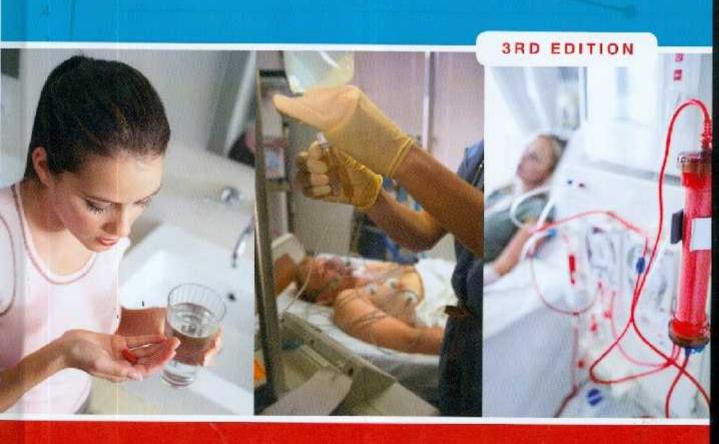
INTERNATIONAL EDITION



APPLIED CLINICAL PHARMACOKINETICS



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 Scattle, Washington

Accession no. M 0151271

Date received 2.5 OCT 2016

Call no. 518.7

BAAAA



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. com.

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 Education 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. Hom, 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.

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 Rata Constant 16
Michaelis-Menten or Saturable
Pharmacokinetics 19
Bioavallanility 20
Problems 22
Answers to Problems 23

2. Clinical Pharmacokinetic Equations and Calculations 27

Introduction 27
One-Compartment Model Equations for Linear
Pharmacokanetics 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 Dusing 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 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 Dusage 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 Pharmacokinetie Computer Programs 357 Doving 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 Texic Concentrations 373 Clinical Monitoring Parameters 375 Basic Clinical Pharmacokinetic Parameters 376 Effects of Disease States and Conditions on Proca namide Pharmacok netics and Dosing 377 Drug Interactions 380 initial Dosage Determination Methods 380 Use of Procainamice and N-Acetylprocainamide Serum Concentrations to Alter Doses 387 Chion Method 393 Bayesian Pharmacokinetie 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 Pachletins 400

9. Quinidine 415

Introduction 415
Therapeutic and Toxic Concentrations 415
Clinical Monitoring Parameters 416
Basic Clinical Pharmacokinetic Parameters 417
Effects or Disease States and Conditions
on Quinidine Pharmacokinetics and Doxing 418
Drug Interactions 420
Initial Doxage 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 Dasing 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 After 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. Ravesian 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
Dusing 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

Levetiracetam 619

Introduction 619 Therapeutic and Toxic Concentrations 621 Clinical Monitor ng Parameters 621 Basic Clinical Pharmacok netic Parameters 622 Effects of Diseases and Conditions on Pharmacokinetics and Dosing 625 Drug Interactions 627 Initial Dosage Determination Methods 628 Use of Levetiracetam Scrum Concentrations to Alter Doses 633 Bayesian Pharmacokinetic Computer Programs 638 Dosing Strategies 639 Special Dosing Considerations 640 Problems 640 Answers to Problems 64

17. Oxcarbazepine/Eslicarbazepine 653

Introduction 653 Oxearbazenine 656. Therapeutic and Toxic Concentrations 656 Clinical Monitoring Parameters 656 Basic Clinical Pharmacokinetic Parameters 656 Effects of Disease States and Conditions. on Pharmacekineries and Dosing 658 Drug Interactions 660 Initial Dosage Determination Methods 651 Use of MHD Serum Concordations to Alter Doses of Oxcarbazepine 664 Bayesian Pharmacokinetics Computer Programs 565 Eslicarbazepine 666 Introduction 666 Therapeutic and Toxic Concentrations 666 Clinical Morntoring Parameters 667 Basic Clinical Pharmacokinetic Parameters 667 Effects of Disease States and Conditions on Pharmacokineries 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
Asswers to Problems 703

19. Tacrolimus 713

Introduction 713 Therapeutic and Toxic Concentrations 713 Clinical Monitoring Parameters 715 Basic Chrical Pharmacokiretic Parameters 716 Effects of Disease States and Conditions on Tacrolimus Pharmacokinetics and Dosing 717 Drug Interactions 717 Initial Desage Determination Methods 7:8 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 727 Clinical Monitoring Parameters 739 Basic Clinical Pharmacokinetic Parameters 740 Effects of Discase States and Conditions on Sirolimus Pharmacokineties and Dosing 741 Drug Interactions 744 Initial Dosage Determination Methods 745 Use of Sirolimus Concentrations to A ter-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 foxe 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
Therapointie 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 894 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

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 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.