure proper indication, and avoid medications with toxic metabolites, or use the least nephrotoxic agents.
2. Alternative medications should be used if potential drug interactions exist.
3. Use caution for drugs with active metabolites that can exaggerate pharmacologic effects in patients with renal impairment.
4. Dosages of drugs cleared renally should be adjusted based on the patient’s renal function (calculated as creatinine clearance or glomerular filtration rate); initial dosages should be determined using published guidelines and adjusted based on patient response or monitoring if appropriate.

The Chronic Kidney Disease Epidemiology Collaboration reviewed the various approaches for GFR measurements based on serum creatinine concentration and other factors (Levey et al, 2009). Based on the same four variables as the MDRD equation, but using a two-slope “spline” to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex, and race, the CKD–EPI equation has less bias than the MDRD equation, especially in patients with higher GFR. In the validation data set, the CKD–EPI equation performed better than the MDRD equation, especially at higher GFR (p < .001 for all subsequent comparisons), with less bias (median difference between measured and estimated GFR, 2.5 vs 5.5 mL/min/1.73 m²). The CKD–EPI creatinine equation is more accurate than the MDRD equation and could replace it for routine clinical use (Levey et al, 2009). No comparison has been made available between the widely used Cockcroft–Gault method and the CKD–EPI method in the more important issue of how to relate the calculated GFR to individual drug clearance in the patient which ultimately determined an optimized drug dosing regimen. A limitation of this method is that the sample contained a limited number of elderly people and racial and ethnic minorities with measured GFR.

DOSE ADJUSTMENT FOR UREMIC PATIENTS

Dose adjustment for drugs in uremic or renally impaired patients should be made in accordance with changes in pharmacodynamics and pharmacokinetics of the drug in the individual patient. Whether renal impairment will alter the pharmacokinetics of the drug enough to justify dosage adjustment is an important consideration. For many drugs that are eliminated primarily by metabolism or biliary
secretion, uremia may not alter pharmacokinetics sufficiently to warrant dosage adjustment.

Active metabolites of the drug may also be formed and must be considered for additional pharmacologic effects when adjusting dose. For some drugs, the free drug concentrations may need to be considered due to decreased or altered protein binding in uremia. Combination products that contain two or more active drugs in a fixed-dose combination may be differentially affected by decreased renal function and thus the use of combination drug products in uremic patients should be discouraged.

The following methods may be used to estimate an initial and maintenance dose regimen. After initiating the dosage, the clinician should continue to monitor the pharmacodynamics and pharmacokinetics of the drug. He or she should also evaluate the patient’s renal function, which may be changing.

### Basis for Dose Adjustment in Uremia

The loading drug dose is based on the apparent volume of distribution of the patient. It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore the loading dose of the drug is the same in uremic patients as in subjects with normal renal function.

The maintenance dose is based on clearance of the drug in the patient. In the uremic patient, the rate of renal drug excretion has decreased, leading to a decrease in total body clearance. Most methods for dose adjustment assume nonrenal drug clearance to be unchanged. The fraction of normal renal function remaining in the uremic patient is estimated from creatinine clearance.

After the remaining total body clearance in the uremic patient is estimated, a dosage regimen may be developed by (1) decreasing the maintenance dose, (2) increasing the dosage interval, or (3) changing both maintenance dose and dosage interval.

Although total body clearance is a more accurate index for drug dosing, the elimination half-life of the drug is more commonly used for dose adjustment because of its convenience. Clearance allows for the prediction of steady-state drug concentrations, while elimination half-life yields information on the time it takes to reach steady-state concentration.

### Nomograms

Nomograms are charts available for use in estimating dosage regimens in uremic patients (Bjornsson, 1986; Chennavasin and Craig Brater, 1981; Tozer, 1974). The nomograms may be based on serum creatinine concentrations, patient data (height, weight, age, gender), and the pharmacokinetics of the drug. As discussed by Chennavasin and Brater (1981), each nomogram has errors in its assumptions and drug database.

Most methods for dose adjustment in renal disease assume that nonrenal elimination of the drug is not affected by renal impairment and that the remaining renal excretion rate constant in the uremic patient is proportional to the product of a constant and the creatinine clearance, $C_{cr}$.

$$k_u = k_{nr} + \alpha C_{cr}$$

(21.14)

where $k_u$ is the nonrenal elimination rate constant and $\alpha$ is a constant. Equation 21.14 is similar to Equation 21.10, where $\alpha = 1/V_D$, and can be used for the construction of a nomogram. Figure 21-3 shows a graphical representation of Equation 21.14 for four different drugs, each with a different renal excretion rate constant. The fractions of drug excreted in the urine unchanged, $f_e$, for drugs A, B, C, and D are 5%, 50%, 75%, and 90%, respectively. A creatinine clearance of ≥80 mL/min is considered an adequate glomerular filtration rate in subjects with normal renal function.
renal function. The uremic elimination rate constant ($k_u$) is the sum of the nonrenal elimination rate constant and the renal elimination rate constant, which is decreased due to renal impairment. If the patient has complete renal shutdown (ie, creatinine clearance = 0 mL/min), then the intercept on the y axis represents the percent of drug elimination due to nonrenal drug elimination routes. Drug $D$, which is excreted 90% unchanged in the urine, has the steepest slope (equivalent to $\alpha$ in Equation 21.14) and is most affected by small changes in creatinine clearance; whereas drug $A$, which is excreted only 5% unchanged in the urine (ie, 95% eliminated by nonrenal routes), is least affected by a decrease in creatinine clearance.

The nomogram method of Welling and Craig (1976) provides an estimate of the ratio of the uremic elimination rate constant ($k_u$) to the normal elimination rate constant ($k_N$) on the basis of creatinine clearance (Fig. 21-4). For this method, Welling and Craig (1976) provided a list of drugs grouped according to the amount of drug excreted unchanged in the urine (Table 21-5). From the $k_u/k_N$ ratio, the uremic dose can be estimated according to Equation 21.15:

$$\text{Uremic dose} = \frac{k_u}{k_N} \times \text{normal dose} \quad (21.15)$$

When the dosage interval $\tau$ is kept constant, the uremic dose is always a smaller fraction of the normal dose. Instead of reducing the dose for a uremic patient, the usual dose is kept constant and the dosage interval $\tau$ is prolonged according to the following equation:

$$\text{Dosage interval in uremia}, \quad \tau_u = \frac{k_N}{k_u} \times \tau_N \quad (21.16)$$

where $\tau_u$ is the dosage interval for the dose in uremic patients and $\tau_N$ is the dosage interval for the dose in patients with normal renal function.

![FIGURE 21-4](image-url)  This nomograph describes the changes in the percentage of normal elimination rate constant (left ordinate) and the consequent geometric increase in elimination half-life (right ordinate) as a function of creatinine clearance. The drugs associated with the individual slopes are given in Table 21-5. (From Welling and Craig, 1976, with permission.)
### TABLE 21-5  Elimination Rate Constants for Various Drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>$k_n$ (h⁻¹)</th>
<th>$k_{nr}$ (h⁻¹)</th>
<th>$k_{nr}/k_n$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Minocycline</td>
<td>0.04</td>
<td>0.04</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>0.25</td>
<td>0.25</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>0.39</td>
<td>0.36</td>
<td>92.3</td>
</tr>
<tr>
<td></td>
<td>Digitoxin</td>
<td>0.114</td>
<td>0.10</td>
<td>87.7</td>
</tr>
<tr>
<td>B</td>
<td>Doxycycline</td>
<td>0.037</td>
<td>0.031</td>
<td>83.8</td>
</tr>
<tr>
<td></td>
<td>Chlortetracycline</td>
<td>0.12</td>
<td>0.095</td>
<td>79.2</td>
</tr>
<tr>
<td>C</td>
<td>Clindamycin</td>
<td>0.16</td>
<td>0.12</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>0.26</td>
<td>0.19</td>
<td>73.1</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>0.22</td>
<td>0.16</td>
<td>72.8</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>0.39</td>
<td>0.28</td>
<td>71.8</td>
</tr>
<tr>
<td>D</td>
<td>Trimethoprim</td>
<td>0.054</td>
<td>0.031</td>
<td>57.4</td>
</tr>
<tr>
<td></td>
<td>Isoniazid (fast)</td>
<td>0.53</td>
<td>0.30</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>Isoniazid (slow)</td>
<td>0.23</td>
<td>0.13</td>
<td>56.5</td>
</tr>
<tr>
<td>E</td>
<td>Dicloxacillin</td>
<td>1.20</td>
<td>0.60</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>Sulfadiazine</td>
<td>0.069</td>
<td>0.032</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole</td>
<td>0.084</td>
<td>0.037</td>
<td>44.0</td>
</tr>
<tr>
<td>F</td>
<td>Nafcillin</td>
<td>1.26</td>
<td>0.54</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>Chlorpropamide</td>
<td>0.020</td>
<td>0.008</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>0.15</td>
<td>0.06</td>
<td>40.0</td>
</tr>
<tr>
<td>G</td>
<td>Colistimethate</td>
<td>0.154</td>
<td>0.054</td>
<td>35.1</td>
</tr>
<tr>
<td></td>
<td>Oxacillin</td>
<td>1.73</td>
<td>0.58</td>
<td>33.6</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>0.021</td>
<td>0.007</td>
<td>33.3</td>
</tr>
<tr>
<td>H</td>
<td>Tetracycline</td>
<td>0.120</td>
<td>0.033</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>Cloxacillin</td>
<td>1.21</td>
<td>0.31</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>Oxytetracycline</td>
<td>0.075</td>
<td>0.014</td>
<td>18.7</td>
</tr>
<tr>
<td>I</td>
<td>Amoxicillin</td>
<td>0.70</td>
<td>0.10</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>1.40</td>
<td>0.19</td>
<td>13.6</td>
</tr>
<tr>
<td>J</td>
<td>Ticarcillin</td>
<td>0.58</td>
<td>0.066</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>Penicillin G</td>
<td>1.24</td>
<td>0.13</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>0.53</td>
<td>0.05</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Carbenicillin</td>
<td>0.55</td>
<td>0.05</td>
<td>9.1</td>
</tr>
</tbody>
</table>
TABLE 21-5  Elimination Rate Constants for Various Drugsa (Continued)

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>$k_N$ (h$^{-1}$)</th>
<th>$k_{nr}$ (h$^{-1}$)</th>
<th>$k_{nr}/k_N$%</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>Cefazolin</td>
<td>0.32</td>
<td>0.02</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>Cephaloridine</td>
<td>0.51</td>
<td>0.03</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Cephalothin</td>
<td>1.20</td>
<td>0.06</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>0.30</td>
<td>0.015</td>
<td>5.0</td>
</tr>
<tr>
<td>L</td>
<td>Flucytosine</td>
<td>0.18</td>
<td>0.007</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>0.28</td>
<td>0.01</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>0.12</td>
<td>0.004</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>0.32</td>
<td>0.010</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Cephalexin</td>
<td>1.54</td>
<td>0.032</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*a$ k_N$ is for patients with normal renal function, $k_{nr}$ is for patients with severe renal impairment, and $k_{nr}/k_N$% = percent of normal elimination in severe renal impairment.

From Welling and Craig (1976), with permission.

PRACTICE PROBLEM

Lincomycin is given at 500 mg every 6 hours to a 75-kg healthy patient. What doses would be used (a) in complete renal shutdown ($Cl_{cr} = 0$) and (b) when $Cl_{cr} = 10$ mL/min?

Solution

To use the nomogram method, follow the steps below:

1. Use Table 21-5 to locate the group to which the drug belongs.
2. Find $k_u/k_N$ at the point corresponding to $Cl_{cr}$ of the patient (see Fig. 21-4).
3. Determine $k_u$ for the patient.
4. Make the dose adjustment in accordance with pharmacokinetic principles.

a. When $Cl_{cr} = 0$,

$$k_u = k_{nr} + k_R$$

In complete renal shutdown ($k_R = 0$),

$$k_u = k_{nr} = 0.06 \text{ h}^{-1}$$ (see Table 21-5, group F)

or find $k_u/k_N$ in Fig. 21-4, group F, at $Cl_{cr} = 0$ mL/min:

$$\frac{k_u}{k_N} = 0.425$$

$$k_u = 0.425 \times 0.15 = 0.0638 \text{ h}^{-1}$$

Uremic dose = 500 mg $\frac{0.0638}{0.15} = 212$ mg every 6 hours

b. At $Cl_{cr} = 10$ mL/min, $k_u/k_N = 0.48$

$$k_{nr} = 0.15 \text{ h}^{-1}$$

$$k_u = (0.48) (0.15) = 0.072 \text{ h}^{-1}$$

Dose = 500 mg $\frac{0.072}{0.15} = 240$ mg

Alternatively,

Dose = (0.48) (500) = 240 mg

Fraction of Drug Excreted Unchanged ($fe$) Methods

For many drugs, the fraction of drug excreted unchanged ($fe$) is available in the literature. Table 21-6 lists various
<table>
<thead>
<tr>
<th>Drug</th>
<th>fe</th>
<th>$t_{1/2 \text{ normal}}$ (h)</th>
<th>Drug</th>
<th>fe</th>
<th>$t_{1/2 \text{ normal}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>0.44 ± 0.11</td>
<td>2.7 ± 0.4</td>
<td>Chlorthalidone</td>
<td>0.65 ± 0.09</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.03 ± 0.01</td>
<td>2.0 ± 0.4</td>
<td>Cimetidine</td>
<td>0.77 ± 0.06</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>0.4</td>
<td>1.3</td>
<td>Clindamycin</td>
<td>0.09–0.14</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>Active metabolite</td>
<td></td>
<td>16–30</td>
<td>Clofibrate</td>
<td>0.11–0.32</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>0.1</td>
<td>2–8</td>
<td>Clonidine</td>
<td>0.62 ± 0.11</td>
<td>8.5 ± 2.0</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>0.005</td>
<td>3.1 ± 1.2</td>
<td>Colistin</td>
<td>0.9</td>
<td>3</td>
</tr>
<tr>
<td>Amantadine</td>
<td>0.85</td>
<td>10</td>
<td>Cyclophosphamide</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.98</td>
<td>2.3 ± 0.4</td>
<td>Cytarabine</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td>Amiloride</td>
<td>0.5</td>
<td>8 ± 2</td>
<td>Dapsone</td>
<td>0.1</td>
<td>20</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.52 ± 0.15</td>
<td>1.0 ± 0.1</td>
<td>Dicloxacillin</td>
<td>0.60 ± 0.07</td>
<td>0.7 ± 0.07</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.4–0.45</td>
<td>12</td>
<td>Digitoxin</td>
<td>0.33 ± 0.15</td>
<td>166 ± 65</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.03</td>
<td>360</td>
<td>Digoxin</td>
<td>0.72 ± 0.09</td>
<td>42 ± 19</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.90 ± 0.08</td>
<td>1.3 ± 0.2</td>
<td>Disopyramide</td>
<td>0.55 ± 0.06</td>
<td>7.8 ± 1.6</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.85</td>
<td>6.3 ± 1.8</td>
<td>Doxycycline</td>
<td>0.40 ± 0.04</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Azlocillin</td>
<td>0.6</td>
<td>1.0</td>
<td>Erythromycin</td>
<td>0.15</td>
<td>1.1–3.5</td>
</tr>
<tr>
<td>Bacampicillin</td>
<td>0.88</td>
<td>0.9</td>
<td>Ethambutol</td>
<td>0.79 ± 0.03</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Baclofen</td>
<td>0.75</td>
<td>3–4</td>
<td>Ethosuximide</td>
<td>0.19</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>0.55</td>
<td>1.5–8.9</td>
<td>Flucytosine</td>
<td>0.63–0.84</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>Bretylium</td>
<td>0.8 ± 0.1</td>
<td>4–17</td>
<td>Flunitrazepam</td>
<td>0.01</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.33</td>
<td>3.5</td>
<td>Furosemide</td>
<td>0.74 ± 0.07</td>
<td>0.85 ± 0.17</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>0.82 ± 0.09</td>
<td>1.1 ± 0.2</td>
<td>Gentamicin</td>
<td>0.98</td>
<td>2–3</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>0.52</td>
<td>0.6 ± 0.3</td>
<td>Griseofulvin</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0.96 ± 0.03</td>
<td>0.77</td>
<td>Hydralazine</td>
<td>0.12–0.14</td>
<td>2.2–2.6</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.80 ± 0.13</td>
<td>1.8 ± 0.4</td>
<td>Hydrochlorothiazide</td>
<td>0.95</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>0.2–0.3</td>
<td>2.0</td>
<td>Indomethacin</td>
<td>0.15 ± 0.08</td>
<td>2.6–11.2</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.5–0.6</td>
<td>1–1.5</td>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>0.88 ± 0.08</td>
<td>0.7 ± 0.13</td>
<td>Rapid acetylators</td>
<td>0.07 ± 0.02</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.92</td>
<td>1.1</td>
<td>Slow acetylators</td>
<td>0.29 ± 0.05</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>0.96</td>
<td>0.9 ± 0.18</td>
<td>Isosorbide dinitrate</td>
<td>0.05</td>
<td>0.5</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.05</td>
<td>2.7 ± 0.8</td>
<td>Kanamycin</td>
<td>0.9</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Chlorphenetermine</td>
<td>0.2</td>
<td>120</td>
<td>Lidocaine</td>
<td>0.02 ± 0.01</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Chlorpropanamide</td>
<td>0.2</td>
<td>36</td>
<td>Lincomycin</td>
<td>0.6</td>
<td>5</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 21-6  Fraction of Drug Excreted Unchanged (fe) and Elimination Half-Life Values (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>fe</th>
<th>( t_{1/2, \text{normal}} (h) )*</th>
<th>Drug</th>
<th>fe</th>
<th>( t_{1/2, \text{normal}} (h) )*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>0.95 ± 0.15</td>
<td>22 ± 8</td>
<td>Prazosin</td>
<td>0.01</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.01</td>
<td>14 ± 5</td>
<td>Primidone</td>
<td>0.42 ± 0.15</td>
<td>8.0 ± 4.8</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.04–0.22</td>
<td>3.2 ± 0.8</td>
<td>Procainamide</td>
<td>0.67 ± 0.08</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.2</td>
<td>22</td>
<td>Propranolol</td>
<td>0.005</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Methicillin</td>
<td>0.88 ± 0.17</td>
<td>0.85 ± 0.23</td>
<td>Quinidine</td>
<td>0.18 ± 0.05</td>
<td>6.2 ± 1.8</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.94</td>
<td>8.4</td>
<td>Rifampin</td>
<td>0.16 ± 0.04</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>0.63 ± 0.10</td>
<td>1.8 ± 0.2</td>
<td>Salicylic acid</td>
<td>0.2</td>
<td>3</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.25</td>
<td>8.2</td>
<td>Sisomicin</td>
<td>0.98</td>
<td>2.8</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>0.1</td>
<td>12</td>
<td>Sotalol</td>
<td>0.6</td>
<td>6.5–13</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>0.75</td>
<td>0.8</td>
<td>Streptomycin</td>
<td>0.96</td>
<td>2.8</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.1 ± 0.02</td>
<td>18 ± 4</td>
<td>Sulfinpyrazone</td>
<td>0.45</td>
<td>2.3</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>0.1</td>
<td>4</td>
<td>Sulfisoxazole</td>
<td>0.53 ± 0.09</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>0.82–0.96</td>
<td>2.5–3.0</td>
<td>Tetracycline</td>
<td>0.48</td>
<td>9.9 ± 1.5</td>
</tr>
<tr>
<td>Nadolol</td>
<td>0.73 ± 0.04</td>
<td>16 ± 2</td>
<td>Thiamphenicol</td>
<td>0.9</td>
<td>3</td>
</tr>
<tr>
<td>Nafacilin</td>
<td>0.27 ± 0.05</td>
<td>0.9–1.0</td>
<td>Thiazinanium</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>0.2</td>
<td>1.0</td>
<td>Theophylline</td>
<td>0.08</td>
<td>9 ± 2.1</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0.67</td>
<td>1.3 ± 0.8</td>
<td>Ticarcillin</td>
<td>0.86</td>
<td>1.2</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>0.98</td>
<td>2.2</td>
<td>Timolol</td>
<td>0.2</td>
<td>3–5</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>0.01</td>
<td>29 ± 7</td>
<td>Tobramycin</td>
<td>0.98</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>Nitrofurantion</td>
<td>0.5</td>
<td>0.3</td>
<td>Tocainide</td>
<td>0.20–0.70 (0.40 mean)</td>
<td>1.6–3</td>
</tr>
<tr>
<td>Nomifensine</td>
<td>0.15–0.22</td>
<td>3.0 ± 1.0</td>
<td>Tolbutamide</td>
<td>0</td>
<td>5.9 ± 1.4</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.75</td>
<td>0.5</td>
<td>Triamterene</td>
<td>0.04 ± 0.01</td>
<td>2.8 ± 0.9</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>0.05</td>
<td>1.5</td>
<td>Trimethoprim</td>
<td>0.53 ± 0.02</td>
<td>11 ± 1.4</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.5</td>
<td>3.0</td>
<td>Tubocurarine</td>
<td>0.43 ± 0.08</td>
<td>2 ± 1.1</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.2</td>
<td>2.5</td>
<td>Valproic acid</td>
<td>0.02 ± 0.02</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>Phenoobarbital</td>
<td>0.2 ± 0.05</td>
<td>86 ± 7</td>
<td>Vancomycin</td>
<td>0.97</td>
<td>5–6</td>
</tr>
<tr>
<td>Pindolol</td>
<td>0.41</td>
<td>3.4 ± 0.2</td>
<td>Warfarin</td>
<td>0</td>
<td>37 ± 15</td>
</tr>
<tr>
<td>Pivampicillin</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>0.88</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Half-life is a derived parameter that changes as a function of both clearance and volume of distribution. It is independent of body size, because it is a function of these two parameters (Cl, \( V_D \)), each of which is proportional to body size. It is important to consider that half-life is the time to eliminate 50% of the “drug” from the body (plasma), not the time in which 50% of the effect is lost.

drugs with their $fe$ values and elimination half-lives. The $fe$ method for estimating a dosage regimen in the uremic patient is a general method that may be applied to any drug whose $fe$ is known.

The Giusti–Hayton (1973) method assumes that the effect of reduced kidney function on the renal portion of the elimination constant can be estimated from the ratio of the uremic creatinine clearance, $Cl_{Cr}^{u}$, to the normal creatinine clearance, $Cl_{Cr}^{N}$:

$$\frac{k_u}{k_N} = \frac{Cl_{Cr}^{u}}{Cl_{Cr}^{N}}$$

(21.17)

where $k_u^u$ is the uremic renal excretion rate constant and $k_N$ is the normal renal excretion rate constant.

$$k_u^u = k_N Cl_{Cr}^{u} / Cl_{Cr}^{N}$$

(21.18)

Because the overall uremic elimination rate constant, $k_u$, is the sum of renal and nonrenal elimination,

$$k_u = k_u^u + k_N$$

(21.19)

$$k_u = k_u^u + k_N \left( \frac{Cl_{Cr}^{u}}{Cl_{Cr}^{N}} \right)$$

Dividing Equation 21.19 by $k_N$

$$\frac{k_u}{k_N} = \frac{k_u^u}{k_N} + \frac{k_N}{k_N} \left( \frac{Cl_{Cr}^{u}}{Cl_{Cr}^{N}} \right)$$

(21.20)

Let $fe = k_u^u/k_N$ = fraction of drug excreted unchanged in the urine and $1 - fe = k_u^u/k_N$ = fraction of drug excreted by nonrenal routes. Substitution into Equation 21.20 yields the Giusti–Hayton equation, where $G$ is the Giusti–Hayton factor, which can be calculated from $fe$ and the ratio of uremic to normal clearance:

$$\frac{k_u}{k_N} = (1 - fe) + fe \left( \frac{Cl_{Cr}^{u}}{Cl_{Cr}^{N}} \right)$$

or

$$\frac{k_u}{k_N} = 1 - fe \left( 1 - \frac{Cl_{Cr}^{u}}{Cl_{Cr}^{N}} \right) = G$$

(21.21)

The Giusti–Hayton equation is useful for most drugs for which the fraction of drug excreted by renal routes has been reported in the literature. The ratio $k_u/k_N$ can be calculated from the fraction of drug excreted by the kidney, normal creatinine clearance, and the creatinine clearance in the uremic patient.

**PRACTICE PROBLEM**

The maintenance dose of gentamicin is 80 mg every 6 hours for a patient with normal renal function. Calculate the maintenance dose for a uremic patient with creatinine clearance of 20 mL/min. Assume a normal creatinine clearance of 100 mL/min.

**Solution**

From the literature, gentamicin is reported to be 100% excreted by the kidney (ie, $fe = 1$). Using Equation 21.21,

$$\frac{k_u}{k_N} = 1 - \left( 1 - \frac{20}{100} \right) = 0.2$$

Because

$$\frac{D_u}{D_N} = \frac{k_u}{k_N} \quad \text{or} \quad D_u = D_N \times \frac{k_u}{k_N}$$

where $D_u$ = uremic dose and $D_N$ = normal dose,

$$D_u = 80 \text{ mg} \times 0.2 = 16 \text{ mg}$$

The maintenance dose is 16 mg every 6 hours. Alternatively, the dosing interval can be adjusted without changing the dose:

$$\frac{\tau_u}{\tau_N} = \frac{k_N}{k_u} \quad \text{or} \quad \tau_u = \tau_N \times \frac{k_N}{k_u}$$

$$\tau_u = 6 \text{ h} \times \frac{1}{0.2} = 30 \text{ h}$$

where $\tau_u$ and $\tau_N$ are dosing intervals for uremic and normal patients, respectively. The patient may be given 80 mg every 30 hours.

Other approaches for using fraction of drug excreted unchanged have been developed by Tozer.
(1974) and Bjornsson (1986). These methods use $fe$ for dosing regimen design and the following equation:

$$Q = 1 - fe (1 - k_f)$$  \hspace{1cm} (21.22)$$

where $Q$ is the dosage adjustment factor, $k_f = Cl_{CR} / Cl_{N}$, and $fe$ is the fraction of unchanged drug excreted renally. Actually $Q$ is exactly the same as $G$ in Equation 21.21, the Giusti–Hayton approach developed in 1973.

The value of $Q$ in Equation 21.22 is multiplied by the normal dose, $D_N$, to give the uremic dose, $D_u$:

$$D_u = Q \times D_N$$  \hspace{1cm} (21.23)$$

All the methods discussed so far assume that nonrenal elimination, $k_{nr}$, is unchanged, thereby ignoring potential side effects resulting from an increase in the half-life of metabolism of the parent drug and/or an accumulation of active metabolites of the drug.

Bodenham and associates (1988) have shown that although lorazepam pharmacokinetics were not significantly altered in patients with chronic renal failure, the clearance of lorazepam glucuronide, a major metabolite, was reduced significantly. Therefore, there are potential sedative side effects in the renally impaired patient as a result of the longer metabolite half-life. Bodenham and co-workers (1988) also cited literature references to potentiation of sedative and analgesic drug effects in renal, liver, and other multisystem disease states.

In addition to pharmacokinetic changes, possible changes in pharmacodynamic effects in patients with renal and other diseases must be considered. Neuromuscular-blocking drugs may be potentiated or antagonized by changes in potassium, phosphate, and hydrogen ion concentration brought about by uremic states. Morphine potentiation has been reported in hypocalcemic states. In many patients, plasma creatinine concentration may not rise for some time, until creatinine clearance has fallen significantly, thereby adding to the uncertainty of any method that depends on plasma $C_{cr}$ for dose adjustment.

**Comparison of Dose Adjustment Methods in Uremic Patients**

All of the methods mentioned previously have similar limitations (see Table 21-2). For example, the drug must follow dose-independent kinetics and the volume of distribution of the drug must remain relatively constant in the uremic patient. It is usually assumed that the nonrenal routes of elimination, such as hepatic clearance, do not change. If there is a change in an active metabolite formation or elimination in uremia, then both parent and active metabolite must be considered when adjusting a dosage regimen for patients with renal disease. Another assumption in the use of these methods is that pharmacologic response is unchanged in the uremic patient. This assumption may be unrealistic for drugs that act differently in the disease state. For example, the pharmacologic response with digoxin is dependent on the potassium level in the body, and the potassium level in the uremic patient may be rather different from that of the normal individual. In a patient undergoing dialysis, loss of potassium may increase the potential of toxic effect of the drug digoxin. For many drugs, studies have shown that the incidence of adverse effects is increased in uremic patients. It is often impossible to distinguish whether the increase in adverse effect is due to a pharmacokinetic change or to a pharmacodynamic change in the receptor sensitivity to the drug. In any event, these observations point out the fact that dose adjustment must be regarded as a preliminary estimation to be followed with further adjustments in accordance with the observed clinical response.

**PRACTICE PROBLEMS**

1. An adult male patient (52 years old, 75 kg) whose serum creatinine is 2.4 mg/dL is to be given gentamicin sulfate for a confirmed Gram-negative infection. The usual dose of gentamicin in adult patients with normal renal function is 1 mg/kg every 8 hours by multiple IV bolus injections. Gentamicin sulfate (Garamycin) is available in 2-mL vials containing 40 mg of gentamicin sulfate per milliliter. Calculate (a) the creatinine clearance in this patient by the Cockcroft–Gault method and (b) the appropriate dosage regimen of gentamicin sulfate for this patient in mg and mL.
Solution

a. The creatinine clearance is calculated by the Cockcroft–Gault method using Equation 21.12:

\[
Cl_{cr} = \frac{(140 - 52)(75)}{72(2.4)} = 38.19 \text{ mL/min}
\]

b. The initial dose of gentamicin sulfate in this patient may be estimated using Equation 21.21. Normal creatinine clearance is assumed to equal 100 mL/min. The fraction of dose excreted unchanged in the urine, \(fe\), is 0.98 for gentamicin sulfate (Table 21-6).

\[
\frac{k_u}{k_N} = Q = 1 - 0.98\left(1 - \frac{38.19}{100}\right) = 0.39
\]

The usual dose of gentamicin sulfate = 1 mg/kg every 8 hours. Therefore, for a 75-kg adult, the usual dose is 75 mg every 8 hours. The uremic dose may be estimated by:

i. Reducing the maintenance dose and keeping the dosing interval constant:

\[
\text{Uremic dose} = \frac{k_u}{k_N} \times \text{normal dose}
\]

Uremic dose = 0.39 \times 75 = 29.25 mg

Give 29.25 mg (about 30 mg) every 8 hours. Because the concentration of gentamicin sulfate solution is 40 mg/mL, 30 mg gentamicin sulfate is equivalent to 0.75 mL.

ii. Increasing the dosing interval and keeping the maintenance dose constant:

\[
\text{Dosage interval in uremia, } \tau_u = \frac{k_N}{k_u} \times \tau_N
\]

\[
\tau_u = 2.564 \times 8 = 20.5 \text{ h}
\]

(2.564 is the reciprocal of 0.39)

Give 75 mg every 20.5 hours.

iii. Change both the maintenance dose and dosing interval. Using the dosing rate \(D_\tau\) = 29.25 mg/8 h = 3.66 mg/h, a dose of 21.9 mg every 6 hours or 43.8 mg every 12 hours will produce the same average steady-state plasma drug concentration.

Although each estimated dosage regimen shown above produces the same average steady-state plasma drug concentration, the peak drug concentration, trough drug concentration, and duration of time in which the drug concentration will be above or below the minimum effective plasma drug concentration will be different. Choice of an appropriate dosage regimen requires consideration of these issues, the patient, and the safety and efficacy of the drug.

2. Calculate the dose adjustment needed for uremic patients with (a) 75% of normal kidney function, (b) 50% of normal kidney function; and (c) 25% of normal kidney function. Make calculations for (1) a drug that is 50% excreted by the kidney, and (2) a drug that is 75% excreted by the kidney.

Solution

The values for percent of normal creatinine clearance in uremic patients with various renal functions are listed in Table 21-7. The percent of dose adjustment in a given uremic state is obtained using the procedure detailed below. The important facts to remember are (1) although the elimination rate constant is usually composed of two components, only the renal component is reduced in a uremic patient, and (2) the kidney function of the uremic patient may be expressed as a percent of normal kidney function. The reduction in the renal elimination rate constant can be estimated from the percent of kidney function remaining in the patient. The steps involved in making the calculations are as follows:

a. Determine \(fe\), or the fraction of drug excreted by the kidney.

b. Determine \(k_u\) by dividing \(Cl_{cr}^u\) of the uremic patient by \(Cl_{cr}^N\).

c. Calculate \(Q\) (Equation 21.22).

d. Multiply \(Q\) by the normal dose to give the fraction of normal dose required for a uremic patient.
3. What is the dose for a drug that is 75% excreted unchanged through the kidney in a uremic patient with a creatinine clearance of 10 mL/min?

**Solution**

\[ fe = 75\% \]

Renal function of uremic patient = \( \frac{10}{100} = 10\% \) normal

Percent of uremic patient’s renal elimination constant = \( 75\% \times 10\% = 7.5\% \) normal

Percent of uremic patient’s overall elimination constant = \( 75\% + (100\% - 75\%) = 7.5\% + 25\% = 32.5\% \)

Therefore, the uremic patient’s dose should be 32.5% of that of normal patient. Table 21-7 provides some calculated dose adjustments for drugs eliminated to various degrees by renal excretion in different stages of renal failure.

**General Clearance Method**

The general clearance method is based on the methods discussed above. This method is popular in clinical settings because of its simplicity. The method assumes that creatinine clearance, \( Cl_{\text{Cr}} \), is a good indicator of renal function and that the renal clearance of a drug, \( Cl_{\text{R}} \), is proportional to \( Cl_{\text{Cr}} \). Therefore, renal drug clearance, \( Cl_{\text{R}}^u \), in the uremic patient is

\[ Cl_{\text{R}}^u = \frac{Cl_{\text{R}}}{Cl_{\text{Cr}}} \times Cl_{\text{R}} \]  

\[ (21.24) \]

\[ Cl_u = Cl_{\text{ur}} + Cl_{\text{R}} \frac{Cl_{\text{R}}^u}{Cl_{\text{Cr}}} \]  

\[ (21.25) \]

where \( Cl_u \) is the total body clearance in the uremic patient.

If the ratio, \( Cl_{\text{R}}^u / Cl_{\text{Cr}}^n \) and \( Cl_{\text{ur}} \) and \( Cl_{\text{R}} \) are known, the total body clearance in the uremic patient may be estimated using Equation 21.25. Alternatively, if the normal total body clearance, \( Cl \), and \( fe \) are known, Equation 21.26 may be obtained by substitution in Equation 21.25:

\[ Cl_u = Cl(1 - fe) + fe \frac{Cl_{\text{R}}^u}{Cl_{\text{Cr}}^n} \]  

\[ (21.26) \]

Equation 21.26 calculates drug clearance in the uremic patient using the fraction of drug excreted unchanged (\( fe \)), total body clearance of the drug (\( Cl \)) in the normal subject, and the ratio of creatinine clearance of the uremic to that of the normal patient.

Dividing Equation 21.26 on both sides by \( Cl \) yields the ratio \( Cl_u / Cl \), reflecting the fraction of the uremic/normal drug dose.

\[ \frac{Cl_u}{Cl} = (1 - fe) + fe \frac{Cl_{\text{R}}^u}{Cl_{\text{Cr}}^n} \]  

\[ (21.27) \]

**PRACTICE PROBLEM**

A 34-year-old, 110-lb female patient is to be given tobramycin for sepsis. The usual dose of tobramycin is 150 mg twice a day by intravenous injection. The

<table>
<thead>
<tr>
<th>Fraction of Drug Excreted Unchanged ( (k_f/k_u) ) or ( fe )</th>
<th>Percent of Normal Dose</th>
<th>50% Normal ( Cl_{\text{Cr}} )</th>
<th>25% Normal ( Cl_{\text{Cr}} )</th>
<th>10% Normal ( Cl_{\text{Cr}} )</th>
<th>0% Normal ( Cl_{\text{Cr}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>87</td>
<td>81</td>
<td>77</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>75</td>
<td>62</td>
<td>55</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>62</td>
<td>44</td>
<td>32</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>0.90</td>
<td>55</td>
<td>32</td>
<td>19</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
creatinine clearance in this patient has decreased to a stable level of 50 mL/min. Calculate the appropriate dose of tobramycin for this patient.

**Solution**

Obtain \( f_e = 0.9 \) from the literature (see Appendix D) and apply Equation 21.27:

\[
\frac{C_l}{C_l} = (1 - f_e) + f_e \frac{C_{lR}}{C_{lR}}
\]

\[
\frac{C_l}{C_l} = 1 - 0.9 + 0.9 \left( \frac{50}{100} \right) = 0.55
\]

Therefore, the dose for the uremic patient = 150 mg \( \times 0.55 = 82.5 \) mg (given twice a day).

**The Wagner Method**

The methods for renal dose adjustment discussed in the previous sections assume that the volume of distribution and the fraction of drug excreted by nonrenal routes are unchanged. These assumptions are convenient and hold true for many drugs. However, in the absence of reliable information assuring the validity of these assumptions, the equations should be demonstrated as statistically reliable in practice. A statistical approach was used by Wagner (1975), who established a linear relationship between creatinine concentration and the first-order elimination constant of the drug in patients. The Wagner method is described in greater detail in the third edition of this book.

This method takes advantage of the fact that the elimination constant for a patient can be obtained from the creatinine clearance, as follows:

\[
k% = a + bC_{lR}
\]  
\[
(21.28)
\]

The values of \( a \) and \( b \) are determined statistically for each drug from pooled data on uremic patients. The method is simple to use and should provide accurate determination of elimination constants for patients when a good linear relationship exists between elimination constant and creatinine concentration. The theoretical derivation of this approach is as follows:

\[
k% = \text{total elimination rate constant}
\]
\[
k_{nr} = \text{nonrenal elimination rate constant (\%)}
\]
\[
k = \text{renal excretion rate constant}
\]
\[
C_l = \text{total body clearance of drug}
\]
\[
R = \frac{C_l}{C_{lR}}
\]  
\[
(21.29)
\]
\[
C_l = R \frac{C_{lR}}{V_D}
\]
\[
k = k_{nr} + \frac{R}{V_D}C_{lR}
\]
\[
100k = 100k_{nr} + \frac{100R}{V_D}C_{lR}
\]
\[
k% = a + bC_{lR}
\]  
\[
(21.30)
\]

Equation 21.30 can also be used with drugs that follow the two-compartment model. In such cases the terminal half-life is used and \( b \), the terminal slope of elimination curve, is substituted for the elimination rate constant, \( k \). Since the equation assumes a constant nonrenal elimination constant \( k_{nr} \) and volume of distribution, any change in these two parameters will result in an error in the estimated elimination constant.

**Frequently Asked Questions**

- What are the advantages and disadvantages of using serum creatinine concentrations for the measurement of renal function?
- What is the most accurate approach for the estimation of glomerular filtration rate?
- Why does each method based on serum creatinine concentrations for dosage adjustment in renal impairment give somewhat different values?
- What are the pharmacokinetic considerations in designing a dosing regimen? Why is dosing once a day for aminoglycosides recommended by many clinicians?

**EXTRACORPOREAL REMOVAL OF DRUGS**

Patients with *end-stage renal disease* (ESRD) and those who have become intoxicated with a drug as a result of drug overdose require supportive treatment to remove the accumulated drug and its metabolites.
Several methods are available for the extracorporeal removal of drugs, including hemoperfusion, hemofiltration, and dialysis. The objective of these methods is to rapidly remove the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the patient.

Patients with impaired renal function may be taking other medication concurrently. For these patients, dosage adjustment may be needed to replace drug loss during extracorporeal drug and metabolite removal.

Dialysis

Dialysis is an artificial process in which the accumulation of drugs or waste metabolites is removed by diffusion from the body into the dialysis fluid. Two common dialysis treatments are peritoneal dialysis and hemodialysis. Both processes work on the principle that as the uremic blood or fluid is equilibrated with the dialysis fluid across a dialysis membrane, waste metabolites from the patient’s blood or fluid diffuse into the dialysis fluid and are removed. The dialysate is balanced with electrolytes and with respect to osmotic pressure. The dialysate contains water, dextrose, electrolytes (potassium, sodium, chloride, bicarbonate, acetate, calcium, etc), and other elements similar to normal body fluids without the toxins.

Peritoneal Dialysis

Peritoneal dialysis uses the peritoneal membrane in the abdomen as the filter. The peritoneum consists of visceral and parietal components. The peritoneum membrane provides a large natural surface area for diffusion of approximately 1 to 2 m² in adults; the membrane is permeable to solutes of molecular weights ≤ 30,000 Da (Merck Manual, 1996–1997). Total splanchnic flow is 1200 mL/min at rest, but only a small portion, approximately 70 mL/min, comes into contact with the peritoneum. Placement of a peritoneal catheter is surgically simpler than hemodialysis and does not require vascular surgery and heparinization. The dialysis fluid is pumped into the peritoneal cavity, where waste metabolites in the body fluid are discharged rapidly. The dialysate is drained and fresh dialysate is reinstalled and then drained periodically. Peritoneal dialysis is also more amenable to self-treatment. However, slower drug clearance rates are obtained with peritoneal dialysis compared to hemodialysis, and thus longer dialysis time is required.

Continuous ambulatory peritoneal dialysis (CAPD) is the most common form of peritoneal dialysis. Many diabetic patients become uremic as a result of lack of control of their diabetes. About 2 L of dialysis fluid is instilled into the peritoneal cavity of the patient through a surgically placed resident catheter. The objective is to remove accumulated urea and other metabolic waste in the body. The catheter is sealed and the patient is able to continue in an ambulatory mode. Every 4 to 6 hours, the fluid is emptied from the peritoneal cavity and replaced with fresh dialysis fluid. The technique uses about 2 L of dialysis fluid; it does not require a dialysis machine and can be performed at home.

Hemodialysis

Hemodialysis uses a dialysis machine and filters blood through an artificial membrane. Hemodialysis requires access to the blood vessels to allow the blood to flow to the dialysis machine and back to the body. For temporary access, a shunt is created in the arm, with one tube inserted into an artery and another tube inserted into a vein. The tubes are joined above the skin. For permanent access to the blood vessels, an arteriovenous fistula or graft is created by a surgical procedure to allow access to the artery and vein. Patients who are on chronic hemodialysis treatment need to be aware of the need for infection control of the surgical site of the fistula. At the start of the hemodialysis procedure, an arterial needle allows the blood to flow to the dialysis machine, and blood is returned to the patient to the venous side. Heparin is used to prevent blood clotting during the dialysis period.

During hemodialysis, the blood flows through the dialysis machine, where the waste material is removed from the blood by diffusion through an artificial membrane before the blood is returned to the body. Hemodialysis is a much more effective method of drug removal and is preferred in situations when rapid removal of the drug from the body is important, as in overdose or poisoning. In practice, hemodialysis is most often used for patients with end-stage renal failure. Early dialysis is appropriate
for patients with acute renal failure in whom resumption of renal function can be expected and in patients who are to be renally transplanted. Other patients may be placed on dialysis according to clinical judgment concerning the patient’s quality of life and risk/benefit ratio (Carpenter and Lazarus, 1994).

Dialysis may be required from once every 2 days to 3 times a week, with each treatment period lasting 2 to 4 hours. The time required for dialysis depends on the amount of residual renal function in the patient, any complicating illness (eg, diabetes mellitus), the size and weight of the patient, including muscle mass, and the efficiency of the dialysis process. Dosing of drugs in patients receiving hemodialysis is affected greatly by the frequency and type of dialysis machine used and by the physicochemical and pharmacokinetic properties of the drug. Factors that affect drug removal in hemodialysis are listed in Table 21-8. These factors are carefully considered before hemodialysis is used for drug removal.

In hemodialysis, blood is pumped to the dialyzer by a roller pump at a rate of 300 to 450 mL/min. The drug and metabolites diffuse from the blood through the semipermeable membrane. In addition, hydrostatic pressure also forces the drug molecules into the dialysate by ultrafiltration. The composition of the dialysate is similar to plasma but may be altered according to the needs of the patient. Many dialysis machines use a hollow fiber or capillary dialyzer in which the semipermeable membrane is made into fine capillaries, of which thousands are packed into bundles with blood flowing through the capillaries and the dialysate is circulated outside the capillaries. The permeability characteristics of the membrane and the membrane surface area are determinants of drug diffusion and ultrafiltration.

The efficacy of hemodialysis membranes for the removal of vancomycin by hemodialysis has been reviewed by De Hart (1996). Vancomycin is an antibiotic effective against most Gram-positive organisms such as *Staphylococcus aureus*, which may be responsible for vascular access infections in patients undergoing dialysis. In De Hart’s study, vancomycin hemodialysis in patients was compared using a cuprophan membrane or a cellulose acetate and polyacrylonitrile membrane. The cellulose acetate and polyacrylonitrile membrane is considered a “high-flux” filter. Serum vancomycin concentrations

<table>
<thead>
<tr>
<th>TABLE 21-8</th>
<th>Factors Affecting Dialyzability of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physicochemical and Pharmacokinetic Properties of the Drug</strong></td>
<td></td>
</tr>
<tr>
<td>Water solubility</td>
<td>Insoluble or fat-soluble drugs are not dialyzed—eg, glutethimide, which is very water insoluble.</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Tightly bound drugs are not dialyzed because dialysis is a passive process of diffusion—eg, propranolol is 94% bound.</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Only molecules with molecular weights of less than 500 are easily dialyzed—eg, vancomycin is poorly dialyzed and has a molecular weight of 1800.</td>
</tr>
<tr>
<td>Drugs with large volumes of distribution</td>
<td>Drugs widely distributed are dialyzed more slowly because the rate-limiting factor is the volume of blood entering the machine—eg, for digoxin, $V_d = 250–300$ L. Drugs concentrated in the tissues are usually difficult to remove by dialysis.</td>
</tr>
<tr>
<td><strong>Characteristics of the Dialysis Machine</strong></td>
<td></td>
</tr>
<tr>
<td>Blood flow rate</td>
<td>Higher blood flows give higher clearance rates.</td>
</tr>
<tr>
<td>Dialysate</td>
<td>Composition of the dialysate and flow rate.</td>
</tr>
<tr>
<td>Dialysis membrane</td>
<td>Permeability characteristics and surface area.</td>
</tr>
<tr>
<td>Transmembrane pressure</td>
<td>Ultrafiltration increases with increase in transmembrane pressure.</td>
</tr>
<tr>
<td>Duration and frequency of dialysis</td>
<td></td>
</tr>
</tbody>
</table>
decreased only 6.3% after dialysis when using the cuprophan membrane, whereas the serum drug concentration decreased 13.6%–19.4% after dialysis with the cellulose acetate and polyacrylonitrile membrane.

In dialysis involving uremic patients receiving drugs for therapy, the rate at which a given drug is removed depends on the flow rate of blood to the dialysis machine and the performance of the dialysis machine. The term dialysance is used to describe the process of drug removal from the dialysis machine. Dialysance is a clearance term similar in meaning to renal clearance, and it describes the amount of blood completely cleared of drugs (in mL/min). Dialysance is defined by the equation

\[ Cl_D = \frac{Q(C_a - C_v)}{C_a} \]  

(21.31)

where \( C_a \) = drug concentrations in arterial blood (blood entering kidney machine), \( C_v \) = drug concentration in venous blood (blood leaving kidney machine), \( Q \) = rate of blood flow to the kidney machine, and \( Cl_D \) = dialysance. Dialysance is sometimes referred to as dialysis clearance.

**PRACTICE PROBLEM**

Assume the flow rate of blood to the dialysis machine is 350 mL/min. By chemical analysis, the concentrations of drug entering and leaving the machine are 30 and 12 µg/mL, respectively. What is the dialysis clearance?

**Solution**

The rate of drug removal is equal to the volume of blood passed through the machine divided by the arterial difference in blood drug concentrations before and after dialysis. Thus,

\[ \text{Rate of drug removal} = 350 \text{ mL/min} \times (30 - 12) \mu g/mL = 6300 \mu g/min \]

Since clearance is equal to the rate of drug removal divided by the arterial concentration of drug,

\[ Cl_D = \frac{6300 \mu g/min}{30 \mu g/mL} = 210 \text{ mL/min} \]

Alternatively, using Equation 21.31,

\[ Cl_D = 350 \text{ mL/min} \times \frac{(30 - 12)}{30} = 210 \text{ mL/min} \]

These calculations show that the two terms are the same. In practice, dialysance has to be measured experimentally by determining \( C_a, C_v \), and \( Q \). In dosing of drugs for patients on dialysis, the average plasma drug concentration of a patient is given by

\[ C_{av}^w = \frac{FD}{(Cl_T + Cl_D)\tau} \]  

(21.32)

where \( F \) represents fraction of dose absorbed, \( Cl_T \) is total body drug clearance of the patient, \( C_{av}^w \) is average steady-state plasma drug concentration, and \( \tau \) is the dosing interval.

In practice, if \( Cl_D \) is 30% or more of \( Cl_T \), adjustment is usually made for the amount of drug lost in dialysis.

The elimination half-life, \( t_{1/2} \), for the drug in the patient off dialysis is related to the remaining total body clearance, \( Cl_T \), and the volume of distribution, \( V_D \), as shown below.

\[ t_{1/2} = \frac{0.693}{Cl_T} V_D \]  

(21.33)

Drugs that are easily dialyzed will have a high dialysis clearance, \( Cl_D \), and the elimination half-life, \( t_{1/2} \), is shorter in a patient on dialysis.

\[ t_{1/2} = \frac{0.693V_D}{Cl_T + Cl_D} \]  

(21.34)

\[ k_{ON} = \frac{Cl_T + Cl_D}{V_D} \]  

(21.35)

where \( k_{ON} \) is the first-order elimination half-life of the drug in the patient on dialysis.

The fraction of drug lost due to elimination and dialysis may be estimated from Equation 21.36.

\[ \text{Fraction of drug lost} = 1 - e^{-(Cl_T + Cl_D)\tau/V_D} \]  

(21.36)

Equation 21.36 is based on first-order drug elimination and the substitution of \( t \) hours for the dialysis period.
Several hypothetical examples illustrating the use of Equation 21.36 have been developed by Gambertoglio (1984). These are given in Table 21-9.

Equation 21.36 shows that as $V_D$ increases, the fraction of drug lost decreases. The fraction of drug lost during a 4-hour dialysis period for phenobarbital and salicylic acid was 0.30 and 0.50, respectively, whereas for digoxin and phenytoin, the fraction of drug lost was only 0.07 and 0.04, respectively. Both phenobarbital and salicylic acid are easily dialyzed because of their smaller volumes of distribution, small molecular weights, and aqueous solubility. In contrast, digoxin has a large volume of distribution and phenytoin is highly bound to plasma proteins, making these drugs difficult to dialyze. Thus, dialysis is not very useful for treating digoxin intoxication, but is useful for salicylate overdose.

An example of the effect of hemodialysis on drug elimination is shown in Fig. 21-5. During the interdialysis period, the patient’s total body clearance is very low and the drug concentration declines slowly. In this example, the drug has an elimination $\frac{1}{2}$-life of 48 hours during the interdialysis period. When the patient is placed on dialysis, the drug clearance (sum of the total body clearance and the dialysis clearance) removes the drug more rapidly.

### CLINICAL EXAMPLES

1. The aminoglycoside antibiotics, such as gentamicin and tobramycin, are eliminated primarily by the renal route. Dosing of these aminoglycosides is adjusted according to the residual renal function in the patient as estimated by creatinine clearance. During hemodialysis or peritoneal dialysis, the elimination half-lives for these antibiotics are significantly decreased. After dialysis, the aminoglycoside concentrations are below the therapeutic range, and the patient needs to be given another dose of the aminoglycoside antibiotic.

2. An adult male (73 years old, 65 kg) with diabetes mellitus is placed on hemodialysis. His residual creatinine clearance is <5 mL/min.
The patient is given tobramycin, an aminoglycoside antibiotic, at a dose of 1 mg/kg by IV bolus injection. Tobramycin is 90% excreted unchanged in the urine, is less than 10% bound to plasma proteins, and has an elimination half-life of approximately 2.2 hours in patients with normal renal function. In this patient, tobramycin has an elimination \( t_{1/2} \) of 50 hours during the interdialysis period and an elimination \( t_{1/2} \) of 8 hours during hemodialysis. The apparent volume of distribution for tobramycin is about 0.33 L/kg. For this patient, calculate (a) the initial plasma antibiotic concentration after the first dose of tobramycin; (b) the plasma drug concentration just before the start of hemodialysis (48 hours after the initial tobramycin dose); (c) the plasma drug concentration at the end of 4 hours of hemodialysis; (d) the amount of drug lost from the body after dialysis; and (e) the tobramycin dose (replenishment dose) needed to be given to the patient after hemodialysis.

**Solution**

a. Initial plasma antibiotic concentration after the first dose of tobramycin:

\[
\text{Patient dose} = \frac{1 \text{mg}}{\text{kg}} \times 65 \text{kg} = 65 \text{mg}
\]

\[
V_d = \frac{0.33 \text{L}}{\text{kg}} \times 65 \text{kg} = 21.45 \text{L}
\]

Plasma drug concentration, \( C_p = \frac{D_0}{V_d} = \frac{65 \text{mg}}{21.45 \text{L}} = 3.03 \text{mg/L} \)

b. Plasma drug concentration just before the start of hemodialysis (48 hours after the initial tobramycin dose): After 48 hours, the plasma drug concentration declines according to first-order kinetics:

\[
C_p = 3.03 e^{-0.693(48)} = 1.58 \text{mg/L}
\]

c. Plasma drug concentration at the end of a 4-hour hemodialysis:

\[
C_p = 1.58 e^{-0.693(4)} = 0.547 \text{mg/L}
\]

d. Amount of drug lost from the body after dialysis:

\[
\text{Amt of drug lost after dialysis = Amt of drug in the body before dialysis – Amt of drug in the body after dialysis}
\]

\[
\frac{15.8 \text{mg}}{L} (21.45 \text{L}) - \frac{5.47 \text{mg}}{L} (21.45) = 22.16 \text{mg}
\]

e. Tobramycin dose (replenishment dose) needed to be given to the patient after hemodialysis: The recommended ranges of peak and trough concentrations of tobramycin (Mathews, 1995) are 5 to 10 mg/L (peak) and 0.5 to <2 mg/L (trough). The usual replenishment dose of tobramycin after hemodialysis is 1 to 1.5 mg/kg. If a replenishment dose of 65 mg (ie, 1 mg/kg) is given to the patient, then the estimated plasma drug concentration is estimated as

Plasma drug concentration after 65 mg given by IV bolus injection

\[
= \frac{65 \text{ mg}}{21.45 \text{ L}} + 0.547 \text{ mg/L} = 3.58 \text{ mg/L}
\]

The patient is given 65 mg of tobramycin by IV bolus injection after completion of hemodialysis to produce a tobramycin plasma concentration of 3.58 mg/L.

### Hemoperfusion

**Hemoperfusion** is the process of removing drug by passing the blood from the patient through an adsorbent material and back to the patient. Hemoperfusion is a useful procedure for rapid drug removal in accidental poisoning and drug overdosage. Because the drug molecules in the blood are in direct contact with the adsorbent material, any molecule that has great affinity for the adsorbent material will be removed. The two main adsorbents used in hemoperfusion include (1) activated charcoal, which adsorbs both polar and nonpolar drug and (2) Amberlite resins. Amberlite resins, such as Amberlite XAD-2 and Amberlite XAD-4, are available as insoluble polymeric beads, each bead containing an agglomerate of cross-linked polystyrene microspheres.
The Amberlite resins have a greater affinity for non-polar organic molecules than does activated charcoal. The important factors for drug removal by hemoperfusion include affinity of the drug for the adsorbent, surface area of the adsorbent, absorptive capacity of the adsorbent, rate of blood flow through the adsorbent, and the equilibration rate of the drug from the peripheral tissue into the blood.

**Hemofiltration**

An alternative to hemodialysis and hemoperfusion is hemofiltration. *Hemofiltration* is a process by which fluids, electrolytes, and small-molecular-weight substances are removed from the blood by means of low-pressure flow through hollow artificial fibers or flat-plate membranes (Bickley, 1988). Because fluid is also filtered out of the plasma during hemofiltration, replacement fluid is administered to the patient for volume replacement. Hemofiltration is a slow, continuous filtration process that removes nonprotein-bound, small molecules (<10,000 Da) from the blood by convective mass transport. The clearance of the drug depends on the sieving coefficient and ultrafiltration rate. Hemofiltration provides a creatinine clearance of approximately 10 mL/min (Bickley, 1988) and may have limited use for drugs that are widely distributed in the body, such as aminoglycosides, cephalosporins, and acyclovir. A major problem with this method is the formation of blood clots within the hollow filter fibers.

**Continuous Renal Replacement Therapy**

Because of the initial loss of fluid that results during hemofiltration, intermittent hemofiltration results in concentration of red blood cells in the resulting reduced plasma volume. Therefore, blood becomes more viscous with a high hematocrit and high colloid osmotic pressure at the distal end of the hemofilter. Pre-dilution may be used to circumvent this problem, but this method is rarely used because of cost and inefficiency.

Continuous replacement therapy allows ongoing removal of fluid and toxins by relying on a patient’s own blood pressure to pump blood through a filter. The continuous filtration is better tolerated by patients than intermittent therapy, provides optimal control of circulating volumes, and provides ongoing toxin removal. Because continuous replacement therapies are hemofiltration methods, replacement fluid must be administered to the patient to replace fluid lost to the hemofiltrate, though the volume of fluid removed can be easily controlled compared to intermittent hemofiltration. Heparin infusions are also provided for anticoagulation.

Continuous renal replacement therapy (CRRT) includes continuous veno-venous hemofiltration (CVVH) and continuous arteriovenous hemofiltration (CAVH). In CAVH, blood passes through a hemofilter that is placed between a cannulated femoral artery and vein. A dialysis filter may be added to CAVH to improve small-molecule clearance. Circulating dialysate on the outside of the filters allows more efficient toxin removal. However, this method is inefficient (10–15 mL filtered per minute) and complex, and is not widely used in comparison to CVVH.

CVVH provides a hemofilter that is placed between cannulated femoral, subclavian, or internal jugular veins. Rather than relying on arterial pressure to filter blood, a pump can be used to provide filtration rates greater than 100 mL/min. Like CAVH, a dialysis filter may be added to CVVH to improve clearance of small molecules.

As with other extracorporeal removal systems, hemofiltration methods can alter drug pharmacokinetics. A study by Hansen et al (2001) showed that acute renal failure patients on CVVH demonstrated a 50% decrease in clearance of levofloxacin. However, because of the high volume and moderate renal clearance of fluoroquinolones, levofloxacin does not require dosing adjustment.

**Drug Removal during Continuous Renal Replacement Therapy**

During CAVH, solutes are removed by convection, in which a sieving coefficient, $S$, reflects the solute removal ability during hemofiltration and is equal to the ratio of solute concentration in the ultrafiltrate to the solute concentration in the retentate. When $S = 1$, solute passes freely through the membrane, whereas
when $S = 0$, the solute is retained in the plasma. $S$ is constant and independent of blood flow; therefore,

$$Cl = S \times \text{rate}_{uf}$$  \hspace{1cm} (21.37)

where rate$_{uf}$ is the ultrafiltration rate. The concentration of drug in the ultrafiltrate is also equal to the unbound drug concentration in the plasma, and so the amount of drug removed during CAVH is

$$\text{Amount removed} = C_p + \alpha \times \text{rate}_{uf}$$  \hspace{1cm} (21.38)

where $\alpha$ = the unbound fraction.

**Frequently Asked Questions**

- **Which pharmacokinetic properties of a drug would predict a greater or lesser rate of elimination in a patient undergoing dialysis?**

- **Drug clearance is often decreased 20–50% in many patients with congestive heart failure (CHF). Explain how it may affect drug disposition.**

**EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS**

Hepatic disease can alter the pharmacokinetics of a drug including the absorption and disposition and the pharmacodynamics including efficacy and safety. Hepatic disease may include common hepatic diseases, such as alcoholic liver disease (cirrhosis) and chronic infections with hepatitis viruses B and C, and less common diseases, such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and $\alpha_1$-antitrypsin deficiency (FDA Guidance for Industry, 2003). In addition, drug-induced hepatotoxicity is the leading cause of acute liver failure in the United States (Chang and Schiano, 2007).

Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may also be excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug-protein binding. Liver disease may also alter kidney function, which can lead to accumulation of a drug and its metabolites even when the liver is not primarily responsible for elimination.

The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. In contrast, creatinine clearance has been used successfully to measure kidney function and renal clearance of drugs. Clinical laboratory tests measure only a limited number of liver functions. Some clinical laboratory tests, such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme tests that detect liver cell damage rather than liver function. Other laboratory tests, such as serum bilirubin, are used to measure biliary obstruction or interference with bile flow. Presently, no single test accurately assesses the total liver function. Usually, a series of clinical laboratory tests are used in clinical practice to detect the presence of liver disease, distinguish among different types of liver disorders, gauge the extent of known liver damage, and follow the response to treatment. A few tests have been used to relate the severity of hepatic impairment to predicted changes in the pharmacokinetic profile of the drug (FDA Guidance, 2003). Examples of these tests include the ability of the liver to eliminate marker drugs such as antipyrine, indocyanine green, monoethylglycine-xylidide, and galactose. Furthermore, endogenous substrates, such as albumin or bilirubin, or a functional measure, such as prothrombin time, have been used for the evaluation of liver impairment.

**Dosage Considerations in Hepatic Disease**

Several physiologic and pharmacokinetic factors are relevant in considering dosage of a drug in patients with hepatic disease (Table 21-10). Chronic disease or tissue injury may change the accessibility of some enzymes as a result of redirection or detour of hepatic blood circulation. Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that subsequently affect plasma drug protein binding and distribution (see Chapter 11). As mentioned, most
Chapter 21

Liver function tests indicate only that the liver has been damaged; they do not assess the function of the cytochrome P-450 enzymes or intrinsic clearance by the liver.

Because there is no readily available measure of hepatic function that can be applied to calculate appropriate doses, enzyme-dependent drugs are usually given to patients with hepatic failure in half-doses, or less. Response or plasma levels then must be monitored. Drugs with flow-dependent clearance are avoided if possible in patients with liver failure. When necessary, doses of these drugs may need to be reduced to as low as one-tenth of the conventional dose, for an orally administered agent. Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, efficacious treatment.

If some of the efflux proteins that normally protect the body against drug accumulation are reduced or not functioning, this could potentially cause hepatic drug injury as drug concentration begins to increase. Compounds that form glucuronide, sulfate, GSH, and other substrates that are involved in phase II metabolism (see Chapter 11) may be depleted during hepatic impairment, potentially interrupting the normal path of drug metabolism. Indeed, even albumin or AAG concentrations can be altered in hepatic impairment and affect drug distribution or drug disposition in many unpredictable ways that can affect drug safety.

