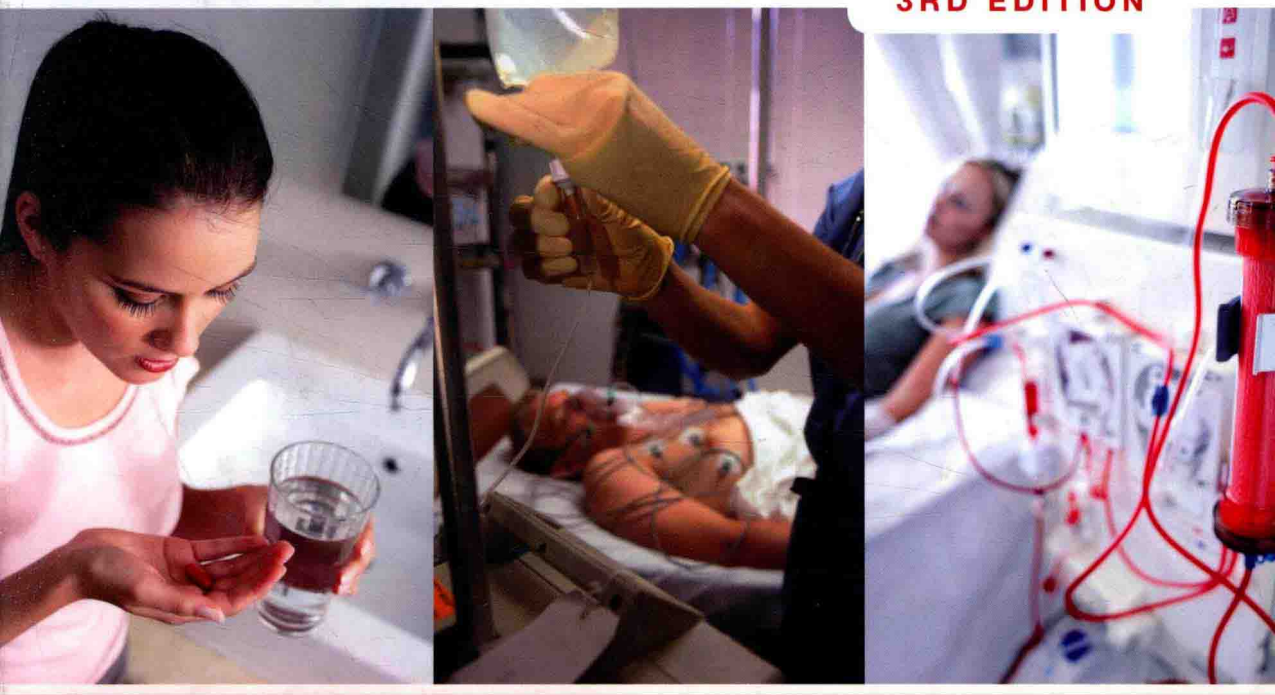
Mc Graw Hill Education

APPLIED CLINICAL PHARMACOKINETICS

3RD EDITION



LARRY A. BAUER

Applied Clinical Pharmacokinetics

Third Edition

Larry A. Bauer, PharmD
Professor
Department of Pharmacy
School of Pharmacy

Adjunct Professor
Department of Laboratory Medicine
School of Medicine
University of Washington
Seattle, Washington

州大学图书馆
藏书章

Mc Graw Hill Education | Medical

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

Applied Clinical Pharmacokinetics, 3rd edition

Copyright © 2014 by McGraw-Hill Education. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

Previous editions copyright © 2008, 2001 by The McGraw-Hill Companies, Inc.

