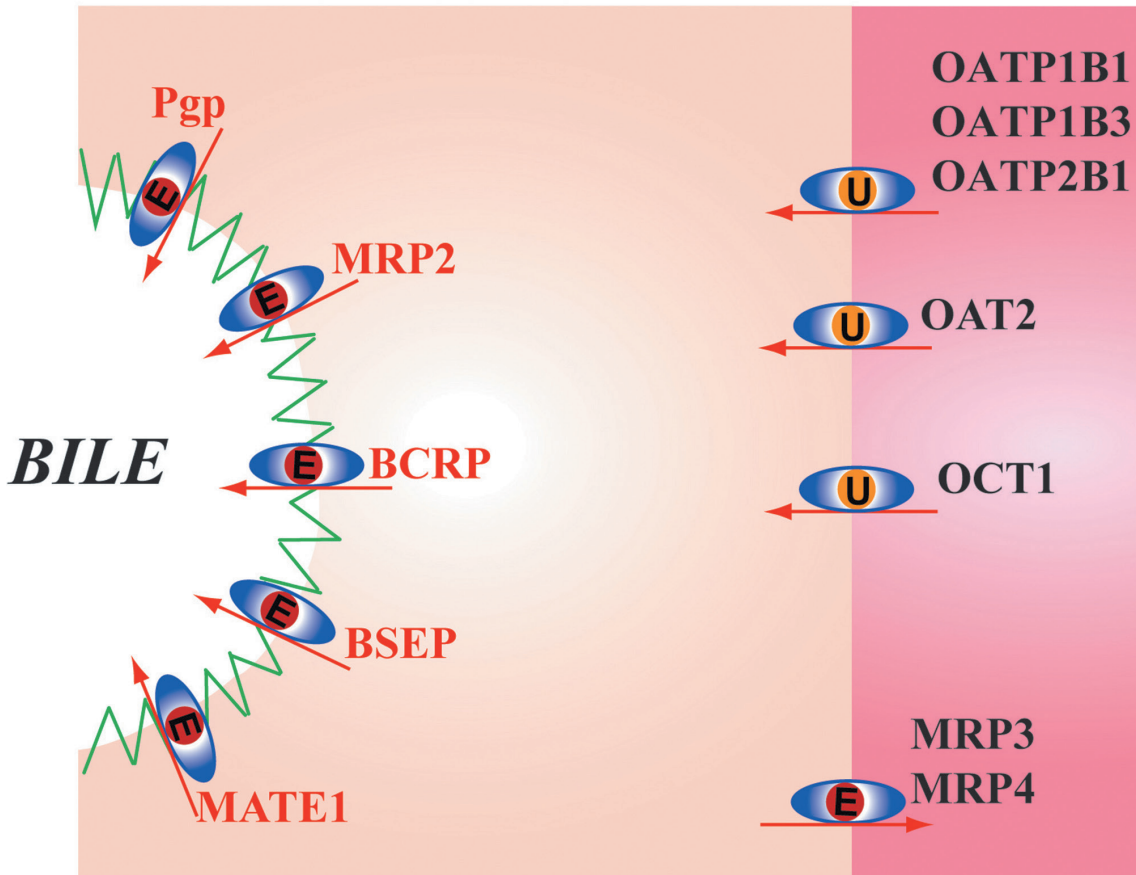
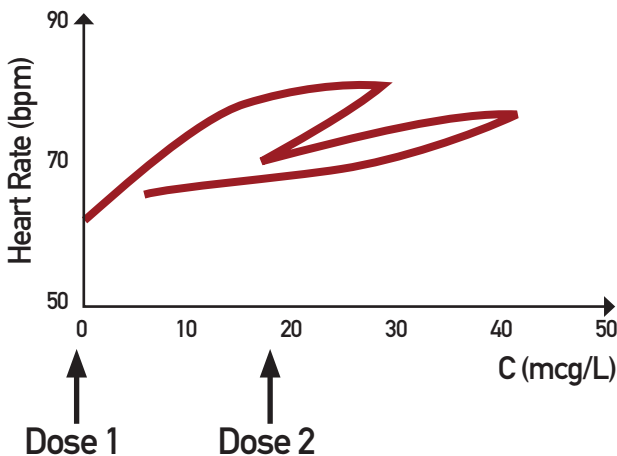


BASIC PHARMACOKINETICS AND PHARMACODYNAMICS



AN INTEGRATED TEXTBOOK AND COMPUTER SIMULATIONS



EDITED BY
SARA E. ROSENBAUM
SECOND EDITION



WILEY

BASIC PHARMACOKINETICS AND PHARMACODYNAMICS

BASIC PHARMACOKINETICS AND PHARMACODYNAMICS

An Integrated Textbook and Computer Simulations

Second Edition

Edited by

SARA E. ROSENBAUM

WILEY

Copyright © 2017 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Names: Rosenbaum, Sara (Sara E.), author, editor.

Title: Basic pharmacokinetics and pharmacodynamics : an integrated textbook and computer simulations / edited by Sara E. Rosenbaum.

Description: Second edition. | Hoboken, New Jersey : John Wiley & Sons, Inc., [2017] | Includes bibliographical references and index.

Identifiers: LCCN 2016031846 (print) | LCCN 2016034126 (ebook) | ISBN 9781119143154 (pbk.) |

ISBN 9781119143161 (pdf) | ISBN 9781119143185 (epub)

Subjects: | MESH: Pharmacokinetics | Pharmacological Phenomena | Computer Simulation

Classification: LCC RM301.5 (print) | LCC RM301.5 (ebook) | NLM QV 38 | DDC 615/.7—dc23

LC record available at <https://lccn.loc.gov/2016031846>

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

To Steve, Molly and Lucy

CONTENTS

Preface	xix
Contributors	xxi
1 Introduction to Pharmacokinetics and Pharmacodynamics	1
<i>Sara E. Rosenbaum</i>	
1.1 Introduction: Drugs and Doses,	2
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,	9
1.3.2 Processes in Pharmacokinetics,	11
1.4 Dose–Response Relationships,	12
1.5 Therapeutic Range,	14
1.5.1 Determination of the Therapeutic Range,	15
1.6 Summary,	18
Reference,	18
2 Passage of Drugs Through Membranes	19
<i>Sara E. Rosenbaum</i>	
2.1 Introduction,	20
2.2 Structure and Properties of Membranes,	20
2.3 Passive Diffusion,	21
2.3.1 Transcellular Passive Diffusion,	23
2.3.2 Paracellular Passive Diffusion,	25
2.4 Carrier-Mediated Processes: Transport Proteins,	26
2.4.1 Uptake Transporters: SLC Superfamily,	27

- 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, 32

References, 33

3 Drug Administration and Drug Absorption 35

Steven C. Sutton

- 3.1 Introduction: Local and Systemic Drug Administration, 36
 - 3.2 Routes of Drug Administration, 37
 - 3.2.1 Common Routes of Local Drug Administration, 37
 - 3.2.2 Common Routes of Systemic Drug Administration, 38
 - 3.3 Overview of Oral Absorption, 41
 - 3.3.1 Anatomy and Physiology of the Oral-Gastric-Intestinal Tract and Transit Time, 41
 - 3.4 Extent of Drug Absorption, 44
 - 3.4.1 Bioavailability Factor, 44
 - 3.4.2 Individual Bioavailability Factors, 45
 - 3.5 Determinants of the Fraction of the Dose Absorbed (F), 46
 - 3.5.1 Disintegration, 46
 - 3.5.2 Dissolution, 46
 - 3.5.3 Formulation Excipients, 50
 - 3.5.4 Adverse Events within the Gastrointestinal Lumen, 50
 - 3.5.5 Transcellular Passive Diffusion, 53
 - 3.5.6 Particulate Uptake, 53
 - 3.5.7 Paracellular Passive Diffusion, 53
 - 3.5.8 Uptake and Efflux Transporters, 54
 - 3.5.9 Presystemic Intestinal Metabolism or Extraction, 58
 - 3.5.10 Presystemic Hepatic Metabolism or Extraction, 60
 - 3.6 Factors Controlling the Rate of Drug Absorption, 61
 - 3.6.1 Dissolution-Controlled Absorption, 63
 - 3.6.2 Membrane Penetration-Controlled Absorption, 63
 - 3.6.3 Overall Rate of Drug Absorption, 63
 - 3.7 Biopharmaceutics Classification System, 64
 - 3.7.1 Intestinal Reserve Length, 64
 - 3.7.2 Biopharmaceutics Classification System (BCS), 64
 - 3.7.3 Biopharmaceutics Drug Disposition Classification System (BDDCS), 65
 - 3.8 Food Effects, 65
- Problems, 66
- References, 67

4 Drug Distribution 71

Sara E. Rosenbaum

- 4.1 Introduction, 72
- 4.2 Extent of Drug Distribution, 72
 - 4.2.1 Distribution Volumes, 74

- 4.2.2 Tissue Binding, Plasma Protein Binding, and Partitioning: Concentrating Effects, 75
- 4.2.3 Assessment of the Extent of Drug Distribution: Apparent Volume of Distribution, 76
- 4.2.4 Plasma Protein Binding, 82
- 4.3 Rate of Drug Distribution, 89
 - 4.3.1 Perfusion-Controlled Drug Distribution, 90
 - 4.3.2 Diffusion or Permeability-Controlled Drug Distribution, 93
- 4.4 Distribution of Drugs to the Central Nervous System, 93
- Problems, 96
- References, 98

5 Drug Elimination and Clearance

99

Sara E. Rosenbaum

- 5.1 Introduction, 100
 - 5.1.1 First-Order Elimination, 101
 - 5.1.2 Determinants of the Elimination Rate Constant and the Half-Life, 102
- 5.2 Clearance, 102
 - 5.2.1 Definition and Determinants of Clearance, 102
 - 5.2.2 Total Clearance, Renal Clearance, and Hepatic Clearance, 104
 - 5.2.3 Relationships among Clearance, Volume of Distribution, Elimination Rate Constant, and Half-Life, 105
 - 5.2.4 Primary and Secondary Parameters, 106
 - 5.2.5 Measurement of Total Body Clearance, 106
- 5.3 Renal Clearance, 108
 - 5.3.1 Glomerular Filtration, 109
 - 5.3.2 Tubular Secretion, 110
 - 5.3.3 Tubular Reabsorption, 113
 - 5.3.4 Putting Meaning into the Value of Renal Clearance, 114
 - 5.3.5 Measurement of Renal Clearance, 115
 - 5.3.6 Fraction of the Dose Excreted Unchanged, 118
- 5.4 Hepatic Elimination and Clearance, 119
 - 5.4.1 Phase I and Phase II Metabolism, 120
 - 5.4.2 The Cytochrome P450 Enzyme System, 121
 - 5.4.3 Glucuronidation, 122
 - 5.4.4 Metabolism-Based Drug–Drug Interactions, 122
 - 5.4.5 Hepatic Drug Transporters and Drug–Drug Interactions, 125
 - 5.4.6 Kinetics of Drug Metabolism, 127
 - 5.4.7 Hepatic Clearance and Related Parameters, 128
- Problems, 139
- References, 142