**Fraction of Drug Metabolized**

Drug elimination in the body may be divided into: (1) fraction of drug excretion unchanged, \( f_e \), and (2) fraction of drug metabolized. The latter is usually estimated from \( 1 - f_e \); alternatively, the fraction of drug metabolized may be estimated from the ratio of \( C_l_h / C_l \), where \( C_l_h \) is hepatic clearance and \( C_l \) is total body clearance. Knowing the fraction of drug eliminated by the liver allows estimation of total body clearance when hepatic clearance is reduced. Drugs with low \( f_e \) values (or, conversely, drugs with a higher fraction of metabolized drug) are more affected by a change in liver function due to hepatic disease.

\[
C_l_h = C_l (1 - f_e) \quad (21.39)
\]

Equation 21.39 assumes that all metabolism occurs in the liver, and all the unchanged drug is excreted in the urine. Assuming linear kinetics are applicable (after determining that there is no enzyme saturation), dosing adjustment may be based on

<table>
<thead>
<tr>
<th>Item</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature and severity of liver disease</td>
<td>Not all liver diseases affect the pharmacokinetics of the drugs to the same extent.</td>
</tr>
<tr>
<td>Drug elimination</td>
<td>Drugs eliminated by the liver &gt;20% are less likely to be affected by liver disease. Drugs that are eliminated mainly via renal route will be least affected by liver disease.</td>
</tr>
<tr>
<td>Route of drug administration</td>
<td>Oral drug bioavailability may be increased by liver disease due to decreased first-pass effects.</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Drug–protein binding may be altered due to alteration in hepatic synthesis of albumin.</td>
</tr>
<tr>
<td>Hepatic blood flow</td>
<td>Drugs with flow-dependent hepatic clearance will be more affected by change in hepatic blood flow.</td>
</tr>
<tr>
<td>Intrinsic clearance</td>
<td>Metabolism of drugs with high intrinsic clearance may be impaired.</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites, may be impaired.</td>
</tr>
<tr>
<td>Pharmacodynamic changes</td>
<td>Tissue sensitivity to drug may be altered.</td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment.</td>
</tr>
</tbody>
</table>
residual hepatic function in patients with hepatic disease, as shown in the following example.

**PRACTICE PROBLEM**

The hepatic clearance of a drug in a patient is reduced by 50% due to chronic viral hepatitis. How is the total body clearance of the drug affected? What should be the new dose of the drug in the patient? Assume that renal drug clearance ($fe = 0.4$) and plasma drug protein binding are not altered.

**Solution**

$RL = \text{residual liver function, estimated by}$

$$[Cl_h^{\textnormal{hepatitis}}] = \frac{RL}{Cl_h^{\textnormal{normal}}},$$

$[Cl_h^{\textnormal{hepatitis}}] = \text{hepatic clearance of drug in patient with hepatitis}$

$Cl_{\textnormal{normal}} = \text{total clearance of drug in normal subject}$

$Cl_{\textnormal{hepatitis}} = \text{total clearance of drug in patient with hepatitis}$

$fe = \text{fraction of drug excreted unchanged}$

$1 - fe = \text{fraction of drug metabolized}$

$[Cl_h^{\textnormal{hepatitis}}] = RL \cdot [Cl_h^{\textnormal{normal}}]$  \hspace{1cm} (21.40)

Substituting for $[Cl_h^{\textnormal{hepatitis}}]$ with $Cl_{\textnormal{normal}}(1 - fe)$

$$[Cl_h^{\textnormal{hepatitis}}] = RL \cdot Cl_{\textnormal{normal}}(1 - fe) \hspace{1cm} (21.40)$$

Assuming no renal clearance deterioration due to hepatitis

$$Cl_{\textnormal{hepatitis}} = [Cl_h^{\textnormal{hepatitis}}] + [Cl_{R}^{\textnormal{normal}}] \hspace{1cm} (21.41)$$

Substituting Equation 21.40 with Equation 21.41 in terms of total body clearance

$$Cl_{\textnormal{hepatitis}} = RL \cdot Cl_{\textnormal{normal}}(1 - fe) + Cl_{\textnormal{normal}}fe \hspace{1cm} (21.42)$$

$$Cl_{\textnormal{hepatitis}} = Cl_{\textnormal{normal}} [RL(1 - fe) + fe] \hspace{1cm} (21.43)$$

$$\frac{D_{\textnormal{hepatitis}}}{D_{\textnormal{normal}}} = \frac{Cl_{\textnormal{hepatitis}}}{Cl_{\textnormal{normal}}} = \frac{RL(1 - fe) + fe}{1} \hspace{1cm} (21.44)$$

where $D_{\textnormal{hepatitis}}$ and $D_{\textnormal{normal}}$ are the doses in a hepatitis patient and in a normal liver function patient, respectively. Substituting in Equation 21.44 with $RL = 0.5$ and $fe = 0.4$,

$$\frac{D_{\textnormal{hepatitis}}}{D_{\textnormal{normal}}} = 0.5(1 - 0.4) + 0.4 = 0.3 + 0.4 = 0.7 \text{ (or 70%)}$$

The adjusted dose of the drug for the hepatic patient is 70% of that for the normal subject as a result of the 50% decrease in hepatic function in the above case ($fe = 0.4$).

An example of a correlation established between actual residual liver function (measured by marker) and hepatic clearance was reported for cefoperazone (Hu et al, 1995) and other drugs in patients with cirrhosis. The method should be applied only to drugs that have linear pharmacokinetics, low protein binding, or that are nonrestrictively bound.

Many variables can complicate dose correction when binding profoundly affects distribution, elimination, and penetration of the drug to the active site. For drugs with restrictive binding, the fraction of free drug must be used to correct the change in free drug concentration and the change in free drug clearance. In some cases, the increase in free drug is partly offset by a larger volume of distribution resulting from the decrease in protein binding. Since there are many variables that complicate dose correction for patients with hepatic disease, dose correction is limited to drugs whose hepatic metabolism is approximated by linear pharmacokinetics.

**Active Drug and the Metabolite**

For many drugs, both the drug and the metabolite contribute to the overall therapeutic response of the patient to the drug. The concentration of both the drug and the metabolite in the body should be known. When the pharmacokinetic parameters of the metabolite and the drug are similar, the overall activity of the drug can become more or less potent as a result of a change in liver function; that is, (1) when the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic-impaired patient because the parent drug concentration will be higher; (2) when the drug is less potent than the metabolite, the overall pharmacologic...
activity in the hepatic patient will decrease because less of the active metabolite is formed.

Changes in pharmacologic activity due to hepatic disease (Table 21-11) may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process. In such cases, the overall pharmacodynamic response may be greatly modified, making it necessary to monitor the response change with the aid of a pharmacodynamic model (see Chapter 19).

### Hepatic Blood Flow and Intrinsic Clearance

Blood flow changes can occur in patients with chronic liver disease (often due to viral hepatitis or chronic alcohol use). In some patients with severe liver cirrhosis, fibrosis of liver tissue may occur, resulting in intra- or extrahepatic shunt. Hepatic arterial-venous shunts may lead to reduced drug fraction of drug extracted (see Chapter 11) and an increase in the bioavailability of drug. In other patients, resistance to blood flow may be increased as a result of tissue damage and fibrosis, causing a reduction in intrinsic hepatic clearance.

The following equation may be applied to estimate hepatic clearance of a drug after assessing changes in blood flow and intrinsic clearance ($Cl_{int}$):

$$ Cl_{h} = \frac{QCl_{int}}{Q + Cl_{int}} \quad (21.45) $$

Alternatively, when both $Q$ and the extraction ratio, $ER$, are known in the patient, $Cl$ may also be estimated:

$$ Cl = Q (ER) \quad (21.46) $$

Unlike changes in renal disease, in which serum creatinine concentration may be used to monitor changes in renal function such as glomerular filtration (GFR), the above physiologic model equation may not be adequate to account for accurate prediction of changes in hepatic clearance. Calculations based on model equations must be corroborated by clinical assessment.

### Pathophysiologic Assessment

In practice, patient information about changes in hepatic blood flow may not be available, because special electromagnetic (Nuxmalo et al, 1978) or ultrasound techniques are required to measure blood flow and are not routinely available. The clinician/pharmacist may have to make an empirical estimate of the blood flow change after examining the patient and reviewing the available liver function tests.

Various approaches have been used diagnostically to assess hepatic impairment. The Child–Pugh (or Child–Turcotte–Pugh) score assesses the overall hepatic impairment as mild, moderate, or severe (Figg et al, 1995; Lucey et al, 1997). The score employs five clinical measures of liver disease including total bilirubin, serum albumin, INR (International Normalized Ratio), ascites, and hepatic encephalopathy (Tables 21-11 and 21-12). Different publications use different measures. Some older references substitute prothrombin time (PT) prolongation for INR. The original classification used nutrition which was later replaced by PT prolongation. The model for end-stage liver disease, or MELD, is a scoring system for assessing the severity of chronic liver disease based on mortality after liver surgery (Cholongitas et al, 2005; Kamath et al, 2007). Unfortunately, neither of these approaches for assessing hepatic disease and hepatic impairment provides direct predictability or correlation with the pharmacokinetics of a drug.

---

**Table 21-11 Child-Pugh Classification of Severity of Liver Disease**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points assigned</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>≤ 2</td>
<td>2–3</td>
<td>&gt;3</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>&gt;3.5</td>
<td>2.8–3.5</td>
<td>&lt;2.8</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time INR</td>
<td>1–3</td>
<td>4–6</td>
<td>&gt;6</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1–2</td>
<td>Grade 3–4</td>
<td></td>
</tr>
</tbody>
</table>

*Modified Child–Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

Data from Trey et al (1966).
While chronic hepatic disease is more likely to change the metabolism of a drug (Howden et al, 1989), acute hepatitis due to hepatotoxin or viral inflammation is often associated with marginal or less severe changes in metabolic drug clearance (Farrel et al, 1978). The clinician should make an assessment based on acceptable risk criteria on a case-by-case basis.

In general, basic pharmacokinetics treats the body globally and more readily applies to dosing estimation. However, drug clearance based on individual eliminating organs is more informative and provides more insight into the pharmacokinetic changes in the disease process. A practical method for dosing hepatic-impaired patients is still in the early stages of development. While the hepatic blood flow model (see Chapter 11) is useful for predicting changes in hepatic clearance resulting from alterations in hepatic blood flow, $Q_h$ and $Q_s$, extrahepatic changes can also influence pharmacokinetics in hepatic-impaired patients. Global changes in distribution may occur outside the liver. Extrahepatic metabolism and other hemodynamic changes may also occur and can be accounted for more completely by monitoring total body clearance of the drug using basic pharmacokinetics. For example, lack of local change in hepatic drug clearance should not be prematurely interpreted as “no change” in overall drug clearance. Reduced albumin and alpha acid glycoprotein (AAG), for example, may change the volume of distribution of the drug and therefore alter total body clearance on a global basis.

### Hormonal Influence

Hormones can also affect the rate of metabolism. In hyperthyroid patients, the rate of metabolism of many drugs is increased, as are, for example, the rates for theophylline, digoxin, and propranolol. In hypothyroid disease, the rate of metabolism of these drugs may be decreased (Table 21-13). In children with human growth hormone (HGH) deficiency, administration of HGH decreases the half-life of theophylline.

### Example

After IV bolus administration of 1 g of cefoperazone to normal and chronic hepatitis patients, urinary excretion of cefoperazone was significantly increased in cirrhosis patients, from 23.95 ± 5.06% for normal patients to 51.09 ± 11.50% in cirrhosis patients (Hu et al, 1995). Explain (a) why there is a change in the percent of unchanged cefoperazone excreted in the urine of patients with cirrhosis, and (b) suggest a quantitative test to monitor the hepatic elimination of cefoperazone (Hint: consult Hu et al, 1994).
Liver Function Tests and Hepatic Metabolic Markers

Drug markers used to measure residual hepatic function may correlate well with hepatic clearance of one drug but correlate poorly with substrate metabolized by a different enzyme within the same cytochrome P-450 subfamily. Some useful marker compounds are listed below.

1. **Aminotransferase** (normal ALT: male, 10–55 U/L; female, 7–30 U/L; normal AST: male, 10–40, U/L; female, 9–25 U/L): Aminotransferases are enzymes found in many tissues that include serum glutamic oxaloacetic transaminase (AST, formerly SGOT) and alanine aminotransferase (ALT, formerly SGPT). ALT is liver specific, but AST is found in liver and many other tissues, including cardiac and skeletal muscle. Leakage of aminotransferases into the plasma is used as an indicator of many types of hepatic disease and hepatitis. The AST/ALT ratio is used in differential diagnosis. In acute liver injury, AST/ALT is 1, whereas in alcoholic hepatitis the AST/ALT > 2.

2. **Alkaline phosphatase** (male, 45–115 U/L; female, 30–100 U/L): Like aminotransferase, alkaline phosphatase (AP) is normally present in many tissues, and it is also present on the canalicular domain of the hepatocyte plasma membrane. Plasma AP may be elevated in hepatic disease because of increased AP production and released into the serum. In cholestasis, or bile flow obstruction, AP release is facilitated by bile acid solubilization of the membranes. Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver, or disease in other tissues such as bone, placenta, or intestine.

3. **Bilirubin** (normal total = 0–1.0 mg/dL; direct = 0–0.4 mg/dL): Bilirubin consists of both a water-soluble, conjugated, “direct” fraction and a lipid-soluble, unconjugated, “indirect” fraction. The unconjugated form is bound to albumin and is therefore not filtered by the kidney. Since impaired biliary excretion results in increases in conjugated (filtered) bilirubin, hepatobiliary disease can result in increases in urinary bilirubin. Unconjugated hyperbilirubinemia results from either increased bilirubin production or defects in hepatic uptake or conjugation. Conjugated hyperbilirubinemia results from defects in hepatic excretion.

4. **Prothrombin time** (PT; normal, 11.2–13.2 sec): With the exception of Factor VIII, all coagulation factors are synthesized by the liver. Therefore, hepatic disease can alter coagulation. Decreases in PT (the rate of conversion of prothrombin to thrombin) therefore is suggestive of acute or chronic liver failure or biliary obstruction. Vitamin K is also important in coagulation, so vitamin K deficiency can also decrease PT.

---

**EXAMPLE**

Paclitaxel, an anticancer agent for solid tumors and leukemia, has extensive tissue distribution, high plasma protein binding (approximately 90%–95%), and variable systemic clearance. Average paclitaxel clearance ranges from 87 to 503 mL/min/m² (5.2–30.2 L/h/m²) with minimal renal excretion of parent drug, 10% (Sonnichsen and Relling, 1994). Paclitaxel is extensively metabolized by the liver to three primary metabolites. Cytochrome P-450 enzymes of the CYP3A subfamily appear to be involved in hepatic metabolism of paclitaxel. What are the precautions in administering paclitaxel to patients with liver disease?

**Solution**

Although paclitaxel has first-order pharmacokinetics at normal doses, its elimination may be saturable in some patients with genetically reduced intrinsic clearance due to CYP3A or CYP2C. The clinical importance of saturable elimination will be greatest when large dosages are infused over a shorter period of time. In these situations, achievable plasma concentrations are likely to cause saturation of binding. Thus, small changes in dosage or infusion duration may result in disproportionately large alterations in paclitaxel systemic exposure, potentially influencing patient response and toxicity.
Hepatic Impairment and Dose Adjustment

Hepatic impairment may not sufficiently alter the pharmacokinetics of some drugs to require dosage adjustment. Drugs that have the following properties are less likely to need dosage adjustment in patients with hepatic impairment (FDA Guidance, 2003):

- The drug is excreted entirely via renal routes of elimination with no involvement of the liver.
- The drug is metabolized in the liver to a small extent (<20%), and the therapeutic range of hepatic clearance will not lead to toxicity of the drug directly or by increasing its interaction with other drugs.
- The drug is gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

For each drug case, the physician needs to assess the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug. For example, Mallikaarjun et al (2008) studied the effects of hepatic or renal impairment on the pharmacokinetics of aripiprazole (Abilify), an atypical antipsychotic used to treat schizophrenia. These investigators concluded that there were no meaningful differences in aripiprazole pharmacokinetics between groups of subjects with normal hepatic or renal function and those with either hepatic or renal impairment. Thus, the adjustment of the aripiprazole dose does not appear to be required in populations with hepatic or renal impairment.

In contrast, Muirhead et al (2002) studied the effects of age and renal and hepatic impairment on the pharmacokinetics, tolerability, and safety of sildenafil (Viagra), a drug used to treat erectile dysfunction). Muirhead et al (2002) observed significant differences in $C_{\text{max}}$ and AUC between the young and the elderly subjects for both the parent drug and the metabolite. In addition, the hepatic impairment study demonstrated that pharmacokinetics of sildenafil was altered in subjects with chronic stable cirrhosis, as shown by a 46% reduction in CL/F and a 47% increase in $C_{\text{max}}$ compared with subjects with normal hepatic function. Sildenafil pharmacokinetics was affected by age and by renal and hepatic impairment, suggesting that a lower starting dose of 25 mg should be considered for patients with severely compromised renal or hepatic function.

Frequently Asked Questions

- How do changes in drug–protein binding affect dose adjustment in patients with renal and/or hepatic disease?
- Which pharmacokinetic properties of a drug are more likely to be affected by renal disease or liver hepatotoxicity?
- Can you quantitatively predict the change in the pharmacokinetics of a drug that normally has high hepatic clearance in a patient with hepatic impairment? Explain.

CHAPTER SUMMARY

The kidney and liver are important organs involved in regulating body fluids, electrolyte balance, removal of metabolic waste, and drug excretion from the body. Impairment of kidney or liver function affects the pharmacokinetics of drugs as well as safety and efficacy. Renal function may be assessed by several methods. Creatinine clearance based on the serum concentration of endogenous creatinine is used most often to measure glomerular filtration rate. Creatinine clearance values must be considered carefully in special populations such as elderly, obese, and emaciated patients. The Crockcroft–Gault method is frequently used to estimate creatinine clearance from serum creatinine concentration. Dose adjustment in renal disease is based on the fraction of drug that is really excreted and generally assumes.
that nonrenal drug elimination remains constant. Different approaches for dose adjustment in renal disease give somewhat different values. Patients with end-stage renal disease (ESRD) and other patients without kidney function require supportive treatment such as dialysis to remove the accumulated drug and its metabolites. The objective of these dialysis methods is to rapidly remove the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the patient. Dosage adjustment may be needed to replace drug loss during extracorporeal drug and metabolite removal. The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. Presently, no single test accurately assesses the total liver function. Various approaches such as the Child–Pugh (or Child–Turcotte–Pugh) score have been used diagnostically to assess hepatic impairment. Hepatic impairment may not sufficiently alter the pharmacokinetics of some drugs to require dosage adjustment. Physicians and/or pharmacists must understand the pharmacokinetic and pharmacodynamic properties of each drug in patients with hepatic and/or renal impairment.

**LEARNING QUESTIONS**

1. The normal dosing schedule for a patient on tetracycline is 250 mg PO (peroral) every 6 hours. Suggest a dosage regimen for this patient when laboratory analysis shows his renal function to have deteriorated from a $Cl_{cr}$ of 90 to 20 mL/min.

2. A patient receiving antibiotic treatment is on dialysis. The flow rate of serum into the kidney machine is 50 mL/min. Assays show that the concentration of drug entering the machine is 5 µg/mL and the concentration of drug in the serum leaving the machine is 2.4 µg/mL. The drug clearance for this patient is 10 mL/min. To what extent should the dose be increased if the average concentration of the antibiotic is to be maintained?

3. Glomerular filtration rate may be measured by either insulin clearance or creatinine clearance.  
   a. Why is creatinine or insulin clearance used to measure GFR?  
   b. Which clearance method, insulin or creatinine, gives a more accurate estimate of GFR? Why?

4. A uremic patient has a urine output of 1.8 L/24 h and an average creatinine concentration of 2.2 mg/dL. What is the creatinine clearance? How would you adjust the dose of a drug normally given at 20 mg/kg every 6 hours in this patient (assume the urine creatinine concentration is 0.1 mg/mL and creatinine clearance is 100 mL/min)?

5. A patient on lincomycin at 600 mg every 12 hours intramuscular was found to have a creatinine clearance of 5 mL/min. Should the dose be adjusted? If so, (a) adjust the dose by keeping the dosing interval constant; (b) adjust the dosing interval and give the same dose; and (c) adjust both dosing interval and dose. What are the significant differences in the adjustment methods?

6. Using the method of Cockcroft–Gault, calculate the creatinine clearance for a woman (38 years old, 62 kg) whose serum creatinine is 1.8 mg/dL.

7. Would you adjust the dose of cephamandole, an antibiotic which is 98% excreted unchanged in the urine, for the patient in Question 6? If so, why?

8. What assumptions are usually made when adjusting a dosage regimen according to the creatinine clearance in a patient with renal failure?

9. The usual dose of gentamicin in patients with normal renal function is 1.0 mg/kg every 8 hours by multiple IV bolus injections. Using the nomogram method (see Fig. 21-4), what
10. A single intravenous bolus injection (1 g) of an antibiotic was given to a male anephric patient (age 68, 75 kg). During the next 48 hours, the elimination half-life of the antibiotic was 16 hours. The patient was then placed on hemodialysis for 8 hours and the elimination half-life was reduced to 4 hours. 

a. How much drug was eliminated by the end of the dialysis period?

b. Assuming the apparent volume of distribution of this antibiotic is 0.5 L/kg, what was the plasma drug concentration just before and just after dialysis?

11. There are several pharmacokinetic methods for adjustment of a drug dosage regimen for patients with uremic disease based on the serum creatinine concentration in that patient. From your knowledge of clinical pharmacokinetics, discuss the following questions.

a. What is the basis of these methods for the calculation of drug dosage regimens in uremic patients?

b. What is the validity of the assumptions upon which these calculations are made?

12. After assessment of the uremic condition of the patient, the drug dosage regimen may be adjusted by one of two methods: (a) by keeping the dose constant and prolonging the dosage interval, $T$, or (b) by decreasing the dose and maintaining the dosage interval constant. Discuss the advantages and disadvantages of adjusting the dosage regimen using either method.

REFERENCES


FDA Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling, FDA, Center for Drug Evaluation and Research (CDER), 2003.


BIBLIOGRAPHY


Chapter Objectives

- Describe the physiologic pharmacokinetic model with equations and underlying assumptions.
- List the difference between the physiologic pharmacokinetic versus the classical compartment model.
- Apply physiologic pharmacokinetic models to model plasma drug concentration and tissue drug distribution in various body organs.
- Describe interspecies scaling and its application in pharmacokinetics and toxicokinetics.
- Define mean residence time (MRT) and explain how the mean residence time of the drug molecules within a dose can be used to calculate the drug clearance of a drug.
- Derive equations that relate the volume of distribution and clearance to MRT after various type routes of drug administration.
- Describe the statistical moment theory and explain how it provides a unique way to study time-related changes in macroscopic events.

The study of pharmacokinetics describes the absorption, distribution, and elimination of the active drug and metabolites in quantitative terms (see Chapter 1). Ideally, a pharmacokinetic model uses the observed time course for drug concentration in the body and, from this data, obtains various pharmacokinetic parameters to predict drug dosing outcomes, pharmacodynamics, and toxicity.

In developing a model, certain underlying assumptions are made by the pharmacokineticist as to the type of pharmacokinetic model, the order of the rate process, the blood flow to a tissue, the method for the estimation of the plasma or tissue volume, and other factors. Even with a more general approach such as model-independent analysis, first-order drug elimination is often assumed in the calculation of $\text{AUC}_{0-\infty}$. In selecting a model for data analysis, the pharmacokineticist may choose more than one method of modeling, depending on many factors, including experimental condition, study design, and completeness of data. The goodness-of-fit to the model and the desired pharmacokinetic parameters are other considerations. Each estimated pharmacokinetic parameter has an inherent variability because of the variability of the biological system and the observed data. Moreover, because pharmacokinetic studies are performed on a limited number of subjects, the estimated pharmacokinetic parameters may not be representative of the entire population.

In spite of difficulties in the construction of these pharmacokinetic models, such models have been extremely useful in describing the time course of drug action, improving drug therapy by enhancing drug efficacy, and minimizing adverse reactions through more accurate dose regimens. Pharmacokinetic models are also applied to the development of new drug delivery systems. Three main types of pharmacokinetic models—physiologic, compartment, and statistical moment approach models—are discussed in this chapter.

The human body is composed of organ systems containing living cells bathed in an extracellular aqueous fluid (see Chapter 10). Both drugs and endogenous substances, such as hormones, nutrients, and oxygen, are transported to the organs by the same network of blood vessels (arteries). The drug concentration within
Explain how MRT is used to calculate the mean dissolution time (MDT), or in vivo mean dissolution time, for a solid drug product.

Explain the difference between model-independent and model-dependent pharmacokinetic analyses.

A target organ depends on plasma drug concentration, the rate of blood flow to an organ, and the rate of drug uptake into the tissue. Physiologically, uptake (accumulation) of drug by organ tissues occurs from the extracellular fluid, which equilibrates rapidly with the capillary blood in the organ. Some drugs cross the plasma membrane into the interior fluid (intracellular water) of the cell (Fig. 22.1).

In addition to drug accumulation, some organs of the body are involved in drug elimination, either by excretion (e.g., kidney) or by metabolism (e.g., liver). The elimination of drug by an organ may be described by drug clearance in the organ (see Chapters 6 and 11). The liver is an example of an organ with drug metabolism and drug uptake (accumulation). Physiologic pharmacokinetic models consider all processes of drug uptake and elimination.

**PHYSIOLOGIC PHARMACOKINETIC MODELS**

Drugs are carried by blood flow from the administration (input) site to various body organs, where the drug rapidly equilibrates with the interstitial water in the organ. Physiologic pharmacokinetic models are mathematical models describing drug movement and disposition in the body based on organ blood flow and the organ spaces penetrated by the drug. In its simplest form, a physiologic pharmacokinetic model considers the drug to be blood flow limited. Drugs are carried to organs by arterial blood and leave organs by venous blood (Fig. 22-2). In such a model, transmembrane movement of drug is rapid, and the capillary membrane does not offer any resistance to drug permeation. Uptake of drug into the tissues is rapid, and a constant ratio of drug concentrations between the organ and the venous blood is quickly established. This ratio is the tissue/blood partition coefficient:

\[ P_{\text{tissue}} = \frac{C_{\text{tissue}}}{C_{\text{blood}}} \]  

(22.1)

where \( P \) is the partition coefficient.

The magnitude of the partition coefficient can vary depending on the drug and on the type of tissue. Adipose tissue, for example, has a high partition for lipophilic drugs. The rate of drug carried to a tissue organ and tissue drug uptake depend on the rate of blood flow to the organ and the tissue/blood partition coefficient, respectively.

The rate of blood flow to the tissue is expressed as \( Q_t \) (mL/min), and the rate of change in the drug concentration with respect to time within a given tissue organ is expressed as

\[
\frac{d(V_{\text{tissue}}C_{\text{tissue}})}{dt} = Q_t(C_{\text{in}} - C_{\text{out}}) 
\]  

(22.2)
Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory

\[
d\left(\frac{V_{\text{tissue}} C_{\text{tissue}}}{dt}\right) = Q_t \left( C_{\text{art}} - C_{\text{ven}} \right) \tag{22.3}
\]

where \( C_{\text{art}} \) is the arterial blood drug concentration and \( C_{\text{ven}} \) is the venous blood drug concentration. \( Q_t \) is blood flow and represents the volume of blood flowing through a typical tissue organ per unit of time.

If drug uptake occurs in the tissue, the incoming concentration, \( C_{\text{art}} \), is higher than the outgoing venous concentration, \( C_{\text{ven}} \). The rate of change in the tissue drug concentration is equal to the rate of blood flow multiplied by the difference between the blood drug concentrations entering and leaving the tissue organ. In the blood flow–limited model, drug concentration in the blood leaving the tissue and the drug concentration within the tissue are in equilibrium, and \( C_{\text{ven}} \) may be estimated from the tissue/blood partition coefficient in Equation 22.1. Substituting in Equation 22.3 with \( C_{\text{ven}} = C_{\text{tissue}} / P_{\text{tissue}} \) yields

\[
d\left(\frac{V_{\text{tissue}} C_{\text{tissue}}}{dt}\right) = Q_t \left( C_{\text{art}} - \frac{C_{\text{tissue}}}{P_{\text{tissue}}} \right) \tag{22.4}
\]

Equation 22.4 describes drug distribution in a noneliminating organ or tissue group. For example, drug distribution to muscle, adipose tissue, and skin is represented in a similar manner by Equations 22.5, 22.6, and 22.7, respectively, as shown below. For tissue organs in which drug is eliminated (Fig. 22.3), parameters representing drug elimination from the liver (\( k_{\text{LIV}} \)) and kidney (\( k_{\text{KID}} \)) are added to account for drug removal through metabolism or excretion. Equations 22.8 and 22.9 are derived similarly to those for the noneliminating organs above.

Removal of drug from any organ is described by drug clearance (\( Cl \)) from the organ. The rate of drug elimination is the product of the drug concentration in the organ and the organ clearance.

\[
\text{Rate of drug elimination} = \frac{V_{\text{tissue}} dC_{\text{tissue}}}{dt} = C_{\text{tissue}} \times Cl_{\text{tissue}}
\]

The rate of drug elimination may be described for each organ or tissue (Fig. 22.4).

\[
\text{Muscle: } \frac{d(V_{\text{MUS}} C_{\text{MUS}})}{dt} = Q_{\text{MUS}} \left( C_{\text{MUS}} - \frac{C_{\text{MUS}}}{P_{\text{MUS}}} \right) \tag{22.5}
\]

\[
\text{Adipose tissue: } \frac{d(V_{\text{FAT}} C_{\text{FAT}})}{dt} = Q_{\text{FAT}} \left( C_{\text{FAT}} - \frac{C_{\text{FAT}}}{P_{\text{FAT}}} \right) \tag{22.6}
\]

\[
\text{Skin: } \frac{d(V_{\text{SKIN}} C_{\text{SKIN}})}{dt} = Q_{\text{SKIN}} \left( C_{\text{SKIN}} - \frac{C_{\text{SKIN}}}{P_{\text{SKIN}}} \right) \tag{22.7}
\]

\[
\text{Liver: } \frac{d(V_{\text{LIV}} C_{\text{LIV}})}{dt} = C_{\text{LIV}} (Q_{\text{LIV}} - Q_{\text{GI}} - Q_{\text{SP}}) + Q_{\text{GI}} \left( C_{\text{GI}} / P_{\text{GI}} \right) \\
+ Q_{\text{SP}} \left( C_{\text{SP}} / P_{\text{SP}} \right) - Q_{\text{LIV}} \left( C_{\text{LIV}} / P_{\text{LIV}} \right) - C_{\text{LIV}} \left( Cl_{\text{LIV}} / P_{\text{LIV}} \right) \tag{22.8}
\]
Kidney: \[
\frac{d(V_{\text{KID}}C_{\text{KID}})}{dt} = Q_{\text{KID}} \left(C_{\text{KID}} - \frac{C_{\text{KID}}}{P_{\text{KID}}} \right) - C_{\text{KID}} \left(\frac{C_{\text{KID}}}{P_{\text{KID}}} \right)
\]

(22.9)

Lung: \[
\frac{d(V_{\text{LU}}C_{\text{LU}})}{dt} = Q_{\text{LU}} \left(\frac{C_{\text{LU}}}{P_{\text{LU}}} \right)
\]

(22.10)

where LIV = liver, SP = spleen, GI = gastrointestinal tract, KID = kidney, LU = lung, FAT = adipose, SKIN = skin, and MUS = muscle.

The mass balance for the rate of change in drug concentration in the blood pool is

\[
\frac{d(V_{\text{LIV}}C_{\text{LIV}})}{dt} = Q_{\text{LIV}} \left(\frac{C_{\text{LIV}}}{P_{\text{LIV}}} \right) + Q_{\text{MUS}} \left(\frac{C_{\text{MUS}}}{P_{\text{MUS}}} \right)_{(\text{muscle})} + Q_{\text{LIV}} \left(\frac{C_{\text{LIV}}}{P_{\text{LIV}}} \right)_{(\text{liver})} + Q_{\text{KID}} \left(\frac{C_{\text{KID}}}{P_{\text{KID}}} \right)_{(\text{kidney})} + Q_{\text{SKIN}} \left(\frac{C_{\text{SKIN}}}{P_{\text{SKIN}}} \right)_{(\text{skin})} + Q_{\text{FAT}} \left(\frac{C_{\text{FAT}}}{P_{\text{FAT}}} \right)_{(\text{adipose})} + Q_{\text{LU}} \left(\frac{C_{\text{LU}}}{P_{\text{LU}}} \right)_{(\text{lung})(\text{blood})} - Q_{s}C_{s}
\]

(22.11)

Lung perfusion is unique because the pulmonary artery returns venous blood flow to the lung, where carbon dioxide is exchanged for oxygen and the blood becomes oxygenated. The blood from the lungs flows back to the heart (into the left atrium) through the pulmonary vein, and the quantity of blood that perfuses the pulmonary system ultimately passes through the remainder of the body. In describing drug clearance through the lung, perfusion from the heart (right ventricle) to the lungs is considered venous blood (Fig. 22-4). Therefore, the terms in Equation 22.11 describing lung perfusion are reversed compared to those for the perfusion of other tissues. With some drugs, the lung is a clearing organ besides serving as a merging pool for venous blood. In those cases, a lung clearance term could be included in the general model.

After intravenous drug administration, drug uptake in the lungs may be very significant if the drug has high affinity for lung tissue. If actual drug clearance is at a much higher rate than the drug clearance accounted for by renal and hepatic clearance, then lung clearance of the drug should be suspected, and a lung clearance term should be included in the equation in addition to lung tissue distribution.

The system of differential equations used to describe the blood flow–limited model is usually solved through computer programs. The Runge–Kutta method is often used in computer methods for using a series of differential equations. Because of the large number of parameters involved in the mass balance, more than one set of parameters may fit the experimental data. This is especially true with human data, in which many of the organ tissue data items are not available. The lack of sufficient tissue data sometimes leads to unconstrained models. As additional data become available, new or refined models are adopted. For example, methotrexate was initially described by
Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory

a flow-limited model, but later work described the model as a diffusion-limited model.

Because invasive methods are available for animals, tissue/blood ratios or partition coefficients can be determined accurately by direct measurement. Using experimental pharmacokinetic data from animals, physiologic pharmacokinetic models may yield more reliable predictions.

Physiologic Pharmacokinetic Model with Binding

The physiologic pharmacokinetic model assumes flow-limited drug distribution without drug binding to either plasma or tissues. In reality, many drugs are bound to a variable extent in either plasma or tissues. With most physiologic models, drug binding is assumed to be linear (not saturable or concentration dependent). Moreover, bound and free drug in both tissue and plasma are in equilibrium. Further, the free drug in the plasma and in the tissue equilibrates rapidly. Therefore, the free drug concentration in the tissue and the free drug concentration in the emerging blood are equal:

\[
C_{b,f} = f_b C_b 
\]

\[
C_{t,f} = f_t C_t 
\]

where \(f_b\) is the blood free drug fraction, \(f_t\) is the tissue free drug fraction, \(C_b\) is the total drug concentration in tissue, and \(C_b\) is the total drug concentration in blood.

Therefore, the partition ratio, \(P_t\), of the tissue drug concentration to that of the plasma drug concentration is

\[
\frac{f_b}{f_t} = \frac{C_b}{C_p} = P_t 
\]

By assuming linear drug binding and rapid drug equilibration, the free drug fraction in tissue and blood may be incorporated into the partition ratio and the differential equations. These equations are similar to those above except that free drug concentrations are substituted for \(C_b\). Drug clearance in the liver is assumed to occur only with the free drug. The inherent capacity for drug metabolism (and elimination) is described by the term \(Cl_{int}\) (see Chapter 11). General mass balance of various tissues is described by Equation 22.16:

\[
\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t (C_{art} - C_{ven})
\]

\[
\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t \left( C_{art} - \frac{C_t}{P_t} \right) \quad (22.16)
\]

or

\[
\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t \left( C_{art} - \frac{f_t}{f_b} C_b \right) \quad (22.17)
\]

For liver metabolism,

\[
\frac{d(V_{LIV} C_{LIV})}{dt} = C_M (Q_{LIV} - Q_{GI} - Q_{SP}) - Q_{LIV} \left( \frac{C_{LIV}}{P_{LIV}} \right) 
\]

\[(hepatic drug elimination)\]

\[
+ Q_{GI} \left( \frac{C_{GI}}{P_{GI}} \right) + Q_{SP} \left( \frac{C_{SP}}{P_{SP}} \right) \quad (22.18)
\]

The mass balance for the drug in the blood pool is

\[
\frac{d(V_b C_b)}{dt} = Q_{MUS} C_{MUS} + Q_{LIV} \left( \frac{C_{LIV}}{P_{LIV}} \right) 
\]

\[(muscle) \quad (liver)\]

\[
+ Q_{KID} \left( \frac{C_{KID}}{P_{KID}} \right) + Q_{SKIN} \left( \frac{C_{SKIN}}{P_{SKIN}} \right) \quad (22.18)
\]

\[(kidney) \quad (skin)\]

\[
+ Q_{FAT} \left( \frac{C_{FAT}}{P_{FAT}} \right) + Q_{LU} \left( \frac{C_{LU}}{P_{LU}} \right) - Q_b C_b 
\]

\[(adipose) \quad (lung) \quad (blood)\]

The influence of binding on drug distribution is an important factor in interspecies differences in pharmacokinetics. In some instances, animal data may predict drug distribution in humans by taking into account the differences in drug binding. For the most part, extrapolations from animals to humans or between species are rough estimates only, and there are many instances in which species differences are not entirely attributable to drug binding and metabolism.
Blood Flow-Limited versus Diffusion-Limited Model

Most physiologic pharmacokinetic models assume rapid drug distribution between tissue and venous blood. Rapid drug equilibrium assumes that drug diffusion is extremely fast and that the cell membrane offers no barrier to drug permeation. If no drug binding is involved, the tissue drug concentration is the same as that of the venous blood leaving the tissue. This assumption greatly simplifies the mathematics involved. Table 22-1 lists some of the drugs that have been described by a flow-limited model. This model is also referred to as the perfusion model.

A more complex type of physiologic pharmacokinetic model is called the diffusion-limited model or the membrane-limited model. In the diffusion-limited model, the cell membrane acts as a barrier for the drug, which gradually permeates by diffusion. Because blood flow is very rapid and drug permeation is slow, a drug concentration gradient is established between the tissue and the venous blood (Lutz and Dedrick, 1985). The rate-limiting step of drug diffusion into the tissue depends on the permeation across the cell membrane rather than blood flow. Because of the time lag in equilibration between blood and tissue, the pharmacokinetic equation for the diffusion-limited model is very complicated.

Application and Limitations of Physiologic Pharmacokinetic Models

The physiologic pharmacokinetic model is related to drug concentration and tissue distribution using physiologic and anatomic information. For example, the effect of a change in blood flow on the drug concentration in a given tissue may be estimated once the model is characterized. Similarly, the effect of a change in mass size of different tissue organs on the redistribution of drug may also be evaluated using the system of physiologic model differential equations generated. When several species are involved, the physiologic model may predict the pharmacokinetics of a drug in humans when only animal data are available. Changes in drug-protein binding, tissue organ drug partition ratios, and intrinsic hepatic clearance may be inserted into the physiologic pharmacokinetic model.

Most pharmacokinetic studies are modeled based on blood samples drawn from various venous sites after either IV or oral dosing. Physiologists have long recognized the unique difference between arterial and venous blood. For example, arterial tension (pressure) of oxygen drives the distribution of oxygen to vital organs. Chiou (1989) and Mather (2001) have discussed the pharmacokinetic issues when differences in drug concentrations in arterial and venous are considered (see Chapter 10). The implication of venous versus arterial sampling is hard to estimate and may be more drug dependent. Most pharmacokinetic models are based on sampling of venous data. In theory, mixing occurs quickly when venous blood returns to the heart and becomes reoxygenated again in the lung. Chiou (1989) has estimated that for drugs that are highly extracted, the discrepancies may be substantial between actual concentration and concentration estimated from well-stirred pharmacokinetic models.

### TABLE 22-1  Drugs Described by Physiologic Pharmacokinetic Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>Anesthetic</td>
<td>Blood, flow limited</td>
<td>Chen and Andrade (1976)</td>
</tr>
<tr>
<td>BSP</td>
<td>Diagnostic</td>
<td>Plasma, flow limited</td>
<td>Luecke and Thomason (1980)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Stimulant</td>
<td>Blood, flow limited</td>
<td>Gabrielson and Bondesson (1987)</td>
</tr>
<tr>
<td>Biperiden</td>
<td>Anticholinergic</td>
<td>Blood, flow limited</td>
<td>Nakashima and Benet (1988)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Antineoplastic</td>
<td>Plasma, multiple metabolite, binding</td>
<td>King et al (1986)</td>
</tr>
</tbody>
</table>


Interspecies Scaling

Various approaches have been used to compare the toxicity and pharmacokinetics of a drug among different species. **Interspecies scaling** is a method used in toxicokinetics and the extrapolation of therapeutic drug doses in humans from nonclinical animal drug studies. **Toxicokinetics** is the application of pharmacokinetics to toxicology and pharmacokinetics for interpolation and extrapolation based on anatomic, physiologic, and biochemical similarities (Mordenti and Chappell, 1989; Bonate and Howard 2000; Mahmood, 2000, 2007; Hu and Hayton, 2001; Evans et al, 2006).

The basic assumption in interspecies scaling is that physiologic variables, such as clearance, heart rate, organ weight, and biochemical processes, are related to the weight or body surface area of the animal species (including humans). It is commonly assumed that all mammals use the same energy source (oxygen) and energy transport systems across animal species (Hu and Hayton, 2001). Interspecies scaling uses a physiologic variable, $y$, that is graphed against the body weight of the species on log–log axes to transform the data into a linear relationship (Fig. 22-5). The general allometric equation obtained by this method is

$$ y = bW^a $$

(22.19)

where $y$ is the pharmacokinetic or physiologic property of interest, $b$ is an allometric coefficient, $W$ is the weight or surface area of the animal species, and $a$ is the allometric exponent. **Allometry** is the study of size.

Both $a$ and $b$ vary with the drug. Examples of various pharmacokinetic or physiologic properties that demonstrate allometric relationships are listed in Table 22-2. In the example shown in Fig. 22-5, methotrexate volume of distribution is related to body weight $B$ of five animal species by the equation $V_β = 0.859B^{0.918}$.

The allometric method gives an empirical relationship that allows for approximate interspecies scaling based on the size of the species. Not considered in the method are certain specific interspecies differences such as gender, nutrition, pathophysiology, route of drug administration, and polymorphisms. Some of these more specific cases, such as the pathophysiologic condition of the animal or human, may preclude pharmacokinetic or allometric predictions.

Interspecies scaling has been refined by considering the aging rate and life span of the species. In terms of physiologic time, each species has a characteristic life span, its **maximum life-span potential** (MLP), which is controlled genetically (Boxenbaum, 1982). Because many energy-consuming biochemical processes, including drug metabolism, vary inversely with the aging rate or life span of the animal, the allometric approach has been used for drugs that are eliminated mainly by hepatic intrinsic clearance.

Through the study of various species in handling several drugs that are metabolized predominantly by the liver, some empirical relationships regarding drug clearance of several drugs have been related mathematically in a single equation. For example, drug hepatic intrinsic clearance of biperiden in rat, rabbit, and dog was extrapolated to humans (Nakashima et al, 1987). Equation 22.20 describes the relationship between biperiden intrinsic clearance with body weight and MLP:

$$ Cl_{int} \times MLP = 1.36 \times 10^7 \times B^{0.892} $$

(22.20)

where MLP is the maximum life-span potential of the species, $B$ is the body weight of the species, and $Cl_{int}$ is the hepatic intrinsic clearance of the free drug.

**FIGURE 22-5** Interspecies correlation between methotrexate volume of distribution $V_β$ and body weight. Linear regression analysis was performed on logarithmically transformed data. (From Boxenbaum, 1982, with permission.)
### TABLE 22-2  Examples of Allometric Relationship for Interspecies Parameters

<table>
<thead>
<tr>
<th>Physiologic or Pharmacokinetic Property</th>
<th>Allometric Exponent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Allometric Coefficient&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal O\textsubscript{2} consumption (mL/h)</td>
<td>0.734</td>
<td>3.8</td>
</tr>
<tr>
<td>Endogenous N output (g/h)</td>
<td>0.72</td>
<td>0.000042</td>
</tr>
<tr>
<td>O\textsubscript{2} consumption by liver slices (mL/h)</td>
<td>0.77</td>
<td>3.3</td>
</tr>
<tr>
<td>Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mL/h)</td>
<td>0.69</td>
<td>8.72</td>
</tr>
<tr>
<td>Inulin (mL/h)</td>
<td>0.77</td>
<td>5.36</td>
</tr>
<tr>
<td>PAH (mL/h)</td>
<td>0.80</td>
<td>22.6</td>
</tr>
<tr>
<td>Antipyrine (mL/h)</td>
<td>0.89</td>
<td>8.16</td>
</tr>
<tr>
<td>Methotrexate (mL/h)</td>
<td>0.69</td>
<td>10.9</td>
</tr>
<tr>
<td>Phenytoin (mL/h)</td>
<td>0.92</td>
<td>47.1</td>
</tr>
<tr>
<td>Aztreonam (mL/h)</td>
<td>0.66</td>
<td>4.45</td>
</tr>
<tr>
<td>Ara-C and Ara-U (mL/h)</td>
<td>0.79</td>
<td>3.93</td>
</tr>
<tr>
<td>Volume of distribution (V\textsubscript{J})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (L/kg)</td>
<td>0.92</td>
<td>0.859</td>
</tr>
<tr>
<td>Cyclophosphamide (L/kg)</td>
<td>0.99</td>
<td>0.883</td>
</tr>
<tr>
<td>Antipyrine (L/kg)</td>
<td>0.96</td>
<td>0.756</td>
</tr>
<tr>
<td>Aztreonam (L/kg)</td>
<td>0.91</td>
<td>0.234</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>0.85</td>
<td>0.0212</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>0.87</td>
<td>0.082</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>0.98</td>
<td>0.0066</td>
</tr>
<tr>
<td>Stomach and intestines weight (g)</td>
<td>0.94</td>
<td>0.112</td>
</tr>
<tr>
<td>Blood weight (g)</td>
<td>0.99</td>
<td>0.055</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>1.01</td>
<td>0.0062</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (min)</td>
<td>0.23</td>
<td>54.6</td>
</tr>
<tr>
<td>Cyclophosphamide (min)</td>
<td>0.24</td>
<td>36.6</td>
</tr>
<tr>
<td>Digoxin (min)</td>
<td>0.23</td>
<td>98.3</td>
</tr>
<tr>
<td>Hexobarbital (min)</td>
<td>0.35</td>
<td>80.0</td>
</tr>
<tr>
<td>Antipyrine (min)</td>
<td>0.07</td>
<td>74.5</td>
</tr>
<tr>
<td>Turnover times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (1/day)</td>
<td>0.30</td>
<td>5.68</td>
</tr>
<tr>
<td>Total body water (1/day)</td>
<td>0.16</td>
<td>6.01</td>
</tr>
<tr>
<td>RBC (1/day)</td>
<td>0.10</td>
<td>68.4</td>
</tr>
<tr>
<td>Cardiac circulation (min)</td>
<td>0.21</td>
<td>0.44</td>
</tr>
</tbody>
</table>

From Ritschel and Banerjee (1986), with permission.
Although further model improvements are needed before accurate prediction of pharmacokinetic parameters can be made from animal data, some interesting results were obtained by Sawada et al (1985) on nine acid and six basic drugs. When interspecies differences in protein–drug binding are properly considered, the volume of distribution of many drugs may be predicted with 50% deviation from experimental values (Table 22-3).

The application of MLP to pharmacokinetics has been described by Boxenbaum (1982). Initially, hepatic intrinsic clearance was considered to be related to volume or body weight. Indeed, a plot of the log drug clearance versus body weight for various animal species resulted in an approximately linear correlation (ie, a straight line). However, after correcting intrinsic clearance by MLP, an improved log–linear relationship was achieved between free drug $\text{Cl}_{\text{int}}$ and body weight for many drugs. A possible explanation for this relationship is that the biochemical processes, including $\text{Cl}_{\text{int}}$, in each animal species are related to the animal’s normal life expectancy (estimated by MLP) through the evolutionary process. Animals with a shorter MLP have higher basal metabolic rates and tend to have higher intrinsic hepatic clearance and thus metabolize drugs faster. Boxenbaum (1982, 1983) postulated a constant “life stuff” in each species, such that the faster the life stuff is consumed, the more quickly the life stuff is used up. In the fourth-dimension scale (after correcting for MLP), all species share the same intrinsic clearance for the free drug.

$$\left(\frac{\text{MLP}}{\text{Cl}_{\text{int}}}ight) = \text{constant} \quad (22.21)$$

$$\text{Cl}_{\text{int}} = aB^b \quad (22.22)$$

Extensive work with caffeine in five species (mouse, rat, rabbit, monkey, and humans) by Bonati and associates (1985) verified this approach. Caffeine is a drug that is metabolized predominantly by the liver. For caffeine,

$$Q = 0.0554 \times B^{0.894}$$

$$L = 0.0370 \times B^{0.849}$$

where $B$ is body weight, $L$ is liver weight, and $Q$ is blood flow.

Hepatic clearance for the unbound drug did not show a direct correlation among the five species. After intrinsic clearance was corrected for MLP (calculation based on brain weight), an excellent relationship was obtained among the five species (Fig. 22-6).

More recently, the subject of interspecies scaling was investigated using $\text{Cl}$ values for 91 substances for several species by Hu and Hayton (2001). These investigators used $Y = a(BW)^b$ in their analysis, similar to Equation 22.19 above but with different symbols: $Y = \text{biological variable}$ dependent on the body weight of the species, $a = \text{allometric coefficient}$, $b = \text{allometric exponent}$, and $BW = \text{body weight}$ of the species. One issue discussed by Hu and Hayton is the uncertainty in the allometric exponent ($b$) of xenobiotic clearance ($\text{CL}$). Published literature has focused on whether the basal metabolic rate scale is a 2/3 or 3/4 power of the body mass ($BW$). When the uncertainty in the determination of a $b$ value is relatively large, a fixed-exponent approach might be feasible according to Hu and Hayton. In this regard, 0.75 might be used for substances that are eliminated mainly by metabolism or by metabolism and excretion combined, whereas 0.67 might apply for drugs that are eliminated mainly by renal excretion. The researchers pointed out that genetic (intersubject) difference may be a limitation for using a single universal constant.

Brightman et al (2006) demonstrated the application of a PK-PD model, based on human parameters to estimate plasma pharmacokinetics of xenobiotics in humans. The model was parameterized through an optimization process, using a training set of in vivo data taken from the literature. On average, the vertical divergence of the predicted plasma concentrations from the observed data was 0.47 log units, on a semilog concentration-time plot. They also evaluated the method against other predictive methods that involve scaling from in vivo animal data. In terms of predicting human clearance for the test set, the model was found to match or exceed the performance of three published interspecies scaling methods, which tend to give overprediction. The article concludes that the generic physiologically based pharmacokinetic model is a means of integrating readily determined in vitro and/or in silico data,
<table>
<thead>
<tr>
<th>Drug</th>
<th>V (L/kg)</th>
<th>Cl (mL/min per kg)</th>
<th>t₁/₂, Z (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Predicted</td>
<td>Percenta</td>
<td>Observed</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.640</td>
<td>0.573 10.5</td>
<td>0.574</td>
</tr>
<tr>
<td>Quinidine</td>
<td>3.20</td>
<td>3.69   22.2</td>
<td>2.91</td>
</tr>
<tr>
<td>Hexobarbital</td>
<td>1.27</td>
<td>0.735 42.1</td>
<td>3.57</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>0.999</td>
<td>1.57   57.2</td>
<td>0.524</td>
</tr>
<tr>
<td>Phenybutazone</td>
<td>0.122b</td>
<td>0.0839c 31.2</td>
<td>0.0205</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.108</td>
<td>0.109 0.926</td>
<td>0.0367</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>0.112</td>
<td>0.116 3.57</td>
<td>0.180</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>11.2b</td>
<td>9.05c 19.2</td>
<td>4.29</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3.62</td>
<td>3.77   4.14</td>
<td>11.2</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>5.56</td>
<td>7.19   29.3</td>
<td>18.3</td>
</tr>
<tr>
<td>Valproate</td>
<td>0.151</td>
<td>0.482 51.6</td>
<td>0.350</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.950</td>
<td>1.44   51.6</td>
<td>0.350</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>0.869</td>
<td>0.878 1.04</td>
<td>0.662</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.649</td>
<td>0.817 25.9</td>
<td>0.0530</td>
</tr>
<tr>
<td>Amobarbital</td>
<td>1.04</td>
<td>1.21   16.3</td>
<td>0.556</td>
</tr>
</tbody>
</table>

a Absolute percent of error.
b The value of VᵦC

c Predicted from the value of VᵦC in the rat.

From Sawada et al (1985), with permission.
Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory

and useful for predicting human xenobiotic kinetics in drug discovery.

**Physiologic versus Compartment Approach**

Compartmental models represent a simplified kinetic approach to describe drug absorption, distribution, and elimination (see Chapters 3 and 4). The major advantage of compartment models is that the time course of drug in the body may be monitored quantitatively with a limited amount of data. Generally, only plasma drug concentrations and limited urinary drug excretion data are available. Compartmental models have been applied successfully to prediction of the pharmacokinetics of the drug and the development of dosage regimens. Moreover, compartmental models are very useful in relating plasma drug levels to pharmacodynamic and toxic effects in the body.

The simplicity and flexibility of the compartment model is the principal reason for its wide application. For many applications, the compartmental model may be used to extract some information about the underlying physiologic mechanism through model testing of the data. Thus, compartment analysis may lead to a more accurate description of the underlying physiologic processes and the kinetics involved. In this regard, compartmental models are sometimes misunderstood, overstretched, and even abused. For example, the tissue drug levels predicted by a compartment model represent only a composite pool for drug equilibration between all tissue and the circulatory system (plasma compartment). However, extrapolation to a specific tissue drug concentration is inaccurate and analogous to making predictions without experimental data. Although specific tissue drug concentration data are missing, many investigators may make general predictions about average tissue drug levels.

Compartment models account accurately for the mass balance of the drug in the body and the amount of drug eliminated. Mass balance includes the drug in the plasma, the drug in the tissue pool, and the amount of drug eliminated after dosage administration. The compartment model is particularly useful for comparing the pharmacokinetics of related therapeutic agents. In the clinical pharmacokinetic literature, drug data comparisons are based on compartment models. Though alternative pharmacokinetic models have been available for approximately 20 years, the simplicity of the compartment model allows easy tabulation of parameters such as $V_D$, $\alpha \frac{1}{2}$, and $\beta \frac{1}{2}$. The alternative pharmacokinetic models, including the physiologic and statistical moment (mean residence time) approaches, are used much less frequently, even though a substantial body of data has been generated using both of these models.

In spite of these advantages, the compartmental model is generally regarded as somewhat empirical and lacking physiologic relevance. Many disease-related changes in pharmacokinetics are the result of physiologic changes, such as impairment of blood flow or a change in organ mass. These pathophysiologic changes are better evaluated using a physiologic-based pharmacokinetic model.

Because of its simplicity, the compartment model often serves as a “first model” that requires further refinement in order to describe the physiologic and drug distribution processes in the body accurately. The physiologic pharmacokinetic model—which accounts for processes of drug distribution, drug binding, metabolism, and drug flow to the body—
organs—is much more realistic. Disease-related changes in physiologic processes are more readily related to changes in the pharmacokinetics of the drug. Furthermore, organ mass, volumes, and blood perfusion rates are often scalable, based on size, among different individuals and even among different species. This allows a perturbation in one parameter and the prediction of changing physiology on drug distribution and elimination.

The physiologic pharmacokinetic model may also be modified to include a specific feature of a drug. For example, for an antitumor agent that penetrates into the cell, both the drug level in the interstitial water and the intracellular water may be considered in the model. Blood flow and tumor size may even be included in the model to study any change in the drug uptake at that site.

The physiologic pharmacokinetic model can calculate the amount of drug in the blood and in any tissues for any time period if the initial amount of drug in the blood is known and the dose is given by IV bolus. In contrast, the tissue compartment in the compartmental model is not related to any actual anatomic tissue groups. The tissue compartment is needed when the plasma drug concentration data are fitted to a multicompartment model. In theory, when tissue drug concentration data are available, the multiple-compartment models may be used to fit both tissue and plasma drug data together, including the drug concentration in a specific tissue. In such a case, the compartment model would mimic the system of equations used in the physiologic model, except that in place of blood flows, transfer constants would be used to describe the mass transfer in the model. The latter approach would probably, at best, yield less useful information than that obtained from the physiologic model.

Physiologic Pharmacokinetic Model Incorporating Hepatic Transporter-Mediated Clearance

It is now well recognized that drug transporters play important roles in the processes of absorption, distribution, and excretion and should be accounted for in models. Predicting human drug disposition, especially when involving hepatic transport, is difficult during drug development. However, drug transport may be a critical process in overall drug disposition in the body such that without a realistic description of transport processes in the body, model accuracy may be deficient. Watanabe et al (2009) describe a model with hepatobiliary excretion mediated by transporters, organic anion-transporting polypeptide (OATP) 1B1 and multidrug resistance–associated protein (MRP) 2, for the HMG-CoA reductase inhibitor drug, pravastatin. While the classical blood flow–based physiologic pharmacokinetic models developed 40 years ago using systems of differential equations that are still useful in describing the mass balance and transfer of drug within major organs, the models are inadequate in light of new discoveries in molecular biology and pharmacogenomics. Drug disposition and drug targeting are better understood based upon using influx/effect and binding mechanisms in micro structures such as interior cellular structures, membrane transporters, surface receptors, genomes, and enzymes. The liver is a complex organ intimately connected to drug transport and bile movement. Compartment concepts are needed to track the mass of drug transfer in and out of those fine structures as shown by the example in Fig. 22-7. Human liver microsomes are used to help predict the metabolic clearance of drugs in the body.

The PBPK model with pravastatin (Watanabe et al, 2009) is used to evaluate the concentration-time profiles for drugs in the plasma and peripheral organs in humans using physiological parameters, subcellular fractions (cells lysed and contents fractionated based on density), and drug-related parameters (unbound fraction and metabolic and membrane transport clearances extrapolated from in vitro experiments). The principle of the prediction was as follows. First, subcellular fractions were obtained by comparing in vitro and in vivo parameters in rats. Then, the in vitro human parameters were extrapolated in vivo using the subcellular fractions obtained in rats. Pravastatin was selected as the model compound because many studies have investigated the mechanisms involved in the drug disposition in rodents, and clinical data after intravenous and oral administration are available.

When multiple drug metabolites are involved, the physiologic model of the cascade events can be
Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory

669

quite complicated and an abbreviated approach may be used. St-Pierre et al (1988) developed a simple one-compartment open model, based on the liver as the only organ of drug disappearance and metabolite formation. The model was used to illustrate the metabolism of a drug to its primary, secondary, and tertiary metabolites. The model encompassed the cascading effects of sequential metabolism (Fig. 22-8). The concentration-time profiles of the drug and metabolites were examined for both oral and intravenous drug administration. Formation of the primary metabolite from drug in the gut lumen, with or without further absorption, and metabolite formation arising from first-pass metabolism of the drug and the primary metabolite during oral absorption were considered. Mass balance equations, incorporating modifications of the various absorption and conversion rate constants, were integrated to provide the explicit solutions.

Frequently Asked Questions

FIGURE 22-7 Schematic diagram of the PBPK model predicting the concentration-time profiles of pravastatin. The liver compartment was divided into five compartments to mimic the dispersion model. Indicated are blood flow (Q), the active hepatic uptake clearance (PS_{act}), the passive diffusion clearance (PS_{dif}), the biliary clearance (PS_{bile}), and the metabolic clearance (CL_{met, int}), human (H), and rat (R). The enterohepatic circulation was incorporated in the case of humans. (From Watanabe et al, 2009, with permission.)
After an intravenous bolus drug dose \((D_0)\), the drug molecules distribute throughout the body. These molecules stay (reside) in the body for various time periods. Some drug molecules leave the body almost immediately after entering, whereas other drug molecules leave the body at later time periods. The term mean residence time (MRT) describes the average time for all the drug molecules to reside in the body.

MRT may be considered also as the mean transit time or mean sojourn time. The residence time for the drug molecules in the dose may be sorted into groups \(i\) \((i = 1, 2, 3, \ldots, m)\) according to their residing time. The total residence time is the summation of the number of molecules in each group \(i\) multiplied by the residence time, \(t_i\), for each group. The summation of \(n_i\) (number of molecules in each group) is the total number of molecules, \(N\). Thus, MRT is the total residence time for all molecules in the body divided by the total number of molecules in the body, as shown in Equation 22.23:

\[
MRT = \frac{\text{total residence time for all drug molecules in body}}{\text{total number of drug molecules}} = \frac{\sum_{i=1}^{m} n_i t_i}{N} \tag{22.23}
\]
where \( n_i \) is the number of molecules and \( t_i \) is the residence time of the \( i \)th group of molecules.

The drug dose (mg) may be converted to the number of molecules by dividing the dose (mg) by 1000 and the molecular weight of the drug to obtain the number of moles of drug, and then multiplying the number of moles of drug by \( 6.023 \times 10^{23} \) (Avogadro’s number) to obtain the number of drug molecules. For convenience, Equation 22.23 may be written in terms of milligrams (instead of molecules) by substitution of \( n_i \) with \( D_{ei} \times f \), where \( D_{ei} \) is the number of drug molecules (as mg) leaving the body with residence time \( t_i \) (\( i = 1, 2, 3, \ldots, m \)). The \( f \) is a conversion factor. The number of molecules or milligrams of drug cancels out in Equation 22.24, showing that MRT is independent of mass:

\[
\text{MRT} = \frac{\sum_{i=1}^{m} D_{ei} \times f}{\sum_{i=1}^{m} D_{ei}} \quad (22.24)
\]

where \( D_{ei} (i = 1, 2, 3, \ldots, m) \) is the amount of drug (mg) in the \( i \)th group with residence time \( t_i \).

Drug molecules may have a residence time ranging from values near zero (eg, 0.1, 0.2) to very large values (100, 1000, 10,000). The number of \( i \) groups may be large and the summation approach to calculate MRT will be only an approximation. Also, for the summation process to be accurate, data must be collected continuously in order not to miss any groups. Integration is an accurate method that replaces summation when the data or function needs to be continuously summed over time.

### Mean Residence Time—IV Bolus Dose

The drug concentration in the body after an IV bolus injection for a drug that follows the pharmacokinetics of a one-compartment model is given by

\[
C_p = \left( \frac{D_p}{V_D} \right) e^{-kt} \quad (22.25)
\]

\[
D_p = D_i e^{-kt} \quad (22.26)
\]

where \( V_D \) is the apparent volume of distribution, \( k \) is the first-order elimination rate constant, and \( t \) is the time after the injection of the drug. The drug exit rate was generated in Table 22-4 with a numerical example until most drug was eliminated.

The rate of change in the amount of drug in the body with respect to time (\( dD_p / dt \)) reflects the rate at which the drug molecules leave the body at any time \( t \). Although all drug molecules enter the body at the

### Table 22-4 Simulated Plasma Data after an IV Bolus Dose, Illustrating Calculation of MRT

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Rate Eliminated ( dD_p / dt ) (mg/h)</th>
<th>Rate Eliminated Time (h) 3 dt (mg/h)</th>
<th>( C_p ) (mg/L)</th>
</tr>
</thead>
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<tr>
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<td>0</td>
<td>100</td>
</tr>
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<td>0.006</td>
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<tr>
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<td>0.005</td>
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<td>0.004</td>
</tr>
<tr>
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<td>0.318</td>
<td>0.003</td>
</tr>
<tr>
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<td>0.002</td>
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<td>0.209</td>
<td>0.002</td>
</tr>
<tr>
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<td>0.004</td>
<td>0.170</td>
<td>0.002</td>
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<tr>
<td>49</td>
<td>0.003</td>
<td>0.137</td>
<td>0.001</td>
</tr>
</tbody>
</table>

\*Drug exiting (first-order rate) tank or body compartment after IV bolus injection. Data generated with Equation 22.25. Dose = 1000 mg, volume = 10 L, \( k = 0.231 \) h\(^{-1}\).