1 2 3 4 5 6 7 8 9 0 DOC/DOC 18 17 16 15 14

ISBN 978-0-07-179458-9
MHID 0-07-179458-1

This book was set in Times by Cenveo® Publisher Services.
The editors were Michael Weitz and Christina M. Thomas.
The production supervisor was Catherine Saggese
Project management was provided by Vastavikta Sharma, Cenveo Publisher Services.
RR Donnelley was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data
Bauer, Larry A., author.
Applied clinical pharmacokinetics / by Larry A. Bauer.—Third edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-07-179458-9 (hardcover : alk. paper)—ISBN 0-07-179458-1 (hardcover : alk. paper)
I. Title.
[DNLM: 1. Pharmacokinetics. 2. Pharmaceutical Preparations—administration & dosage. QV 38]
RM301.5
615'.7—dc23

2013029778

International Edition ISBN 978-1-25-925141-2; MHID 1-25-925141-1. Copyright © 2014. Exclusive rights by McGraw-Hill Education, for manufacture and export. This book cannot be re-exported from the country to which it is consigned by McGraw-Hill Education. The International Edition is not available in North America.

McGraw-Hill Education books are available at special quantity discounts to use premiums and sales promotions, or for use in corporate training programs. To contact a representative please visit the Contact Us pages at www.mhprofessional.com.

Dedication

Third time's a charm . . . right? Through the planned and unexpected, the little things and the big things, the pleasant side trips and trying travails, family are what make it all worthwhile. Thank you (S.P.B., L.A.B., and L.E.B.) for all of your love and support that helped make the third edition a reality.

Thanks for the huge amount of support and assistance from my colleagues. You guys help each and every day, whether it is insight on a new drug interaction, discussion of an interesting patient case, or the latest sports scores: John R. Horn, Douglas J. Black, Lingtak-Neander Chan, Danny D. Shen, and, of course, Philip D. Hansten.

"It's pretty far, but it doesn't seem like it."—Yogi Berra

—L.A.B.

About the Author

Larry A. Bauer, PharmD, is a Professor at the University of Washington School of Pharmacy and has been on the faculty since 1980. He also holds an adjunct appointment at the same rank in the Department of Laboratory Medicine where he is a toxicology consultant. He received a Bachelor of Science in Pharmacy degree (1977, Magna Cum Laude) from the University of Washington and a Doctor of Pharmacy degree (1980) from the University of Kentucky under the supervision of Dr. Robert Blouin. He also completed an ASHP-accredited hospital pharmacy residency (1980) specializing in clinical pharmacokinetics from A. B. Chandler Medical Center at the University of Kentucky under the preceptorship of Dr. Paul Parker. Dr. Bauer is a fellow of the American College of Clinical Pharmacology and the American College of Clinical Pharmacy.

Dr. Bauer's specialty area is in clinical pharmacokinetics, and he teaches courses and offers clinical clerkships in this area. His research interests include the pharmacokinetics and pharmacodynamics of drug interactions, the effects of liver disease and age on drug metabolism, and computer modeling of population pharmacokinetics. He has over 165 published research papers, abstracts, books and book chapters. Dr. Bauer is a member of several clinical pharmacology and clinical pharmacy professional organizations. He was Consulting Editor of Clinical Pharmacy (1981–1990), Field Editor of ASHP Signal (1981–1983), and a member of the Editorial Board of Clinical Pharmacology and Therapeutics. Recently, he completed an appointment to the Editorial Board of Antimicrobial Agents and Chemotherapy and, he reviews for many other scientific publications. Dr. Bauer has precepted three post-doctoral fellows in clinical pharmacokinetics who currently have faculty appointments in schools of pharmacy or positions in the pharmaceutical industry.

此为试读,需要完整PDF请访问: www.ertongbook.com

Foreword

As a pharmacist for 36 years, I am rarely surprised about most things that happen in my professional life. However, I continue to be amazed by the depth and breadth of both the practice and research efforts in the area of therapeutic drug monitoring. As I write this, it is baseball season, so perhaps that eternal philosopher says it best:

> "In theory, there is no difference between theory and practice. In practice, there is."—Yogi Berra

Antibiotics usually take front-and-center attention in clinical pharmacokinetics. While the aminoglycosides continue to develop quietly, vancomycin is demanding more attention as pharmacokinetic/pharmacodynamic (PK/PD) relationships are uncovered and pathogen MICs push upward (short version: the bacteria are winning).