6 Compartmental Models in Pharmacokinetics

145

Sara E. Rosenbaum

- 6.1 Introduction, 146

- 6.2 Expressions for Component Parts of the Dose–Plasma Concentration Relationship, 146
 - 6.2.1 Effective Dose, 146
 - 6.2.2 Rate of Drug Absorption, 147
 - 6.2.3 Rate of Drug Elimination, 148
 - 6.2.4 Rate of Drug Distribution, 148
- 6.3 Putting Everything Together: Compartments and Models, 149
 - 6.3.1 One-Compartment Model, 149
 - 6.3.2 Two-Compartment Model, 150
 - 6.3.3 Three-Compartment Model, 150
- 6.4 Examples of Complete Compartment Models, 152
 - 6.4.1 Intravenous Bolus Injection in a One-Compartment Model with First-Order Elimination, 152
 - 6.4.2 Intravenous Bolus Injection in a Two-Compartment Model with First-Order Elimination, 153
 - 6.4.3 First-Order Absorption in a Two-Compartment Model with First-Order Elimination, 154
- 6.5 Use of Compartmental Models to Study Metabolite Pharmacokinetics, 155
- 6.6 Selecting and Applying Models, 156
- Problems, 157
- Suggested Readings, 157

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

159

Sara E. Rosenbaum

- 7.1 Introduction, 160
- 7.2 One-Compartment Model, 160
- 7.3 Pharmacokinetic Equations, 162
 - 7.3.1 Basic Equation, 162
 - 7.3.2 Half-Life, 163
 - 7.3.3 Time to Eliminate a Dose, 163
- 7.4 Simulation Exercise, 163
- 7.5 Application of the Model, 165
 - 7.5.1 Predicting Plasma Concentrations, 165
 - 7.5.2 Duration of Action, 166
 - 7.5.3 Value of a Dose to Give a Desired Initial Plasma Concentration, 167
 - 7.5.4 Intravenous Loading Dose, 167
- 7.6 Determination of Pharmacokinetic Parameters Experimentally, 168
 - 7.6.1 Study Design for the Determination of Parameters, 168
 - 7.6.2 Pharmacokinetic Analysis, 169
- 7.7 Pharmacokinetic Analysis in Clinical Practice, 173
- Problems, 174
- Suggested Reading, 176

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

177

Sara E. Rosenbaum

- 8.1 Introduction, 178

- 8.2 Tissue and Compartmental Distribution of a Drug, 179
 - 8.2.1 Drug Distribution to the Tissues, 179
 - 8.2.2 Compartmental Distribution of a Drug, 180
 - 8.3 Basic Equation, 181
 - 8.3.1 Distribution: A , α , and the Distribution $t_{1/2}$, 182
 - 8.3.2 Elimination: B , β , and the $\beta t_{1/2}$, 182
 - 8.4 Relationship Between Macro and Micro Rate Constants, 183
 - 8.5 Primary Pharmacokinetic Parameters, 183
 - 8.5.1 Clearance, 184
 - 8.5.2 Distribution Clearance, 184
 - 8.5.3 Volume of Distribution, 186
 - 8.6 Simulation Exercise, 188
 - 8.7 Determination of the Pharmacokinetic Parameters of the Two-Compartment Model, 191
 - 8.7.1 Determination of Intercepts and Macro Rate Constants, 191
 - 8.7.2 Determination of the Micro Rate Constants: k_{12} , k_{21} , and k_{10} , 193
 - 8.7.3 Determination of the Primary Pharmacokinetic Parameters, 193
 - 8.8 Clinical Application of the Two-Compartment Model, 194
 - 8.8.1 Measurement of the Elimination Half-Life in the Postdistribution Phase, 194
 - 8.8.2 Determination of the Loading Dose, 195
 - 8.8.3 Evaluation of a Dose: Monitoring Plasma Concentrations and Patient Response, 197
- Problems, 197
Suggested Readings, 199

9 Pharmacokinetics of Extravascular Drug Administration

201

Dr. Steven C. Sutton

- 9.1 Introduction, 202
- 9.2 First-Order Absorption in a One-Compartment Model, 203
 - 9.2.1 Model and Equations, 203
 - 9.2.2 Parameter Determination, 205
 - 9.2.3 Absorption Lag Time, 210
 - 9.2.4 Flip-Flop Model and Sustained-Release Preparations, 212
 - 9.2.5 Determinants of T_{\max} and C_{\max} , 212
- 9.3 Modified Release and Gastric Retention Formulations, 214
 - 9.3.1 Impact of the Stomach, 214
 - 9.3.2 Moisture in the Gastrointestinal Tract, 215
- 9.4 Bioavailability, 215
 - 9.4.1 Bioavailability Parameters, 215
 - 9.4.2 Absolute Bioavailability, 217
 - 9.4.3 Relative Bioavailability, 217
 - 9.4.4 Bioequivalence, 217
 - 9.4.5 Single-Dose Crossover Parallel and Steady-State Study Designs, 219
 - 9.4.6 Example Bioavailability Analysis, 219
- 9.5 *In Vitro-In Vivo* Correlation, 219
 - 9.5.1 Definitions, 219

- 9.5.2 Assumptions, 220
- 9.5.3 Utility, 220
- 9.5.4 Immediate Release IVIVC, 220
- 9.5.5 Modified Release IVIVC, 221
- 9.6 Simulation Exercise, 222
- Problems, 223
- References, 224

10 Introduction to Noncompartmental Analysis 225

Sara E. Rosenbaum

- 10.1 Introduction, 225
- 10.2 Mean Residence Time, 226
- 10.3 Determination of Other Important Pharmacokinetic Parameters, 229
- 10.4 Different Routes of Administration, 231
- 10.5 Application of Noncompartmental Analysis to Clinical Studies, 232
- Problems, 234

11 Pharmacokinetics of Intravenous Infusion in a One-Compartment Model 237

Sara E. Rosenbaum

- 11.1 Introduction, 238
- 11.2 Model and Equations, 239
 - 11.2.1 Basic Equation, 239
 - 11.2.2 Application of the Basic Equation, 241
 - 11.2.3 Simulation Exercise: Part 1, 241
- 11.3 Steady-State Plasma Concentration, 242
 - 11.3.1 Equation for Steady-State Plasma Concentrations, 242
 - 11.3.2 Application of the Equation, 242
 - 11.3.3 Basic Formula Revisited, 243
 - 11.3.4 Factors Controlling Steady-State Plasma Concentration, 243
 - 11.3.5 Time to Steady State, 244
 - 11.3.6 Simulation Exercise: Part 2, 245
- 11.4 Loading Dose, 246
 - 11.4.1 Loading-Dose Equation, 246
 - 11.4.2 Simulation Exercise: Part 3, 248
- 11.5 Termination of Infusion, 248
 - 11.5.1 Equations for Termination Before and After Steady State, 248
 - 11.5.2 Simulation Exercise: Part 4, 249
- 11.6 Individualization of Dosing Regimens, 249
 - 11.6.1 Initial Doses, 249
 - 11.6.2 Monitoring and Individualizing Therapy, 250
- Problems, 252

12 Multiple Intravenous Bolus Injections in the One-Compartment Model 255

Sara E. Rosenbaum

- 12.1 Introduction, 256
- 12.2 Terms and Symbols Used in Multiple-Dosing Equations, 257

- 12.3 Monoexponential Decay During a Dosing Interval, 259
 - 12.3.1 Calculation of Dosing Interval to Give Specific Steady-State Peaks and Troughs, 260
- 12.4 Basic Pharmacokinetic Equations for Multiple Doses, 260
 - 12.4.1 Principle of Superposition, 260
 - 12.4.2 Equations that Apply Before Steady State, 261
- 12.5 Steady State, 262
 - 12.5.1 Steady-State Equations, 263
 - 12.5.2 Average Plasma Concentration at Steady State, 264
 - 12.5.3 Fluctuation, 267
 - 12.5.4 Accumulation, 267
 - 12.5.5 Time to Reach Steady State, 269
 - 12.5.6 Loading Dose, 270
- 12.6 Basic Formula Revisited, 270
- 12.7 Pharmacokinetic-Guided Dosing Regimen Design, 270
 - 12.7.1 General Considerations for Selection of the Dosing Interval, 270
 - 12.7.2 Protocols for Pharmacokinetic-Guided Dosing Regimens, 272
- 12.8 Simulation Exercise, 276
- Problems, 277
- Reference, 278

13 Multiple Intermittent Infusions

279

Sara E. Rosenbaum

- 13.1 Introduction, 279
- 13.2 Steady-State Equations for Multiple Intermittent Infusions, 281
- 13.3 Monoexponential Decay During a Dosing Interval: Determination of Peaks, Troughs, and Elimination Half-Life, 284
 - 13.3.1 Determination of Half-Life, 284
 - 13.3.2 Determination of Peaks and Troughs, 286
- 13.4 Determination of the Volume of Distribution, 286
- 13.5 Individualization of Dosing Regimens, 289
- 13.6 Simulation, 289
- Problems, 290

14 Multiple Oral Doses

293

Sara E. Rosenbaum

- 14.1 Introduction, 293
- 14.2 Steady-State Equations, 294
 - 14.2.1 Time to Peak Steady-State Plasma Concentration, 295
 - 14.2.2 Maximum Steady-State Plasma Concentration, 296
 - 14.2.3 Minimum Steady-State Plasma Concentration, 296
 - 14.2.4 Average Steady-State Plasma Concentration, 296
 - 14.2.5 Overall Effect of Absorption Parameters on a Steady-State Dosing Interval, 297
- 14.3 Equations Used Clinically to Individualize Oral Doses, 298
 - 14.3.1 Protocol to Select an Appropriate Equation, 298
- 14.4 Simulation Exercise, 300
- References, 301

15 Nonlinear Pharmacokinetics	303
<i>Sara E. Rosenbaum</i>	
15.1 Linear Pharmacokinetics, 304	
15.2 Nonlinear Processes in Absorption, Distribution, Metabolism, and Elimination, 306	
15.3 Pharmacokinetics of Capacity-Limited Metabolism, 307	
15.3.1 Kinetics of Enzymatic Processes, 307	
15.3.2 Plasma Concentration–Time Profile, 309	
15.4 Phenytoin, 310	
15.4.1 Basic Equation for Steady State, 311	
15.4.2 Estimation of Doses and Plasma Concentrations, 313	
15.4.3 Influence of K_m and V_{max} and Factors That Affect These Parameters, 314	
15.4.4 Time to Eliminate the Drug, 316	
15.4.5 Time to Reach Steady State, 317	
15.4.6 Individualization of Doses of Phenytoin, 318	
Problems, 321	
References, 322	
16 Introduction to Pharmacogenetics	323
<i>Dr. Daniel Brazeau</i>	
16.1 Introduction, 324	
16.2 Genetics Primer, 324	
16.2.1 Basic Terminology: Genes, Alleles, Loci, and Polymorphism, 324	
16.2.2 Population Genetics: Allele and Genotype Frequencies, 326	
16.2.3 Quantitative Genetics and Complex Traits, 327	
16.3 Pharmacogenetics, 328	
16.3.1 Pharmacogenetics of Drug-Metabolizing Enzymes, 330	
16.3.2 Pharmacogenetics of Drug Transporters, 333	
16.4 Genetics and Pharmacodynamics, 334	
16.4.1 Drug Target Pharmacogenetics, 334	
16.5 Summary, 335	
Reference, 335	
Suggested Readings, 335	
17 Models Used to Predict Drug–Drug Interactions for Orally Administered Drugs	337
<i>Sara E. Rosenbaum</i>	
17.1 Introduction, 338	
17.2 Mathematical Models for Inhibitors and Inducers of Drug Metabolism Based on <i>In Vitro</i> Data, 340	
17.2.1 Reversible Inhibition, 340	
17.2.2 Time-Dependent Inhibition, 341	
17.2.3 Induction, 345	
17.3 Surrogate <i>In Vivo</i> Values for the Unbound Concentration of the Perpetrator at the Site of Action, 345	
17.3.1 Surrogate Measures of Hepatic Inhibitor and Inducer Concentrations, 346	