\*Total drug exited = average rate \( \times dt \) and sum total.

\*Total drug residence time (expressed as mg/h) = rate \( \times t \) \( \times dt \) and sum total.
same time, the exit time, or the residing time, for each molecule is different. Equation 22.27 is obtained by taking the derivative of Equation 22.26, with all the drug molecules exiting the body from \( t = 0 \) to \( \infty \) (Table 22-4):

\[
\frac{dD}{dt} = -kD_0 e^{-kt} \tag{22.27}
\]

Alternatively, the rate of drug molecules exiting at any time \( t \) is given by

\[
\frac{dDe}{dt} = -\frac{dD}{dt} = kD_0 e^{-kt} \tag{22.28}
\]

Rearranging yields

\[
D_0 e^{-kt} dt = \frac{dDe}{k} \tag{22.29}
\]

At any time \( t \), \( dDe \) molecules exit. Therefore, multiplying Equation 22.29 by \( t \) on both sides yields the residence for each molecule exiting with a residence time \( t \). Summation of the residence time for each drug molecule, and division by the total number of molecules, estimates the mean residence time (Equation 22.30):

\[
\frac{\int_0^\infty D_0 e^{-kt} t \, dt}{D_0} = \int_0^\infty kD_0 e^{-kt} t \, dt \tag{22.30}
\]

\[
\text{MRT} = \int_0^\infty k e^{-kt} t \, dt \tag{22.31}
\]

As shown in Equation 22.30, the MRT is related to the product of the elimination rate constant \( k \) and the function describing drug elimination in the body. MRT is the integrated normalized form of the differential function representing drug amount (or concentration) in the body. The term differential probability is used to reflect that the function is a probability density function (PDF), which represents the residence time probability of a molecule in the population. The mean residence time is the normalized (divided by \( D_0 \)) differential of the function governing drug elimination in the body. When a function is normalized, it becomes dimensionless, without units.

Equation 22.30 was derived in terms of amount of drug. Because \( D_0 = C_p^0 V_D \), substituting for \( D_0 \) with \( C_p^0 V_D \) into the right side of Equation 22.30 yields

\[
\int_0^\infty \frac{dD}{dt} \, dt = \int_0^\infty \frac{kC_p^0 e^{-kt} dt}{C_p^0} \tag{22.32}
\]

Equation 22.32 may be used to determine MRT directly or may be rearranged to Equation 22.33 by dividing the numerator and denominator by \( k \) to yield a moment equation.

\[
\text{MRT} = \frac{\int_0^\infty \frac{dD}{dt} \, dt}{D_0} = \frac{\int_0^\infty \frac{C_p^0 e^{-kt} t \, dt}{C_p^0/k}}{C_p^0/k} \tag{22.33}
\]

The plasma concentration equation [function \( f(t) \)] multiplied by time and integrated from \( 0 = \infty \) gives a term called the first moment of the plasma drug curve. The denominator is the area under the curve, \( \text{AUC}_0^\infty \). The \( \text{AUC}_0^\infty \) is equal to \( \int_0^\infty C_p dt \) or \( D_0/V_D k \). Because \( C_p^0 = D_0/V_D \), the denominator of Equation 22.33 is the \( \text{AUC}_0^\infty \) of the time–concentration curve \( ( \text{AUC}_0^\infty = D_0/k V_D ) \); see Chapter 6. Equation 22.33 is used in pharmacokinetics to determine MRT; the equation is abbreviated in the literature as shown in Equation 22.34:

\[
\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \tag{22.34}
\]

where AUMC is the area under the (first) moment-versus-time curve from \( t = 0 \) to infinity. AUC is the area under plasma time-versus-concentration curve from \( t = 0 \) to infinity. AUC is also known as the zero moment curve. Table 22-5 shows how summation may be used to calculate MRT from generated data when the function is known.

**EXAMPLE**

A drug that follows the kinetics of a one-compartment model is given by IV bolus injection at a dose of 1000 mg. The drug has an elimination rate constant of 0.231 h\(^{-1}\) and a volume of distribution of 10 L. The body is considered a single compartment with no drug permanently bound in the body. (Use Table 22-4 for this problem; 50 data points were generated with Equation 22.25 for \( C_p \) and Equation 22.28 for \( dDe/dt \).)
The example is basically a verification of Equation 22.30. The approximation shows that when the function is not known, MRT may be estimated from the rate of drug excreted or from the plasma drug concentration–time curve. In practice, unless the entire dose is known, there is no

| TABLE 22-5 | Equations and Parameters Used in Generating Data for Fig. 22.8. Summation Method Was Used to Mimic Actual Calculation of MRT by the Moment Method

<table>
<thead>
<tr>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$j = 0, \ldots, 50$ Number of groups summed</td>
</tr>
<tr>
<td>$t_j = 1 \times j$ Residence time $t_j$</td>
</tr>
<tr>
<td>$k = 0.231$</td>
</tr>
<tr>
<td>Dose = 1000 mg</td>
</tr>
<tr>
<td>Volume = 10 L</td>
</tr>
<tr>
<td>$Db_i = 1000 \times \exp(-kt_i)$ Equation showing drug in body at $t_i$</td>
</tr>
<tr>
<td>$De_i = 1000k \times \exp(-kt_i)$ Equation showing drug exiting at $t_i$</td>
</tr>
<tr>
<td>$rt_i = De_i \times t_i$</td>
</tr>
<tr>
<td>$\sum_i rt_i = 4.31 \times 10^3$ Total residence time found by summation, $MRT = \frac{4310}{1004.43} = 4.29 h$</td>
</tr>
</tbody>
</table>

