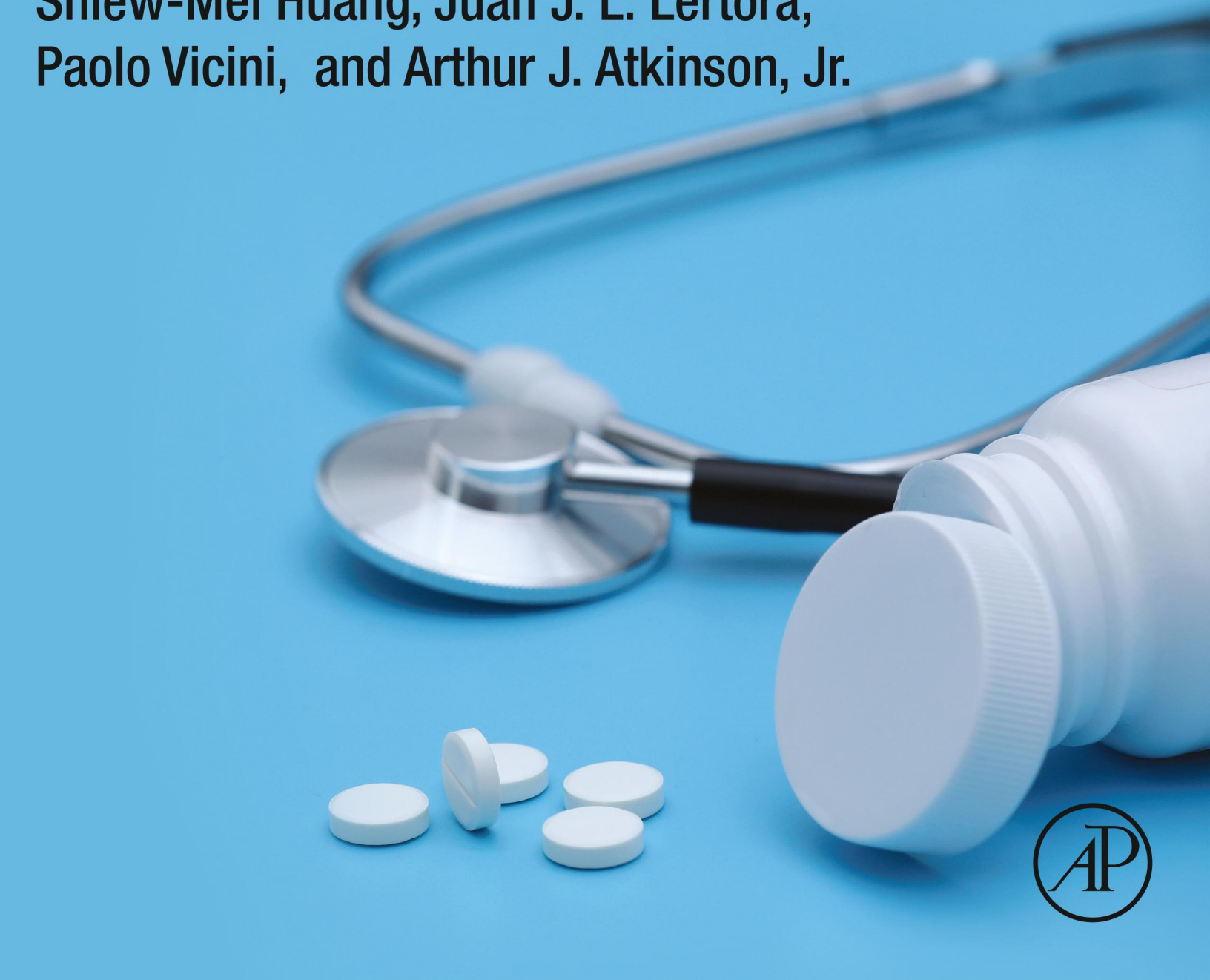
Fourth Edition

# *Atkinson's Principles of*

# CLINICAL PHARMACOLOGY

Shiew-Mei Huang, Juan J. L. Lertora,
Paolo Vicini, and Arthur J. Atkinson, Jr.



# Atkinson's Principles of Clinical Pharmacology

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# Atkinson's Principles of Clinical Pharmacology

Fourth Edition

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# Preface to the first edition

The rate of introduction of new pharmaceutical products has increased rapidly over the past decade, and details learned about a particular drug become obsolete as it is replaced by newer agents. For this reason, we have chosen to focus this book on the principles that underlie the clinical use and contemporary development of pharmaceuticals. It is assumed that the reader will have had an introductory course in pharmacology and also some understanding of calculus, physiology, and clinical medicine.

This book is the outgrowth of an evening course that has been taught for the past 3 years at the NIH Clinical Center. Wherever possible, individuals who have lectured in the course have contributed chapters corresponding to their lectures. The organizers of this course are the editors of this book and we also have recruited additional experts to assist in the review of specific chapters. We also acknowledge the help of William A. Mapes in preparing much of the artwork. Special thanks are due to Donna Shields, Coordinator for the ClinPRAT training program at NIH, whose attention to myriad details has made possible both the successful conduct of our evening course and the production of this book. Finally, we were encouraged and patiently aided in this undertaking by Robert M. Harington and Aaron Johnson at Academic Press.

# Preface to the fourth edition

In the two decades since the first edition of *Principles of Clinical Pharmacology* was published, major advances have been made in our understanding of many areas of this discipline, including pharmacogenetics/pharmacogenomics, drug transporters, the mechanism of adverse drug reactions, and biomarkers. The primary physical base of clinical pharmacology has also migrated from academia to the pharmaceutical industry and the U.S. Food and Drug Administration (FDA), where the discipline plays an increasingly prominent role in the development and regulation of new pharmaceuticals. Evidence for this transition is provided by the proliferation of FDA Guidance Documents that are cited in many chapters of the current edition of our text. However, as in previous editions, some linkage remains with the online lecture series that continues to be offered by the Clinical Center at the National Institutes of Health.[a]

We are indebted to the authors from previous editions who returned to update their chapters. However, the recent advances in clinical pharmacology have been paralleled by a change in the demographics of the discipline. This is reflected in our text by the addition of many new scientists to our roster of chapter authors. Our editorial leadership has also evolved in order to maintain its relevance and vitality. In launching this new edition of the textbook, the editorial team and the publisher wish to acknowledge the pioneering work of Dr. Arthur J. Atkinson, Jr., who conceived the first edition as an introductory textbook emphasizing fundamental principles to guide drug discovery, drug development, drug regulation, and drug utilization in clinical medicine. His outstanding leadership and dedication to this educational endeavor is thus recognized by the present edition being published as *Atkinson's Principles of Clinical Pharmacology*.

Many of the illustrations in the text appeared originally in *Clinical Pharmacology and Therapeutics*, and we thank the American Society for Clinical Pharmacology and Therapeutics for allowing us to reproduce these free of charge. Finally, special thanks are due the Elsevier Production Staff who together provided the ongoing support that has been invaluable for the successful production of this book.

[a] https://ocr.od.nih.gov/courses/principles-clinical-pharmacology.html.