- 17.3.2 Surrogate Measures of Intestinal Inhibitor and Inducer Concentrations, 346
- 17.4 Models Used to Predict DDIs *In Vivo*, 347
 - 17.4.1 Introduction, 347
 - 17.4.2 Basic Predictive Models: R Values, 348
 - 17.4.3 Predictive Models Incorporating Parallel Pathways of Elimination (fm), 350
 - 17.4.4 Models Incorporating Intestinal Extraction, 354
 - 17.4.5 Models Combining Multiple Actions of Perpetrators, 358
- 17.5 Predictive Models for Transporter-Based DDIs, 359
 - 17.5.1 Kinetics of Drug Transporters, 359
- 17.6 Application of Physiologically Based Pharmacokinetic Models to DDI Prediction: The Dynamic Approach, 362
- 17.7 Conclusion, 362
- Problems, 363
- References, 364

18 Introduction to Physiologically Based Pharmacokinetic Modeling 367

Sara E. Rosenbaum

- 18.1 Introduction, 368
- 18.2 Components of PBPK Models, 369
- 18.3 Equations for PBPK Models, 369
- 18.4 Building a PBPK Model, 373
- 18.5 Simulations, 377
- 18.6 Estimation of Human Drug-Specific Parameters, 378
 - 18.6.1 Tissue Plasma Partition Coefficient, 379
 - 18.6.2 Volume of Distribution, 379
 - 18.6.3 Clearance, 380
- 18.7 More Detailed PBPK Models, 381
 - 18.7.1 Permeability-Limited Distribution, 381
 - 18.7.2 Drug Transporters, 383
 - 18.7.3 Models for Oral Absorption, 386
 - 18.7.4 Reduced Models, 387
- 18.8 Application of PBPK Models, 387
- References, 388

19 Introduction to Pharmacodynamic Models and Integrated Pharmacokinetic–Pharmacodynamic Models 391

Drs. Diane Mould and Paul Hutson

- 19.1 Introduction, 392
- 19.2 Classic Pharmacodynamic Models Based on Receptor Theory, 393
 - 19.2.1 Receptor Binding, 394
 - 19.2.2 Concentration-Response Models, 395
- 19.3 Direct Effect Pharmacodynamic Models, 402
 - 19.3.1 E_{\max} and Sigmoidal E_{\max} Models, 402
 - 19.3.2 Inhibitory I_{\max} and Sigmoidal I_{\max} Models, 404
 - 19.3.3 Linear Adaptations of the E_{\max} and I_{\max} Model, 404

19.4	Integrated PK–PD Models: Intravenous Bolus Injection in the One-Compartment Mode and the Sigmoidal E_{\max} Model, 406	
19.4.1	Simulation Exercise, 409	
19.5	Pharmacodynamic Drug–Drug Interactions, 410	
19.5.1	Simulation Exercise, 410	
	Problems, 411	
	References, 412	
20	Semimechanistic Pharmacokinetic–Pharmacodynamic Models	413
	<i>Drs. Diane Mould and Paul Hutson</i>	
20.1	Introduction, 414	
20.2	Hysteresis and the Effect Compartment, 416	
20.2.1	Simulation Exercise, 419	
20.3	Physiological Turnover Models and Their Characteristics, 419	
20.3.1	Points of Drug Action, 421	
20.3.2	System Recovery After Change in Baseline Value, 421	
20.4	Indirect Effect Models, 422	
20.4.1	Introduction, 422	
20.4.2	Characteristics of Indirect Effect Drug Responses, 424	
20.4.3	Characteristics of Indirect Effect Models Illustrated Using Model I, 426	
20.5	Other Indirect Effect Models, 432	
20.5.1	Transit Compartment Models, 435	
20.5.2	Model for Hematological Toxicity of Anticancer Drugs, 439	
20.5.3	Alternate Parameterizations of Transit Models, 442	
20.6	Models of Tolerance, 442	
20.6.1	Introduction to Pharmacologic Tolerance, 442	
20.6.2	Counter-Regulatory Force Tolerance Model, 444	
20.6.3	Precursor Pool Model of Tolerance, 447	
20.7	Irreversible Drug Effects, 450	
20.7.1	Application of the Turnover Model to Irreversible Drug Action, 450	
20.8	Disease Progression Models, 452	
20.8.1	Drug Pharmacokinetics, 452	
20.8.2	Pharmacodynamics, 452	
20.8.3	Disease Activity Models, 453	
20.8.4	Disease Progression Models, 453	
	Problems, 459	
	References, 465	
Appendix A	Review of Exponents and Logarithms	469
	<i>Sara E. Rosenbaum</i>	
A.1	Exponents, 469	
A.2	Logarithms: Log and Ln, 470	
A.3	Performing Calculations in the Logarithmic Domain, 471	
A.3.1	Multiplication, 471	
A.3.2	Division, 472	

A.3.3	Reciprocals, 472	
A.3.4	Exponents, 472	
A.4	Calculations Using Exponential Expressions and Logarithms, 472	
A.5	Decay Function: e^{-kt} , 474	
A.6	Growth Function: $1 - e^{-kt}$, 475	
A.7	Decay Function in Pharmacokinetics, 475	
	Problems, 476	
Appendix B	Rates of Processes	479
	<i>Sara E. Rosenbaum</i>	
B.1	Introduction, 479	
B.2	Order of a Rate Process, 480	
B.3	Zero-Order Processes, 480	
B.3.1	Equation for Zero-Order Filling, 480	
B.3.2	Equation for Zero-Order Emptying, 481	
B.3.3	Time for Zero-Order Emptying to Go to 50% Completion, 481	
B.4	First-Order Processes, 482	
B.4.1	Equation for a First-Order Process, 482	
B.4.2	Time for 50% Completion: the Half-Life, 483	
B.5	Comparison of Zero- and First-Order Processes, 484	
B.6	Detailed Example of First-Order Decay in Pharmacokinetics, 484	
B.6.1	Equations and Semilogarithmic Plots, 484	
B.6.2	Half-Life, 485	
B.6.3	Fraction or Percent Completion of a First-Order Process Using First-Order Elimination as an Example, 485	
B.7	Examples of the Application of First-Order Kinetics to Pharmacokinetics, 487	
Appendix C	Creation of Excel Worksheets for Pharmacokinetic Analysis	489
	<i>Sara E. Rosenbaum</i>	
C.1	Measurement of AUC and Clearance, 489	
C.1.1	Trapezoidal Rule, 490	
C.1.2	Excel Spreadsheet to Determine $AUC_{0 \rightarrow \infty}$ and Clearance, 491	
C.2	Analysis of Data from an Intravenous Bolus Injection in a One-Compartment Model, 494	
C.3	Analysis of Data from an Intravenous Bolus Injection in a Two-Compartment Model, 496	
C.4	Analysis of Oral Data in a One-Compartment Model, 498	
C.5	Noncompartmental Analysis of Oral Data, 501	
Appendix D	Derivation of Equations for Multiple Intravenous Bolus Injections	505
	<i>Sara E. Rosenbaum</i>	
D.1	Assumptions, 505	

D.2	Basic Equation for Plasma Concentration After Multiple Intravenous Bolus Injections, 505	
D.3	Steady-State Equations, 508	
Appendix E	Enzyme Kinetics: Michaelis–Menten Equation and Models for Inhibitors and Inducers of Drug Metabolism	509
	<i>Sara E. Rosenbaum and Roberta S. King</i>	
E.1	Kinetics of Drug Metabolism: The Michaelis–Menten Model, 510	
E.1.1	Overview, 510	
E.1.2	Assumptions for Validity of Michaelis–Menten Model, 510	
E.1.3	K_m and V_{max} , 511	
E.1.4	Derivation of the Michaelis–Menten Equation, 511	
E.1.5	Summary, Practical Considerations, and Interpretations, 513	
E.1.6	Relationship Between Intrinsic Clearance and the Michaelis–Menten Parameters, 514	
E.2	Effect of Perpetrators of DDI on Enzyme Kinetics and Intrinsic Clearance, 515	
E.2.1	Reversible Inhibition, 515	
E.2.2	Time-Dependent Inhibition, 518	
E.2.3	Enzyme Induction, 524	
	References, 526	
Appendix F	Summary of the Properties of the Fictitious Drugs Used in the Text	527
	<i>Sara E. Rosenbaum</i>	
Appendix G	Computer Simulation Models	529
	<i>Sara E. Rosenbaum</i>	
	Glossary of Terms	531
	Index	537

PREFACE

The goal of the second edition of *Basic Pharmacokinetics and Pharmacodynamics* is to update and strengthen existing chapters of the book and to add additional chapters in response to recent trends in the application of pharmacokinetics and pharmacodynamics in clinical practice and pharmaceutical research.

Notable areas of update and expansion include both the text and the interactive computer models associated with drug transporters and hepatic clearance. Additionally, the chapters on drug absorption/bioavailability and pharmacodynamics have been updated, expanded and strengthened to reflect the importance of these topics and the need to cover the material both comprehensively and in a manner compatible with their present application. I felt that these areas would be most effectively strengthened by experts in each of the fields. To this end, I am delighted that Dr. Steven Sutton, who has had extensive experience as a researcher in the pharmaceutical industry and as an educator at the College of Pharmacy, University of New England, agreed to take over Chapters 3 and 9 that cover drug absorption and bioavailability. I am also delighted that Drs. Diane Mould and Paul Hutson agreed to revamp and expand the chapters on pharmacodynamics (Chapters 19 and 20). Dr. Mould of Projections Research Inc is a well-known pharmacokinetic and pharmacodynamic modeler, who has extensive experience in the application of pharmacodynamic models. Dr. Hutson from University of Wisconsin, School of Pharmacy, is similarly experienced and was able to provide an academic perspective to the overhaul of this material.

Owing to the increasing prominence of personalized and precision medicine, it has become important that clinical pharmacists and researchers in pharmaceutical fields have a basic knowledge of pharmacogenomics. Dr. Daniel Brazeau, an experienced educator and researcher in this area from the College of Pharmacy, University of New England, graciously agreed to write an introductory chapter on pharmacogenetics for the second edition. In response to the increasing use and diverse application of physiologically based pharmacokinetic (PBPK) modeling that has occurred over the last 15 years, it has become essential for modern students of pharmacokinetics to have a foundation in this topic. Chapter 18 introduces PBPK models and describes how they are built and applied. The third new chapter in the second edition presents the predictive models used to evaluate drug–drug

interaction (DDI) risk using *in vitro* data. These models are used increasingly by pharmaceutical companies and drug regulators to try to reduce the large health risks and costs posed by DDIs. While not all readers of the book will need to apply these models professionally, an understanding of this topic will allow students to better understand and appreciate the mechanism, characteristics, and varied outcome of DDIs. Finally, in order to provide interested students with a foundation to this latter chapter, the second edition includes an appendix on basic enzyme kinetics and the mathematical basis of the predictive models. My colleague at the College of Pharmacy, Dr. Roberta King, an expert in drug metabolism, collaborated in the preparation of this material. Each of the new chapters is supported by new interactive computer models.

It is hoped that the second edition of this textbook provides a comprehensive and thorough presentation of all essential topics in the contemporary application of pharmacokinetics and pharmacodynamics. While not all chapters will be necessary for the immediate needs of all audiences, collectively the book should serve as a valuable reference for the future.