*MATLAB was used for calculation. Complete data generated are listed in Table 22-4.

```
EXAMPLE

1. Calculate the MRT of the drug molecules in the body using the moment method. Assume AUC is 432.9 (mg/L)/h and AUMC is 1865.465 (mg/L)h^2.

2. Calculate MRT using the total residence times of all molecules exited and divide by the total dose. Compare the answer to part 1.

Solution

1. Using the equation $MRT = \frac{AUMC}{AUC}$,

   $MRT = \frac{1865.465 \text{ (mg/L)h}^2}{432.9 \text{ (mg/L)h}} = 4.309 h$

2. The residence time for most of the drug molecules exiting from the body ($t = 0$ to $\infty$) is approximated by the first 50 points (only few drug molecules remained in the body after 50 hours). Total residence time is the sum of the number of molecules at each exit time point multiplied by the time. The mean residence time is the sum of all the residence times for all

   drug molecules divided by the total number of molecules (Equation 22.23). Multiplying columns 1 and 2 yields column 3:

   Total drug molecule residence time = 4310 mg/h

   Sum of drug exited = 1004.43 mg

   The sum of drug exited was obtained by averaging the rate of drug exited for each time point and multiplied by the time interval, 1 hour in this case; then sum up to obtain the total drug excreted. See Table 22-4.

   $MRT = \frac{4310}{1004.43} = 4.29 h$
assurance that all drug molecules are excreted through the plasma compartment if multiple compartments are involved.

MRT may also be calculated using the compartmental approach by considering the MRT for a drug after IV bolus injection as the reciprocal of the elimination rate constant, \( k \). In this case, MRT is inversely related to the elimination constant, and MRT = 1/\( k \). Therefore, MRT = 1/0.231 h\(^{-1} \) = 4.329 h. MRT was estimated earlier as 4.309 hours using the moment method. The slightly smaller value for the MRT here is due to approximation in the summation of the moment area and AUC.

Using the method of MRT = AUMC/AUC, MRT may be estimated using the AUC calculated from the \( C_p \) versus time curve (Table 22-4). Alternatively, the MRT can be estimated accurately using integration when the function that describes plasma drug concentrations is known (Table 22-5). A plot of \( D_e \) and \( C_p \) versus time, and the moment curve \( D_e \times t \) versus \( t \), are shown in Fig. 22-9. For drugs that follow the kinetics of a one-compartment model with drug elimination only from the plasma, MRT may be calculated by either the area method or from the first moment curve. In data analysis, the function that governs drug disposition is generally not known, and the MRT is generally calculated from the plasma drug concentration–time curve.

### STATISTICAL MOMENT THEORY

Statistical moment theory provides a unique way to study time-related changes in macroscopic events. A macroscopic event is considered the overall event brought about by the constitutive elements involved. For example, in chemical processing, a dose of tracer molecules may be injected into a reactor tank to track the transit time (residence time) of materials that stay in the tank. The constitutive elements in this example are the tracer molecules, and the macroscopic events are the residence times shared by groups of tracer molecules. Each tracer molecule is well mixed and distributes noninteractively and randomly in the tank.

Using the method of MRT = AUMC/AUC, MRT may be estimated using the AUC calculated from the \( C_p \) versus time curve (Table 22-4). Alternatively, the MRT can be estimated accurately using integration when the function that describes plasma drug concentrations is known (Table 22-5). A plot of \( D_e \) and \( C_p \) versus time, and the moment curve \( D_e \times t \) versus \( t \), are shown in Fig. 22-9. For drugs that follow the kinetics of a one-compartment model with drug elimination only from the plasma, MRT may be calculated by either the area method or from the first moment curve. In data analysis, the function that governs drug disposition is generally not known, and the MRT is generally calculated from the plasma drug concentration–time curve.

**FIGURE 22-9** Plot of (A) drug eliminated versus time; (B) \( C_p \) versus time; and (C) \( D_e \times t \) versus time. The data generated for these plots are tabulated in Table 22-4. The actual equations and parameters used are listed in Table 22-5.
In the one-compartment model, AUC divided by \( C_0 \) also yields MRT (432.896/100 = 4.33 hours). This example is another way to calculate MRT, as will be demonstrated later. MRT may also be computed by integrating \( f(t)/C_0 \) (Fig. 22-10B). However,
if \( f(t) \) represents a two- or multicompartment function, the computed MRT using this method is only for the central compartment, whereas using the AUMC/AUC approach leads to an MRT for the body (a larger value). The latter method treats the molecules as a single population within the body, tracking them only as they exit and without supposing any knowledge of molecular exchanges between the plasma and tissue compartments.

In the previous discussion, Equation 22.34 was derived to estimate MRT without applying the concept of probability density functions. However, the equation may be rearranged in the form of a PDF, as in Equation 22.31. This result is plotted in Fig. 22-10C for comparison. The moment theory facilitates calculation of MRT and related parameters from the kinetic function, as discussed below.

A probability density function \( f(t) \) multiplied by \( t^m \) and integrated over time yields the moment curve (Equation 22.35). The moment curve shows the characteristics of the distribution.

\[
\mu_m \text{ or } m\text{th moment} = \int_{0}^{\infty} t^m f(t) \, dt \tag{22.35}
\]

where \( f(t) \) is the probability density function, \( t \) is time, and \( m \) is the \( m\)th moment.

For example, when \( m = 0 \), substituting for \( m = 0 \) yields Equation 22.36, called the zero moment, \( \mu_0 \):

\[
\mu_0 = \int_{0}^{\infty} f(t) \, dt \tag{22.36}
\]

If the distribution is a true probability function, the area under the zero moment curve is 1.

Substituting into Equation 22.35 with \( m = 1 \), Equation 22.37 gives the first moment \( \mu_1 \)

\[
\mu_1 = \int_{0}^{\infty} t f(t) \, dt \tag{22.37}
\]

The area under the curve \( f(t) \) times \( t \) is called the AUMC, or the \textit{area under the first moment curve}. The first moment, \( \mu_1 \), defines the \textit{mean} of the distribution.

Similarly, when \( m = 2 \), Equation 22.35 becomes the second moment, \( \mu_2 \):

\[
\mu_2 = \int_{0}^{\infty} t^2 f(t) \, dt \tag{22.38}
\]

where \( \mu_2 \) defines the variance of the distribution. Higher moments, such as \( \mu_3 \) or \( \mu_4 \), represent skewness and kurtosis of the distribution. Equation 22.35 is therefore useful in characterizing families of moment curves of a distribution.

The principal use of the moment curve is the calculation of the MRT of a drug in the body. The elements of the distribution curve describe the distribution of drug molecules after administration and the residence time of the drug molecules in the body.

In Equation 22.31, the plasma equation, \( f(t) = C_p e^{-kt} \), was converted to a PDF [ie, \( f(t) = ke^{-kt} \)]. It can be shown that \( \mu_0 \) for this function = 1 (total probability adds up to 1 by summing the zero moment), and the mean of the function is the area under the first moment curve (the mean is the MRT).

By comparison, Equation 22.25 is not a true PDF, because its mean is not given by the AUMC, and its AUC is not 1. Nonetheless, Equation 22.34 may be used to calculate MRT independent of the PDF concept, although some confusion over its application appears in the literature.

---

### Example

An antibiotic was given to two subjects by an IV bolus dose of 1000 mg. The drug has a volume of distribution of 10 L and follows a one-compartment model with an elimination constant of (1) 0.1 h \(^{-1}\) and (2) 0.2 h \(^{-1}\) in the two subjects. Determine the MRT from each \( C_p \) versus time curve (Table 22-6) and compare your values with the MRT determined by taking the reciprocal of \( k \).

**Solution**

**Noncompartmental Approach** (MRT = AUMC/AUC)

1. From Table 22-6, multiply each time point with the corresponding plasma \( C_p \) to obtain points for the moment curve. Use the trapezoid rule and sum the area to obtain the area under the moment curve (AUMC) for subject 1. Also, determine the area under the plasma curve using the trapezoid rule.
<p>| Subjects 1 and 2 |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>(C_1)</th>
<th>(C_2)</th>
<th>(t)</th>
<th>AUMC1</th>
<th>AUMC2</th>
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<td>12</td>
<td>361.433</td>
</tr>
<tr>
<td>13</td>
<td>27.253</td>
<td>7.427</td>
<td>13</td>
<td>354.291</td>
</tr>
<tr>
<td>14</td>
<td>24.660</td>
<td>6.081</td>
<td>14</td>
<td>345.236</td>
</tr>
<tr>
<td>15</td>
<td>22.313</td>
<td>4.979</td>
<td>15</td>
<td>334.695</td>
</tr>
<tr>
<td>16</td>
<td>20.190</td>
<td>4.076</td>
<td>16</td>
<td>323.034</td>
</tr>
<tr>
<td>17</td>
<td>18.268</td>
<td>3.337</td>
<td>17</td>
<td>310.562</td>
</tr>
<tr>
<td>18</td>
<td>16.530</td>
<td>2.732</td>
<td>18</td>
<td>297.538</td>
</tr>
<tr>
<td>19</td>
<td>14.957</td>
<td>2.237</td>
<td>19</td>
<td>284.180</td>
</tr>
<tr>
<td>20</td>
<td>13.534</td>
<td>1.832</td>
<td>20</td>
<td>270.671</td>
</tr>
<tr>
<td>21</td>
<td>12.246</td>
<td>1.500</td>
<td>21</td>
<td>257.158</td>
</tr>
<tr>
<td>22</td>
<td>11.080</td>
<td>1.228</td>
<td>22</td>
<td>243.767</td>
</tr>
<tr>
<td>23</td>
<td>10.026</td>
<td>1.005</td>
<td>23</td>
<td>230.595</td>
</tr>
<tr>
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<td>9.072</td>
<td>0.823</td>
<td>24</td>
<td>217.723</td>
</tr>
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<td>25</td>
<td>8.208</td>
<td>0.674</td>
<td>25</td>
<td>205.212</td>
</tr>
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<td>26</td>
<td>7.427</td>
<td>0.552</td>
<td>26</td>
<td>193.111</td>
</tr>
<tr>
<td>27</td>
<td>6.721</td>
<td>0.452</td>
<td>27</td>
<td>181.455</td>
</tr>
<tr>
<td>28</td>
<td>6.081</td>
<td>0.370</td>
<td>28</td>
<td>170.268</td>
</tr>
<tr>
<td>29</td>
<td>5.502</td>
<td>0.303</td>
<td>29</td>
<td>159.567</td>
</tr>
<tr>
<td>30</td>
<td>4.979</td>
<td>0.248</td>
<td>30</td>
<td>149.361</td>
</tr>
</tbody>
</table>

(Continued)
The steps are as follows.

**a.** Multiply each \( C_p \) by \( t \) as in column 5 of Table 22-6.

**b.** Sum all \( C_p \times t \) values, and find the area under the moment curve (AUMC)—that is, 9986.45 (\( \mu g/mL \)h^2).

**c.** Estimate the tail area of the moment curve (beyond the last data point) using the equation

\[
AUMC_{pp} = C_p t + \frac{C_p}{k^2} \quad (22.39)
\]

Substituting the last data point, \( C_p = 0.00454 \) \( \mu g/mL \), the last time point, 100 hours, and the last moment curve point, 0.454 (\( \mu g/mL \)h):

\[
\text{Tail AUMC} = 0.454 \times \frac{0.00454}{0.1^2} = 4.99(\mu g/mL)h^2
\]

Total AUMC = 9986.46 + 4.99 = 9991.45(\( \mu g/mL \))h^2

(Note that \( k \) is determined from the slope to be 0.1 h^-1.)

**d.** Estimate AUC using the trapezoid rule from columns 1 and 2 (AUC = 1000.79 (\( \mu g/mL \))h).

**2.** From the tabulated results, summing up column 6, AUMC 2 = 2491.68 (\( \mu g/mL \))h^2. AUC for patient 2 = 500 (\( \mu g/mL \))h (calculated from the

---

**TABLE 22-6 Simulated Data for a Drug Administered by IV Bolus**

(Continued)

<table>
<thead>
<tr>
<th>Subjects 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_p )</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>91</td>
</tr>
<tr>
<td>92</td>
</tr>
<tr>
<td>93</td>
</tr>
<tr>
<td>94</td>
</tr>
<tr>
<td>95</td>
</tr>
<tr>
<td>96</td>
</tr>
<tr>
<td>97</td>
</tr>
<tr>
<td>98</td>
</tr>
<tr>
<td>99</td>
</tr>
<tr>
<td>100</td>
</tr>
</tbody>
</table>

Note the corresponding AUMC for the two subjects in the last two columns.

*(1) k = 0.1 h^-1, (2) k = 0.2 h^-1.*
Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory

one or more tissue or peripheral compartments. The assumptions are (1) that the drug is eliminated only from the central compartment and (2) that all drug is eliminated by a linear process (constant clearance). The MRT for a multicompartment model drug is the summation of the residence time of the drug in each compartment,

\[ MRT_{\text{body}} = MRT_{c} + MRT_{p1} + MRT_{p2} + \ldots + MRT_{pn} \]  
(22.40)

where \( MRT_{pi} \) represents MRT in the \( i \)th peripheral or tissue compartments and \( MRT_{c} = MRT \) for the central compartment.

MRT for the body may be calculated from the plasma concentration curve using AUMC/AUC as discussed earlier, because the body (including all compartments) may be treated as a single compartment. \( MRT_{c} \) is known as the mean residence time or mean transit time for the central compartment. This is calculated by \( \frac{\text{AUC}}{C_{0p}} \), where AUC is the area under the plasma drug concentration curve and \( C_{0p} \) is the initial plasma drug concentration at time = 0.

Derivation of \( MRT_{c} \)

Let

- \( D_{e} \) = amount of drug eliminated at time \( t \)
- \( D_{0} \) = dose or drug at time zero
- \( D_{p} \) = amount of drug in the plasma compartment from which drug is eliminated at time \( t \)
- \( C_{p} \) = drug concentration in the plasma compartment (volume, \( V_{D} \))

At time \( t \), \( dD_{e} \) units of drug are eliminated, the residence time is \( t \, dD_{e} \), and integrating from 0 to \( D_{e}^{*} \) yields the total residence time (see the numerator of Equation 22.41). Integrating \( D_{e} \) will yield the total units of drug eliminated (see the denominator of Equation 22.41), and MRT is obtained by dividing the total residence time by the total units of drugs. If elimination occurs only from the central compartment, then at any instant \( dt \), \( dD_{e} = -dD_{p} \).

\[ MRT_{c} = \frac{\int_{0}^{D_{e}^{*}} t \, dD_{e}}{\int_{0}^{D_{e}^{*}} dD_{p}} = \frac{\int_{0}^{D_{0}} t \, dD_{p}}{\int_{0}^{D_{0}} dD_{p}} \]  
(22.41)

MRT for Multicompartment Model with Elimination from the Central Compartment

The moment theory provides a means for calculating MRT for the body from plasma drug concentration data obtained for drugs that follow one-compartment models. In this section, the MRT is determined for a drug that has a plasma (central) compartment and one or more tissue or peripheral compartments. The assumptions are (1) that the drug is eliminated only from the central compartment and (2) that all drug is eliminated by a linear process (constant clearance). The MRT for a multicompartment model drug is the summation of the residence time of the drug in each compartment.

\[ MRT_{\text{body}} = MRT_{c} + MRT_{p1} + MRT_{p2} + \ldots + MRT_{pn} \]  
(22.40)

where \( MRT_{pi} \) represents MRT in the \( i \)th peripheral or tissue compartments and \( MRT_{c} = MRT \) for the central compartment.

MRT for the body may be calculated from the plasma concentration curve using AUMC/AUC as discussed earlier, because the body (including all compartments) may be treated as a single compartment. \( MRT_{c} \) is known as the mean residence time or mean transit time for the central compartment. This is calculated by \( \frac{\text{AUC}}{C_{0p}} \), where AUC is the area under the plasma drug concentration curve and \( C_{0p} \) is the initial plasma drug concentration at time = 0.

Derivation of \( MRT_{c} \)

Let

- \( D_{e} \) = amount of drug eliminated at time \( t \)
- \( D_{0} \) = dose or drug at time zero
- \( D_{p} \) = amount of drug in the plasma compartment from which drug is eliminated at time \( t \)
- \( C_{p} \) = drug concentration in the plasma compartment (volume, \( V_{D} \))

At time \( t \), \( dD_{e} \) units of drug are eliminated, the residence time is \( t \, dD_{e} \), and integrating from 0 to \( D_{e}^{*} \) yields the total residence time (see the numerator of Equation 22.41). Integrating \( D_{e} \) will yield the total units of drug eliminated (see the denominator of Equation 22.41), and MRT is obtained by dividing the total residence time by the total units of drugs. If elimination occurs only from the central compartment, then at any instant \( dt \), \( dD_{e} = -dD_{p} \).

\[ MRT_{c} = \frac{\int_{0}^{D_{e}^{*}} t \, dD_{e}}{\int_{0}^{D_{e}^{*}} dD_{p}} = \frac{\int_{0}^{D_{0}} t \, dD_{p}}{\int_{0}^{D_{0}} dD_{p}} \]  
(22.41)
Since

$$tdC_p = -C_p dt$$

and

$$\int_0^t dC_p = C_p^0$$

$$\text{MRT}_C = \frac{\int_0^\infty tV dC_p}{\int_0^\infty V dC_p} = \frac{\int_0^\infty dC_p}{\int_0^\infty dC_p}$$

$$(22.42)$$

$$\text{MRT}_p = \frac{\text{AUMC}}{\text{AUC}} - \frac{\text{AUC}}{C_p^0}$$

$$(22.44)$$

The plasma drug concentrations of a drug that follows a two-compartment model after IV bolus were simulated with the following parameters (Nagashima and Benet, 1988) and the plasma concentration equation for the two-compartment model. Determine MRT for the plasma and tissue compartments and verify Equation 22.43. Use these parameters: $$a = 2.2346$$, $$b = 0.4654$$, $$k = 0.946$$ (overall elimination constant from the central compartment), $$k_{12} = 0.655$$, $$k_{21} = 1.1$$ (all rate constants in h$^{-1}$). Also, $$V_p = 10$$ L, $$D_0 = 1000$$ mg, $$C_0 = 100$$ µg/mL.

Using the above parameters, the plasma drug concentration, $$C_p$$, at any point is given by Equation 22.45 (Table 22-7) and is plotted in Fig. 22-12.

$$C_p = 100 \left[ \left( \frac{k_{12} - a}{b - a} \right) e^{-at} + \left( \frac{k_{21} - b}{a - b} \right) e^{-bt} \right]$$

$$(22.45)$$

The AUMC is found by determining the $$C_p \times t$$ at each point and summing up for the entire curve.
physiologic pharmacokinetic models, mean residence time, and statistical moment theory

681

Table 22-7 Simulated Data Showing How to Calculate MRT from AUMC/AUC; 50 Points Were Generated Using Two-Compartment Equation after IV Bolus

<table>
<thead>
<tr>
<th>t</th>
<th>Cp</th>
<th>AUC</th>
<th>Cp*t</th>
<th>AUMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>21.076</td>
<td>0</td>
<td>2.144</td>
</tr>
<tr>
<td>0.25</td>
<td>68.611</td>
<td>14.752</td>
<td>17.153</td>
<td>5.232</td>
</tr>
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<td>0.5</td>
<td>49.404</td>
<td>10.838</td>
<td>24.702</td>
<td>6.585</td>
</tr>
<tr>
<td>0.75</td>
<td>37.302</td>
<td>8.338</td>
<td>27.976</td>
<td>7.170</td>
</tr>
<tr>
<td>1</td>
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<td>29.386</td>
<td>7.419</td>
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<tr>
<td>1.25</td>
<td>23.974</td>
<td>5.508</td>
<td>29.968</td>
<td>7.513</td>
</tr>
<tr>
<td>1.5</td>
<td>20.092</td>
<td>4.658</td>
<td>30.138</td>
<td>7.523</td>
</tr>
<tr>
<td>1.75</td>
<td>17.170</td>
<td>4.006</td>
<td>30.048</td>
<td>7.475</td>
</tr>
<tr>
<td>2</td>
<td>14.876</td>
<td>3.485</td>
<td>29.752</td>
<td>7.377</td>
</tr>
<tr>
<td>10</td>
<td>0.342</td>
<td>0.081</td>
<td>3.416</td>
<td>0.817</td>
</tr>
<tr>
<td>10.25</td>
<td>0.304</td>
<td>0.072</td>
<td>3.117</td>
<td>0.745</td>
</tr>
<tr>
<td>10.5</td>
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<td>0.064</td>
<td>2.842</td>
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</tr>
<tr>
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<td>0.241</td>
<td>0.057</td>
<td>2.590</td>
<td>0.619</td>
</tr>
<tr>
<td>11</td>
<td>0.214</td>
<td>0.051</td>
<td>2.359</td>
<td>0.563</td>
</tr>
<tr>
<td>11.25</td>
<td>0.191</td>
<td>0.045</td>
<td>2.148</td>
<td>0.513</td>
</tr>
<tr>
<td>11.5</td>
<td>0.17</td>
<td>0.040</td>
<td>1.954</td>
<td>0.467</td>
</tr>
<tr>
<td>11.75</td>
<td>0.151</td>
<td>0.036</td>
<td>1.778</td>
<td>0.424</td>
</tr>
<tr>
<td>12</td>
<td>0.135</td>
<td>0.032</td>
<td>1.616</td>
<td>0.386</td>
</tr>
<tr>
<td>12.25</td>
<td>0.12</td>
<td>0.028</td>
<td>1.469</td>
<td>0.35</td>
</tr>
<tr>
<td>Total sum of column</td>
<td>106.6</td>
<td>177.915</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The AUMC = 177.915 and the AUC = 106.6. The MRT of the drug in the body is 1.67 hours. MRT of the drug in the plasma is \( \frac{AUC}{C_0} = \frac{106.6}{100} = 1.066 \) hours. The MRT for the tissue compartment is 1.67 – 1.066 = 0.604 hour.

From statistical moment theory, MRT is the mean of the statistical distribution, \( k \times \frac{C_p}{C_0} \times dt \), where \( k \) is the elimination constant and each \( C_p \) has been normalized by dividing by \( C_0 \) (to give a PDF). MRT for the body is then simply the first moment of the distribution:

\[
\text{MRT} = \int_0^{t_f} \frac{100}{C_0} \left( \frac{k_{21}}{b-a} \right) e^{-at} + \left( \frac{k_{21}}{a-b} \right) e^{-bt} \ dt
\]

\((22.46)\)

MRT = 1.687 hours

The answer should agree with that given above, by AUMC/AUC. The second method illustrates the relationship of the plasma concentration data and the PDF. Because \( k \) (the elimination constant from the central compartment) is not known from plasma data, the second approach
is not applied directly. The PDF approach may also be used to determine MRT or mean residence time from the central compartment. Taking the derivative of the two-compartment equation for plasma drug concentration yields a PDF; this function may be calculated directly using software such as MATHCAD. Integration of the result yields MRT = 1.066 hours (the mean of the PDF), the same as that calculated using \( \frac{AUC}{C_0} \). AUMC/AUC of the differential function also yields an MRT of 1.066 hours.

In contrast, when AUMC/AUC is applied to the plasma drug concentration equation directly, AUC/\( C^0_p \) yields 1.066 hours, while AUMC/AUC yields 1.687 hours. The latter approach has caused some controversy in the literature because two different definitions were independently derived that apply independently during calculation. When the PDF approach is applied, this confusion is avoided. When the PDF is applied to the equation describing the drug in the body, an MRT of 1.687 hours is obtained, which is the sum of MRT in the tissue and the plasma compartment. In each case, MRT is simply the mean of the distribution that has a definite variance. The MRT may still be calculated without any knowledge of the distribution function, in which case the MRT is the ratio of two area-under-the-curve terms used in calculating \( V_{ss} \) or \( Cl \). The two approaches are contrasted below.

### Analysis Based on \( f(t) \), the Function Describing Plasma Drug Concentration

\[
f(t) = \frac{(k_{21}-a)e^{-at}}{b-a} + \frac{(k_{23}-b)e^{-bt}}{a-b}
\]

\[
\int_0^{50} f(t) dt = \frac{AUC_0}{C_0} = 1.058
\]

\[
\int_0^{50} f(t) dt = \frac{AUMC_0}{AUC} = 1.784
\]

\[
\frac{AUMC}{AUC} = 1.784 \quad \frac{1}{1.058} = 1.688
\]

\[
\text{MRT} = \frac{AUC}{C_0} = \frac{1.058}{1} = 1.058
\]

### Analysis Based on Differential Function, \( f'(t) \), the Derivative of \( f(t) \)

\[
g(t) = \frac{(k_{21}-a)e^{-at}}{b-a}(a) + \frac{(k_{23}-b)e^{-bt}}{a-b}(b)
\]

\[
\int_0^{50} g(t) dt = \frac{AUMC_0}{C_0} = 1.058 \quad \text{(MRT from PDF)}
\]

\[
\int_0^{50} g(t) dt = \frac{AUC_0}{C_0} = 1
\]

\[
\frac{AUMC}{AUC} = \frac{1.058}{1} = 1.058 \quad \text{(MRT using AUMC/AUC)}
\]

The first approach depends on \( C^0_p \) evaluation. The second approach allows two ways to evaluate MRT. The two approaches agree with each other.
The Model-Independent and Model-Dependent Nature of MRT

MRT evaluated from AUMC/AUC assumes that most drugs are excreted through the central compartment or that they are metabolized in highly vascular tissues that kinetically are considered part of the central compartment. For drugs eliminated through tissues that are not part of the central compartment, the MRT calculated by AUMC/AUC is smaller than that calculated by considering both peripheral and central compartment elimination.

Compare models A and B generated by Nakashima and Benet (1988) in Fig. 22-13 and Table 22-8. Both models A and B have identical rate constants except that model B has an elimination rate constant, \( k_{20} \), from the peripheral compartment. MRT calculated using the new approach, referred to as MRT (new), is 1.687 hours for model A and 2.212 hours for model B. The new equation for MRT (new) of model B is

\[
MRT_{\text{new}}(\text{new}) = \frac{\text{AUMC}}{\text{AUC}} + \frac{k_{20} V_2}{E_2 Cl} \tag{22.47}
\]

where \( k_{20} \) = the elimination rate for drug eliminated in compartment 2; \( V_2 \) = the distribution volume of compartment 2; \( E_2 \) = the sum of rate constants exiting from compartment 2 (in model B, \( E_2 = k_{20} + k_{21} \)); \( Cl \) = total body clearance; \( MRT_c \) = MRT from the central compartment; \( MRT_p \) = MRT from the peripheral or tissue compartment, also referred to as MRT; \( MRT = \text{AUMC}/\text{AUC} \); and \( MRT_{\text{new}} \) = MRT as calculated with correction for peripheral elimination.

The equation also applies for other multicomartment models. For a three-compartment model, Fig. 22-13 (model E), a third term is added to Equation 22.47 to reflect drug exiting in compartment 3, as in Equation 22.48.

\[
MRT_{\text{new}}(\text{new}) = \frac{\text{AUMC}}{\text{AUC}} + \frac{k_{20} V_2}{E_2 Cl} + \frac{k_{30} V_3}{E_3 Cl} \tag{22.48}
\]

From Table 22-8, MRT (new) calculated using Equations 22.47 and 22.48 is model dependent. The original MRT calculated using AUMC/AUC yields the same MRT value of 1.687 hours for models A, B, and C. The original method, frequently quoted as a model-independent method for calculating MRT from plasma data, in effect, treats the body as a single unit from which drugs are eliminated from the plasma pool regardless of the true nature of the model. Unfortunately, it is not possible to know, from plasma data alone, whether drug elimination occurs in the peripheral compartment. Therefore, it is not possible to interpret unambiguously the calculated MRT parameters without making some assumptions. Benet and Galeazzi (1979) and Nakashima and Benet (1988) showed that MRT is related to \( V_{SS} \) and clearance (Equation 22.49), as illustrated in Table 22-8. The clearances among models A, B, and

![FIGURE 22-13](66485457-66485438) The three possible linear two-compartment open models and two possible three-compartment models. In each case, the concentration in compartment 1 (the central compartment) represents the measurable concentration of drug. (From Nakashima and Benet, 1988, with permission.)
C are identical, showing that clearance is site independent and may be calculated through MRT. However, the three-compartment model clearances were clearly different.

\[ \text{MRT} = \frac{\text{Cl}}{V_{ss}} \]  

(22.49)  

MRT is useful in calculating the steady-state volume of distribution and additional parameters in compartmental and other models. In the compartmental models, MRT may give some idea of how long the drug molecules stay in the peripheral compartment. For example, for the drug digoxin, MRT for the body is 49.5 hours; for the central and peripheral compartments, 

Table 22-8 Parameter Values for Models Depicted in Fig. 22-11 Consistent with the Following Equations: \( C_p = 64.131e^{-2.2346t} + 35.869e^{-0.4654t} \) for Models A, B, and C; and \( C_p = 53.55e^{-0.1212t} + 18.4e^{0.0361t} + 28.013e^{-0.01049t} \) for Models D and E.
MRT is 3.68 hours and 45.8 hours as calculated (Veng-Pedersen, 1989). The peripheral MRT is the mean total time the drug molecules spend in the peripheral tissue, considering the first entry as well as possibly subsequent entries into the peripheral tissue from the central, general systemic circulation. An overview of MRT values for various pharmacokinetic models is given in Table 22-9.

### Mean Absorption Time (MAT) and Mean Dissolution Time (MDT)

After IV bolus injection, the rate of systemic drug absorption is zero, because the drug is placed directly into the bloodstream. The MRT calculated for a drug after IV bolus injection basically reflects the elimination rate processes in the body. After oral drug administration, the MRT is the result of both drug absorption and elimination. The relationship between the mean absorption time, MAT, and MRT is given by

\[
\text{MAT} = \text{MRT}_{\text{oral}} - \frac{1}{k}
\]

For a one-compartment model, \( \text{MRT}_{\text{IV}} = 1/k \):

\[
\text{MAT} = \text{MRT}_{\text{oral}} - \frac{1}{k}
\]

### Table 22-9 Mean Residence Time for Different Pharmacokinetic Models

<table>
<thead>
<tr>
<th>Model</th>
<th>MRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-compartment bolus IV</td>
<td>( \frac{1}{k} )</td>
</tr>
<tr>
<td>One-compartment oral bolus</td>
<td>( \frac{1}{k_1} + \frac{1}{k} )</td>
</tr>
<tr>
<td>Two-compartment bolus IV</td>
<td>( \frac{(k_{1z} + k_{z1})}{kk_{z1}} )</td>
</tr>
<tr>
<td>Two-compartment oral bolus</td>
<td>( \frac{1}{k_1} + \frac{(k_{1z} + k_{z1})}{kk_{z1}} )</td>
</tr>
<tr>
<td>One-compartment infusion (for period t)</td>
<td>( \frac{1}{k} + \frac{t}{2} )</td>
</tr>
<tr>
<td>Two-compartment IV bolus</td>
<td>( \frac{A_1}{a^2} + \frac{A_2}{b^2} )</td>
</tr>
</tbody>
</table>

*Alternatively, this may be calculated as \( \frac{1}{a} + \frac{1}{b} - \frac{1}{k_1} \).*


In some cases, IV data are not available and an MRT for a solution may be calculated. The mean dissolution time (MDT), or in vivo mean dissolution time, for a solid drug product is

\[
\text{MDT}_{\text{solid}} = \text{MRT}_{\text{solid}} - \text{MRT}_{\text{solution}} \quad (22.52)
\]

MDT reflects the time the drug to dissolve in vivo. Equation 22.52 calculates the in vivo dissolution time for a solid drug product (tablet, capsule) given orally. MDT has been evaluated for a number of drug products. MDT is most readily estimated for the drugs that follow the kinetics of a one-compartment model. MDT is considered model independent because MRT is model independent. MDT has been used to compare the in vitro dissolution versus in vivo bioavailability for immediate-release and extended-release drug products (see Chapters 14 and 17). Even with complete experimental data, the parameters obtained are quite dependent on the method of computation method employed.

**Example**

Data for ibuprofen (Gillespie et al, 1982) are shown in Table 22-10. Serum concentrations for ibuprofen after a capsule and a solution are tabulated as a function of time in Tables 22.11 and 22.12.

The MRT was determined using the trapezoid method and Equation 22.43. The MRT for the solution was 2.63 hours and for the product was 4.48 hours. Therefore, MDT for the product is 4.48 – 2.63 = 1.85 hours.

\[
\text{MAT}_{\text{solution}} = \text{MRT}_{\text{solution}} - \frac{1}{k} = 2.63 - \frac{1}{0.455} = 2.2 \text{ h}
\]

\[
\text{MAT}_{\text{product}} = \text{MRT}_{\text{product}} - \frac{1}{k} = 4.48 - \frac{1}{0.347} = 4.48 - 2.88 = 1.6 \text{ h}
\]

Applying Equation 22.52 directly (Riegelman and Collier, 1980),

\[
\text{MDT} = 4.48 - 2.63 = 1.85 \text{ h}
\]
TABLE 22-10  Serum Concentrations for Capsule Ibuprofen

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$C_p$</th>
<th>$C_p t$</th>
<th>$tC_p \Delta t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.167</td>
<td>0.06</td>
<td>0.01002</td>
<td>0.000836</td>
</tr>
<tr>
<td>0.333</td>
<td>3.59</td>
<td>1.195</td>
<td>0.1000</td>
</tr>
<tr>
<td>0.50</td>
<td>7.79</td>
<td>3.895</td>
<td>0.425</td>
</tr>
<tr>
<td>1</td>
<td>13.3</td>
<td>13.300</td>
<td>4.298</td>
</tr>
<tr>
<td>1.5</td>
<td>14.5</td>
<td>21.750</td>
<td>8.762</td>
</tr>
<tr>
<td>2</td>
<td>16.9</td>
<td>33.80</td>
<td>63.887</td>
</tr>
<tr>
<td>3</td>
<td>16.6</td>
<td>49.80</td>
<td>85.46</td>
</tr>
<tr>
<td>4</td>
<td>11.9</td>
<td>47.60</td>
<td>48.70</td>
</tr>
<tr>
<td>6</td>
<td>6.31</td>
<td>37.86</td>
<td>85.46</td>
</tr>
<tr>
<td>8</td>
<td>3.54</td>
<td>28.32</td>
<td>66.18</td>
</tr>
<tr>
<td>10</td>
<td>1.36</td>
<td>13.60</td>
<td>41.92</td>
</tr>
<tr>
<td>12</td>
<td>0.63</td>
<td>7.56</td>
<td>21.16</td>
</tr>
</tbody>
</table>

$\text{Total AUMC} = 382.695$

$k = 0.347 \text{h}^{-1}$; $AUC_C = 91.5$

$AUMC_{\text{of tail piece}} = \frac{(0.63)(12)}{0.347} = 21.79 + 5.23 = 27.02$

$AUC_C' = 280.695 + 27.02 = 409.72$

$MRT_{\text{product}} = \frac{409.72}{91.5} = 4.48 \text{h}$

Data adapted from Gillespie et al (1982), with permission.

TABLE 22-11  Serum Concentrations for Solution Ibuprofen

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$C_p$</th>
<th>$C_p t$</th>
<th>$tC_p \Delta t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.167</td>
<td>17.8</td>
<td>2.973</td>
<td>0.248</td>
</tr>
<tr>
<td>0.333</td>
<td>29.0</td>
<td>9.657</td>
<td>1.048</td>
</tr>
<tr>
<td>0.50</td>
<td>29.7</td>
<td>14.85</td>
<td>2.046</td>
</tr>
<tr>
<td>1</td>
<td>25.7</td>
<td>25.7</td>
<td>10.14</td>
</tr>
<tr>
<td>1.5</td>
<td>19.7</td>
<td>29.55</td>
<td>13.81</td>
</tr>
<tr>
<td>2</td>
<td>17.0</td>
<td>34.0</td>
<td>15.88</td>
</tr>
<tr>
<td>3</td>
<td>11.0</td>
<td>33.0</td>
<td>33.50</td>
</tr>
<tr>
<td>4</td>
<td>7.1</td>
<td>28.4</td>
<td>30.70</td>
</tr>
<tr>
<td>6</td>
<td>3.82</td>
<td>22.92</td>
<td>51.33</td>
</tr>
<tr>
<td>8</td>
<td>1.44</td>
<td>11.52</td>
<td>34.45</td>
</tr>
<tr>
<td>10</td>
<td>0.57</td>
<td>5.70</td>
<td>17.22</td>
</tr>
<tr>
<td>12</td>
<td>0.38</td>
<td>4.56</td>
<td>10.26</td>
</tr>
</tbody>
</table>

$\text{Total AUMC} = 220.64$

$k = 0.455 \text{h}^{-1}$; $AUC_S = 88.5$

$AUMC_{\text{of tailpiece, extrapolation to } t} = \frac{(0.38)(12)}{0.445} + 0.38 + 0.445^2$

$= 10.02 + 1.84 = 11.86$

$AUC_S = 220.64 + 11.86 = 232.50 \text{ (μg/mL) h}$

$MRT_{\text{solute}} = \frac{232.50}{88.5} = 2.63 \text{h}$

Data adapted from Gillespie et al (1982), with permission.

TABLE 22-12  Parameters for Capsule and Solution Ibuprofen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Capsule</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>(μg/mL)h</td>
<td>92.55</td>
<td>85.50</td>
</tr>
<tr>
<td>AUMC</td>
<td>(μg/mL)h$^2$</td>
<td>396.1</td>
<td>210.5</td>
</tr>
<tr>
<td>$k_a$</td>
<td>h$^{-1}$</td>
<td>0.46</td>
<td>4.90</td>
</tr>
<tr>
<td>$k$</td>
<td>h$^{-1}$</td>
<td>0.47</td>
<td>0.437</td>
</tr>
<tr>
<td>MRT</td>
<td>Hours</td>
<td>4.28</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Parameters were calculated from data of Gillespie et al (1982).
SELECTION OF PHARMACOKINETIC MODELS

Several objectives should be considered when using mathematical models to study rate processes (e.g., pharmacokinetics of a drug). The primary objective in developing a model is to conceptualize the kinetic process in a quantitative manner that can be tested experimentally (see Chapter 1). A model that cannot be tested is weak and will not improve or yield new knowledge about the process. In contrast, a wrong model that can be tested may be useful if the proposed hypotheses and its subsequent rejection leads to the correct model. To be statistically vigorous, a hypothesis or model is tested with the null hypothesis ($H_0$) (Appendix A). Only after rejection of the null hypothesis (tested beyond chance probability) is the hypothesis accepted. When the null hypothesis is rejected, the probability (e.g., $p < 0.05$) means that the chance of error is less than 5% and the hypothesis or model is accepted. In fitting data using linear regression, the correlation of coefficient, $r^2$, is calculated, where $r^2$ is an indication of how well the data are predicted by the model. For example, $r = 0.9$ or $r^2 = 0.81$ indicates that 81% of the data agree with the model. The $r^2$ is not always a very good criterion. The sum of the squared differences (between the observed and predicted data) is a better criterion.

Adequate experimental design and the availability of valid data are important considerations in model selection and testing. For example, the experimental design should determine whether a drug is being eliminated by saturable (dose-dependent) or simple linear kinetics. A plot of metabolic rate versus drug concentration can be used to determine dose dependence, as in Figure 22-14. Metabolic rate can be measured at various drug concentrations using an in vitro system (see Chapter 11). In Fig. 22-14, curve $B$, saturation occurs at higher drug concentration.

For illustration, consider the drug concentration–time profile for a drug given by IV bolus. The combined metabolic and distribution processes may result in profiles like those in Fig. 22-15. Curve $A$ represents a slow initial decline due to saturation and a faster terminal decline as drug concentration decreases. Curve $C$ represents a dominating distributive phase masking the effect of nonlinear metabolism. Finally, a combination of $A$ and $C$ may approximate a rough overall linear decline (curve $B$). Notice that the drug concentration–time profile is shared by many different processes and that the goodness-of-fit is not an adequate criterion for adopting a model. For example, concluding linear metabolism based only on curve $B$ would be incorrect. Contrary to common belief, complex models tend to mask opposing variables that must be isolated and tested through better experimental designs. In this case, a constant infusion until steady-state experiment would yield information on saturation without the influence of initial drug distribution.

![Image of Metabolic rate versus drug concentration](image1)

**FIGURE 22-14** Metabolic rate versus drug concentration. Drug $A$ follows first-order pharmacokinetics, whereas drug $B$ follows nonlinear pharmacokinetics and saturation occurs at higher drug concentrations.

![Image of Plasma drug concentration profiles](image2)

**FIGURE 22-15** Plasma drug concentration profiles due to distribution and metabolic process. (See text for description of $A$, $B$, and $C$.)
The use of pharmacokinetic models has been critically reviewed by Rescigno and Beck (1987) and by Riggs (1963). These authors emphasize the difference between model building and simulation. A model is a secondary system designed to test the primary system (real and unknown). The assumptions in a model must be realistic and consistent with physical observations. On the other hand, a simulation may emulate the phenomenon without resembling the true physical process. A simulation without identifiable support of the physical system does little to aid understanding of the basic mechanism. The computation has only hypothetical meaning.

For example, the data in Fig. 22-16 may be described by three different equations: a straight line, a hyperbola, and an equation with trigonometric functions. Without physical support, the model gives little understanding of the mechanisms involved. Regression or data fitting (computation of parameters of a given equation so that divergence of the data from the equation is minimized) is considered to be modulation. All forms of modulation represent data manipulation and, as such, decrease information. Information comes from observations and observations only. If more points were available in this example, we could distinguish different processes if the data represent a straight line. Simulations within the realm of data allow for the determination of a quantitative relationship that is useful but does not actually increase understanding of the underlying physiologic processes governing the sojourn of the drug in the body.

Data dredging, such as manipulating the data to influence a stated study objective or model, is considered statistically undesirable because it may lead to a biased or a nonobjective analysis of the study. Ideally, statisticians prefer that details such as inclusion and exclusion criteria, the number of subjects per group, and the method of analysis or modeling be designed with sufficient power written into the protocols in advance. Pharmacokineticists are interested in understanding underlying kinetic processes that yield the results (data); statisticians are more interested in knowing that the conclusions drawn are real and not the result of random distribution.

It is perhaps refreshing to reexamine the basic paradigm of pharmacokinetics, or kinetics, which may be described as “observing how a given process changes over time.” For example, by monitoring a change in the drug concentration in a patient over time, drug absorption and elimination from the patient may be modeled. If a statistician wishes to extrapolate the conclusion to a larger population, he or she may choose to enroll a sufficient number of subjects, and consider inclusion or exclusion criteria such as age, sex, other diseases, and genetics.

Basic pharmacokinetic concepts should be simple with few assumptions. The clinician may choose to weigh the risk of extrapolating the data and conclusions from a study with a few patients to a larger patient population. With recent advances in genetics, there are thousands of known genomic and environmental factors that may potentially influence disease and pharmacotherapy. The combination of genetic and environmental factors is very large and may make it very difficult to apply average information to an individual subject (see Chapter 12). However, the concept of adjusting dosing based on individual pharmacokinetic/pharmacodynamic information is still the most reliable approach to optimize dosing and drug efficacy and avoid toxicity. Ultimately, individual pharmacokinetic information will be combined with pharmacogenetic information obtained from the patient to allow the development of even better models to improve drug therapy.
CHAPTER SUMMARY

Physiologically based PK-PD models use a system of differential equations to describe drug transfer and accumulation in various tissues or organs in the body. Published data in the physiologic literature regarding size (mass) of organs and blood flow to each organ and body mass are used. Drug elimination in key organs is based on clearance concepts. The generic PK-PD model is useful as a crude model for rough estimates of plasma concentration versus time profiles after IV administration assuming no protein binding, specific transporters, or any unusual drug specific disposition characteristics. Despite this limitation, the PK-PD model is used when no kinetic or efficacy information is available for a drug when given the first time in humans. Typically, animal data about protein binding, drug efflux, and CYPs are used to fill in missing information due to the lack of human tissue data. Drug development methods such as Caco-2 cells, liver microsome metabolism, and binding to human serum proteins are also used to gather in vitro data about the drug in order to improve the accuracy of in vivo projection when using PK models. Toxicology data from animals are also collected to evaluate whether the first dose in humans is safe or not. Subsequently, single-dose and dose escalation studies, done under close medical supervision, will generate the first set of human PK data, which may then be used to refine the PK model in man. MRT (mean residence time) is a statistical approach that treats drug molecules as individual units that move through organ and body spaces according to kinetic principles, and allows independent development of many equations that are familiar to classical kineticists. MRT allows the determination of the time for mean residence of the molecules (eg, dose administered) in the body according to its route of administration. The variance of the residence time can also be determined based on statistical moment theory based on probability density function. The MRT approach allows another way of computing the clearance and volume of distribution of a drug through the derived equations. These equations are preferred by some scientists and are applied to AUC and clearance computation of new drugs. The approach is often referred to as the noncompartmental approach although all computation methods applied some form of interpolation or extrapolation at some stage of data analysis and parameter determination. An important consideration that should be kept in mind is the impact of the assumptions of the method rather than the semantics.

LEARNING QUESTIONS

1. After an intravenous dose (500 mg) of an antibiotic, plasma–time concentration data were collected and the area under the curve was computed to be 20 mg/L h. The area was found to be 100 mg/L h².

   a. What is the mean residence time of this drug?
   b. What is the clearance of this drug?
   c. What is the steady-state volume of distribution of this drug?
2. Why is MRT calculated from moment and AUC curves (i.e., $\frac{[\text{AUMC}]_{\infty}}{\text{AUC}_{\infty}}$) rather than $\frac{[\text{AUC}]_{\infty}}{C_0}$ directly, as the term was defined in Equation 22.43? 

3. If the data in Question 1 above are fit to a one-compartment model with an elimination $k$ that is found to be 0.25 hour, MRT may be calculated simply as $1/k$. What different assumptions are used in here versus Question 1? 

4. What are the principal considerations in interspecies scaling? 

5. What are the key considerations in fitting plasma drug data to a pharmacokinetic model? 

REFERENCES


Physiologic Pharmacokinetic Models, Mean Residence Time, and Statistical Moment Theory


BIBLIOGRAPHY


PROBABILITY

Probability is widely applied to measure risk associated with disease and drug therapy. Risk factor is a condition or behavior that increases the chance of developing disease in a healthy subject over a period of time. An example could be the risk of developing lung cancer over time with tobacco smoking. Another example of risk factor is the possibility of developing hearing loss after receiving an aminoglycoside antibiotic for a period of time.

The term relative risk (RR) or risk ratio is the most frequently used probability term to measure association of risk with exposure (to a drug or a behavior). Risk factors may be genetic, environmental, or behavioral. They have important implications in both pharmacokinetics and drug therapy (see Chapter 12). Risk factors may be casual or merely a marker that increases the probability of a disease.

\[
RR = \frac{\text{risk (exposed)}}{\text{risk (unexposed)}}
\]

\[
RR = \frac{\text{disease probability of exposed}}{\text{disease probability of unexposed}}
\]

Often risk information is collected in a controlled manner over a period of time by survey, either from the past or forward in time. In a prospective cohort study (also known as a cohort study, prospective, follow-up, or longitudinal study), a cohort of healthy subjects exposed to different levels of a suspected risk is followed forward in time to determine the incidence of risk in each group. For example, in a hypothetical study, the risk of thrombophlebitis was studied in a group of randomly selected women: 500 women taking and 500 matched women not taking a birth control pill for 10 years. The RR of 10 for thrombophlebitis was calculated from a risk of thrombophlebitis in women exposed to the birth control pill versus women not exposed to the drug using a dichotomous 2 × 2 table as shown in Table A-1, where A and B are the number of subjects who developed thrombophlebitis. The probability of exposed in this case is A/(A + B) and that of not exposed is C/(C + D). In this case, assume the exposed risk is 0.025 and the not-exposed risk is 0.0025. Then RR = 0.025/0.0025 = 10. Thus, the relative risk of thrombophlebitis in women on the birth control pill for 10 years is 10 for this group of women studied.

A second method of studying risk is the historical or retrospective cohort study, which looks backward in time to determine the present risk. The cohort of exposed and unexposed subjects is retrieved from past records to determine risk outcome. In the next section relative risks are described in terms of odds, a similar concept that is also widely applied.

ODDS

The probability of drawing an ace from a deck of cards is 4/52, or 1/13 for a deck of cards containing 4 aces in 52 cards. The odds of drawing an ace is the number of times an ace will be drawn divided by the number of times it will not be drawn. The odds are

\[
\text{ODDS} = \frac{4/52}{48/52} = \frac{4}{48} = \frac{1}{12}
\]

This can be read as a 1:12 odds of drawing an ace. The absence of four aces in the denominator makes the difference in the odds outcome. Odds are numerically not equal to probability as defined.
The point may be illustrated by considering the opening of a standard deck of cards, one card at a time. For example, we may encounter 4 aces after 40 cards are opened, before the entire deck is open. We can see that the number of cards opened (we stopped at 40 cards) becomes a factor in the odds obtained. In this case, after opening the first 40 cards, 4 cards were aces and 36 cards were not aces. The odds are $4/36 = 1/9$ instead of $1/12$ as calculated for 52 cards. Using this analogy, it is inappropriate to pick sample sizes that do not reflect the natural risk course of the disease or drug treatment involved. If we decide to sample only 40 cards, stop sampling, and then calculate the odds (or RR in observing a disease), the results will be in error. In statistics, the sample size and how samples represent the population at large are important considerations for accurate determination of the RR of a disease or drug treatment.

A common approach to studying risk outcome is the case-control study (also known as the retrospective study). In the case-control study, the exposure histories of two groups of subjects are selected on the basis of whether or not they develop a particular disease (eg, thrombophlebitis), in order to evaluate disease frequency resulting from drug (eg, the pill) exposure. The investigator selects the size of the subject population that has the disease or is disease free to determine exposure to the risk factor. The number of subjects who do and do not have the disease may not necessarily reflect the natural frequency of the disease. It is therefore improper to compute a “relative risk (RR)” from the odds ratio (OR) for a case-control study, because the investigator can manipulate the size of the relative risk.

$$OR = \frac{\text{odds of case exposure}}{\text{odds of case unexposed}}$$

If the disease is rare, then $OR = RR$. When the sample size is large, the difference between OR and RR diminishes.

In statistical analysis, it is important to guard against selection error or bias. Investigators may look harder for cancer, for example, in smokers than in a control group of healthy subjects. The resultant disparity is often called surveillance bias. In a case-control group there may also be recall bias; for example, medical history taken on surgical lung cancer (case) may be more likely to contain information on smoking than other type of surgical controls (Knapp and Miller, 1992).

### EXPERIMENTAL DESIGN AND COLLECTION OF DATA

Statistics have important applications in scientific studies, whether in studies involving hypothesis testing or in finding ways to improve a product. Statistical design is widely used at the experimental planning stage. Later, when data are collected, statistical methods are applied for data analysis and to help draw conclusions from the studies.

Experimental design may be simple or may involve an elaborate model. The method may be

---

**TABLE A-1  Tabulation from a Hypothetical Cohort Study of Female Subjects on the Pill—With and without Developing Thrombophlebitis for 10 Years**

<table>
<thead>
<tr>
<th>Risk factor present (+ Thrombophlebitis)</th>
<th>Negative Outcome (‐ Thrombophlebitis)</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor absent (eg, not taking the pill—not exposed)</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Subtotal</td>
<td>A + C</td>
<td>B + D</td>
</tr>
</tbody>
</table>
applied to optimize a drug or drug product based on a set of criteria (Deming and Morgan, 1987). Experimental design may be used to optimize an analytical method to separate a drug from impurities, such as an HPLC method. In pharmacokinetics, experimental design is used to design better sampling time for drawing blood samples for drug analysis in pharmacokinetic parameter estimation. A common approach to optimizing a drug product is the factorial design. For example, we may be interested in determining whether 0%, 0.25%, 0.5%, 0.75%, or 1% of magnesium stearate should be formulated into a tablet granulation to allow adequate flow of the tablet granulation mixture during manufacturing. This problem may be viewed as a simple one-factorial-design experiment to determine the amount of lubricant needed to provide best powder flow (1 factor × 5 lubricant levels). The object of the experimental design is to try to pick the tablet lubricant level that will result in the optimal powder flow from the hopper to the die cavity during tablet compression.

In practice, tablet granulation flow is more complex. Moisture level, particle size, and tackiness (of the drug substance) are other factors that influence flow. We may decide to reduce the increment level and select the lubricant levels to 0%, 0.5%, and 1% only. This provides three lubricant levels—high, medium, and low—for each factor. We then can apply a factorial design of 4 factors at 3 levels, which involves $4^3 = 64$ trials in the above case to generate a geometric response space that represents all the factors involved. The full factorial design is tedious, so a reduced design, the fractional factorial design, is often used. How to reach the optimal point efficiently when several factors are involved is a problem for many optimization experiments.

The identical concept for optimizing flow can be applied to optimizing the media composition supporting antibiotic production by fermentation using Streptomyces or a new microbe engineered by recombinant DNA. The factorial design may be employed to find the optimum composition for the growth medium. Factorial design yields knowledge about the system but is tedious. An alternative approach to carry out the optimization is the sequential simplex method, which optimizes the factors through sequentially planned experiments. This method is often applied in parameter estimation from data using computerized iteration algorithms. In designing experiments, it is important to know the factors involved and the range of each factor. How much change in drug concentration is occurring in plasma samples over an hour or in a minute? How much difference in drug concentrations can the analytical method detect? Good design requires some knowledge of the system and a strategy to obtain data for analysis that saves time and resources.

The same principle applies to human clinical studies. In clinical trials, studies are often done with a limited number of subjects, due to either cost or the availability of subjects who meet the study requirements. Based on good clinical practices, the study subjects are selected according to exclusion and inclusion criteria that are written into the protocol. All subjects must give informed consent to be in the study. Since most studies are done over a period of time, it is important to ensure that both the treatment and control groups are balanced and to avoid any temporal influence. For example, in bioequivalency trials, adequate time (wash-out time) between study dosing periods is allowed for the drug to be eliminated from the subject and to avoid residual effects due to carryover of the drug from the first dosing period to the next dosing period.

All scientific studies must be designed properly to obtain valid conclusions that may be applied to the population intended. The experimental design of a study includes the following:

1. A clearly stated hypothesis for the study
2. Assurance that the samples have been randomly selected
3. Control of all experimental variables
4. Collection of adequate data to allow experimental testing of the hypothesis

For example, we may wish to test the hypothesis that the average weight of young males is greater than the average weight of females in the United States. First, we may decide that young male and female subjects aged 18 to 24 will be selected and other ages excluded. The subjects are randomly selected from a pool of subjects who are not inter-related in a way that might affect their body weights. We may want to exclude subjects with certain diseases...
(exclusion criteria). A sufficient number of subjects must be selected (sampled) randomly so that the total number of subjects (sample size) represents the general population in the United States. The need for randomization is easily understood but often poorly met because of the difficulties in recruiting subjects, or in the methods used for recruiting. For example, if all the subjects in this example are randomly recruited from one health club in a given city, the samples will not be typical of the population intended even though the subjects are randomly selected. Are we too ambitious to include the population of the entire United States? Second, many of the subjects exercise at the health club to lose weight, and this may not be representative of the general population. A true sample is one selected randomly from the population of the entire country without connection with any variable that affects their weights.

The identification of all covariates in a study is generally difficult and requires thorough consideration. The subject of sample size, inclusion criteria, and exclusion criteria are major considerations in experimental design that will affect the statistical outcome. After careful consideration, we may realize that there are many variables to be considered and may wish to modify the scope to tailor the study objectives more efficiently.

Age, gender, genetic background, and health of the subjects are important variables in clinical drug testing. The statistical design of a study is based on the study objectives. Each study should have clearly stated objectives and an appropriate study design indicating how the study is to be performed. Often, the population may be subdivided according to the objectives of the study. For example, a new drug for the treatment of Alzheimer’s disease in the elderly may initially be tested in male subjects aged 55 and above. Later, clinical studies might test the drug in other patient populations. Many different statistical designs are possible. Some of these designs control experimental variables better than others. Specific statistical designs are given in other chapters and in standard statistical texts.

The quality of the data is very important and may be controlled by the researcher and the method of measurement. For example, if the weights of the young males and females in the example above are obtained using different scales, the investigator must ascertain that each scale weighs the subject accurately. Accuracy refers to the closeness of the observation (i.e., observed weight) to the actual or true value. Reproducibility or precision refers to the closeness of repeated measurements.

**ANALYSIS AND INTERPRETATION OF DATA**

The objective of data analysis is to obtain as much information about the population as possible based on the sample data collected. A common method for analyzing data of a sample population is to classify the data and then plot the frequency of occurrence of all the samples. For example, the frequency of weight distribution of a class of students may be plotted in the form of a histogram that relates frequency to weight (Fig. A-1).

An important observation in this example is that the weight of most students lies in the middle of the weight distribution. There is a common tendency for most sample values to occur around the mean. This is described in the central limit theorem, which states that the frequency of the values of measurements drawn randomly from a population tends to approximate a bell-shaped curve or normal distribution. Extensive data collection is needed to determine the distributional nature of a sample population. Once the parameters of a distribution are determined, the probability of a given sample’s occurrence in the population may be calculated.

**FIGURE A-1** Weight distribution of 120 students.
DESCRIPTIVE TERMS

Descriptive terms are used in statistics to generalize the nature of the data and provide a measure of central tendency. The mean or average is the sum of the observations divided by the number, \( n \), of observations (Table A-2). The median is the middle value of the observation between the highest and lowest value. The mode is the most frequently occurring value. The term range is used to describe the dispersion of the observations and is the difference between the highest and lowest values. For data that are distributed as a normal distribution (discussed below), the mean, median, and mode have the same value.

THE NORMAL DISTRIBUTION

If data are plotted according to the frequency of occurrence, a pattern for the distribution of the data is observed. Most data approximate a normal or Gaussian distribution. The normal distribution is a bell-shaped curve that is symmetric on both sides of the mean. Statistical tests that assume the data follow normal distribution patterns are known as parametric tests. Nonparametric tests do not make any assumption about the central tendency of the data and may be used to analyze data without assuming normal distribution. Nonparametric tests require no assumption of normality and are less powerful. Examples are the Wilcoxon test and the side test.

The shape of the normal distribution is determined by only two parameters, the population mean and the variance, both of which may be estimated from the samples. The variance is a measure of the spread or variability of the sample. Many biologic and physical random variables are described by the normal distribution (or may be transformed to a normal distribution). These may include the weight and height of humans and animal species, the elimination half-lives of many drugs in a population of patients, the duration of a telephone call, and other variables. In statistics, the item investigated is termed the random variable. For convenience, the standardized normal distribution is introduced to allow easy probability calculation when the standard deviation is known (Fig. A-2). The probability of a sample value occurring from 1 standard deviation (SD) above to 1 SD below the mean is 68% (\( z \) of –1 to +1). This value is calculated by finding the probability corresponding to \( z = -1 \) and \( z = 1 \) from curve B in Fig. A-2 as follows:

- Probability between \( z \) of –4 to –1 is 0.16.
- Probability between \( z \) of –4 to +1 is 0.84.
- Therefore, the probability between \( z \) of –1 and +1 is 0.84 – 0.16 = 0.68 or 68%.

The area representing probability between any two points on the normal distribution is calculated from this graph. In practice, a cumulative standardized normal distribution table is used to allow better accuracy.

Standard deviation measures the variability of a group of data. SD for \( n \) number of measurements is calculated according to the following equation:

\[
SD = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}}
\]  

(A.1)

### TABLE A-2  Descriptive Statistics for a Set of Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Descriptive Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Sum = 1274</td>
</tr>
<tr>
<td>25</td>
<td>Mean = 57.9</td>
</tr>
<tr>
<td>29</td>
<td>Mode = 67</td>
</tr>
<tr>
<td>35</td>
<td>Median = 62</td>
</tr>
<tr>
<td>37</td>
<td>( n = 22 )</td>
</tr>
<tr>
<td>42</td>
<td>Range = 21–91</td>
</tr>
<tr>
<td>45</td>
<td>SD = 20.3</td>
</tr>
<tr>
<td>49</td>
<td>RSD = 35.1%</td>
</tr>
<tr>
<td>56</td>
<td>75</td>
</tr>
<tr>
<td>57</td>
<td>88</td>
</tr>
<tr>
<td>61</td>
<td>91</td>
</tr>
</tbody>
</table>

*The data represent a set of measurements (observations) in a study. The descriptive terms are often used to describe the data. Each term is defined in the text.*

SD, standard deviation; RSD, relative standard deviation.
where $\bar{x}$ is the mean, $x_i$ is the observed value, and $n$ is the number of observations (data). The standard deviation is often calculated by computer or calculator and gives an indication of the spread of data (see Fig. A-2). A larger standard deviation indicates that the spread of data about the mean is larger compared to data with the same mean but with a smaller standard deviation.

Relative standard deviation or coefficient of variation allows comparison of the variance of measurements. The standard deviation is divided by the mean to give the relative standard deviation (RSD) or coefficient of variation (CV):

$$RSD = \frac{SD}{\bar{x}}$$  \hspace{1cm} (A.2)

The RSD may be expressed as a percent or %CV by multiplying the RSD by 100. This is commonly known as percent standard deviation or percent variation.

The difference between the mean, $\bar{x}$, and each observed datum, $x_i$, is the deviation from the mean. Because the deviation from the mean can be either negative or positive, the deviations are squared and summed to give an estimation of the total spread or deviation of the data from the mean. The term, $\sum_{i} (x_i - \bar{x})^2$ is the sum of the squares. This term incorporates measurement error as well as inherent variance of the samples. If a single sample is measured several times, the sum of the squares should be very small if the method of measurement is reproducible.

The concept of least squares for minimizing error due to model fitting is fundamental in many statistical methods.

**CONFIDENCE LIMIT**

If normal distribution of the data is assumed, the probability of a random variable in the population can be calculated. For example, data that fall within 1 SD above and below the mean ($\bar{x} \pm 1$ SD) represent approximately 68% of the data, whereas data that fall within 2 SD above and below the mean ($\bar{x} \pm 2$ SD) represent approximately 95% of the data. In the examples below, the random variable in which we are interested is the diameters of drug particles measured from a powdered drug sample lot.

**EXAMPLE**

The particle size of a powdered drug sample was measured. The average (mean) particle size was 130 $\mu$m with a standard deviation of 20 $\mu$m.

1. Determine the range of particle sizes that represents the middle 68% of the powdered drug.

**Solution**

From a normal distribution table or Fig. A-2, 68% of the middle particles represent 34% above and below the mean, corresponding to the mean $\pm 1$ SD.
In the above example, the calculation shows that most of the particles lie around the mean. To be 95% certain, simply extend from the mean ± 2 SD. This approach estimates the 95% confidence limit. A 95% confidence limit implies that if an experiment is performed 100 times, 95% of the data will be in this range above and below the mean.

This example shows how to reconstruct a population based on the two parameters, mean and variance (approximated by the SD). A more common application is the estimation of experimental data such as assay measurements. Such 95% confidence limits are often calculated from the standard deviation to estimate the reliability of the assay measurement.

In the example above, the mean for the particle size was 130 μm and the SD was 20 mm. Therefore, from Equation A.2, the RSD = 20/130 or 0.15. The RSD may be expressed as a percent or %CV by multiplying the RSD by 100.

As mentioned, accuracy refers to the agreement with the observed value or measurement in a group of data and the actual or true value of the population. Unfortunately, the true value is unknown in many studies. The term precision refers to the reproducibility of the data or the variation within a set of measurements. Data that are less precise will demonstrate a larger variance or a larger relative standard deviation, whereas more precise data will have a smaller variance.

2. Determine the range of particle sizes that represents the middle 95% of the powdered drug.

**Solution**

95% ± 2 or 47.5% on each side of the mean, corresponding to ±2 SD (Fig. A-2)

Smallest particle size = 130 – (2 × 20) = 90 μm

Largest particle size = 130 + (2 × 20) = 170 μm

Therefore, 95% of the particles will have a particle size ranging from 90 to 170 μm.

---

**EXAMPLE**

A lot of 10-mg tablets was assayed five times by three students (Fig. A-3). Which student assayed the tablets most accurately?

**Solution**

The mean and SD of assays by each student were determined. Because the same lot was assayed, the difference in SD among the students is attributed to assay variations. Student A is closest to the target—that is, the labeled claimed dose (LCD) of 10 mg. Student C is most precise (with the smallest %SD), but is consistently off target.

The data obtained by Student C is considered biased because all the observed data are above 10 mg. Data are also considered biased if all the observed data are below the true value of 10 mg.

Bias refers to a systematic error when the measurement is consistently not on target. Repeated measurements may be very reproducible (precise) but miss the target. In the example above, Student C was most precise, but Student A was most accurate. In determining accuracy and precision, a standard (known sample) is usually prepared and assayed several times to determine the variation due to assay errors. In the example above, we assumed that the students used known 10-mg standard tablets. If the tablets were unknown samples, it would not be possible to conclude which student was more accurate, because the true value would be unknown. In practice, assay methods are validated for precision and accuracy based on known standards before unknown samples (eg, plasma samples) are assayed.

In the analysis and interpretation of data, statistics makes inferences about a population using experimental data gathered in a sample. After analysis of data, the statistician calculates the likelihood or probability that a given result would happen. *Probability (p)* is the fraction of the population indicating that a given result or event would occur by random sampling or chance. For example, if p < 0.05, then the likelihood that a result occurs by random sampling is 5/100, 1/20, or 5%. By convention, if the
Appendix A

Appendix A

statistical inference produces a p value of 0.05 or less, it is considered atypical or uncommon of the population. As shown in Fig. A-1, the probability of finding a student weighing above 250 lb is small \( p < 0.05 \), and we may conclude (somewhat erroneously) that a student who weighs 250 lb is significantly different from the rest. This concept for determining the probability of how typical a given sample value occurs in a population may be extended to hypothesis testing. Hypothesis testing estimates the probability of whether a given value is typical of the control group or of the treated group.

**STATISTICAL DISTRIBUTIONS AND APPLICATION**

The frequency distribution of some data does not appear to be symmetrically shaped. The term \textit{skewness} relates to the asymmetry of the data. The data distribution may be skewed to the left or right of the mean. In many pharmacologic studies, the sample size in the study is small, and the investigator cannot always be certain that the data obtained from the study are normally distributed. An incorrect assumption of a normal distribution may lead to a biased conclusion. In such cases, a nonparametric test may be used, because it does not make any assumption about the underlying test except that it may be continuous.

During data analysis, a value or observation may be observed that is several standard deviations above or below the mean; such a value is called an \textit{outlier}. A value that is an outlier is difficult to use statistically. An observed value that deviates far from the majority of the data may indicate non-normal distribution, an error in measurement, or an error in data entry. If an error is found during checking, it should be corrected. In general, outlier values should not be excluded from the statistical analysis. Some investigators use log transformation of the data to make the distribution of the data appear to be more normally distributed. A geometric mean is obtained after log transformation of the data. In some cases, with sufficient data collection, a bimodal distribution may be observed. For example, the acetylation of isoniazid in humans follows a bimodal distribution, indicating two populations consisting of fast acetylators and slow acetylators. In this study, if the data were obtained from subjects of whom all but one were fast acetylators, then the single datum for the slow acetylator might be considered an outlier (and possibly be discarded from the data analysis).

When a specific distribution is not known, it may be possible to use the bootstrap/jackknife method. A \textit{bootstrap} is a paradoxical means of getting started on something when you need some of that something in order to get started. The concept derives from the
phrase “to pull oneself up by one’s bootstraps.” Rather than attributing an assumption to the distribution, the actual data collected will be used to extrapolate further about the larger population it represents. Instead of collecting more samples by actual experiment, one simply puts all the data into a “virtual bag” and randomly samples (not actually taking the original data out) from the bag until the desired number of samples is collected to yield a glimpse of what the population will be like. The method was a great innovation by Bradley Efron and is easily adapted to many applications with computer technology. The basic bootstrap method is essentially the same. The method has worked well and has been modified for many practical applications where assumption of specific distribution failed (Efron et al, 1993). It should be appreciated that the nature of the data from an original study is new and unknown. The greatest difficulty facing the investigator is characterizing the distribution and applying it to a proper model. The bootstrap method avoids the problem of assuming the wrong distribution. In Chapter 22, statistical distribution is discussed with further application to pharmacokinetics.

