



Second Edition

Applied
Clinical
Pharmacokinetics

LARRY A. BAUER

**APPLIED CLINICAL
PHARMACOKINETICS**

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APPLIED CLINICAL PHARMACOKINETICS

Second Edition

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For all of the late dinners, all of the even later bedtimes, and all of the understanding, forgiveness, unconditional love, and support, I continue to be eternally grateful to my wife (S.P.B.) and my daughters (L.A.B. and L.E.B.) for allowing me the time and effort to produce another edition.

Isn't it supposed to get easier each time?

—L.A.B.

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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 his Bachelor of Science in Pharmacy degree (1977) from the University of Washington and his 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; 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 155 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*. Currently, he is on the editorial board of *Antimicrobial Agents and Chemotherapy* and reviews for many other scientific publications. Dr. Bauer has precepted three postdoctoral fellows in clinical pharmacokinetics who currently have faculty appointments in schools of pharmacy or positions in the pharmaceutical industry.

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PREFACE

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 pharmaceuticals, 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
June 6, 2000

Part I

BASIC CONCEPTS

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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 which 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 (e.g., 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 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

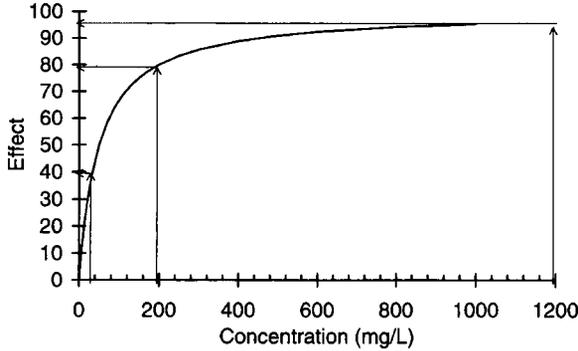


FIGURE 1-1 The relationship between drug concentration and response is usually a hyperbolic function: $\text{Effect} = (E_{\max} \cdot C)/(EC_{50} + C)$, where E_{\max} is the maximum effect and EC_{50} is the drug concentration where the drug effect equals $E_{\max}/2$. After a dosage change is made 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 five-fold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L).

increase in pharmacological effect that one observes in a patient as the dose is increased 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 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 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 which will increase after a dose is given (due to drug absorption from the gastrointestinal 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