Immunosuppressants continue to be the number one category of monitored drugs in our health care system, and sirolimus makes its debut in this edition of the book. Of course, being a large transplant center contributes to this trend, but it is a rare clinician that doesn't encounter transplant patients and their medications on a routine basis.

While being a static area for quite some time, the next generation anticonvulsants are finally coming into their own. Updated treatment guidelines put these agents squarely in the spotlight, and the increase in serum concentration monitoring for these medications has been impressive. The challenge with these newer drugs is the role that therapeutic drug monitoring will play in their therapy because the concentration-response relationships are not as well defined for them compared to the older agents. Lamotrigine, levetiracetam, oxcarbazepine, and eslicarbazepine are included in this edition.

As for me, preparation for the fourth edition begins today.

Larry A. Bauer, PharmD
May 17, 2014

From *Applied Clinical Pharmacokinetics*, Second Edition

Upon beginning my thirtieth year as a pharmacist, the number of new approaches that continue to be developed for therapeutic drug monitoring impresses me. The second edition of *Applied Clinical Pharmacokinetics* includes new methods to dose immunosuppressants (2-hour postdose cyclosporine concentrations, area under the curve methods for cyclosporine and tacrolimus), and the elevation of what were new methods of dosing antibiotics to the mainstream (extended interval and area under the curve methods for aminoglycosides, trough-only monitoring for vancomycin). Other additions include more complete coverage of pediatric patients, dosing during hemoperfusion, an overview of methods preceding the initial and dosage adjustment sections, and a dosing strategies section that groups together initial and dosage adjustment techniques into a logical sequence. Of course, relevant sections, examples, problems, and references have been updated as needed for each chapter. However, one thing that remains unchanged is the general organization and philosophy of the book (please see the excerpt from the first edition following this section).

> Bernard of Chartres used to say that we are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size.—in Metalogicon (1159 A.D.), by John of Salisbury.

Depending on one's point of view, the discipline of therapeutic drug monitoring is entering its fifth decade. Some brilliant scientists and practitioners who have made significant contributions to the area (and whose names are in the reference list or attached to the methods recommended in this text) and changed the lives of countless patients are no longer with us. I extend my humble thanks to all of these exceptional individuals for making things a little bit clearer and a lot easier for the rest of us.

Larry A. Bauer, PharmD
June 2008

From *Applied Clinical Pharmacokinetics*, First Edition

The structure of this book is uniform for each chapter and is derived from my lectures in clinical pharmacokinetics. The introduction, which consists of a brief discussion of the clinical pharmacology and mechanism of action for the drug, is followed by sections that describe the therapeutic concentration range and anticipated adverse effects for the drug as well as a general monitoring scheme for the agent. Clinical monitoring parameters for therapeutic response and toxicity and basic clinical pharmacokinetic parameters for the compound are discussed next. The next sections describe the effects of disease states and conditions on the pharmacokinetics and dosing of the drug, and drug interactions that may occur with concurrent use of other agents. Each chapter concludes with a comprehensive presentation (with examples) of various methods to compute initial drug doses and to modify drug therapy regimens using serum concentrations to adjust doses. All dosing methods used in this text are ones that are published in peer-reviewed literature. Additionally, they are techniques that I have personal clinical experience with and have produced acceptable results in my practice and clinical clerkships. Finally, problems (with solutions) are included for each chapter so that the various dosing methods can be practiced. The problems are made up of brief clinical vignettes which, given a brief background, request that initial doses be computed or that dosage regimens be modified using drug concentrations.

This text is meant to teach clinical pharmacokinetic and therapeutic drug monitoring techniques to all clinical practitioners regardless of professional background. Pharmacists, physicians, nurse practitioners, and physician assistants are among the individuals who could benefit from the text. With the advent of the almost-universal Doctor of Pharmacy degree in colleges of pharmacy, this book could be used in a pharmaceutics, pharmacokinetics, therapeutics, or clinical pharmacy course sequence. It is also possible to use this textbook in a self-directed manner to teach oneself or review important concepts and techniques. Every effort was made to make the chapters "student-friendly." Abbreviations are held to an absolute minimum. When abbreviations are used, they are defined near the place where they are used. Rather than using appendices, important information is repeated in each drug section so that readers do not need to jump from section to section for critical data. Multiple dosage computation and adjustment techniques for each drug, ranging from the simplest to the sophisticated, are presented. The easiest pharmacokinetic equations that produce accurate results are used in each instance.