The normal, binomial, Poisson, chi-square distributions are frequently applied in statistics and engineering. Some distributions are related mathematically. References for further information are listed at the end of this appendix.

Statistical analysis is referred to as a statistical test when the data are formulated for hypothesis testing. The most common test involves the Student’s t-test, which is a test of means of two groups assuming the same variance. If the variances are different, the Student’s t-test will be a t-test with unequal variance. When the sample size increases to very large, the t-distribution approaches the normal distribution. The t-test becomes more powerful if the subjects meet the criteria for a paired t-test. The F-test is a simple test of variance of two groups. When more groups are involved, analysis of variance may be applied.

For this reason, all drugs under development in clinical studies are monitored for side effects and rare events. After FDA approval and marketing, pharmaco-vigilance is needed to ensure safety in the larger population of patients who will be using the drug.

In testing the effect of a drug across different groups, the term interaction is often heard. An effect is a difference in treatment response, and an interaction is a difference in differences. Examples might be treatment-by-center interactions, or treatment-by-gender interactions. When large interactions are noted, it is not appropriate to combine groups and make an overall assessment of the treatment effect statistically. Clinical trials often involve pivotal and supporting studies. An analysis that combines multiple studies to obtain an overall result, such as an overall estimate of the size of the treatment effect of a drug, is termed meta-analysis.

**HYPOTHESIS TESTING**

Hypothesis testing is an objective way of analyzing data and determining whether the data support or reject the hypothesis postulated. For example, we might want to test the hypothesis that a given steroid causes a weight increase. We want to test this hypothesis using two groups of healthy volunteers, one group (treated) that took the given steroid and another (control) that took no drug. The two hypotheses generated are as follows:

- $H_0$: There is no difference in weight between the treated and control groups (null hypothesis).
- $H_1$: There is a difference in weight between the treated and control groups (alternative hypothesis).

The null hypothesis, $H_0$, states that there is no difference between the treatments. The experimental data will either reject or fail to reject (accept) the null hypothesis. If the null hypothesis is rejected, then the alternative hypothesis is accepted, since there are only two possibilities. A simple hypothesis testing data from two groups is the two-sample Student’s t-test involving a control group and a treated group (the t-distribution approximates the normal distribution and is commonly used).

The data for the study (simulated) are shown in Fig. A-4 using 120 students in the control and treated
groups. The mean weight of the treated group is about 175 lb, whereas the mean weight for the control group is about 155 lb. There is a shift to the right in the weight distribution of the treated group. However, a considerable overlapping (shaded area) in weights is observed, making it difficult to reject the null hypothesis. In practice, $H_0$ is rejected at a known level of uncertainty called the level of significance. A level of 5% ($\alpha = 0.05$) is considered statistically significant, and a level of 1% ($\alpha = 0.01$) is considered highly significant. Commonly, this level of significance is reported as $p < 0.05$ or $p < 0.01$, respectively, to indicate the different levels of significance. Because uncertainty is involved, whenever the null hypothesis is rejected or accepted, the level of significance is stated. A significance level of 25% ($p < 0.25$) in the above example suggests that there is a 25% probability that the weight change is not due to drug treatment. A 25% probability is a level far too large to reject the $H_0$ with certainty. The level of significance is therefore related to the probability of incorrectly rejecting $H_0$ when it should have been accepted. This level of error is called Type I error. Whenever a decision is made, there is the possibility of making the wrong decision. Four possible decisions for a statistical test may be made (Table A-3). A Type II error is committed when $H_0$ is accepted as being true when it should have been rejected. In contrast, a Type I error is committed when $H_0$ is rejected when it should have been accepted.

The probability of committing a Type I error is defined as the significance level of the statistical test, and is denoted as $p$ or $\alpha$ (alpha). The probability of a Type II error, denoted as $\beta$ (beta), can also be computed.

The power test determines the probability that the statistical test results in the rejection of the null hypothesis if $H_0$ is really false. The larger the power, the more sensitive are the tests. Because power is defined as $1 - \beta$, the larger the $\beta$-error (Type II error), the weaker is the power. The power of the test would equal $1 - \beta$ for a particular power.

To reduce Type I or Type II errors, the sample sizes need to be increased or the assay method improved. Because time, expense, and ethical concerns for performing a study are important issues, the investigator generally tries to keep the sample size (usually the number of subjects in a clinical study) to a minimum. The variability within the samples, number of samples (sample size), and desired level of significance will affect the power of the statistical test. Usually, the greater the variability within the samples, the larger will be the sample size needed to obtain sufficient power.

**TABLE A-3  Decisions Based on a Statistical Test**

<table>
<thead>
<tr>
<th></th>
<th>Accept Null Hypothesis ($H_0$)</th>
<th>Reject Null Hypothesis ($H_0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_0$ true</td>
<td>Correct decision</td>
<td>Type I error</td>
</tr>
<tr>
<td>$H_1$ true</td>
<td>Type II error</td>
<td>Correct decision</td>
</tr>
</tbody>
</table>

**ANALYSIS OF VARIANCE (ONE-WAY)**

When more than two data sets are compared, analysis of variance (ANOVA) is used to determine the probability of the data sets being identical or different among groups. One-way analysis of variance is a method for testing the differences between the population means of $k$ treatment groups, where each group $i (i = 1, 2, \ldots, k)$ consists of $n_i$ observations $X_{ij} (j = 1, 2, \ldots, n_i)$. For example, we may want to test whether there is a difference in the peak plasma level of a drug resulting from the administration of three different dosage forms—solution, capsule, and tablet. If we decide to have three groups of 20 patients per group, $i = 1, 2, 3, j = 1, 2, \ldots, 20$, and the observation
in each group will be $X_{ij}$. The formulas for calculation are as follows:

- **Sum of observation in group**
  \[ \sum_j x_{ij} \]

- **Total sum of squares**
  \[ SS = \sum_i \left( \sum_j x_{ij}^2 \right) - \frac{\left( \sum_i \sum_j x_{ij} \right)^2}{\sum_i n_i} \]

- **Total sum of squares**
  \[ TSS = \sum_i \left( \sum_j x_{ij}^2 \right) - \frac{\left( \sum_i \sum_j x_{ij} \right)^2}{\sum_i n_i} \]

- **Error sum squares (ESS)**
  \[ ESS = SS - TSS \]

The value of the $F$-statistic is

\[ F = \frac{DF_2 \times TSS}{DF_1 \times ESS} = \frac{TSS/DF_1}{ESS/DF_2} \]

Alternatively, $F$ is expressed as the ratio of treatment mean squares (TMS)/error mean squares (EMS):

\[ F = \frac{TSS/DF_1}{ESS/DF_2} = \frac{TMS}{EMS} \]

Error degrees of freedom $DF_1 = k - 1$

Error degrees of freedom $DF_2 = \sum_{j=1}^k n_j - k$

ANOVA is a test for a difference in means between two or more groups. It is very similar to the $t$-test, which tests for a difference between two groups. It is applicable when several groups are involved. An ANOVA on two groups is analogous to a two-sample $t$-test. ANOVA assumes that the groups have equal variances and that the outcome is normally distributed within each group. These assumptions are less important when one has large samples and equal sample sizes for each group (as with the $t$-test). If one rejects the null hypothesis in the ANOVA, one can conclude that the groups are not all equal, but the test does not yield any information on each pair of comparisons.

After completion of the study and statistical analysis of the data, the investigator must decide whether any statistically significant difference in the data groups has clinical relevance. For example, it may be possible to demonstrate that a new antihypertensive agent lowers the systolic blood pressure in patients by 10 mm Hg and that this effect is statistically significant ($p < 0.05$) using the appropriate statistical test. From these results and statistical treatment of the data, the principal investigator must decide whether the study is clinically relevant and whether the drug will be efficacious for its intended use. An example of ANOVA can be found in Chapter 15, Table 15-5.

In clinical tests involving a comparison of a drug to a control, it is important to establish some criteria in advance with the clinicians. What is the size of the difference ($\Delta$) that is considered clinically meaningful? How large should the sample size be in order to have adequate statistical power? If the variance is large, a large sample may be needed. On the other hand, “over-powering” may occur if the study sample size is so large that an extremely small treatment effect could be found statistically significant but not clinically useful. When two similar studies testing the treatment effect of a drug find different results and conclusions, as is sometimes reported in the literature, it is important to look for study flaws and biases. If an estimate is biased, it means that it is not accurately estimating the true value (true mean, true median, true standard deviation, etc). It may be due to a flaw in the study design, conduct, or analysis. Any of these can shift the results in favor of either the new drug or the control. Is the drug tested...
in one of the studies using an old standard of care? A new drug believed by most physicians to be superior can influence the result. Bias includes not blinding the study or having many dropouts, especially if the dropouts are due to the study drug. The consequence of the study bias may lead to a drug that may be found statistically better than the control but not clinically important. Clinical judgment should be used to evaluate the magnitude of the treatment and eliminate over-powering. This is especially important for superiority trials of new drugs. Most clinical trials for regulatory purposes are quality checked or audited to ensure accuracy. On the other hand, the literature or information published, although useful, may not be adequately reviewed or does not always meet statistical design requirements. It is important for the pharmacist to check the source of information and determine whether test methods are validated.

**POWER TEST**

A Type I error may be observed when the result of an ANOVA rejects the null hypothesis when it should have been accepted. The power of a statistical hypothesis test provides a high level of certainty that the correct decision was made—that is, to reject the null hypothesis when it is actually false. The power of a hypothesis test is the probability of not committing a Type II error. It is calculated by subtracting the probability of a Type II error from 1, usually expressed as:

\[
\text{Power} = 1 - P(\text{Type II error}) = 1 - \beta
\]

The values for the power test range from 0 to 1. Ideally, the values for the power test should have a high power or value close to 1. To calculate the power of a given test, it is necessary to specify \(\alpha\) (the probability that the test will lead to the rejection of the hypothesis tested when that hypothesis is true) and to specify a specific alternative hypothesis. Usually, \(\alpha\) is set at 0.05. The power test is influenced by sample size and by intrasubject variability. For drugs whose bioavailability demonstrates high intrasubject variability (>30% CV), a larger number of subjects (larger sample size) is required to obtain a high power (>0.95).

**BIOEQUIVALENCE STUDIES**

Statistics have wide application in bioequivalence studies for the comparison of drug bioavailability for two or more drug products (see Chapter 15). The FDA has published two Guidance for Industry for the statistical determination of bioequivalence (1992, 2001) that describe the comparison between a test (T) and reference (R) drug product. These trials are needed for approval of new or generic drugs. If the drug formulation changes, bioequivalence studies may be needed to compare the new drug formulation to the previous drug formulation. For new drugs, several investigational formulations may be used at various stages, or one formulation with several strengths must show equivalency by extent and rate (e.g., 2 × 250-mg tablet vs 1 × 500-mg tablet, suspension vs capsule, immediate-release vs extended-release product). The blood levels of the drug are measured for both the new and the reference formulation. The derived pharmacokinetic parameters, such as maximum concentration \(C_{\text{max}}\) and area under the curve (AUC), must meet accepted statistical criteria for the two drugs to be considered bioequivalent. In bioequivalence trials, a 90% confidence interval of the ratio of the mean of the new formulation to the mean of the old formulation (Test/Reference) is calculated. That confidence interval needs to be completely within 0.80 to 1.25 for the drugs to be considered bioequivalent. Adequate power should be built into the design and validated methods used for analysis of the samples. Typically, both the rate (reflected by \(C_{\text{max}}\)) and extent (AUC) are tested. The ANOVA may also reveal any sequence effects, period effects, treatment effects, or inter- and intrasubject variability. Because of the small subject population usually employed in bioequivalence studies, the ANOVA uses log-transformed data to make an inference about the difference of the two groups.

**PHARMACOKINETIC MODELS**

In data analysis involving a model, the number of data points should exceed the number of parameters in the model with a sufficient degree of freedom. Otherwise, the model is unconstrained and the parameters estimated are not valid.
REFERENCES


Appendix B: Applications of Computers in Pharmacokinetics

Improvements in the quantitative analysis of drugs in biological tissues, such as plasma, and the increasing sophistication of computers and software along with access to the Internet have greatly accelerated the development of pharmacokinetics. Computer software programs now allow for the rapid solution of complicated pharmacokinetic equations and rapid modeling of pharmacokinetic processes. Computers simplify tedious calculations and allow more time for the development of new approaches to data analysis and pharmacokinetic modeling. In addition, computer software is used for the development of experimental study designs, statistical data treatment, data manipulation, graphical representation of data, pharmacokinetic model simulation, and projection or prediction of drug action. Furthermore, computers are used frequently for written reports, documentation, and archiving.

A variety of computers are now available. Personal computers (PCs) may be used independently or linked together into local networks (LANs) that share many application software packages. Each type of computer has an operating system (OS), which is a collection of programs that allocates resources and enables algorithms (well-defined rules or processes for solving a problem in a finite number of steps) to be processed. Windows, Mac OS, and more recently, LINUX, are examples of commonly used operating systems. Most PC users have access to the Internet via a modem or through wireless that allows PCs to access remote information at various sites on the Internet that provide a variety of free or commercial pharmacokinetic (PK) programs.

A computer package or software is a program of instructions written in a computer language. This software is needed to run the computer. The computer operating system must support the computer language of the software. In the past, computer users needed to be competent in computer programming and usually had knowledge of at least one computer language such as Pascal, C, or Basic. As a result of the availability of various commercial and noncommercial pharmacokinetic applications and spreadsheets, such as Excel, very little computer programming is required for many applications in pharmacokinetics. Some examples are given below.

PHARMACOKINETIC SOFTWARE

Pharmacokinetic software consists of computer programs designed for computation and easy solution of pharmacokinetic problems. Not all computer programs satisfy the user’s full requirements, but many provide the following.

1. **Fitting drug concentration–time data to a series of pharmacokinetic models, and choosing the one that best describes the data statistically:** Typically, a least-squares program is employed, in which the sum of squared differences between observed data points and theoretic prediction is minimized. Usually, a mathematical procedure is used iteratively (repetitively) to achieve a minimum in the sum of squares (convergence). Some data may allow easier convergence with one procedure rather than another. The mathematical method employed should be reviewed before use.

2. **Fitting data into a pharmacokinetic or pharmacodynamic model defined by the user:** This method is by far the most useful, because any list of prepared models is often limited. The flexibility of user-defined models allows continuous refinement of the model as new experimental
information becomes available. Some software merely provides a utility program for fitting the data to a series of polynomials. This utility program provides a simple, quantitative way of relating the variables, but offers little insight into the underlying pharmacokinetic processes.

3. Simulation: Some software programs generate data based on a model with parameter input by the user. When the parameters are varied, new data are generated based on the model chosen. The user is able to observe how the simulated model data matches the experimental observed data. Because pharmacokinetic processes are conveniently described by systems of differential equations, the simulation process involves a numerical solution of the equation with predefined precision.

4. Experimental design: To estimate the parameters of any model, the experimental design of the study must have points appropriately spaced to allow curve description and modeling. Although statisticians stress the need for proper experimental design, little information is generally available for experimental design in pharmacokinetics when a study is performed for the first time. For the first pharmacokinetic study, an empirical or a statistical experiment design is necessarily based on assumptions that may later prove to be wrong.

5. Clinical pharmacokinetic applications: Some software programs are available for the clinical monitoring of narrow-therapeutic-index drugs (ie, critical-dose drugs) such as the aminoglycosides, other antibiotics, theophylline, or antiarrhythmics. These programs may include calculations for creatinine clearance using the Cockcroft–Gault equation (see Chapter 21), dosage estimation, pharmacokinetic parameter estimation for the individual patient, and pharmacokinetic simulations.

6. Computer programs for teaching: Software applications for teaching have been reviewed by Charles and Duffull (2001). These authors taught a course in which students used downloaded free ware. Pharmacalc and PharmaSim may be used for pharmacokinetic computations. SAAM II or Stella and ModelMaker may be used for “system dynamics.” The latter takes into account stochastic processes in the simulation and may be more suitable when variability is considered to be an important factor in a clinical situation. Other software reviewed includes ADAPT for use in parameter estimation, simulation, and experimental (sample schedule) design.

VALIDATION OF SOFTWARE PACKAGES

Software used for data analysis such as statistical and pharmacokinetic calculations should be validated with respect to the accuracy, quality, integrity, and security of the data. One approach for determining the accuracy of the data analysis is to compare the results obtained from two different software packages using the same set of data (Heatherington et al, 1998). Because software packages may have different functionalities, different results (eg, pharmacokinetic parameter estimates) may be obtained.

PHARMACOKINETIC SOFTWARE

Various pharmacokinetic programs (software) are available on the Internet. These programs may not have been validated by the programmer. Thus, the user is responsible for validating the program. Other programs are available from commercial suppliers. Dr. David Bourne of the University of Oklahoma has compiled a listing of pharmacokinetic programs, general references in pharmacokinetics, pharmaco-dynamics, and other information, available at www.boomer.org. The website www.cpb.uokhsc.edu/pkin/soft.html lists numerous pharmacokinetic software packages with user comments. Students should consult the site for updated information.

Popular Programs

Some popular commercially available computer software programs are listed below. Other PK programs are available. The listing of these software packages is not an endorsement by the authors. The descriptions may not represent the latest versions.
New features are often added or old features improved. The user should contact the program vendor directly for more information.

**WinNonlin**

WinNonlin (www.pharsight.com) is a powerful least-squares program for parameter estimation. Both a user-defined model and a library of over 20 compartmental models are available. The program accepts both differential and regular (analytical) equations. Users may select the Hartley-modified or Levenberg-type Gauss–Newton algorithm or the (Nelder and Mead) simplex algorithm for minimizing the sum of squared residuals. Some training is needed. Until its commercial release, Nonlin was installed mostly on mainframe computers. WinNonlin includes additional features and was designed to run on PCs. PCGRAPH (Version 4) was bundled to improve the quality of the plots from previous versions of Nonlin. Compartmental models, curve fitting, and simulations are specially designed for pharmacokinetics.

WinNonlin is Windows-based software for pharmacokinetic, pharmacodynamic, and noncompartmental analysis. It is designed for easy interfacing and secure data management with PkS Suite. WinNonlin can calculate individual bioequivalences for all of the common replicated crossover designs. WinNonMix is associated software for population pharmacokinetic analysis. WinNonlin has an improved user interface that makes it easier to use and to interface with other Windows applications. WinNonlin is relatively easy to use for modeling or noncompartmental analysis of data files and handles large numbers of subjects or profiles. WinNonlin’s input and output data may be managed via Excel (Microsoft)-compatible spreadsheet files. The Noncompartmental Analysis module computes derived pharmacokinetic parameters ($\text{AUC}_0\rightarrow\tau$, $\text{AUC}_0\rightarrow\infty$, $C_{\text{max}}$, cumulative excretion, etc). PCNonlin’s extensive library of models for nonlinear regression and parameter estimation are included in this software. Standard descriptive statistics and confidence intervals are determined from datasets.

**SAS**

SAS (www.sas.com) is an all-purpose data analysis system with a flexible application-development language. SAS Graph allows for multidimension plots, for bar, pie, and contour charts, and for all sorts of other graphs. Over 5000 SAS products are reported to be available. Various “procs” (subroutines) are available for statistics as well as general linear and nonlinear regression models. There are over 80 procedures for univariate descriptive statistics; $t$-test, chi-square, correlation, autoregression, multidimensional scaling, nonparametric test, factor analysis, and discriminant and stepwise analysis. SAS runs in many user environments, including PCSAS for personal computers. A special startup interface, ASSIST, facilitates beginners who are unfamiliar with the default batch data entry.


**The R Foundation for Statistical Computing**

R (www.r-project.org/foundation/) is a language and environment for statistical computing and graphics. R provides a wide variety of statistical (linear and nonlinear modeling, classical statistical tests, time-series analysis, classification, clustering, etc.) and graphical techniques for data handling and model analysis. It originated in Bell Laboratories and is now maintained as a nonprofit software by a private foundation. It is highly applicable to PK applications. The S language is often the vehicle of choice for research in statistical methodology, and R provides an open source route to participation in that activity.

**Scientist**

Scientist® (www.micromath.com) is specifically designed to fit model equations to experimental data. Other programs focus on technical graphics, symbolic manipulation, matrix operations, or worksheets for engineering calculations. Scientist is a general mathematical modeling application that can perform nonlinear least-squares minimization and simulation.
Models can consist of both analytic and differential equations. The software has many functions with pharmacokinetic applications. Scientist is menu-driven and very suitable for student use; it fits data to models, mono-, bi-, and tri-exponentials based on model selection criteria (Akaike Information Criteria). A good statistics menu is available for AUC, $C_{\text{max}}$, $t_{\text{max}}$, and mean residence time. The program gives initial parameter estimates and final parameters after iteration. However, the program does not handle differential equations or user-defined models. Plot outputs are available, as are pharmacokinetic curve stripping, and least-squares parameter optimization. The original software was written for PC DOS but has now been replaced by a Windows version with additional features.

The Scientist Pharmacokinetic Library is a set of pharmacokinetic models that can be used to simulate analyze pharmacokinetic data. The Pharmacokinetic Library includes one- and two-compartment models expressed as mono-, bi-, and tri-exponential equations. The models include bolus input, constant rate IV input, first-order or Michaelis–Menten output, and both single- and multiple-dose models.

PKAnalyst® for Windows is designed to simulate and perform parameter estimation for pharmacokinetic models. Built-in models can calculate micro rate constants for compartmental models, analyze saturable (Michaelis–Menten) kinetics, handle bolus and zero-/first-order input for finite and infinite time periods, and produce concentration/effect Sigmoid-Emax diagrams, including, parameter estimation and statistical data analysis.

Kinetics

Kineticawww.adeptnordic.com/products/lab/kinetica/) provides noncompartmental analysis to population pharmacokinetic–pharmacodynamic analyses. It offers fast high-throughput data analysis for clinical, preclinical, discovery, drug metabolism, and drug delivery settings.

NONMEM

NONMEM (Nonlinear Mixed Effects Model), developed by S. L. Beal and L. B. Sheiner, is a statistical program used for fitting parameters in population pharmacokinetics. The NONMEM program first appeared in 1979. It is useful in evaluating relationships between pharmacokinetic parameters and demographic data such as age, weight, and disease state. Average population parameters and intersubject variance are estimated. The program fits the data of all the subjects simultaneously and estimates the parameters and their variances. The parameters are useful in estimating doses for individuals based on population pharmacokinetics with calculated risks. A regression program is written in ANSI (American National Standards Institute) Fortran 77 for mainframe computers.

The NONMEM program itself is a general (noninteractive) regression program which can be used to fit many different types of data. PREDPP consists of subroutines that can be used by NONMEM to compute predictions for population pharmacokinetics. NM-TRAN is a preprocessor, allowing control and other needed inputs and error messages to NONMEM/PREDPP.

PK Solutions

PK Solutions (www.summitpk.com/pksolutions/pksolutions.htm) is an automated Excel-based program that does single- and multiple-dose pharmacokinetic data analysis of concentration–time data from biological samples (blood, serum, plasma, lymph, etc) following intravenous or extravascular routes of administration. The program provides comprehensive tables of the most widely used and published pharmacokinetic parameters with the ease of a few mouse clicks. PK Solutions calculates results using noncompartmental (area) and compartmental (exponential terms) methods without presuming any specific compartmental model. Multiple-dose and steady-state parameters are automatically projected from single-dose results.

GastroPLUS

GastroPlus® (www.simulations-plus.com) is a computer simulation program that predicts the rate and extent of drug absorption from the gastrointestinal tract. The program simulates the absorption, pharmacokinetics, and pharmacodynamics for drugs in human and preclinical species. The underlying model
Applications of Computers in Pharmacokinetics

is the Advanced Compartmental Absorption and Transit (ACAT) model. Features include a variety of dosage forms: intravenous (bolus or infusion), immediate release (tablet, capsule, suspension, solution, lingual spray, and sublingual tablet) and controlled release (gastric retention, dispersed release, integral tablet, enteric-coated tablet and capsule, and buccal patch), and in vitro–in vivo correlation for immediate- or controlled-release formulations.

Other Pharmacokinetic Programs

There are a variety of software programs on the Internet including instructional programs, drug–drug interaction programs, clinical pharmacokinetic programs for specific drugs and disease states, etc. The user must decide whether the particular software program has been validated when deciding to accept the results of the program.

ELECTRONIC SPREADSHEETS

For general computation, many programs, such as electronic spreadsheets, are very adaptable to calculation and pharmacokinetic curve plotting. Electronic spreadsheets software programs such as Microsoft Excel are easy to use. Data are entered in columns (referred to alphabetically as A, B, C, ...) and rows (referred to numerically as 1, 2, 3, ...). Data are generally displayed on screen and can be selected by moving the arrow keys followed by pressing the Return or Enter key. An example of a Microsoft Excel worksheet to generate time–concentration data after n doses of a drug given orally according to a one-compartment model is given in Fig. B-1. The parameter inputs are in column B, time is in column D, and concentration is in column E.

EXAMPLE 1

From a series of time–concentration data (Fig. B-2, rows A and B), determine the elimination rate constant using the regression feature of MS Excel.

**Solution**

a. Type in the time and concentration data shown in columns A and B (see Fig. B-2).

b. Convert in column C all concentration data to ln concentration. Data point #1 may be omitted because ln of zero cannot be determined.

c. From the main menu, select Insert:
   Select function
   SLOPE
   Y data range (select last 4 value)
   X data range (select last 4 value)
   The slope, given in Fig. B-2 is –0.1. In this case, the ln concentration is plotted versus time, and the slope is simply the elimination rate constant.
   **Note:** To check this result, students may be interested in simulating the data with dose = 10,000 µg/kg, V_D = 1000 mL/kg, k_a = 0.8 h⁻¹, and k_e = 0.1 h⁻¹.

EXAMPLE 2

Generate some data for a two-compartment model using two differential equations. Initial conditions are dose = 1, V = 1, and k_{12} = 0, k_{21} = 1, and k = 3.

**Solution**

The data may be generated with MathCAD (Fig. B-3). Note that k_{12} is abbreviated as k_1, k_{21} is abbreviated as k_2, and k is abbreviated as k_3 in the program for simplicity. Also, dC_p/dt = F(t, x, y); x = C_p; y = C_t; t = time; and dC_t/dt = G(t, x, y).

Model Fitting

An example of a set of oral plasma data was fitted to a one-compartment model by RSTRIP (Fig. B-4). The software makes an initial estimate as well as a final parameter after several iterations. An example of some oral plasma data was generated with PCNonlin (Figs. B-5A, B, C).

EXAMPLE 3

After a drug is administered orally, a series of plasma drug concentration–time data may be fitted to a one-compartment model, to estimate the
Appendix B

FIGURE B-1 Example of a Microsoft Excel spreadsheet used to calculate time–concentration data according to an oral one-compartment model after \( n \) doses.

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FIGURE B-2 A sample spreadsheet showing a set of time–concentration data being analyzed to obtain the slope or the elimination constant. Note: Only four points from the terminal part of the curve were regressed [\( t \) versus \( \ln (\text{conc}) \)].
Applications of Computers in Pharmacokinetics

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SOLVING A SYSTEM OF DIFFERENTIAL EQUATIONS

k_1 = 0.2 \quad k_2 = 1 \quad k_3 = 3

\kappa \text{ and } \gamma \text{ are functions of the time variable } t, \text{ and } F \text{ and } G \text{ are the derivatives } dx/dt \text{ and } dy/dt.

\begin{align*}
F(t,x,y) &= k_2 \cdot \gamma - [k_3 + k_1] \\
G(t,x,y) &= k_1 \cdot x - k_2 \cdot \gamma
\end{align*}

\begin{align*}
\text{start} &= 0 \\
\text{endt} &= 4 \\
\text{n} &= 100 \\
\text{interval} &= \text{inlx} = 1 \\
\text{inly} &= 0
\end{align*}

**FIGURE B-3** A sample of the MathCAD application program used to solve the two-differential equation for a two-compartment model after IV bolus dose. (The first 10 data points are shown.)

**FIGURE B-4** Sample output from RSTRIP pharmacokinetic software showing a good fit of the theoretical data to actual data (columns 2 and 3). The parameters estimated are given in the top right-hand corner.
LISTING OF INPUT COMMANDS

MODEL 3, 'ONE'

MODEL 3

REMARK ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT

REMA

REMA NO. PARAMETER CONSTANT SECONDARY PARM.

REMA

REMA 1 VOLUME DOSE AUC

REMA 2 K01 K01 HALF LIFE

REMA 3 K10 K10 HALF LIFE

REMA 4 TMAX

REMA 5 CMAX

REMA

COMM

NFARM 3

NCON 1

MSEC 5

PNAME 'VOLUME', 'K01', 'K10'

PNAME'S 'AUC', 'K01-HL', 'K10-HL', 'TMAX', 'CMAX'

END

TEMP

Z=CON(1)

Y=P(1)

K01=P(2)

K10=P(3)

T=X

END

FUNC1

COE=D*K01/(V*(K01-K10))

P=COEF*(DEXP(-K10*T)-DEXP(-K01*T))

END

SECO

S(1)=D/V/K10

S(2)=DEXP(.5)/K01

S(3)=DEXP(.5)/K10

TMAX=(DEXP(K01/K10)/(K01-K10))

S(4)=TMAX

S(5)=D/V*DEXP(-K10*TMAX)

END

SCM

CONS 250

INIT 100.7, 1.03, .13

NOBS 9

DATA

BEGIN

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS VOLUME K01 K10

0 1.34180 100.7 1.03 0 .1300

1 .13681 100.7 .5689 .1706

2 .359976E-01 100.7 .4396 .1788

3 .357194E-01 100.7 .4439 .1795

4 .357049E-01 100.7 .4442 .1791

5 .356635E-01 99.63 .4392 .1816

6 .356553E-01 99.63 .4383 .1815

TAU = .1900E-04 RANK = 3 COND = 2481.

CONVERGENCE ACHIEVED

RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN .000100

6 .356553E-01 99.57 .4377 .1817

FIGURE B-5A Sample output from PCNONLIN showing data fitted to Model 3, a one-compartment model with first-order absorption and first-order elimination.
Applications of Computers in Pharmacokinetics

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*** SUMMARY OF NONLINEAR ESTIMATION ***

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CORRECTED SUM OF SQUARED OBSERVATIONS = 1.28889
SUM OF SQUARED RESIDUALS = 1.28889
SUM OF WEIGHTED SQUARED RESIDUALS = .35623E-01
S = .770857E-01 WITH 6 DEGREES OF FREEDOM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ESTIMATE</th>
<th>STANDARD ERROR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>13.814898</td>
<td>.847009</td>
</tr>
<tr>
<td>K01-HL</td>
<td>1.583474</td>
<td>.425680</td>
</tr>
<tr>
<td>K10-HL</td>
<td>3.813757</td>
<td>.917038</td>
</tr>
<tr>
<td>TMAX</td>
<td>3.437115</td>
<td>.217994</td>
</tr>
<tr>
<td>CMAX</td>
<td>1.345203</td>
<td>.040455</td>
</tr>
</tbody>
</table>

FIGURE B-5B  Sample output from PCNONLIN.
absorption rate constant, elimination rate constant, and volume of distribution. Other pharmacokinetic parameters of interest may also be calculated using the NONLIN program, as shown in Fig. B-5. Three parameters were estimated—\( V \), \( k_{01} \), and \( k_{10} \)—representing volume of distribution, \( k_a \), and \( k \) (see model). Initial estimates were derived from either curve stripping or feathering. Dose is \( \text{CON (1)} \). In this case, \( \text{NOBS} = 9 \), showing that there are 9 data points. There is only one function that describes the model \( \text{FUNC 1} \). \( S(1) \) represents the calculation of \( \text{AUC} \), \( S(2) \) the calculation of absorption, and \( S(3) \) the calculation of elimination half-life.

**REFERENCES**


**BIBLIOGRAPHY**


APPENDIX C: Solutions to Frequently Asked Questions (FAQs) and Learning Questions

Frequently Asked Questions, FAQs, are commonly asked questions to stimulate discussion and understanding of particular topics. Only a few of the FAQs at the ends of the chapters of this textbook are answered here. In some cases, an FAQ may have several answers that discuss the topic from different viewpoints. Thus, the answer provided in each chapter may be only one of several possible approaches. The use of questions and answers that broadly discuss a topic is a useful teaching tool that provides an integrated approach to learning through active class participation.

CHAPTER 1

Frequently Asked Questions

Why are drug concentrations more often measured in plasma rather than whole blood or serum?

• Blood is composed of plasma and red blood cells (RBCs). Serum is the fluid obtained from blood after it is allowed to clot. Serum and plasma do not contain identical proteins. RBCs may be considered a cellular component of the body in which the drug concentration in the serum or plasma is in equilibrium, in the same way as with the other tissues in the body. Whole blood samples are generally harder to process and assay than serum or plasma samples. Plasma may be considered a liquid tissue compartment in which the drug in the plasma fluid equilibrates with drug in the tissues and cellular components.

At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?

• The exact site of drug action is generally unknown for most drugs. The time needed for the drug to reach the site of action, produce a pharmacodynamic effect, and reach equilibrium are deduced from studies on the relationship of the time course for the drug concentration and the pharmacodynamic effect. Often, the drug concentration is sampled during the elimination phase after the drug has been distributed and reached equilibrium. For multiple-dose studies, both the peak and trough drug concentrations are frequently taken.

Learning Questions

1. The plasma drug level–time curve describes the pharmacokinetics of the systemically absorbed drug. Once a suitable pharmacokinetic model is obtained, plasma drug concentrations may be predicted following various dosage regimens such as single oral and IV bolus doses, multiple-dose
regimens, IV infusion, etc. If the pharmacokinetics of the drug relates to its pharmacodynamic activity (or any adverse drug response or toxicity), then a drug regimen based on the drug’s pharmacokinetics may be designed to provide optimum drug efficacy. In lieu of a direct pharmacokinetic—pharmacodynamic relationship, the drug’s pharmacokinetics describes the bioavailability of the drug including inter- and intrasubject variability; this information allows for the development of drug products that consistently deliver the drug in a predictable manner.

2. The purpose of pharmacokinetic models is to relate the time course of the drug in the body to its pharmacodynamic and/or toxic effects. The pharmacokinetic model also provides a basis for drug product design, the design of dosage regimens, and a better understanding of the action of the body on the drug.

3. (Figure C-1)

4. a. Nine parameters: $V_1, V_2, V_3, k_{12}, k_{21}, k_e, k_m, k_u$
   
   b. Compartment 1 and compartment 3 may be sampled.
   
   c. $k = k_b + k_m + k_e$
   
   d. $\frac{dC_1}{dt} = k_{21}C_2 - (k_{12} + k_m + k_e + k_b)C_1$

6. **Table 1**

<table>
<thead>
<tr>
<th>Compartment 1</th>
<th>Compartment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_1$</td>
<td>$C_2$</td>
</tr>
</tbody>
</table>

a. $C_1$ and $C_2$ are the total drug concentration in each compartment, respectively. $C_1 > C_2$ may occur if the drug concentrates in compartment 1 due to protein binding (compartment 1 contains a high amount of protein or special protein binding), due to partitioning (compartment 1 has a high lipid content and the drug is poorly water soluble), if the pH is different in each compartment and the drug is a weak electrolyte (the drug may be more ionized in compartment 1), or if there is an active transport mechanism for the drug to be taken up into the cell (eg, purine drug). Other explanations for $C_1 > C_2$ may be possible.

b. Several different experimental conditions are needed to prove which of the above hypotheses is the most likely cause for $C_1 > C_2$. These experiments may use in vivo or in vitro methods, including intracellular electrodes to measure pH in vivo, protein-binding studies in vitro, and partitioning of drug in chloroform/water in vitro, among others.

c. In the case of protein binding, the total concentration of drug in each compartment may be different (eg, $C_1 > C_2$) and, at the same time, the free (nonprotein-bound) drug concentration may be equal in each compartment—assuming that the free or unbound drug is easily diffusible. Similarly, if $C_1 > C_2$ is due to differences in pH and the nonionized drug is easily diffusible, then the nonionized drug concentration may be the same in each compartment. The total drug concentrations will be $C_1 = C_2$ when there is similar affinity for the drug and similar conditions in each compartment.

d. The total amount of drug, $A$, in each compartment depends on the volume, $V$, of the compartment and the concentration, $C$, of the drug in the compartment. Since the amount of drug ($A$) = concentration ($C$) times volume ($V$), any condition that causes the product, $C_1V_1 \neq C_2V_2$, will result in $A_1 \neq A_2$. Thus, if $C_1 = C_2$ and $V_1 \neq V_2$, then $A_1 \neq A_2$.

**CHAPTER 2**

**Frequently Asked Questions**

*How do I know my graph is first order when plotted on semilog paper?*
• A semilog plot spaces the data at logarithmic intervals on the y axis and rectangular (evenly spaced) intervals on the x axis. The paper comes in one or more cycles. Two-cycle semilog paper covers two logarithmic intervals (e.g., 1–100). The semilog scale does not start with zero.

I plotted the plasma drug concentration versus time data on semilog paper, and got a slope with an incorrect \( k \). Why?

• A common error in using logs is failing to remember that \( \ln x = 2.3 \log x \). For the slope formula using a semilog plot,

\[
slope = \frac{\log y_2 - \log y_1}{x_2 - x_1} = -\frac{k}{2.3}
\]

\( k = -\text{slope} \times 2.3 \) (Did you forget the 2.3 factor?)

Alternatively, if you determine the slope with natural logs,

\[
slope = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} = -k
\]

\( k = -\text{slope} \) (You should not use the 2.3 factor in this case.)

I performed linear regression on \( t \) versus \( \ln C_p \). How do I determine the \( C_0 \) from the intercept?

• Use the natural antilog of the intercept, or the inverse of ln.

**Learning Questions**

1. a. Zero-order process (Fig. C-2).
   b. Rate constant, \( k_0 \);

   **Method 1**
   Values obtained from the graph (see Fig. C-2):

<table>
<thead>
<tr>
<th>( t ) (min)</th>
<th>( A ) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>80</td>
<td>41</td>
</tr>
</tbody>
</table>

   \(-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{y_2 - y_1}{x_2 - x_1}\)

   \(-k_0 = \frac{41 - 71}{80 - 40} = 0.75 \text{ mg/min}\)

   \( k_0 = 0.81 \text{ mg/min} \)

   Notice that the negative sign shows that the slope is declining.

   **Method 2**
   By extrapolation:

   \( A_0 = 103.5 \text{ at } t = 0; A = 71 \text{ at } t = 40 \text{ min} \)

   \( A = k_0 t + A_0 \)

   \( 71 = -40k_0 + 103.5 \)

   \( k_0 = 0.81 \text{ mg/min} \)

   Notice that the answer differs in accordance with the method used.

c. \( t_{1/2} \)

   For zero-order kinetics, the larger the initial amount of drug \( A_0 \), the longer the \( t_{1/2} \).

   **Method 1**

   \[
t_{1/2} = \frac{0.5A_0}{k_0}
   \]

   \( t_{1/2} = \frac{0.5(103.5)}{0.78} = 66 \text{ min} \)

   **Method 2**

   The zero-order \( t_{1/2} \) may be read directly from the graph (see Fig. C-2):
At \( t = 0 \), \( A_0 = 103.5 \) mg.
At \( t_{1/2} \), \( A = 51.8 \) mg.

Therefore, \( t_{1/2} = 66 \) min.

d. The amount of drug, \( A \), does extrapolate to zero on the \( x \) axis.

e. The equation of the line is

\[
A = -k_0 t + A_0 \\
A = -0.78t + 103.5
\]

2. a. First-order process (Fig. C-3).

b. Rate constant, \( k \):

**Method 1**
Obtain the first-order \( t_{1/2} \) from the semilog graph (see Fig. C-3):

<table>
<thead>
<tr>
<th>( t ) (minute)</th>
<th>( A ) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>53</td>
<td>15</td>
</tr>
</tbody>
</table>

\( t_{1/2} = 23 \) min

\[
k = \frac{0.693}{t_{1/2}} = \frac{0.693}{23} = 0.03 \text{ min}^{-1}
\]

**Method 2**

\[
\text{Slope} = -k = \frac{\log Y_2 - \log Y_1}{X_2 - X_1}
\]

\[
k = \frac{-2.3(\log 15 - \log 30)}{53 - 30} = 0.03 \text{ min}^{-1}
\]

c. \( t_{1/2} = 23 \) min (see Method 1 above).

d. The amount of drug, \( A \), does not extrapolate to zero on the \( x \) axis.

e. The equation of the line is

\[
\log A = -\frac{-kt}{2.3} + \log A_0
\]

\[
\log A = -\frac{0.03t}{2.3} + \log 78
\]

\[
A = 78e^{-0.03t}
\]

On a rectangular plot, the same data show a curve (not plotted).

3. a. Zero-order process (Fig. C-4).

b. \( k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} \)
Values obtained from the graph (see Fig. C-4):

<table>
<thead>
<tr>
<th>$t$ (h)</th>
<th>$C$ ($\mu g/mL$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>80</td>
</tr>
<tr>
<td>4.2</td>
<td>60</td>
</tr>
</tbody>
</table>

It is always best to plot the data. Obtain a regression line (ie, the line of best fit), then use points $C$ and $t$ from that line.

$$-k_0 = \frac{60 - 80}{4.2 - 1.2}$$

$$k_0 = 6.67 \mu g/mL/h$$

c. By extrapolation:
At $t_o$, $C_0 = 87.5 \mu g/mL$.

d. The equation (using a ruler only) is

$$A = -k_0 t + A_0 = -6.67t + 87.5$$

A better fit to the data may be obtained by using a linear regression program. Linear regression programs are available on spreadsheet programs such as excel.

4. Given:

<table>
<thead>
<tr>
<th>$C$ (mg/mL)</th>
<th>$t$ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>30</td>
</tr>
</tbody>
</table>

a. $\log C = -\frac{k t}{2.3} + \log C_0$

$$\log 75 = -\frac{30k}{2.3} + \log 300$$

$$k = 0.046 \text{ days}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.046} = 15 \text{ days}$$

b. Method 1

300 mg/mL = $C_0$ at $t = 0$

75 mg/mL = $C$ at $t = 30$ days

225 mg/mL = difference between initial and final drug concentration

$$k_0 = \frac{225 \text{ mg/mL}}{30 \text{ days}} = 7.5 \text{ mg/mL/d}$$

The time, $t_{1/2}$, for the drug to decompose to one-half $C_0$ (from 300 to 150 mg/mL) is calculated by (assuming zero order)

$$t_{1/2} = \frac{150 \text{ mg/mL}}{7.5 \text{ mg/mL/day}} = 20 \text{ days}$$

Method 2

$$C = -k_0 t + C_0$$

75 = $-30k_0 + 300$

$$k_0 = 7.5 \text{ mg/mL/d}$$

At $t_{1/2}$, $C = 150 \text{ mg/mL}$

150 = $-7.5t_{1/2} + 300$

$$t_{1/2} = 20 \text{ days}$$

Method 3

A $t_{1/2}$ value of 20 days may be obtained directly from the graph by plotting $C$ against $t$ on rectangular coordinates.

5. Assume the original concentration of drug to be 1000 mg/mL.

Method 1

<table>
<thead>
<tr>
<th>$C_0$ (mg/mL)</th>
<th>No. of Half-Lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>500</td>
<td>1</td>
</tr>
<tr>
<td>250</td>
<td>2</td>
</tr>
<tr>
<td>125</td>
<td>3</td>
</tr>
<tr>
<td>62.5</td>
<td>4</td>
</tr>
<tr>
<td>31.3</td>
<td>5</td>
</tr>
</tbody>
</table>

$99.9\%$ of 1000 = 999

Concentration of drug remaining = $0.1\%$ of 1000

1000 – 999 = 1 mg/mL

It takes approximately 10 half-lives to eliminate all but $0.1\%$ of the original concentration of drug.
Immediately after the drug dissolves, the drug degrades at a constant, or zero-order rate. Since concentration is equal to mass divided by volume, it is necessary to calculate the initial drug concentration (at \( t = 0 \)) to determine the original volume in which the drug was dissolved. From the data, calculate the zero-order rate constant, \( k_0 \):

\[
-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{0.45 - 0.3}{2.0 - 0.5} = 0.1 \text{ mg/mL h}
\]

Then calculate the initial drug concentration, \( C_0 \), using the following equation:

\[
C = -k_0 t + C_0
\]

At \( t = 2 \) h,

\[
0.3 = -0.1 \times 2 + C_0
\]

\( C_0 = 0.5 \text{ mg/mL} \)

Alternatively, at \( t = 0.5 \) h,

\[
0.45 = -0.1 \times 0.5 + C_0
\]

\( C_0 = 0.5 \text{ mg/mL} \)

Since the initial mass of drug \( D_0 \) dissolved is 300 mg and the initial drug concentration \( C_0 \) is 0.5 mg/mL, the original volume may be calculated from the following relationship:

\[
C_0 = \frac{D_0}{V}
\]

\[
0.5 \text{ mg/mL} = \frac{300 \text{ mg}}{V(\text{mL})}
\]

\( V = 600 \text{ mL} \)

The volume of the culture tube is not important. In 8 hours (480 minutes), the culture tube is completely full. Because the doubling time for the cells is 2 minutes (ie, one \( t_{1/2} \)), then in 480 minutes less 2 minutes (478 minutes) the culture tube is half full of cells.
10. Data are often reported as the mean ± standard deviation or SD (see Fig. A-2, Appendix A). One SD above and below the mean represents 95% of the population, assuming a normal distribution of the data. In this example,

\[
\text{Mean} + 2\text{SD} = 9.8 \text{ L} + 8.4 \text{ L} = 18.2 \text{ L} \\
\text{Mean} - 2\text{SD} = 9.8 \text{ L} - 8.4 \text{ L} = 1.4 \text{ L}
\]

Thus, 95% of the population would have a volume of distribution approximately ranging from 1.4 to 18.2 L.

11. The answer is A. Each of the equations is in the form of \( y = Ae^{kt} \), where \( k \) is the slope of the line connecting the data points. A positive slope indicates that the direction of the line is slanted upward from left to right, whereas a negative slope indicates that the line slants downward (declines) from left to right. Answer C would have a rising slope.

12. The answer is C. Recall that \( e^{-kt} = \frac{1}{e^{kt}} \), and that, as \( k \) or \( t \) gets larger, the fraction, \( \frac{1}{e^{kt}} \), gets smaller (for both A and B). (Note: You may check the values using your calculator.)

13. The answer is D. You cannot obtain a log from a negative number.

14. The answer is B. Substitute the same value for \( t \) in each example and note your answers.

**CHAPTER 3**

**Frequently Asked Questions**

What is the difference between a rate and a rate constant?

- A rate represents the change in amount or concentration of drug in the body per time unit. For example, a rate equal to –5 mg/h means the amount of drug is decreasing at 5 mg/h. A positive or negative sign indicates that the rate is increasing or decreasing, respectively. Rates may be zero order, first order, or higher orders. For a first-order rate, the rate of change of drug in the body is determined by the product of the elimination rate constant, \( k \), and by the amount of drug remaining in the body, ie, rate = \(-kD_B\), where \( k \) represents “the fraction” of the amount of drug in the body that is eliminated per hour. If \( k = 0.1 \text{ h}^{-1} \) and \( D_B = 10 \text{ mg} \), then the rate = \( 0.1 \text{ h}^{-1} \times 10 \text{ mg} = 1 \text{ mg/h} \). The rate constant in this example shows that one-tenth of the drug is eliminated per hour, whatever amount of drug is present in the body. For a first-order rate, the rate states the absolute amount eliminated per unit time (which changes with the amount of drug in the body), whereas the first-order rate constant, \( k \), gives a constant fraction of drug that is eliminated per unit time (which does not change with the amount of drug in the body).

Why does \( k \) always have the unit 1/time (eg, h\(^{-1}\)), regardless of what concentration unit is plotted?

- The first-order rate constant \( k \) has no concentration or mass units. In the calculation of the slope, \( k \), the unit for mass or concentration is canceled when taking the log of the number:

\[
\text{Slope} = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} = \frac{\ln (y_2/y_1)}{x_2 - x_1}
\]

If a drug is distributed in the one-compartment model, does it mean that there is no drug in the tissue?

- The one-compartment model uses a single homogeneous compartment to represent the fluid and the vascular tissues. This model ignores the heterogeneity of the tissues in the body, so there is no merit in predicting precise tissue drug levels. However, the model provides useful insight into the mass balance of drug distribution in and out of the plasma fluid in the body. If \( V_D \) is larger than the physiologic vascular volume, the conclusion is that there is some drug outside the vascular pool, ie, in the tissues. If \( V_D \) is small, then there is little extravascular tissue drug storage, except perhaps in the lung, liver, kidney, and heart. With some knowledge about the lipophilicity of the drug and an understanding of blood flow and perfusion within the body, a postulation may be made as to which organs are involved in storing the extravascular drug. The concentration of a biopsy sample may support or refute the postulation.
How is clearance related to the volume of distribution and $k$?

• Clearance is the volume of plasma fluid that is cleared of drug per unit time. Clearance may also be derived for the physiologic model as the fraction of drug that is eliminated by an organ as blood flows through it. The former definition is equivalent to $Cl = kV_D$ and is readily adapted to dosing since $V_D$ is the volume of distribution. If the drug is eliminated solely by metabolism in the liver, then $Cl_L = Cl$. $Cl_H$ is usually estimated by the difference between $Cl - Cl_R$. $Cl_H$ is directly estimated by the product of the hepatic blood flow and the extraction ratio.

If we use a physiologic model, are we dealing with actual volumes of blood and tissues? Why do volumes of distribution emerge for drugs that often are greater than the real physical volume?

• Since mass balance (ie, relating dose to plasma drug concentration) is based on volume of distribution rather than blood volume, the compartment model is used in determining dose. Generally, the total blood concentrations of most drugs are not known, since only the plasma or serum concentration is assayed. Some drugs have an RBC/plasma drug ratio much greater than 1, making the application of the physiologic model difficult without knowing the apparent volume of distribution.

**Learning Questions**

1. The $C_p$ decreased from 1.2 to 0.3 $\mu$g/mL in 3 hours.

<table>
<thead>
<tr>
<th>$t$ (h)</th>
<th>$C_p$ (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

$$\log C_p = -\frac{kt}{2.3} + \log C_0^j$$

$$\log 0.3 = -\frac{k(3)}{2.3} + \log 1.2$$

$k = 0.462 \text{ h}^{-1}$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.462}$$

$t_{1/2} = 1.5 \text{ h}$

These data may also be plotted on a semilog graph and $t_{1/2}$ obtained from the graph.

2. Dose (IV bolus) = 6 mg/kg $\times$ 50 kg = 300 mg

a. 

$$V_D = \frac{\text{dose}}{C_p^0} = \frac{300 \text{ mg}}{8.4 \mu \text{g/mL}} = \frac{300 \text{ mg}}{8.4 \text{ mg/L}} = 35.7 \text{ L}$$

(1) Plot the data on semilog graph paper and use two points from the line of best fit.

<table>
<thead>
<tr>
<th>$t$ (h)</th>
<th>$C_p$ (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

(2) 

$t_{1/2}$ (from graph) = 4 h

$$k = \frac{0.693}{4} = 0.173 \text{ h}^{-1}$$

b. 

$C_p^0 = 8.4 \mu \text{g/mL}$  $C_p = 2 \mu \text{g/mL}$  $k = 0.173 \text{ h}^{-1}$

$$\log C_p = -\frac{kt}{2.3} + \log C_0^p$$

$$\log 2 = -\frac{0.173t}{2.3} + \log 8.4$$

$t = 8.29 \text{ h}$

Alternatively, time $t$ may be found from a graph of $C_p$ versus $t$.

c. Time required for 99.9% of the drug to be eliminated:

(1) Approximately 10 $t_{1/2}$

$$t = 10(4) = 40 \text{ h}$$

(2) $C_p^0 = 8.4 \mu \text{g/mL}$

With 0.1% of drug remaining,

$$C_p = 0.001 \times 8.4 \mu \text{g/mL} = 0.0084 \mu \text{g/mL}$$

$k = 0.173 \text{ h}^{-1}$
\[
\log 0.0084 = \frac{-0.173t}{2.3} + \log 8.4
\]

\[t = 39.9\text{ h}\]

d. If the dose is doubled, then \(C^0_p\) will also double. However, the elimination half-life or first-order rate constant will remain the same. Therefore,

\[C^0_p = 16.8\ \mu g/mL \quad C_p = 2\ \mu g/mL \quad k = 0.173\text{ h}^{-1}\]

\[
\log 2 = \frac{0.173t}{2.3} + \log 16.8
\]

\[t = 12.3\text{ h}^{-1}\]

Notice that doubling the dose does not double the duration of activity.

3. \(D_0 = 200\text{ mg}\)

\(V_D = 10\%\) of body weight = 0.1 (80 kg)

\[= 8000\text{ mL} = 8\text{ L}\]

At 6 hours:

\[C_p = 1.5\text{ mg} / 100\text{ mL}\]

\[V_D = \frac{\text{drug in body} (D_b)}{C_p}\]

\[D_b = C_p V_D = \frac{1.5}{100}\text{ mL} (8000\text{ mL}) = 120\text{ mg}\]

\[
\log D_b = -\frac{k t}{2.3} + \log D^0_b
\]

\[\log 120 = -\frac{k(6)}{2.3} + \log 200\]

\[k = 0.085\text{ h}^{-1}\]

\[t_{1/2} = \frac{-0.693}{k} = 0.693 = 8.1\text{ h}\]

4. \(C_p = 78e^{-0.46t}\) (the equation is in the form \(C_p = C^0_pe^{-kt}\))

\[\ln C_p = \ln 78 - 0.46t\]

\[
\log C_p = -\frac{0.46t}{2.3} + \log 78
\]

Thus, \(k = 0.46\text{ h}^{-1}, C^0_p = 78\ \mu g / mL\).

a. \(t_{1/2} = \frac{0.693}{k} = 0.693 = 1.5\text{ h}\)

b. \(V_D = \frac{\text{dose}}{C^0_p} = \frac{300,000\ \mu g}{78\ \mu g/mL} = 3846\text{ mL}\)

Dose = 4 mg/kg × 75 kg = 300 mg

c. (1) \(\log C_p = \frac{0.46(4)}{2.3} + \log 78 = 1.092\)

\[C_p = 12.4\ \mu g/mL\]

(2) \(C_p = 78e^{-0.46(4)} = 78e^{-1.84} = 78 (0.165)\)

\[C_p = 12.9\ \mu g/mL\]

d. At 4 hours:

\[D_b = C_p V_D = 12.4\ \mu g / mL \times 3846\text{ mL}\]

\[= 47.69\text{ mg}\]

e. \(V_D = 3846\text{ mL}\)

Average weight = 75 kg

Percent body wt = (3.846 kg/75 kg) × 100

= 5.1%

The apparent \(V_D\) approximates the plasma volume.

f. \(C_p = 2\ \mu g/mL\)

Find \(t\).

\[\log 2 = -\frac{0.46t}{2.3} + \log 78\]

\[t = -\frac{2.3 (\log 2 - \log 78)}{0.46}\]

\[t = 7.96\text{ h} = 8\text{ h}\]

Alternate Method

\[2 = 78e^{-0.46t}\]

\[\frac{2}{78} = e^{-0.46t}\]
Method 2
The equation for a first-order elimination after IV bolus injection is

$$\log D_B = \frac{-kt}{2.3} + \log D_0$$

where

- $D_B =$ amount of drug remaining in the body
- $D_0 =$ dose = 200 mg
- $k =$ elimination rate constant
  $$k = \frac{0.693}{t_{1/2}} = 0.1155 \text{ h}^{-1}$$
- $t =$ 24 h

$$\log D_B = \frac{-0.1155(24)}{2.3} + \log 200$$

$D_B = 12.47 \text{ mg} = 12.5 \text{ mg}$

$\% \text{ of drug lost} = \frac{200 - 12.5}{200} \times 100 = 93.75\%$

6. For first-order elimination kinetics, one-half of the initial quantity is lost each $t_{1/2}$. The following table may be developed:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Number of $t_{1/2}$</th>
<th>Amount of Drug in Body (mg)</th>
<th>Percent of Drug in Body</th>
<th>Percent of Drug Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>200</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>50</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>25</td>
<td>12.5</td>
<td>87.5</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>12.5</td>
<td>6.25</td>
<td>93.75</td>
</tr>
</tbody>
</table>

Method 1
From the above table the percent of drug remaining in the body after each $t_{1/2}$ is equal to 100% times $(1/2)^n$, where $n$ is the number of half-lives, as shown below:

<table>
<thead>
<tr>
<th>Number of $t_{1/2}$</th>
<th>Percent of Drug in Body</th>
<th>Percent of Drug Remaining in Body after $n \cdot t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>$100 \times 1/2$</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>$100 \times 1/2 \times 1/2$</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>$100 \times 1/2 \times 1/2 \times 1/2$</td>
</tr>
<tr>
<td>$n$</td>
<td>100 $(1/2)^n$</td>
<td></td>
</tr>
</tbody>
</table>

Percent of drug remaining $\frac{100}{2^n}$, where $n =$ number of $t_{1/2}$

Percent of drug excreted $= 100 - \frac{100}{2^n}$

At 24 hours, $n = 4$, since $t_{1/2} = 6$ h.

Percent of drug lost $= 100 - \frac{100}{16} = 93.75\%$

7. The zero-order rate constant for alcohol is 10 mL/h. Since the specific gravity for alcohol is 0.8,

$$0.8 \text{ g/mL} = \frac{x(\text{g})}{10 \text{ mL}}$$

$$x = 8 \text{ g}$$

Therefore, the zero-order rate constant, $k_0$, is 8 g/h.

Drug in body at $t = 0$:

$$D_B^0 = C_P V_D = \frac{210 \text{ mg}}{0.100 \text{ L}} \times (0.60)(75 \text{ L}) = 94.5 \text{ g}$$

Drug in body at time $t$:

$$D_B = C_P V_D = \frac{100 \text{ mg}}{0.100 \text{ L}} \times (0.60)(75 \text{ L}) = 45.0 \text{ g}$$
For a zero-order reaction:

\[ D_B = -k_D t + D_B^0 \]
\[ 45 = -8t + 94.5 \]
\[ t = 6.19 \text{ h} \]

8. a. \[ C_p^0 = \frac{\text{dose}}{V_d} = \frac{500 \text{ mg}}{(0.1 \text{ L/kg})(55 \text{ kg})} = 90.9 \text{ mg/L} \]

b. \[ \log D_B = \frac{-kt}{2.3} + \log D_B^0 \]
\[ \log D_B = \frac{(0.693 / 0.75)(4)}{2.3} + \log 500 \]
\[ D_B = 12.3 \text{ mg} \]

c. \[ \log 0.5 = \frac{-(0.693 / 0.75)t}{2.3} + \log 90.0 \]
\[ t = 5.62 \text{ h} \]

9. \[ \log D_B = \frac{-kt}{2.3} + \log D_B^0 \]
\[ \log 25 = \frac{-k(8)}{2.3} + \log 100 \]
\[ k = 0.173 \text{ h}^{-1} \]
\[ t_{1/2} = \frac{0.693}{0.173} = 4 \text{ h} \]

10. \[ \log D_B = \frac{-kt}{2.3} + \log D_B^0 \]
\[ = \frac{(-0.693 / 8)(24)}{2.3} + \log 600 \]
\[ D_B = 74.9 \text{ mg} \]

Percent drug lost = \( \frac{600 - 74.9}{600} \times 100 \)
\[ = 87.5\% \]

\[ C_p \text{ at } t = 24 \text{ hours:} \]
\[ C_p = \frac{74.9 \text{ mg}}{(0.4 \text{ L/kg})(62 \text{ kg})} = 3.02 \text{ mg/L} \]

11. The total drug concentration in the plasma is not usually equal to the total drug concentration in the tissues. A one-compartment model implies that the drug is rapidly equilibrated in the body (in plasma and tissues). At equilibrium, the drug concentration in the tissues may differ from the drug concentration in the body because of drug protein binding, partitioning of drug into fat, differences in pH in different regions of the body causing a different degree of ionization for a weakly dissociated electrolyte drug, an active tissue uptake process, etc.

12. Set up the following table:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>( D_s ) (mg)</th>
<th>( \frac{dD_s}{dt} ) mg/h</th>
<th>mg/h</th>
<th>( t^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100/4</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>26/4</td>
<td>6.5</td>
<td>6</td>
</tr>
</tbody>
</table>

The elimination half-life may be obtained graphically after plotting mg/h versus \( t^* \). The \( t_{1/2} \) obtained graphically is approximately 2 hours.

\[ \log \frac{dD_B}{dt} = \frac{-kt}{2.3} + \log k D_B^0 \]
\[ \text{Slope} = \frac{-k}{2.3} = \frac{\log Y_2 - \log Y_1}{X_2 - X_1} = \frac{\log 6.5 - \log 25}{6 - 2} \]
\[ k = 0.336 \text{ h}^{-1} \]
\[ t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.336} = 2.06 \text{ h} \]

**CHAPTER 4**

**Frequently Asked Questions**

Are “hypothetical” or “mathematical” compartment models useful in designing dosage regimens in the clinical setting? Does “hypothetical” mean “not real”?
• *Mathematical* and *hypothetical* are indeed vague and uninformative terms. Mathematical equations are developed to calculate how much drug is in the vascular fluid, as well as outside the vascular fluid (ie, extravascular or in the tissue pool). *Hypothetical* refers to an unproven model. The assumptions in the compartmental models simply imply that the model simulates the mass transfer of drug between the circulatory system and the tissue pool. The mass balance of drug moving out of the plasma fluid is described even though we know the tissue pool is not real (the tissue pool represents the virtual tissue mass that receives drug from the blood). While the model is a less-than-perfect representation, we can interpret it, knowing its limitations. All pharmacokinetic models need interpretation. We use a model when there are no simple ways to obtain needed information. As long as we know the model limitations (ie, that the tissue compartment is not the brain or the muscle!) and stay within the bounds of the model, we can extract useful information from it. For example, we may determine the amount of drug that is stored outside the plasma compartment at any desired time point. After an IV bolus drug injection, the drug distributes rapidly throughout the plasma fluid and more slowly into the fluid-filled tissue spaces. Drug distribution is initially rapid and confined to a fixed fluid volume known as the \( V_p \) or the initial volume. As drug distribution expands into other tissue regions, the volume of the penetrated spaces increases, until a critical point (steady state) is obtained when all penetrable tissue regions are equilibrated with the drug. Knowing that there is heterogenous drug distribution within and between tissues, the tissues are grouped into compartments to determine the amount of drugs in them. Mass balance, including drug inside and outside the vascular pool, accounts for all body drug storage \( (D_B = D_t + D_p) \). Assuming steady state, the tissue drug concentration is equal to the plasma drug concentration, \( C_{PSS} \), and one may determine size of the tissue volume using \( D_t/C_{PSS} \). This volume is really a “numerical factor” that is used to describe the relationship of the tissue storage drug relative to the drug in the blood pool. The sum of the two volumes is the steady-state volume of distribution.

The product of the steady-state concentration, \( C_{PSS} \), and the \( (V_D)_{ss} \) yields the amount of drug in the body at steady state. The amount of drug in the body at steady state is considered vital information in dosing drugs clinically. Students should realize that tissue drug concentrations are not predicted by the model. However, plasma drug concentration is fully predictable after any given dose once the parameters become known. Initial pharmacokinetic parameter estimation may be obtained from the literature using comparable age and weight for a specific individual.

*If physiologic models are better than compartment models, why not just use physiologic models?*

• A physiologic model is a detailed representation of drug disposition in the body. The model requires blood flow, extraction ratio, and specific tissue and organ size. This information is not often available for the individual. Thus, the less sophisticated compartment models are used more often.

*Since clearance is the term most often used in clinical pharmacy, why is it necessary to know the other pharmacokinetic parameters?*

• Clearance is used to calculate the steady-state drug concentration and to calculate the maintenance dose. However, clearance alone is not useful in determining the maximum and minimum drug concentrations in a multiple-dosing regimen.

*What is the significance of the apparent volume of distribution?*

• Apparent volumes of distribution are not real tissue volumes, but rather reflect the volume in which the drug is contained. For example,

\[
V_p = \text{initial or plasma volume} \\
V_t = \text{tissue volume} \\
(V_D)_{SS} = \text{steady-state volume of distribution (most often listed in the literature).}
\]

The steady-state drug concentration multiplied by \( (V_D)_{SS} \) yields the amount of drug in the body. \( (V_D)_{B} \) is a volume usually determined from area under the curve (AUC), and differs from \( (V_D)_{SS} \) somewhat in magnitude. \( (V_D)_{B} \) multiplied by \( b \) gives clearance of the drug.
What is the error assumed in a one-compartment model compared to a two-compartment or multi compartment model?

- If the two-compartment model is ignored and the data are treated as a one-compartment model, the estimated values for the pharmacokinetic parameters are distorted. For example, during the distribution phase, the drug declines rapidly according to distribution $\alpha$ half-life, while in the elimination (terminal) part of the curve, the drug declines according to a $\beta$ elimination half-life.

What kind of improvement in terms of patient care or drug therapy is made using the compartment model?

- Compartment models have been used to develop dosage regimens and pharmacodynamic models. Compartment models have improved the dosing of drugs such as digoxin, gentamicin, lidocaine, and many others. The principal use of compartment models in dosing is to simulate a plasma drug concentration profile based on pharmacokinetic (PK) parameters. This information allows comparison of PK parameters in patients with only two or three points to a patient with full profiles using generated PK parameters.

Learning Questions

1. Equation for the curve:

$$C_p = 52e^{-1.39t} + 18e^{-0.135t}$$

$$k = 0.41 \text{ h}^{-1} \quad k_{12} = 0.657 \text{ h}^{-1} \quad k_{21} = 0.458 \text{ h}^{-1}$$

2. Equation for the curve:

$$C_p = 28e^{-0.63t} + 10.5e^{-0.46t} + 14e^{-0.077t}$$

Note: When feathering curves by hand, a minimum of three points should be used to determine the line. Moreover, the rate constants and $y$ intercepts may vary according to the individual’s skill. Therefore, values for $C_p$ should be checked by substitution of various times for $t$, using the derived equation. The theoretical curve should fit the observed data.

3. $C_p = 11.14 \mu g/mL$.

4. The initial decline in the plasma drug concentration is due mainly to uptake of drug into tissues. During the initial distribution of drug, some drug elimination also takes place. After the drug has equilibrated with the tissues, the drug declines at a slower rate because of drug elimination.

5. A third compartment may indicate that the drug has a slow elimination component. If the drug is eliminated by a very slow elimination component, then drug accumulation may occur with multiple drug doses or long IV drug infusions. Depending on the blood sampling, a third compartment may be missed. However, some data may fit both a two- and a three-compartment model. In this case, if the fit for each compartment model is very close statistically, the simpler compartment model should be used.

6. Because of the heterogeneity of the tissues, drug equilibrates into the tissues at different rates and different drug concentrations are usually observed in the different tissues. The drug concentration in the “tissue” compartment represents an “average” drug concentration and does not represent the drug concentration in any specific tissue.

7. $C_p = Ae^{-at} + Be^{-bt}$

After substitution,

$$C_p = 4.62e^{-8.94t} + 0.64e^{-0.19t}$$

a. $V_p = \frac{D_0}{A + B} = \frac{75,000}{4.62 + 0.64} = 14,259 \text{ mL}$

b. $V_t = \frac{V_p k_{12}}{k_{21}} = \frac{(14,259)(6.52)}{(1.25)} = 74,375 \text{ mL}$

c. $k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)}$

$$k_{12} = \frac{(4.62)(0.64)(0.19 - 8.94)^2}{(4.62 + 0.64)(4.62)(0.19) + (0.64)(8.94)}$$

$$k_{12} = 6.52 \text{ h}^{-1}$$
8. The tissue compartments may not be sampled directly to obtain the drug concentration. Theoretical drug concentration, \( C_t \), represents the average concentration in all the tissues outside the central compartment. The amount of drug in the tissue, \( D_t \), represents the total amount of drug outside the central or plasma compartment. Occasionally \( C_t \) may be equal to a particular tissue drug concentration in an organ. However, this \( C_t \) may be equivalent by chance only.

9. The data were analyzed using computer software called RSTRIP, and found to fit a two-compartment model:

\[
A (1) = 2.0049 \quad A (2) = 6.0057
\]

(two preexponential values)

\[
k (1) = 0.15053 \quad k (2) = 7.0217
\]

(two exponential values)

The equation that describes the data is

\[
C_p = 2.0049 e^{-0.15053 t} + 6.0057 e^{-7.0217 t}
\]

The coefficient of correlation = 0.999 (very good fit).

The model selection criterion = 11.27 (good model).

The sum of squared deviations = 9.3 x 10^{-5} (there is little deviation between the observed data and the theoretical value).

\[
\alpha = 7.0217 \text{ h}^{-1}, \quad \beta = 0.15053 \text{ h}^{-1}
\]

10. a. Late-time samples were taken in some patients, yielding data that resulted in a monoexponential elimination profile. It is also possible that a patient’s illness contributes to impaired drug distribution.

b. The range of distribution half-lives is 30 to 45 minutes.

c. None. Tissue concentrations are not generally well predicted from the two-compartment model. Only the amount of drug in the tissue compartment may be predicted.

