CONTENTS

Preface xvii

1 Introduction to Pharmacokinetics and Pharmacodynamics 1

1.1 Introduction: Drugs and Doses, 1
1.2 Introduction to Pharmacodynamics, 3
   1.2.1 Drug Effects at the Site of Action, 3
   1.2.2 Agonists, Antagonists, and Concentration–Response Relationships, 6
1.3 Introduction to Pharmacokinetics, 9
   1.3.1 Plasma Concentration of Drugs, 10
   1.3.2 Processes in Pharmacokinetics, 11
1.4 Dose–Response Relationships, 13
1.5 Therapeutic Range, 14
   1.5.1 Determination of the Therapeutic Range, 16
1.6 Summary, 18

2 Passage of Drugs Through Membranes 20

2.1 Introduction, 20
2.2 Structure and Properties of Membranes, 21
2.3 Passive Diffusion, 22
   2.3.1 Transcellular Passive Diffusion, 24
   2.3.2 Paracellular Passive Diffusion, 26
2.4 Carrier-Mediated Processes: Transport Proteins, 27
   2.4.1 Uptake Transporters: SLC Superfamily, 28
   2.4.2 Efflux Transporters: ABC Superfamily, 29
   2.4.3 Characteristics of Transporter Systems, 31
3 Drug Administration, Absorption, and Bioavailability

3.1 Introduction: Local and Systemic Drug Administration, 37
3.2 Common Routes of Systemic Drug Administration, 37
   3.2.1 Intravascular Direct Systemic Administration, 37
   3.2.2 Extravascular Parenteral Routes, 38
   3.2.3 Other Extravascular Routes, 38
3.3 Overview of Oral Absorption, 40
3.4 Extent of Drug Absorption, 41
   3.4.1 Bioavailability Factor, 41
   3.4.2 Individual Bioavailability Factors, 42
3.5 Determinants of the Bioavailability Factor, 43
   3.5.1 Disintegration, 43
   3.5.2 Dissolution, 43
   3.5.3 Formulation Excipients, 43
   3.5.4 Adverse Events Within the Gastrointestinal Lumen, 44
   3.5.5 Transcellular Passive Diffusion, 46
   3.5.6 Paracellular Passive Diffusion, 47
   3.5.7 Uptake and Efflux Transporters, 47
   3.5.8 Presystemic Intestinal Metabolism or Extraction, 50
   3.5.9 Presystemic Hepatic Metabolism or Extraction, 52
3.6 Factors Controlling the Rate of Drug Absorption, 53
   3.6.1 Dissolution-Controlled Absorption, 54
   3.6.2 Membrane Penetration-Controlled Absorption, 55
   3.6.3 Overall Rate of Drug Absorption, 55
3.7 Biopharmaceutics Classification System, 55

4 Drug Distribution

4.1 Introduction, 61
4.2 Extent of Drug Distribution, 61
   4.2.1 Distribution Volumes, 62
   4.2.2 Tissue Binding and Plasma Protein Binding: Concentrating Effects, 64
   4.2.3 Assessment of the Extent of Drug Distribution: Apparent Volume of Distribution, 65
   4.2.4 Plasma Protein Binding, 72
4.3 Rate of Drug Distribution, 79
   4.3.1 Perfusion-Controlled Drug Distribution, 80
   4.3.2 Diffusion-Controlled Drug Distribution, 82
4.4 Distribution of Drugs to the Central Nervous System, 83

Problems, 86
References, 87
5 Drug Elimination and Clearance

5.1 Introduction, 89
  5.1.1 First-Order Elimination, 90
  5.1.2 Determinants of the Elimination Rate Constant and the
       Half-Life, 91
5.2 Clearance, 91
  5.2.1 Definition and Determinants of Clearance, 91
  5.2.2 Total Clearance, Renal Clearance, and Hepatic Clearance, 94
  5.2.3 Relationships Among Clearance, Volume of Distribution,
       Elimination Rate Constant, and Half-Life, 95
  5.2.4 Primary and Secondary Parameters, 96
5.3 Renal Clearance, 97
  5.3.1 Glomerular Filtration, 97
  5.3.2 Tubular Secretion, 98
  5.3.3 Tubular Reabsorption, 100
  5.3.4 Putting Meaning into the Value of Renal Clearance, 101
5.4 Hepatic Clearance, 102
  5.4.1 Phase I and Phase II Metabolism, 103
  5.4.2 The Cytochrome P450 Enzyme System, 104
  5.4.3 Glucuronidation, 105
  5.4.4 Drug–Drug Interactions, 106
  5.4.5 Hepatic Drug Transporters, 107
  5.4.6 Kinetics of Drug Metabolism, 109
  5.4.7 Hepatic Clearance, 111
5.5 Measurement of Clearances, 115
  5.5.1 Total Body Clearance, 115
  5.5.2 Renal Clearance, 117
  5.5.3 Fraction of the Drug Excreted Unchanged, 120

