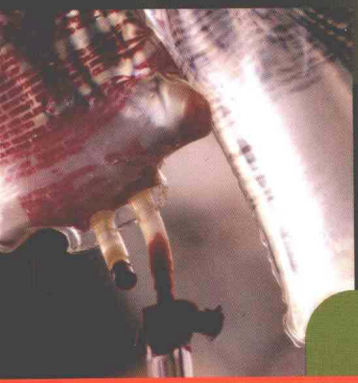
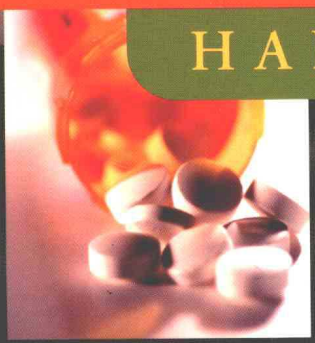


CLINICAL PHARMACOKINETICS HANDBOOK



- Patient-specific regimen and monitoring criteria
- User-friendly calculation methods
- Latest techniques and equations
- Dosing in special populations
- Drug-by-drug coverage

LARRY A. BAUER

CLINICAL PHARMACOKINETICS HANDBOOK

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To my wife (S.P.B.)
for her unwavering, unlimited support and caring for over 25 years
and
to my daughters (L.A.B. & L.E.B.)
for their no-holds-barred, every-day-is-a-new-opportunity approach to life—you both constantly teach me new things.

P.S. Dad, this one's for you.

About the Author

Larry A. Bauer, Pharm.D., 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. He also completed an ASHP-accredited hospital pharmacy residency (1980), specializing in clinical pharmacokinetics, at A. B. Chandler Medical Center at the University of Kentucky, under the preceptorship of Dr. Paul Parker and under the guidance of Dr. Robert Blouin. Dr. Bauer is a fellow of the American College of Clinical Pharmacology and 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, the effects of renal disease and dialysis on drug elimination, and computer modeling of population pharmacokinetics. He has over 140 published research papers, abstracts, and book chapters. Also, he is author of the textbook entitled *Applied Clinical Pharmacokinetics* (McGraw-Hill, 2001). Dr. Bauer is a member of several clinical pharmacology and clinical pharmacy professional organizations. He is a reviewer for several scientific publications, was Consulting Editor of *Clinical Pharmacy* (1981–1990) and Field Editor of *ASHP Signal* (1981–1983), and is currently on the Editorial Boards of *Clinical Pharmacology and Therapeutics* and *Antimicrobial Agents and Chemotherapy*. 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.

Preface

After writing *Applied Clinical Pharmacokinetics*, something unanticipated happened. While passing through the intensive care unit of our hospital, I encountered several advanced clerkship students who were carrying the textbook with them while on patient rounds. Later, on the same trip through the hospital, a couple of staff clinical pharmacists congratulated me on publishing the textbook, and one asked when a handbook with similar content would be available. I began considering ideas for such a handbook on that day.

My original concept was to write a handbook that focused solely on the dosing aspects of each drug, omitting other material that was included in the textbook. However, when I made a prototype for a couple of drugs that followed this plan and gave copies to a few clerkship students and clinical pharmacists, they all requested a handbook format that followed the one in the textbook. Clerkship students and beginning practitioners found the additional information for all drugs to be useful, while more advanced practitioners found the extra material helpful for drugs that they didn't use very often.

Based on this limited market research, *Clinical Pharmacokinetics Handbook* is an updated distillation of the information in *Applied Clinical Pharmacokinetics* that can easily be carried in a lab coat pocket in patient care areas. The handbook follows the same format as the textbook, it contains most of the same information (but in an outline form), and it uses many of the same patient examples for the various dosing techniques. As a result, previous users of the textbook will feel very comfortable with the format of the material. New users will find that each drug-specific chapter follows the same logical format, so that similar information about different medications can be easily found.