I would like to thank the many scientists who generously gave of their time and provided me with information and input in many areas. I would especially like to thank Dr. Karthik Venkatakrishnan for his valuable input on the chapter on predictive models for DDIs. I would also like to thank and recognize the wonderful work of Pragati Nahar who prepared the custom color figures in the book, including the figure used on the cover. I would also like to thank many undergraduate and graduate students at URI who helped in a variety of ways especially Jamie Chung who provided valuable support for the preparation of the materials, and Benjamin Barlock and Rohitash Jamwal for their input in the creation of the simulation models. Finally, I would like to thank Jonathan Rose at Wiley for his patience, understanding, and responsiveness in the preparation of this edition.

CONTRIBUTORS

Daniel Brazeau Daniel Brazeau is a Research Associate Professor at the University of New England. He holds joint appointments in the Department of Pharmaceutical Sciences in the College of Pharmacy and Department of Biomedical Sciences in the College of Osteopathic Medicine. Dr. Brazeau is a Director of UNE's Genomics Core, a research training core providing the expertise, technologies and most importantly, training support for faculty and students. He received his B.S. and M.S. in Biology from the University of Toledo and earned his Ph.D. in Biological Sciences (1989) from the University at Buffalo. After completing postdoctoral training in population genetics at the University of Houston, he was a Research Assistant Professor in the Department of Zoology at the University of Florida and Director of the University of Florida's Genetic Analysis Laboratory in the Interdisciplinary Research Center for Biotechnology. For 10 years prior to joining UNE, he was a Research Associate Professor in the Department of Pharmaceutical Sciences at the University at Buffalo and Director of the University at Buffalo's Pharmaceutical Genetics Laboratory. Dr. Brazeau's research interests involve the areas of population molecular genetics and genomics. He teaches courses in molecular genetics methodologies and a required course in pharmacogenomics for graduate and pharmacy professional students. Dr. Brazeau is also a participating scientist in the National Science Foundation's Geneticist-Educator Network Alliances (GENA) working with high school science teachers to incorporate genetics into the classroom.

Paul Hutson Paul Hutson, whose baccalaureate and master's degrees are in biochemistry and chemistry, respectively, completed an oncology/pharmacokinetics fellowship at St. Jude Children's Research Hospital in Memphis. He was a Faculty Member at the University of Illinois for 5 years before moving to the University of Wisconsin School of Pharmacy in Madison in 1988. He now practices pharmacy with the oncology and palliative care group at the UW Hospital and Clinics and is an Associate Member of the UW Carbone Cancer Center. His three course offerings at the School of Pharmacy are Clinical Pharmacokinetics, Pediatric Pharmacotherapy, and Dietary Supplements, and he supervises an Advanced Pharmacy Practice Experience (APPE) in basic pharmacometrics. Dr. Hutson

provides pharmacometric modeling services to the pharmaceutical industry and to University of Wisconsin—Madison investigators through its CTSA-funded Institute for Clinical and Translational Research.

Roberta S. King Roberta S. King is an Associate Professor at the University of Rhode Island, College of Pharmacy. Her research expertise is in metabolism and enzymology focusing on individual variation in activity of the drug-metabolizing enzymes. She teaches Drug Metabolism and Structure-based Drug Design.

Dr. Mould Dr. Mould obtained her bachelors degree at Stevens Institute of Technology in 1984 in Chemistry and Chemical Biology. She received her Ph.D. in Pharmaceutics and Pharmaceutical Chemistry at The Ohio State University (OSU) in 1989. She spent 26 years as a pharmacokineticist in industry where she specialized in population pharmacokinetic/pharmacodynamic modeling and was an Associate Research Professor at Georgetown University. She has conducted population PK/PD analyses of hematopoietic agents, monoclonal antibodies, anticancer and antiviral agents, antipsychotic, cardiovascular, and sedative/hypnotic agents. Dr Mould is involved in clinical trial simulation and optimal study design in drug development. She was a member of the Scientific Advisory Group for PharSight, where she assisted in development of clinical trial simulation software.

Currently, Dr Mould is President of Projections Research Inc., a consulting company offering pharmacokinetic and pharmacometric services. She is also the founder of iDose LLC, a company that develops systems to individualize doses of drugs that are difficult to manage. She has published 62 peer-reviewed articles, 16 book chapters, made 97 national and international presentations, and presented six podium sessions on advanced modeling and simulation approaches. Dr Mould has authored 97 posters at both national and international meetings. She is an Adjunct Professor at the University of Rhode Island (URI), OSU, and the University of Florida, and teaches an annual class on disease progression modeling at the National Institutes of Health. Dr Mould taught nine courses (OSU, URI, and SUNY Buffalo) on specialized aspects of population pharmacokinetic and dynamic modeling. She is a member of the editorial board for Journal of Pharmacokinetics and Pharmacodynamics, Clinical Pharmacology and Therapeutics, and Clinical Pharmacology and Therapeutics Pharmacometrics and Systems Pharmacology. Dr. Mould is a member of the Board of Regents for the American College of Clinical Pharmacology and is a Chairman of the Publications committee for this organization. She is a Fellow of the American College of Clinical Pharmacology and the American Association of Pharmaceutical Sciences.

Steven C. Sutton Steven (Steev) C. Sutton, B.S. Pharmacy, Ph.D., University of New England, Portland, Maine Dr. Sutton is an Associate Professor and Chair of Pharmaceutics, College of Pharmacy, University of New England in Portland, Maine. He received his B.S. in Pharmacy from Massachusetts College of Pharmacy and a Ph.D. in Pharmaceutical Sciences from the State University of New York at Buffalo, New York. Dr Sutton began his career in the pharmaceutical industry working for CIBA-Geigy in Ardsley, NY (now Novartis), for INTERx in Lawrence, KS (then a part of Merck), and for Pfizer in Groton, CT, before embarking in a second career—that of academia—at the University of New England College of Pharmacy in Portland in 2009. Dr. Sutton founded the AAPS Oral Absorption Focus Group and in 2003, he became a Fellow of the AAPS. His research interests include predicting active pharmaceutical ingredient concentration–time profile in human after oral administration from chemical structure, modeling, and simulation of oral absorption of low permeability and/or low aqueous soluble compounds, *in vitro*—*in vivo* correlation of orally

administered controlled release dosage forms, species differences in gastrointestinal (GI) physiology, and transport of nanoparticles across the GI epithelium. Dr. Sutton has authored or coauthored over 120 book chapters, abstracts of work in progress, invited presentations, and patents.

1

INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

SARA E. ROSENBAUM

- 1.1 Introduction: Drugs and Doses
 - 1.2 Introduction to Pharmacodynamics
 - 1.2.1 Drug Effects at the Site of Action
 - 1.2.1.1 Interaction of a Drug with Its Receptor
 - 1.2.1.2 Postreceptor Events
 - 1.2.2 Agonists, Antagonists, and Concentration–Response Relationships
 - 1.3 Introduction to Pharmacokinetics
 - 1.3.1 Plasma Concentration of Drugs
 - 1.3.2 Processes in Pharmacokinetics
 - 1.4 Dose–Response Relationships
 - 1.5 Therapeutic Range
 - 1.5.1 Determination of the Therapeutic Range
 - 1.6 Summary
- Reference

Objectives

The material in this chapter will enable the reader to:

1. Define pharmacodynamics and pharmacokinetics
2. Understand the processes that control the dose–response relationship
3. Gain a general appreciation of how mathematical expressions in pharmacodynamics and pharmacokinetics can be used for the rational determination of optimum dosing regimens

Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations,
Second Edition. Edited by Sara E. Rosenbaum.
© 2017 John Wiley & Sons, Inc. Published 2017 by John Wiley & Sons, Inc.

1.1 INTRODUCTION: DRUGS AND DOSES

Drugs may be defined as chemicals that alter physiological or biochemical processes in the body in a manner that makes them useful in the treatment, prevention, or cure of diseases. Based on this definition, any useful drug must affect body physiology or biochemistry. By extension, any useful drug must, if used inappropriately, possess the ability to do harm. Drug action begins with administration of the drug (input) and concludes with the biological response (output, which can be a beneficial and/or an adverse effect). The inputs (dose, frequency of administration, and route of administration) must be selected carefully to optimize the onset, intensity, and duration of therapeutic effects for a particular disease condition. At the same time, the inputs selected must minimize any harmful effects of drugs.

The design of optimum dosing regimens requires a complete understanding of the processes and steps that translate the input into the output. It also requires an understanding of how the input–output relationship may be influenced by individual patient characteristics that may exist at the very beginning of therapy, as well as conditions that may arise during the course of drug therapy. These will include the age and weight of the patient, the presence of other diseases, genetic factors, concurrent medications, and changes in the disease being treated over time.

The material presented in this book will address and explain why, as shown in Table 1.1, there is such tremendous variability in the value of drug doses and dosing frequencies among therapeutic drugs. Additionally, it will address why different routes of administration are used for different drugs and different indications (Table 1.1).

The steps between drug input and the emergence of the response can be broken down into two phases: pharmacokinetic and pharmacodynamic. The *pharmacokinetic phase* encompasses all the events between the administration of a dose and the achievement of drug concentrations throughout the body. The *pharmacodynamic phase* encompasses all the events between the arrival of the drug at its site of action and the onset, magnitude, and duration of the biological response (Figure 1.1). The rational design of optimum dosing regimens must be based on a thorough understanding of these two phases and will, ideally, include the development of one or more mathematical expressions for the relationship between dose and the time course of drug response.

Optimum drug administration is important not only for ensuring good patient outcomes in clinical practice, but also in the design of clinical trials during drug development. The

TABLE 1.1 Examples of Common Daily Doses and Dosing Intervals

Drug	Daily Dose (mg)	Dose Frequency (h)	Route
Calcium carbonate	3000	2	Oral
Ibuprofen	1600	6	Oral
Vancomycin (for MRSA ^a)	2000	12	Intravenous
Amoxicillin	750	8	Oral
Vancomycin (for pseudomembranous colitis)	1000	6	Oral
Atenolol	100	24	Oral
Fluoxetine	20	24	Oral
Ramipril	10	12	Oral
Digoxin	0.250	24	Oral
Chloroquine	300	Weekly	Oral

^aMethicillin-resistant *Staphylococcus aureus*.

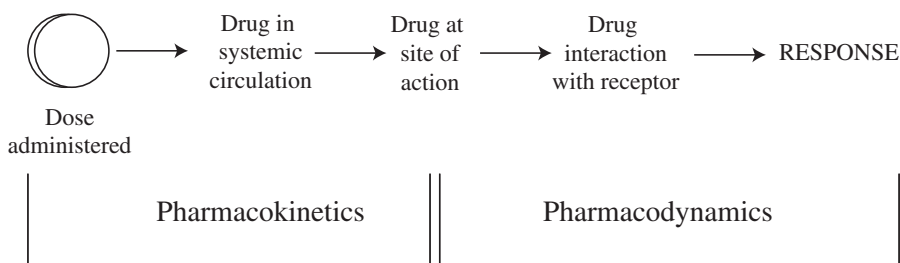


FIGURE 1.1 The two phases of drug action. The pharmacokinetic phase is concerned with the relationship between the value of the dose administered and the value of the drug concentrations achieved in the body; the pharmacodynamic phase is concerned with the relationship between drug concentrations at the site of action and the onset, intensity, and duration of drug response.

cost of drug research and development is enormous, so it is critical that all drug candidates selected for human trials are evaluated in the most efficient, cost-effective manner possible.