d. No. At steady state, the rate in and the rate out of the tissues is the same, but the drug concentrations are not necessarily the same. The plasma and each tissue may have different drug binding.

e. None. Only the pooled tissue is simulated by the tissue compartment.

### Frequently Asked Questions

**What is the main reason for giving a drug by slow IV infusion?**

- Slow IV infusion may be used to avoid side effects due to rapid drug administration. For example, intravenous immune globulin (human) may cause a rapid fall in blood pressure and possible anaphylactic shock in some patients when infused rapidly. Some antisense drugs also cause a rapid fall in blood pressure when injected via rapid IV into the body. The rate of infusion is particularly important in administering antiarrhythmic agents in patients. The rapid IV bolus injection of many drugs (eg, lidocaine) that follow the pharmacokinetics of multiple-compartment models may cause an adverse response due to the initial high drug concentration in the central (plasma) compartment before slow equilibration with the tissues.

**Why do we use a loading dose to rapidly achieve therapeutic concentration for a drug with a long elimination half-life instead of increasing the rate of drug infusion or increasing the size of the infusion dose?**

- The loading drug dose is used to rapidly attain the target drug concentration, which is approximately the steady-state drug concentration. However, the loading dose will not maintain the steady-state
level unless an appropriate IV drug infusion rate or maintenance dose is also used. If a larger IV drug infusion rate or maintenance dose is given, the resulting steady-state drug concentration will be much higher and will remain sustained at the higher level. A higher infusion rate may be administered if the initial steady-state drug level is inadequate for the patient.

What are some of the complications involved with IV infusion?

• The common complications associated with intravenous infusion include phlebitis and infections at the infusion site caused by poor intravenous techniques or indwelling catheters.

### Learning Questions

1. **a.** To reach 95% of $C_{SS}$:

$$4.32t_{1/2} = (4.32)(7) = 30.2 \text{ h}$$

**b.** $D_L = C_{SS}V_D$

$$= (10)(0.231)(65,000) = 150 \text{ mg}$$

**c.** $R = C_{SS}V_D k = (10)(15,000)(0.099)$

$$= 14.85 \text{ mg/h}$$

**d.** $Cl_T = V_D \times k = (15,000)(0.099) = 1485 \text{ mL/h}$

**e.** To establish a new $C_{SS}$ will still take 4.32$t_{1/2}$. However, the $t_{1/2}$ will be longer in renal failure.

**f.** If $Cl_T$ is decreased by 50%, then the infusion rate $R$ should be decreased proportionately:

$$R = 10(0.50)(1485) = 7.425 \text{ mg/h}$$

2. **a.** The steady-state level can be found by plotting the IV infusion data. The plasma drug–time curves plateau at 10 $\mu$g/mL. Alternatively, $V_D$ and $k$ can be found from the single IV dose data:

$$V_D = 100 \text{ mL/kg} \quad k = 0.2 \text{ h}^{-1}$$

**b.** Using equations developed in Example 2 in the first set of examples in Chapter 5:

$$0.95 \frac{R}{V_D k} = \frac{R}{V_D k}(1 - e^{-kt})$$

$$0.95 = 1 - e^{-0.2t}$$

$$0.05 = e^{-0.2t}$$

$$t_{95\% ss} = \frac{\ln 0.05}{-0.2} = 15 \text{ h}$$

**c.** $Cl_T = V_D k \quad V_D = \frac{D_L}{C_P}$

$$Cl_T = 100 \times 0.2 \quad V_D = \frac{1000}{10} = 100 \text{ mL/kg}$$

$$Cl_T = 20 \text{ mL/kg h}$$

**d.** The drug level 4 hours after stopping the IV infusion can be found by considering the drug concentration at the termination of infusion as $C_P^0$. At the termination of the infusion, the drug level will decline by a first-order process.

$$C_P = C_P^0 e^{-kt}$$

$$C_P = 9.9e^{-(0.2)(4)}$$

$$C_P = 4.5 \mu g/mL$$

**e.** The infusion rate to produce a $C_{SS}$ of 10 $\mu$g/mL is 0.2 mg/kg/h. Therefore, the infusion rate needed for this patient is

$$0.2 \text{ mg/kg h} \times 75 \text{ kg} = 15 \text{ mg/h}$$

**f.** From the data shown, at 4 hours after the start of the IV infusion, the drug concentration is 5.5 $\mu$g/mL; the drug concentration after an IV bolus of 1 mg/kg is 4.5 $\mu$g/mL. Therefore, if a 1-mg dose is given and the drug is then infused at 0.2 mg/kg/h, the plasma drug concentration will be $4.5 + 5.5 = 10 \mu g/mL$. 
3. Infusion rate $R$ for a 75-kg patient:

\[ R = (1 \text{ mg/kg h})(75 \text{ kg}) = 75 \text{ mg/h} \]

Sterile drug solution contains 25 mg/mL. Therefore, 3 mL contains $(3 \text{ mL}) \times (25 \text{ mg/mL})$, or 75 mg. The patient should receive 3 mL (75 mg)/h by IV infusion.

4. \( C_{SS} = \frac{R}{V D} k = C_{SS} V D k \)

\[ R = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg}) \left( \frac{0.693}{3 \text{ h}} \right) \]

\[ = 173.25 \text{ mg/h} \]

Drug is supplied as 125 mg/mL. Therefore,

\[ 125 \text{ mg/mL} = \frac{173.25 \text{ mg}}{X} \]

\[ X = 1.386 \text{ mL} \]

\[ R = 1.386 \text{ mL/h} \]

\[ D_L = C_{SS} V D = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg}) \]

\[ = 750 \text{ mg} \]

5. \[ C_{SS} = \frac{R}{k V D} = \frac{R}{C_{T}} \]

a. \[ C_{T} = \frac{R}{C_{SS}} = \frac{5.3 \text{ mg/kg h} \times 71.71 \text{ kg}}{17 \text{ mg/L}} \]

\[ = 22.4 \text{ L/h} \]

b. At the end of IV infusion, \( C_p = 17 \mu g/mL \). Assuming first-order elimination kinetics:

\[ C_p = C_p e^{-k t} \]

\[ 1.5 = 17 e^{-k (2.5)} \]

\[ 0.0882 = e^{-2.5 k} \]

In 0.0882 = −2.5 \( k \)

\[ -2.43 = -2.5 \]

\[ k = 0.971 \text{ h}^{-1} \]

\[ t_{1/2} = \frac{0.693}{0.971} = 0.714 \text{ h} \]

c. \[ Cl_T = k V D \quad V D = \frac{Cl_T}{k} \]

\[ V D = \frac{22.4}{0.971} = 23.1 \text{ L} \]

d. Probenecid blocks active tubular secretion of cephradine.

6. At steady state, the rate of elimination should equal the rate of absorption. Therefore, the rate of elimination would be 30 mg/h. The \( C_{SS} \) is directly proportional to the rate of infusion \( R \), as shown by

\[ C_{SS} = \frac{R}{k V D} \quad k V D = \frac{R}{C_{SS}} \]

\[ \frac{R_{old}}{C_{SS,old}} = \frac{R_{new}}{C_{SS, new}} \]

\[ = \frac{30 \text{ mg/h}}{40 \text{ mg/h}} = \frac{20 \mu g/mL}{C_{SS, new}} \]

\[ C_{SS, new} = 26.7 \mu g/mL \]

The new elimination rate will be 40 mg/h.

7. a. \( R = C_{SS} k V D \)

\[ R = (20 \text{ mg/L})(0.693/8 \text{ h})(1.5 \text{ L/kg})(75 \text{ kg}) \]

\[ = 194.9 \text{ mg/h} \]

\[ R = 195 \text{ mg/h/ 15 mg/mL} = 13 \text{ mL/h} \]

b. \( D_L = C_{SS} V D = (20)(1.5)(75) = 2250 \text{ mg} \)

given by IV bolus injection

c. The loading dose is given to obtain steady-state drug concentrations as rapidly as possible.

d. 15 mL of the antibiotic solution contains 225 mg of drug. Thus, an IV infusion rate of 15 mL/h is equivalent to 225 mg/h. The \( C_{SS} \) achieved by the manufacturer’s recommendation is

\[ C_{SS} = \frac{R}{k V D} = \frac{225}{(0.0866)(112.5)} = 23.1 \text{ mg/L} \]
The theoretical $C_{SS}$ of 23.1 mg/L is close to the desired $C_{SS}$ of 20 mg/L. Assuming a reasonable therapeutic window, the manufacturer’s suggested starting infusion rate is satisfactory.

**CHAPTER 6**

**Frequently Asked Questions**

**What’s the difference between clearance and the rate of drug elimination?**

- Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process. Drug clearance (body clearance, total body clearance, or $Cl_r$) considers the entire body as a single drug-eliminating system from which many unidentified elimination processes may occur. The drug elimination rate is defined as the amount of drug removed per time unit (eg, mg/min). Since drug elimination is generally first order, the drug elimination rate is not a constant and depends upon the amount of drug remaining in the body. In contrast, for first-order drug elimination clearance is a constant and is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time.

**What is the difference between drug clearance and creatinine clearance?**

- With most drugs, total body clearance (often termed “clearance”) is the sum of renal and nonrenal clearances. Creatinine is an endogenous marker that accumulates in the blood when renal function is impaired. Creatinine is excreted by glomerular filtration and is not reabsorbed. Creatinine clearance is a measure of glomerular filtration rate. Renal clearance is therefore proportional to creatinine clearance but not equal to it, since most drugs are reabsorbed to some extent, and some drugs are actively secreted.

**What is an independent parameter in a model? Is clearance an independent parameter of the physiologic model? How is clearance related to parameters in the compartment model?**

- A parameter is a model-based numerical constant estimated statistically from the data. Model parameters are used generally to make predictions about the behavior of the real process. A parameter is termed independent if the parameter is not dependent on other parameters of the model. In the classical one-compartment model, $k$ and $V_D$ are independent model parameters, and $t_{1/2}$ and $Cl$ are regarded as derived parameters. In the physiologic model, $Cl$ and $V_D$ are regarded as independent model parameters, while $k$ is a dependent parameter since $k$ depends on $Cl/V_D$. In practice, both $Cl$ and $k$ are dependent on various physiologic factors, such as blood flow, drug metabolism, renal secretion, and drug reabsorption. Most biologic events are the result of many events that are described more aptly as mutually interacting rather than acting independently. Thus, the underlying elimination process may be adequately described as fraction of drug removed per minute ($k$) or as volume of fluid removed per minute ($Cl$).

**Learning Questions**

3. a. $Cl_T = V_D k = V_D \frac{0.693}{t_{1/2}}$

   Average $Cl_T = \frac{(30)(0.693)}{3.4} = 6.11 \text{ L/h}$

   Upper $Cl_T$ limit $= \frac{(30)(0.693)}{1.8} = 11.55 \text{ L/h}$

   Lower $Cl_T$ limit $= \frac{(30)(0.693)}{6.8} = 3.06 \text{ L/h}$

b. $Cl_r = k \frac{V_D}{0.36} = 0.36 \text{ L/h}$

   $k_e = \frac{0.36}{30} = 0.012 \text{ h}^{-1}$

   $Cl_{nr} = Cl_T - Cl_r$

   $Cl_{nr} = 6.11 - 0.36 = 5.75 \text{ L/h}$

   $Cl_{nr} = k_m V_D$

   $k_m = \frac{5.75}{30} = 0.192 \text{ h}^{-1}$
4. a. Apparent $V_D = (0.21) (78,000 \text{ mL})$

\[ = 16,380 \text{ mL} \]

\[ C_{\text{T}} = k V_D \]

\[ C_{\text{T}} = \left( \frac{0.693}{2} \right) (16,380) \]

\[ C_{\text{T}} = 5676 \text{ mL/h} = 94.6 \text{ mL/min} \]

b. $k_c = 70\%$ of the elimination constant

\[ k_c = (0.7) \left( \frac{0.693}{2} \right) = 0.243 \text{ h}^{-1} \]

\[ C_{\text{h}} = k_c V_D \]

\[ C_{\text{h}} = (0.243) (16,380) = 3980 \text{ mL/h} \]

\[ = 66.3 \text{ mL/min} \]

c. Normal GFR = creatinine clearance = 122 mL/min

\[ Cl_R \text{ of drug} = 66.3 \text{ mL} \]

Because the $Cl_R$ of the drug is less than the creatinine clearance, the drug is filtered at the glomerulus and is partially reabsorbed.

5. a. During intravenous infusion, the drug levels will reach more than 99% of the plasma steady-state concentration after seven half-lives of the drug.

\[ Cl_{\text{T}} = \frac{R}{C_{\text{ss}}} \]

\[ = \frac{300,000}{11} \mu g/\text{h} = 27,272 \text{ mL/h} \]

b. $Cl_{\text{T}} = k V_D$

\[ V_D = \frac{27,272}{0.693} = 39,354 \text{ mL} \]

c. Since $k_m = 0 \quad k_c = k$

\[ Cl_{\text{T}} = Cl_R = 27,272 \text{ mL/h} \]

b. $Cl_{\text{kv}} = 70\%$ of the elimination constant

\[ k_e = \frac{0.693}{2} = 0.243 \text{ h}^{-1} \]

\[ Cl_{\text{h}} = k_e V_D \]

\[ Cl_{\text{h}} = (0.243) (16,380) = 3980 \text{ mL/h} \]

\[ = 66.3 \text{ mL/min} \]

c. Since $k_m = 0 \quad k_c = k$

\[ Cl_{\text{T}} = Cl_R = 27,272 \text{ mL/h} \]

d. $Cl_{\text{R}} = 27,272 \text{ mL/h} = 454 \text{ mL/min}$

Normal GFR is 100 to 130 mL/min. The drug is probably filtered and actively secreted in the kidney.

6. $Cl_R = \frac{\text{excretion rate}}{C_p} = \frac{200 \text{ mg/2 h}}{2.5 \text{ mg/100 mL}}$

\[ Cl_R = 4000 \text{ mL/h} \]

7. $Cl_{\text{T}} = \frac{R}{C_{\text{ss}}}$

\[ Cl_{\text{T}} = \frac{5.3 \text{ mg/kg h}}{17 \text{ mg/L}} = 0.312 \text{ L/kg h} \]

For a 71.7-kg adult,

\[ Cl_T = (0.312 \text{ L/kg h}) (71.7 \text{ kg}) = 22.4 \text{ L/h} \]

11. From the data, determine urinary rate of drug excretion per time period by multiplying urinary volume by the urinary concentration for each point. Average $C_p$ for each period by taking the mean of two consecutive points (see Table). Plot $dD/dt$ versus $C_p$ to determine renal clearance from slope. The renal clearance from slope is 1493.4 mL/h (Fig. C-5).
To determine the total body clearance by the area method, the area under the plasma concentration curve \([AUC]\) must be calculated and summed. The tailpiece is extrapolated because the data are not taken to the end. A plot of \(\log C_p\) versus \(t\) (Fig. C-6) yields a slope of \(k = 0.23\) h\(^{-1}\). The tailpiece of area is extrapolated using the last data point divided by \(k\) or \(31.55/0.23 = 137.17\) μg/mL/h.

### Table C-6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma Concentration (μg/mL)</th>
<th>Urinary Volume (mL)</th>
<th>Urinary Concentration (μg/mL)</th>
<th>Urinary Rate, (dD_u/dt) (μg/h)</th>
<th>Average (C_p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>250.00</td>
<td>100.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>198.63</td>
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<td>2680.00</td>
<td>334,999.56</td>
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<td>1901.20</td>
<td>266,168.41</td>
<td>178.23</td>
</tr>
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<td>100.00</td>
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<td>141.61</td>
</tr>
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<td>80.00</td>
<td>2100.35</td>
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<td>112.51</td>
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<td>250.00</td>
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<td>170.00</td>
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<td>160.00</td>
<td>526.74</td>
<td>84,278.70</td>
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<td>31.55</td>
<td>400.00</td>
<td>133.01</td>
<td>53,203.77</td>
<td>35.63</td>
</tr>
</tbody>
</table>

Subtotal area (0–9 h) 953.97
Tailpiece (9–∞ h) 137.17
Total area (0–∞) 1091.14

Total clearance = \(C_l = \frac{FD_u}{[AUC]_0} = \frac{2,500,000}{1091.14} = 2,291.2\) mL/h

Because total body clearance is much larger than renal clearance, the drug is probably also excreted by a nonrenal route.

Nonrenal clearance = 2291.2 – 1493.4 = 797.8 mL/h

The easiest way to determine clearance by a compartmental approach is to estimate \(k\) and \(V_D\) from the graph. \(V_D\) is 10 L and \(k\) is 0.23 h\(^{-1}\). Total clearance is 2300 mL/min (a slightly different value when compared with the area method).

### Chapter 7

**Frequently Asked Questions**

*If drug absorption is simulated using the oral one-compartment model, would a larger absorption rate constant result in a greater amount of drug absorbed?*
The fraction of drug absorbed, $F$, and the absorption rate constant, $k_a$, are independent parameters. A drug in an oral solution may have a more rapid rate of absorption compared to a solid drug product. If the drug is released from the drug product slowly or is formulated so that the drug is absorbed slowly, the drug may be subjected to first-pass effects, degraded in the gastrointestinal tract, or eliminated in the feces so that less drug (smaller $F$) may be absorbed systemically compared to the same drug formulated to be absorbed more rapidly from the drug product.

**How do you explain that $k_a$ is often greater than $k$ with most drugs?**

- A drug with a rate of absorption slower than its rate of elimination will not be able to obtain optimal systemic drug concentrations to achieve efficacy. Such drugs are generally not developed into products. However, the aprtment $k_a$ for drugs absorbed from controlled release products (Chapter 17) may be smaller, but the initial rate of absorption from the GI tract is faster than the rate of drug elimination since $-K_{D_{GI}}$.

**What is the absorption half-life of a drug and how is it determined?**

- For drugs absorbed by a first-order process, the absorption half-life is $0.693/k_a$. Although drug absorption involves many stochastic (system-based random) steps, the overall rate process is often approximated by a first-order process, especially with oral solutions and immediate-release drug products such as compressed tablets or capsules. The determination of the absorption rate constant, $k_a$, is most often calculated by the Wagner-Nelson method for drugs, which follows a one-compartment model with first-order absorption and first-order elimination.

**In switching a drug from IV to oral dosing, what is the most important consideration?**

- The fraction of drug absorbed may be less than 1 (ie, 100% bioavailable) after oral administration. In some cases, there may be a different salt form of the drug used for IV infusion compared to the salt form of the drug used orally. Therefore, a correction is needed for the difference in MW of the two salt forms.

**Drug clearance is dependent on dose and area under the time–drug concentration curve. Would drug clearance be affected by the rate of absorption?**

- Total body drug clearance and renal drug clearance are generally not affected by drug absorption from most absorption sites. In the gastrointestinal tract, a drug is absorbed via the hepatic portal vein to the liver and may be subject to hepatic clearance.

**Learning Questions**

1. **a.** The elimination rate constant is $0.1 \text{ h}^{-1} (t_{1/2} = 6.93 \text{ h}).$
   
   **b.** The absorption rate constant, $k_a$, is $0.3 \text{ h}^{-1}$ (absorption half-life = 2.31 h).

   The calculated $t_{\text{max}} = \frac{\ln (k_a / k)}{k_a - k} = 5.49 \text{ h}$.

   **c.** The y intercept was observed to be 60 ng/mL. Therefore the equation that fits the observed data is

   $$C_p = 60 \left( e^{-0.3t} - e^{-0.1t} \right)$$

   **Note:** Answers obtained by “hand” feathering the data on semilog graph paper may vary somewhat depending on graphing skills and skill in reading data from a graph.

2. **By direct observation of the data, the $t_{\text{max}}$ is 6 hours and the $C_{\text{max}}$ is 23.01 ng/mL. The apparent volume of distribution, $V_p$, is obtained from the intercept, $I$, of the terminal elimination phase, and substituting $F = 0.8$, $D = 10,000,000$ ng, $k_a = 0.3 \text{ h}^{-1}$, $k = 0.1 \text{ h}^{-1}$:

   $$I = \frac{Fk_D D_0}{V_p (k_a - k)}$$

   $$60 = \frac{(0.8)(0.3)(10,000,000)}{V_p(0.3 - 0.1)}$$

   $$V_D = 200 \text{ L}$$

3. **The percent-of-drug-unabsorbed method is applicable to any model with first-order elimination, regardless of the process of drug input. If**
the drug is given by IV injection, the elimination rate constant, \( k \), may be determined accurately. If the drug is administered orally, \( k \) and \( k_a \) may flip-flop, resulting in an error unless IV data are available to determine \( k \). For a drug that follows a two-compartment model, an IV bolus injection is used to determine the rate constants for distribution and elimination.

4. After an IV bolus injection, a drug such as theophylline follows a two-compartment model with a rapid distribution phase. During oral absorption, the drug is distributed during the absorption phase, and no distribution phase is observed. Pharmacokinetic analysis of the plasma drug concentration data obtained after oral drug administration will show that the drug follows a one-compartment model.

5. The equations for a drug that follows the kinetics of a one-compartment model with first-order absorption and elimination are

\[
C_p = \frac{FD_0 k_a}{V_D (k_a - k)} (e^{-kt} - e^{-k'_{a}t})
\]

\[t_{max} = \frac{\ln(k_a/k)}{k_a - k}
\]

As shown by these equations:

a. \( t_{max} \) is influenced by \( k_a \) and \( k \) and not by \( F \), \( D_0 \), or \( V_D \).

b. \( C_p \) is influenced by \( F \), \( D_0 \), \( V_D \), \( k_a \), and \( k \).

6. A drug product that might provide a zero-order input is an oral controlled-release tablet or a transdermal drug delivery system (patch). An IV drug infusion will also provide a zero-order drug input.

7. The general equation for a one-compartment open model with oral absorption is

\[
C_p = \frac{FD_0 k_a}{V_D (k_a - k)} (e^{-kt} - e^{-k'_{a}t})
\]

From \( C_p = 45(e^{-0.17t} - e^{-1.5t}) \),

\[
\frac{FD_0 k_a}{V_D (k_a - k)} = 45
\]

\[k = 0.17 \text{ h}^{-1}
\]

\[k_a = 1.5 \text{ h}^{-1}
\]

8. a. Drug A

\[t_{max} = \frac{\ln(1.0 / 0.2)}{1.0 - 1.2} = 2.01 \text{ h}
\]

Drug B

\[t_{max} = \frac{\ln(0.2 / 1.0)}{0.2 - 1.0} = 2.01 \text{ h}
\]

b. \( C_{max} = \frac{FD_0 k_a}{V_D (k_a - k)} (e^{-k'_{max}} - e^{-k_{max}}) \)

Drug A

\[C_{max} = \frac{(1)(500)(1)}{(-10)(1 - 2)} (e^{-0.2(1)} - e^{-1(1)}) = 33.4 \mu g/mL
\]

Drug B

\[C_{max} = \frac{(1)(500)(0.2)}{(20)(0.2 - 1.0)} (e^{-0.2(1)} - e^{-1(1)}) = 3.34 \mu g/mL
\]

9. a. The method of residuals using manual graphing methods may give somewhat different answers depending on personal skill and the quality of the graph paper. Values obtained by the computer program ESTRIP gave the following estimates:

\[k_a = 2.84 \text{ h}^{-1} \quad k = 0.186 \text{ h}^{-1} \quad t_{1/2} = 3.73 \text{ h}
\]

b. A drug in an aqueous solution is in the most absorbable form compared to other oral dosage forms. The assumption that \( k_a > k \) is generally true for drug solutions and immediate-release oral dosage forms such as compressed tablets and capsules. Drug absorption from extended-release dosage forms may have
To demonstrate unequivocally which slope represents the true \( k \), the drug must be given by IV bolus or IV infusion, and the slope of the elimination curve obtained.

c. The Loo–Riegelman method requires IV data. Therefore, only the method of Wagner–Nelson may be used on these data.

d. Observed \( t_{\text{max}} \) and \( C_{\text{max}} \) values are taken directly from the experimental data. In this example, \( C_{\text{max}} \) is 85.11 ng/mL, which occurred at a \( t_{\text{max}} \) of 1.0 hour. The theoretical \( t_{\text{max}} \) and \( C_{\text{max}} \) are obtained as follows:

\[
t_{\text{max}} = \frac{2.3 \log(k_{a}/k)}{k_{a} - k} = \frac{2.3 \log(2.84/0.186)}{2.84 - 0.186} = 1.03 \text{ h}
\]

\[
C_{\text{max}} = \frac{FD_{0}k_{a}}{V_{D}(k_{a} - k)} (e^{-k_{a}t_{\text{max}}} - e^{-k_{a}t_{\text{max}}})
\]

where \( FD_{0}k_{a}/V_{D}(k_{a} - k) \) is the \( y \) intercept equal to 110 ng/mL and \( t_{\text{max}} = 1.03 \text{ h} \).

\[
C_{\text{max}} = (110) (e^{-0.186(1.0)} - e^{-2.84(1.03)})
\]

\[
C_{\text{max}} = 85 \text{ ng/mL}
\]

e. A more complete model-fitting program, such as WINNONLIN, is needed to fit the data statistically to a one-compartment model.

**CHAPTER 8**

**Frequently Asked Questions**

Is the drug accumulation index \( R \) applicable to any drug given by multiple doses or only to drugs that are eliminated slowly from the body?

- **Accumulation index**, \( R \), is a ratio that indicates steady-state drug concentration to the drug concentration after the first dose. The accumulation index does not measure the absolute size of overdosing; it measures the amount of drug cumulation that can occur due to frequent drug administration.

Factors that affect \( R \) are the elimination rate constant, \( k \), and the dosing interval, \( \tau \). If the first dose is not chosen appropriately, the steady-state level may still be incorrect. Therefore, the first dose and the dosing interval must be determined correctly to avoid any significant drug accumulation. The accumulation index is a good indication of accumulation due to frequent drug dosing, applicable to any drug, regardless of whether the drug is bound to tissues.

**What are the advantages/disadvantages for giving a drug by constant IV infusion, intermittent IV infusion, or multiple IV bolus injections? What drugs would most likely be given by each route of administration? Why?**

- Some of the advantages of administering a drug by constant IV infusion include the following: (1) A drug may be infused continuously for many hours without disturbing the patient. (2) Constant infusion provides a stable blood drug level for drugs that have a narrow therapeutic index. (3) Some drugs are better tolerated when infused slowly. (4) Some drugs may be infused simultaneously with electrolytes or other infusion media in an acute-care setting. Disadvantages of administering a drug by constant IV infusion include the following: (1) Some drugs are more suitable to be administered as a bolus IV injection. For example, some reports show that an aminoglycoside given once daily resulted in fewer side effects compared with dividing the dose into two or three doses daily. Due to drug accumulation in the kidney and adverse toxicity, aminoglycosides are generally not given by prolonged IV infusions. In contrast, a prolonged period of low drug level for penicillins and tetracyclines may not be as efficacious and may result in a longer cure time for an infection. The pharmacodynamics of the individual drug must be studied to determine the best course of action. (2) Drugs such as nitroglycerin are less likely to produce tolerance when administered intermittently versus continuously.

Why is the steady-state peak plasma drug concentration often measured sometime after an IV dose is given in a clinical situation?
• After an IV bolus drug injection, the drug is well distributed within a few minutes. In practice, however, an IV bolus dose may be administered slowly over several minutes or the drug may have a slow distribution phase. Therefore, clinicians often prefer to take a blood sample 15 minutes or 30 minutes after IV bolus injection and refer to that drug concentration as the peak concentration. In some cases, a blood sample is taken an hour later to avoid the fluctuating concentration in the distributive phase. The error due to changing sampling time can be large for a drug with a short elimination half-life.

Is a loading dose always necessary when placing a patient on a multiple-dose regimen? What are the determining factors?

• A loading or priming dose is used to rapidly raise the plasma drug concentration to therapeutic drug levels to obtain a more rapid pharmacodynamic response. In addition, the loading dose along with the maintenance dose allows the drug to reach steady state concentration quickly, particularly for drugs with long elimination half-lives.

An alternative way of explaining the loading dose is based on clearance. After multiple IV dosing, the maintenance dose required is based on $Cl$, $C_{ss}$, and $\tau$.

$$C_{ss} = \frac{Dose}{\tau \times Cl}$$

$$Dose = C_{ss} \times \tau \times Cl$$

If $C_{ss}$ and $\tau$ are fixed, a drug with a smaller clearance requires a smaller maintenance dose. In practice, the dosing interval is adjustable and may be longer for drugs with a small $Cl$ if the drug does not need to be dosed frequently. The steady-state drug level is generally determined by the desired therapeutic drug.

Does a loading dose significantly affect the steady-state concentration of a drug given by a constant multiple-dose regimen?

• The loading dose will affect only the initial drug concentrations in the body. Steady-state drug levels are obtained after several elimination half lives (eg, 4.32 $t_{1/2}$ for 95% steadystate level). Only 5% of the drug contributed by the loading dose will remain at 95% steady state. At 99% steady-state level, only 1% of the loading dose will remain.

Learning Questions

1. $V_D = 0.20$ (50 kg) = 10,000 mL

a. $D_{max} = \frac{D_0}{1 - f} = \frac{50 \text{ mg}}{1 - e^{-\left(0.6932\right)\left(8\right)}} = 53.3 \text{ mg}$

$$C_{max} = \frac{D_{max}}{V_D} = \frac{53.3 \text{ mg}}{10,000 \text{ mL}} = 5.33 \mu g/mL$$

b. $D_{min} = 53.3 - 50 = 3.3 \text{ mg}$

$$C_{min} = \frac{3.3 \text{ mg}}{10,000 \text{ mL}} = 0.33 \mu g/mL$$

c. $C_{av} = \frac{FD_0 \times 1.44 t_{1/2}}{V_D \times \tau} = \frac{(50) (1.44) (2)}{(10,000) (8)} = 1.8 \mu g/mL$

2. a. $D_0 = \frac{C_{av} V_D \times \tau}{1.44 t_{1/2}}$

$$= \frac{(10) (40,000) (6)}{(1.44) (5)} = 333 \text{ mg every 6 h}$$

b. $\tau = \frac{FD_0 \times 1.44 t_{1/2}}{V_D \times C_{av}} = \frac{(225,000) (1.44) (5)}{(40,000) (10)} = 4.05 \text{ h}$

6. Dose the patient with 200 mg every 3 hours.

$$D_t = \frac{D_0}{1 - e^{-\left(\frac{t}{\tau}\right)}} = \frac{200}{1 - e^{-\left(\frac{3}{0.23}\right)(3)}} = 400 \text{ mg}$$
Notice that $D_L$ is twice the maintenance dose, because the drug is given at a dosage interval equal approximately to the $t_{1/2}$ of 3 hours.

8. The plasma drug concentration, $C_p$, may be calculated at any time after $n$ doses by Equation 8.21 and proper substitution.

$$C_p = \frac{D_0}{V_D} \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau}$$

$$C_p = \frac{200}{40} \left( \frac{1}{1 - e^{-0.347(4)}} \right) e^{-0.347(4)}$$

$$= 4.63 \text{ mg/L}$$

Alternatively, one may conclude that for a drug whose elimination $t_{1/2}$ is 2 hours, the predicted plasma drug concentration is approximately at steady state after 3 doses or 12 hours. Therefore, the above calculation may be simplified to the following:

$$C_p = \frac{D_0}{V_D} \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau}$$

$$C_p = \frac{200}{40} \left( \frac{1}{1 - e^{-0.347(4)}} \right) e^{-0.347(4)}$$

$$= 4.71 \text{ mg/L}$$

9. $C_{\text{max}}^w = \frac{D_0}{V_D} \left( 1 - e^{-k\tau} \right)$

where

$V_D = 20\%$ of 82 kg = (0.2) (82) = 16.4 L

$k = (0.693/3) = 0.231 \text{ h}^{-1}$

$D_0 = V_D C_{\text{max}}^w (1 - e^{-k\tau}) = (16.4) (10) (1 - e^{-0.231(8)})$

a. $D_0 = 138.16 \text{ mg to be given every 8 h}$

b. $C_{\text{min}}^w = C_{\text{max}}^w (e^{-k\tau}) = (10) (e^{-0.231(8)})$

$$= 1.58 \text{ mg/L}$$

c. $C_{\text{av}}^w = \frac{D_0}{kV_D\tau} = \frac{138.16}{(0.231) (16.4) (8)}$

$$= 4.56 \text{ mg/L}$$

d. In the above dosage regimen, the $C_{\text{min}}^w$ of 1.59 mg/L is below the desired $C_{\text{min}}^w$ of 2 mg/L. Alternatively, the dosage interval, $\tau$, could be changed to 6 hours.

$$D_0 = V_D C_{\text{max}}^w (1 - e^{-k\tau}) = (16.4) (10) (1 - e^{-0.231(6)})$$

$$D_0 = 123 \text{ mg to be given every 6 h}$$

$$C_{\text{min}}^w = C_{\text{max}}^w (e^{-k\tau}) = (10) (e^{-0.231(6)}) = 2.5 \text{ mg/L}$$

$$C_{\text{av}}^w = \frac{D_0}{kV_D\tau} = \frac{123}{(0.231)(16.4)(6)} = 5.41 \text{ mg/L}$$

10. a. $C_{\text{av}}^w = \frac{FD_0}{kV_D\tau}$

Let $C_{\text{av}}^w = 27.5 \text{ mg/L}$

$$D_0 = C_{\text{av}}^w kV_D\tau = \frac{(27.5)(0.693/10.6)(0.5)(78)}{0.77}$$

$$= 546.3 \text{ mg}$$

$D_0 = 546.3 \text{ mg every 6 h}$

b. If a 500-mg capsule is given every 6 hours,

$$C_{\text{av}}^w = \frac{FD_0}{kV_D\tau} = \frac{(0.77)(500)(0.693/10.6)(0.5)(78)}{0.77}$$

$$= 25.2 \text{ mg/L}$$

c. $D_L = \frac{D_M}{1 - e^{-k\tau}} = \frac{500}{1 - e^{0.654(6)}} = 1543 \text{ mg}$

$D_L = 3 \times 500 \text{ mg capsules} = 1500 \text{ mg}$

**CHAPTER 9**

**Frequently Asked Questions**

*Why is it important to monitor drug levels carefully for dose dependency?*

- A patient with concomitant hepatic disease may have decreased biotransformation enzyme activity. Infants and young subjects may have immature hepatic enzyme systems. Alcoholics may
have liver cirrhosis and lack certain coenzymes. Other patients may experience enzyme saturation at normal doses due to genetic polymorphism. Pharmacokinetics provides a simple way to identify nonlinear kinetics in these patients and to estimate an appropriate dose. Finally, concomitant use of other drugs may cause nonlinear pharmacokinetics at lower drug doses due to enzyme inhibition.

**What are the main differences in pharmacokinetic parameters between a drug that follows linear pharmacokinetics and a drug that follows nonlinear pharmacokinetics?**

- A drug that follows linear pharmacokinetics generally has a constant elimination half-life and a constant clearance with an increase in the dose. The steady-state drug concentrations and AUC are proportional to the size of the dose. Nonlinear pharmacokinetics results in dose-dependent $Cl_t$, $t_{1/2}$, and AUC. Nonlinear pharmacokinetics are often described in terms of $V_{max}$ and $K_M$.

**What is the cause of nonlinear pharmacokinetics that is not dose related?**

- **Chronopharmacokinetics** is the main cause of nonlinear pharmacokinetics that is not dose related. The time-dependent or temporal process of drug elimination can be the result of rhythmic changes in the body. For example, nortriptyline and theophylline levels are higher when administered between 7 and 9 AM compared to between 7 and 9 PM after the same dose. Biological rhythmic differences in clearance cause a lower elimination rate in the morning compared to the evening. Other factors that cause nonlinear pharmacokinetics may result from enzyme induction (eg, carbamazepine) or enzyme inhibition after multiple doses of the drug. Furthermore, the drug or a metabolite may accumulate following multiple dosing and affect the metabolism or renal elimination of the drug.

**What are the main differences between a model based on Michaelis–Menten kinetic ($V_{max}$ and $K_M$) and the physiologic model that describes hepatic metabolism based on clearance?**

- The physiologic model based on organ drug clearance describes nonlinear drug metabolism in terms of blood flow and intrinsic hepatic clearance (Chapter 11). Drugs are extracted by the liver as they are presented by blood flow. The physiologic model accounts for the sigmoid profile with changing blood flow and extraction, whereas the Michaelis–Menten model simulates the metabolic profile based on $V_{max}$ and $K_M$. The Michaelis–Menten model was applied mostly to describe in-vitro enzymatic reactions. When $V_{max}$ and $K_M$ are estimated in patients, blood flow is not explicitly considered. This semiempirical method was found by many clinicians to be useful in dosing phenytoin. The organ clearance model was more useful in explaining clearance change due to impaired blood flow. In practice, the physiologic model has limited use in dosing patients because blood flow data for patients are not available.

**Learning Questions**

2. Capacity-limited processes for drugs include:
   - Absorption
     - Active transport
   - Intestinal metabolism by microflora
   - Distribution
     - Protein binding
   - Elimination
     - Hepatic elimination
     - Biotransformation
     - Active biliary secretion
   - Renal excretion
     - Active tubular secretion
     - Active tubular reabsorption

4. $C_P^0 = \frac{dose}{V_D} = \frac{10,000 \mu g}{20,000 \text{ mL}} = 0.5 \mu g / \text{ mL}$

   From Equation 9.1,

   $\text{Elimination rate} = -\frac{dC_P}{dt} = \frac{V_{max} C_P}{K_M + C_P}$
Because $K_M = 50 \mu g/mL$, $C_p << K_M$ and the reaction rate is first order. Thus, the above equation reduces to Equation 9.3.

$$\frac{-dC_p}{dt} = \frac{V_{max} C_p}{K_M} = k' C_p$$

$$k' = \frac{V_{max}}{K_M} = \frac{20 \mu g/h}{50 \mu g} = 0.4 h^{-1}$$

For first-order reactions,

$$t_{1/2} = \frac{0.693}{k'} = \frac{0.693}{0.4} = 1.73 h$$

The drug will be 50% metabolized in 1.73 hours.

7. When INH is coadministered, plasma phenytoin concentration is increased due to a reduction in metabolic rate $v$. Equation 9.1 shows that $v$ and $K_M$ are inversely related ($K_M$ in denominator). An increase in $K_M$ will be accompanied by an increase in plasma drug concentration. Figure 9-4 shows that an increase in $K_M$ is accompanied by an increase in amount of drug in the body at any time $t$. Equation 9.4 relates drug concentration to $K_M$, and it can be seen that the two are proportionally related, although they are not linearly proportional to each other due to the complexity of the equation. An actual study in the literature shows that $k$ is increased severalfold in the presence of INH in the body.

8. The $K_M$ has the units of concentration. In laboratory studies, $K_M$ is expressed in moles per liter, or micromoles per milliliter, because reactions are expressed in moles and not milligrams. In dosing, drugs are given in milligrams and plasma drug concentrations are expressed as milligrams per liter or micrograms per milliliter. The units of $K_M$ for pharmacokinetic models are estimated from $in vivo$ data. They are therefore commonly expressed as milligrams per liter, which is preferred over micrograms per milliliter because dose is usually expressed in milligrams. The two terms may be shown to be equivalent and convertible. Occasionally, when simulating amount of drug metabolized in the body as a function of time, the amount of drug in the body has been assumed to follow Michaelis–Menten kinetics, and $K_M$ assumes the unit of $D_o$ (eg, mg). In this case, $K_M$ takes on a very different meaning.

**CHAPTER 10**

Frequently Asked Questions

How does a physical property, such as partition coefficient, affect drug distribution?

- Partitioning refers to the relative distribution of a drug in the lipid and aqueous phases. Generally, a high partition coefficient ($P_{oil/water}$) favors tissue distribution and leads to a larger volume of distribution. Partitioning is a major factor that, along with protein binding of a drug, determines drug distribution.

What are the causes of a long distribution half-life for a body organ if blood flow to the tissue is rapid?

- Generally, the long distribution half-life is caused by a tissue/organ that has a high drug concentration, due either to intracellular drug binding or high affinity for tissue distribution. Alternatively, the drug may be metabolized slowly within the tissue or the organ may be large and have a high capacity for organ uptake.

How long does it take for a tissue organ to be fully equilibrated with the plasma? How long for a tissue organ to be half-equilibrated?

- The distribution half-life determines the time it takes for a tissue organ to be equilibrated. It takes 4.32 distribution half-lives for the tissue organ to be 95% equilibrated and one distribution half-life for the drug to be 50% equilibrated. The concept is analogous to reaching steadystate during drug infusion (see Chapter 5).

When a body organ is equilibrated with drug from the plasma, the drug concentration in that organ should be the same as that of the plasma. True or false?

- The answer is False. The free drug concentrations in the tissue and plasma are the same after
equilibration, but the total drug concentration in the tissue is not the same as the total drug concentration in the plasma. The bound drug concentration may vary depending on local tissue binding or the lipid solubility of the drug. Many drugs have a long distributive phase due to tissue drug binding or lipid solubility. Drugs may equilibrate slowly into these tissues and then be slowly eliminated. Drugs with limited tissue affinity are easily equilibrated. Some examples of drugs with a long distributive phase are discussed in relation to the two-compartment model (see Chapter 4).

What is the parameter that tells when half of the protein binding sites are occupied?

- The ratio, $r$, is defined as the ratio of the number of moles of drug bound to the number of moles of protein in the system. For a simple case of one binding site, $r$ reflects the proportion of binding sites occupied; $r$ is affected by (1) the association binding constant, (2) the free drug concentration, and (3) the number of binding sites per mole of protein. When $[D]$, or free drug concentration, is equal to 1 (or the dissociation constant $K_a(2n – 1)$), the protein is 50% occupied for a drug with 1:1 binding according to Equation 10.19. (This can be verified easily by substituting for $[D]$ into the right side of the equation and determining $r$.) For a drug with $n$ similar binding sites, binding occurs at the extent of 1:2 of bound drug:protein when $[D] = 1/ [K_a(2n – 1)]$. This equation, however, reflects binding in vitro when drug concentration is not changing; therefore, its conclusions are somewhat limited.

Do all drugs that bind proteins lead to clinically significant interactions?

- No. For some drugs, protein binding does not affect the overall distribution of other drugs. Typically, if a drug is highly bound, there is an increased chance of a significant change in the fraction of free drug when binding is altered.

Which macromolecules participate in drug–protein binding?

- Albumin, $\alpha_1$-acid glycoprotein, and lipoprotein. For some drugs and hormones, there may be a specific binding protein.

How does drug–protein binding affect drug elimination?

- Most drugs are assumed to be restrictively bound, and binding reduces drug clearance and elimination. However, some nonrestrictively bound drugs may be cleared easily. Changes in binding do not affect the rate of elimination of these drugs. Some drugs, such as some semisynthetic penicillins that are bound to plasma protein, may be actively secreted in the kidney. The elimination rates of these drugs are not affected by protein binding.

What are the factors to consider when adjusting the drug dose for a patient whose plasma protein concentration decreases to half that of normal?

- It is important to examine why the albumin level is reduced in the patient. For example, is the reduced albumin level due to uremia or hepatic dysfunction? In general, reduced protein binding will increase free drug concentration. Any change in drug clearance should be considered before reducing the dose, since the volume of distribution may be increased, partially offsetting the increase in free drug concentration.

How does one distinguish between the distribution phase and the elimination phase after an IV injection of a drug?

- In general, the early phase after an IV bolus dose is the distributive phase. The elimination phase occurs in the later phase, although distribution may continue for some drugs, especially for a drug with a long elimination half-life. The elimination phase is generally more gradual, since some drug may be returned to the blood from the tissues as drug is eliminated from the body.

Learning Questions

1. The zone of inhibition for the antibiotic in serum is smaller due to drug–protein binding.
2. Calculate $r(D)$ versus $r$, then graph the results on rectangular coordinates.

<table>
<thead>
<tr>
<th>$r$</th>
<th>$r/D \times 10^4$</th>
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<tbody>
<tr>
<td>0.4</td>
<td>1.21</td>
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<tr>
<td>0.8</td>
<td>0.90</td>
</tr>
<tr>
<td>1.2</td>
<td>0.60</td>
</tr>
<tr>
<td>1.6</td>
<td>0.30</td>
</tr>
</tbody>
</table>

The $y$ intercept = $nK_a = 1.5 \times 10^4$.

The $x$ intercept = $n = 2.$

Therefore, $K_a = 1.5 \times 10^4/2 = 0.75 \times 10^4$

$K_a$ may also be found from the slope.

8. The liver is important for the synthesis of plasma proteins. In chronic alcoholic liver disease or cirrhosis, fewer plasma proteins are synthesized in the liver, resulting in a lower plasma protein concentration. Thus, for a given dose of naproxen, less drug is bound to the plasma proteins, and the total plasma drug concentration is smaller.

10. Protein binding may become saturated at any drug concentration in patients with defective proteins or when binding sites are occupied by metabolic wastes generated during disease states (e.g., renal disease). Diazoxide is an example of nonlinear binding at therapeutic dose.

11. The answer is False. The percent bound refers to the percent of total drug that is bound. The percent bound may be ≥ 99% for some drugs. Saturation may be better estimated using the Scatchard plot approach and by examining “$r$,” which is the number of moles of drug bound divided by the number of moles of protein. When $r$ is 0.99, most of the binding sites are occupied. The $f_b$, or fraction of bound drug, is useful for determining $f_u/f_u = 1 - f_b$.

12. Adenosine is extensively taken up by cells including the blood elements and the vascular endothelium. Adenosine is rapidly metabolized by deamination and/or is used as AMP in phosphorylation. Consequently, adenosine has a short elimination half-life.

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CHAPTER 11

Frequently Asked Questions

Why do we use the term hepatic drug clearance to describe drug metabolism in the liver?

- Hepatic drug clearance describes drug metabolism in the liver and accounts for both the effect of blood flow and the intrinsic ability of the liver to metabolize a drug. Hepatic drug clearance is added to renal clearance and other clearances to obtain total (body) clearance, which is important in determining the maintenance dose of a drug. Hepatic drug clearance is often considered nonrenal clearance when it is measured as the difference between total clearance and renal clearance.

Please explain why many drugs with significant metabolism often have variable bioavailability.

- Most orally administered drugs pass through the liver prior to systemic absorption. The rate of blood flow can greatly affect the extent of drug that reaches the systemic circulation. Also, intrinsic metabolism may differ among individuals and may be genetically determined. These factors may cause drug levels to be more erratic for drugs that undergo extensive metabolism compared to drugs that are excreted renally.

The metabolism of some drugs is affected more than others when there is a change in protein binding. Why?

- Protein synthesis may be altered by liver dysfunction. In general, when drug–protein binding is reduced, the free drug may be metabolized more easily. However, some drugs may be metabolized regardless of whether the drug is bound or free (for discussion of nonrestrictive binding, see Chapter 10). In such cases, there is little change in pharmacodynamic activity due to changes in drug–protein binding.

Give some examples that explain why the metabolic pharmacokinetics of drugs are important in patient care.

- Erythromycin, morphine, propranolol, various steroids, and other drugs have large metabolic
clearance. In hepatic disease, highly potent drugs that have a narrow therapeutic index should be monitored carefully. Troglitazone (Rezulin), for example, is a drug that can cause severe side effects in patients with liver dysfunction; liver transaminase should be monitored in diabetic patients.

**Learning Questions**

1. **a.**

\[ k = k_m + k_e + k_b = 0.20 + 0.25 + 0.15 \]

\[ = 0.60 \text{ h}^{-1} \]

\[ t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.60} = 1.16 \text{ h} \]

b. \[ k = k_m + k_e = 0.45 \text{ h}^{-1} \]

\[ t_{1/2} = 1.54 \text{ h} \]

c. \[ k = 0.35 \text{ h}^{-1} \]

\[ t_{1/2} = 1.98 \text{ h} \]

d. \[ k = 0.80 \text{ h}^{-1} \]

\[ t_{1/2} = 0.87 \text{ h} \]

2. **a.** \[ k = 0.347 \text{ h}^{-1} \]

\[ k_e = (0.9)(0.347) = 0.312 \text{ h}^{-1} \]

b. Renal excretion, 90% of the drug is excreted unchanged.

5. Normal hepatic clearance, \( Cl_H \):

\[ Cl_H = Q \left( \frac{Cl_{int}}{Q + Cl_{int}} \right) \]

\[ Q = 1.5 \text{ L/min} \]

\[ Cl_{int} = 0.040 \text{ L/min} \]

\[ Cl_H = 1.5 \left( \frac{0.040}{1.5 + 0.040} \right) = 0.039 \text{ L/min} \]

a. Congestive heart failure:

\[ Cl_H = 1.0 \left( \frac{0.040}{1.0 + 0.040} \right) = 0.038 \text{ L/min} \]

b. Enzyme induction:

\[ Cl_H = 1.5 \left( \frac{0.090}{1.5 + 0.090} \right) = 0.085 \text{ L/min} \]

**Note:** A change in blood flow, \( Q \), did not markedly affect \( Cl_H \) for a drug with low \( Cl_{int} \).

6. Normal hepatic clearance:

\[ Cl_H = 1.5 \left( \frac{12}{1.5 + 12} \right) = 1.33 \text{ L/min} \]

Congestive heart failure (CHF):

\[ Cl_H = 1.0 \left( \frac{12}{1.0 + 12} \right) = 0.923 \text{ L/min} \]

a. \[ Cl_H = Q(ER) = Q \left( \frac{Cl_{int}}{Q + Cl_{int}} \right) \]

\[ ER = \frac{Cl_{int}}{Q + Cl_{int}} \]

Normal ER = \[ \frac{12}{1.5 + 12} = 0.89 \text{ L/min} \]

CHF ER = \[ \frac{12}{1.0 + 12} = 0.92 \text{ L/min} \]

b. \[ F = 1 – ER = 1 – 0.89 \]

\[ F = 0.11 \text{ or } 11\% \]

10. **a.** Because <0.5% of the unchanged drug is excreted in the urine, hepatic clearance nearly approximates total body clearance.

\[ Cl_H = Cl_T = kV_D = \left( \frac{0.693}{3.9} \right)(4.3)(80) \]

\[ = 61.1 \text{ L/h} \]

b. \[ Cl_H = Q \times ER \]

\[ Q = (1.5 \text{ L/min}) (60 \text{ min}) = 90 \text{ L/h} \]

\[ ER = 61.1/90 = 0.68. \]

11. **a.** \[ Cl_T = kV_D \left( \frac{0.693}{1.6} \right)(0.78)(81) = 27.4 \text{ L/h} \]

b. \[ Cl_R = k_eV_D \]

\[ K_e = 0.12k = 0.12 \left( \frac{0.693}{1.6} \right) = 0.052 \text{ h}^{-1} \]

\[ Cl_R = (0.052)(0.78)(81) = 3.29 \text{ L/h} \]
Alternatively,

\[ Cl_R = f_c Cl_T \]

\[ Cl_R = 0.12 \times Cl_T = (0.12) \times (27.4) = 3.29 \text{ L/h} \]

c. \[ Cl_{hi} = Cl_T - Cl_R = 27.4 - 3.29 = 24.11 \text{ L/h} \]

**CHAPTER 13**

**Frequently Asked Questions**

*What is an “absorption window”?*

- An absorption window refers to the segment of the gastrointestinal tract from which the drug is well absorbed and beyond which the drug is either poorly absorbed or not absorbed at all. After oral administration, most drugs are well absorbed in the duodenum and to a lesser extent in the jejunum. A small amount of drug absorption may occur from the ileum.

*Why are some drugs absorbed better with food whereas the oral absorption of other drugs is slowed or decreased by food?*

- Food, particularly food with a high fat content, stimulates the production of bile, which is released into the duodenum. The bile helps to solubilize a lipid-soluble drug, thereby increasing drug absorption. Fatty food also slows gastrointestinal motility, resulting in a longer residence time for the drug to be absorbed from the small intestine.

*Are drugs that are administered as an oral solution completely absorbed from the gastrointestinal tract?*

- After oral administration, the drug in solution may precipitate in the gastrointestinal tract. The precipitated drug needs to redissolve before it can be absorbed. Some drug solutions are prepared with a co-solvent, such as alcohol or glycerin, and form coarse crystals on precipitation that dissolve slowly, whereas other drugs precipitate into fine crystals that redissolve rapidly. The type of precipitate is influenced by the solvent, by the degree of agitation, and by the physical environment. *In vitro* mixing and dilution of the drug solution in artificial gastric juice, artificial intestinal juice, or in other pH buffers may predict the type of drug precipitate that is formed.

In addition, drugs dissolved in a highly viscous solution (e.g., simple syrup) may have slower absorption because of the viscosity of the solution. Furthermore, drugs that are readily absorbed across the gastrointestinal membrane may not be completely bioavailable (i.e., 100% systemic absorption) due to first-pass effects (discussed in Chapter 11). Finally, drugs that are absorbed by saturable mechanisms may have concentrations exceeding the capacity of the intestine to absorb all the drug within the absorption window.

*What factors contribute to a delay in drug absorption?*

- The major biologic factor that delays gastrointestinal drug absorption is a delay in gastric emptying time. Any factor that delays stomach emptying time, such as fatty food, will delay the drug entering into the duodenum from the stomach and, thereby, delay drug absorption.

**Learning Questions**

1. In the presence of food, undissolved aspirin granules larger than 1 mm are retained up to several hours longer in the stomach. In the absence of food, aspirin granules are emptied from the stomach within 1 to 2 hours. When the aspirin granules empty into the duodenum slowly, drug absorption will be as slow as with a sustained-release drug product. Enteric-coated aspirin granules taken with an evening meal may provide relief of pain for arthritic patients late into the night.

2. The answer is b. A basic drug formulated as a suspension will depend on stomach acid for dissolution as the basic drug forms a hydrochloric acid (HCl) salt. If the drug is poorly soluble, adding milk may neutralize some acid so that the drug may not be completely dissolved. Making an HCl salt rather than a suspension of the base ensures that the drug is soluble without being dependent on stomach HCl for dissolution.

3. Protein drugs are generally digested by proteolytic enzymes present in the GI tract and...
therefore are not adequately absorbed by the oral route. Protein drugs are most commonly given parenterally. Other routes of administration, such as intranasal and rectal administration, have had some success or are under current investigation for the systemic absorption of protein drugs.

4. The answer is c. Raising the pH of an acid drug above its pKₐ will increase the dissociation of the drug, thereby increasing its aqueous solubility.

5. The large intestine is most heavily populated by bacteria, yeasts, and other microflora. Some drugs which are not well absorbed in the small intestine are metabolized by the microflora to products that are absorbed in the large bowel. For example, drugs with an azo link (e.g., sulfasalazine) are cleaved by bacteria in the bowel and the cleaved products (e.g., 5-aminosalicylic acid and sulfapyridine) are absorbed. Other drugs, such as antibiotics (e.g., tetracyclines), may destroy the bacteria in the large intestine, resulting in an overgrowth of yeast (e.g., Candida albicans) and leading to a yeast infection. Destruction of the microflora in the lower bowel can also lead to cramps and diarrhea.

6. First-pass effects are discussed more fully in Chapter 11. Alternative routes of drug administration such as buccal, inhalation, sublingual, intranasal, and parenteral will bypass the first-pass effects observed after oral drug administration.

7. Although antacid statistically decreased the extent of systemic drug absorption (p < .05) as shown by an AUC₀–₄₉ of 349 ± 108 pg h/mL, compared to the control (fasting) AUC₀–₄₉ value of 417 ± 135 pg h/mL, the effect of antacid is not clinically significant. A high-fat diet decreased the rate of systemic drug absorption, as shown by a longer tₚₜₛ value (64 minutes) and lower Cₚₜₛ value (303 pg/mL).

**CHAPTER 14**

**Frequently Asked Questions**

What physical or chemical properties of a drug substance are important in designing a drug for (a) oral administration or (b) parenteral administration?

- For optimal drug absorption after oral administration, the drug should be water soluble and highly permeable so it can be absorbed throughout the gastrointestinal tract. Ideally, the drug should not change into a polymorphic form that could affect its solubility. The drug should be stable in both gastric and intestinal pH and preferably should not be hygroscopic.

  For parenteral administration, the drug should be water soluble and stable in solution, preferably at autoclave temperature. The drug should be nonhygroscopic and preferably should not change into another polymorphic form.

For a lipid-soluble drug that has very poor aqueous solubility, what strategies could be used to make this drug more bioavailable after oral administration?

- A lipid-soluble drug may be prepared in an oil-in-water (o/w) emulsion or dissolved in a nonaqueous solution in a soft gelatin capsule. A co-solvent may improve the solubility and dissolution of the drug.

For a weak ester drug that is unstable in highly acid or alkaline solutions, what strategies could be used to make this drug more bioavailable after oral administration?

- The rate of hydrolysis (decomposition) of the ester drug may be reduced by formulating the drug in a co-solvent solution. A reduction in the percent of the aqueous vehicle will decrease the rate of hydrolysis. In addition, the drug should be formulated at the pH in which the drug is most stable.

**Learning Questions**

1. The rate-limiting steps in the oral absorption of a solid drug product are the rate of drug dissolution within the gastrointestinal tract and the rate of permeation of the drug molecules across the intestinal mucosal cells. Generally, disintegration of the drug product is rapid and not rate limiting. Water-soluble drugs dissolve rapidly in the aqueous environment of the gastrointestinal tract, so the permeation of the intestinal mucosal cells may be the rate-limiting step. The drug absorption
rate may be altered by a variety of methods, all of which depend on knowledge of the biopharmaceutical properties of the drug and the drug product and on the physiology of the gastrointestinal tract. Drug examples are described in detail in this chapter and in Chapter 13.

2. Most drugs are absorbed by passive diffusion. The duodenum area provides a large surface area and blood supply that maintains a large drug concentration gradient favorable for drug absorption from the duodenum into the systemic circulation.

3. If the initial drug absorption rate, \( \frac{dD_A}{dt} \), was slower than the drug elimination rate, \( \frac{dD_E}{dt} \), then therapeutic drug concentrations in the body would not be achieved. It should be noted that the rate of absorption is generally first order, \( \frac{dD_A}{dt} = D_0 k_a \), where \( D_0 \) is the drug dose which is great initially. Even if \( k_a < k \), the initial drug absorption rate may be greater than the drug elimination rate. After the drug is absorbed from the absorption site, \( \frac{dD_A}{dt} \leq \frac{dD_E}{dt} \).

4. A drug prepared as an oral aqueous drug solution is generally the most bioavailable. However, the same drug prepared as a well-designed immediate-release tablet or capsule may have similar bioavailability. In the case of an oral drug solution, there is no dissolution step; the drug molecules come into contact with intestinal membrane, and the drug is rapidly absorbed. As a result of first-pass effects (discussed in Chapter 11), a drug given in an oral drug solution may not be 100% bioavailable. If the drug solution is formulated with a high solute concentration—such as sorbitol solution, which yields a high osmotic pressure—gastric motility may be slowed, thus slowing the rate of drug absorption.

5. Anticholinergic drugs prolong gastric emptying, which will delay the absorption of an enteric-coated drug product.

6. Erythromycin may be formulated as enteric-coated granules to protect the drug from degradation at the stomach pH. Enteric-coated granules are less affected by gastric emptying and food (which delays gastric emptying) compared to enteric-coated tablets.

**CHAPTER 15**

**Frequently Asked Questions**

Why are preclinical animal toxicology studies and clinical efficacy drug studies in human subjects not required by the FDA to approve a generic drug product as a therapeutic equivalent to the brand-name drug product?

- Preclinical animal toxicology and clinical efficacy studies were performed on the marketed brand drug product as part of the New Drug Application (NDA) prior to FDA approval. These studies do not have to be repeated for the generic bioequivalent drug product. The manufacturer of the generic drug product must submit an Abbreviated New Drug Application (ANDA) to the FDA, demonstrating that the generic drug product is a therapeutic equivalent (see definitions in Chapter 15) to the brand drug product.

What do sequence, washout period, and period mean in a crossover bioavailability study?

- The sequence is the order in which the drug products (ie, treatments) are given (eg, brand product followed by generic product or vice versa). Sequence is important to prevent any bias due to the order of the treatments in the study. The term washout refers to the time for total elimination of the dose. The time for washout is determined by the elimination half-life of the drug. Period refers to the drug-dosing day on which the drug is given to the subjects. For example, for Period 1, half the subjects receive treatment A, brand product, and the other half of the subjects receive treatment B, generic product.

Why does the FDA require a food intervention (food effect) study for generic drug products before granting approval?

- Manufacturers are required to perform a food-intervention bioavailability study on all drugs whose bioavailability is known to be affected by food. In addition, a food-intervention bioavailability study is required on all modified-release products since (1) the modified-release formulation (eg, enteric coating, sustained-release coating)
4. Plot the data on both rectangular and semi-log graph paper. The following answers were obtained from estimates from the plotted plasma level–time curves. More exact answers may be obtained mathematically by substitution into the proper formulas.

a. 1.37 hours  
b. 13.6 hours  
c. 8.75 hours  
d. 5 hours  
e. 4.21 μg/mL  
f. 77.98 μg h/mL

5. **Drug Product**

<table>
<thead>
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<th>Subject</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Week 3</th>
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<td>B</td>
<td>C</td>
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<tr>
<td>6</td>
<td>B</td>
<td>A</td>
<td>C</td>
</tr>
</tbody>
</table>

6. **a. Absolute bioavailability**

\[ \frac{D_{u,PO}^{u,PO}}{D_{u,IV}^{u,IV}} = \frac{340}{40} / \frac{200}{2} = 0.85 \text{ or } 85\% \]

**b. Relative bioavailability**

\[ \frac{D_{u,PO}^{u,PO}}{D_{u,IV}^{u,PO}} = \frac{360}{4} / \frac{380}{4} = 0.947 \text{ or } 94.7\% \]

7. The fraction of drug absorbed systemically is the absolute bioavailability.

\[ \frac{\% \text{ of dose excreted after PO}}{\% \text{ of dose excreted after IV}} = \frac{48\%}{75\%} = 0.64 \]

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**Learning Questions**

3. **a.** Oral solution: The drug is in the most bioavailable form.  
   **b.** Oral solution: Same reason as above.
   **c.** Absolute bioavailability
   \[ \frac{[AUC]_{soln}}{[AUC]_{IV}} = \frac{145}{10} / \frac{29}{2} = 1.0 \]
   **d.** Relative bioavailability
   \[ \frac{[AUC]_{tab}}{[AUC]_{soln}} = \frac{116}{10} / \frac{145}{10} = 0.80 \]
   **e.** (1) \( C_p^0 = 6.67 \mu g/mL \) (by extrapolation of IV curve)
   \[ V_D = \frac{2000 \mu g/kg}{6.67 \mu g/mL} = 300 \text{ mL/kg} \]
   (2) \( t_{1/2} = 3.01 \text{ h} \)
   (3) \( k = 0.23 \text{ h}^{-1} \)
   (4) \( Cl_T = kV_D = 69 \text{ mL/kg h} \)
Appendix C

CHAPTER 16

Frequently Asked Questions

Three batches of ibuprofen tablets, 200 mg, are manufactured by the same manufacturer using the same equipment. Each batch meets the same specifications. Does meeting specifications mean that each batch of drug product contains the identical amount of ibuprofen?

- Specifications provide a quantitative limit (acceptance criteria) to a test product (e.g., the total drug content must be within ±5% or the amount of impurities in the drug substance must not be more than [NMT] 1%). Thus, one batch of nominally 200-mg ibuprofen tablets may contain an average content of 198 mg, whereas the average content for another batch of 200-mg ibuprofen tablets may have an average content of 202 mg. Both batches meet a specification of ±5% and would be considered to meet the label claim of 200 mg of ibuprofen per tablet.

What should a manufacturer of a modified-release tablet consider when making a qualitative or quantitative change in an excipient?

- The manufacturer must consider whether the excipient is critical or not critical to drug release. If the excipient (e.g., starch) is not critical to drug release (i.e., a non-release-controlling excipient), then small changes in the starch concentration, generally less than 3% of the total target dosage form weight, is unlikely to affect the formulation quality and performance. A qualitative change in the excipient may affect drug release and thus will have significant effect on the formulation performance.

CHAPTER 17

Frequently Asked Questions

Are extended-release drug products always more efficacious than immediate-release drug products containing the same drug?

- Extended-release drug products have many advantages compared to immediate-release drug products, as discussed in Chapter 14. However, an extended-release drug product of a drug that has a long elimination half-life (e.g., chlorpheniramine maleate, digoxin, levothyroxine) has no advantage over the same drug given in an immediate-release (conventional) drug product. For some drugs, the clinical rationale for an extended-release drug product that provides a long-sustained drug level is not established. Nitroglycerin, for example, is less likely to produce tolerance with intermittent dosing compared with dosing by a continuous-release product. For some antibiotics there is also a specific duration of postantibiotic effect, during which bactericidal activity continues even when the plasma drug level is depleted. Some drugs are better tolerated with a “pulse” type of drug input into the body.

What are the advantages and disadvantages of a zero-order rate for drug absorption?

- A zero-order rate for drug absorption will give more constant plasma drug concentrations with minimal fluctuations between peak and trough levels compared to first-order drug absorption. Depending on the therapeutic window for the drug and the relationship between the pharmacokinetics and pharmacodynamics of the drug, zero-order drug absorption may not always be more efficacious than first-order absorption.

Learning Questions

1. a. For many drugs, the plasma drug concentration is proportional to the drug concentration at the receptor site and the pharmacodynamic effect. By maintaining a prolonged, constant plasma drug concentration, the pharmacodynamic effect is also maintained.

b. A drug that releases at a zero-order rate and is absorbed at a zero-order rate provides a more constant plasma drug concentration compared to a first-order drug release.

2. a. Both A and B release drug at a zero-order rate (straight line). Curve B shows that 100% of drug is released in 12 hours, or about 8.3% per hour.

b. Product C.

c. Product C initially releases drug at a zero-order rate (first 3 hours).
Solutions to Frequently Asked Questions (FAQs) and Learning Questions

751

Glycosylation is the addition of a carbohydrate group to the molecule. For example, Betaseron (interferon β-1A) is not glycosylated, whereas Avonex (interferon β-1B) is glycosylated. Glycosylation will increase the water solubility and the molecular weight of the drug. Although both drugs are β-interferons, glycosylation affects the pharmacokinetics, the stability, and the efficacy of these drugs.

What kind of biological drugs are available and how are they used? Is this similar or different from small molecule drugs?

The distribution of a biotechnology compound depends on its physicochemical characteristics. Many peptides, proteins, and nucleotides have polar chains so that a major portion of the drug is distributed in the extracellular fluid with a volume of 7 to 15 L. Drugs that easily penetrate into the cell have higher volumes of distribution, about 15 to 45 L, due to the larger volume of intracellular fluid.

CHAPTER 19

Frequently Asked Questions

Explain why doubling the dose of a drug does not double the pharmacodynamic effect of the drug.

Doubling a dose does not double the drug response (or the pharmacodynamic effect). The pharmacodynamic effect of a drug is proportional to the log of the plasma drug concentration—usually within 20% to 80% of the maximal response. Near the maximal pharmacodynamic effect, doubling the dose may only cause a very small increase in effect. No further increase in pharmacodynamic effect is achieved by an increase in dose once the maximum pharmacodynamic effect, $E_{\text{max}}$, is obtained.

What kind of biological drugs are available and how are they used? Is this similar or different from small molecule drugs?

The distribution of a biotechnology compound depends on its physicochemical characteristics. Many peptides, proteins, and nucleotides have polar chains so that a major portion of the drug is distributed in the extracellular fluid with a volume of 7 to 15 L. Drugs that easily penetrate into the cell have higher volumes of distribution, about 15 to 45 L, due to the larger volume of intracellular fluid.

CHAPTER 18

Frequently Asked Questions

What is the most frequent route of administration of biologic compounds?

- The most frequent route of administration for biologic compounds is parenteral (eg, IM or IV). For example, β-Interferon for multiple sclerosis is given IM to allow gradual drug release into the systemic circulation.

What is the effect of glycosylation on the activity of a biologic compound? Give an example.

- Glycosylation is the addition of a carbohydrate group to the molecule. For example, Betaseron (interferon β-1A) is not glycosylated, whereas Avonex (interferon β-1B) is glycosylated. Glycosylation will increase the water solubility and the molecular weight of the drug. Although both drugs are β-interferons, glycosylation affects the pharmacokinetics, the stability, and the efficacy of these drugs.

"What is meant by a hysteresis loop? Why do some drugs follow a clockwise hysteresis loop and other drugs follow a counterclockwise hysteresis loop?"

- For many drugs, the drug responses over time plotted versus plasma drug concentrations produce a loop-shaped (hysteresis loop) profile. The hysteresis loop shows that the plasma drug concentration is not...
always a good indicator of drug response. A clockwise hysteresis loop shows that response decreases with time and may be the result of drug tolerance or formation of an antagonistic metabolite.

What is meant by an effect compartment? How does the effect compartment differ from pharmacokinetic compartments, such as the central compartment and the tissue compartment?

• The effect compartment is postulated to describe the pharmacodynamics of drugs that are not well described by drug concentration in the plasma compartment. The effect compartment is assumed to be the receptor site in the body for drug response. Drug concentration in this site is referred to as drug concentration in the effect compartment. The amount of drug in the effect compartment is relatively small and is insignificant compared to the amount of drug in other tissues. Drug elimination from the effect compartment is governed by $k_{ee}$, a first-order rate constant that is estimated from the pharmacodynamic data. Drug concentration in the effect compartment may be equilibrated with the central compartment when a steady-state plasma drug concentration is reached.

Learning Questions

1. a. True. Drug concentration is more precise because an identical dose may result in different plasma drug concentration in different subjects due to individual differences in pharmacokinetics.

b. True. The kinetic relationship between drug response and drug concentration is such that the response is proportional to log concentration of the drug.

c. True. The data show that after IV bolus dose, the response begins at the same point, indicating that the initial plasma drug concentration is the same. In uremic patients, the volume of distribution may be affected by changes in protein binding and electrolyte levels, which may range from little or no effect to strongly affecting the $V_D$.

d. False. The drug is likely to be excreted through the kidney, since the slope (elimination) is reduced in uremic patients.

e. True. Assuming that the volume of distribution is unchanged, the starting pharmacologic response should be the same if the receptor sensitivity is unchanged. In a few cases, receptor sensitivity to the drug can be altered in uremic patients. For example, the effect of digoxin will be more intense if the serum potassium level is depleted.

2. These antibiotics inhibit β-lactamase by irreversible binding to the enzyme protein via an acylation reaction, similar to antibiotic binding to the protein in the cell wall. β-Lactamase breaks the cyclic amide bond of the antibiotics.

3. Several answers are possible.

a. Pharmacokinetic considerations: Subsequent doses induce the hepatic drug metabolizing enzymes (auto-induction), thereby decreasing the elimination half-life, resulting in lower steady-state drug concentrations.

b. Pharmacodynamic considerations: The patient develops tolerance to the drug, resulting in the need for a higher dose to produce the same effect.

5. CNS drugs.

6. An allergic response to a drug may be unpredictable and does not generally follow a dose–response relationship.

7. PAT (postantibiotic time) is the time for continued antibacterial activity even though the plasma antibiotic concentration has fallen below MEC, or minimum effective concentration.

8. AUC/MIC or AUIC is a pharmacokinetic parameter incorporating MIC together in order to provide better prediction of antibiotic response (cure percent). An example is ciprofloxacin. AUIC is a good predictor of percent cure in infection treated at various dose regimens.

CHAPTER 20

Frequently Asked Questions

Can therapeutic drug monitoring be performed without taking blood samples?

• Therapeutic drug monitoring (TDM) may be performed by sampling other biologic fluids, such as
solutions to frequently asked questions (FAQs) and learning questions

753

• With the Bayesian approach, the estimates of patient parameters are constrained more narrowly, to allow easier parameter estimation based on information provided from the population. The information is then combined with one or more serum concentrations from the patient to obtain a set of final patient parameters (generally Cl and \( V_D \)). When no serum sample is taken, the Bayesian approach is reduced to a priori model using only population parameters.

Why is pharmacokinetics important in studying drug interactions?

• Pharmacokinetics provides a means of studying whether an unusual drug action is related to pharmacokinetic factors, such as drug disposition, distribution, or binding, or is related to pharmacodynamic interaction, such as a difference in receptor sensitivity, drug tolerance, or some other reason. Many drug interactions involving enzyme inhibition, stimulation, and protein binding were discovered as a result of pharmacokinetic, pharmacogenetic, and pharmacodynamic investigations.