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Chapter 1

# Introduction to clinical pharmacology

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*Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago.*

Rudolph Buchheim, Beitrage zur Arzneimittellehre, 1849 [1]

## Background

*Clinical pharmacology* can be defined as the study of drugs in humans. Clinical pharmacology often is contrasted with basic pharmacology. Yet *applied* is a more appropriate antonym for *basic* [2]. In fact, many basic problems in pharmacology can only be studied in humans. This text will focus on the basic principles of clinical pharmacology. Selected applications will be used to illustrate these principles, but no attempt will be made to provide an exhaustive coverage of applied therapeutics. Other useful supplementary sources of information are listed at the end of this chapter.

Leake [3] has pointed out that pharmacology is a subject of ancient interest but is a relatively new science. Reidenberg [4] subsequently restated Leake's listing of the fundamental problems with which the science of pharmacology is concerned:

1. The relationship between dose and biological effect.
2. The localization of the site of action of a drug.
3. The mechanism(s) of action of a drug.
4. The absorption, distribution, metabolism, and excretion of a drug.
5. The relationship between chemical structure and biological activity.

These authors agree that pharmacology could not evolve as a scientific discipline until modern chemistry provided the chemically pure pharmaceutical products that are needed to establish a quantitative relationship between drug dosage and biological effect.

Clinical pharmacology has been termed a bridging discipline because it combines elements of classical pharmacology with clinical medicine. The special competencies of individuals trained in clinical pharmacology have equipped them for productive careers in academia, the pharmaceutical industry, and governmental agencies, such as the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). Reidenberg [4] has pointed out that clinical pharmacologists are concerned both with the optimal use of existing medications and with the scientific study of drugs in humans. The latter area includes both evaluation of the safety and efficacy of currently available drugs and development of new and improved pharmacotherapy.

### Optimizing use of existing medicines

As the opening quote indicates, the concern of pharmacologists for the safe and effective use of medicine can be traced back at least to Rudolph Buchheim (1820–79), who has been credited with establishing pharmacology as a laboratory-based discipline [1]. In the United States, Harry Gold and Walter Modell began in the 1930s to provide the foundation for the modern discipline of clinical pharmacology [5]. Their accomplishments include the invention of the double-blind design for clinical trials [6], the use of effect kinetics to measure the absolute bioavailability of digoxin and characterize the time course of its chronotropic effects [7], and the founding of *Clinical Pharmacology and Therapeutics*.

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Few drugs have focused as much public attention on the problem of adverse drug reactions as thalidomide, which was first linked in 1961 to catastrophic outbreaks of phocomelia by Lenz in Germany and McBride in Australia [8]. Although thalidomide had not been approved at that time for use in the United States, this tragedy prompted passage in 1962 of the Harris-Kefauver Amendments to the Food, Drug, and Cosmetic Act. This act greatly expanded the scope of the FDA's mandate to protect the public health. The thalidomide tragedy also provided the major impetus for developing a number of NIH-funded academic centers of excellence that have shaped contemporary clinical pharmacology in this country. These US centers were founded by a generation of vigorous leaders, including Ken Melmon, Jan Koch-Weser, Lou Lasagna, John Oates, Leon Goldberg, Dan Azarnoff, Tom Gaffney, and Leigh Thompson. Colin Dollery and Folke Sjöqvist established similar programs in Europe. In response to the public mandate generated by the thalidomide catastrophe, these leaders quickly reached consensus on a number of theoretically preventable causes that contribute to the high incidence of adverse drug reactions [5]. These include:

1. Inappropriate polypharmacy.
2. Failure of prescribing physicians to establish and adhere to clear therapeutic goals.
3. Failure of medical personnel to attribute new symptoms or changes in laboratory test results to drug therapy.
4. Lack of priority given to the scientific study of adverse drug reaction mechanisms.
5. General ignorance of basic and applied pharmacology and therapeutic principles.

The important observations also were made that, unlike the teratogenic reactions caused by thalidomide, most adverse reactions encountered in clinical practice occurred with drugs that had been in clinical use for a substantial period of time, rather than newly introduced, drugs, and were dose related, rather than idiosyncratic [5, 9, 10].

Recognition of the considerable variation in response of different patients treated with standard drug doses has provided the impetus for the development of what has been called "personalized medicine" [11] or, more recently, "precision medicine" [12]. Despite the recent introduction of these terms, they actually describe a continuing story that can be divided into three chapters in which different complementary technologies were developed and are being applied to improve patient therapy by coping with this variability [13]. In the earliest chapter, laboratory methods were developed to measure drug concentrations in patient blood samples and to guide therapy, an approach now termed "therapeutic drug monitoring" [10]. The routine availability of these measurements then made it possible to apply pharmacokinetic principles in routine patient care to achieve and maintain these drug concentrations within a prespecified therapeutic range. Despite these advances, *serious adverse drug reactions* (defined as those adverse drug reactions that require or prolong hospitalization, are permanently disabling, or result in death) continue to pose a severe problem and have been estimated to occur in 6.7% of hospitalized patients [14]. Although this figure has been disputed, the incidence of adverse drug reactions probably is still higher than is generally recognized [15]. In the third chapter that is still being written, genetic approaches are being developed and applied to meet both this challenge and to improve the efficacy and safety of drug therapy [16]. Thus pharmacogenetics is being used to identify slow drug-metabolizing patients who might be at increased risk for drug toxicity and rapid metabolizers who might not respond when standard drug doses are prescribed. In a parallel development, pharmacogenomic methods are increasingly used to identify subsets of patients who will either respond satisfactorily or be at increased risk of an adverse reaction to a particular drug.

The fact that most adverse drug reactions occur with commonly used drugs focuses attention on the last of the preventable causes of these reactions: the inadequate training that prescribing physicians receive in pharmacology and therapeutics. Buchheim's comparison of surgery and medicine is particularly apt in this regard [5]. Most US medical schools provide their students with only a single course in pharmacology that traditionally is part of the second-year curriculum, when students lack the clinical background that is needed to support detailed instruction in therapeutics. In addition, Sjöqvist [17] has observed that most academic pharmacology departments have lost contact with drug development and pharmacotherapy. As a result, students and residents acquire most of their information about drug therapy in a haphazard manner from colleagues, supervisory house staff and attending physicians, pharmaceutical sales representatives, and whatever independent reading they happen to do on the subject. This unstructured process of learning pharmacotherapeutic technique stands in marked contrast to the rigorously supervised training that is an accepted part of surgical training, in which instantaneous feedback is provided whenever a retractor, let alone a scalpel, is held improperly.

## Evaluation and development of medicines

Clinical pharmacologists have made noteworthy contributions to the evaluation of existing medicines and development of new drugs. In 1932 Paul Martini published a monograph entitled *Methodology of Therapeutic Investigation* that summarized his experience in scientific drug evaluation and probably entitles him to be considered the "first clinical pharmacologist" [18]. Martini described the use of placebos, control groups, stratification, rating scales, and the "n of 1" trial design,

and emphasized the need to estimate the adequacy of sample size and to establish baseline conditions before beginning a trial. He also introduced the term "clinical pharmacology." Gold [6] and other academic clinical pharmacologists also have made important contributions to the design of clinical trials. More recently, Sheiner [19] outlined a number of improvements that continue to be needed in the use of statistical methods for drug evaluation, and asserted that clinicians must regain control over clinical trials in order to ensure that the important questions are being addressed.