I remain convinced that the ideal approach to therapeutic drug monitoring is matching the best initial dosage and dosage adjustment techniques to the individual patient and the desired therapeutic goals. However, to provide some guidance in selecting methods that work well together, I have provided a new section entitled "Dosing Strategies." This section links together an initial dosing approach with a dose adjustment method that practitioners can consider during the treatment of patients. However, as long as the limitations for each dosing technique are adhered to, any of the initial dosing methods can be coupled with any of the dosing adjustment methods to achieve individualized drug dosage regimens.

From *Applied Clinical Pharmacokinetics*

Being a practitioner for over 20 years, I have had an opportunity to see the development of therapeutic drug monitoring almost from its inception. What began in the late 1960s and early 1970s as a way to optimize cardiac glycoside and aminoglycoside antibiotic treatment for patients has, in the 21st century, blossomed into an integral part of patient care for many drugs. On any given

day, our clinical laboratory reports the results of over 200 patient drug concentration assays to clinicians.

My strong belief is 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, Pharm.D.

Contents

1 | BASIC CONCEPTS

1 Clinical Pharmacokinetic and Pharmacodynamic Concepts

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 (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.
  - *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 (Figure 1-1).

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).
- 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 steady-state serum or blood concentrations are often used to assess patient response and to compute new dosage regimens.
- If a patient is administered several different doses until steady state is established, and steady-state serum concentrations are obtained from the patient after each dosage level, it is possible to determine a pattern of drug accumulation (Figure 1-3). If a plot of steady-state concentration versus dose yields a straight line, the drug is said to follow *linear pharmacokinetics.* In this situation, steady-state serum concentrations increase or decrease proportionally with dose.

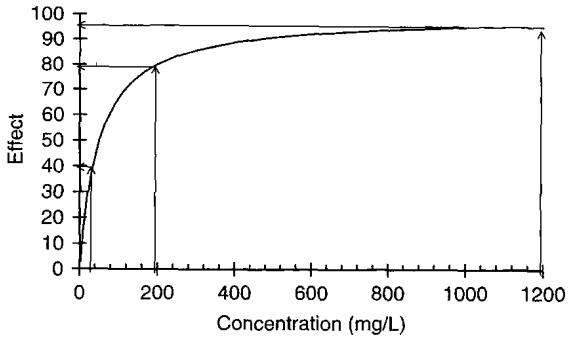

FIG. 1-1 The relationship between drug concentration and response is usually a hyperbolic function: Effect = $(E_{max} \cdot C)/(EC_{50} + C)$, where E_{max} is the maximum effect and EC_{50} is the drug concentration when the drug effect equals $E_{max}/2$. After a dosage change is made and drug concentrations 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.

- If a patient has been taking a medication long enough for steady state to have been established, and it is determined that a dosage adjustment is necessary because of lack of drug effect or the presence of drug toxicity, steady-state drug concentrations will change in proportion to dose for drugs that follow linear pharmacokinetics.
- When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow *nonlinear pharmacokinetics*.

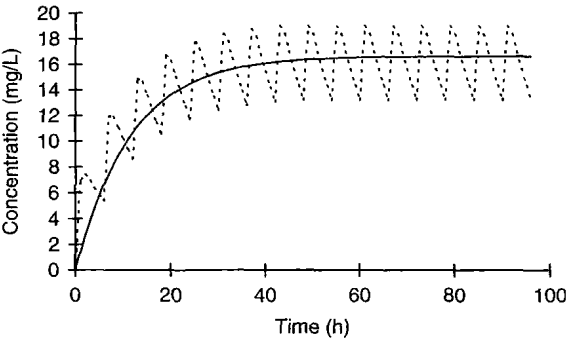

FIG. 1-2 When medications are given on a continuous basis, serum concentrations increase until the rate of drug administration equals the elimination rate. For the intravenous infusion, serum concentrations increase in a smooth pattern until steady state is achieved (solid line). During oral dosing of an equivalent amount, the serum concentrations oscillate around the intravenous profile, increasing during drug absorption and decreasing after absorption is complete and elimination takes place (dashed line).