Problems, 121
References, 124

6 Compartmental Models in Pharmacokinetics

6.1 Introduction, 127
6.2 Expressions for Component Parts of the Dose–Plasma
    Concentration Relationship, 127
  6.2.1 Effective Dose, 127
  6.2.2 Rate of Drug Absorption, 128
  6.2.3 Rate of Drug Elimination, 129
  6.2.4 Rate of Drug Distribution, 129
6.3 Putting Everything Together: Compartments and Models, 130
  6.3.1 One-Compartment Model, 130
  6.3.2 Two-Compartment Model, 131
  6.3.3 Three-Compartment Model, 131
6.4 Examples of Complete Compartment Models, 133
  6.4.1 Intravenous Bolus Injection in a One-Compartment Model
       with First-Order Elimination, 133
CONTENTS

6.4.2 Intravenous Bolus Injection in a Two-Compartment Model with First-Order Elimination, 134
6.4.3 First-Order Absorption in a Two-Compartment Model with First-Order Elimination, 135

6.5 Use of Compartmental Models to Study Metabolite Pharmacokinetics, 136

6.6 Selecting and Applying Models, 137

Problems, 138
Recommended Reading, 138

7 Pharmacokinetics of an Intravenous Bolus Injection in a One-Compartment Model 139

7.1 Introduction, 140
7.2 One-Compartment Model, 140
7.3 Pharmacokinetic Equations, 142
  7.3.1 Basic Equation, 142
  7.3.2 Half-Life, 143
  7.3.3 Time to Eliminate a Dose, 143
7.4 Simulation Exercise, 144
7.5 Application of the Model, 145
  7.5.1 Predicting Plasma Concentrations, 145
  7.5.2 Duration of Action, 146
  7.5.3 Value of a Dose to Give a Desired Initial Plasma Concentration, 147
  7.5.4 Intravenous Loading Dose, 147
7.6 Determination of Pharmacokinetic Parameters Experimentally, 148
  7.6.1 Study Design for the Determination of Parameters, 149
  7.6.2 Pharmacokinetic Analysis, 149
7.7 Pharmacokinetic Analysis in Clinical Practice, 153
Problems, 155
Recommended Reading, 157

8 Pharmacokinetics of an Intravenous Bolus Injection in a Two-Compartment Model 158

8.1 Introduction, 159
8.2 Tissue and Compartmental Distribution of a Drug, 159
  8.2.1 Drug Distribution to the Tissues, 159
  8.2.2 Compartmental Distribution of a Drug, 160
8.3 Basic Equation, 162
  8.3.1 Distribution: $A$, $\alpha$, and the Distribution $t_{1/2}$, 163
  8.3.2 Elimination: $B$, $\beta$, and the Beta $t_{1/2}$, 163
8.4 Relationship Between Macro and Micro Rate Constants, 164
8.5 Primary Pharmacokinetic Parameters, 165
  8.5.1 Clearance, 165
  8.5.2 Distribution Clearance, 166
  8.5.3 Volume of Distribution, 167
8.6 Simulation Exercise, 170
8.7 Determination of the Pharmacokinetic Parameters of the Two-Compartment Model, 173
  8.7.1 Determination of Intercepts and Macro Rate Constants, 173
  8.7.2 Determination of the Micro Rate Constants: $k_{12}, k_{21},$ and $k_{10}$, 175
  8.7.3 Determination of the Primary Pharmacokinetic Parameters, 175
8.8 Clinical Application of the Two-Compartment Model, 176
  8.8.1 Measurement of the Elimination Half-Life in the Postdistribution Phase, 176
  8.8.2 Determination of the Loading Dose, 177
  8.8.3 Evaluation of a Dose: Monitoring Plasma Concentrations and Patient Response, 179
Problems, 180
Recommended Reading, 181

9 Pharmacokinetics of Extravascular Drug Administration 182
  9.1 Introduction, 183
  9.2 Model for First-Order Absorption in a One-Compartment Model, 184
    9.2.1 Model and Equations, 184
    9.2.2 Determination of the Model Parameters, 186
    9.2.3 Absorption Lag Time, 192
    9.2.4 Flip-Flop Model and Sustained-Release Preparations, 192
    9.2.5 Determinants of $T_{\text{max}}$ and $C_{\text{max}}$, 194
  9.3 Bioavailability, 195
    9.3.1 Bioavailability Parameters, 195
    9.3.2 Absolute Bioavailability, 197
    9.3.3 Relative Bioavailability, 198
    9.3.4 Bioequivalence, 198
    9.3.5 Example Bioavailability Analysis, 198
  9.4 Simulation Exercise, 198
Problems, 199
Recommended Reading, 200