Contemporary drug development is a complex process that is conventionally divided into preclinical research and development and a number of clinical development phases, as shown in Fig. 1.1 for small molecule drugs licensed by the US FDA [20]. After a drug candidate is identified and put through in vitro screens and animal testing, an Investigational New Drug application (IND) is submitted to the FDA. When the IND is approved, Phase 1 clinical development begins with a limited number of studies in healthy volunteers or patients. The goal of these studies is to establish a range of tolerated doses and to characterize the drug candidate's pharmacokinetic properties and initial toxicity profile. If these results warrant further development of the compound, short-term Phase 2 studies are conducted in a selected group of patients to obtain evidence of therapeutic efficacy and to explore patient therapeutic and toxic responses to several dose regimens. These dose-response relationships are used to design longer Phase 3 trials to confirm therapeutic efficacy and document safety in a larger patient population. The material obtained during preclinical and clinical development is then incorporated in a New Drug Application (NDA) that is submitted to the FDA for review. The FDA may request clarification of study results or further studies before the NDA is approved and the drug can be marketed. Adverse drug reaction monitoring and reporting is mandated after NDA approval. Phase 4 studies, conducted after NDA approval, may include studies to support FDA licensing for additional therapeutic indications or "over-the-counter" (OTC) sales directly to consumers. The development pathway of biologic products is similar and leads to submission of a Biologics License Application (BLA).

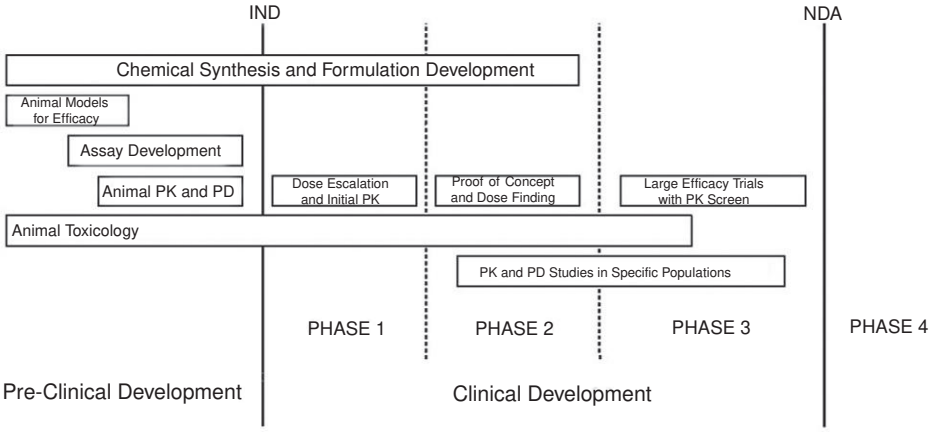


**FIG. 1.1** The process of new drug development in the United States. (PK indicates pharmacokinetic studies; PD indicates studies of drug effect or pharmacodynamics.) Further explanation is provided in the text. *(Modified from Peck CC, Barr WH, Benet LZ, Collins J, Desjardins RE, Furst DE, et al. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. Clin Pharmacol Ther 1992;51:465–473.)*

Although the expertise and resources needed to develop new drugs are primarily concentrated in the pharmaceutical industry, clinical investigators based in academia have played an important catalytic role in championing the development of a number of drugs [21]. For example, dopamine was first synthesized in 1910 but the therapeutic potential of this compound was not recognized until 1963 when Leon Goldberg and his colleagues provided convincing evidence that dopamine mediated vasodilation by binding to a previously undescribed receptor [22]. These investigators subsequently demonstrated the clinical utility of intravenous dopamine infusions in treating patients with hypotension or shock unresponsive to plasma volume expansion. This provided the basis for a small pharmaceutical firm to bring dopamine to market in the early 1970s.

Academically based clinical pharmacologists have a long tradition of interest in drug metabolism. Drug metabolism generally constitutes an important mechanism by which drugs are converted to inactive compounds that usually are more rapidly excreted than the parent drug. However, some drug metabolites have important pharmacologic activity. This was first demonstrated in 1935 when the antibacterial activity of prontosil was found to reside solely in its metabolite, sulfanilamide (Fig. 1.2) [23]. Advances in analytical chemistry over the last 30 years have made it possible to measure on a routine basis plasma concentrations of drug metabolites as well as parent drugs. Further study of these metabolites has demonstrated that several of them have important pharmacologic activity that must be considered for proper clinical interpretation of plasma concentration measurements [24].

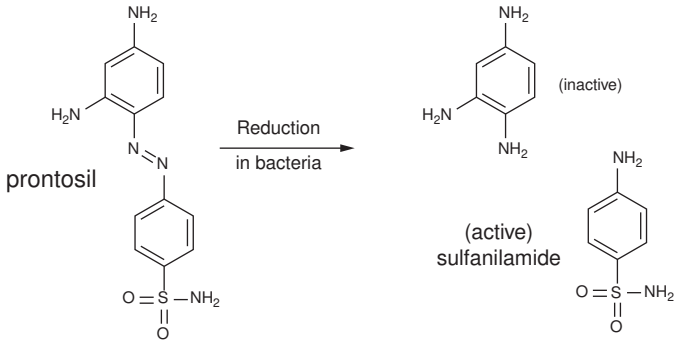


**FIG. 1.2** Azo-reduction of prontosil to form sulfanilamide and 1,2,4-triaminobenzene.

In some cases, clinical pharmacologists have demonstrated that drug metabolites have pharmacologic properties that make them preferable to marketed drugs. For example, when terfenadine (Seldane), the prototype of nonsedating antihistamine drugs, was reported to cause *torsades de pointes* and fatality in patients with no previous history of cardiac arrhythmia, Woosley and his colleagues [25] proceeded to investigate the electrophysiologic effects of both terfenadine and its carboxylate metabolite (Fig. 1.3). These investigators found that terfenadine like quinidine, an antiarrhythmic drug with known propensity to cause *torsades de pointes* in susceptible individuals, blocked the delayed rectifier potassium current. However, terfenadine carboxylate, which actually accounts for most of the observed antihistaminic effects when patients take terfenadine, was found to be devoid of this proarrhythmic property. These findings provided the impetus for commercial development of the carboxylate metabolite as a safer alternative to terfenadine. This metabolite is now marketed as fexofenadine (Allegra).

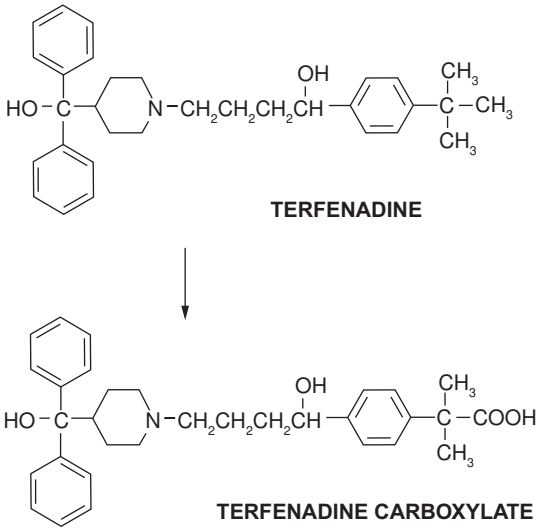


**FIG. 1.3** Chemical structures of terfenadine and its carboxylate metabolite. The acid metabolite is formed by oxidation of the *t*-butyl side chain of the parent drug.