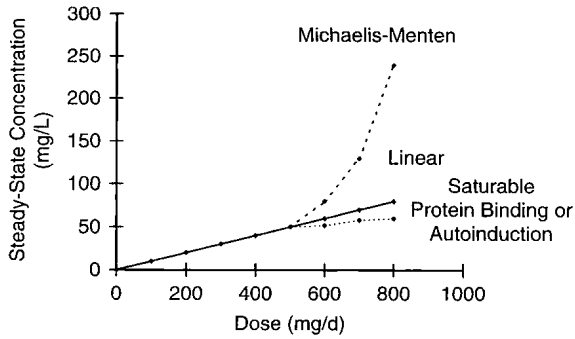

FIG. 1-3 When doses are increased for most drugs, steady-state concentrations increase in a proportional fashion, leading to linear pharmacokinetics (solid line). However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (upper dashed line), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (lower dashed line), saturable plasma protein binding or autoinduction are likely explanations.

- When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the processes removing the drug from the body have become saturated. This phenomenon is known as *saturable or Michaelis-Menten pharmacokinetics*. Phenytoin[2] follows Michaelis-Menten pharmacokinetics.
- When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations. Some drugs, such as valproic acid,[3] *saturate plasma protein binding sites* so that as the dosage is increased, steady-state serum concentrations increase less than expected. Other drugs, such as carbamazepine,[4] increase their own rate of metabolism from the body as dose is increased, so steady-state serum concentrations increase less than anticipated. This process is known as *autoinduction* of drug metabolism.

CLEARANCE

- Clearance (Cl) determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css):

$$MD = Css \cdot Cl$$

- Target steady-state concentrations are usually chosen from previous studies in patients that have determined minimum effective concentrations and maximum concentrations that produce the desired pharmacological effect but avoid toxic side effects. This range of steady-state concentrations is known as the *therapeutic range* for the drug. The therapeutic range should be considered as an initial guideline for drug concentrations in a specific patient; drug dose and steady-state concentrations should then be titrated and individualized based on therapeutic response.

- The liver is most often the organ responsible for drug metabolism, while in most cases the kidney is responsible for drug elimination. The majority of drug metabolism is catalyzed by enzymes contained in the microsomes of hepatocytes known as the cytochrome P-450 enzyme system. The kidney eliminates drugs by glomerular filtration and tubular secretion in the nephron.
- Table 1-1 lists the cytochrome P-450 enzymes responsible for the majority of drug oxidative metabolism in humans, along with examples of known substrates, inhibitors, and inducers.[5] Also, some ethnic groups are deficient in certain enzyme families to a varying extent, and this information is included.
- P-glycoprotein (PGP) is a transport protein that is responsible for the active secretion of drugs into the bile, urine, and gastrointestinal tract. Table 1-2 lists PGP substrates, inhibitors, and inducers.
- The clearance for an organ, such as the liver or kidney, that metabolizes or eliminates drugs is determined by the blood flow to the organ and the ability of the organ to metabolize or eliminate the drug[6]. The drug clearance for an organ is equal to the product of the blood flow to the organ and the extraction ratio of the drug (Figure 1-4).
  - Liver blood flow (LBF) and renal blood flow (RBF) are each ~1– 1.5 L/min in adults with normal cardiovascular function. The ability of an organ to remove or extract the drug from the blood or serum is usually measured by determining the extraction ratio (ER), which is the fraction of drug removed by the organ, and is computed by measuring the concentrations of the drug entering (C_{in}) and leaving (C_{out}) the organ:

$$ER = \frac{(C_{in} - C_{out})}{C_{in}}$$

- Another way to think of hepatic clearance (Cl_H) is to recognize that its value is a function of the intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance, Cl'_{int}); the fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α_1-acid glycoprotein, or lipoproteins, but is present in the unbound, or "free," state (unbound fraction of drug, f_B); and liver blood flow (LBF):

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl_{int})}{LBF + (f_B \cdot Cl_{int})}$$

VOLUME OF DISTRIBUTION

- Volume of distribution (V) determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered (Figure 1-5):

$$LD = Css \cdot V$$

  - It is rare to know the exact volume of distribution for a patient, because it is necessary to administer a dose on a previous occasion in order to have computed this parameter. Thus, usually an average volume of distribution measured in other patients with similar demographics (age, weight, gender, etc.) and medical conditions (renal failure, liver failure, heart failure, etc.) is used to estimate a loading dose (Figure 1-6). As a result, most patients will not actually attain steady state after a loading dose, but it can be hoped that serum drug concentrations will be high enough that the patient will experience the pharmacological effect of the drug.