It is my strong belief that clinical pharmacokinetics cannot be practiced in a vacuum. Individuals interested in using these dosing techniques for their patients must also be excellent clinical practitioners. Although it is true that "kinetics = dose," clinicians must be able to select the best drug therapy among many choices and appropriately monitor patients for therapeutic response, adverse drug effects, potential drug interactions, disease states and conditions that alter drug dosage, and so on. Thus, it is not acceptable to simply suggest a dose and walk away from the patient, satisfied that the job has been done. It is my sincere hope that this book will help clinicians increase their knowledge in the area of therapeutic drug monitoring and improve care to their patients.

Larry A. Bauer, PharmD
May 17, 2014

Contents

About the Author ix
Foreword x
From Applied Clinical Pharmacokinetics, *Second Edition* xi
From Applied Clinical Pharmacokinetics, *First Edition* xii

I. Basic concepts

1. Clinical Pharmacokinetic and Pharmacodynamic Concepts 3

Introduction 3
Linear Versus Nonlinear Pharmacokinetics 3
Clearance 6
Volume of distribution 14
Half-life and Elimination Rate Constant 16
Michaelis-Menten or Saturable Pharmacokinetics 19
Bioavailability 20
Problems 22
Answers to Problems 23

2. Clinical Pharmacokinetic Equations and Calculations 27

Introduction 27
One-Compartment Model Equations for Linear Pharmacokinetics 27
Designing Individualized Dosage Regimens Using One-Compartment Model Equations 38
Multicompartment Models 41
Michaelis-Menten Equations for Saturable Pharmacokinetics 41
Calculation of Clearance, Volume of Distribution, and Half-life in Pharmacokinetic Research Studies 42
Problems 43
Answers to Problems 44

3. Drug Dosing in Special Populations: Renal and Hepatic Disease, Dialysis, Heart Failure, Obesity, and Drug Interactions 49

Introduction 49
Renal Disease 49
Hepatic Disease 56
Heart Failure 64
Dialysis 65
Hemodialysis 67
Hemofiltration 71
Peritoneal Dialysis 73
Obesity 74
Drug Interactions 76
Problems 79
Answers to Problems 81

II. Antibiotics

4. The Aminoglycoside Antibiotics 89

Introduction 89
Therapeutic and Toxic Concentrations 89
Clinical Monitoring Parameters 92
Basic Clinical Pharmacokinetic Parameters 93
Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing 95
Drug Interactions 100
Initial Dosage Determination Methods 100
Use of Aminoglycoside Serum Concentrations to Alter Dosages 121
Bayesian Pharmacokinetic Computer Programs 146
Dosing Strategies 149
Special Dosing Considerations 150
Problems 152
Answers to Problems 156

5. Vancomycin 197

Introduction 197
Therapeutic and Toxic Concentrations 197
Clinical Monitoring Parameters 200
Basic Clinical Pharmacokinetic Parameters 201

Effects of Disease States and Conditions on Vancomycin Pharmacokinetics and Dosing 202
Drug Interactions 205
Initial Dosage Determination Methods 205
Use of Vancomycin Serum Concentrations to Alter Dosages 224
Area Under the Curve Method 241
Bayesian Pharmacokinetic Computer Programs 244
Dosing Strategies 246
Problems 247
Answers to Problems 250