The potential impact of pharmacogenetics on drug prescribing and development is illustrated by the example of tamoxifen, a selective estrogen receptor modifier that has been used as therapy and recurrence prevention in patients with breast cancer. As shown in Fig. 1.4, tamoxifen is converted by cytochrome P450 (CYP) enzymes to several metabolites that have more potent antiestrogenic activity than the parent compound. Although 4-hydroxy-tamoxifen had been thought to be the primary pharmacologically active tamoxifen metabolite, Flockhart and colleagues [26] demonstrated that endoxifen plasma concentrations averaged more than 10 times those of 4-hydroxy-tamoxifen in women treated with tamoxifen and that both compounds had equal in vitro potency in suppressing breast cancer cell proliferation. Unfortunately, there is still no agreement on the clinical utility of using genotype biomarkers to assess the extent of endoxifen formation to guide breast cancer therapy with tamoxifen, so therapeutic monitoring of endoxifen plasma concentrations is being evaluated for this purpose [27, 28]. These findings also have provided the rationale for current efforts to develop endoxifen as a replacement for tamoxifen that would not be subject to pharmacogenetic variation or drug interactions affecting CYP2D6 activity [29, 30].

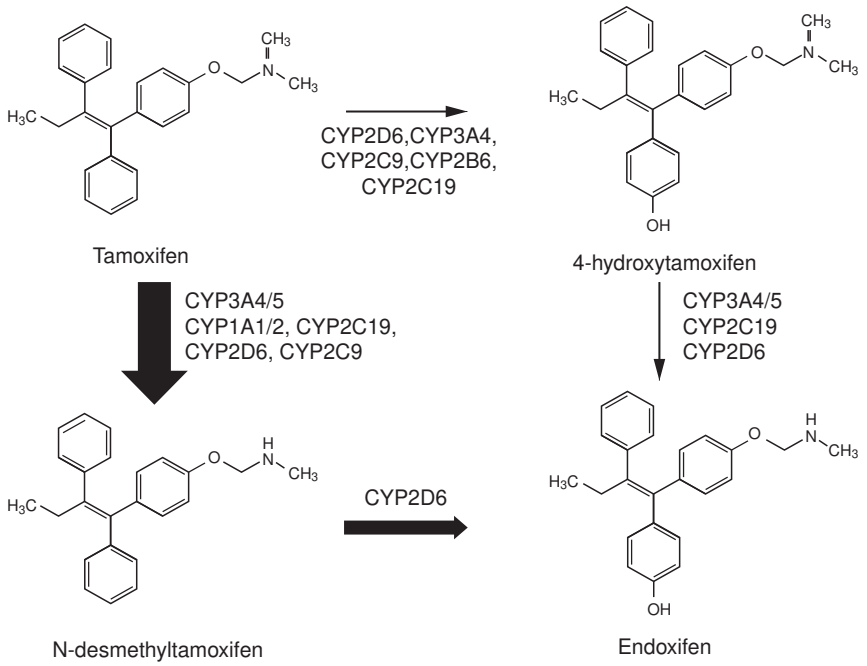


**FIG. 1.4** Partial metabolic pathway of tamoxifen showing metabolite structures and the CYP enzymes involved. The relative contribution of each metabolic step is indicated by the thickness of the *arrows*.

## Pharmacokinetics

*Pharmacokinetics* is defined as the quantitative analysis of the processes of drug absorption, distribution, and elimination that determine the time course of drug action in response to an administered drug dose. *Pharmacodynamics* deals with the mechanism of drug action. Hence, pharmacokinetics and pharmacodynamics constitute two major subdivisions of pharmacology.

Since as many as 70%–80% of adverse drug reactions are dose related [9], our success in preventing these reactions is contingent on our grasp of the principles of pharmacokinetics that provide the scientific basis for dose selection. This becomes critically important when we prescribe drugs that have a narrow therapeutic index. Pharmacokinetics is inescapably mathematical. Although 95% of pharmacokinetic calculations required for clinical application are simple algebra, some understanding of calculus is required to fully grasp the principles of pharmacokinetics.

### The concept of clearance

Because pharmacokinetics comprises the first few chapters of this book and figures prominently in subsequent chapters, we will pause here to introduce the clinically most important concept in pharmacokinetics: the concept of *clearance*. In 1928 Möller et al. [31] observed that, above a urine flow rate of 2 mL/min, the rate of urea excretion by the kidneys is proportional to the amount of urea in a constant volume of blood. They introduced the term "clearance" to describe this proportionality and defined urea clearance as the volume of blood which one minute's excretion serves to clear of urea. Since then, creatinine clearance ($CL_{CR}$) has become most commonly used in clinical practice when renal functional status is directly measured and is calculated from the following equation:

$$CL_{CR} = UV/P$$

where $U$ is the concentration of creatinine excreted over a certain period of time in a measured volume of urine ($V$) and $P$ is the serum concentration of creatinine. This is really a first-order differential equation since $UV$ is simply the rate at which creatinine is being excreted in urine ($dE/dt$). Hence,

$$dE/dt = CL_{CR} \cdot P$$

If, instead of looking at the rate of creatinine excretion in urine, we consider the rate of change of creatinine in the body ($dX/dt$), we can write the following equation:

$$dX/dt = I - CL_{CR} \cdot P \tag{1.1}$$

Here $I$ is the rate of *synthesis* of creatinine in the body and $CL_{CR} \cdot P$ is the rate of creatinine *elimination*. At steady state, these rates are equal and there is no change in the total body content of creatinine ($dX/dt = 0$), so:

$$P = I/CL_{CR} \tag{1.2}$$

This equation explains why it is hazardous to estimate the status of renal function solely from serum creatinine results in patients who have a reduced muscle mass and a concomitant decline in creatinine synthesis rate. For example, creatinine synthesis rate may be substantially reduced in elderly patients, so it is not unusual for serum creatinine concentrations in these patients to remain within normal limits, even though renal function is markedly impaired.

## Clinical estimation of renal function

In routine clinical practice, it is not practical to collect the urine samples that are needed to measure creatinine clearance directly. However, creatinine clearance in adult patients can be estimated either from a standard nomogram or from equations such as that proposed by Cockcroft and Gault [32]. For men, creatinine clearance can be estimated from this equation as follows:

$$CL_{CR}(\text{mL/min}) = \frac{(140 - \text{age})(\text{weight in kg})}{72(\text{serum creatinine in mg/dL})} \tag{1.3}$$

For women, this estimate should be reduced by 15%. By comparing Eq. (1.2) with Eq. (1.3), we see that the terms *(140 − age)(weight in kg)/72* simply provide an estimate of the creatinine formation rate in an individual patient.