10 Introduction to Noncompartmental Analysis 201
  10.1 Introduction, 201
  10.2 Mean Residence Time, 202
  10.3 Determination of Other Important Pharmacokinetic Parameters, 205
  10.4 Different Routes of Administration, 207
  10.5 Application of Noncompartmental Analysis to Clinical Studies, 208
Problems, 210

11 Pharmacokinetics of Intravenous Infusion in a One-Compartment Model 212
  11.1 Introduction, 213
  11.2 Model and Equations, 214
    11.2.1 Basic Equation, 214
13 Multiple Intermittent Infusions  254
  13.1 Introduction, 254
  13.2 Steady-State Equations for Multiple Intermittent Infusions, 256
  13.3 Monoexponential Decay During a Dosing Interval: Determination of Peaks, Troughs, and Elimination Half-Life, 259
    13.3.1 Determination of Half-Life, 259
    13.3.2 Determination of Peaks and Troughs, 261
  13.4 Determination of the Volume of Distribution, 261
  13.5 Individualization of Dosing Regimens, 264
  13.6 Simulation Exercise, 265
    Problems, 265

14 Multiple Oral Doses  267
  14.1 Introduction, 267
  14.2 Steady-State Equations, 268
    14.2.1 Time to Peak Steady-State Plasma Concentration, 269
    14.2.2 Maximum Steady-State Plasma Concentration, 270
    14.2.3 Minimum Steady-State Plasma Concentration, 271
    14.2.4 Average Steady-State Plasma Concentration, 271
    14.2.5 Overall Effect of Absorption Parameters on a Steady-State Dosing Interval, 272
  14.3 Equations Used Clinically to Individualize Oral Doses, 272
    14.3.1 Protocol to Select an Appropriate Equation, 273
  14.4 Simulation Exercise, 274
    References, 265

15 Nonlinear Pharmacokinetics  277
  15.1 Linear Pharmacokinetics, 277
  15.2 Nonlinear Processes in Absorption, Distribution, Metabolism, and Elimination, 280
  15.3 Pharmacokinetics of Capacity-Limited Metabolism, 281
    15.3.1 Kinetics of Enzymatic Processes, 282
    15.3.2 Plasma Concentration–Time Profile, 283
  15.4 Phenytoin, 284
    15.4.1 Basic Equation for Steady State, 285
    15.4.2 Estimation of Doses and Plasma Concentrations, 287
    15.4.3 Influence of $K_m$ and $V_{max}$ and Factors That Affect These Parameters, 289
    15.4.4 Time to Eliminate the Drug, 290
    15.4.5 Time to Reach Steady State, 291
    15.4.6 Individualization of Doses of Phenytoin, 292
    Problems, 295
    References, 296
16 Introduction to Pharmacodynamic Models and Integrated Pharmacokinetic-Pharmacodynamic Models

16.1 Introduction, 298
16.2 Classic Pharmacodynamic Models Based on Traditional Receptor Theory, 299
  16.2.1 Receptor Binding, 300
  16.2.2 Response-Concentration Models, 302
16.3 Empirical Pharmacodynamic Models Used Clinically, 307
  16.3.1 Sigmoidal $E_{\text{max}}$ and $E_{\text{max}}$ Models, 308
  16.3.2 Linear Adaptations of the $E_{\text{max}}$ Model, 310
16.4 Integrated PK-PD Models: $E_{\text{max}}$ Model Combined with a PK Model for Intravenous Bolus Injection in a One-Compartment Model, 312
  16.4.1 Simulation Exercise, 314
16.5 Hysteresis and the Effect Compartment, 315
  16.5.1 Simulation Exercise, 318
Problems, 319
References, 321