III. Cardiovascular Agents

6. Digoxin 293

Therapeutic and Toxic Concentrations 293
Clinical Monitoring Parameters 295
Basic Clinical Pharmacokinetic Parameters 296
Effects of Disease States and Conditions on Digoxin Pharmacokinetics and Dosing 296
Drug Interactions 299
Initial Dosage Determination Methods 300
Pharmacokinetic Dosing Method 301
Use of Digoxin Serum Concentrations to Alter Dosages 309
Bayesian Pharmacokinetic Computer Programs 313
Dosing Strategies 315
Special Dosing Considerations 316
Problems 320
Answers to Problems 322

7. Lidocaine 339

Introduction 339
Therapeutic and Toxic Concentrations 339
Clinical Monitoring Parameters 342
Basic Clinical Pharmacokinetic Parameters 342
Effects of Disease States and Conditions on Lidocaine Pharmacokinetics and Dosing 343
Drug Interactions 347
Initial Dosage Determination Methods 347
Use of Lidocaine Serum Concentrations to Alter Doses 353
Bayesian Pharmacokinetic Computer Programs 357
Dosing Strategies 359
Use of Lidocaine Booster Doses to Immediately Increase Serum Concentrations 359
Problems 360
Answers to Problems 361

8. Procainamide/*N*-acetyl Procainamide 373

Introduction 373
Therapeutic and Toxic Concentrations 373
Clinical Monitoring Parameters 375
Basic Clinical Pharmacokinetic Parameters 376
Effects of Disease States and Conditions on Procainamide Pharmacokinetics and Dosing 377
Drug Interactions 380
Initial Dosage Determination Methods 380
Use of Procainamide and *N*-Acetylprocainamide Serum Concentrations to Alter Doses 387
Chiou Method 393
Bayesian Pharmacokinetic Computer Programs 394
Use of Procainamide Booster Doses to Immediately Increase Serum Concentrations 396
Dosing Strategies 397
Conversion of Procainamide Doses From Intravenous to Oral Route of Administration 397
Problems 398
Answers to Problems 400

9. Quinidine 415

Introduction 415
Therapeutic and Toxic Concentrations 415
Clinical Monitoring Parameters 416
Basic Clinical Pharmacokinetic Parameters 417
Effects of Disease States and Conditions on Quinidine Pharmacokinetics and Dosing 418
Drug Interactions 420
Initial Dosage Determination Methods 421
Use of Quinidine Serum Concentrations to Alter Doses 426
Dosing Strategies 432
Conversion of Quinidine Doses From One Salt Form to Another 433
Problems 434
Answers to Problems 435

IV. Anticonvulsants

10. Phenytoin/Fosphenytoin 447

Introduction 447
Therapeutic and Toxic Concentrations 449
Clinical Usefulness of Unbound Phenytoin Concentrations 450
Clinical Monitoring Parameters 453

Basic Clinical Pharmacokinetic Parameters 453
Impact of Altered Plasma Protein Binding on Phenytoin Pharmacokinetics 457
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 458
Drug Interactions 460
Initial Dosage Determination Methods 462
Literature-Based Recommended Dosing 466
Use of Phenytoin Serum Concentrations to Alter Doses 468
Bayesian Pharmacokinetic Computer Programs 481
Dosing Strategies 483
Use of Phenytoin Booster Doses to Immediately Increase Serum Concentrations 483
Problems 485
Answers to Problems 486

11. Carbamazepine 503

Introduction 503
Therapeutic and Toxic Concentrations 503
Clinical Monitoring Parameters 506
Basic Clinical Pharmacokinetic Parameters 506
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 508
Drug Interactions 509
Initial Dosage Determination Methods 510
Use of Carbamazepine Serum Concentrations to Alter Doses 511
Bayesian Pharmacokinetic Computer Programs 512
Problems 512
Answers to Problems 513

12. Valproic Acid 517

Introduction 517
Therapeutic and Toxic Concentrations 517
Clinical Monitoring Parameters 521
Basic Clinical Pharmacokinetic Parameters 521
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 523
Drug Interactions 524
Initial Dosage Determination Methods 526
Use of Valproic Acid Serum Concentrations to Alter Doses 530
Pharmacokinetic Parameter Method 532
Bayesian Pharmacokinetic Computer Programs 534
Dosing Strategies 536
Problems 537
Answers to Problems 538