Since the Cockcroft-Gault equation was introduced, there has been substantial improvement in reducing the variability and analytical bias in automated methods for measuring creatinine concentrations and these measurements are now calibrated to values obtained by isotope dilution mass spectrometry [33]. In addition, the Cockcroft-Gault equation overestimates true glomerular filtration rate (GFR) as measured by inulin clearance because creatinine is secreted by the renal tubule in addition to being filtered at the glomerulus [34]. For these reasons, data from the Modification of Diet in Renal Disease (MDRD) Study have been used by Levey and colleagues [35] to develop a series of equations that more accurately estimate GFR from standardized serum creatinine measurements and other patient characteristics. This group of investigators [36] has used measured renal clearance of iothalamate as a reference to compare GFR estimates and drug dosing recommendations based on the Cockcroft-Gault equation with those obtained using the following 4-variable version of the MDRD Study equation:

$$\text{GFR} = 175 \times \text{SCR}^{-1.154} \times \text{age}^{-0.203} \times 1.212\ (\text{if African American}) \times 0.742\ (\text{if female})$$

Standardized serum creatinine (SCR) measurements were used in both equations without correcting the Cockcroft-Gault equation for this change in analytical precision. Nonetheless, the concordance rates of dosing recommendations for a panel of 15 medications were 88% for the MDRD Study equation and 85% for the Cockcroft-Gault equation when compared with measured GFR. Consequently, the authors recommended basing drug dosing adjustments in patients with impaired renal function on more recent GFR estimating equations rather than on the Cockcroft-Gault equation. Subsequent estimating equations have been developed to extend the prediction range from patients with chronic kidney disease and GFR less than 60 mL/min/1.73 $m^2$ to individuals with higher GFR (CKD-EPI) [37] and to incorporate serum concentration of cystatin C, another endogenous GFR marker [38].

Neither the Cockcroft-Gault equation nor the previously described GFR estimating equations can be used to estimate creatinine clearance in pediatric patients because muscle mass has not reached the adult proportion of body weight. Therefore, Schwartz and colleagues [39, 40] developed the following equation to predict creatinine clearance in these patients:

$$CL_{CR}\left(\text{mL/min/1.73 m}^2\right) = \frac{k \cdot L(\text{in cm})}{\text{plasma creatinine in mg/dL}}$$

where $L$ is the body length and $k$ varies by age and sex. For children 1–13 years of age, the value of $k$ had been 0.55 but Schwartz et al. [41] have revised this to 0.413, to reflect the introduction of SCR measurements. The original Schwartz formula also recommended discrete values of $k$ for neonates and children under 1 year of age (0.45), and for females (0.57) and males (0.70) between the ages of 13 and 20. Pottel et al. [42] subsequently proposed the following modification of the Schwartz formula in which $k$ for children between 1 and 14 years of age is expressed as the following age-dependent continuous variable:

$$k = 0.0414 \times \ln(\text{age}) + 0.3018$$

In all these equations body length is used as a surrogate for muscle mass in order to estimate creatinine generation rate.

The assessment of renal function in the elderly also has been problematic and this dilemma prompted the Berlin Initiative Study (BIS) to develop two separate equations for patients aged 70 years or older that were modeled on iohexol clearance as a GFR reference [43]. The first equation (BIS1) is creatinine based and includes age and sex as additional variables:

$$\text{GFR} = 3736 \times \text{SCR}^{-0.87} \times \text{age}^{-0.95} \times 0.82\,(\text{if female})$$

A second equation was developed that included measurement of cystatin C but was not deemed as suitable for routine clinical use because of the high cost of cystatin C analysis. A subsequent attempt also has been made to develop an SCR-based equation for estimating GFR as a continuous function across all age groups [44]. However, these latter methods have not been independently validated nor used to guide drug dosage and a recent review of four different methods found that each had limited accuracy [45].

The 2012 clinical guidelines issued by the Kidney Disease: Improving Global Outcomes (KDIGO) group [46] recommend that clinical laboratories report GFR using the 2009 CKD-EPI equations and that an estimating equation incorporating cystatin C be used if confirmation is needed in patients without "markers of kidney damage." Fortunately, CKD-EPI equation results can be automatically calculated by clinical laboratories but are normalized to a body surface area of 1.73 $m^2$, requiring further calculation to obtain a result that is more consistent with an individual patient's muscle mass. Given this complexity, the simpler Cockcroft and Gault equation still finds widespread use among clinicians involved in patient care. Unfortunately, estimating equations based on serum creatinine measurements are inaccurate in patients whose renal function is changing rapidly, for example in acute renal failure, [47], and frequently underestimate GFR in trauma and burn patients or in those requiring intensive care in whom augmented renal clearance is common, so measured creatinine clearance must be relied on [48]. On the other hand, creatinine clearance is likely to overestimate renal function in patients with low creatinine production due to cirrhosis, cachexia, or age-related skeletal muscle atrophy [47].

## Dose-related toxicity often occurs when impaired renal function is unrecognized

Failure to appreciate that a patient has impaired renal function is a frequent cause of dose-related adverse drug reactions with digoxin and other drugs that normally rely primarily on the kidneys for elimination. As presented in Table 1.1, an audit of patients with high plasma concentrations of digoxin (≥3.0 ng/mL) demonstrated that 19 of 44, or 43% of 44 patients with digoxin toxicity had serum creatinine concentrations within the range of normal values, yet had estimated creatinine clearances less than 50 mL/min [49]. Hence, assessment of renal function is essential if digoxin and many other drugs are to be used safely and effectively, and is an important prerequisite for the application of clinical pharmacologic principles to patient care.

**TABLE 1.1 Status of renal function in 44 patients with digoxin toxicity.**

| | $CL_{CR}$ (mL/min) | | |
|---|---|---|---|
| Serum creatinine (mg/dL) | ≥50 | <50 | % |
| ≤1.7 | 4 | 19 | 52% |
| >1.7 | 0 | 21 | 48% |

Data from Piergies AA, Worwag EM, Atkinson AJ Jr. A concurrent audit of high digoxin plasma levels. Clin Pharmacol Ther 1994;55:353–358.

Decreases in renal function are particularly likely to be unrecognized in older patients whose creatinine clearance declines as a consequence of aging rather than overt kidney disease. It is for this reason that the Joint Commission on Accreditation of Healthcare Organization has placed the estimation or measurement of creatinine clearance in patients of 65 years of age or older at the top of its list of indicators for monitoring the quality of medication use [50]. Fortunately, computerized laboratory reporting systems have been programmed to automatically report MDRD or CKD-EPI estimates of GFR, a task that was relatively easy to accomplish because these calculations can be performed without access to patient weight. This undoubtedly is an important advance in that it should increase prescriber awareness of a patient's renal functional status.

Although the developers of the MDRD equation advocated its further use in calculating drug dosage [36], there is a substantial existing body of published dosing guidelines that are based on the Cockcroft-Gault equation. In the final

analysis, it may not matter in most cases which equation is used as the basis for adjusting oral doses of many drugs as the accuracy of either equation in estimating renal function generally exceeds the level of adjustment permitted by available oral formulations, or even the accuracy with which tablets can be split.

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Bruton LL, Hilal-Dandan R, Knollman B, editors. Goodman & Gilman's The pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill; 2018.

