Applied Clinical Pharmacokinetics

Third Edition

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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.

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VI. Other Drugs

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.

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