

BASIC PHARMACOKINETICS AND PHARMACODYNAMICS

**An Integrated Textbook and
Computer Simulations**

SARA ROSENBAUM



WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

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	

- 2.4.4 Simulation Exercise, 32
- 2.4.5 Clinical Examples of Transporter Involvement in Drug Response, 33

3 Drug Administration, Absorption, and Bioavailability **36**

- 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
- Problems, 56
- References, 57

4 Drug Distribution **60**

- 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	88
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	126
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	

- 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 , α , and the Distribution $t_{1/2}$, 163
 - 8.3.2 Elimination: B , β , 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_{\max} and C_{\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	

- 11.2.2 Application of the Basic Equation, 216
- 11.2.3 Simulation Exercise: Part 1, 216
- 11.3 Steady-State Plasma Concentration, 217
 - 11.3.1 Equation for Steady-State Plasma Concentrations, 217
 - 11.3.2 Application of the Equation, 217
 - 11.3.3 Basic Formula Revisited, 218
 - 11.3.4 Factors Controlling Steady-State Plasma Concentration, 218
 - 11.3.5 Time to Steady State, 219
 - 11.3.6 Simulation Exercise: Part 2, 220
- 11.4 Loading Dose, 221
 - 11.4.1 Loading-Dose Equation, 221
 - 11.4.2 Simulation Exercise: Part 3, 223
- 11.5 Termination of Infusion, 223
 - 11.5.1 Equations for Termination Before and After Steady State, 223
 - 11.5.2 Simulation Exercise: Part 4, 224
- 11.6 Individualization of Dosing Regimens, 224
 - 11.6.1 Initial Doses, 224
 - 11.6.2 Monitoring and Individualizing Therapy, 225
- Problems, 227

12 Multiple Intravenous Bolus Injections in the One-Compartment Model 230

- 12.1 Introduction, 231
- 12.2 Terms and Symbols Used in Multiple-Dosing Equations, 232
- 12.3 Monoexponential Decay During a Dosing Interval, 234
 - 12.3.1 Calculation of Dosing Interval to Give Specific Steady-State Peaks and Troughs, 235
- 12.4 Basic Pharmacokinetic Equations for Multiple Doses, 236
 - 12.4.1 Principle of Superposition, 236
 - 12.4.2 Equations That Apply Before Steady State, 236
- 12.5 Steady State, 238
 - 12.5.1 Steady-State Equations, 238
 - 12.5.2 Average Plasma Concentration at Steady State, 240
 - 12.5.3 Fluctuation, 242
 - 12.5.4 Accumulation, 243
 - 12.5.5 Time to Reach Steady State, 244
 - 12.5.6 Loading Dose, 245
- 12.6 Basic Formula Revisited, 245
- 12.7 Pharmacokinetic-Guided Dosing Regimen Design, 246
 - 12.7.1 General Considerations for Selection of the Dosing Interval, 246
 - 12.7.2 Protocols for Pharmacokinetic-Guided Dosing Regimens, 247
- 12.8 Simulation Exercise, 251
- Problems, 253
- References, 253

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	297
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_{\max} and E_{\max} Models, 308	
16.3.2 Linear Adaptations of the E_{\max} Model, 310	
16.4 Integrated PK–PD Models: E_{\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 $AUC_{0 \rightarrow \infty}$ 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

PREFACE

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