*This is the standard reference textbook of pharmacology. It contains good introductory presentations of the general principles of pharmacokinetics, pharmacodynamics and therapeutics. Appendix II contains a useful tabulation of the pharmacokinetic properties of many commonly-used drugs.*

Carruthers SG, Hoffman BB, Melmon KL, Nierenberg DW, editors. Melmon and Morrelli's Clinical pharmacology. 4th ed. New York: McGraw-Hill; 2000.

*This is the classic textbook of clinical pharmacology with introductory chapters devoted to general principles and subsequent chapters covering different therapeutic areas. A final section is devoted to core topics in clinical pharmacology.*

Waldman SA, Terzic A, editors. Pharmacology and therapeutics: principles to practice. Philadelphia: Saunders-Elsevier; 2009.

*This is an introductory textbook that is divided into initial chapters that present pharmacologic principles and later chapter that are devoted to therapeutic applications in a wide number of clinical areas.*

### Pharmacokinetics

Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker; 1982.

*This is a standard reference in pharmacokinetics and is the one most often cited in the "methods section" of papers that are published in journals covering this area.*

Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics: concepts and applications. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.

*This is a well-written book that is very popular as an introductory text.*

### Drug metabolism

Pratt WB, Taylor P, editors. Principles of drug action: the basis of pharmacology. 3rd ed. New York: Churchill Livingstone; 1990.

*This book is devoted to basic principles of pharmacology and has good chapters on drug metabolism and pharmacogenetics.*

### Drug therapy in special populations

Evans WE, Schentag JJ, Jusko WJ, editors. Applied pharmacokinetics: principles of therapeutic drug monitoring. 3rd ed. Vancouver, WA: Applied Therapeutics; 1992.

*This book contains detailed information that is useful for individualizing dose regimens of a number of commonly-used drugs.*

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*This book describes how the basic principles of clinical pharmacology currently are being applied in the process of drug development.*

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The American Board of Clinical Pharmacology (ABCP). http://www.abcp.net/.

Chapter 2

# Clinical pharmacokinetics

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Pharmacokinetics is a valuable adjunct for prescribing and evaluating patient therapy with many drugs, particularly those that have a *narrow therapeutic index*, the ratio of toxic/therapeutic drug concentrations. In addition, pharmacokinetics plays an important role in the conduct of both basic and applied pharmacological research, and is an essential component of the drug development process. For most clinical and many other applications, pharmacokinetic analyses can be simplified by representing drug distribution within the body by a *single compartment* in which drug concentrations are uniform [1]. Clinical application of pharmacokinetics usually entails relatively simple calculations, carried out in the context of what has been termed *the target concentration strategy*. We shall begin by discussing this strategy.

## The target concentration strategy

The rationale for measuring concentrations of drugs in plasma, serum, or blood is that *concentration-response* relationships are often less variable than are *dose-response* relationships [2]. This is true because individual variation in the processes of drug absorption, distribution, and elimination affects dose-response relationships, but not the relationship between free (nonprotein-bound) drug concentration in plasma water and intensity of effect (Fig. 2.1). The rationale of therapeutic drug monitoring was first elucidated over 90 years ago when Otto Wuth recommended monitoring bromide levels in patients treated with this drug [3]. However, its more widespread clinical application has been possible only

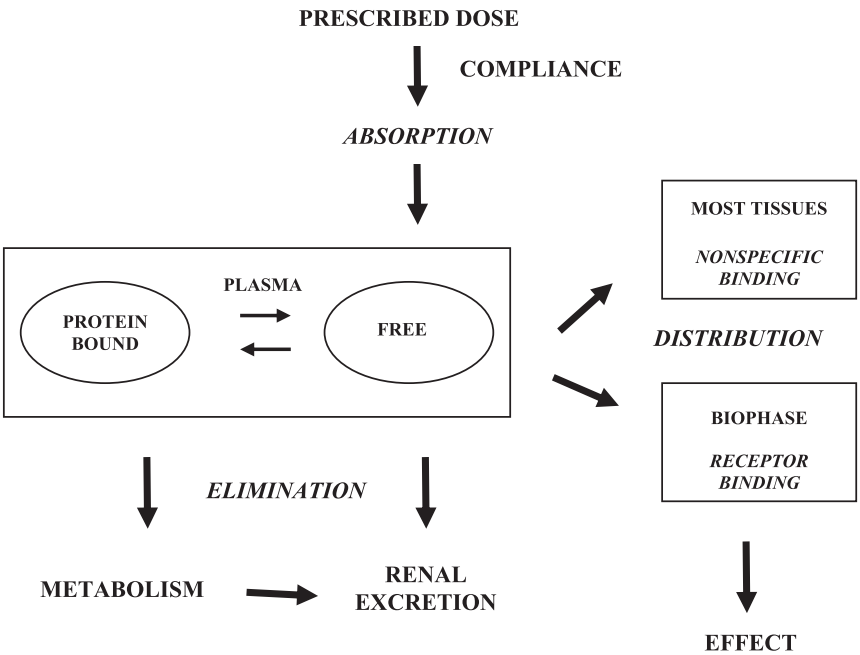


**FIG. 2.1** Diagram of factors that account for variability in observed effects when standard drug doses are prescribed. Some of this variability can be compensated for by using plasma concentration measurements to guide dose adjustments.

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because major advances have been made over the past 50 years in developing analytical methods capable of routinely measuring drug concentrations in patient serum, plasma, or blood samples, and because of increased understanding of basic pharmacokinetic principles [4, 5]

Because most adverse drug reactions are dose related, therapeutic drug monitoring has been advocated as a means of improving therapeutic efficacy and reducing drug toxicity [6]. Drug concentration monitoring is most useful when combined with pharmacokinetic/pharmacogenetic-based dose selection in an integrated management plan as outlined in Fig. 2.2. This approach to drug dosing is termed the *target concentration strategy*. Pharmacokinetics has been most useful in estimating initial drug doses, particularly for loading doses and for maintenance doses of drugs that are primarily eliminated by renal excretion, and in making subsequent dose adjustments based on plasma concentration measurements. Recent advances in pharmacogenetics and pharmacogenomics are finding increasing clinical utility in guiding drug selection and in providing dose estimates for drugs that are primarily eliminated by certain metabolic pathways.