The application of pharmacokinetic and pharmacodynamic principles to this process has been shown to enhance the selection of optimum doses and optimum designs of phase II clinical trials.

1.2 INTRODUCTION TO PHARMACODYNAMICS

Pharmaco- comes from the Greek word for “drug,” *pharmakon*, and *dynamics* means “of or relating to variation of intensity.” *Pharmacodynamics (PD)* is the study of the magnitude of drug response. In particular, it is the study of the onset, intensity, and duration of drug response and how these are related to the concentration of a drug at its site of action. An overview of some basic drug terminology and the drug response–concentration relationship is provided below.

1.2.1 Drug Effects at the Site of Action

Note that although some references and textbooks distinguish the terms drug *effect* and drug *response*, this distinction has not been adopted universally. In this book, *effect* and *response* are used interchangeably.

1.2.1.1 Interaction of a Drug with Its Receptor

Drug response is initiated by a chemical interaction between a drug and a special binding site on a macromolecule in a tissue. This macromolecule is known as a drug *receptor*. The drug–receptor interaction results in a conformational change in the receptor, which results in the generation of a stimulus that ultimately leads to a biochemical or physiological response (Figure 1.2). Most receptors (over 95%) are proteins; however, other types of receptors exist such as the DNA receptors of the alkylating agents used in cancer chemotherapy. The drug–receptor interaction involves chemical bonding, which is usually reversible in nature and can be expressed using the law of mass action (Figure 1.2). Thus, at the site of action, the drug binds to its receptor and equilibrium is established between the bound and the unbound drug. As the drug is eliminated from the body and removed from its site of action, it dissociates from the receptor, which is left unchanged, and the response dissipates.

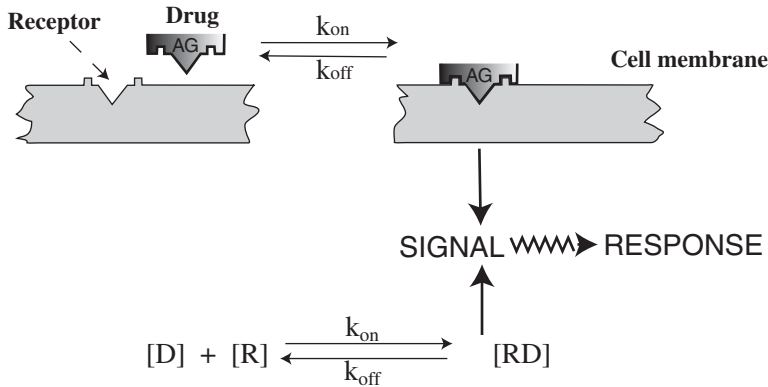


FIGURE 1.2 Drug–receptor interaction. Here, AG signifies a drug agonist, $[D]$ is the free drug concentration (not bound to the receptor), R is the concentration of free receptors, $[RD]$ is the concentration of the drug–receptor complex, and k_{on} and k_{off} are the rate constants for the forward and backward processes, respectively.

In contrast, a few drugs form *irreversible* covalent bonds with their receptors. For example, aspirin inhibits platelet aggregation by inhibiting the formation of thromboxane in the platelets. It accomplishes this by binding covalently to and blocking the catalytic activity of cyclooxygenase, the enzyme that produces thromboxane. The effect of a single dose of aspirin will persist long after the drug has been removed from its site of action and will continue until new cyclooxygenase molecules are synthesized, which can then resume the production of thromboxane. Other examples of drugs that bind irreversibly to their receptors include the alkylating agents mentioned above and proton pump inhibitors, such as omeprazole, which block the secretion of gastric acid by binding irreversibly to the H^+ , K^+ -ATPase pumps of parietal cells.

The drug–receptor interaction is highly dependent on the chemical structure of both the drug and the receptor and, therefore, small changes in the structure of the drug can reduce or destroy activity. For example, the drug–receptor interaction can distinguish between the *R*- and *S*-isomers of drugs that have chiral carbon atoms. Usually, one isomer is much more active than the other. The *S*-isomer of warfarin, for example, is two to five times more active than the *R*-isomer. The development and promotion of *S*-omeprazole (Nexium) is based on the premise that the *S*-isomer has the higher affinity for the binding site and thus offers therapeutic advantages over preparations containing racemic mixtures (equal quantities of each isomer) of omeprazole, such as Prilosec and its generic equivalents.

Receptors are assumed to exist for all active endogenous compounds (*natural ligands*) such as neurotransmitters and hormones. The interaction between natural ligands and their receptors controls and/or regulates physiological and biochemical processes in the body. In most cases, drugs mimic or antagonize the actions of endogenous ligands by interacting with their cognate receptors. For example, epinephrine is a natural ligand that interacts with β_2 -adrenergic receptors in bronchial smooth muscle to bring about bronchial dilation. Albuterol, a drug, also interacts with this receptor to produce bronchial dilation. Acetylcholine transmits signals through a synapse by interacting with its nicotinic receptor found on postsynaptic neuronal membranes. This interaction, which is mimicked by the drug nicotine, results in the production of a response called an action potential.

It should be noted that there are a few drugs that do not act on receptors but that exert their action by bringing about *physicochemical changes* in the body. For example, conventional

antacids, such as calcium carbonate, act as buffers to reduce acidity in the stomach and polyethylene glycol, an osmotic laxative, acts by preventing the absorption of water in the large intestine.

1.2.1.2 Postreceptor Events

Drugs almost always bring about some type of change in the *intracellular environment* of cells, but the lipophilic cell membrane presents a physical barrier to most drugs and endogenous ligands. As a result, most receptors are located on the cell membrane itself. The stimulus generated from the interaction of the drug with the membrane bound receptor has to be relayed to the inside of the cell. The relaying of the initial stimulus, known as *coupling* or *signal transduction*, often involves a cascade of different steps during which the initial signal may be amplified or diminished. Some important transduction mechanisms are summarized below (see Figure 1.3).

1. Interaction of a drug with a receptor can lead directly to the opening or closing of an *ion channel* that lies across a cell membrane. In this case, the signal is relayed by changes in the ion concentration within the cell. For example, the interaction of acetylcholine with its nicotinic receptor results in the opening of an ion channel allowing Na^+ to move into the cell thus, initiating the production of an action potential.
2. Signal transduction for a large number of drugs involves the *activation of a G-protein* (guanine nucleotide-binding protein). The drug–receptor interaction on the membrane triggers the activation of a G-protein on the cytoplasmic side of the membrane, which then initiates a series of events that culminate in the biological response. Activated G-protein can produce a variety of effects, including stimulation or inhibition of enzymes, and the opening or closing of ion channels. These events usually result in changes in the concentration of an intracellular compound known as the

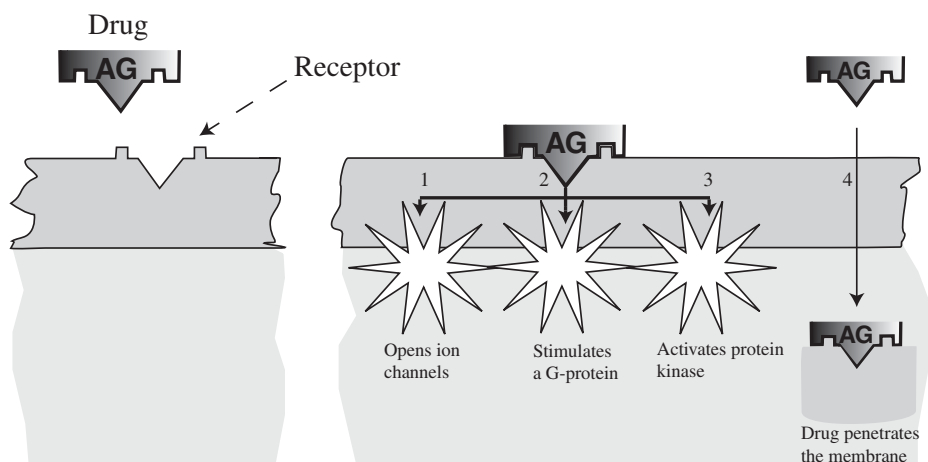


FIGURE 1.3 Diagrammatic representations of how a drug receptor interaction brings about intracellular events. The intracellular relay of the initial signal resulting from the interaction of a drug with a membrane-bound receptor can be accomplished in one of three ways: (1) the direct opening of ion channels; (2) the activation of a G-protein that may lead to the activation of another enzyme or to a modulation of an ion channel; (3) the activation of protein kinase. Alternatively, (4), some drugs are able to penetrate membranes and directly activate intracellular receptors.

second messenger. Examples of second messengers include cyclic adenosine-3',5'-monophosphate (cAMP), calcium, and phosphoinositides. The second messengers then relay the response further through a series of complex steps. For example, the interaction of catecholamines such as norepinephrine with certain β -receptor subtypes involves G-protein activation. This then stimulates adenylate cyclase to convert adenosine triphosphate to cAMP, which acts as the second messenger. Subsequent events include the stimulation of specific protein kinases, activation of calcium channels, and modification of cellular proteins. Other examples of G-protein-coupled receptors are the action of acetylcholine on its muscarinic receptors and the action of serotonin on its 5-HT receptors.

3. The interaction of a drug with its receptor can also result in the stimulation of a receptor-associated enzyme, tyrosine kinase. The activated tyrosine kinase phosphorylates key macromolecules, which are often a part of the receptor itself, to relay the signal. Insulin and peptide growth factors, for example, use this form of signal transduction.

Some drugs are lipophilic enough to penetrate the cell membrane, while others may be transported across the cell membrane by uptake transporters. Drugs that are able to enter a cell can interact directly with intracellular receptors. Examples of drugs that act on intracellular receptors include many steroids such as glucocorticoid steroids, sex hormones, and thyroid hormones. The HMG-CoA reductase inhibitors (commonly known as *statins*) and metformin also act within the cell (hepatocyte) and both are dependent on uptake transporters to deliver them to the intracellular space and their site of action.

1.2.2 Agonists, Antagonists, and Concentration–Response Relationships

A drug that mimics the endogenous receptor ligand to activate the receptor is referred to as an *agonist*. The typical relationship between the drug effect and the agonist concentration at the receptor site is shown in Figure 1.4a. Note that as the concentration of the drug increases, the effect increases. At *low concentrations*, there is a linear relationship between concentration and effect (i.e., the response is proportional to the concentration). At higher drug

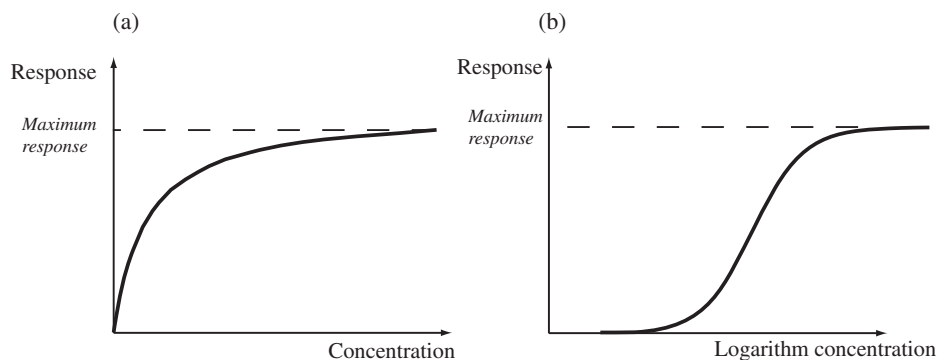


FIGURE 1.4 Plots of response versus drug concentration: (a) on a linear scale and (b) on a semilogarithmic scale.

concentrations, increases in concentration bring about much smaller changes in effect (the *law of limited returns*). Eventually, at very high concentrations, the effect achieves a maximum value and then remains constant and independent of concentration. In this area of the curve, increases in concentration will not result in further increases in response. This relationship is observed because response is generated by a saturable, capacity-limited process. For example, the response may be limited by the number of receptors that a tissue contains. At low drug concentrations, there are many free receptors and as the drug concentration increases, the drug can bind to the free receptors and response can increase proportionally. At higher concentrations, more and more of the receptors are occupied. As a result, increases in the drug concentration produce much less increase in effect. Eventually, all of the receptors are occupied (or saturated) and a maximum effect is observed. To accommodate a wide range of concentrations, the relationship between effect and concentration is usually plotted on a semilogarithmic scale, which transforms the plot to a sigmoidal shape (Figure 1.4b).