17 Mechanism-Based Integrated Pharmacokinetic-Pharmacodynamic Models 323

17.1 Introduction, 324
17.2 Alternative Models for Drug-Receptor Interaction: Operational Model of Agonism, 325
  17.2.1 Simulation Exercise, 329
17.3 Physiological Turnover Model and Its Characteristics, 329
  17.3.1 Points of Drug Action, 330
  17.3.2 System Recovery After Change in Baseline Value, 330
17.4 Indirect Effect Models, 331
  17.4.1 Characteristics of Indirect Effect Drug Responses, 333
  17.4.2 Characteristics of Indirect Effect Models Illustrated Using Model I, 334
  17.4.3 Other Indirect Models, 340
17.5 Transduction and Transit Compartment Models, 340
  17.5.1 Simulation Exercise, 343
17.6 Tolerance Models, 344
  17.6.1 Counter-regulatory Force Model, 345
  17.6.2 Precursor Pool Model of Tolerance, 348
17.7 Irreversible Drug Effects, 350
  17.7.1 Application of the Turnover Model to Irreversible Drug Action, 350
  17.7.2 Model for Hematological Toxicity of Anticancer Drugs, 352
17.8 Disease Progression Models, 356
  17.8.1 Generation of Drug Response, 356
  17.8.2 Drug Interaction with a Disease, 356
  17.8.3 Disease Progression Models, 356
Problems, 360
References, 365
Appendix A  Review of Exponents and Logarithms  368
A.1 Exponents, 368
A.2 Logarithms: log and ln, 369
A.3 Performing Calculations in the Logarithmic Domain, 370
  A.3.1 Multiplication, 370
  A.3.2 Division, 371
  A.3.3 Reciprocals, 371
  A.3.4 Exponents, 371
A.4 Calculations Using Exponential Expressions and Logarithms, 371
A.5 Decay Function: $e^{-kt}$, 373
A.6 Growth Function: $1 - e^{kt}$, 374
A.7 Decay Function in Pharmacokinetics, 374
Problems, 375

Appendix B  Rates of Processes  377
B.1 Introduction, 377
B.2 Order of a Rate Process, 378
B.3 Zero-Order Processes, 378
  B.3.1 Equation for Zero-Order Filling, 378
  B.3.2 Equation for Zero-Order Emptying, 379
  B.3.3 Time for Zero-Order Emptying to Go to 50% Completion, 379
B.4 First-Order Processes, 380
  B.4.1 Equation for a First-Order Process, 380
  B.4.2 Time for 50% Completion: The Half-Life, 381
B.5 Comparison of Zero- and First-Order Processes, 382
B.6 Detailed Example of First-Order Decay in Pharmacokinetics, 382
  B.6.1 Equations and Semilogarithmic Plots, 382
  B.6.2 Half-Life, 383
  B.6.3 Fraction or Percent Completion of a First-Order Process Using First-Order Elimination as an Example, 384
B.7 Examples of the Application of First-Order Kinetics to Pharmacokinetics, 385

Appendix C  Creation of Excel Worksheets for Pharmacokinetic Analysis  387
C.1 Measurement of AUC and Clearance, 387
  C.1.1 Trapezoidal Rule, 388
  C.1.2 Excel Spreadsheet to Determine $AUC_{0\to\infty}$ and Clearance, 389
C.2 Analysis of Data from an Intravenous Bolus Injection in a One-Compartment Model, 393
C.3 Analysis of Data from an Intravenous Bolus Injection in a Two-Compartment Model, 394
C.4 Analysis of Oral Data in a One-Compartment Model, 398
C.5 Noncompartmental Analysis of Oral Data, 399

Appendix D  Derivation of Equations for Multiple Intravenous Bolus Injections 403
D.1 Assumptions, 403
D.2 Basic Equation for Plasma Concentration After Multiple Intravenous Bolus Injections, 403
D.3 Steady-State Equations, 406

Appendix E Summary of the Properties of the Fictitious Drugs Used in the Text  407

Appendix F Computer Simulation Models  409

Glossary of Abbreviations and Symbols  410

Index  415
The behavior and characteristics of therapeutic drugs vary enormously. For example, doses differ more than a thousandfold. Some drugs must be taken three times a day, others once daily, and some every month. The response to some therapies occurs immediately, whereas for others it may take days or even weeks for the response to be apparent. Some drugs must be taken with food; others must be taken on an empty stomach. Concurrent medications interact with some drugs but not with others. The study of pharmacokinetics (the dose–concentration relationship) and pharmacodynamics (the concentration–response relationship), which have been referred to as the pillars of clinical pharmacology, unlocks the mystery of this behavior and brings clarity to diverse patterns of drug action. The goal of this book is to provide straightforward, uncomplicated, but comprehensive coverage of the essentials of pharmacokinetics and pharmacodynamics. I hope the book will enable a large and diverse group of students to develop an interest in this subject and gain a better understanding of the properties and behaviors of drugs.

Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations is an introductory textbook suitable to accompany courses in pharmacokinetics, pharmacodynamics, and clinical pharmacology in pharmacy and medical schools. It is also directed toward people in the pharmaceutical field who want to gain an understanding of this area through self-study. The book is organized and written with several objectives in mind. First, as an introductory textbook, the intent is to present the material in as simple a way as possible, without compromising the accuracy and scope of the material. I think it is important that students not be overwhelmed during their initial exposure. Interested students can always find more advanced literature. Second, simulations are integrated into the text to allow students to visualize important concepts and to promote understanding. Pharmacokinetics and pharmacodynamics are subjects that must be approached with the goal of understanding, not memorizing, the material. The text provides exercises to guide readers through simulations, but readers are also encouraged to experiment with simulations on their own. A third goal is to balance the qualitative side of pharmacokinetics with the quantitative side, or equations. Although only a fraction