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[5]

Cytochrome P-450 enzyme	Substrates	Inhibitors	Inducers
CYP1A2	Acetaminophen Caffeine Clozapine Imipramine Ondansetron Phenacetin Ropinirole Tacrine Theophylline (R)-Warfarin Zileuton	Allopurinol Cimetidine Ciprofloxacin Enoxacin Erythromycin Fluvoxamine Isoniazid	Carbamazepine Charcoal-broiled meat Phenobarbital Primidone Rifampin Tobacco smoke
CYP2C9	Celecoxib Chlorpropamide Diclofenac Dronabinol Flurbiprofen Fluvastatin Glimepiride Glipizide Glyburide Ibuprofen Indomethacin Irbesartan Losartan Meloxicam Naproxen Nateglinide Phenytoin Piroxicam Ritonavir Rosiglitazone Tolbutamide Torsemide (S)-Warfarin Zafirlukast	Amiodarone Cimetidine Clopidogrel Cotrimoxazole Delavirdine Disulfiram Efavirenz Fluconazole Fluvastatin Fluvoxamine Gemfibrozil Imatinib Isoniazid Itraconazole Ketoconazole Metronidazole Sulfinpyrazole Zafirlukast	Barbiturates Carbamazepine Phenobarbital Phenytoin Primidone Rifampin
CYP2C19 PM: ~4% Caucasians ~20% Japanese & Chinese	Carisoprodol Desmethyldiazepam Diazepam Hexobarbital Imipramine Lansoprazole (S)-Mephenytoin Omeprazole Pantoprazole Pentamidine Phenytoin Propranolol Rabeprazole Selegiline Sertraline (R)-Warfarin	Cimetidine Delavirdine Efavirenz Felbamate Fluconazole Fluoxetine Fluvoxamine Omeprazole Ticlopidine	Artemisinin Barbiturates Phenytoin Rifampin

(Continued)

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[5] (*Continued*)

Cytochrome P-450 enzyme	Substrates	Inhibitors	Inducers
CYP2D6 PM: ~8% Caucasians ~1% Japanese & Chinese	Alprenolol Amitriptyline Carvedilol Chlorpromazine Clomipramine Codeine Debrisoquin Desipramine Dextromethorphan Dihydrocodeine Encainide Fentanyl Flecainide Fluoxetine Fluvoxamine Fluphenazine Haloperidol Hydrocodone Imipramine Labetalol Maprotiline Methamphetamine Metoprolol Mexiletine Nortriptyline Oxycodone Paroxetine Perhexiline Perphenazine Promethazine Propafenone Propoxyphene Propranolol Risperidone Sertraline Sparteine Thioridazine Timolol Tolterodine Tramadol Trazodone Venlafaxine	Amiodarone Bupropion Chloroquine Cimetidine Citalopram Diphenhydramine Fluoxetine Imatinib Paroxetine Perphenazine Propafenone Propoxyphene Quinacrine Quinidine Quinine Ritonavir Sertraline Terbinafine Thioridazine	
CYP2E1	Acetaminophen Chlorzoxazone Enflurane Ethanol Halothane Isoflurane Isoniazid	Disulfiram	Ethanol Isoniazid
CYP3A4	Alfentanil Alprazolam Amiodarone Amlodipine	Clarithromycin Clotrimazole Danazol Delavirdine	Barbiturates Carbamazepine Dexamethasone Griseofulvin

(*Continued*)