What are the major considerations in therapeutic drug monitoring?

• The major considerations in TDM include the pathophysiology of the patient, the blood sample collection, and the data analysis. Clinical assessment of patient history, drug interaction, and demographic factors are all part of a successful program for therapeutic drug monitoring.

What is meant by population pharmacokinetics? What advantages does population pharmacokinetics have over classical pharmacokinetics?

• Most pharmacokinetic models require well-controlled studies in which many blood samples are taken from each subject and the pharmacokinetic parameters estimated. In patient care situations, only a limited number of blood samples is collected, which does not allow for the complete determination of the drug’s pharmacokinetic profile in the individual patient. However, the data from blood samples taken from a large demographic sector are more reflective of the disease states and pharmacogenetics of the patients treated. Population pharmacokinetics allow data from previous patients to be used in addition to the limited blood sample from the individual patient. The type of information obtained is less constrained and is sometimes dependent on the model and algorithm used for analysis. However, many successful examples have been reported in the literature.

Why is it possible to estimate individual pharmacokinetic parameters with just a few data points using the Bayesian method?

• With the Bayesian approach, the estimates of patient parameters are constrained more narrowly, to allow easier parameter estimation based on information provided from the population. The information is then combined with one or more serum concentrations from the patient to obtain a set of final patient parameters (generally Cl and \( V_D \)). When no serum sample is taken, the Bayesian approach is reduced to a priori model using only population parameters.

Learning Questions

1. Steady-state drug concentrations are achieved in approximately 5 half-lives. For a drug with a half-life of 36 hours, steady-state drug concentrations are achieved in approximately 180 hours (or 7.5 days). Thus, dose adjustment in patients is difficult for drugs with very long half-lives. In contrast, steady-state drug concentrations are achieved in approximately 20 to 30 hours (or 1 day) for drugs whose half-lives are 4 to 6 hours.

2. \[ C_{\text{max}}^{\infty} = \frac{D_0}{V_D} \left( \frac{1}{1 - e^{-\frac{t}{\tau}}} \right) \]

\[ C_{\text{max}}^{\infty} = \frac{250,000}{42,000} \left( \frac{1}{1 - e^{-\left(\frac{6}{0.34}\right)}} \right) \]

\[ C_{\text{max}}^{\infty} = \frac{250,000}{42,000} \left( \frac{1}{0.998} \right) = 5.96 \mu g/mL \]
At steady state, the peak concentration of penicillin G will be 5.96 μg/mL.

3. \( C_{av}^\infty = \frac{D}{k \tau} = \frac{250,000}{(0.99)(20,000)(6)} = 2.10 \, \mu g/mL \)

Free drug concentration at steady state = 2.10(1 - 0.97) = 0.063 μg/mL.

4. \( C_{av}^\infty = \frac{1.44D_0^{1/2}}{V_0\tau} \)

For the Normal Patient:
\( V_0 = (0.392)(1)(1000) = 392 \, mL/kg \)

\( C_{av}^\infty = \frac{(1.44)(D_0)(1)(1.49)}{(392)(6)} = 2 \, \mu g/mL \)
\( D_0 = \frac{(392)(6)(2)}{(1.44)(1.49)} = 2192 \, \mu g/kg = 2.2 \, mg/kg \)

For the Uremic Patient:
\( V_0 = (23.75)(1) (1000) = 237.5 \, mL/kg \)

\( C_{av}^\infty = \frac{(1.44)(D_0)(1)(1.49)}{(237.5)(6)} = 2 \, \mu g/mL \)
\( D_0 = \frac{(2)(237.5)(6)}{(1.44)(6.03)} = 328.2 \, \mu g/kg \)

\( = 0.3 \, mg/kg \)

5. a. \( V_0 = 306,000 \, mL \)
Dose = 0.5 × 10^6 ng

\( C_{av}^\infty = \frac{(1.44)(DFt_{1/2})}{V_0\tau} = \frac{(1.44)(0.5 \times 10^6)(0.56)(0.95)}{(306,000)(1)} = 1.25 \, ng/mL \)

b. The patient is adequately dosed.

c. \( F = 1; \) using the above equation, the \( C_{av}^\infty \) is 2.2 ng/mL; although still effective, the \( C_{av}^\infty \) will be closer to the toxic serum concentration of 3 ng/mL.

6. The \( Cl_{cr} \) for this patient shows normal kidney function.

\( t_{1/2} = 2 \, h \quad k = 0.693/2 = 0.3465 \, h^{-1} \)
\( V_D = 0.2 \, L/kg \times 80 \, kg = 16 \, L \)

a. \( C_{av}^\infty = \frac{D_0 / V_D}{1 - e^{-k\tau}} = \frac{250 / 16}{1 - e^{-(0.3465)(8)}} = 16.68 \, mg/L \)

\( C_{av}^\infty = C_{av}^\infty e^{-kt} = 16.68e^{-(0.3465)(8)} = 1.04 \, mg/L \)

The dosage regimen of 250 mg every 8 hours gives a \( C_{max}^\infty \) above 16 mg/L and a \( C_{min}^\infty \) below 2 mg/L. Therefore, this dosage regimen is not correct.

b. Several trials might be necessary to obtain a more optimal dosing regimen. One approach is to change the dosage interval, \( \tau \), to 6 hours and to calculate the dose, \( D_0^\infty \):

\( D_0 = C_{max}^\infty V_D (1 - e^{-k\tau}) \)

\( = (16)(16)(1 - e^{-(0.3465)(6)}) = 224 \, mg \)

\( C_{min}^\infty = C_{max}^\infty e^{-kt} = 16e^{-(0.3465)(6)} = 2 \, mg/L \)

A dose of 224 mg given every 6 hours should achieve the desired drug concentrations.

10. Assume desired \( C_{av}^\infty = 0.0015 \, \mu g/mL \) and \( \tau = 24 \, h. \)

\( C_{av}^\infty = \frac{FD_0^{1/2}}{V_D\tau} \)
\( D_0 = \frac{C_{av}^\infty V_D\tau}{F1.44t_{1/2}} \)
\( D_0 = \frac{(0.0015)(4)(68)(24)}{(0.80)(1.44)(30)} = 0.283 \, mg \)

Give 0.283 mg every 24 hours.

a. For a dosage regimen of one 0.30-mg tablet daily

\( C_{av}^\infty = \frac{(0.80)(0.3)(1.44)(30)}{(4)(68)(24)} = 0.0016 \, \mu g/mL \)

which is within the therapeutic window.
Solutions to Frequently Asked Questions (FAQs) and Learning Questions

755

b. A dosage regimen of 0.15 mg every 12 hours would provide smaller fluctuations between \( C_{\text{max}} \) and \( C_{\text{min}} \) compared to a dosage regimen of 0.30 mg every 24 hours.

c. Since the elimination half-life is long (30 hours), a loading dose is advisable.

\[
D_L = D_m \left( \frac{1}{1 - e^{-\tau}} \right)
\]

\[
D_L = 0.30 \left( \frac{1}{1 - e^{-(0.693/30)(24)}} \right) = 0.70 \text{ mg}
\]

For cardiotonic drugs related to the digitalis glycosides, it is recommended that the loading dose be administered in several portions with approximately half the total as the first dose. Additional fractions may be given at 6- to 8-hour intervals, with careful assessment of the clinical response before each additional dose.

d. There is no rationale for a controlled-release drug product because of the long elimination half-life of 30 hours inherent in the drug.

11. a. \[
C_{av} = \frac{FD_{D}1.44t_{1/2}}{V_{D}^2}
\]

\[
C_{av} = \frac{(1500)(1.44)(6)}{(1.3)(62)(4)} = 39.6 \mu \text{g/mL}
\]

b. \[
D_L = D_m \left( \frac{1}{1 - e^{-\tau}} \right)
\]

c. A \( D_L \) of 4.05 g is needed, which is equivalent to eight tablets containing 0.5 g each.

d. The time to achieve 95% to 99% of steady state is, approximately, \( 5t_{1/2} \) without a loading dose. Therefore,

\[5 \times 6 = 30 \text{ h}\]

12. a. \[
C_{ss} = \frac{R}{kV_D} \quad R = C_{ss}kV_D
\]

\[
R = (5) \left( \frac{0.693}{2} \right)(0.173)(75) = 22.479 \text{ mg/h}
\]

\[
D_L = C_{ss}V_D = (5)(0.173)(75) = 64.875 \text{ mg}
\]

b. \[
\frac{R_{\text{old}}}{C_{SS, \text{old}}} = \frac{R_{\text{new}}}{C_{SS, \text{new}}}
\]

\[
\frac{22.479}{2} = \frac{R_{\text{new}}}{5} \quad R_{\text{new}} = 56.2 \text{ mg/h}
\]

c. \( 4.32t_{1/2} = 4.32(2) = 8.64 \text{ h} \)

13. \( t_{1/2} = 8 \text{ h} \quad k = 0.693/8 = 0.0866 \text{ h}^{-1} \)

\[
V_D = (1.5 \text{ L/kg})(75 \text{ kg}) = 112.5 \text{ L}
\]

\[
C_{SS} = 20 \mu \text{g/mL}
\]

a. \( R = C_{SS}V_D = (20)(0.0866)(112.5) = 194.85 \text{ mg/h} \)

b. \( D_L = C_{SS}V_D = (20)(112.5) = 2250 \text{ mg} \)

Alternatively, \( D_L = R/k = 194.85/0.0866 = 2250 \text{ mg} \)

c. 0.2 mL of a 15-mg/mL solution contains 3 mg.

\[
R = 3 \text{ mg/h/kg} \times 75 \text{ kg} = 225 \text{ mg/h}
\]

\[
C_{SS} = \frac{R}{kV_D} = \frac{225}{(0.0866)(112.5)} = 23.1 \text{ mg/L}
\]

The proposed starting infusion rate given by the manufacturer should provide adequate drug concentrations.

CHAPTER 21

Frequently Asked Questions

What are the main factors that influence drug dosing in renal disease?

• Renal disease can cause profound changes in the body that must be evaluated by assessing the patient’s condition and medical history. Renal dysfunction is often accompanied by reduced protein–drug binding and by reduced glomerular filtration rate in the kidney. Some changes in hepatic clearance may also occur. While there is no accurate method for predicting the resulting \( \text{in vivo} \) changes, a decrease in albumin may increase \( f_a \), or the fraction of free plasma drug concentration in the body. The \( f_a \) is estimated from \( f_a = 1 - f_b \), where \( f_b \) is the fraction of bound plasma drug. For the uremic patient, the fraction of drug
bound \( f'_b \) is affected by a change in plasma protein: \( f'_b/f_b = p' \times 4.4 \), where \( p \) is the normal plasma protein concentration (4.4 g/dL assuming albumin is the protein involved) and \( p' \) is the uremic plasma protein concentration; \( f'_b \) is the fraction of drug bound in the uremic patient. Since \( f'_u \) or the fraction of unbound drug is increased in the uremic patient, the free drug concentration may be increased and sometimes lead to more frequent side effects. On the other hand, an increase in plasma free drug in the uremic patient is offset somewhat by a corresponding increase in the volume of distribution as plasma protein–drug binding is reduced. Reduction in GFR is more definite; it is invariably accompanied by a reduction in drug clearance and by an increase in the elimination half-life of the drug.

Name and contrast the two methods for adjusting drug dose in renal disease.

- Two approaches to dose adjustment in renal disease are the clearance method and the elimination rate constant method. The methods are based on estimating either the uremic \( Cl_R \) or uremic \( k_R \) after the creatinine clearance is obtained in the uremic patient.

What are the pharmacokinetic considerations in designing a dosing regimen? Why is dosing once a day for aminoglycosides recommended by many clinicians?

- Aminoglycosides are given as a larger dose spaced farther apart (once daily). Keeping the same total daily dose of the aminoglycoside improves the response (efficacy) and possibly lessens side effects in many patients. Model simulation shows reduced exposure (AUC) to the effect compartment (toxicity), while the activity is not altered. The higher drug dose produces a higher peak drug concentration. In the case of gentamicin, the marketed drug is chemically composed of three related, but distinctly different, chemical components, which may distribute differently in the body.

How do changes in drug–protein binding affect dose adjustment in patients with renal and/or hepatic disease?

- Hepatic disease may reduce albumin and \( \alpha_1 \)-acid glycoprotein (AAG) concentrations resulting in decreased drug protein binding. Blood flow to the liver may also be affected. Generally, for a drug with linear binding, \( f_u \) may be increased as discussed in FAQ #1. Consult Chapter 10 also for a discussion of restrictive clearance of drugs. Examples of binding to AAG are the protease inhibitors for AIDS.

Drug clearance is often decreased 20–50% in many patients with congestive heart failure (CHF). Explain how it may affect drug disposition.

- Congestive heart failure (CHF) can reduce renal or hepatic blood flow and decrease hepatic and renal drug clearance. In CHF, less blood flow is available in the splanchnic circulation to the small intestine and may result in less systemic drug bioavailability after oral drug administration. Severe disturbances to blood flow will affect the pharmacokinetics of many drugs. Myocardiac infarction (MI) is a clinical example which often causes drug clearance to be greatly reduced, especially for drugs with large hepatic extraction.

Learning Questions

1. The normal dose of tetracycline is 250 mg PO every 6 hours. The dose of tetracycline for the uremic patient is determined by the \( k/u/k_N \) ratio, which is determined by the kidney function, as in Fig. 21-5. From line H in the figure, at \( Cl_{Cf} \) of 20 mL, \( k/u/k_N = 40\% \). In order to maintain the average concentration of tetracycline at the same level as in normal patients, the dose of tetracycline must be reduced.

\[
\frac{D_u}{D_N} = \frac{k}{k_N} = 40\% 
\]

\[
D_u = (250)(0.40) = 100 \text{ mg}
\]

2. The drug in this patient is eliminated by the kidneys and the dialysis machine. Therefore,

Total drug clearance = \( Cl_T + Cl_D \)
Using Equation 21.31,

\[ Cl_d = \frac{Q(C_a - C_x)}{C_a} \]

\[ Cl_d = \frac{50 (5 - 2.4)}{5} = 26 \text{ mL/min} \]

Total drug clearance = 10 + 26 = 36 mL/min

Since the drug clearance is increased from 10 to 36 mL/min, the dose should be increased if dialysis is going to continue. Since dose is directly proportional to clearance,

\[ \frac{D_a}{D_N} = \frac{36}{10} = 3.6 \]

The new dose should be 3.6 times the dose given before dialysis if the same level of antibiotics is to be maintained.

4. The creatinine clearance of a patient is determined experimentally by using Equation 21.11,

\[ Cl_{Cr} = \frac{C_u V \times 100}{C_{Cr} \times 1440} \]

\[ Cl_{Cr} = (0.1) (1800) (100) = 5.68 \text{ mL/min} \]

(2.2) (1440)

Assuming that the normal \( Cl_{Cr} \) in this patient is 100 mL/min, the uremic dose should be 5.7% of the normal dose, since kidney function is drastically reduced:

\[ (0.057) (20 \text{ mg/kg}) = 1.14 \text{ mg/kg given every 6 hours} \]

5. From Fig. 21-5, line F, at a \( Cl_{Cr} \) of 5 mL/min,

\[ \frac{k_u}{k_N} = 45\% \]

a. The dose given should be as follows:

\[ (0.45) (600 \text{ mg}) = 270 \text{ mg every 12 hours} \]

b. Alternatively, the dose of 600 mg should be given every

\[ 12 \times \frac{100}{45} = 26.7 \text{ h} \]

c. Since it may be desirable to give the drug once every 24 hours, both dose and dosing interval may be adjusted so that the patient will still maintain an average therapeutic blood level of the drug, which can then be given at a convenient time. Using the equation for \( C_{av}^\infty \),

\[ C_{av}^\infty = \frac{D_0}{k V_0 \tau} \]

\[ D_0 = 600 \text{ mg} \]

\[ \tau = 26.7 \text{ h} \]

\[ C_{av}^\infty = \frac{600}{k V_0 \times 26.7} \]

To maintain \( C_{av}^\infty \) the same, calculate a new dose, \( D_N \), with a new dosing interval, \( \tau_N \), of 24 hours.

\[ C_{av}^\infty = \frac{D_N}{k V_0 (24)} \]

Thus,

\[ \frac{600}{26.7} = \frac{D_N}{(24)} \]

Therefore,

\[ D_N = \frac{24}{26.7} \times 600 = 539 \text{ mg} \]

The drug can also be given at 540 mg daily.

6. For females, use 85% of the \( Cl_{Cr} \) value obtained in males.

\[ Cl_{Cr} = \frac{0.85 [140 - \text{age(year)}] \text{ body weight (kg)}}{72 \times (Cl_{Cr})} \]

\[ Cl_{Cr} = \frac{0.85 [140 - 38] 62}{(72)(1.8)} = 41.5 \text{ mL/min} \]

9. Gentamycin is listed in group K (Table 21.5). From the nomogram in Figure 21-5,

\[ Cl_{Cr} = 20 \text{ mL/min} \quad \frac{k_u}{k_N} = 25\% \]
Uremic dose = 25% of normal dose = (0.25) (1 mg/kg) = 0.25 mg/kg
For a 72-kg Patient:
Uremic dose = (0.25) (75) = 18.8 mg
The patient should receive 18.8 mg every 8 hours by multiple IV bolus injections.

**10. a.** During the first 48 hours postdose, $t_{1/2} = 16$ h.
For IV bolus injection, assuming first-order elimination:

\[ D_B = D_0 e^{-kt} \]

\[ D_B = 1000 e^{-0.693/16} \] (48)

\[ D_B = 125 \text{ mg remaining in body} \]
just before dialysis

During dialysis, $t_{1/2} = 4$ h, and

\[ D_B = 125 e^{-0.693/4(8)} = 31.3 \text{ mg after dialysis} \]

**b.** $V_D = (0.5 \text{ L/kg})(75\text{kg}) = 37.5 \text{ L}$
Drug concentration just before dialysis:

\[ C_p = 125/37.5 \text{ L} = 3.33 \text{ mg/L} \]

Drug concentration just after dialysis:

\[ C_p = 31.3/37.5 \text{ L} = 0.83 \text{ mg/L} \]

**CHAPTER 22**

**Frequently Asked Questions**

*Why are differential equations used to describe physiologic models?*

- Differential equations are used to describe the rate of drug transfer between different tissues and the blood. Differential equations have the advantage of being very adaptable to computer simulation without a lot of mathematical manipulations.

*Why do we assume that drug concentrations in venous and arterial blood are the same in pharmacokinetics?*

- After an IV bolus drug injection, a drug is diluted rapidly in the venous pool. The venous blood is oxygenated in the lung and becomes arterial blood. The arterial blood containing the diluted drug then perfuses all the body organs through the systemic circulation. Some drug diffuses into the tissue and others are eliminated. In cycling through the body, the blood leaving a tissue (venous) generally has a lower drug concentration than the perfusing blood (arterial). In practice, only venous blood is sampled and assayed. Drug concentration in the venous blood rapidly equilibrates with the tissue and will become arterial blood in the next perfusion cycle (seconds later) through the body. In pharmacokinetics, the drug concentration is assumed to decline smoothly and continuously. The difference in drug concentration between arterial and venous blood reflects drug uptake by the tissue, and this difference may have important consequences in drug therapy, such as tumor treatment.

*Why is statistical moment used in pharmacokinetics?*

- Statistical moment is adaptable to mean residence time calculation and is widely used in pharmacokinetics.

*Why is MRT used in pharmacokinetics?*

- Mean residence time (MRT) represents the average staying time of the drug in a body organ or compartment as the molecules diffuse in and out. MRT is an alternative concept used to describe how long a drug stays in the body. The main advantage of MRT is that it is based on probability and is consistent with how drug molecules behave in the physical world. Concentration in a heterogeneous region of the body may be hard to pinpoint.

**Learning Questions**

1. **a.** $\text{MRT} = \frac{[\text{AUMC}]_0}{[\text{AUC}]_0} = \frac{100 \text{ (mg/L) h}^2}{25 \text{ (mg/L) h}} = 4 \text{ h}$

   **b.** $\text{Cl}_T = \frac{D_0}{[\text{AUC}]_0} = \frac{500 \text{ mg}}{20 \text{ (mg/L) h}} = 25 \text{ L/h}$

   **c.** $V_{ss}$ may be calculated using Equation 22.49:

   \[ \text{MRT} = \frac{\text{Cl}_T}{V_{ss}} \]

   Therefore,

   \[ V_{ss} = \frac{\text{Cl}_T}{\text{MRT}} = \frac{25}{4} = 6.25 \text{ L} \]
2. MRT is not calculated directly based on its definition \((\text{AUC}/C_0)\), because it is not possible to determine \(C_0\) except with simple data involving a one-compartment model. Based on rigorous derivation, \(C_0\) is not \(C_p^0\) except in a one-compartment IV bolus dose; rather, it is the concentration \(D_T/V_D\) which is equal to \(C_p = C_p^0\) in the simple IV bolus dose. With oral absorption data, it is not possible to determine \(D_T/V_D\) without using a model.

3. If the data in Problem 1 are fitted to obtain \(k\), and \(k = 0.25 \text{ h}^{-1}\),

\[
\text{MRT} = \frac{1}{k} = \frac{1}{0.25} = 4 \text{ h}
\]

Although the answer agrees with the result calculated above using a noncompartmental approach, the calculation now uses an equation with assumptions of the one-compartment model for IV bolus.

4. The principal considerations in interspecies scaling are size, protein–drug binding, and maximum lifespan potential (MLP) of the species.

5. The model assumptions should be consistent with known information about the system. The number of model parameters should not exceed the available data, and an adequate degree of freedom should be present to test for lack of fit. The law of parsimony should apply at all times.
Appendix D: Guiding Principles for Human and Animal Research

ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

The Declaration of Helsinki, first published in 1964 by the World Medical Association, established recommendations guiding medical doctors in biomedical research involving human subjects (www.wma.net/e/policy/b3.htm). The Declaration governs international research ethics and defines rules for “research combined with clinical care” and “non-therapeutic research.” The Declaration of Helsinki has been revised periodically and is the basis of Good Clinical Practices used today. A copy of the latest revision is reproduced in this Appendix. The Declaration of Helsinki addressed the following issues:

• “Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights.”
• Research protocols should be clearly formulated into an experimental protocol and reviewed by an independent committee prior to initiation.
• Informed consent from all research participants is necessary.
• Research should be conducted by medically/scientifically qualified individuals.
• Risks should not exceed benefits.

The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, was published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research on April 18, 1979 (http://ohsr.od.nih.gov/mpa/belmont.php3). The Belmont Report identifies three principles, or general prescriptive judgments, that are relevant to research involving human subjects.

Boundaries Between Practice and Research

1. Practice refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.
2. Research designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, eg, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.
3. Experimental is when a clinician departs in a significant way from standard or accepted practice. The fact that a procedure is “experimental,” in the sense of new, untested, or different, does not automatically place it in the category of research.

Basic Ethical Principles

1. Respect for persons
2. Beneficence
3. Justice
Applications

1. Informed consent
2. Assessment of risks and benefits
3. Selection of subjects

The United States' Code of Federal Regulations (CFR) publishes regulations for the protection of human subjects. Title 45 Code of Federal Regulations Part 46 (45CFR46) contains federal regulations which directly apply to most human research done in the United States and are intended to protect all human subjects. 45CFR46 does the following:

• Defines activities that are subject to regulation.
• Details the composition and function of an Institutional Review Board (IRB).
• Describes expedited review procedures.
• Lists the criteria for review of research.
• Provides a detailed description of the informed consent process, including waivers.
• Describes the process for documenting consent, including waivers.
• There are three subparts of the regulations that include additional protections for vulnerable populations:
  Pregnant women, fetuses, and neonates
  Prisoners
  Children

Various resources concerning ethics involving human subjects research and Institutional Review Boards (IRBs) have been collected by the National Institutes of Health (www.nih.gov/sigs/bioethics/IRB.html).

GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

Animal experiments are to be undertaken only with the purpose of advancing knowledge. Consideration should be given to the appropriateness of experimental procedures, species of animals used, and number of animals required.

Only animals that are lawfully acquired shall be used in the laboratory, and their retention and use shall be in every case in compliance with federal, state, and local laws and regulations and in accordance with the NIH Guide.

Animals in the laboratory must receive every consideration for their comfort; they must be properly housed, fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during all surgical procedures. Where recovery from anesthesia is necessary during the study, acceptable technique to minimize pain must be followed. Muscle relaxants or paralytics are not anesthetics and they should not be used alone for surgical restraint. They may be used for surgery in conjunction with drugs known to produce adequate analgesia. Where use of anesthetics would negate the results of the experiment, such procedures should be carried out in strict accordance with the NIH Guide. If the study requires the death of the animal, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.


**DECLARATION OF HELSINKI**

*World Medical Association Declaration of Helsinki*

*Ethical Principles for Medical Research Involving Human Subjects*

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964; amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000


**Introduction**

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.
Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information, and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits, and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain
from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations, and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient–physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective,
the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician’s judgement it offers hope of saving life, reestablishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
Appendix E: Popular Drugs and Pharmacokinetic Parameters
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Availability (%)</th>
<th>Urinary Excretion (%)</th>
<th>Bound in Plasma (%)</th>
<th>Clearance (mL/min)</th>
<th>Volume of Distribution (L)</th>
<th>Half-Life (h)</th>
<th>Effective Concentrations</th>
<th>Toxic Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>88 ± 15</td>
<td>3 ± 1</td>
<td>0</td>
<td>350 ± 100</td>
<td>67 ± 8</td>
<td>2.0 ± 0.4</td>
<td>10–20 µg/mL</td>
<td>&gt;300 µg/mL</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>15–30 0.59 (0.58–0.98)</td>
<td>75 ± 10</td>
<td>15 ± 4</td>
<td>330 ± 80</td>
<td>48 ± 13</td>
<td>2.4 ± 0.7</td>
<td>Very long</td>
<td>Related to bone turnover</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>88 ± 16</td>
<td>20</td>
<td>71 ± 3</td>
<td>0.74 ± 0.14 mL/min/kg</td>
<td>0.72 ± 0.12 L/Kg</td>
<td>12 ± 2</td>
<td>20–40 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Alteplase (TPA)</td>
<td>—</td>
<td>Low</td>
<td>—</td>
<td>10 ± 4 mL/min/kg</td>
<td>0.1 ± 0.01 L/Kg</td>
<td>0.08 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>98</td>
<td>4</td>
<td>91 ± 42</td>
<td></td>
<td>19 ± 4</td>
<td>2.3 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>93 ± 10</td>
<td>86 ± 8</td>
<td>18</td>
<td>180 ± 28</td>
<td>15 ± 2</td>
<td>1.7 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>2–5</td>
<td>&gt;90</td>
<td>32 ± 14</td>
<td></td>
<td>53 ± 36</td>
<td>18 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>62 ± 17</td>
<td>82 ± 10</td>
<td>18 ± 2</td>
<td>270 ± 50</td>
<td>20 ± 5</td>
<td>1.3 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>68 ± 3</td>
<td>1.4 ± 1.2</td>
<td>49</td>
<td>650 ± 80</td>
<td>11 ± 2</td>
<td>0.25 ± 0.3</td>
<td>See salicylic acid</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>56 ± 30</td>
<td>94 ± 8</td>
<td>&lt;5</td>
<td>170 ± 14</td>
<td>67 ± 11</td>
<td>6.1 ± 2.0</td>
<td>1 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>50</td>
<td>57 ± 8</td>
<td>14–22</td>
<td>410 ± 250</td>
<td>120 ± 49</td>
<td>4.3 ± 1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>65</td>
<td>38 ± 11</td>
<td>30 ± 6</td>
<td>840 ± 100</td>
<td>57 ± 13</td>
<td>2.2 ± 0.5</td>
<td>50 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;70</td>
<td>&lt;1</td>
<td>74 ± 3</td>
<td>89 ± 37</td>
<td>98 ± 26</td>
<td>15 ± 5</td>
<td>6.5 ± 3 µg/mL</td>
<td>&gt;9 µg/mL</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>90 ± 9</td>
<td>91 ± 18</td>
<td>14 ± 3</td>
<td>300 ± 80</td>
<td>18 ± 2</td>
<td>0.90 ± 0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>52</td>
<td>71 ± 3</td>
<td>470 ± 120</td>
<td>18 ± 8</td>
<td>0.57 ± 0.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>75–90</td>
<td>25 ± 15</td>
<td>53 ± 5</td>
<td>170 ± 14</td>
<td>66 ± 4</td>
<td>2.7 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloridiazepoxide&lt;sup&gt;e&lt;/sup&gt;</td>
<td>100</td>
<td>&lt;1</td>
<td>96.5 ± 1.8</td>
<td>38 ± 34</td>
<td>21 ± 2</td>
<td>10 ± 3</td>
<td>&gt;0.7 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Chloroquine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>89 ± 16</td>
<td>61 ± 4</td>
<td>61 ± 9</td>
<td>750 ± 120</td>
<td>13,000 ± 4600</td>
<td>8.9 ± 3.1 days</td>
<td>15–30 ng/mL</td>
<td>0.25 µg/mL</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>&gt;90</td>
<td>20 ± 18</td>
<td>96 ± 1</td>
<td>2.1 ± 0.4</td>
<td>6.8 ± 0.8</td>
<td>33 ± 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>62 ± 6</td>
<td>62 ± 20</td>
<td>19</td>
<td>540 ± 130</td>
<td>70 ± 14</td>
<td>1.9 ± 0.3</td>
<td>0.8 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>60 ± 12</td>
<td>65 ± 12</td>
<td>40</td>
<td>420 ± 84</td>
<td>130 ± 28</td>
<td>4.1 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Method</td>
<td>Normal Range</td>
<td>Unit</td>
<td>Lower Limit</td>
<td>Upper Limit</td>
<td>Note</td>
<td></td>
<td></td>
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<tr>
<td>------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td>62 ± 11</td>
<td>ng/mL</td>
<td>20</td>
<td>210 ± 84</td>
<td>0.2–2 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td>&lt;1</td>
<td>ng/mL</td>
<td>93 ± 2</td>
<td>410 ± 70</td>
<td>100–400 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td>&lt;1</td>
<td>ng/mL</td>
<td>98.7 ± 0.2</td>
<td>27 ± 4</td>
<td>&gt;400 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diflunisal</td>
<td></td>
<td>6 ± 3</td>
<td>ng/mL</td>
<td>99.9 ± 0.01</td>
<td>0.1 ± 0.02</td>
<td>300–400 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitoxin</td>
<td></td>
<td>&gt;90</td>
<td>ng/mL</td>
<td>32 ± 15</td>
<td>97 ± 1</td>
<td>&gt;35 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td>70 ± 13</td>
<td>ng/mL</td>
<td>60 ± 11</td>
<td>25 ± 5</td>
<td>&gt;2 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td>44 ± 10</td>
<td>ng/mL</td>
<td>&lt;4</td>
<td>78 ± 3</td>
<td>&gt;10 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dirithromycin</td>
<td></td>
<td>10% (6–14)</td>
<td>mg/mL</td>
<td>17–25</td>
<td>10–30</td>
<td>44 (16–65)</td>
<td></td>
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<tr>
<td>Disopyramide</td>
<td></td>
<td>83 ± 11</td>
<td>mg/mL</td>
<td>55 ± 6</td>
<td>84 ± 28</td>
<td>&gt;8 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>35 ± 25</td>
<td>mg/mL</td>
<td>12 ± 7</td>
<td>84 ± 3</td>
<td>&gt;3 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td></td>
<td>77 ± 8</td>
<td>mL/min</td>
<td>79 ± 3</td>
<td>&lt;5</td>
<td>&gt;10 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td>77 ± 8</td>
<td>µg/mL</td>
<td>25 ± 15</td>
<td>0</td>
<td>&gt;100 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>—</td>
<td>µg/mL</td>
<td>3 ± 2</td>
<td>0.19 ± 0.04</td>
<td>10–100 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famiclovir</td>
<td></td>
<td>77 ± 8</td>
<td>µg/mL</td>
<td>74 ± 9</td>
<td>&lt;20</td>
<td>&gt;2.5 µg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td></td>
<td>45 ± 14</td>
<td>µg/mL</td>
<td>67 ± 15</td>
<td>17 ± 7</td>
<td>13 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>&gt;60</td>
<td>µg/mL</td>
<td>&lt;2.5</td>
<td>94</td>
<td>&lt;500 ng/mL</td>
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<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td>61 ± 17</td>
<td>µg/mL</td>
<td>66 ± 7</td>
<td>98.8 ± 0.2</td>
<td>25 µg/mL</td>
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<tr>
<td>Ganciclovir</td>
<td></td>
<td>3</td>
<td>µg/mL</td>
<td>73 ± 31</td>
<td>1–2</td>
<td>4.3 ± 1.6</td>
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<tr>
<td>Gentamicin</td>
<td></td>
<td>&gt;90</td>
<td>µg/mL</td>
<td>&lt;10</td>
<td>90 ± 25</td>
<td>&gt;5 µg/mL</td>
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<tr>
<td>Hydralazine</td>
<td></td>
<td>20–60</td>
<td>µg/mL</td>
<td>87</td>
<td>3900 ± 900</td>
<td>&gt;1 µg/mL</td>
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<tr>
<td>Imipramine</td>
<td></td>
<td>40 ± 12</td>
<td>µg/mL</td>
<td>&lt;2</td>
<td>90.1 ± 1.4</td>
<td>&gt;1 µg/mL</td>
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<tr>
<td>Indinavir</td>
<td></td>
<td>~3</td>
<td>µg/mL</td>
<td>~3</td>
<td></td>
<td>&gt;1 µg/mL</td>
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<tr>
<td>Indomethacin</td>
<td></td>
<td>98</td>
<td>µg/mL</td>
<td>15 ± 8</td>
<td>90</td>
<td>&gt;5 µg/mL</td>
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<tr>
<td>Drug</td>
<td>Oral Availability (%)</td>
<td>Urinary Excretion (%)</td>
<td>Bound in Plasma (%)</td>
<td>Clearance (mL/min)</td>
<td>Volume of Distribution (L)</td>
<td>Half-Life (h)</td>
<td>Effective Concentrations</td>
<td>Toxic Concentrations</td>
</tr>
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</tr>
<tr>
<td>Labetalol</td>
<td>18 ± 5</td>
<td>&lt;5</td>
<td>50</td>
<td>1750 ± 700</td>
<td>660 ± 240</td>
<td>4.9 ± 2.0</td>
<td>0.13 µg/mL</td>
<td>&gt;6 µg/mL</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>35 ± 11</td>
<td>2 ± 1</td>
<td>70 ± 5</td>
<td>640 ± 170</td>
<td>77 ± 28</td>
<td>1.8 ± 0.4</td>
<td>1.5–6 µg/mL</td>
<td>&gt;2 µg/mL</td>
</tr>
<tr>
<td>Lithium</td>
<td>100</td>
<td>95 ± 15</td>
<td>0</td>
<td>25 ± 8</td>
<td>55 ± 24</td>
<td>22 ± 8</td>
<td>0.5–1.25 mEq/L</td>
<td>&gt;2 meq/L</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>97 ± 2</td>
<td>65 ± 9</td>
<td>10</td>
<td>3.3 ± 0.5 mL/min/kg</td>
<td>2.3 ± 0.3 L/kg</td>
<td>8.0 ± 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>&lt;5</td>
<td>Negligible</td>
<td>95</td>
<td>4–18 mL/min/kg</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Meperidine</td>
<td>52 ± 3</td>
<td>1–25</td>
<td>58 ± 9</td>
<td>1200 ± 350</td>
<td>310 ± 60</td>
<td>3.2 ± 0.8</td>
<td>0.4–0.7 µg/mL</td>
<td>10 µM</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>70 ± 27</td>
<td>48 ± 18</td>
<td>34 ± 8</td>
<td>150 ± 60</td>
<td>39 ± 13</td>
<td>7.2 ± 2.1</td>
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<tr>
<td>Metoprolol</td>
<td>38 ± 14</td>
<td>10 ± 3</td>
<td>11 ± 1</td>
<td>1050 ± 210</td>
<td>290 ± 50</td>
<td>3.2 ± 0.2</td>
<td>25 ng/mL</td>
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<tr>
<td>Metronidazole</td>
<td>99 ± 8</td>
<td>10 ± 2</td>
<td>10</td>
<td>90 ± 20</td>
<td>52 ± 7</td>
<td>8.5 ± 2.9</td>
<td>3–6 µg/mL</td>
<td>&gt;2.0 µg/mL</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>87 ± 13</td>
<td>4–15</td>
<td>63 ± 3</td>
<td>6.3 ± 2.7 mL/min/kg</td>
<td>4.9 ± 0.5 L/kg</td>
<td>9.2 ± 2.1</td>
<td>0.5–2.0 µg/mL</td>
<td>&gt;2.0 µg/mL</td>
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<tr>
<td>Midazolam</td>
<td>44 ± 17</td>
<td>56 ± 26</td>
<td>95 ± 2</td>
<td>460 ± 130</td>
<td>77 ± 42</td>
<td>1.9 ± 0.6</td>
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<tr>
<td>Morphine</td>
<td>24 ± 12</td>
<td>6–10</td>
<td>35 ± 2</td>
<td>1600 ± 700</td>
<td>230 ± 60</td>
<td>1.9 ± 0.5</td>
<td>65 ng/mL</td>
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<tr>
<td>Moxalactam</td>
<td>76 ± 12</td>
<td>50</td>
<td>120 ± 30</td>
<td>—</td>
<td>19 ± 6</td>
<td>2.1 ± 0.7</td>
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</tr>
<tr>
<td>Nifedipine</td>
<td>50 ± 13</td>
<td>0</td>
<td>96 ± 1</td>
<td>490 ± 130</td>
<td>55 ± 15</td>
<td>1.8 ± 0.4</td>
<td>47 ± 20 ng/mL</td>
<td>&gt;30 µg/mL</td>
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<td>Nortriptyline</td>
<td>51 ± 5</td>
<td>2 ± 1</td>
<td>92 ± 2</td>
<td>500 ± 130</td>
<td>1300 ± 300</td>
<td>31 ± 13</td>
<td>50–140 ng/mL</td>
<td>&gt;500 ng/mL</td>
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<tr>
<td>Notilnicin</td>
<td>—</td>
<td>80–90</td>
<td>&lt;10</td>
<td>1.3 ± 0.2 mL/min/kg</td>
<td>0.2 ± 0.02 L/kg</td>
<td>2.3 ± 0.7</td>
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<td>Phenobarbital</td>
<td>100 ± 11</td>
<td>24 ± 5</td>
<td>51 ± 3</td>
<td>4.3 ± 0.9</td>
<td>38 ± 2</td>
<td>4.1 ± 0.8 days</td>
<td>10–25 µg/mL</td>
<td>&gt;30 µg/mL</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90 ± 3</td>
<td>2</td>
<td>89 ± 23</td>
<td>Dose-dependent</td>
<td>45 ± 3</td>
<td>Dose-dependent</td>
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<td></td>
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<tr>
<td>Pravastatin</td>
<td>18 ± 8</td>
<td>47 ± 7</td>
<td>43–48</td>
<td>3.5 ± 2.4 mL/min/kg</td>
<td>0.46 ± 0.04 L/kg</td>
<td>1.8 ± 0.8</td>
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<tr>
<td>Prazosin</td>
<td>68 ± 17</td>
<td>&lt;1</td>
<td>95 ± 1</td>
<td>210 ± 20</td>
<td>42 ± 9</td>
<td>2.9 ± 0.8</td>
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<tr>
<td>Procainamide</td>
<td>83 ± 16</td>
<td>67 ± 8</td>
<td>16 ± 5</td>
<td>350–840</td>
<td>130 ± 20</td>
<td>3.0 ± 0.6</td>
<td>3–14 µg/mL</td>
<td>&gt;14 µg/mL</td>
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<td>Drug</td>
<td>Cmax</td>
<td>IC50</td>
<td>Cmin</td>
<td>Vdmax</td>
<td>CL</td>
<td>T1/2</td>
<td>Elimination</td>
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<tr>
<td>Propranolol</td>
<td>26 ± 10</td>
<td>&lt;0.5</td>
<td>87 ± 6</td>
<td>840 ± 210</td>
<td>270 ± 40</td>
<td>3.9 ± 0.4</td>
<td>20 ng/mL</td>
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<tr>
<td>Pyridostigmine</td>
<td>14 ± 3</td>
<td>80–90</td>
<td>87 ± 3</td>
<td>600 ± 120</td>
<td>77 ± 21</td>
<td>1.9 ± 0.2</td>
<td>50–100 ng/mL</td>
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<tr>
<td>Quinidine</td>
<td>80 ± 15</td>
<td>18 ± 5</td>
<td>87 ± 3</td>
<td>190 ± 80</td>
<td>6.2 ± 1.8</td>
<td>2–6 μg/mL</td>
<td>&gt;8 μg/mL</td>
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<tr>
<td>Ranitidine</td>
<td>52 ± 11</td>
<td>69 ± 6</td>
<td>15 ± 3</td>
<td>730 ± 80</td>
<td>91 ± 28</td>
<td>2.1 ± 0.2</td>
<td>100 ng/mL</td>
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<td>Ribavirin</td>
<td>45 ± 5</td>
<td>35 ± 8</td>
<td>0</td>
<td>5 ± 1.0 mL/min/kg</td>
<td>9.3 ± 1.5 L/kg</td>
<td>28 ± 7</td>
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<td>Rifampin</td>
<td>7 ± 3</td>
<td>89 ± 1</td>
<td>57 ± 3</td>
<td>200 ± 110</td>
<td>68 ± 25</td>
<td>3.5 ± 0.8</td>
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<tr>
<td>Ritonavir</td>
<td>&lt;5</td>
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<tr>
<td>Salicylic acid</td>
<td>100</td>
<td>2–30</td>
<td>80–90</td>
<td>14±</td>
<td>12 ± 2</td>
<td>10–15</td>
<td>150–300 μg/mL</td>
<td>&gt;200 μg/mL</td>
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<tr>
<td>Saquinavir</td>
<td>&lt;5</td>
<td>Negligible</td>
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<tr>
<td>Sotalol</td>
<td>90–100</td>
<td>&gt;75</td>
<td>0</td>
<td>7.6 mL/min/kg</td>
<td>2.0 ± 0.4 L/kg</td>
<td>12 ± 3</td>
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<tr>
<td>Sulfamethoxazole</td>
<td>100</td>
<td>14 ± 2</td>
<td>62 ± 5</td>
<td>15 ± 1.4</td>
<td>10 ± 5</td>
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<tr>
<td>Sulfisoxazole</td>
<td>96 ± 14</td>
<td>49 ± 8</td>
<td>91 ± 1</td>
<td>23 ± 3.5</td>
<td>10.5 ± 1.4</td>
<td>6.6 ± 0.7</td>
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<tr>
<td>Sumatriptan</td>
<td>14 ± 5 (oral)</td>
<td>22 ± 4</td>
<td>14–21</td>
<td>0.65 ± 0.1 L/kg</td>
<td>1.9 ± 0.3</td>
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<td>Tamoxifen</td>
<td>—</td>
<td>&lt;1</td>
<td>&gt;98</td>
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<tr>
<td>Terbutaline</td>
<td>14 ± 2</td>
<td>56 ± 4</td>
<td>20</td>
<td>240 ± 40</td>
<td>125 ± 15</td>
<td>14 ± 2</td>
<td>2.3 ± 1.8 ng/mL</td>
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<td>Tetracycline</td>
<td>77</td>
<td>58 ± 8</td>
<td>65 ± 3</td>
<td>120 ± 20</td>
<td>105 ± 6</td>
<td>11 ± 1.5</td>
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<tr>
<td>Theophylline</td>
<td>96 ± 8</td>
<td>18 ± 3</td>
<td>56 ± 4</td>
<td>48 ± 21</td>
<td>35 ± 11</td>
<td>8.1 ± 2.4</td>
<td>10–20 μg/mL</td>
<td>&gt;20 μg/mL</td>
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<tr>
<td>Tobramycin</td>
<td>90</td>
<td>&lt;10</td>
<td>77</td>
<td>18 ± 6</td>
<td>2.2 ± 0.1</td>
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<tr>
<td>Tocainide</td>
<td>89 ± 5</td>
<td>38 ± 7</td>
<td>10 ± 15</td>
<td>180 ± 35</td>
<td>210 ± 15</td>
<td>14 ± 2</td>
<td>6–15 μg/mL</td>
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<tr>
<td>Tolbutamide</td>
<td>93 ± 10</td>
<td>96 ± 1</td>
<td>17 ± 3</td>
<td>7 ± 1</td>
<td>5.9 ± 1.4</td>
<td>80–240 μg/mL</td>
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<tr>
<td>Trimethoprim</td>
<td>100</td>
<td>69 ± 17</td>
<td>44</td>
<td>150 ± 40</td>
<td>130 ± 15</td>
<td>11 ± 1.4</td>
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<tr>
<td>Tubocurarine</td>
<td>63 ± 35</td>
<td>50 ± 8</td>
<td>135 ± 42</td>
<td>27 ± 8</td>
<td>20.6 ± 1.1</td>
<td>0.6 ± 0.2 μg/mL</td>
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<tr>
<td>Valproic acid</td>
<td>100 ± 10</td>
<td>1.8 ± 2.4</td>
<td>93 ± 1</td>
<td>7.7 ± 1.4</td>
<td>9.1 ± 2.8</td>
<td>14 ± 3</td>
<td>30–100 μg/mL</td>
<td>&gt;150 μg/mL</td>
</tr>
<tr>
<td>Vancocmycin</td>
<td>79 ± 11</td>
<td>30 ± 10</td>
<td>98 ± 7</td>
<td>27 ± 4</td>
<td>5.6 ± 1.8</td>
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</table>

(Continued)
### TABLE E-1 Pharmacokinetic and Pharmacodynamic Parameters for Selected Drugs (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Availability (%)</th>
<th>Urinary Excretion (%)</th>
<th>Bound in Plasma (%)</th>
<th>Clearance (mL/min/kg)</th>
<th>Volume of Distribution (L)</th>
<th>Half-Life (h)</th>
<th>Effective Concentrations</th>
<th>Toxic Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>22 ± 8 (oral)</td>
<td>&lt;3</td>
<td>90 ± 2</td>
<td>15 ± 6</td>
<td>5.0 ± 2.1 L/kg</td>
<td>4.0 ± 1.5</td>
<td>120 ± 20 mg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 ± 13 (sublingual)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>93 ± 8</td>
<td>&lt;2</td>
<td>99 ± 1</td>
<td>3.2 ± 1.7</td>
<td>9.8 ± 4.2 L/kg</td>
<td>37 ± 15</td>
<td></td>
<td>2.2 ± 0.4 μg/mL</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>88 ± 17</td>
<td>65 ± 17</td>
<td>&lt;4</td>
<td>4.1 ± 1.2 mL/min/kg</td>
<td>0.53 ± 0.13 L/kg</td>
<td>2.0 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>63 ± 13</td>
<td>18 ± 5</td>
<td>&lt;25</td>
<td>26 ± 6 mL/min/kg</td>
<td>1.4 ± 0.4 L/kg</td>
<td>1.1 ± 0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The values in this table represent the parameters determined when the drug is administered to healthy normal volunteers or to patients who are generally free from disease except for the condition for which the drug is being prescribed. The values presented here are data compiled from Hardman JG: Design and optimization of dosage regimens: Pharmacokinetic data. In: Goodman and Gilman’s The Pharmacological Basis of Therapeutics. 9th ed. Gilman AG et al (editors). McGraw-Hill, 1995. This source must be consulted for the effects of disease states on the pertinent pharmacokinetic parameters.*

**For a standard 70-kg person.**

**No pharmacodynamic values are given for antibiotics since these vary depending upon the infecting organism.**

**One or more metabolites are active. Clearance given for aspirin is for conversion to the active metabolite, salicylic acid; see that compound for further clearance data.**

**The values are within the therapeutic range for drugs exhibiting dose-dependent pharmacokinetics.**


Dirithromycin:
Erythropoietin:
Indinavir:
Alendronate:
Protease inhibitors:
Zidovudine, zalcitabine, and saquinavir:
Index

Page numbers followed by f indicate figures; page numbers followed by t indicate tables.

A
AAGP. See \( \alpha_1 \), Acid glycoprotein
Abbreviated New Drug Application (ANDA), 441, 748
bioequivalence studies for, 427, 427t, 428t
bioequivalence study waiver, 429–430
NDA compared with, 427, 427t
review of, 429, 429f
ABC transporters. See ATP-binding cassette transporters
Abilify. See Aripiprazole
Absolute bioavailability, 283–286, 406–407, 749
Absorption, 736–738, 747–748.
See also Oral absorption;
Physiologic absorption
administration route and,
321–324, 323r–324t
bioavailability and
bioequivalence problems, 414
disintegration compared with dissolution and,
363–364
in drug product design, 321, 333–334
first-order, 133f, 134–137,
136f, 137f, 736–738, 750–751
absorption and elimination rate constant effects on
maximum concentration, 143–144, 143t, 144f,
736–738
nonlinear elimination with,
192–193
rate constant determination,
137–147, 138f, 139f,
141f, 141t, 143t, 144f,
145f, 146r, 147t, 736–738
in GI tract, 339, 340f, 746
double-peak phenomenon,
347–348, 347f
emptying time, 341–342,
342f
food effects on, 343–347,
344r, 345f, 346f, 746–747
GI motility, 339–341, 340f,
341t
GI perfusion, 342–343
intestinal motility, 342
inhibition of, 596
of lipid-soluble drugs,
390–391, 747
lubricant effect on, 370, 370f
models for estimation of, 145
CRFA, 147–148, 148f
Loo–Riegelman method,
145–147, 145f, 146t,
147t, 738
particle size and, 366r, 367
pharmacokinetics of, 131–133,
132f
rate of, 541, 542r, 746–747
dissolution rate compared with, 381–382, 381f, 382f
ER drug products, 499, 500f
rate-limiting steps in, 363–
365, 364f, 365f, 747–748
solubility, pH, and, 366, 366r,
746–747
stability, pH, and, 366–367,
366r, 746–747
zero-order, 133–134, 737,
750–751
clinical application, 134,
134f
nonlinear elimination with,
192
Absorption enhancers, 397,
492–493
Absorption phase, of plasma
drug concentration–time
curve, 132, 132f
Absorption rate constants
determination of, 736–738
elimination rate constant
flip-flop with, 139–140,
139f, 737
lag time and, 138–139, 139f
with method of residuals,
137–138, 138f, 736
with modified Wagner–
Nelson method, 144–145
practice problem, 141r, 142
Absorption rate constants, determination of (Cont.):
with two-compartment oral absorption data, 145–147, 145f, 146t, 147t
with urinary data, 142–143
with Wagner–Nelson method, 140–142, 141f, 736, 738
maximum concentration, time to maximum concentration, and AUC response to, 143–144, 143f, 736–738
significance of, 133
Absorption window, 474, 746
Absorptive pressure, 208
Accumulation, 153–157, 154f, 155t, 156f, 157r, 158f, 158t, 159f
clinical example, 157–158
in tissues, 210–211
Accumulation half-life, 156–157, 157t
Accumulation index, 156, 166, 738
Accuracy, 572, 696, 699
Acetaminophen, 6, 52, 270, 271f
drug interactions of, 594
metabolism of, 269, 270f, 270t, 517, 743
protein binding of, 219
Acetanilide, 271f
Acetophenetidin, 271f
Acetylation, 273, 276, 303
Achlorhydric patients, 352
Achromycin V. See Tetracycline hydrochloride
α, Acid glycoprotein (AAGP), 220r, 221, 223–224, 232, 743
altered concentrations of, 238r, 245–246
Acids. See Weak acids
Acquired multidrug resistance, 311
Activated charcoal, 643
Active targeting, 519
Active transport, 329–330, 330f
Active tubular secretion, 111–112, 113r
Acute pharmacodynamic effect, 411–412, 411f, 412f
Adaptive dosing, 600–601
Adaptive model, 577
Adipose tissue. See Fat
Adjustment. See Dosage adjustment
Administration route, 253. See also specific routes
absorption and, 321–324, 323t–324t
determination of, 583, 583t
ADR. See Adverse drug reaction
Adrenal tissue, 209–210, 209f, 210f
β-Adrenergic antagonists, nonlinear pharmacokinetics of, 190, 190f
Adverse drug reaction (ADR) absorption pharmacokinetics and, 132–133
genetic differences involved in, 308, 309t
GI, 391
with IV bolus injections, 53
with lidocaine, 85–86
nonlinear pharmacokinetics causing, 195–196
in TDM, 575–576
viral, 597
Adverse effect, 462–463
Adverse event. See Adverse drug reaction
Adverse response, 543
Affinity, 208, 211, 329
Agenerase. See Amprenavir
Aging. See Elderly
Agnost, 527–529
Ajinmaline, 551–553, 552f
Alamino transfersases (ALT), 645
Albumin, 220–221, 220r, 226r, 227, 237, 238r, 517, 743
Albuterol, 312, 567
Alendronate sodium (Fosamax®), 346–347
Alfentanil, 231–232, 552, 553f
Alkaline phosphatase, 650
Allegra. See Fexofenadine
Alleles, 307, 316
Allergic response, 543, 752
Allometry, 663, 664t
Allosteric binding, 237, 241, 528
Allosteric effects, 549
Allosteric site, 260
ALT. See Alanine aminotransferases
Amberlite resins, 643–644
Ambien. See Zolpidem tartrate
Aminoglycosides, 77
dialysis removal of, 642–643
in elderly, 586–587
elimination rate constant and apparent volume of distribution of, 165–166
nonlinear pharmacokinetics of, 177, 194
in obese patients, 589
renal impairment dose adjustments for, 625, 756
Aminophylline, 98–99, 579
Aminotransferase, 650
Amiodarone, 76
Ammonium chloride, 112
Amobarbital, 222
Amorphous forms, 367
Amount of drug remaining to be excreted method. See Sigma-minus method
Amoxicillin, 73, 170
Amoxicillin/clavulanate (Augmentin Bid-875), 170
Amphetamine, 113, 211, 270, 274
Ampicillin, 368
Amprenavir (Agenerase), 245–246
Amrinone, 729–730
Analysis of variance (ANOVA), 424, 702–704
ANDA. See Abbreviated New Drug Application
Anhydrous state, 367
Animal studies ethical principles in, 762
interspecies scaling in, 663–667, 663f, 664t, 666r, 667f, 759
ANOVA. See Analysis of variance
Antacids, 112, 353, 596–597, 747
Antagonist, 527–529
Antibiotics, 538. See also specific drugs
dose determination for, 580
in elderly, 586–587
in infants and children, 585
MIC in dosing of, 170
pharmacokinetic/pharmacodynamic relationships and,
539–540, 539f, 539r, 540f
renal impairment dose adjustments for, 625, 756
Anticancer drugs, 540–541, 540f, 541f. See also specific drugs
Anticholinergic drugs, 352–353, 748
Antihypertensive drugs, 195. See also specific drugs
Antiloga, 22
Antithrombin effect, 557–558, 558f
Antipsychotics, 352–353, 748
Antisense oligonucleotide drugs, 513
Apparent volume of distribution. See also Clearance and volume of distribution ratio
of aminoglycosides, 165–166
clearance relationship with, 125–126, 126t
elimination half-life relationship with, 228–229
IV infusion for determination of, 100
in multicompartment models, 70–73, 71t, 728
in noncompartmental model, 52
in one-compartment open model, 44–46, 44f, 50, 723–725
calculation of, 46–47, 46f
significance of, 47–48, 47t
in physiologic drug distribution model, 213,
217–218, 218f, 219f, 724
calculation of, 213–216, 214f, 215t
in complex biological systems, 216–217, 217f
practice problem, 216
of popular drugs, 768–772f
protein binding of drugs and, 222–223, 223f
clinical example, 226–227
effect of changing plasma protein, 222–225
at steady state, 72, 101–103
in two-compartment open model, 70–73, 71t
central compartment volume, 70–71, 71t, 74
extrapolated volume, 72
practical focus, 75–77
practice problem, 73–74, 73f
significance of, 74–75
steady state volume, 72
tissue compartment volume, 75
volume by area, 72–73
Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), 385, 437–440, 438r, 440r
Approximation, 21
Area, volume of distribution by, 72–73
Area under the curve (AUC), 8, 8f, 25–26, 406
absorption rate constants determined with,
140–142, 141f, 736–738
apparent volume of distribution calculated from,
46–47
clearance determined from, 52
elimination and absorption rate constant effects on,
143–144, 143r, 144f, 736–738
in linearity determination, 198–199, 199f
in MRT calculations, 672–679, 680f, 681–682
in multiple-dosage regimens, 160
Area under the first moment curve (AUMC), 672, 676, 677r–678r, 678–682, 680f
Aripiprazole (Abilify), 337, 651
Aspirin, 52, 270, 345f, 346
absorption of, 357, 746
ADRs of, 597
dissolution rate compared with absorption rate of, 381–382f
pharmacodynamic model of, 557–558, 558f
protein binding of, 243
Assays, in TDM, 571–573
Association constant, 232–236, 234f, 235f, 236f, 743–744
AST. See Aspartate aminotransferase
Asynthetic reactions. See Phase I reactions
Atomoxetine, 191
ATP-binding cassette (ABC) transporters, 76, 312, 331
Augmentin Bid-875. See Amoxicillin/clavulanate
AUIC, 752
INDEX

AUMC. See Area under the first moment curve
Auto-induction, 193–194, 279–280
Auto-inhibition, 193–194
Autoregulation, 110, 110f
Azithromycin (Zithromax), 82, 102–103, 226
Azo drugs, 269

B
BACPACs. See Bulk actives postapproval changes
Bactrim. See Sulfamethoxazole/trimethoprim
Balsalazide, 322, 324r, 339
Barbiturates, 278
Base. See Weak base
Bayesian theory, 598–600, 600f, 753
adaptive method for dosing with feedback, 600–601
Bayes estimator, 601, 602f, 602r
comparison of Bayes, least-squares, steady-state, and Chiou methods, 602–603, 603f, 604r
BCS. See Biopharmaceutical Classification System
BDDCS. See Biopharmaceutical Drug Disposition Classification System
Beads, 484–486, 486r
Bell-shaped curve. See Normal distribution
Belmont Report, 761
Benzocaine, 270
Benzodiazepines, 231
Beta phase. See Elimination phase
Bias, 694, 699
Bicarbonate, 112
Bicillin, 53
Biexponential profiles, 63, 84, 84f
Biliary clearance, 292
Biliary excretion, 291–292, 291f, 291r
Biliary clearance estimation, 292
clinical example, 292–293
enterohepatic circulation, 292
inhibition of, 596
significance of, 292
Bilirubin, 650
Binding. See also Protein binding of drugs
allosteric, 237, 241, 528
Binding constants, 232–233
graphic determination of, 744
in vitro methods, 233–234, 233f, 234f, 235f
in vivo methods, 234–236
Binding sites, 232–233, 743
drug interactions due to competition for, 237, 241
graphic determination of, 744
in vitro methods, 233–234, 233f, 234f, 235f
in vivo methods, 234–236
Bioavailability, 2, 440, 745, 747–749
absolute, 283–286, 406–407, 749
biopharmaceutic factors in, 361–363, 747–748
blood flow effects on, 284–286, 284r, 286f
drug design considerations, 388, 747–748
drug products where, may be self-evident, 432–433
drug products with possible problems with, 413–414
food effects on, 344r, 345f
of IR drug products, 473, 473f
nonlinear pharmacokinetics and, 196
transporter role in, 293–294, 293f
Bioavailability studies, 403
of ER drug products, 416, 499–500
occupancy time, 499, 500f
pharmacokinetic profile, 499
rate of drug absorption, 499, 500f
steady-state plasma drug concentration, 499
methods for assessing, 407–413, 408t
acute pharmacodynamic effect, 411–412, 411f, 412f
clinical observations, 412
in-vitro studies, 412–413
plasma drug concentration, 408–410, 409f, 410f
urinary drug excretion data, 410, 410f, 411f
purpose of, 405–406
relative and absolute bioavailability, 406–407, 749
special concerns in, 436–437, 436r, 437r
Bioequivalence, 440–441, 748–749
bases for determining, 413
of biopharmaceuticals, 522–523
drug products where, may be self-evident, 432–433
drug products with possible problems with, 413–414
Bioequivalence interval, 424
Bioequivalence requirement, 440
Bioequivalence studies, 403, 413–414
for ANDA, 427, 427r, 428t
clinical example, 422–423
clinical significance of, 435
crossover study designs for, 418–423
clinical endpoint, 421
Latin-square crossover designs, 418–419, 418r, 419r, 749
multiple-dose, 420–421
nonreplicate, parallel, 420
in patients maintained on reference, 421–422, 422f
replicated, 419
scaled average, 419–420
data evaluation, 423–424
ANOVA, 424
pharmacokinetic, 423
statistical, 423
two one-sided tests
procedure, 423–424, 424r
design and evaluation of, 414–417
analytical methods, 417
combination drug products, 416–417
extended-release formulations, 416
objectives, 414
RLD, 416
study considerations, 414–416, 415r
of ER drug products, 499–500
example of, 424–427, 425f, 425r, 426f, 426r, 427r
methods for assessing, 408r
possible surrogate markers for, 437, 437r
special concerns in, 436–437, 436r, 437r
statistics in, 704
study designs, 417–418
fasting study, 417
food intervention study, 417–418, 748
waivers of, 429–430
Bioequivalent drug products, 440–441
Biologic drugs. See Biopharmaceuticals
Biologic specimen, 6
Biological systems, volume of distribution in, 216–217, 217f
Biomarkers, 307, 316, 530
clinical considerations for, 531–532
clinical endpoints, pharmacodynamics, and, 531, 532r
pharmacogenomic, 315r, 532
Biopharmaceuticals, 1–3, 2f, 3t, 506, 507r–508t. See also Biotechnology
bioequivalence and comparability of, 522–523
follow on, 522
generic, 433–434
pharmacokinetics of, 521–522
Biopharmaceutical Classification System (BCS), 383, 431–433, 431r
BDDCS, 432
disintegration test for, 364
dissolution, 432
drug products where bioavailability or bioequivalence may be self-evident, 432–433
permeability, 432
solubility, 431–432
Biopharmaceutical Disposition Classification System (BDDCS), 432
Biopharmaceutics, 361, 747–748
basis of, 362
bioavailability and, 361–363, 747–748
dissolution and drug release testing, 370–374, 371r
dissolution profile comparisons, 386, 386f
dose and dosage form, 363
drug design considerations, 387, 387r
drug product stability, 386–387
of ER drug products, 473–475
large intestine, 475
small intestine and transit time, 474–475
stomach, 474
formulation factors, 368–370, 368r, 369r, 370f
IVIVC, 380–386
physicochemical properties, 366–368, 366r, 367f, 368f, 747–748
QbD integration with, 455
455f
review, 427–429, 429r
Biosimilar drug products. See Generic biologics
Biosimilarity, interchangeability of, 433–434
Biotechnology, 505–514, 751
gene therapy, 512–513
miRNA, 513–514
monoclonal antibodies, 506, 507r–508r, 508–509, 509r, 510f, 511r–512r, 512
oligonucleotide drugs, 513
protein drugs, 506, 507r–508r
Biotransformation. See Metabolism
Biowaiver, 429–430
Biperiden, 663
Bitolterol mesylate (Tornalate), 485–486
Black box warnings, 315r
Bleomycin, 391
Blood, 717
drug concentration in measurement of, 6–7, 7t
units of expression for, 33
Blood flow
bioavailability relationship with, 284–286, 284r, 286r
to GI tract, 342–343, 349
hepatic, in hepatic disease, 648, 756
hepatic and intrinsic clearance relationships with, 286–287
hepatic clearance of protein-bound drugs relationship with, 289–290, 289f
to liver, 265, 266f, 267f
metabolism relationship with, 284–286, 284r, 286r
physiologic drug distribution and, 208–210, 208f, 208r, 209f, 210f
renal, 109–110, 110f
to tissues, 63r
Blood flow models. See Physiologic models
Blood urea nitrogen (BUN), 622
Blood–brain barrier, 212–213
Blood-flow-limited model. See Perfusion-limited models
Index

BMI. See Body mass index
Body clearance. See Clearance
Body mass index (BMI), 589
Body surface area (BSA), 34
Bolus administration. See Intravenous bolus administration; Loading dose
Bootstrap, 700
Bound in plasma parameters, 768–772
Bovine spongiform encephalopathy (BSE), 455–456, 456
Bowman’s capsule, 109
Brain, 212–213
Brand name, 441
BSA. See Body surface area
BSE. See Bovine spongiform encephalopathy
Buccal tablets, 392
Buffering agents, 366, 391
Bulk actives postapproval changes (BACPACs), 463
BUN. See Blood urea nitrogen
Bupivacaine, 246
Bupropion hydrochloride (Wellbutrin), 170–171, 498
Buserelin acetate (Suprefact), 395
Butorphanol tartrate (Stadol NS), 395

C
Caco-2 cells, 350
CAD. See Cyclic antidepressant drugs
Caffeine, 277, 665, 667
Calcium, 353
Calculators, 20–21
Calculus, 24
differential, 24
integral, 24–26, 25
Capacity, of enzyme, 179
Capacity-limited, binding-insensitive drugs, 290, 290
Capacity-limited and binding-sensitive drugs, 290, 290
Capacity-limited elimination, 181–191, 182f, 183r, 184f, 185f, 186f, 186r, 188f, 189f, 190f
Capacity-limited metabolism, 177–179, 741
Capacity-limited pharmacokinetics, 181–182, 182f, 183r
clinical focus, 191
determination of Michaelis constant and maximum elimination rate, 184–188, 184f, 185f, 186f, 186r, 188f, 741
elimination half-life in, 189
interpretation of Michaelis constant and maximum elimination rate, 188–189, 189f, 741
practice problems, 183–184
CAPD. See Continuous ambulatory peritoneal dialysis
Capillaries, 205–207, 206f, 207r
Capillary membranes, 211–212
Carbamazepine, 177, 194, 278, 279, 315f
Carprofen, 274
Carrier-mediated transport, 329–333, 330f, 331r, 332f, 333r
Carriers. See Drug carriers
Case-control study, 694
Catenary model, 13–14, 13f
CAVH. See Continuous arteriovenous hemofiltration
Cefamandole, 610, 754
CEFazolin, 222–223, 223f, 333
Cefoperazone, 222–223, 223f, 647, 649
Cefotaxime, 539, 540f
Cefotetan, 222–223, 223f
Cefpodoxime proxetil, 346
Celiac disease, 352
Cell, drug distribution within, 212
Cell membranes
drug passage across
carrier-mediated transport, 329–333, 330f, 331r, 332f, 333r
passive diffusion, 326–329, 327f, 329f, 329r
nature of, 324–326, 325f, 326f
permeability of, 211–212
Central compartment, 62–66, 65f, 730
distribution in, 215, 742–743
elimination from, 77
MRT calculations in, 679–682, 681
renal clearance in, 124
volume of distribution of, 70–71, 71f
Central limit theorem, 696
Cephalosporins, 218, 222–223, 223f, 333
hypersensitivity to, 543
pharmacokinetic/pharmacodynamic relationships and, 539–540, 539f
protein binding of, 227, 227f
repetitive IV injections of, 162
Cephalothin, 264–265, 264
Cephradine (Velosef), 732
Cerebral spinal fluid (CSF), 212–213
CFR. See Code of Federal Regulations
cGMPs. See Current Good Manufacturing Practices
Chemical name, 441
Chemistry, Manufacturing, and Controls (CMC), 459, 460f
Cheng–Prusoff equation, 262
CHF. See Congestive heart failure
Child–Pugh classification, 648, 648r
Children
dose determination in, 584–585, 585r
renal impairment in, 624, 624f
Child–Turcotte classification, 648, 649r
in hepatic disease, 648
of protein-bound drugs, 289, 289f
IV infusion for determination of, 94, 99–100, 731–732
models of
dose and dosage interval determination, 582–583
dose determination, 579–580
dosing frequency determination, 581–582
dosing in obese patients, 588–590
drug interactions in absorption inhibition, 596
altered renal reabsorption due to urinary pH changes, 596–597
MAO inhibition, 595–596
metabolism induction, 596
metabolism inhibition, 594–595
pharmacokinetics of, 590–594, 590f
plasma drug concentration in response to dose and dosage interval changes, 580–581
popPK in, 4, 597–598, 753
adaptive method for dosing with feedback, 600–601
analysis of population pharmacokinetic data, 603–605
Bayes estimator, 601, 602f, 602r
Bayesian theory introduction, 598–600, 600f, 753
clinical example of, 606–607, 606r
Clinical pharmacokinetics, PopPK in (Cont.):
  comparison of Bayes, least-squares, steady-state, and Chiou methods, 602–603, 603r, 604r
decision analysis involving diagnostic test, 607–608, 607t, 608r
model selection criteria, 607 practical focus, 4–5, 5f
regional pharmacokinetics in, 608–609
TDM, 4, 567–568, 567f, 567t, 752–753
ADRs and, 575–576
clinical example, 574–575
dosage adjustment in, 574
dosage regimen design for, 568–569
drug assay in, 571–573
drug concentration measurements in, 570–571, 571t, 575
drug pharmacokinetics in, 569–570
drug product in, 570
drug selection for, 568, 569t
patient compliance in, 570
patient response evaluation in, 570
pharmacokinetic evaluation in, 573–574, 573r
serum drug concentration monitoring in, 574
Clinical pharmacokinetic services (CPKS), 4. See also Therapeutic drug monitoring
Clinical toxicology, 5–6
Clobazam, 231
Clockwise hysteresis, 552–556, 553f
Clopidogrel (Plavix), 335
Clozapine, 312
CMC. See Chemistry, Manufacturing, and Controls
CMVs. See Critical manufacturing variables
Cocaine, 9, 81r, 541–542, 552, 553f
Cockcroft and Gault method, 623–626, 623f, 635–636, 757
Code of Federal Regulations (CFR), 762
Codeine, 270, 277, 308, 310–311
Cohort study, 693
Colchicine, 62, 730
Colon, 339
Colonic drug delivery, 392–393
Combination drug products, 416–417
Comparative dissolution profiles, 430
Compartment models, 11–14, 12f, 13f, 61, 728–730.
  See also specific models of IV bolus administration, determination of, 79–80, 80f
  physiologic models compared with, 667–668, 717
Competitive inhibition, 259f, 260, 260f
Compliance, in TDM, 570
Computers, 20–21, 707. See also Software
electronic spreadsheets, 711, 712f, 713f, 714f, 715f, 716
Concentration. See also Plasma drug concentration calculations for, 34–35, 34t
drug response relationship with, 4–5, 5f
measurement of, 6
biologic specimen sampling, 6
blood, plasma, or serum concentrations, 6–7, 7t, 9–10
forensic measurements, 9
plasma drug concentration–time curve, 7–8, 7f, 8f, 717
saliva concentrations, 9
significance of, 9–10
in TDM, 570–571, 571t, 575
tissue concentrations, 8
urine and feces concentrations, 8–9
monitoring of, 574
units of expression for, 33, 34t
Concerta. See Methylphenidate
Conditional probability curves, 599, 600f
Confidence interval approach.
  See Two one-sided tests procedure
Confidence limit, 698–700, 700f
Congestive heart failure (CHF), 352, 756
Conjugation reactions. See Phase II reactions
Constant IV infusion, 163–164, 738
Constrained data, 15
Continuous ambulatory peritoneal dialysis (CAPD), 639
Continuous arteriovenous hemofiltration (CAVH), 644
Continuous process verification, 465
Continuous renal replacement therapy (CRRT), 644
Continuous veno-venous hemofiltration (CVVH), 644
Controlled-release drug product, 470, 471t
Convective transport, 336
Convolution, 144–145
Cooperative effects, 549
Cooperativity, 233
Coordinates
  rectangular, 26–28, 26f, 28f
  semilog, 26–28, 27f, 719
Core tablets, 487
Corticosteroids, 546, 547f, 548f
Coumarin, 279
Counterclockwise hysteresis, 552–553, 553f
<table>
<thead>
<tr>
<th>Term</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPKS. See Clinical pharmacokinetic services</td>
<td>781</td>
</tr>
<tr>
<td>CPP. See Critical process parameters</td>
<td></td>
</tr>
<tr>
<td>Creatinine, 111, 621, 733. See also Serum creatinine concentration</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
</tr>
<tr>
<td>dose adjustment based on, 622–623, 755–758</td>
<td></td>
</tr>
<tr>
<td>in adults, 623–624, 623f, in children, 624, 624f</td>
<td></td>
</tr>
<tr>
<td>eGFR using MDRD or CKD–EPI equations, 625–626</td>
<td></td>
</tr>
<tr>
<td>GFR measurements for, 626–627, 626t</td>
<td></td>
</tr>
<tr>
<td>practice problems, 624–625, 625t</td>
<td></td>
</tr>
<tr>
<td>in elderly, 588</td>
<td></td>
</tr>
<tr>
<td>elimination rate constant relationship with, 628–629, 628f, 629f</td>
<td></td>
</tr>
<tr>
<td>renal function classification based on, 629t</td>
<td></td>
</tr>
<tr>
<td>CRFA. See Cumulative relative fraction absorbed</td>
<td></td>
</tr>
<tr>
<td>Critical dose drugs. See Narrow therapeutic index drugs</td>
<td></td>
</tr>
<tr>
<td>Critical manufacturing variables (CMVs), 2, 453–454, 462</td>
<td></td>
</tr>
<tr>
<td>Critical process parameters (CPP), 453–454</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease, 339, 352</td>
<td></td>
</tr>
<tr>
<td>Cross tolerance, 542</td>
<td></td>
</tr>
<tr>
<td>Crossover study designs for bioequivalence, 418–423 clinical endpoint, 421</td>
<td></td>
</tr>
<tr>
<td>Latin-square crossover designs, 418–419, 418f, 419t, 749</td>
<td></td>
</tr>
<tr>
<td>multiple-dose, 420–421 nonreplicate, parallel, 420</td>
<td></td>
</tr>
<tr>
<td>in patients maintained on reference, 421–422, 422f replicated, 419</td>
<td></td>
</tr>
<tr>
<td>scaled average, 419–420</td>
<td></td>
</tr>
<tr>
<td>CRRT. See Continuous renal replacement therapy</td>
<td></td>
</tr>
<tr>
<td>CSF. See Cerebral spinal fluid Cumulative amount of drug excreted in urine, 410, 410f</td>
<td></td>
</tr>
<tr>
<td>Cumulative relative fraction absorbed (CRFA), 147–148, 148f</td>
<td></td>
</tr>
<tr>
<td>Current Good Manufacturing Practices (cGMPs), 458, 458t</td>
<td></td>
</tr>
<tr>
<td>Curve fitting, 26–29, 26f, 29f</td>
<td></td>
</tr>
<tr>
<td>CVVH. See Continuous venovenous hemofiltration</td>
<td></td>
</tr>
<tr>
<td>Cyclic antidepressant drugs (CAD), 277–278</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, 160, 275–276</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A, 16f</td>
<td></td>
</tr>
<tr>
<td>Cylinder method, 372t, 376</td>
<td></td>
</tr>
<tr>
<td>Cytochrome P-450 (CYP450), 191, 268</td>
<td></td>
</tr>
<tr>
<td>CYP1A2, 311</td>
<td></td>
</tr>
<tr>
<td>CYP2C9, 311</td>
<td></td>
</tr>
<tr>
<td>CYP2C19, 311</td>
<td></td>
</tr>
<tr>
<td>CYP2D6, 191, 277, 279, 310–311</td>
<td></td>
</tr>
<tr>
<td>CYP3A, 275–277, 279</td>
<td></td>
</tr>
<tr>
<td>drug interactions of, 191, 593–594</td>
<td></td>
</tr>
<tr>
<td>induction of, 279–280, 280r, 596</td>
<td></td>
</tr>
<tr>
<td>polymorphisms of, 276–278, 277r, 305, 310–311</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Data analysis for linearity determination, 198–200, 198f, 199t statistics in, 694, 694f</td>
<td></td>
</tr>
<tr>
<td>Data collection, 694–696</td>
<td></td>
</tr>
<tr>
<td>Data dredging, 688</td>
<td></td>
</tr>
<tr>
<td>Debrisoquine, 277, 308, 310</td>
<td></td>
</tr>
<tr>
<td>Decision analysis, for diagnostic tests, 607–608, 607r, 608r</td>
<td></td>
</tr>
<tr>
<td>Declaration of Helsinki, 761, 762–765</td>
<td></td>
</tr>
<tr>
<td>Deconvolution, 145</td>
<td></td>
</tr>
<tr>
<td>Definite integral, 25</td>
<td></td>
</tr>
<tr>
<td>Delayed release drug products, 392, 470, 471r</td>
<td></td>
</tr>
<tr>
<td>DELS. See Difference extended least-squares Deoxyribonucleic acid (DNA), 505</td>
<td></td>
</tr>
<tr>
<td>Depakene. See Valproic acid</td>
<td></td>
</tr>
<tr>
<td>Dependent variable, 10</td>
<td></td>
</tr>
<tr>
<td>Descriptive model, 558</td>
<td></td>
</tr>
<tr>
<td>Descriptive terms, 697, 697</td>
<td></td>
</tr>
<tr>
<td>Design space, 454, 465</td>
<td></td>
</tr>
<tr>
<td>Desipramine, 191, 278</td>
<td></td>
</tr>
<tr>
<td>Desolvated solvates, 367</td>
<td></td>
</tr>
<tr>
<td>Determinate errors, 33</td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine hydrochloride injection (Precedex®), 221</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan, 277</td>
<td></td>
</tr>
<tr>
<td>Diagnostic tests, decision analysis involving, 607–608, 608r</td>
<td></td>
</tr>
<tr>
<td>Dialysance, 641</td>
<td></td>
</tr>
<tr>
<td>Dialysis, 639–641, 640r</td>
<td></td>
</tr>
<tr>
<td>clinical examples, 642–643</td>
<td></td>
</tr>
<tr>
<td>practice problem, 641–642, 642f, 642r</td>
<td></td>
</tr>
<tr>
<td>Dialysis clearance, 641, 756–758</td>
<td></td>
</tr>
<tr>
<td>Diazepam (Valium), 541, 581</td>
<td></td>
</tr>
<tr>
<td>drug interactions of, 594–595</td>
<td></td>
</tr>
<tr>
<td>elimination of, 230–231</td>
<td></td>
</tr>
<tr>
<td>pharmacogenetics of, 315</td>
<td></td>
</tr>
<tr>
<td>protein binding of, 221–222</td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin, 610, 754</td>
<td></td>
</tr>
<tr>
<td>Dicumarol, 10, 329</td>
<td></td>
</tr>
<tr>
<td>Diet. See Food</td>
<td></td>
</tr>
<tr>
<td>Difference extended least-squares (DELS), 605</td>
<td></td>
</tr>
<tr>
<td>Difference factor, 386</td>
<td></td>
</tr>
<tr>
<td>Differential calculus, 24</td>
<td></td>
</tr>
<tr>
<td>Differential equations, 758</td>
<td></td>
</tr>
<tr>
<td>Differential probability, 672</td>
<td></td>
</tr>
<tr>
<td>Diffusion, 205–208, 206f, 207r across cell membranes, 326–329, 327f, 329f, 329t facilitated, 330</td>
<td></td>
</tr>
<tr>
<td>protein binding and, 226r</td>
<td></td>
</tr>
<tr>
<td>Diffusion cells method, 372r, 377, 377f</td>
<td></td>
</tr>
<tr>
<td>Diffusion coefficient, 327–328</td>
<td></td>
</tr>
</tbody>
</table>
Diffusion-limited models, 208, 208f, 661–662, 662r
Diffunisal, 588
Digestive phase, 474
Digoxin (Lanoxin), 10, 14, 610, 754
absorption of, 332, 353
accumulation of, 211
affinity of, 329
dialysis removal of, 642
distribution and elimination
half-lives of, 81r
distribution of, 210, 218
dosing frequency of, 581
drug interactions of, 282, 335, 596
loading dose of, 75–76
MRT of, 684–685
in obese patients, 589
TDM of, 574–575
two-compartment model for
distribution of, 68–69, 68r, 69r, 70r, 80
in uremic patients, 635
Dilaudid. See Hydromorphone
Dipyridamole, 347–348, 347f
Direct method, for determination
of Michaelis constant and
maximum elimination
rate, 187–188
Dirithromycin, 228–229
Disassociation constant, 223–232
Disease states. See also specific
states
absorption in, 351–352
Disintegration, 364
dissolution and absorption
compared with, 363–364
testing of, 364, 364f
Disopyramide, 274
Dispersion of data, 697
Displacement
drug interactions arising from,
246–247
protein binding of drugs and,
241–244, 242f, 244r
Dissolution, 364
BCS and, 432
bioavailability and bioequivalence problems, 414
clinical performance and,
383–384
disintegration compared with
absorption and, 363–364
of ER drug products, 472, 472f, 750–751
excipients and, 368, 369r
lubricant effect on, 370, 370f
plasma concentration
compared with, 382, 382f, 383f
profile comparisons,
386, 386f
rate of
absorption rate compared
with, 381–382, 381f, 382f
permeation rate and, 383
serum concentration compared
with, 383, 383f
solubility and, 364–365, 365f
steps in, 365, 365f
Dissolution in reactive medium, 369
Dissolution test, 365, 370–374, 371r
apparatus for, 372–373, 372r
development and validation
of, 371–374, 372r, 373r, 373r

discriminating, 371, 384
of enteric-coated products,
377
of ER drug products, 497, 497f, 750–751
mechanical calibration for,
378
medium for, 373–374
meeting requirements for,
378–379, 378r, 379r
methods for, 372r, 374–376, 375f
cylinder, 372r, 376
diffusion cells, 372r, 377, 377f
flow-through-cell, 372r, 376
intrinsic dissolution method,
377
paddle method, 372r,
374–375, 375f
paddle-over-disk, 372r, 376
peristalsis method, 377
reciprocating cylinder, 372r,
375
reciprocating disk, 372r,
376
rotating basket, 372r, 374
rotating bottle method, 372r,
376
for novel/special dosage
forms, 377–378
performance verification test
for, 378
for phenytoin, 384–385
variable control problems in,
379–380
Distribution. See also Apparent
volume of distribution;
Physiologic drug
distribution
within cells, 212
in central compartment, 215,
742–743
after IV bolus administration,
743
nonlinear elimination com-
bined with, 191–193
response and, 544–545, 544f,
545f, 546r
statistical, 696–698, 698f,
700–701
Distribution equilibrium, 64
Distribution half-life, 80, 81r,
208–210, 208r, 209r, 210f, 742
Distribution phase
length of, 84–85, 85f
significance of, 85
in two-compartment open
model, 64–65, 64f
DNA. See Deoxyribonucleic acid
Docetaxel, 351
Dosage
biopharmaceutic consider-
ations for, 363
determination of, 579,
582–583
in elderly, 585–588, 587f
in infants and children, 584–585, 585r
in obese patients, 588–590
practice problems, 580
drug design considerations, 388–389
of drugs with biexponential profiles, 84, 84f
duration of activity and elimination half-life relationships, 537, 537f
duration of activity relationship with, 536
plasma drug concentration response to, 580–581