Many agonists are able to produce the system's maximum response without fully occupying all the receptors. In these systems, the maximum response of the drug must be the result of some other saturable, capacity-limited process that occurs after receptor binding. These tissues or systems are said to have *spare receptors*. Experimentally, the presence of spare receptors can be demonstrated by destroying some of the receptors. If an agonist is still able to produce a maximum response, the system must contain spare receptors.

The efficiency with which a drug's interaction with the receptor is converted into the initial stimulus or biosignal is a function of the number of receptors at the site of action and a drug's *intrinsic efficacy*. Intrinsic efficacy can be defined as the magnitude of the stimulus produced per unit receptor occupied. The value of the stimulus that results from a specific concentration of a drug is also a function of the drug's affinity for its receptors. *Affinity* can be defined as the extent or fraction to which a drug binds to receptors at any given drug concentration. Drugs that have high affinity require less drug to produce a certain degree of binding and to elicit a certain response compared to drugs with low affinity. Affinity is one of the factors that determines *potency* (see Chapter 19).

A drug that binds to a receptor but does not activate it is referred to as an *antagonist*. The presence of an antagonist at the receptor site blocks the action of the agonist (Figure 1.5). Higher concentrations of the agonist are needed to displace the antagonist and to produce the effect that is elicited when the antagonist was absent. The antagonist shifts the concentration–response curve of an agonist to the right (Figure 1.6). At sufficiently high concentrations of the antagonist, the agonist's action may be blocked completely and the effect of even high concentrations of the agonist is reduced to zero. Some drugs bind to

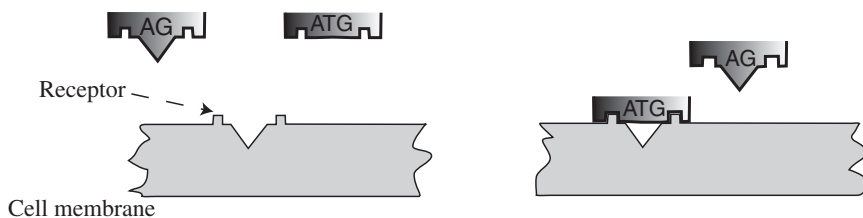


FIGURE 1.5 Diagrammatic representation of the action of an antagonist. The antagonist (ATG) binds to the receptor but does not produce a signal. Its presence on the receptor blocks the action of agonists (AG), including the natural ligand.

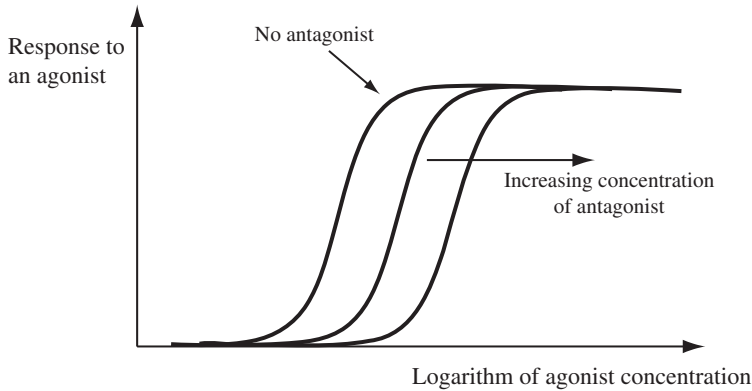


FIGURE 1.6 Plot of response versus logarithm concentration for an agonist in the absence and presence of increasing concentrations of an antagonist.

receptors, but the binding is less efficient and a full response cannot be achieved even when the drug's concentration is very high and all the receptors are occupied (Figure 1.7). These drugs are referred to as *partial agonists*. A partial agonist will block the effect of a full agonist. In the presence of high concentrations of a partial agonist, the action of a full agonist can be reduced to the maximum response elicited by the partial agonist. Clinically, partial agonists are used to act as buffers to avoid full stimulation of a system. Examples of partial agonists include several β -blockers, including pindolol, and the opioid buprenorphine. The latter is a partial agonist on the μ -opioid receptors and is considered a safer alternative to morphine because it does not produce as much respiratory depression (see Chapter 19).

In summary, drug action is mediated primarily by the interaction of a drug with membrane-bound receptors at its site of action. This produces conformational changes in the receptor, which lead to the generation of an initial signal. The signal is then relayed to the intracellular environment by means of a variety of transduction processes. The response increases with increases in drug concentration until enough receptors are occupied to generate the maximal response. The response to a specific concentration of drug is dependent on drug-specific properties (e.g., intrinsic efficacy and affinity) and tissue-specific properties (e.g., number or density of receptors and amplification or diminution of the initial signal during transduction). An important goal in a study of pharmacodynamics is to derive

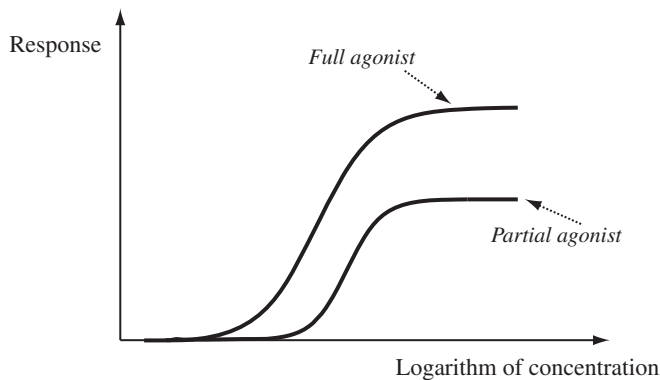


FIGURE 1.7 Plot of response versus logarithm concentration for a full and a partial agonist.

a mathematical expression for the magnitude of drug response as a function of drug concentration:

$$E = f_{PD}(C) \quad (1.1)$$

where E is the drug effect or response, C is the drug concentration, and f_{PD} is a pharmacodynamic function that links these two variables and contains the drug-specific parameters of intrinsic efficacy and affinity. In equation (1.1), E is the *dependent variable* because it is dependent on all the other components of the equation. The drug concentration at the site of action (C) is the *independent variable* because it is independent of all the other components of equation (1.1). This expression would allow the effect to be estimated at any drug concentration and allow the required concentrations for optimum response to be identified.

1.3 INTRODUCTION TO PHARMACOKINETICS

Pharmaco- comes from the Greek word for “drug,” *pharmakon*, and *kinetics* comes from the Greek word for “moving,” *kinetikos*. *Pharmacokinetics (PK)* is the study of drug movement into, around, and out of the body. By extension, it involves the study of drug absorption, distribution, and elimination (metabolism and excretion) (ADME).

Pharmacokinetics involves the study of how drugs enter the body, distribute throughout the body, and leave the body. It is concerned with the driving forces for these processes and the rate at which they occur. Pharmacokinetics is the study of the *time course of drug concentrations in body compartments*. From a therapeutic perspective, the drug concentration at the site of action is by far the most important: Concentrations should be sufficiently high to produce a response but not so high as to produce toxicity. Since it is not possible to routinely measure this concentration clinically, the *plasma concentration* of the drug is the main focus in pharmacokinetics. It is often assumed that the *plasma concentration reflects the drug concentration at the site of action*. This is generally true and the relationship is often linear. Increases or decreases in the plasma concentration will be reflected by proportional increases or decreases at the site of action, respectively. However, as discussed in subsequent chapters, this is not always the case and a more complex relationship between these two concentrations may exist. It is important to note that although changes in the plasma concentration will usually result in proportional changes in the drug concentration at the site of action, the reverse is not true. Because the amount of drug that is delivered to the site of action is usually such a very small fraction of the total amount of drug in the body (in other tissues and the systemic circulation), local changes in the amount of drug at the site of action are generally not reflected by noticeable changes in the plasma concentration.

1.3.1 Plasma Concentration of Drugs

As stated above, pharmacokinetics is concerned with the body’s exposure to a drug and how drug concentrations change over time. For the most part, drug concentrations in the plasma are the focus in pharmacokinetics. The rationale for this is twofold. First, blood is one of the few body fluids that can be obtained and analyzed repeatedly for drug concentrations at specified times after the administration of a dose. The concentration of drug in whole blood is not commonly used in pharmacokinetics because blood is a complex physical system that consists of red blood cells, white blood cells, and platelets suspended in plasma water. Blood with the cellular elements removed, either by centrifugation (plasma) or clotting

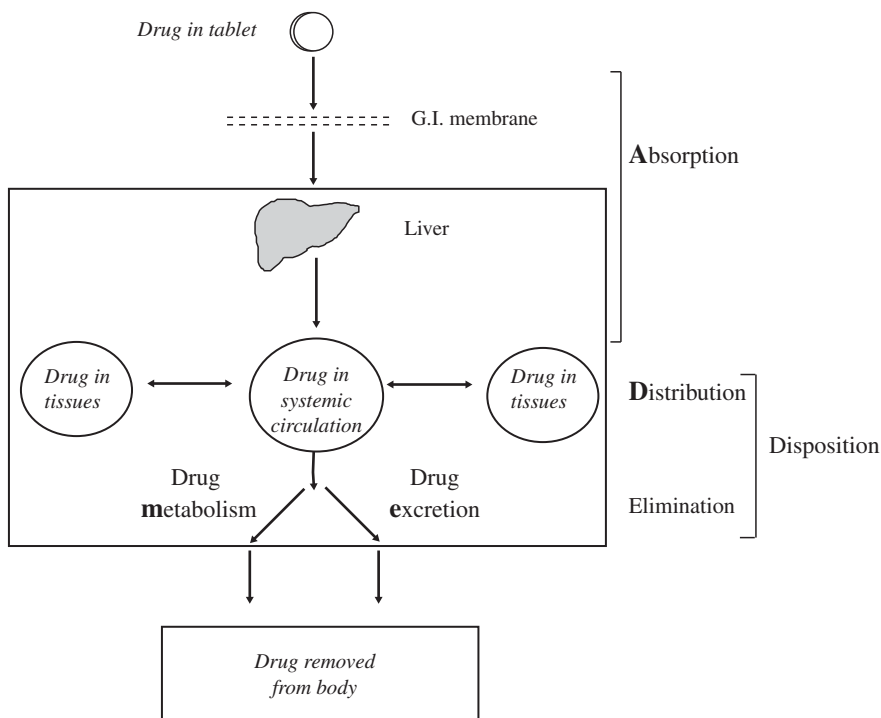


FIGURE 1.8 Processes of drug absorption, distribution, and elimination (metabolism and excretion) (ADME). Drug contained within the tablet must undergo absorption. It must penetrate the gastrointestinal membrane and pass through the liver before reaching the systemic circulation. Once in the blood, it has the opportunity to distribute to the tissues, including the site of action. As soon as drug is present in the systemic circulation, it is subject to elimination. This occurs primarily in the liver and kidneys, where drugs undergo metabolism and/or excretion, respectively. The fate of a drug in the systemic circulation (distribution and elimination) is referred to as drug disposition.