13. Phenobarbital/Primidone 549

Introduction 549
Therapeutic and Toxic Concentrations 549
Clinical Monitoring Parameters 551
Basic Clinical Pharmacokinetic Parameters 552
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 552
Drug Interactions 554
Initial Dosage Determination Methods 554
Use of Phenobarbital and Primidone Serum Concentrations to Alter Doses 559
Bayesian Pharmacokinetic Computer Programs 562
Dosing Strategies 563
Problems 564
Answers to Problems 565

14. Ethosuximide 573

Introduction 573
Therapeutic and Toxic Concentrations 575
Clinical Monitoring Parameters 575
Basic Clinical Pharmacokinetic Parameters 576
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 576
Drug Interactions 577
Initial Dosage Determination Methods 577
Use of Ethosuximide Serum Concentrations to Alter Doses 580
Bayesian Pharmacokinetic Computer Programs 583
Dosing Strategies 585
Problems 585
Answers to Problems 586

15. Lamotrigine 593

Introduction 593
Therapeutic and Toxic Concentrations 595
Clinical Monitoring Parameters 595
Basic Clinical Pharmacokinetic Parameters 596
Effects of Diseases and Conditions on Pharmacokinetics and Dosing 597
Drug Interactions 600
Initial Dosage Determination Methods 603
Use of Lamotrigine Serum Concentrations to Alter Doses 607
Selection of Appropriate Pharmacokinetic Model and Equations 608
Bayesian Pharmacokinetics Computer Programs 609
Special Dosing Considerations 610
Problems 610
Answers to Problems 611

此为试读,需要完整PDF请访问: www.ertongbook.com

16. Levetiracetam 619

Introduction 619
Therapeutic and Toxic Concentrations 621
Clinical Monitoring Parameters 621
Basic Clinical Pharmacokinetic Parameters 622
Effects of Diseases and Conditions on Pharmacokinetics and Dosing 625
Drug Interactions 627
Initial Dosage Determination Methods 628
Use of Levetiracetam Serum Concentrations to Alter Doses 633
Bayesian Pharmacokinetic Computer Programs 638
Dosing Strategies 639
Special Dosing Considerations 640
Problems 640
Answers to Problems 641

17. Oxcarbazepine/Eslicarbazepine 653

Introduction 653
Oxcarbazepine 656
Therapeutic and Toxic Concentrations 656
Clinical Monitoring Parameters 656
Basic Clinical Pharmacokinetic Parameters 656
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 658
Drug Interactions 660
Initial Dosage Determination Methods 661
Use of MHD Serum Concentrations to Alter Doses of Oxcarbazepine 664
Bayesian Pharmacokinetics Computer Programs 665
Eslicarbazepine 666
Introduction 666
Therapeutic and Toxic Concentrations 666
Clinical Monitoring Parameters 667
Basic Clinical Pharmacokinetic Parameters 667
Effects of Disease States and Conditions on Pharmacokinetics and Dosing 668
Drug Interactions 670
Initial Dosage Determination Methods 671
Use of Serum Concentrations to Alter Doses of Eslicarbazepine 672
Bayesian Pharmacokinetics Computer Programs 674
Problems 674
Answers to Problems 675

V. Immunosuppressants

18. Cyclosporine 685

Introduction 685
Therapeutic and Toxic Concentrations 685
Clinical Monitoring Parameters 687
Basic Clinical Pharmacokinetic Parameters 688
Effects of Disease States and Conditions on Cyclosporine Pharmacokinetics and Dosing 690
Drug Interactions 690
Initial Dosage Determination Methods 691
Use of Cyclosporine Concentrations to Alter Doses 694
Bayesian Pharmacokinetic Computer Programs 699
Dosing Strategies 701
Problems 701
Answers to Problems 703