response relationship with, 534–536, 534f, 535f, 536f, 544–545, 544f, 545f, 546r, 751–752
strategies for, 4–5, 5f, 34–35, 34f
Dosage adjustment
in hepatic disease, 645–646, 646r, 651, 755–758
in renal impairment, 617, 619r, 755–758
clearance-based, 620, 756
elimination rate constant-based, 620–621, 756
extracorporeal removal of drugs, 638–645, 640r, 642f, 642r
general approaches for, 618–621, 619r
GFR measurement, 621–622, 626–627, 626r
pharmacokinetic considerations, 617–618
serum creatinine concentration and creatinine clearance, 622–627, 623f, 624f, 625r, 626r
for uremic patients, 627–638, 628f, 629f, 630r–631l, 632r–633r, 637r, 755–758
in TDM, 574
Dosage form
biopharmaceutic considerations for, 363
for ER drug products, 475
Dosage interval, 153–154, 157, 158r
determination of, 582–583
plasma drug concentration response to, 580–581
Dosage regimen. See also
Multiple-dosage regimens
design of, 576, 752–755
empirical regimens, 578
individualized regimens, 576–577
nomograms and tabulations in, 577–578, 757–758
population-based, 577
regimens based on partial pharmacokinetic parameters, 577
individualization of, 566
schedules, 169–170, 169f, 170f, 172, 173r
Dose ratio, 169, 169f
Dose-dependent pharmacokinetics. See Nonlinear pharmacokinetics
Dose-dumping, 346, 346f, 476
Dosing frequency, 389, 581–582
Double reciprocal plot, 234, 234f
Double-peak phenomenon, 347–348, 347f
Doxorubicin, 212
Doxycycline, 227, 228t
Drug accumulation. See Accumulation
Drug carriers, 514–519
albumin, 517
lipoproteins, 517
liposomes, 517–518, 518f
polymeric delivery systems, 515–517, 515f, 516f
protein drugs, 507r–508r, 514–515
Drug clearance. See Clearance
Drug concentration. See Concentration
Drug concentration–time curve, 7–8, 7f, 8f, 406. See also
Plasma drug concentration–time curve
Drug delivery
albumin, 517
of biopharmaceuticals, 506
colonic, 392–393
floating, 490
lipoproteins, 517
liposomes, 517–518, 518f
oral, 390, 394–395, 456r
osmotic, 488–489, 488f, 489r, 490f
polymeric delivery systems, 515–517, 515f, 516f
of protein drugs, 507r–508r, 514–515
rectal, 393
targeted, 519–521, 751
drugs for, 520
general considerations in, 519
oral immunization, 521
site-specific carrier, 520
target site, 519
targeting agents, 520
transdermal, 134, 134f, 396–397, 397r, 490–493, 491r, 492f
vaginal, 393
Drug disposition, 3
Drug distribution. See Distribution
Drug elimination. See Elimination
Drug excretion. See Excretion
Drug exposure, 160
for anticancer drugs, 540–541, 540f, 541f
Circadian rhythms and, 194–195
drug response and, 5
protein binding and, 244–245
response relationship with, 558–559
Drug in body
absorption and, 131–132, 132f
Drug in body (Cont.):
for capacity-limited drug after IV bolus dose, 181–182, 182f
in multiple-dosage regimens, 158–161, 159f
in one-compartment open model, 44, 44f, 726
physiologic drug distribution
and, 217–218
Drug interactions
in clinical pharmacokinetics
absorption inhibition, 596
altered renal reabsorption
due to urinary pH changes, 596–597
biliary excretion inhibition, 596
MAO inhibition, 595–596
metabolism induction, 596
metabolism inhibition in, 594–595
pharmacokinetics of, 590–594, 590r, 591r–592r
practical focus, 597
of CYP450 enzymes, 191, 593–594
during drug absorption, 352–353
in GI tract, 334–336, 336f
during hepatic metabolism, 278–279, 278r, 279r, 280f
auto-induction and
time-dependent pharmacokinetics, 279–280
clinical example, 282
drug interaction example, 275–276
enzyme variations, 276
genetic variations, 276–278, 277f
transporter-based interactions, 280–282, 281f
protein binding causing competition for binding sites, 237, 241
displacement, 246–247
sources of, 590f
of statins, 261–262, 275–276
Drug metabolism. See Metabolism
Drug Price Competition and Patent Term Restoration Act of 1984, 433
Drug products, 1, 441. See also specific products
bioequivalent, 440–441
with possible bioavailability and bioequivalence problems, 413–414
risks from, 451–452, 452f
in TDM, 570
Drug product design, 2, 3f
absorption in, 321, 333–334
efficiency, 397
bioavailability for, 388, 747–748
biopharmaceutics for, 387, 387f
buccal and sublingual tablets, 392
colonic drug delivery, 392–393
dose considerations for, 388–389
dosing frequency considerations for, 389
GI side effects, 391
inhalation drug products, 390
IR and MR drug products, 392
lipid-soluble drugs, 390–391
nasal drug products, 395, 396f
parenteral drug products, 393–394, 394f
pharmacodynamics for, 387
pharmacokinetics for, 388
physiocalchemical considerations for, 366f, 387–388, 747–748
rectal and vaginal drug delivery, 393
route of administration, 389, 389f
SUPAC, 397–398
transdermal drug products, 396–397, 397f
Drug product performance, 1, 442
dissolution and, 383–384
drug product quality and, 451–452, 452f
excipient effect on, 455–456, 456f
BSE in gelatin, 455–456, 456f
gelatin capsules stability, 456
in vitro, 370–374, 371f
in vivo, 403–405, 404f, 405f, 748–749
Drug product quality, 451, 750
Drug product performance and, 452, 452f
problems with, 464, 464f, 465f
Drug product selection, 441
Drug recalls, 460, 460f
Drug response. See Response
Drug review process, 427–430, 428f, 429f, 456f, 748–749
Drug–protein binding. See Protein binding of drugs
Drug–receptor theory, 544–545, 544f, 545f, 546f
Drug-specific transporters. See Transporters
Duodenum, 338
Duration of activity, 8
dose and elimination half-life effects on, 537, 537f
dose relationship with, 536
elimination half-life effect on, 537–539, 538f, 538f
Dynamic range, 572
Electronic spreadsheets, 711.
Electrolyte balance, 227.
Elderly, 585–588, 587f.
Efflux transporters, 311–312, 331–333, 332f, 333r, 350f, 351, 351f.
Effective concentrations. See also Minimum effective concentration of popular drugs, 768r–772t.
Effective renal plasma flow (ERPF), 112.
Efflux transporters, 311–312, 331–333, 332f, 333r, 350f, 351, 351f.
eGFR. See Estimated GFR.
Elderly, 585–588, 587f.
Electrolyte balance, 227.
Electronic spreadsheets, 711, 712f, 713f, 714f, 715f, 716.
Elimination, 107–108, 733–735. See also Clearance.
biliary excretion, 291–292, 291f, 291t.
biliary clearance estimation, 292.
clinical example, 292–293.
enterohepatic circulation, 292.
inhibition of, 596.
significance of, 292.
capacity-limited, 181–191, 182f, 183r, 184f, 185f, 186f, 186r, 188f, 189f, 190f.
from central compartment, 77.
MRT calculations in, 679–682, 681r, 682f.
dialysis effects on, 641–642, 642f, 642r.
enzymatic, saturable, 179–181, 180r.
extrahepatic drug metabolism, 253.
first-order elimination, 253–254.
fraction of drug excreted unchanged, 254–255, 255f.
fraction of drug metabolized, 254–255, 255f.
practical focus, 255.
first-order, 48–52, 253–254, 726.
bio transformation pathways, 270–275, 270r, 271f, 272f, 272r, 273f, 274r, 275f, 275r, 303.
bio transformation reactions, 269–270, 269r.
blood flow and intrinsic clearance relationships with, 286–287.
drug interactions during, 275–282, 277r, 278r, 279r, 280r, 281r.
enzymes involved in, 267–268, 268f, 274–278, 275r, 277r.
exterohepatic metabolism, 256–257.
first-pass effects, 282–287, 284r, 286r, 289f.
in hepatic disease, 648.
liver anatomy and physiology, 265–267, 265r, 266f, 267f.
of protein-bound drugs, 287–290, 289f, 290f, 743.
transporter role in, 293–294, 293f.
in infants and children, 584, 585r.
after IV bolus administration, 743.
nonlinear, 191–193.
in one-compartment open model as amount per time unit, 48.
as fraction eliminated per time unit, 48f, 49.
as volume per time unit, 48–49, 48f.
clinical example, 230–231.
restrictive and nonrestrictive elimination, 229–230.
volume of distribution relationship with, 228–229.
rate of, 108, 179–180, 180r.
clinical application, 114.
practice problems, 114.
renal clearance and, 118–120, 119f, 120f.
zero-order, 48, 726–727.
Elimination half-life apparent volume of distribution relationship with, 228–229.
of capacity-limited drug, 189.
dialysis effects on, 641, 642f.
distribution half-life relation with, 80, 81r.
dose and duration of activity relationships with, 537, 537f.
duration of activity response to, 537–539, 538f, 538r.
in multiple-dosage regimens, 156–157, 156f, 157f, 158r.
for various drugs, 632r–633r.
Elimination phase of plasma drug concentration–time curve, 64–65, 64f, 132, 132f.
Elimination phase (Cont.):
in two-compartment open model, 77
  clearance and, 73–74
  of plasma drug concentration–time curve, 64–65, 64f
Elimination rate constants, 253–254
  absorption rate constant flip-flop with, 139–140, 139f, 737
  of aminoglycosides, 165–166
clearance relationship with, 125–126, 126f
creatinine clearance relationship with, 628–629, 628f, 629f
  maximum concentration, time to maximum concentration, and AUC response to, 143–144, 143f, 144f, 736–738
  in noncompartmental model, 52
  in one-compartment open model, 44–45, 44f, 45f, 724, 726–727
  in renal impairment, dose adjustment based on, 620–621, 756
  in two-compartment open model, 77
  urinary excretion data for calculation of, 53–57, 54f, 55f, 56f, 57f
  clinical application, 56–57, 56f
  practice problems, 54–56, 54f, 55f
  for various drugs, 630–631t
ELS. See Extended least-squares method
Empirical dosage regimens, 578
Empirical model, 11, 558
Emptying, gastric, 341–342, 342f
Enantiomers, metabolism of, 274, 274t, 275f
Endocytosis, 335, 336f
Endoplasmic reticulum, 268
Endpoints
  clinical, 531, 532t
  surrogate, 531, 558
End-stage renal disease (ESRD)
extracorporeal removal of drugs in, 638
  protein binding of drugs in, 239t–240t
Enteral administration routes, 329–324t
Enteral system, 337
Enteric-coated products, 470–471
dissolution test of, 377
  for GI side effects, 391
Enterohepatic circulation, 292
Enzymes. See also Capacity-limited pharmacokinetics
capacity of, 179
  hepatic, 267–268, 268f
  CYP450 genetic variations, 276–278, 277t
  species differences in, 274–275, 275t
  variation of, 276
  induction of, 279–280, 278t
  CYP450 induction, 279–280, 280t, 596
  in drug interactions, 596
  inhibition of, 278, 278t
  in drug interactions, 594–595
  kinetics of, 259–262, 259f, 260f
  MAO inhibition, 595–596
  saturation of, 179–181, 180t
Enzyme kinetics. See
  Michaelis–Menten kinetics
Equilibration half-life, 541, 542r
Equivalence, 441, 462
ER drug products. See Extended-release drug products
Ergometrine, 81r
ERPF. See Effective renal plasma flow
Error, 33, 702, 704
Erythrocytes, 222
Erythromycin, 297, 345f, 346, 745–746, 748
dissolution testing of, 372, 373f
  hydrates of, 368
Erythropoietin, 322
Esomeprazole (Nexium), 334–335
Esophagus, 337–338
ESRD. See End-stage renal disease
Estimated GFR (eGFR), 625–626
Estimation, 20–21
Estraderm, 397
Ethical principles
  for animal studies, 762
  for human research, 761–762
  Declaration of Helsinki, 761, 762–765
Ethynyl estradiol (EE), 134, 134f
Etoposide, 82–83
Etretinate, 210
Eulexin®. See Flutamide
Excipients, 362, 750. See also Absorption enhancers
bioavailability and bioequivalence problems, 414
drug product performance effect of, 455–456, 456f
  BSE in gelatin, 455–456, 456f
gelatin capsules stability, 456
  functional properties with, 368–370, 368t, 369t, 370f
Excretion, 107. See also Renal drug excretion
  biliary, 291–292, 291f, 291t
  biliary clearance estimation, 292
  clinical example, 292–293
  enterohepatic circulation, 292
  inhibition of, 596
  significance of, 292
Excretion rate method. See Rate method
Exocytosis, 335–336, 336f
Experiment, 761
Experimental design, 694–696
Exponents, 21–23
Exposure. See Drug exposure
Extended least-squares (ELS) method, 601
Extended-release (ER) drug products, 170, 392, 469, 471r, 750–751
advantages and disadvantages of, 475–476
bioavailability study for, 416, 499–500
occupancy time, 499, 500f
pharmacokinetic profile, 499
rate of drug absorption, 499, 500f
steady-state plasma drug concentration, 499
bioequivalence study for, 499–500
biopharmaceutic factors of, 473–475
large intestine, 475
small intestine and transit time, 474–475
stomach, 474
clinical efficacy and safety of, 498
clinical examples of, 480
dissolution rates of, 472, 472f, 750–751
dosage form selection for, 475
evaluation of, 495–499
clinical considerations, 498
dissolution studies, 497, 497r, 750–751
IVIVC, 497
pharmacodynamic and safety considerations, 496–497, 496f, 497f
pharmacokinetic studies, 497–498
generic substitution of, 498–499
with immediate release component, 479–480
kinetics of, 476–478, 478f
pharmacokinetic simulation of, 478–480, 478f, 479f
plasma drug concentration of, 473, 473f
statistical evaluation of, 500
types of, 480–495, 481t, 482r–483t
combination products, 493–494
core tablets, 487
drug release from matrix, 480–483, 483f
gastroretentive system, 489–490
gum-type matrix tablets, 483–484
implants and inserts, 494
ion-exchange products, 486–487
microencapsulation, 487–488
nanotechnology derived drugs, 494–495
osmotic drug delivery system, 488–489, 488f, 489t, 490f
parenteral dosage forms, 494
polymeric matrix tablets, 484
prolonged-action tablets, 486
slow release pellets, beads, or granules, 484–486, 486t
transdermal drug delivery system, 490–493, 491t, 492f
Extracorporeal removal of drugs, 638–639
dialysis, 639–641, 640r, 756–758
clinical examples, 642–643
practice problem, 641–642, 642f, 642t
hemofiltration, 644–645
hemoperfusion, 643–644
Extraction ratio, 283–284, 284r, 286t, 287–290, 289f
Extrahepatic drug metabolism, 253, 256–257
first-order elimination, 253–254
fraction of drug excreted unchanged, 254–255, 255f
fraction of drug metabolized, 254–255, 255f
practical focus, 255
Extrapolated volume of distribution, 72
Extrapolation, 29
Extravascular route, 363
Extrusion-spheronization, 485
F
Facilitated diffusion, 330
Factorial design, 695
Famotidine (Pepcid), 347
Fasting study, for bioequivalence, 417, 424–427, 425
Fat
drug accumulation in, 211
drug distribution to, 209, 209f
elimination by, 659–660, 660f
FDA. See Food and Drug Administration
Feathering. See Method of residuals
Feces, 8–9
Feedback, dosing with, 600–601
Felodipine (Plendil), 587–588, 587f
Fentanyl, 322, 392, 552, 553f
Fexofenadine (Allegra), 595
Fick’s law of diffusion, 31, 207, 327–328
Filtration fraction, 110
Filtration pressure. See Hydrostatic pressure
First moment, 672, 674, 676, 681
First-order absorption, 133f, 134–137, 136f, 137f, 736–738, 750–751
First-order absorption (Cont.):
- absorption and elimination rate constant effects on maximum concentration, time to maximum concentration, and AUC, 143–144, 143r, 144f, 736–738
- nonlinear elimination with, 192–193
- rate constant determination, 736–738
- elimination rate constant flip-flop, 139–140, 139f, 737
- lag time and, 138–139, 139f with method of residuals, 137–138, 138f, 736
- with modified Wagner–Nelson method, 144–145
- practice problem, 141r, 142
- with two-compartment oral absorption data, 145–147, 145f, 146r, 147r
- with urinary data, 142–143
- with Wagner–Nelson method, 140–142, 141f, 736, 738

First-order conditional estimate (FOCE), 604–605

First-order elimination, 48–52, 253–254, 726

First-order half-life, 38–39, 38f, 720–722

First-order reactions, 37–38, 37f, 38f, 38r, 720–722

First-pass effects, 282, 747

- absolute bioavailability, 283–286
- blood flow, intrinsic clearance, and hepatic clearance relationships in, 286–287
- blood flow effects on bioavailability and liver metabolism, 284–286, 284r, 286r, 286t
evidence of, 282–283
- liver extraction ratio, 283–284, 284r, 286r, 287–290, 289f

Fixed model, 577

Flecainide, 277

- Flip-flop, of absorption and elimination rate constants, 139–140, 139f, 737
- Floating drug delivery system, 490

Flow models. See Physiologic models

Flow-dependent metabolism, 267, 290

Flow-limited model. See Perfusion-limited models

Flow-through-cell method, 372, 376

Fluconazole, 393

- Fluid mosaic model, 326
- Fluid volume, in body, 205–206, 206f

- Fluid-bed coating, 485
- FluMist, 395
- Flunitrazepam, 231
- Fluorouracil (FU), 194
- Fluoxetine, 278
- Flutamide (Eulexin®), 210, 257
- Fluvastatin sodium (Lescol®), 286
- Fluvoxamine, 195–196, 311, 594

FOCE. See First-order conditional estimate

Follow on biologics, 523

Follow-up study, 693

Food
- drug disposition and, 597
- GI absorption and, 334–347, 344r, 345f, 346f, 746–747

Food and Drug Administration (FDA). See also
- Abbreviated New Drug Application; New Drug Application
- Approved Drug Products with Therapeutic Equivalence Evaluations, 385, 437–440, 438r, 440t
- BCS, 383, 431–433, 431r
- bioavailability study guidance, 405, 412–413

bioequivalence study guidance, 413–416
generic biologics guidance, 434

Food intervention study, 417–418, 748

Forensic drug measurements, 9

Formal experimental design, 465

Formulation factors, 368–370, 368t, 369r, 370f

Fosamax®, See Alendronate sodium

Fraction of dose in body, 158–159, 159f

Fraction of drug excreted, 124–125

Fraction of drug excreted unchanged, 254–255, 255f
dose adjustment based on, 631, 632–633, 634–635

Fraction of drug excreted, 634–635

Fraction of drug excreted unchanged, 646–647

Fractional factorial design, 695

Free drug concentration, 230

Frequency. See Dosing frequency

FU. See Fluorouracil

Furosemide (Lasix), 218, 223, 352

G

Gamma scintigraphy, 348

Gantrisin. See Sulfisoxazole

Garamycin. See Gentamicin sulfate

Gastric emptying time, 339, 340f, 746
double-peak phenomenon, 347–348, 347f
emptying time, 341–342, 342f

Gastrointestinal therapeutic systems (GITS), 488–489, 488f, 489r, 490f
intermittent IV infusion of, 164–165
nonlinear pharmacokinetics
of, 194
in obese patients, 589
in uremic patients, 634,
757–758
Gentamicin sulfate (Garamycin),
635–636
GFR. See Glomerular filtration
rate
GI tract. See Gastrointestinal tract
GITS. See Gastrointestinal therapeutic systems
Giusti–Hayton method, 634
Gleevec. See Imatinib mesylate
Glial cells, 211–212
Glomerular filtration, 111–112,
113
clearance by, 119–120, 119r,
120
urine formation and, 110–111,
111
Glomerular filtration rate (GFR),
109–111, 110f
in elderly, 588
MDRD or CKD–EPI equations for estimation of,
625–626
measurement of, 621–622,
626–627, 626r
renal function classification
based on, 625r
Glomerulus, 108, 109
Glutathione, 273, 273f
Glycosylation, 751
Good Manufacturing Practices
(GMPs), 458, 458r
Gradumet, 484
Granules, 484–486, 486r
Grapefruit juice, 279, 279r, 353,
597
Graphs, 26, 26f, 27f, 719–723
curve fitting, 26–29, 26f, 29f
determination of order, 29
practice problems, 29–31
slope determination, 27–29,
28f, 29f
Graphic determination
of binding constants and sites,
744
in vitro methods, 233–234,
233f, 234f, 235f
in vivo methods,
234–236
of renal clearance, 121–122,
121f, 122f
Griseofulvin, 343, 345f
Gum-type matrix tablets,
483–484
H
Haldol. See Haloperidol
Half-life. See also Elimination
half-life
accumulation, 156–157,
157r
distribution, 80, 81r,
208–210, 208r, 208t,
209r, 210f, 742
equilibration, 541, 542r
first-order, 38–39, 38f,
720–722
IV single dose for calculation
of, 50–52, 724–727
of popular drugs, 768–772
time to reach steady state drug
concentration and,
93, 93r
zero-order, 39, 719–721
Haloperidol (Haldol), 394, 569,
583
Haplotype, 307–308,
316
Haptens, 508–509
Hatch-Waxman Act, 433
Heidelberg capsule, 349
Hematocrit, 109
Hemodialysis, 758
drug elimination during,
639–642, 640r, 642r
protein binding of drugs in,
239–240r
Hemofiltration, 644–645
Hemoperfusion, 643–644
Henderson–Hasselbalch
equation, 112–113, 328
Hepatic clearance, 122, 255–256, 744–746
biotransformation pathways, 270, 270t
acetylation, 273, 276, 303
enantiomer metabolism, 274, 274t, 275f
mercapturic acid
conjugation, 273, 273f
phase I reactions, 270, 271f
phase II reactions, 270–273, 270t, 271f, 272f, 272t, 273f
regioselectivity, 274
species differences in, 274–275, 275r
biotransformation reactions, 269–270, 269t
blood flow and intrinsic clearance relationships with, 286–287
drug interactions during, 278–279, 278r, 279r, 280r
auto-induction and
time-dependent pharmacokinetics, 279–280
clinical example, 282
drug interaction example, 275–276
enzyme variations, 276
genetic variations, 276–278, 277r
transporter-based interactions, 280–282, 281t
enzymes involved in, 267–268, 268f, 274–278, 275t, 277t
extrahepatic metabolism, 256–257
first-pass effects, 282
absolute bioavailability, 283–286
blood flow, intrinsic clearance, and hepatic clearance relationships in, 286–287
blood flow effects on bioavailability and liver metabolism, 284–286, 284t, 286r
evidence of, 282–283
liver extraction ratio, 283–284, 284r, 286r, 287–290, 289f
in hepatic disease, 648
liver anatomy and physiology, 265–267, 265r, 266f, 267f
Michaelis–Menten kinetics of, 257–259, 257f, 258f, 259f–260f, 741
clinical example, 261–262
enzyme inhibition kinetics, 259–262, 259f, 260f
metabolite kinetics for one-compartment model drugs, 262–264, 262f, 264f
metabolite kinetics for two-compartment model drugs, 264–265, 264f, 265f
practice problem, 263–264, 264f
of protein-bound drugs, 287–288, 743
blood flow changes, 289–290, 289f
changes in, 290, 290f
intrinsic clearance changes, 289, 289f
transporter role in, 293–294, 293f
Hepatic disease, 755–758
classification of, 648, 648t, 649t
pharmacokinetics in, 645–646
for active drugs with metabolites, 647–648, 648t
dosage adjustment in, 645–646, 646t, 651, 755–758
fraction of drug metabolized, 646–647
hepatic blood flow and intrinsic clearance, 648, 756
hormonal influence on, 649, 649t
liver function tests and hepatic markers, 650
pathophysiological assessment of, 648–649, 648t, 649f
practice problem, 647
Herbal remedies, 593
Herceptin, 302
Heroin, 9
Heterozygous cell, 307
hFSH. See Human follicle-stimulating hormone
High-extraction ratio drugs, 287, 289–290, 289f
Higuchi equation, 483
Hill equation, 548
Historical cohort study, 693
HIV–AIDS, 352
HMG-CoA reductase inhibitors. See Statins
Homozygous cell, 307
Hormonal influence, on metabolism, 649, 649t
Housekeeper contractions, 474
Hypersensitivity, 543
Hypothesis, null, 687, 701
Hypothesis testing, 701–702, 702f, 702r
Hypothetical models, 728
Hysteresis, 552–556, 553f, 554f, 555f, 751–752
clinical example, 556–557, 557f
simulation of, 556, 556f

I
Ibuprofen, 558, 558f, 685–686, 686t
IBW. See Ideal body weight
ICH. See International Conference on Harmonization
Ideal body weight (IBW), 589, 622
IgG1 kappa mAb, 81t
Ileum, 338–339
IM injection. See Intramuscular
Imatinib mesylate (Gleevec), 308, 315t
Imipramine, 218, 223, 277–278, 290
Immediate-release (IR) drug products, 392
bioavailability of, 473, 473f
Imodium. See Loperamide
Implants, 494
In vitro drug product performance, 370–374, 371t
In vitro graphic determination, of binding constants and sites, 233–234, 233f, 234f, 235f
In vitro–in vivo correlation (IVIVC), 380–386
BCS, 383
discriminating dissolution test, 384
dissolution and clinical performance, 383–384
of ER drug products, 497
failure of, 384–386, 384tr, 385f
level A correlation, 380, 381f
level B correlation, 380
level C correlation, 381–383
dissolution rate compared with absorption rate, 381, 381f
percent of drug dissolved compared with percent absorbed, 381f, 382, 382f
plasma concentration compared with percent of drug dissolved, 382, 382f, 383f
serum concentration compared with percent of drug dissolved, 383, 383f
In vitro–in vivo relationship (IVIVR), 383
In vivo drug product performance, 403–405, 404f, 405f, 748–749
In vivo graphic determination, of binding constants and sites, 234–236
Independent variable, 10
Indeterminate errors, 33
Indinavir, 212, 352, 593
Indirect effect, 529, 553
Individualization, of dosage regimens, 566
Individualized regimens, design of, 576–577
Indomethacin, 391
Induction, 278–280, 278t
CYP450 induction, 279–280, 280t, 596
in drug interactions, 596
Infants, 584–585, 585t
Influx transporters, 330–331, 331f
Infusion. See Intravenous
Inhalation drug delivery, 354–355
Inhalation drug products, 395–396, 396f
Inhibition of absorption, 596
of biliary excretion, 596
of enzymes, 278, 278t
in drug interactions, 594–595
kinetics of, 259–262, 259f, 260f
MAO inhibition, 595–596
Initial volume of distribution, 70–71, 71r, 74
Inserts, 494
Institutional Review Board (IRB), 415
Insulin, 10, 322, 336, 354, 506, 583
absorption of, 357, 746–747
oral delivery of, 390
TDM of, 567
Integral calculus, 24–26, 25f
Integrated pharmacologic response, 545
Interchangeability, biosimilarity v., 433–434
Interdigestive phase, 474
Interferon, 506, 507t–508t
Interferon-β, 595
Intermittent IV infusion, 163, 163t
clinical example, 164–165
superposition of several IV infusion doses, 163–164, 165t
International Conference on Harmonization (ICH), 459
Interpolation, 29
Interspecies scaling, 663–667, 663f, 664f, 666t, 667f, 759
Intestinal absorption, 746–747
transporters in, 330–333, 331t, 332f, 333f
Intestinal motility, 342
Intestinal permeability, 349–351, 350f, 351f
Intramuscular (IM) injection clinical example, 394–395
design considerations for, 393–394, 394f
Intravenous (IV) bolus administration, 323t
ADRs with, 53
design considerations for, 393–394, 394f
determination of compartment models of, 79–80, 80f
Intravenous (IV) bolus administration (Cont.):
distribution and elimination phases after, 743
dose and duration of activity relationship in, 536
MRT of, 671–672, 671t, 673t, 674f
multicompartment models of, 61–63, 63t, 728–730
clinical application, 80–82, 81f, 84–86, 84f
determination of, 79–80, 80f
practical application, 84–85, 85f
practical focus, 80, 81t
practice problem, 82–83
one-compartment open model of, 43–44, 44f, 723–727
apparent volume of distribution in, 44–48, 44f, 46f, 47r, 50, 723–725
calculation of elimination rate constant from urinary excretion data, 53–57, 54f, 55f, 56f, 727
capacity-limited drug elimination, 181–191, 182f, 183r, 184f, 185f, 186f, 186r, 188f, 189f, 190f
clearance in, 48–52, 48f, 724
clinical application, 43
elimination rate constant in, 44–45, 44f, 45f, 724, 726–727
practical focus, 50–52
three-compartment open model of, 77, 77f, 78f, 729–730
clinical applications, 78–79, 78t
two-compartment open model of, 61, 63–66, 64f, 65f, 729–730
apparent volume of distribution in, 70–77, 71r, 73f
clearance in, 72–74, 73f, 76–77
clinical application, 68, 68t, 69r, 70f
elimination rate constant in, 77
method of residuals, 66–68, 67f, 67r, 729
practical focus, 69–70
practice problems, 68–69, 73–74, 73f
relation between distribution and elimination half-life, 80, 81t
Intravenous (IV) infusion, 91, 323t, 730–733
apparent volume of distribution estimated from, 100
clearance estimated from, 94, 99–100, 731–732
constant, 163–164, 738
calculation between oral dosing and, 578–579
elimination half-life calculated from, 95–96, 99–100
intermittent, 163, 163t
clinical example, 164–165
superposition of several IV infusion doses, 163–164, 165t
loading dose plus, 730–732
one-compartment open model of, 96–98, 97f
two-compartment model of, 101, 101f
one-compartment model of, 91–92
loading dose combined with, 96–98, 97f
steady state drug concentration in, 92–94, 92f, 93f, 93t
plasma drug concentration–time curve for, 91, 92f, 93f
practice problems, 98–100
rate of, 730–733
total body clearance after, 126
two-compartment model of, 100–101
apparent volume of distribution in, 101–103
loading dose combined with, 101, 101f
practical focus, 102–103
Intravenous (IV) injections, repetitive, 158–161, 159r
eyearly or late dose administration during, 162–163
missed dose during, 161–162
Intrinsic activity, 527, 529
Intrinsic clearance
blood flow and hepatic clearance relationships with, 286–287
in hepatic disease, 648
of protein-bound drugs, 289, 289f
Intrinsic dissolution method, 377
Intrinsic multidrug resistance, 311
Inulin, 111, 118, 119r, 621
Invasive sampling methods, 6
Invirase. See Saquinavir mesylate
In-vivo perfusion studies, of GI tract, 349
Ion-exchange products, 486–487
Ion-pair formation, 336
Iontophoresis, 397, 493
IR drug products. See Immediate-release drug products
IRB. See Institutional Review Board
Irreversible drug–protein binding, 219
Isoniazid, 201, 273, 276, 308, 742
Isoproterenol, 2, 270, 274
hysteresis of, 552
metabolism of, 269
rate constant flip-flop with, 140
Isotretinoin, 62
Isozymes, CYP450, 268, 276–278, 277r, 305, 310–311
INDEX 793

IV bolus administration. See Intravenous bolus administration
IV infusion. See Intravenous infusion
IV injections. See Intravenous injections
IVIVC. See In vitro–in vivo correlation
IVIVR. See In vitro–in vivo relationship

J
Jaundice, 213
Jejunum, 338

K
Kanamycin, 586
Ketocconazole, 275, 279, 335
Kidney
anatomic considerations of, 108–109, 108f, 109f
blood supply to, 109–110
drug distribution to, 209–210, 209f, 210f
elimination by, 660, 660f
glomerular filtration and urine formation, 110–111, 111f
regulation of blood flow, 110, 110f
Kidney disease. See Renal impairment
Kinetica, 710
Kupffer cells, 267

L
Lag time, for drug absorption, 138–139, 139f
Lanoxin. See Digoxin
Large intestine, 475
Lasix. See Furosemide
Late dose administration, 162–163
Latin-square crossover designs, 418–419, 418f, 419f, 749
Law of diminishing return, 548
Law of mass action, 232, 527
Law of parsimony, 28–29
Lean body weight (LBW), 589–590, 622
Least-squares method, 28, 30, 300–303, 603f, 604r
Leflunomide, 292–293
Lescol®. See Fluvastatin sodium
Level of significance, 702
Levocarnitine (Livostin), 395
Levodopa, 270
Levofoxacin, 644
Levotyroxine sodium (Levoxin, Synthroid), 422–423
Librium. See Chlordiazepoxide
Lidocaine, 79, 609
ADRs involving, 85–86
distribution and elimination half-lives of, 80, 81f
drug interactions of, 246–247
IV infusion of, 100
perfusion model of, 15, 15f
population data on, 605
protein binding of, 242, 242f, 246–247
Lifecycle, 465
Ligand, 528
Lincomycin, 631
Linear regression, 28, 30
Linearity, 572
determination of, 198–200, 198f, 199f
Lineweaver–Burk equation, 259, 259f
Linezolid (Zyvox), 595–596
Lipid bilayer, 325
Lipid-soluble drugs, absorption of, 390–391, 747
Lipoproteins, 220r, 221–222, 223f, 517, 743
Liposomes, 495, 517–518, 518f
Liquid drug products, 368–369, 369f
Lithium, 81f, 587
Liver
anatomy and physiology of, 265–267, 265f, 266f, 267f
determination of, 255–264
elimination by, 659–660, 660f
Liver disease. See Hepatic disease
Liver extraction ratio, 283–284, 284f, 287–290, 289f
Liver function tests, 650
Livostin. See Levocabastine
Loading dose, 628, 730–732
of digoxin, 75–76
IV infusion plus, 730–732
one-compartment open model of, 96–98, 97f
two-compartment model of, 101, 101f
in multiple-dosage regimens, 168–169, 169f, 739
practice problems, 98–99
Local activity, 362
Local anesthetics, 246
Locus, 307
Log linear regression, 31
Logarithms, 21–23, 719, 723
Longitudinal study, 693
Loo–Riegelman method, 145–147, 145f, 146t, 147f, 738
Loperamide (Imodium), 79
Lorazepam, 556–557, 557f, 635
L-Oros Softcap, 489, 490f
Lovastatin (Mevacor®), 275–276
Low-extraction ratio drugs, 287, 289–290, 289f
Low extraction ratio drugs, 287, 289–290, 289f
LSD. See Lysergic acid diethylamide
Lubricant
absorption effect of, 370, 370f
dissolution effect of, 370, 370f
Lung, elimination by, 660, 660f
Lysergic acid diethylamide (LSD), 535, 536f
M
mAbs. See Monoclonal antibodies
Macrolides, 539–540, 539f, 539r
Macroscopic events, 674
Maintenance dose, 168–169, 169f, 628, 739–740
Mammillary model, 12–13, 13f, 62
MAO. See Monoamine oxidase
MAOIs. See Monoamine oxidase inhibitors
Marijuana, 9, 56
Mathematical models, 728 Matrix, 480–481 Matrix tablets, 480–483, 483f gum-type, 483–484 polymeric, 484 Maximum effect model, 548–549, 548f, 549f
Maximum life-span potential (MLP), 663, 665, 667f
biotransformation pathways, 270–275, 270r, 271f, 272f, 272r, 273f, 274r, 275f, 275r, 303

biotransformation reactions, 269–270, 269f

blood flow and intrinsic clearance relationships with, 286–287
drug interactions during, 275–282, 277r, 278r, 279r, 280r, 281r

enzymes involved in, 267–268, 268f, 274–278, 275r, 277r

extrahepatic metabolism, 256–257

first-pass effects, 282–287, 284r, 286r, 289f

liver anatomy and physiology, 265–267, 265f, 266f, 267f

Michaelis–Menten kinetics of, 257–265, 257f, 258f, 259f–260f, 262f, 264f, 265f, 741

of protein-bound drugs, 287–290, 289f, 290f

transporter role in, 293–294, 293f

hormonal influence on, 649, 649f

induction of, 596

inhibition of, 594–595

velocity of, 258–259

Metabolites

in hepatic disease, 648, 648f

kinetics of

for one-compartment model drugs, 262–264, 262f, 264f

for two-compartment model drugs, 264–265, 264f, 265f

physiologic models incorporating, 669, 670f

Metastable, 368

Method A and B, 377

Method of residuals, 66–68, 67f, 67r, 729

absorption rate constants determined with, 137–138, 138f, 736

Methotrexate, 14, 660–661, 663, 663f

Methylphenidate (Concerta), 480, 488, 499, 500r

Metoclopramide, 353

Metoprolol, 190, 190f, 308

Mevacor®. See Lovastatin

Mexiletine, 246–247, 605

MFOs. See Mixed-function oxidases

Miacalcin, 395

MIC. See Minimum inhibitory concentration

Michaelis constant, 179–181, 742

in hepatic clearance, 257–259, 257f, 259f

enzyme inhibition, 260–261

in one-compartment model with IV bolus injection determination of, 184–188, 184f, 185f, 186f, 186r, 188f

elimination response to, 182, 183f

interpretation of, 188–189, 189f

Michaelis–Menten kinetics, 179–181

of hepatic clearance, 257–259, 257f, 258f, 259f–260f, 741

clinical example, 261–262

enzyme inhibition kinetics, 259–262, 259f, 260f

metabolite kinetics for one-compartment model drugs, 262–264, 262f, 264f

metabolite kinetics for two-compartment model drugs, 264–265, 264f, 265f

practice problem, 263–264, 264f

in one-compartment model with IV bolus injection, 181–182, 182f, 183r

clearance in, 189–190, 190f

clinical focus, 191
determination of Michaelis constant and maximum elimination rate, 184–188, 184f, 185f, 186f, 186r, 188f, 741

elimination half-life in, 189

interpretation of Michaelis constant and maximum elimination rate, 188–189, 189f, 741

practice problems, 183–184

Micro RNA (miRNA), 513–514

Microconstants, 64–65

Microencapsulation, 487–488

Microparticles, 516

Microsome, 268

Midazolam, 231

Milrinone, 80, 81

Minimum detectable limit (MDL), 572

Minimum effective concentration (MEC), 2

during multiple-dosage regimens, 153

on plasma drug concentration–time curve, 7–8, 7f, 8f

protein binding of drugs and, 242

Minimum inhibitory concentration (MIC), 170

Minimum quantifiable level (MQL), 572

Minimum toxic concentration (MTC), 4

during multiple-dosage regimens, 153

on plasma drug concentration–time curve, 7–8, 7f, 8f

miRNA. See Micro RNA

Missed dose, 161–162, 170

Mixed agonist-antagonist, 529

Mixed drug elimination, 192

Mixed-effect statistical model, 605

Mixed-function oxidases (MFOs), 267–268, 268f
MLP. See Maximum life-span potential
Mode, 697
Model fitting, with electronic spreadsheets, 711, 713f, 714f, 715f, 716
Model-dependent nature, of MRT, 683–685, 683f, 684r, 685r
Model-independent clearance estimation, 117–118, 117f
renal clearance, 122–123
Model-independent nature, of MRT, 683–685, 683f, 684r, 685r
Modification of Diet in Renal Disease (MDRD) formula, 625–627
Modified Wagner–Nelson method, 144–145
Modified-release (MR) drug products, 392, 469–473, 471r, 750–751. See also Extended-release drug products
Modified-release parenteral dosage forms, 394
Moments. See also Statistical moment theory of plasma drug concentration–time curve, 672–674, 673r, 674f
Monoamine oxidase (MAO), 268, 595–596
Monoamine oxidase inhibitors (MAOIs), 191
Monoclonal antibodies (mAbs), 506, 507r–508r, 508–509, 509r, 510f, 511r–512r, 512
Monogenic disorders, 306
Morphine, 6, 256, 569, 635
Motility
GI, 339–341, 340f, 341r
intestinal, 342
Moxalactam, 70, 71r, 80–82, 81f, 222–223, 223f
MQL. See Minimum quantifiable level
MR drug products. See Modified-release drug products
MRT. See Mean residence time
MTC. See Minimum toxic concentration
MTM. See Medication therapy management
Mucomyst. See N-acetylcysteine
Multicompartment models. See also Three-compartment open model; Two-compartment open model for IV bolus administration, 61–63, 63r, 728–730
clinical application, 80–82, 81f, 84–86, 84f
determination of, 79–80, 80f
practical application, 84–85, 85f
practical focus, 80, 81r
practice problem, 82–83
MRT calculations in, 679–682, 681r, 682f
renal clearance in, 124
Multidrug resistance, 311–312, 331, 350f, 351, 351f
Multiple-dosage regimens, 153, 738–740
clinical example, 170–171
drug accumulation in, 153–158, 154f, 155r, 156f, 157r, 158r
intermittent IV infusion, 163, 163r
clinical example, 164–165
superposition of several IV infusion doses, 163–164, 165r
loading dose in, 168–169, 169f, 739
oral regimens, 166–168
practice problems, 171–173, 173r
repetitive IV injections, 158–161, 159r
early or late dose administration during, 162–163
missed dose during, 161–162
schedules of, 169–170, 169f, 170f, 172, 173r
Multiple-dose bioequivalence crossover study, 420–421
Multisource drug product, 404–405, 405f
Muscle
drug distribution to, 209–210, 209f, 210f
elimination by, 659–660, 660f
Mutations, 303
N
N-acetylcysteine (Mucomyst), 273
Nanoparticles, 516
Nanotechnology derived drugs, 494–495
Narrow therapeutic index (NTI) drugs, 566
Nasacort AQ. See Triamcinolone acetonide
Nasal drug delivery, 354
Nasal drug products, 395, 396
Natural logarithm, 22, 719
NDA. See New Drug Application
Negative formulary, 438
Negativity predictability, 608
Nelfinavir, 212
Nephrons, 108–109, 109f
Nephrotic syndrome, 239–240r
Neuromuscular-blocking drugs, 635
New Drug Application (NDA), 748
ANDA compared with, 427, 427r
Nexium. See Esomeprazole
NGMN. See Norelgestromin
Niacin (Niaspan), 192, 541
Nicotine, 541
Nicotrol, 395
Nifedipine (Procardia XL), 439, 440r, 488, 595
Nitrates, 542–543
Nitroglycerin, 284, 322, 337, 491–492, 583
Nomograms, 577–578
for creatinine clearance, 623–624, 623f, 624f
for dose adjustment for uremic patients, 628–629, 628f, 629f, 630–631r, 757–758
Noncompartmental model, 52, 117–118
MRT calculations in, 676–679
Noncompetitive inhibition, 259f, 260
Noninvasive sampling methods, 6
Nonlinear mixed-effect model (NONMEM), 604–605
software, 710
Nonlinear pharmacokinetics, 6, 177–179, 178r, 179f, 740–742
adverse reactions and toxicity due to, 195–196
bioavailability of drugs with, 196
chronopharmacokinetics and time-dependent pharmacokinetics, 193–194, 194r, 741
Circadian rhythms and drug exposure, 194–195
clinical focus, 195
determination of linearity, 198–200, 198f, 199r
in one-compartment model distribution with nonlinear elimination, 191–192
clinical focus, 192
first-order absorption and nonlinear elimination, 192–193
mixed drug elimination, 192
two-compartment model with nonlinear elimination, 192–193
zero-order input and nonlinear elimination, 192
in one-compartment model with IV bolus injection, 181–182, 182r, 183r
clearance in, 189–190, 190f
clinical focus, 191
determination of Michaelis constant and maximum elimination rate, 184–188, 184f, 185f, 186f, 186r, 188f, 741
elimination half-life in, 189
interpretation of Michaelis constant and maximum elimination rate, 188–189, 189f, 741
practice problems, 183–184
protein-bound drugs with, 196–197, 196f, 246
one-compartment model drugs, 197–198, 197f
reasons for, 200, 740–741
saturable enzymatic elimination processes, 179–181, 180r
NONMEM. See Nonlinear mixed-effect model
Nonparametric tests, 697
Nonpareil seeds, 485
Nonreplicate, parallel bioequivalence study, 420
Nonrestrictive clearance, 287–288
Nonrestrictive elimination, 229–230
Nonreversible response, 527
Nonsteroid anti-inflammatory drugs (NSAIDs), elimination of, 230
Norelgestromin (NGMN), 134, 134f
Normal distribution, 696–698, 698f
Nortriptyline, 223
Noyes–Whitney equation, 24, 365
NSAIDs. See Nonsteroid anti-inflammatory drugs
NTI drugs. See Narrow therapeutic index drugs
Null hypothesis, 687, 701
Nutrients, drug absorption affected by, 353
O
Obese patients
dose adjustment for renal impairment in, 622–624
dose determination in, 588–590
Occancy concept, 527–530
Occupancy time, of ER drug products, 499, 500f
Odds, 693–694, 694f
ODT. See Orally disintegrating tablets
Older adults. See Elderly
Oligonucleotide drugs, 513
OLS method. See Ordinary least-squares method
Omeprazole (Prilosec), 334–335, 338, 353
One-compartment open model, 11–13, 12f, 13f
absorption rate constants determined from, 140–142, 141f, 736–738
for distribution, nonlinear elimination combined with, 191–193
elimination in
as amount per time unit, 48
as fraction eliminated per time unit, 48f, 49
as volume per time unit, 48–49, 48f
for IV bolus administration, 43–44, 44f, 723–727
apparent volume of distribution in, 44–48, 44f, 46f, 47f, 50, 723–725
capacity-limited drug elimination, 181–191, 182f, 183r, 184f, 185f, 186f, 186r, 188f, 189f, 190f
One-compartment open model, for IV bolus administration (Cont.):
clearance in, 48–52, 48f, 724
clinical application, 43
elimination rate constant in, 44–45, 44f, 45f, 724
practical focus, 50–52
urinary excretion data for elimination rate constant calculation in, 53–57, 54f, 55f, 56f, 727
for IV infusion, 91–92
loading dose combined with, 96–98, 97f
steady state drug concentration in, 92–94, 92f, 93f, 93r
of metabolites, 262–264, 262f, 264f
of protein-bound drugs with nonlinear pharmacokinetics, 197–198, 197f
One-way ANOVA, 702–704
Onset time, 8
Open system, 12
Opiates, 542–543
Oral absorption, 336, 736–738
anatomic and physiologic considerations, 336–339, 337f
during drug product development, 333–334
first-order model of, 133f, 134–137, 136f, 137f
rate constant determination, 137–147, 138f, 139f, 141f, 141r, 143r, 144f, 145f, 146r, 147r
GI tract absorption, 339–348, 340f, 341r, 342f, 344r, 345f, 346f, 347f, 746–747
models for estimation of, 145
CRFA, 147–148, 148f
Loo–Riegelman method, 145–147, 145f, 146f, 147r, 738
pharmacokinetics of, 131–133, 132f
rate constants for determination of, 137–147, 138f, 139f, 141f, 141r, 143r, 144f, 145f, 146f, 147r
significance of, 133 steps of, 361, 747
zero-order model of, 133–134, 134f
Oral availability, of popular drugs, 768–772
Oral cavity, 337
Oral delivery
clinical example, 394–395
common excipients for, 456f
drug product considerations for, 390
of insulin, 390
Oral dosage regimens
conversion between IV infusion and, 578–579
multiple doses, 166–168
Oral immunization, 521
Oral route, 323r
Orally disintegrating tablets (ODT), 392, 470, 471f
Orange Book, See Approved Drug Products with Therapeutic Equivalence Evaluations
Order of reaction
determination of, 29
probability concept and, 33–34
Ordinary least-squares (OLS) method, 601, 603
Organs
blood flow to, 208r
drug accumulation in, 210–211
drug uptake by, 208–210, 208f, 208r, 209f, 210f
elimination by, 51–52, 659–660, 660f
Organ clearance, 116–117, 116f, 117f
Orosomucoid, See α1 Acid glycoprotein
Ortho Evra, 134, 134f
Osmotic drug delivery system, 488–489, 488f, 489r, 490f
Osmotic pump systems, 349
OTC drugs. See Over-the-counter drugs
Outlier, 700
Over-the-counter (OTC) drugs, 566
Oxazepam, 231
Oxicams, 230
Oxymetazoline, 227, 228
Paclitaxel (Taxol), 76, 350f, 650
Paddle method, 372, 374–375, 375f
Paddle-over-disk method, 372
Pan coating, 485
Paracellular drug diffusion, 325, 325f, 329
Parameter, 733
Parametric tests, 697
Parenteral administration routes, 323r
Parenteral drug products, 393–394, 394f, 747
clinical example, 394–395
modified-release, 394, 494
Parkinson’s disease, 352
Paroxetine (Prozac), 157–158
Paroxetine hydrochloride (Paxil), 191
Partial agonist, 527–529
Partial pharmacokinetic parameters, dosage regimens based on, 577
Particle size
bioavailability and bioequivalence problems, 414
drug absorption and, 366r, 367
Partition coefficient
drug, 209–211, 209f, 210f, 327, 742
tissue/blood, 658–659
Passive targeting, 519
PAT. See Postantibiotic time; Process analytical technology
Patient, determination of Michaelis constant and maximum elimination rate in, 186–187, 188f, 741
Patient compliance, in TDM, 570
Patient response, in TDM, 570
Paxil. See Paroxetine hydrochloride
PDF. See Probability density function
Peak plasma concentration. See Maximum plasma concentration
Pediatric dosing. See Children Peeling. See Method of residuals Pellets, 484–486, 486t
Penicillin, 610, 753
clearance of, 115, 125
distribution of, 218
dosing frequency of, 581–582 in elderly, 586
hypersensitivity to, 543
in infants and children, 584–585
protein binding of, 228
renal excretion of, 112
Pentobarbital, 222
Pepcid. See Famotidine
Percent of drug dissolved, 381f, 382–383, 382f, 383f
Percent of drug unabsorbed, 140–142, 141f, 736–737
Percent standard deviation, 698
Performance verification test (PVT), 378
Perfusion models. See Physiologic models
Perfusion pressure, 110
Perfusion studies, of GI tract, 349
Perfusion-limited models, 208, 208f, 290, 290f, 659–662, 662t
Period, 419, 748
 Peripheral compartment. See Tissue compartment
Peristalsis method, 377
Peritoneal dialysis, 639
Permeability
BCS and, 432
of cell and capillary membranes, 211–212
intestinal, 349–351, 350f, 351f
Permeability-limited models. See Diffusion-limited models
Permeation enhancers. See Absorption enhancers
Permeation rate, 383
P-gp transporters, 76, 79, 212, 331–333, 333r, 350f, 351, 351f
drug interactions involving, 281–282, 281t
gender differences in, 222
genetic polymorphism of, 311–312
physiologic models incorporating, 668
pH
renal excretion and, 112–113, 113t
renal reabsorption and, 596–597
solubility, drug absorption, and, 366, 366t, 746–747
stability, drug absorption, and, 366–367, 366t, 746–747
Phagocytosis, 335
Pharmaceutical alternatives, 441
Pharmaceutical development, 453–455
CMV and CPP, 453–454
PAT, 454–455
QbD, 453, 453t
biopharmaceutics integration with, 455, 455f
Pharmaceutical equivalents, 441
Pharmaceutical substitution, 442
Pharmacodynamics, 5
drug design considerations, 387
of ER drug products, 496–497, 496f, 497f
pharmacokinetics and, 527, 751–752
biomarker considerations, 531–532
biomarkers, pharmacodynamics, and clinical endpoints, 531, 532t
clinical examples, 539–541, 539f, 539r, 540f, 541f
distribution and pharmacologic response, 544–545, 544f, 545f, 546f
dose and elimination half-life effects on duration of activity, 536
dose–response relationship, 534–536, 534f, 535f, 536f, 544–545, 544f, 545f, 546f, 751–752
drug tolerance and physical dependency, 542–543
drug–receptor theory, 544–545, 544f, 545f, 546f
elimination half-life effect on duration of activity, 537–539, 538f, 538t
hypersensitivity and adverse response, 543
pharmacogenomic biomarkers in drug labels, 315r, 532
PK–PD model development, 532–533, 533r
practice problem, 536–537
rate of absorption and pharmacodynamic response, 541, 542t
receptor occupancy concept, 527–530
receptors for drugs, 530–531
protein binding of drugs and, 241–244, 242f, 244t
Pharmacogenetics, 276, 301–303, 304r, 316–317
ADRs and, 308, 309r
clinical example, 315–316
pharmacokinetics/
pharmacodynamics and, 313–315, 315r
polymorphisms and, 303–306, 304r, 305f, 306f
CYP450, 276–278, 277r, 305, 310–311
in drug targets, 312–313, 313r, 314f
transporter, 311–312
Pharmacogenetics/
pharmacogenomics, 313–315, 315r
Pharmacogenomics, 301, 306–308, 317
Pharmacogenomic biomarkers, 315r, 532
Pharmacokinetics, 3–4, 301. See also Clinical pharmacokinetics; Non-linear pharmacokinetics of absorption, 131–133, 132f
basics of, 10–15, 12f, 13f, 14f, 15f, 16f
of biopharmaceuticals, 521–522
capacity-limited, 181–182, 182f, 183r
clearance in, 189–190, 190f
clinical focus, 191
determination of Michaelis constant and maximum elimination rate, 184–188, 184f, 185f, 186f, 186r, 188f, 741
elimination half-life in, 189
interpretation of Michaelis constant and maximum elimination rate, 188–189, 189f, 741
practice problems, 183–184
drug design considerations, 388
of drug interactions, 590–594, 590r, 591r–592r
in hepatic disease, 645–646
for active drugs with metabolites, 647–648, 648r
dosage adjustment in, 645–646, 646r, 651, 755–758
fraction of drug metabolized, 646–647
hepatic blood flow and intrinsic clearance, 648, 756
hormonal influence on, 649, 649r
liver function tests and hepatic markers, 650
pathophysiologic assessment of, 648–649, 648r, 649r
practice problem, 647
pharmacodynamics and, 527, 751–752
biomarker considerations, 531–532
biomarkers, pharmacodynamics, and clinical endpoints, 531, 532r
clinical examples, 539–541, 539f, 539r, 540f, 541f
distribution and pharmacologic response, 544–545, 544f, 545f, 546r
dose and duration of activity relationship, 536
dose and elimination half-life effects on duration of activity, 537, 537f
dose–response relationship, 534–536, 534f, 535f, 536f, 544–545, 544f, 545f, 546r
drug tolerance and physical dependency, 542–543
drug–receptor theory, 544–545, 545f, 546r
elimination half-life effect on duration of activity, 537–539, 538f, 538r
hypersensitivity and adverse response, 543
pharmacogenomic biomarkers in drug labels, 315r, 532
PK–PD model development, 532–533, 533r
practice problem, 536–537
rate of absorption and pharmacodynamic response, 541, 542r
receptor occupancy concept, 527–530
receptors for drugs, 530–531
Pharmacokinetic evaluation, in TDM, 573–574, 573r
Pharmacokinetic models, 657–658
MRT for, 685r
physiologic, 658–661, 659f, 660f, 741, 758–759
application and limitations of, 662
with binding, 661
compartment approach compared with, 667–668
diffusion-limited model, 208, 208f, 661–662, 662t
flow-limited model, 208, 208f, 290, 290f, 659–662, 662t
with hepatic transporter-mediated clearance, 668–669, 669f, 670f
interspecies scaling, 663–667, 663f, 664t, 666t, 667f, 759
purpose of, 718
selection of, 687–689, 687f, 688f
statistics in, 704
Pharmacokinetic parameters, 10–12
of ER drug products, 499
of haloperidol, 394
of various drugs, 666, 768t–772t
Pharmacokinetic studies of bioequivalence studies, 423
of ER drug products, 497–498
Pharmacokinetic tolerance, 542
Pharmacokinetic–pharmacodynamic (PK–PD) models, 529–530
with effect compartment, 550–551, 550f
receptors in development of, 532–533, 533t
Pharmacokinetics/pharmacodynamics, pharmacogenetics and, 313–315, 315t
Phase I reactions, 270, 271f
Phase II reactions, 270–273, 270t, 271f, 272f, 272t, 273f
Phenobarbital
dialysis removal of, 642
drug interactions of, 278
excretion of, 291
metabolism of, 276
Phenothiazine, 211, 352–353
Phenotype, 307, 317
Phenylbutazone, 270
Phenylbutazone, 270
drug interactions of, 237
elimination of, 230
protein binding of, 235f, 243
Phenylpropanolamine, 541
Phenytoin
AUC of, 409
dialysis removal of, 642
dissolution test requirements for, 384–385
dosing frequency of, 581
metabolism of, 269, 276
nonlinear pharmacokinetics of, 177, 181, 186–188, 187f, 190, 201, 742
protein binding of, 222, 231
pH–partition hypothesis, 329
Physical dependency, 542–543
Physicochemical properties, 366–368
drug design considerations, 366t, 387–388
particle size and drug absorption, 366t, 367
polymorphism, solvates, and absorption, 366t, 367–368, 367f, 368f
solubility, pH, and drug absorption, 366, 366t, 746–747
Physiologic absorption, 746–747
administration route and, 321–324, 323t–324t
cell membranes in

drug passage across,
326–333, 327f, 329f, 329t, 330f, 331r, 332f, 333r
nature of, 324–326, 325f, 326f
clinical examples, 351, 351f
disease states affecting, 351–352
drug interactions affecting, 352–353
drug interactions in GI tract, 334–336, 336f
drug product design and, 321
inhalation drug delivery, 354–355
methods for studying gamma scintigraphy, 348
intestinal permeability studies, 349–351, 350f, 351f
in-vivo GI perfusion studies, 349
markers, 348–349
osmotic pump systems, 349
RDDCs, 349
nasal drug delivery, 354
nutrients affecting, 353
oral, 336
anatomic and physiologic considerations, 336–339, 337f
during drug product development, 333–334
GI tract absorption, 339–348, 340f, 341f, 342f, 344r, 345f, 346f, 347f, 746–747
topical and transdermal drug delivery, 355
Physiologic drug distribution, 205–206, 206f, 207r, 742–744
apparent volume of, 213, 217–218, 218f, 219f, 724
calculation of, 213–216, 214f, 215r
in complex biological systems, 216–217, 217f
practice problem, 216
Physiologic drug distribution
(Cont.):
cell and capillary membrane permeability, 211–212
within cells and tissues, 212
clinical focus, 213
to CSF and brain, 212–213
diffusion, 205–208, 206f, 207r
distribution half-life, blood flow, and drug uptake by organs, 208–210, 208f, 208r, 209f, 210f
drug accumulation, 210–211
gender differences in, 222
hydrostatic pressure, 206–208
modeling of, 247
of protein-bound drugs, 217–218, 217f, 227–229, 227f, 228f, 241–244, 242f, 244r
Physiologic models, 11, 14–15, 14f, 15f, 16f, 728, 741
of clearance, 116–117, 116f, 117f
compartment models compared with, 667–668, 717
pharmacokinetic, 658–661, 659f, 660f, 758–759
application and limitations of, 662
with binding, 661
compartment approach compared with, 667–668
diffusion-limited model, 208, 208f, 661–662, 662r
flow-limited model, 208, 208f, 290, 290f, 659–662, 662r
with hepatic transporter-mediated clearance, 668–669, 669f, 670f
interspecies scaling, 663–667, 663f, 664r, 666r, 667f, 759
volume of distribution in, 724
Pinocytosis, 335–336
PK Solutions, 710
PK–PD models. See Pharmacokinetic–pharmacodynamic models
Plasma, 717
Plasma compartment. See Central compartment
Plasma drug concentration, 6–7, 7f, 9–10, 408–410, 408r, 409f, 410f. See also Steady state drug concentration
dose and dosage interval changes affecting, 580–581
of ER drug products, 473, 473f
during multiple-dosage regimens, 153–157, 155r, 156f, 158r, 161, 172, 173r, 739–740
intermittent IV infusion, 163–165
oral regimens, 166–168
repetitive IV injections, 158–163, 159r
after oral dosing, 135–136, 135f, 136f
peak plasma drug concentration, 408
percent of drug dissolved compared with, 382, 382f, 383f
physiologic drug distribution and, 217–218
in saturable enzymatic elimination processes, elimination rate response to, 179–180, 180r
of sustained-release drug products, 472, 472f
time of peak plasma concentration, 408, 409f
units of expression for, 33
Plasma drug concentration–time curve
absorption phase of, 132, 132f
AUC of, 408–410, 409f, 410f
clearance determined from, 52 distribution phase length on, 84–85, 85f
elimination phase of, 64–65, 64f, 132, 132f
first moment of, 672
for IV infusion, 91, 92f, 93f
measurements using, 7–8, 7f, 8f, 717
of multiple-dosage regimens, 154, 156f
for oral dosing, 135–136, 135f, 136f
postabsorption phase of, 132, 132f
of protein-bound drugs with nonlinear pharmacokinetics, 196–198, 196f, 197f
sampling time and, 717
during saturation, 179, 179f
in three-compartment open model, 77, 78f
in two-compartment open model, 63–68, 64f, 67f
Plasma flow, renal, 109
Plasma protein binding. See Protein binding of drugs
Plavix. See Clopidogrel
Plendil. See Felodipine
Polyclonal antibodies, 509
Polygenic disorders, 306
Polymeric delivery systems, 515–517, 515f
Polymeric matrix tablets, 484
Polymorphic genes, 307
Polymorphism. See Genetic polymorphism
PopPK. See Population pharmacokinetics
Population averages, dosage regimens based on, 577
Population pharmacokinetics (PopPK), 4, 597–598, 753
adaptive method for dosing with feedback, 600–601
analysis of population pharmacokinetic data, 603–605
Bayes estimator, 601, 602f, 602r
Protein binding of drugs (Cont.): nonlinear pharmacokinetics due to, 196–197, 196f, 246 one-compartment model drugs, 197–198, 197f physiologic pharmacokinetic models with, 661 renal clearance and, 125 renal clearance in response to, 125 Protein drugs, 506, 507r–508r formulation and delivery of, 507r–508r, 514–515 Prothrombin time (PT), 650 Proton pump inhibitors, 353 Prozac. See Paroxetine PSA. See Pressure-sensitive adhesive Pseudoephedrine, 132–133 PT. See Prothrombin time Purine drugs, accumulation of, 211 Purinethol. See Mercaptopurine PVT. See Performance verification test Pyrimidine drugs, accumulation of, 211

INDEX

805

model-independent methods, 122–123
in multicompartmental models, 124
practice problem, 123, 123f, 124–125
for protein-bound drugs, 125
renal drug excretion and, 118
glomerular filtration and active secretion, 120, 120f
glomerular filtration and reabsorption, 120
glomerular filtration only, 119, 119r
Renal drug excretion, 111–114, 113r, 253–255, 255f, 733–735
clinical application, 114
practice problems, 114
renal clearance and, 118
glomerular filtration and active secretion, 120, 120f
glomerular filtration and reabsorption, 120
glomerular filtration only, 119, 119r
Renal impairment with aging, 588
dose adjustment in, 617, 619t, 755–758
clearance-based, 620, 756
elimination rate constant-based, 620–621, 756
extracorporeal removal of drugs, 638–645, 640r, 642f, 642r
general approaches for, 618–621, 619r
GFR measurement, 621–622, 626–627, 626r
pharmacokinetic considerations, 617–618
serum creatinine concentration and creatinine clearance, 622–627, 623f, 624f, 625t, 626r
for uremic patients, 627–638, 628f, 629f, 630r–631r, 632r–633r, 637t, 755–758
moxalactam disodium response to, 80–82, 81f
protein binding of drugs in, 221–222, 239r–240r
reduced drug clearance in, 72–73, 73f
two-compartment modeling of drug distribution in, 68–69, 68t, 69, 70f
Renal plasma flow (RPF), 109
Repeat-action tablet, 472
Repetitive IV injections, 158–161, 159
early or late dose administration during, 162–163
missed dose during, 161–162
Replicated crossover bioequivalence study, 419
Reproducibility, 696
RES. See Reticuloendothelial system
Research with animals ethical principles in, 762
interspecies scaling in, 663–667, 663f, 664r, 666t, 667f, 759
boundaries of, 761
with humans, 761–762
Declaration of Helsinki, 761, 762–765
Residence time. See Mean residence time
Response, 10, 701
distribution and, 544–545, 544f, 545f, 546t
dose relationship with, 534–536, 534f, 535f, 536f, 544–545, 544f, 545f, 546r, 751–752
drug concentration relationship with, 4–5, 5f
drug exposure and, 5
exposure relationship with, 558–559
hysteresis of, 552–556, 553f, 554f, 555f, 751–752
clinical example, 556–557, 557f
simulation of, 556, 556f
pharmacodynamic, 541, 542f
pharmacodynamic response, 10
systemic exposure and, 540–541, 540f, 541f
in TDM, 570
variability in, 568t
Restrictive clearance, 287–288
Restrictive elimination, 229–230
Reticuloendothelial system (RES), 267
Retrospective cohort study, 693
Retrospective study, 694
Reversible drug–protein binding, 219
RhG-CSF. See Recombinant human granulocyte-colony stimulating factor
Rifamipin, 278–279
Risk factor, 693
Risk management, 459–460
drug manufacturing requirements, 459, 460t
drug recalls and withdrawals, 460, 460r
process validation, 459–460
regulatory and scientific considerations, 459
Risks from medicines, 451–452, 452f
Risperidone, 191
Ritonavir, 282
RLD. See Reference listed drug
Rotating basket method, 372r, 374
Rotating bottle method, 372r, 376
Route of administration drug design considerations, 389, 389f
extravascular, considerations for, 363
of local activity, 362
RPF. See Renal plasma flow
INDEX

RSD. See Relative standard deviation
Ruggeness, 573
Runge–Kutta method, 660

S
Safety considerations, of ER drug products, 496–497, 496f, 497f
Salicylates, 6, 409
nonlinear pharmacokinetics of, 177, 181, 192
Salicylic acid, 270
absorption of, 328–329, 329f, 329f
dialysis removal of, 642
protein binding of, 234, 235f
renal excretion of, 113
Salicyluric acid, 140
Saliva, 9
Sampling, 6
Sampling error, 33
Sandostatin, 395
Saquinavir, 212
Saquinavir mesylate (Invirase®), 224, 278–279
SAS, 709
Saturable enzymatic elimination, 179–181, 180f. See also Capacity-limited pharmacokinetics
Saturation, 177–179, 740–742. See also Capacity-limited pharmacokinetics
Scaled average bioequivalence crossover study, 419–420
Scale-up and postapproval changes (SUPAC), 397–398, 404, 404f, 461–463, 461f
adverse effect, 462–463
assessment of effects of change, 462
BACPACs, 463
CMVs, 462
equivalence, 462
practical focus, 463–464
changes in batch size, 464
quantitative change in excipients, 463, 463f
Scatchard plot, 234, 234f, 235f, 744
Schedules, dosing, 169–170, 169f, 170f, 172, 173f
Scientist software, 709–710
Scopolamine (Transderm Scop), 396–397
SD. See Standard deviation
Second moment, 676
Sedan. See Terfenadine
Selection bias, 694
Selective serotonin reuptake inhibitors (SSRIs)
ADRs of, 308
drug interactions of, 191, 278
Semilog coordinates, 26–28, 27f, 719
Sensitivity, 572, 608
Sensitivity slope, 555
Sepsis, moxalactam disodium pharmacokinetics in patients with, 80–82, 81f
Sequence, 419, 748–749
Sequential simplex method, 695
Serotonin syndrome, 191, 596
Serum, 717
drug concentration in, 6–7, 7f, 9–10
percent of drug dissolved compared with, 383, 383f
units of expression for, 33
Serum creatinine concentration, dose adjustment based on, 622–623
in adults, 623–624, 623f
in children, 624, 624f
eGFR using MDRD or CKD–EPI equations, 625–626
GFR measurements for, 626–627, 626f
practice problems, 624–625, 625f
Side effect. See Adverse drug reaction
Siersback–Nielsen method, 623, 623f
Sieving coefficient, 644–645
Sigma-minus method, 55–56, 55f
Sigmoid maximum effect model, 549, 550f
Significant figures, 32–33
Sildenafil (Viagra), 651
Similarity factor, 386
Single-nucleotide polymorphism (SNP), 307–308
Sink conditions, 373
siRNA. See Small, interfering RNA
Site-dependent metabolism, 267
Site-specific drug delivery. See Targeted drug delivery
Skewness, 702
Skin
drug distribution to, 209, 209f
elimination by, 659–660, 660f
Slope determination, 27–29, 28f, 29f
Slow release pellets, beads, or granules, 484–486, 486t
Slow-erosion core tablet, 487
Small, interfering RNA (siRNA), 513–514
Small intestine, 474–475
SNP. See Single-nucleotide polymorphism
Sodium valproate (VPA), 191
Software, for pharmacokinetic calculations, 20–21, 707–708
GastroPLUS, 710–711
Kinetica, 710
NONMEM, 710
PK Solutions, 710
R Foundation for Statistic Computing, 709
SAS, 709
Scientist, 709–710
validation of, 708
WinNonlin, 709
Solid drug products, excipients used in, 368–369, 368f
Solubility, 364
BCS and, 431–432
bioavailability and bioequivalence problems, 414
dissolution and, 364–365, 365f
pH, drug absorption, and, 366, 366f, 746–747
Solubility–pH profile, 366
Solute carrier transporters, 312
Solvates, 367–368
absorption and, 366f, 367–368, 367f, 368f
Sonophoresis, 493
SOPs. See Standard Operating Procedures
Sorbitrate, 392
Sparteine, 308
Species
hepatic biotransformation enzyme variation with, 274–275, 275f
scaling among, 663–667, 663f, 664f, 666f, 667f
Specifications, 453–455, 459–460, 462, 750
Specificity, 572, 608
Specified impurity, 465
Spray dry coating, 485
Spreadsheets
electronic, 711, 712f, 713f, 714f, 715f, 716
pharmacokinetic calculations using, 24
SSRIs. See Selective serotonin reuptake inhibitors
St. John’s wort, 593, 596
Stability, 572–573
bioavailability and bioequivalence problems, 414
demonstration of, 386–387 of gelatin capsules, 456
Stability–pH profile, 366
Stadol NS. See Butorphanol tartrate
Stagnant layer, 365, 365f
Standard deviation (SD), 33, 697–698, 723
Standard Operating Procedures (SOPs), 458, 458f
Standard two-stage (STS) method, 605
Statins, drug interactions of, 261–262, 275–276
Statistics, 693
bioequivalence studies, 704
certainty limit, 698–700, 700f
data analysis and interpretation, 696, 696f
descriptive terms, 697, 697f
distributions, 696–698, 698f, 700–701
experimental design and data collection, 694–696
fundamentals of, 33–34
hypothesis testing, 701–702, 702f, 702f
normal distribution, 696–698, 698f
odds, 693–694, 694f
pharmacokinetic models, 704
power test, 702, 704
probability, 693
Statistical evaluation of bioequivalence studies, 423
of ER drug products, 500
Statistical moment theory, 674–679, 675f
MAT and MDT, 685–686, 686f
model-independent and model-dependent nature of MRT, 683–685, 683f, 684f, 685f
MRT for multicompartment models with central compartment elimination, 679–682, 681f, 682f
Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design, 415
Steady state
apparent volume of distribution at, 72, 101–103
clearance relationship with, 100
Steady state drug concentration, 91
during IV infusion, 730–733
apparent volume of distribution at, 101–103
one-compartment model of, 92–94, 92f, 93f, 93r
two-compartment model of, 100–103, 101f
during loading dose plus IV infusion, 730–732
one-compartment model of, 96–98, 97f
two-compartment model of, 101, 101f
in multiple-dosage regimens, 154–157, 172, 173t, 739–740
Steady-state method, 602–603, 603f
Steady-state plasma drug concentration, of ER drug products, 499
Stereoselectivity, 274, 274f
Stomach, 338, 474
STS method. See Standard two-stage method
Student’s t-test, 701
Study submission, 427–430, 427t, 428t, 429f, 429f
dissolution study waiver, 429–430
bioequivalence study waiver, 429–430
Streptococcus pneumoniae, 114
Sulfadiazine, 273
Sulfamethoxazole/trimethoprim (Bactrim), 114
Sulfasalazine, 269
Sulfisoxazole (Gantrisin), 273, 611, 754–755
distribution of, 223
renal excretion of, 114
INDEX

Sulfonamides, 235f
Sum of squares, 698
SUPAC. See Scale-up and postapproval changes
Superposition principle, 154, 155r
for several IV infusion doses, 163–164, 165r
Suprefact. See Buserelin acetate
Suramin, protein binding of, 244
Surface area, bioavailability, and bioequivalence problems, 414
Surrogate endpoints, 531, 558
Surrogate markers, 437, 437r, 749
Surveillance bias, 694
Sustained-release drug products, 472, 472f, 750–751
Synthetic reactions. See Phase II reactions
Synthroid. See Levothyroxine sodium
Systemic clearance. See Clearance

T
Tabulations, 577–578
Tachyphylaxis, 543
Tacrolimus, 335
Tagamet. See Cimetidine
Target drug concentration, 568–569
during multiple-dosage regimens, 153
steady-state, 93
Targeted drug delivery, 519–521, 751
drugs for, 520
general considerations in, 519
oral immunization, 521
site-specific carrier, 520
target site, 519
targeting agents, 520
Targeted-release drug products, 470, 471r, 472
Taxol. See Paclitaxel
Tazobactam, 559, 752
TBW. See Total body weight
TCAs. See Tricyclic antidepressants
TDM. See Therapeutic drug monitoring
Teniposide, 540–541, 540f, 541f
Tenoxicam, 229
Terfenadine (Seldane), 595
Tetracycline, 756
absorption of, 347
accumulation of, 211
in bones and teeth, 329
metabolism of, 310
multiple-oral-dose regimens of, 167–168
protein binding of, 227–228, 228r
Tetracycline hydrochloride (Achromycin V), 174, 740
Theophylline, 4, 34–35, 485, 486r, 729
absorption of, 346, 346f, 348, 737
Bayesian methods applied to, 599–601, 600f
clearance of, 733
compartment models of, 79
conversion from IV infusion to oral dosing of, 578–579
distribution and elimination half-lives of, 80, 81r
dosage regimen of, 578
drug interactions of, 278, 595
food interaction with, 597
IV infusion of, 99, 100
maximum effect model of, 548, 549f
metabolism of, 269, 276, 284, 287
multiple-dosage regimens of, 169, 169f, 174, 739
TDM of, 567, 567f, 574
Therapeutic alternatives, 442
Therapeutic drug monitoring (TDM), 4, 567–568, 567f, 567r, 752–753
ADRs and, 575–576
clinical example, 574–575
dosage adjustment in, 574
dosage regimen design for, 568–569
drug assay in, 571–573
drug concentration measurements in, 570–571, 571r, 575
drug pharmacokinetics in, 569–570
drug product in, 570
drug selection for, 568, 568it
patient compliance in, 570
patient response evaluation in, 570
pharmacokinetic evaluation in, 573–574, 573r
serum drug concentration monitoring in, 574
Therapeutic equivalence evaluation codes, 438–439, 438r
for nifedipine extended release-tablets, 439, 440r
Therapeutic equivalents, 442
Therapeutic index, 8
Therapeutic substitution, 442
Therapeutic window, 8
Thiopental, 14
Three-compartment open model, 718
for IV bolus administration, 77–79, 77f, 78f, 78r, 729–730
MRT calculations in, 683–684, 683r
for nifedipine extended release-tablets, 439, 440r
Therapeutic equivalents, 442
Therapeutic index, 8
Therapeutic substitution, 442
Therapeutic window, 8
Thiopental, 14

Tight junctions, 325, 325r

Time for peak plasma concentration, 8, 135–136, 408, 409r
elimination and absorption rate constant effects on, 143–144, 143r, 144f, 736–738
Time to reach steady state drug concentration in multiple-dosage regimens, 158r
in one-compartment model, 92–94, 92f, 93f, 93r
INDEX

809

Time-dependent pharmacokinetics, 193–194, 194r, 741
Circadian rhythms and drug exposure, 194–195
clinical focus, 195
drug interactions and,
279–280
Timolol, 190, 190f

Tissues
accumulation in, 210–211
blood flow to, 63f
centration in, 8
distribution to, 208–210, 208f, 208r, 209f, 210f
distribution within, 212
elimination by, 51–52,
659–660, 660f
Tissue compartment, 62, 64–66,
65f, 730
apparent volume of distribution in, 75
distribution in, 215, 215r,
742–743
MRT for, 680–682, 681r, 682f
TMP/SMX. See Trimethoprim-
sulfamethoxazole

Tobramycin, 578
dialysis removal of, 642–643
dose determination for, 580
nonlinear pharmacokinetics of, 194
in uremic patients, 637–638
Tocainamide, 549, 550f
Tolazamide, 148, 148f
Tolbutamide, 223, 312
tolerance, 542
Topical drug delivery, 355
Tornalate. See Bitolterol mesylate
Torsades de pointes, 595
Total body clearance, 114, 122–126, 733–735. See also Clearance
after IV infusion, 126
practice problem, 123, 123f
Total body weight (TBW), 622
Total predictability, 608
Total time for drug to be excreted, 410, 411f

Toxic concentrations. See also
Minimum toxic concentration
of popular drugs, 768r–772r
Toxicity, nonlinear
pharmacokinetics causing, 195–196
Toxicokinetics, 5–6, 663
Toxicology, 5–6

Transcellular absorption, 325, 325f
Transderm Scop. See Scopolamine
Transdermal drug delivery, 134,
134f, 324r, 490–493, 491r, 492f
absorption in, 355
drug product considerations for, 396–397, 397r
Transdermal Therapeutic Systems (TTS), 492
Transfer constants, 64–66
Transgene, 512
Transport protein, 336
Transporters, 350–351, 350f, 351f

ABC, 76, 331
in carrier-mediated intestinal absorption, 330–333,
331r, 332f, 333r
drug interactions based on,
280–282, 281r

geic polymorphism of,
311–312
in hepatic clearance and
bioavailability, 293–294,
293f
P-gp, 76, 79, 212, 331–333,
333r, 350f, 351, 351f
drug interactions involving,
281–282, 281r
gender differences in, 222
genetic polymorphism of,
311–312
physiologic models
incorporating, 668
physiologic pharmacokinetic models incorporating, 668–669, 669f, 670f

Trapezoid rule, 25–26
Triamcinolone acetonide
(Nasacort AQ), 395
Tricyclic antidepressants
(TCAs), 6, 352–353
distribution of, 218
metabolism of, 308, 310
Trimazosin, 554, 554f, 555f
Trimethoprim-sulfamethoxazole
(TMP/SMX), 539–540,
539f, 539r
TTS. See Transdermal Therapeutic Systems
Tubocurarine, 535, 535f, 546
Tubular reabsorption, 112–113,
113r, 120
Two one-sided tests procedure,
423–424, 424r
Two-compartment open model,
12–13, 13f, 718
absorption rate constants
determined from, 145–147, 145f, 146r, 147r
elimination phase in, 77
clearance and, 73–74
of plasma drug concentration–time curve, 64–65, 64f
for IV bolus administration,
61, 63–66, 64f, 65f, 729–730
apparent volume of distribution in, 70–77,
71r, 73f
clearance in, 72–74, 73f,
76–77
clinical application, 68, 68r,
69r, 70f
elimination rate constant in, 77
method of residuals, 66–68,
67f, 67r, 729
practical focus, 69–70
practice problems, 68–69,
73–74, 73f
relation between
distribution and elimination half-life, 80,
81r

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INDEX

Two-compartment open model

(Cont.):
of IV infusion, 100–101
apparent volume of
distribution in, 101–103
loading dose combined
with, 101, 101f
practical focus, 102–103
of metabolites, 264–265, 264f,
265f
MRT calculations in,
680–682, 681r, 682f, 683f
with nonlinear elimination,
192–193
renal clearance in, 124
Type I error, 702, 704
Type II error, 702, 704

U
Uncompetitive inhibition, 259f
Unidentified impurity, 465
Unit membrane theory, 325
United States Pharmacopeia
National Formulary
(USP-NF), 459
Units of measurement, 31–33, 32r,
34r
Uremia, 617–618
dose adjustment for, 627–628,
755–758
fraction of drug excreted
unchanged methods, 631,
632r–633r, 634–635
general clearance method, 635
method comparison, 635
nomograms for, 628–629,
628f, 629f, 630r–631t,
757–758
practice problems, 631,
634–638, 637r
Wagner method, 638
Urinary excretion data, 410, 410f,
411f
absorption rate constants deter-
mined with, 142–143
cumulative amount of drug
excreted in urine, 410,
410f
elimination rate constant
calculated from, 53–57,
54f, 55f, 56f, 727
clinical application, 56–57,
56f
practice problems, 54–56,
54f, 55f
of popular drugs, 768r–772r
rate of drug excretion, 410,
411f
total time for drug to be
excreted, 410, 411f
validity of, 56–57, 56f
Urine
drug concentration in, 8–9
formation of, 110–111, 111r
pH of
renal excretion and,
112–113, 113r
renal reabsorption and,
596–597
USP-NF. See United States
Pharmacopeia National
Formulary
V
Vaginal drug delivery, 393
Validity, of urinary excretion
data, 56–57, 56f
Valium. See Diazepam
Valproic acid (Depakene), 197,
218
Vancomycin, 625, 640–641
Variable, 10
Variance, 697
Velocity of metabolism,
258–259
Velocity of reaction, 258
Velosef. See Cephradine
Venous drug concentrations,
247, 662, 758
Verapamil, 76, 195, 596
Viagra. See Sildenafil
Vinblastine, 76, 277
Vince alkaloids, 277
Vincristine, 76
Vindesine, 277
Viral ADRs, 597
Vitamin B-12, 353
Vitamin K, 597
Volume of distribution. See
Apparent volume of
distribution
VPA. See Sodium valproate
W
Wagner method, 638
Wagner–Nelson method,
140–142, 141f, 736,
738. See also Modified
Wagner–Nelson
method
Waivers, of bioequivalence
studies, 429–430
Warfarin, 4, 545
distribution of, 223
drug interactions of, 237, 597
elimination of, 230
indirect effect of, 553
metabolism of, 310–311
population data fitting for,
606–607, 606f
TDM of, 567
Washout period, 419, 748
Wash-out time, 695
Water volume, in body, 205–206,
206f
Weak acids
absorption of, 746–747
diffusion of, 328
renal excretion of,
112–113
Weak base
absorption of, 746–747
diffusion of, 328
renal excretion of, 113
Weighted least-squares (WLS)
approach, 598, 600
Wellbutrin. See Bupropion
hydrochloride
Well-stirred models, 230, 247
Wild type genes, 307
WinNonlin, 709
WLS approach. See Weighted
least-squares approach
World Medical Association,
Declaration of Helsinki,
761, 762–765
<table>
<thead>
<tr>
<th><strong>X</strong></th>
<th>Xanthine oxidase, 268</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xenobiotics, 267</td>
</tr>
<tr>
<td></td>
<td>Xylocaine, 285, 583</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>Zantac®, See Ranitidine</td>
</tr>
<tr>
<td></td>
<td>Zero moment, 676</td>
</tr>
</tbody>
</table>

Zero moment curve, 672

Zero-order absorption, 133–134, 737, 750–751

Clinical application, 134, 134f

Nonlinear elimination with, 192

Zero-order elimination, 48, 726–727

Zero-order half-life, 39, 719–721

Zero-order reactions, 35–38, 36f, 38t, 719–722

Zithromax. See Azithromycin

Zolpidem tartrate (Ambien), 480

Zyvox. See Linezolid