(serum), is preferred. The collection of plasma requires the use of an anticoagulant such as heparin. However, heparin can interfere with the assay of some drugs. In these cases (e.g., for measuring digoxin concentration), serum rather than plasma is used as the reference fluid. In this book, no distinction will be made between plasma and serum, and the term *plasma concentration* will be used almost universally.

The second rationale for focusing on plasma concentrations in pharmacokinetics is that the circulatory system is the central fluid for the receipt and distribution of drugs (Figure 1.8). All drug input processes conclude when drug reaches the plasma, and all *disposition* (distribution and elimination) *processes* begin once drug is present in the plasma. Thus, drugs at absorption sites such as the gastrointestinal tract or subcutaneous tissue are absorbed into the circulatory system. Once in the blood, drugs undergo distribution to various tissues in the body and undergo elimination primarily through the liver and/or kidneys.

Plasma or plasma water consists of small dissolved molecules (e.g., glucose, ions, nutrients, and drugs) and suspended substances such as proteins, which are too large to dissolve. Many drugs can *bind* or *associate* with the plasma proteins. The binding is reversible and may be expressed according to the *law of mass action*:



where D is the free drug concentration, P is the concentration of the protein not involved in binding, DP is the concentration of the drug–protein complex, and k_1 and k_2 are the rate constants for the forward and backward reaction, respectively.

Thus, many drugs exist in the plasma in an equilibrium between two forms: one component dissolved in the plasma water (*free drug*) and one component associated with or bound to plasma proteins (*bound drug*). The term *plasma concentration* (C_p) in pharmacokinetics refers to the total drug concentration of the drug, that is, the bound plus the free drug. Total drug concentrations are reported routinely because they are much easier and less expensive to measure than free drug concentrations. However, as presented in subsequent chapters, the free concentration is the clinically important component: Only free unbound drug is able to pass biological membranes, interact with the receptor, and generate a pharmacological response.

1.3.2 Processes in Pharmacokinetics

Pharmacokinetics involves the study of the processes that affect the plasma concentration of a drug at any time after the administration of a dose. These processes are summarized in Figure 1.8. Most drugs are administered orally as tablets. A *tablet* is a compressed powder mass that consists of the active drug, which usually comprises only a small portion of the overall tablet, and other compounds required for either the manufacture of the tablet (i.e., diluents and lubricants) or to optimize the characteristics of the finished product (i.e., color, taste, and hardness). Once a tablet is swallowed, it enters the stomach, where the drug contained within the hard powder mass must be exposed and released. The tablet must first disintegrate into small particles to enable the drug to dissolve in the gastrointestinal fluid. These initial processes of disintegration and dissolution are part of *biopharmaceutics*, which may be defined as the study of how a drug's chemical and physical properties influence both the administration of the drug and the pharmacokinetic behavior of the dosage form *in vivo*. When the drug is dissolved in the gastrointestinal fluid, it has the opportunity to pass across the epithelial cell lining of the gastrointestinal membrane and get taken up into the blood on the other side. Once in the circulatory system, the drug has to pass through the liver, which is a major organ of drug elimination. The absorbed drug may undergo elimination by *metabolism during its first pass through the liver*. After passing through the liver, the drug is taken to the heart, which pumps the drug throughout the entire circulatory system. At this point, the drug has been *absorbed*. The rate and extent of absorption of a drug are very important determinants of the early plasma concentrations of a drug. Rapid rates of absorption will promote high early plasma concentrations. Once the heart pumps the drug around the body, the drug is given the opportunity to *distribute* to all the tissues, including the biophase or site of action. A drug's distribution pattern, particularly the rate and extent to which it distributes to the tissues, is also an important determinant of the early plasma concentrations. If a drug distributes extensively to the tissues, little drug will be left in the plasma and the plasma concentration will be low. The plasma concentration will also be influenced by drug *elimination*, which occurs as soon as the drug is in the plasma. The main pathways of elimination are *hepatic metabolism* and *renal excretion*. The process of drug elimination will continue to affect the plasma concentration until the drug has been removed from the body completely.

In summary, a drug's pharmacokinetics are determined by the simultaneous processes of ADME (Figure 1.8). The combined processes of drug elimination and drug distribution or the fate of a drug once it is present in the body is referred to as *drug disposition*

TABLE 1.2 Pharmacokinetic Processes That Control the Dose–Plasma Concentration Relationship after the Consumption of a Tablet

	Process	Type of Process
1	Release of drug: tablet disintegration	Biopharmaceutics
2	Dissolution of tablet	Biopharmaceutics
3	Absorption of drug through gastrointestinal membrane into the blood	Absorption
4	Passage through the liver	Absorption
5	Entry to systemic circulation	Absorption
6	Distribution to the biophase	Biophase distribution
7	Distribution throughout the body	Distribution
8	Elimination (metabolism and excretion)	Elimination

(Figure 1.8). The individual pharmacokinetic steps associated with the administration of a tablet are summarized in Table 1.2.

The goal of pharmacokinetics is to study each of the ADME processes with the aim of:

1. Identifying the drug and patient factors that determine the rate and extent of each process. Topics to be considered include:
 - How does a drug's lipophilicity influence absorption, distribution, and elimination?
 - What factors determine a drug's distribution pattern?
 - Is the whole of a dose absorbed into the body?
 - Does a drug get to every tissue in the body?
 - To what extent, do drugs undergo renal as opposed to hepatic elimination?
 - How are pharmacokinetic processes affected by patient characteristics, such as the age of the patient, renal or hepatic impairment, ethnicity, and genetics?
2. Identifying a way to quantify or summarize each process in ADME using a single parameter. Issues to be considered include:
 - How can the extent of absorption of a drug be quantified?
 - How can the extent to which a drug distributes the tissues be quantified?
3. Deriving a mathematical expression for the rate of each process in ADME and for the overall relationship between a drug's plasma concentration and time after any dose:

$$C_p = f_{PK}(\text{dose, time}) \quad (1.3)$$

where C_p is the plasma concentration, and f_{PK} is a function that contains expressions and parameters for ADME. In equation (1.3), C_p is the dependent variable because it is dependent on all the other components of the equation, time is the independent variable, and dose is a constant in a given situation.

1.4 DOSE–RESPONSE RELATIONSHIPS

It will become apparent in subsequent chapters that for most drugs, *the drug concentration in the body at any time is proportional to the dose*. As a result, plots of response at a certain time as a function of dose (Figure 1.9) resemble the plots of response versus concentration

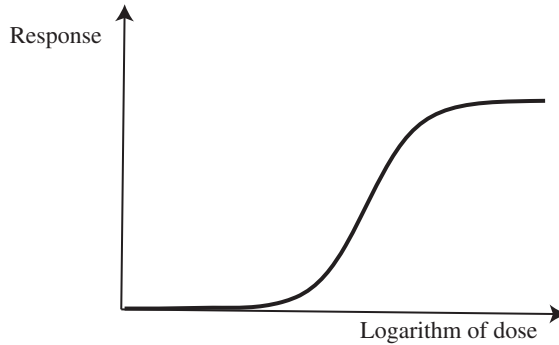


FIGURE 1.9 Graph of response versus logarithm of dose.

(Figure 1.4): A hyperbolic plot is often observed on the linear scale, and a sigmoidal plot is observed on the semilogarithmic scale. Thus, dose–response curves are analogous, but not identical, to pharmacodynamic concentration–effect curves.

In contrast to the plots of response versus concentration, which are purely dependent on a drug’s pharmacodynamics, a dose–response curve is a function of both the drug’s pharmacodynamic characteristics (intrinsic efficacy and affinity) and its pharmacokinetic characteristics (the fraction of the dose absorbed, the extent to which a drug distributes throughout the body, etc.). Note that low doses produce no effect, and as the maximum response is approached, increasing the dose produces little change in the response (limiting returns). Based on the characteristics shown in Figure 1.9, doses must be selected to avoid the subtherapeutic areas of the plot and to avoid doses that approach or lie on the plateau that provide little or no additional benefit over lower doses. Most drugs also produce toxicity at higher concentrations, and it is important that doses are selected that minimize this toxicity. The toxicity may be an extension of the drug’s pharmacological action (e.g., the major adverse effects of warfarin, digoxin, and anticholinergic drugs), in which case it is important to avoid areas on the dose–response curve close to the maximum effect. Alternatively, the toxicity may arise because the drug may interact with multiple receptors of different types, particularly at higher concentrations, to produce undesired effects. Examples of this type of toxicity include muscle toxicity associated with the statins and drowsiness associated with first-generation antihistamines. The development of models and mathematical expressions of the pharmacokinetic and pharmacodynamic phases of drug response provides an opportunity for the rational selection of optimum dosing regimens.

The expression for a drug’s pharmacokinetics [equation (1.3)] can be combined with the expression for a drug’s pharmacodynamics [equation (1.1)] to produce a *complete expression for the dose–response relationship*:

$$E = f_{PD} (f_{PK} (\text{dose, time})) \quad (1.4)$$

Note that in this equation, the plasma concentration of the drug (C_p) has been substituted for the drug concentration at the site of action (C) in the pharmacodynamic equation. This assumes that the concentration at the site is always proportional to the plasma concentration. The validity and limitations of this are discussed in subsequent chapters. Equation (1.4) enables the full time course of drug response to be estimated after any dose. It could also be used to estimate the dose and dosing interval to produce optimum response. If these relationships are identified early in the course of drug development, they can be used to

determine optimum doses for clinical trials. This in turn will increase the efficiency of trials, reduce the time for drug development, and decrease the price of these highly costly studies. The expressions can also be used to simulate response data for situations not yet studied clinically. For example, if a drug's pharmacokinetics and pharmacodynamics are known after a single dose, it is possible to use a combined PK–PD equation to simulate the response that may be expected during multiple dosing therapy. Simulations can be performed using different dosing regimens to try to obtain an estimate of what may be the most effective dosing regimen.

1.5 THERAPEUTIC RANGE

In vivo pharmacodynamic studies aimed at developing mathematical expressions of drug response are relatively new. Historically, *in vivo* pharmacodynamic studies have been very difficult to perform. Some reasons for this are presented below:

1. It is difficult to obtain precise measurements of drug response. Meaningful models and mathematical expressions for drug response require that response data be collected on a continuous scale. The data must also possess a reasonable degree of precision. All-or-none responses and subjective data, based largely on a patient's or a physician's opinion, have limited value in this application. The response to only a handful of drugs (e.g., anticoagulants and hypoglycemic agents) meets these criteria. In the last 10–20 years, this problem has been overcome by the development and use of biomarkers (see Chapter 19) of drug response. *Biomarkers* are parallel changes in the levels or intensities of concrete measurable biological molecules or other effects that have been found to be predictably associated with a drug's biological response. Examples of biomarkers may include cells, proteins, antibodies, body temperature, or features of an electroencephalograph.
2. The mathematical expressions derived from pharmacodynamic models are mainly nonlinear and could not be applied to clinical data until computer software became available for nonlinear regression analysis.
3. Each drug or drug class has a unique mechanism of action and way of relaying or coupling the initial drug effect. Signal transduction may take less than a second for some drugs, several minutes for others, or up to several hours for others. As a result, summarizing the characteristics of the concentration–response relationship can be complex.
4. In many cases, a drug's response lags behind the plasma concentration. This can confound the concentration–response relationship and add an additional layer of complexity to modeling response as a function of plasma concentration.