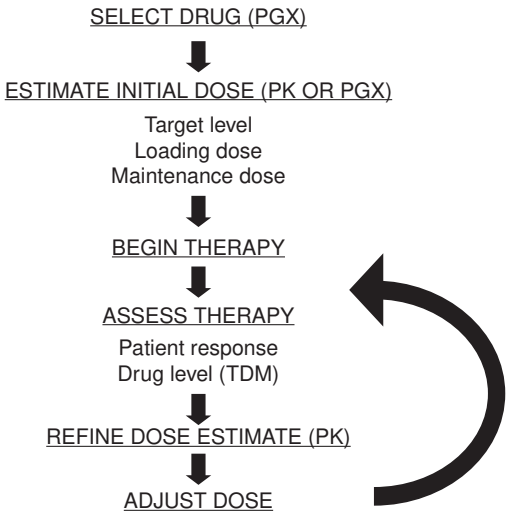



**FIG. 2.2** Target concentration strategy in which pharmacogenetics (PGX), pharmacokinetics (PK), and drug concentration measurements (TDM) are integral parts of a therapeutic approach that extends from initial drug selection and dose estimation to subsequent patient monitoring and dose adjustment. *(Reproduced with permission from Atkinson AJ Jr. Individualization of drug therapy: an historical perspective. Transl Clin Pharmacol 2014;22:52–54.)*

## Monitoring serum concentrations of digoxin as an example

Given the advanced state of modern chemical and immunochemical analytical methods, the greatest current challenge is the establishment of the range of drug concentrations in blood, plasma, or serum that correlate reliably with therapeutic efficacy or toxicity. This challenge is exemplified by the results shown in Fig. 2.3 that are taken from the attempt by Smith and Haber

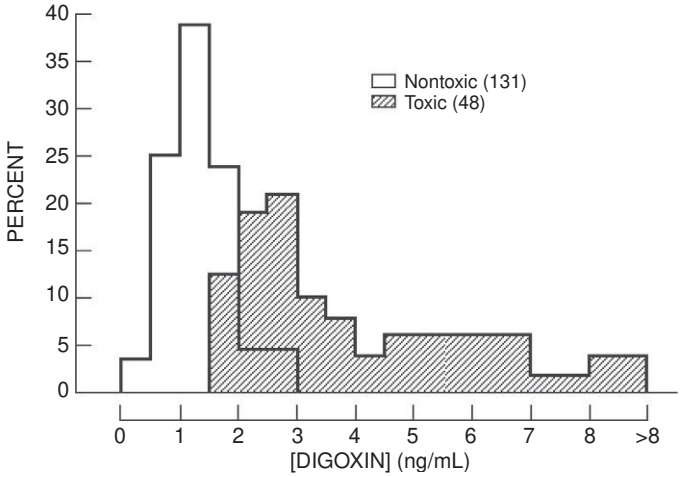



**FIG. 2.3** Superimposed frequency histograms in which serum digoxin concentrations are shown for 131 patients without digoxin toxicity and 48 patients with electrocardiographic evidence of digoxin toxicity. *(Reproduced with permission from Smith TW, Haber E. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. J Clin Invest 1970;49:2377–2386.)*

[7] to correlate serum digoxin levels with clinical manifestations of toxicity. It can be seen that no patient in this study with digoxin levels below 1.6 ng/mL was toxic and that all patients with digoxin levels above 3.0 ng/mL had evidence of digoxin intoxication. However, there was a large intermediate range between 1.6 and 3.0 ng/mL in which patients could be either nontoxic or toxic. Accordingly, laboratory reports of digoxin concentration have traditionally been accompanied by the following guidelines:

| | |
|---|---|
| Usual therapeutic range | 0.8–1.6 ng/mL |
| Possibly toxic levels | 1.6–3.0 ng/mL |
| Probably toxic levels | >3.0 ng/mL |

Additional clinical information is often necessary to interpret drug concentration measurements that are otherwise equivocal. Thus Smith and Haber found that all toxic patients with serum digoxin levels less than 2.0 ng/mL had coexisting coronary heart disease, a condition known to predispose the myocardium to the toxic effects of this drug. Conversely, 4 of the 10 nontoxic patients with levels above 2.0 ng/mL were being treated with antiarrhythmic drugs that might have suppressed electrocardiographic evidence of digoxin toxicity.

Although traditional digoxin serum level recommendations were based largely on studies in which digoxin toxicity or intermediate inotropic endpoints were measured, more recent studies have focused on correlating digoxin serum levels with the long-term clinical outcome of patients treated with this drug. The Digitalis Investigation Group trial, in which nearly 1000 patients were enrolled, has forced a major revaluation of digoxin dosing guidelines [8]. The investigators concluded that, compared to placebo, digoxin therapy decreased the need for hospitalization and reduced the incidence of death from congestive heart failure, but not overall mortality. Post hoc analysis of this data indicated that all-cause mortality was only lessened in men whose serum digoxin concentrations ranged from 0.5 to 0.9 ng/mL [9]. Higher levels were associated with progressively greater mortality and did not confer other clinical benefit. Based on the pharmacokinetic properties of digoxin, one would expect levels in this range to be obtained with a daily dose of 0.125 mg. However, most patients with serum digoxin levels in this range were presumed to be taking a 0.25-mg daily digoxin dose, a dose that in patients with normal renal function generally provides a steady-state plasma level of 1.4 ng/mL. In addition, the serum digoxin levels were only measured in a subset of the patients at a single time point, whereas outcomes were followed for a duration of 28–58 months [10].

As a result of subsequent observational studies and meta-analyses, a revised therapeutic range of 0.5–0.9 ng/mL has been recommended with a 56% increase in mortality risk being observed with levels $\geq$1.2 ng/mL [11, 12]. The strongest support for using digoxin is to control rapid heart rate in patients with atrial fibrillation whose blood pressure is only marginally adequate [12]. Digoxin is also recommended for patients with congestive heart failure and reduced cardiac ejection fraction as it has been shown to reduce mortality, morbidity, and hospitalization frequency. However, it has been estimated that only 20% of patients hospitalized for congestive heart failure in recent years were receiving digoxin therapy, whereas in the 1990s more than two-thirds of heart failure patients entering clinical trials were being treated with this drug [13]. In part, this decrease reflects the advent of more effective diuretics and other drugs that unload the left ventricle [12]. However, this may also reflect the fact that appropriate monitoring of digoxin plasma levels and knowledge of pharmacokinetics required to use digoxin safely and effectively is regarded as too much of an inconvenience by most clinicians. So some cardiologists have advocated creating a cadre of dedicated medical heart failure specialists who would have the requisite expertise in these areas [13].

## General indications for drug concentration monitoring

Unfortunately, controlled studies documenting the clinical benefit of drug concentration monitoring are limited. In addition, one could not justify concentration monitoring for all prescribed drugs even if this technical challenge could be met. Thus drug concentration monitoring is most helpful for drugs that have a narrow therapeutic index and that have no clinically observable effects that can be easily monitored to guide dose adjustment. Generally accepted indications for measuring drug concentrations are as follows:

1. To evaluate concentration-related toxicity
   - Unexpectedly slow drug elimination
   - Accidental or purposeful overdose
   - Surreptitious drug taking
   - Dispensing errors

2. To evaluate lack of therapeutic efficacy
   - Patient noncompliance with prescribed therapy
   - Poor drug absorption
   - Unexpectedly rapid drug elimination
3. To ensure that the dose regimen is likely to provide effective prophylaxis.
4. To use pharmacokinetic principles to guide dose adjustment.

Unfortunately, dose-related adverse reactions still occur frequently with digoxin, phenytoin, and many other drugs for which drug concentration measurements are routinely available. The persistence in contemporary practice of these adverse reactions most likely reflects inadequate understanding of basic pharmacokinetic principles. This is illustrated by the following case history [4]:

> *A 39-year-old man with mitral stenosis was hospitalized for mitral valve replacement. He had a history of chronic renal failure resulting from interstitial nephritis and was maintained on hemodialysis. His mitral valve was replaced with a prosthesis and digoxin therapy was initiated postoperatively in a dose of 0.25 mg/day. Two weeks later, he was noted to be unusually restless in the evening. The following day, he died shortly after he received his morning digoxin dose. Blood was obtained during an unsuccessful resuscitation attempt, and the measured plasma digoxin concentration was 6.9 ng/mL.*

Later in this chapter we will demonstrate that the ostensibly surprising delayed onset of this fatal adverse event was pharmacokinetically consistent with this initial therapeutic decision.

