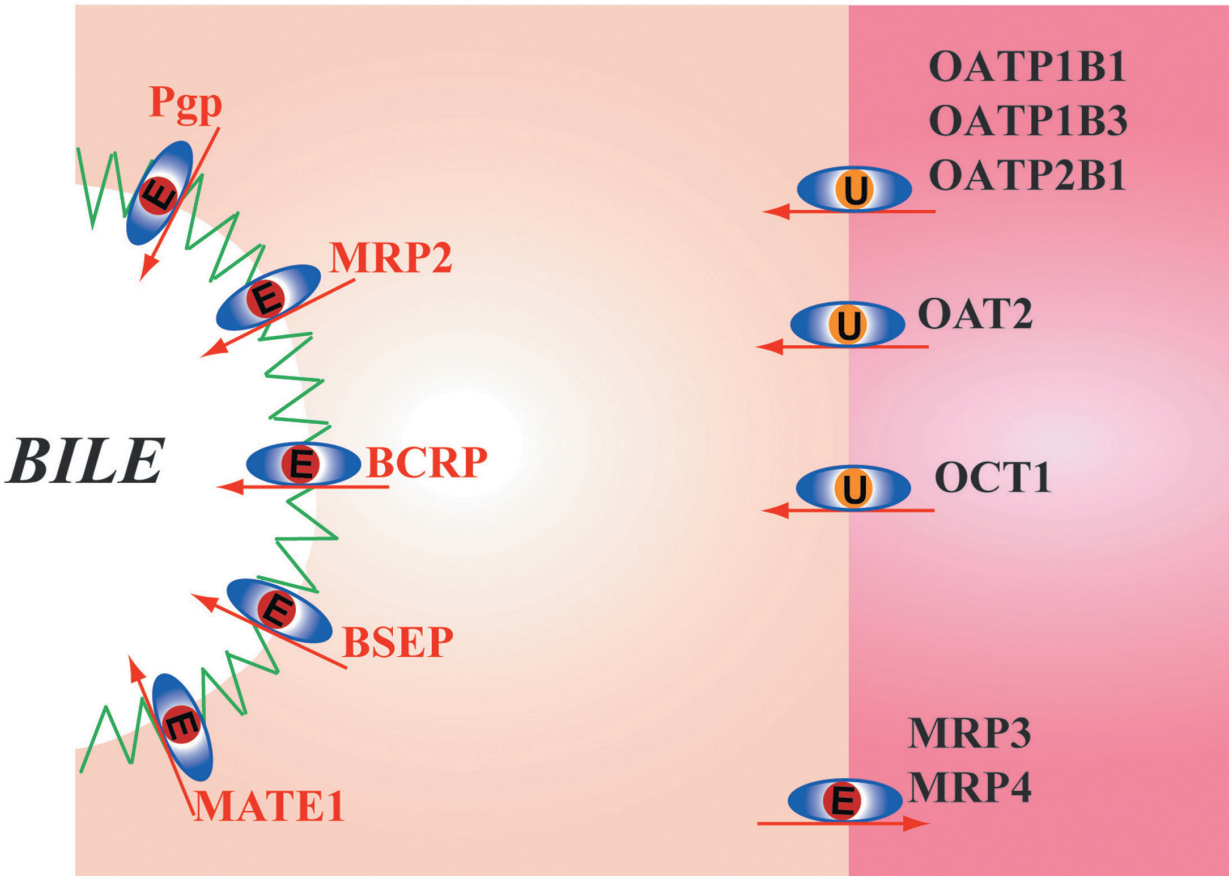
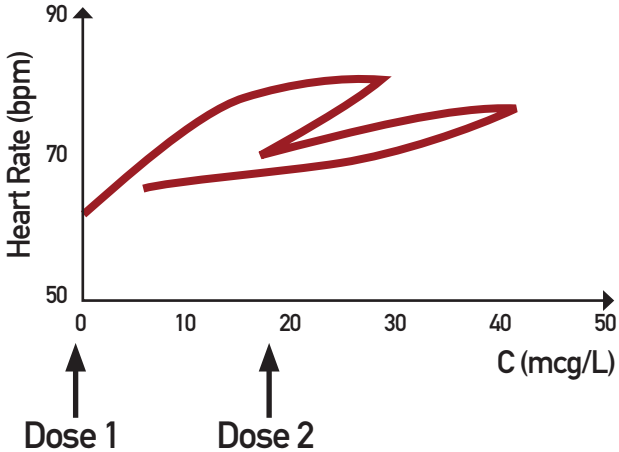
BASIC PHARMACOKINETICS AND PHARMACODYNAMICS



AN INTEGRATED TEXTBOOK AND COMPUTER SIMULATIONS



EDITED BY
SARA E. ROSENBAUM

SECOND EDITION

with website

WILEY

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An Integrated Textbook and Computer Simulations

Second Edition

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SARA E. ROSENBAUM

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To Steve, Molly and Lucy

CONTENTS

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

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.

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

[a]Methicillin-resistant *Staphylococcus aureus*.

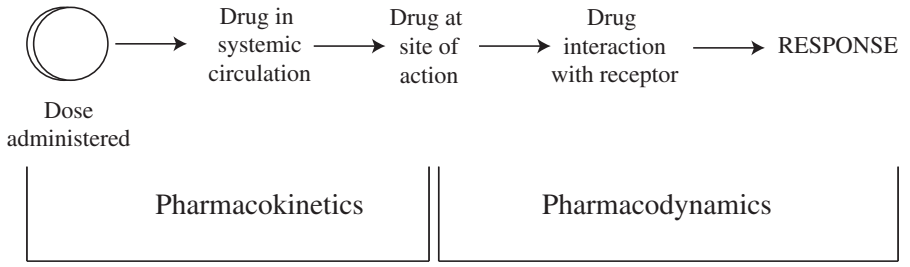

FIGURE 1.1 The two phases of drug action. The pharmacokinetic phase is concerned with the relationship between the value of the dose administered and the value of the drug concentrations achieved in the body; the pharmacodynamic phase is concerned with the relationship between drug concentrations at 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," *pharmackon*, 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.

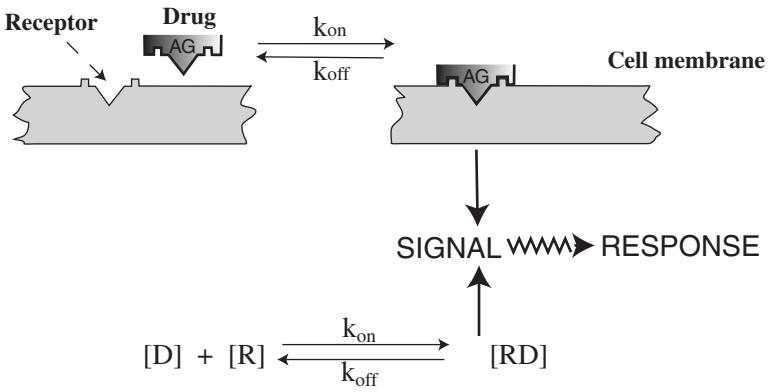

FIGURE 1.2 Drug–receptor interaction. Here, AG signifies a drug agonist, [D] is the free drug concentration (not bound to the receptor), *R* is the concentration of free receptors, [*RD*] is the concentration of the drug–receptor complex, and k_{on} and k_{off} are the rate constants for the forward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