By contrast, pharmacokinetic studies are relatively simple to perform. Blood is easily sampled, drug assays for most drugs are fairly easily developed, and the data analysis is relatively straightforward and could be performed even before the wide availability of computers and software for pharmacokinetic analysis, by linearizing the mathematical expressions and analyzing the data using simple linear regression analysis. Furthermore, the pharmacokinetics of most drugs can be modeled using one of about three basic well-established models. As a result, pharmacokinetic studies and modeling have been a central part of the drug development process for decades. In order to use pharmacokinetic models for the design of dosing regimens, it is necessary to have target-optimal plasma concentrations

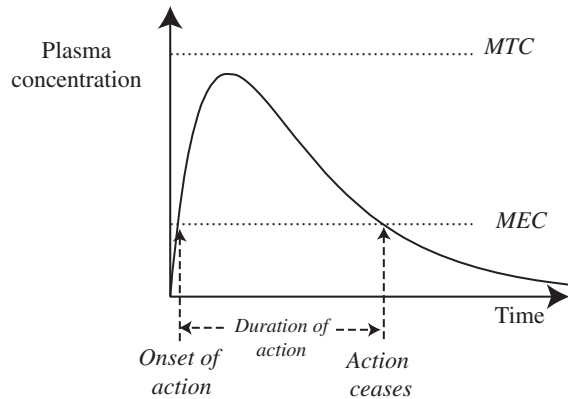


FIGURE 1.10 Therapeutic range. The therapeutic range of a drug is the range of plasma concentrations bounded by a lower minimum effective concentration (MEC) and an upper maximum tolerated concentration (MTC). The typical plasma concentration–time profile observed with the administration of a single oral dose is also shown. The therapeutic range allows the onset and duration of action of a drug to be estimated.

or some idea of the concentration–response relationship. In the absence of mathematical expressions for this relationship, a very simple approach for linking drug concentrations to response was developed and termed the *therapeutic range*. The therapeutic range is defined as the range of plasma concentrations that are associated with optimum response and minimal toxicity in most patients. Most commonly, the goal of therapy is to maintain drug concentrations within the therapeutic range at all times. There are a small number of drugs for which this is not desirable, such as certain antibiotics and drugs like nitroglycerin, where tolerance develops with continuous exposure to the drug.

The therapeutic range is illustrated in Figure 1.10, which shows:

- The *minimum effective concentration* (MEC) is the lower boundary for effective drug concentrations; plasma concentrations below the MEC have a high probability of being subtherapeutic.
- The *maximum tolerated concentration* (MTC) is the upper boundary for optimum drug concentrations; plasma concentrations above the MTC have a high probability of producing adverse effects or toxicity.
- The *onset of action* of a drug, which may be estimated as the time it takes for plasma concentrations to reach the MEC.
- The *duration of action* of a drug, which may be estimated as the time during which plasma concentrations remain within the therapeutic range.

1.5.1 Determination of the Therapeutic Range

To apply the therapeutic range appropriately, and to understand both its value and limitations, it is necessary to appreciate how it is typically derived. It is usually determined by studying the effects of a drug in a large population and noting the plasma concentrations at which patients:

- experience therapeutic effects;
- experience side effects or toxicity.

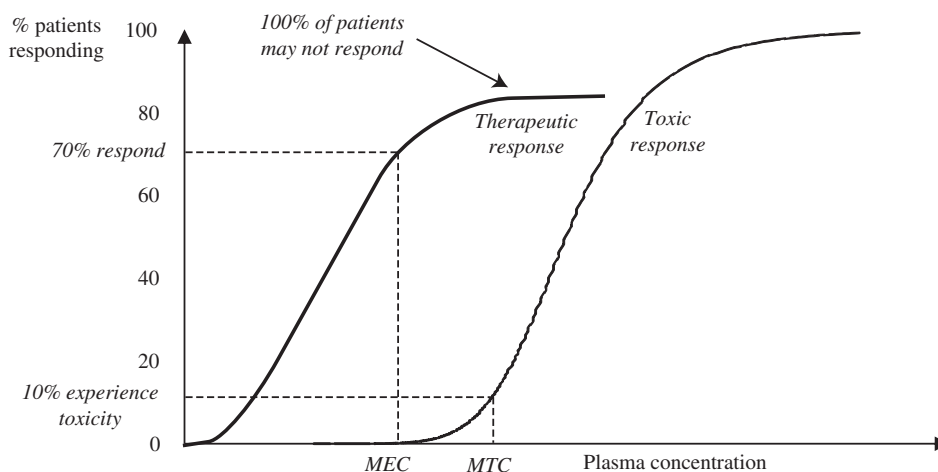


FIGURE 1.11 Identification of the therapeutic range. A drug's therapeutic range is based on studying the concentrations associated with response and toxicity in a large group of patients. The MEC is selected at a concentration at which a large fraction of the population respond (70% is used in the diagram). The MTC is selected at a concentration where a significant fraction of the population experience toxicity. In the diagram, the MTC was selected at the concentration where 10% of the population experience toxicity.

The cumulative plot of the percentage of all patients who experience a therapeutic response is then plotted as a function of plasma concentration (Figure 1.11). The cumulative plot of the percentage of patients experiencing adverse effects at the various concentrations is then added to the same graph (Figure 1.11). Similar sigmoidal shapes are obtained for both curves, but the plot for toxicity is always displaced to the right. Higher concentrations are needed for adverse compared to therapeutic effects (if this were not the case, the drug would not be of therapeutic value). A frequent characteristic of these plots is that although 100% of patients experience toxicity if concentrations are high enough, fewer than 100% of patients experience therapeutic effects even at high concentrations. Patients who do not respond therapeutically even to high concentrations are referred to as *nonresponders*.

This plot is then used to estimate a drug's therapeutic range. The MEC and MTC are usually chosen at concentrations where a high percentage of patients experience a therapeutic effect and a small percentage of patients experience toxicity, respectively. The specific concentrations selected for the MEC and the MTC will depend on the margin of safety and the risk–benefit ratio acceptable for a given indication. For example, the MTC for an over-the-counter analgesic or nonsteroidal anti-inflammatory drug will be chosen at a concentration associated with much less toxicity than that of a drug used to treat a life-threatening condition such as cancer. In Figure 1.11, the MEC was selected as the concentration at which 70% of the population experienced a therapeutic benefit, and the MTC was selected as the concentration at which 10% of the population experienced some adverse effects.

The therapeutic range has been enormously useful clinically, particularly in helping clinicians determine optimum doses of drugs that have both narrow therapeutic ranges and wide interpatient variability in dose requirements. Examples of these drugs are shown in Table 1.3. A dose that is optimum for one patient (i.e., a dose that gives plasma concentrations in the therapeutic range) may produce concentrations below the MEC in a second patient and produce concentrations above the MTC in a third patient. As a result, doses are

TABLE 1.3 Therapeutic Ranges of Example Drugs [1]

Drug	Therapeutic Range
Cyclosporine	100–400 ^a µg/L, whole blood HPLC ^b analysis
Digoxin	0.5–2 ^c µg/L
Lithium	0.6–1.5 mEq/L
Phenytoin	10–20 mg/L
Tacrolimus	5–20 ^a µg/L, whole blood
Theophylline	5–15 mg/L

^aDepending on the time after transplant, the type of transplant, and the preference of the center.

^bHigh-performance liquid chromatography.

^cDepending on the indication.

frequently individualized by measuring plasma concentrations achieved by a typical dose and then applying pharmacokinetic principles to calculate a dose that will provide concentrations in the therapeutic range.

It is, however, important to recognize that the therapeutic range has limitations, which include:

1. It represents the range of concentrations that are optimum for most people. Certain patients will, however, experience therapeutic effects at concentrations below the MEC, and others will experience toxicity below the MTC. Some patients never respond therapeutically to a drug even at concentrations well above the MTC.
2. It does not incorporate a graded concentration-related response (i.e., a response that increases with increases in concentration). It is an all-or-nothing response: Patients are predicted to respond when the plasma concentration is within the established therapeutic plasma concentration range and not to respond when the plasma concentration is below the MEC.
3. It only applies to plasma concentrations that are in equilibrium with the drug concentrations at the site of action. It can take a long time for some drugs to distribute to their site of action. For example, it takes about 6–8 h for digoxin to fully distribute to its site of action (the myocardium of the heart). During this distribution period, the therapeutic range will not apply. For example, serum concentrations above the MTC in this period will not necessarily be associated with toxicity.

Therapeutic Index (TI) or Therapeutic Ratio Like the therapeutic range, the TI or therapeutic ratio is a way to express the safety margin offered by a drug. It is the ratio of the dose of the drug that produces toxicity in 50% of patients to the dose of the drug that produces therapeutic response in 50% of patients:

$$TI = \frac{TD_{50}}{ED_{50}} \quad (1.5)$$

where TD_{50} is the dose that produces toxicity in half the patients, and ED_{50} is the therapeutic or effective dose in half the patients. If, for example, a drug has a TI of 100, the toxic dose is about 100 times larger than the effective dose and the drug has a wide safety margin. Conversely, a TI of 3 would indicate a small margin of safety. A drug with a small therapeutic ratio will have a narrow therapeutic range.

1.6 SUMMARY

In summary:

- *Pharmacokinetics* may be defined as a study of the relationship between drug concentration and time after the administration of a given dose. It involves the study of all the processes that affect this relationship: that is, a drug's ADME. Pharmacokinetics represents the first stage in the process of drug response.
- In pharmacokinetics, the plasma concentrations of a drug are usually studied. A goal is to derive a mathematical expression for the relationship between the plasma concentration, dose, and time:

$$C_p = f_{PK}(\text{dose, time}) \quad (1.6)$$

where C_p is the plasma concentration of the drug, and f_{PK} is a function that describes the relationships among C_p , dose, and time. The function incorporates the drug's pharmacokinetic parameters.

- *Pharmacodynamics* may be defined as a study of the relationship between drug concentration at the site of action and the onset, duration, and intensity of response to the drug. The pharmacodynamic phase constitutes the second and final step in drug response.
- A goal is to derive a mathematical expression for the relationship between the response and the drug concentration:

$$E = f_{PD}(C) \quad (1.7)$$

where E is the drug effect or response, C is the concentration at the site of action, and f_{PD} is a function that describes the relationship between the two and incorporates a drug's pharmacodynamic parameters.

- Integrating pharmacokinetics and pharmacodynamics covers the entire dose–response relationship. Mathematical expressions for the pharmacokinetic and pharmacodynamic phases can be combined to provide a complete mathematical expression of the dose–response relationship:

$$E = f_{PD}(f_{PK}(\text{dose, time})) \quad (1.8)$$

- Equation (1.8) provides a complete expression for the time course of drug response. It will allow the drug response to be calculated at any time after any dose. It will allow optimum dosing regimens to be determined and can be used to simulate drug response data in situations not studied clinically.

REFERENCE

1. Bauer, L. A. (2008) *Applied Clinical Pharmacokinetics*, 2nd ed., McGraw-Hill, New York.