19. Tacrolimus 713

Introduction 713
Therapeutic and Toxic Concentrations 713
Clinical Monitoring Parameters 715
Basic Clinical Pharmacokinetic Parameters 716
Effects of Disease States and Conditions on Tacrolimus Pharmacokinetics and Dosing 717
Drug Interactions 717
Initial Dosage Determination Methods 718
Use of Tacrolimus Concentrations to Alter Doses 720
Bayesian Pharmacokinetic Computer Programs 724
Dosing Strategies 726
Problems 727
Answers to Problems 728

20. Sirolimus 737

Introduction 737
Therapeutic and Toxic Concentrations 737
Clinical Monitoring Parameters 739
Basic Clinical Pharmacokinetic Parameters 740
Effects of Disease States and Conditions on Sirolimus Pharmacokinetics and Dosing 741
Drug Interactions 744
Initial Dosage Determination Methods 745
Use of Sirolimus Concentrations to Alter Doses 749
Bayesian Pharmacokinetic Computer Programs 753
Dosing Strategies 754
Problems 754
Answers to Problems 756

VI. Other Drugs

21. Lithium 767

Introduction 767
Therapeutic and Toxic Concentrations 767
Clinical Monitoring Parameters 768
Basic Clinical Pharmacokinetic Parameters 769
Effects of Disease States and Conditions on Lithium Pharmacokinetics 770
Drug Interactions 770
Initial Dosage Determination Methods 771
Use of Lithium Serum Concentrations to Alter Dosages 780
Dosing Strategies 783
Problems 784
Answers to Problems 785

22. Theophylline 797

Introduction 797
Therapeutic and Toxic Concentrations 797
Clinical Monitoring Parameters 798
Basic Clinical Pharmacokinetic Parameters 800
Effects of Disease States and Conditions on Theophylline Pharmacokinetics and Dosing 800
Drug Interactions 803
Initial Dosage Determination Methods 804
Use of Theophylline Serum Concentrations to Alter Doses 812
Chiou Method 818
Bayesian Pharmacokinetic Computer Programs 820
Dosing Strategies 822
Use of Theophylline Booster Doses to Immediately Increase Serum Concentrations 822
Conversion of Theophylline Doses From Intravenous to Oral Route of Administration 823
Removal of Theophylline Body Stores in Management of Theophylline Overdose 824
Problems 825
Answers to Problems 826

Index 847

BASIC CONCEPTS

1 Clinical Pharmacokinetic and Pharmacodynamic Concepts

INTRODUCTION

Clinical pharmacokinetics is the discipline that applies pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens that optimize the therapeutic response of a medication while minimizing the chance of an adverse drug reaction. Pharmacokinetics is the study of the *absorption*, *distribution*, *metabolism*, and *excretion* of drugs.[1] When drugs are given extravascularly (eg, orally, intramuscularly, applied to the skin via a transdermal patch, etc), *absorption* must take place for the drug molecules to reach the systemic circulation. In order to be absorbed, the drug molecules must pass through several physiological barriers before reaching the vascular system. For example, when a medication is given orally, the drug dosage form must release drug molecules via dissolution, and the molecules must pass through the various layers of the gastrointestinal (GI) tract where they enter capillaries. *Distribution* occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart. *Metabolism* is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a *metabolite*. The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects. *Excretion* is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.

Pharmacodynamics is the relationship between drug concentration and pharmacological response. It is extremely important for clinicians to realize that the change in drug effect is usually not proportional to the change in drug dose or concentration (Figure 1-1). For example, when a drug dose or concentration is increased from a baseline value, the increase in pharmacological effect is greater when the initial dose or concentration is low compared to the change in drug effect observed when the initial dose or concentration is high. Thus, the increase in pharmacological effect that one observes in a patient as the dose is incremented is subject to the law of diminishing returns and will eventually reach a maximum. The reason that most drugs follow this pattern is because their pharmacological effect is produced by forming a complex with a drug receptor. Once the drug-receptor complex is formed, the pharmacological effect is expressed. Often, toxic side effects of drugs follow the same type of dose- or concentration-response relationship, albeit shifted to the right on the dose or concentration axis. In clinical situations, patients may need to tolerate some drug side effects in order to obtain the maximal pharmacological effect of the agent.

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

When drugs are given on a constant basis, such as a continuous intravenous infusion or an oral medication given every 12 hours, serum drug concentrations increase until the rate of drug administration equals the rate of drug metabolism and excretion. At that point, serum drug concentrations become constant during a continuous intravenous infusion or exhibit a repeating pattern over each dosage interval for medications given at a scheduled time (Figure 1-2). For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic

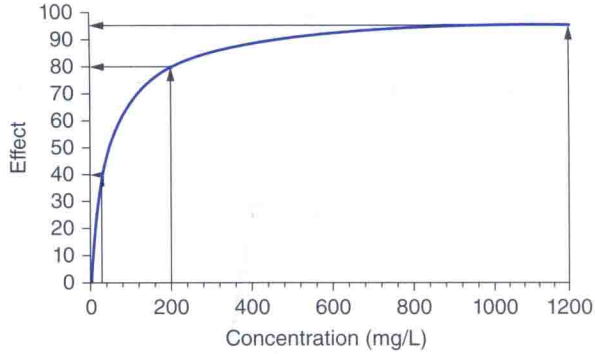


FIGURE 1-1 The relationship between drug concentration and response is usually a hyperbolic function: Effect = $(E_{max} \cdot C)/(EC_{50} + C)$, where E_{max} is the maximum effect and EC_{50} is the drug concentration where the drug effect equals $E_{max}/2$. After a dosage change is made and drug concentrations increase, the drug effect does not change proportionally. Further, the increase in pharmacological effect is greater when the initial concentration is low compared to the change in drug effect observed when the initial concentration is high. In this graph, the drug effect changes ~50% (from ~40 to 80 units) with a fivefold increase in concentrations at low levels (from ~40 to 200 mg/L), but only ~20% (from ~80 to 95 units) when the same fivefold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L).

metabolism and renal excretion equals 50 mg/h. If cyclosporine is given orally at a dose of 300 mg every 12 hours, cyclosporine blood concentrations will follow a repeating pattern over the dosage interval that will increase after a dose is given (because of drug absorption from the GI tract) and decrease after absorption is complete. This repeating pattern continues and eventually drug concentrations for each dosage interval become superimposable when the amount of cyclosporine absorbed into the body from the GI tract equals the amount removed by hepatic metabolism over each dosage interval. Regardless of the mode of drug administration, when the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value. This equilibrium condition is known as *steady-state* and is extremely important in clinical pharmacokinetics because usually steady-state serum or blood concentrations are used to assess patient response and compute new dosage regimens.

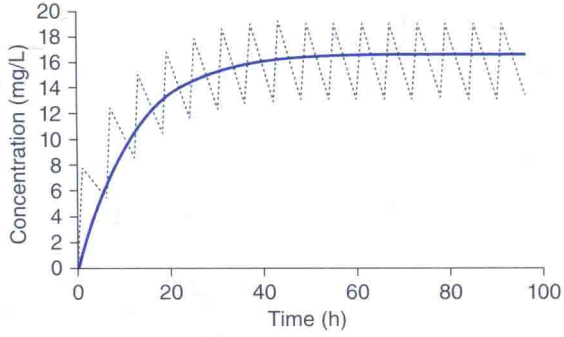


FIGURE 1-2 When medications are given on a continuous basis, serum concentrations increase until the rate of drug administration equals the elimination rate. In this case, the solid line shows serum concentrations in a patient receiving intravenous theophylline at a rate of 50 mg/h (*solid line*) and oral theophylline 300 mg every 6 hours (*dashed line*). Because the oral dosing rate (dose/dosage interval = 300 mg/6 h = 50 mg/h) equals the intravenous infusion rate, the drug accumulation patterns are similar. For the intravenous infusion, serum concentrations increase in a smooth pattern until steady-state is achieved. During oral dosing, the serum concentrations oscillate around the intravenous profile, increasing during drug absorption and decreasing after absorption is complete and elimination takes place.

此为试读，需要完整PDF请访问：www.ertongbook.com