## Concepts underlying clinical pharmacokinetics

Pharmacokinetics provides a scientific basis for dose selection, and the process of dose regimen design can be used to illustrate with a single-compartment model the basic concepts of *apparent distribution volume* ($V_d$), *elimination half-life* ($t_{1/2}$), and *elimination clearance* ($CL_E$). A schematic diagram of this model is shown in Fig. 2.4 along with the two primary pharmacokinetic parameters of distribution volume and elimination clearance that characterize it.

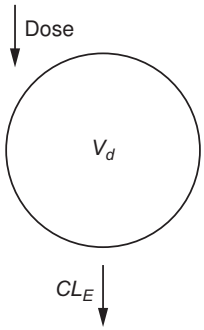



**FIG. 2.4** Diagram of a single-compartment model in which the primary kinetic parameters are the apparent distribution volume of the compartment ($V_d$) and the elimination clearance ($CL_E$).

### Initiation of drug therapy (concept of apparent distribution volume)

Sometimes drug treatment is begun with a loading dose to produce a rapid therapeutic response. Thus a patient with atrial fibrillation might be given a 0.375 mg intravenous loading dose of digoxin as initial therapy to control ventricular rate. The expected plasma concentrations of digoxin are shown in Fig. 2.5. Inspection of this figure indicates that the log plasma-concentration-vs.-time curve eventually becomes a straight line. This part of the curve is termed the *elimination phase*. By extrapolating this elimination-phase line back to time zero, we can estimate the plasma concentration ($C_0$) that would have occurred if the loading dose were instantaneously distributed throughout the body. Measured plasma digoxin concentrations lie above the back-extrapolated line for several hours because distribution equilibrium actually is reached only slowly after a digoxin dose is administered. This part of the plasma-level-vs.-time curve is termed the *distribution phase*. This phase reflects the underlying *multicompartmental* nature of digoxin distribution from the intravascular space to peripheral tissues.

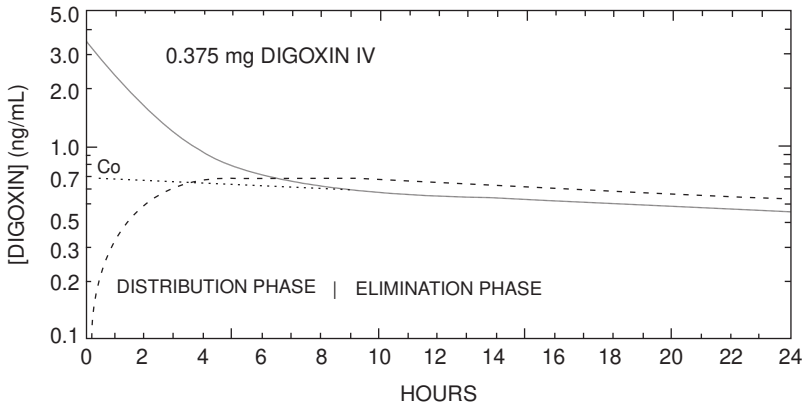



**FIG. 2.5** Simulation of plasma (*solid line*) and tissue (*heavy dashed line*) digoxin concentrations after intravenous administration of a 0.375-mg loading dose to a 70-kg patient with normal renal function. A value of 0.7 ng/mL for $C_0$ is estimated by back-extrapolating (*dotted line*) the elimination-phase plasma concentrations. A value of 536 L for $V_d$ is calculated by dividing the administered drug dose by this estimate of $C_0$, as shown in the text. Tissue concentrations are referenced to the apparent distribution volume of a peripheral compartment that represents tissue distribution. *(Simulation based on pharmacokinetic model of Reuning RH, et al. Role of pharmacokinetics in drug dosage adjustment. I. Pharmacologic effect kinetics and apparent volume of distribution of digoxin. J Clin Pharmacol New Drugs 1973;13:127–141.)*

As shown in Fig. 2.5, the back-extrapolated estimate of 0.7 ng/mL for $C_0$ can be used to calculate the apparent volume ($V_{d(extrap)}$) of a hypothetical single compartment into which digoxin distribution occurs:

$$V_{d\,(extrap)} = \text{Loading dose}/C_0 \tag{2.1}$$

In this case,

$$V_{d(extrap)} = 0.375\,\text{mg}/0.7\,\text{ng/mL}$$
$$V_{d(extrap)} = 536\,\text{L}$$

This distribution volume is much larger than anatomically possible. However, this discrepancy occurs because digoxin has a much higher binding affinity for tissues than for plasma, and the *apparent* distribution volume is the volume of *plasma* that would be required to provide the observed dilution of the loading dose. Despite this anomaly, the concept of distribution volume is clinically useful because it defines the relationship between plasma concentration and the total amount of drug in the body. Further complexity arises from the fact that $V_{d(extrap)}$ is only one of three different distribution volume estimates that we will encounter. Because the distribution process is neglected in calculating this volume, it represents an overestimate of the sum of the volumes of the individual compartments involved in drug distribution.

The time course of the myocardial effects of digoxin parallels its concentration profile in peripheral tissues (Fig. 2.5), so there is a delay between the attainment of peak plasma digoxin concentrations and the observation of maximum inotropic and chronotropic effects. The range of therapeutic and toxic digoxin concentrations has been estimated from observations made during the elimination phase, so blood should not be sampled for digoxin assay until distribution equilibrium is nearly complete. In clinical practice, this means waiting for at least 6 h after a digoxin dose has been administered. In an audit of patients with measured digoxin levels of 3.0 ng/mL or more, it was found that nearly one-third of these levels were not associated with toxicity but reflected procedural error, in that blood was sampled less than 6 h after digoxin administration [14].

For other drugs, such as thiopental [15] or lidocaine [16], the locus of pharmacologic action (termed the *biophase* in classical pharmacology) is in rapid kinetic equilibrium with the intravascular space. The distribution phase of these drugs represents their somewhat slower distribution from intravascular space to pharmacologically inert tissues, such as skeletal muscle. In this way, the pharmacological effects of single doses of these drugs may be rapidly terminated by the process of distribution even though only a small fraction of the dose has been eliminated from the body. Plasma levels of these drugs reflect therapeutic and toxic effects throughout the dosing interval and blood can be obtained for drug assay without waiting for the elimination phase to be reached.

## Continuation of drug therapy (concepts of elimination half-life and clearance)

After starting therapy with a loading dose, maintenance of a sustained therapeutic effect usually necessitates administering additional drug doses to replace the amount of drug that has been excreted or metabolized. Fortunately, the elimination of most drugs is a *first-order* process in that the rate of drug elimination is directly proportional to the drug concentration in plasma.

## *Elimination half-life*

It is convenient to characterize the elimination of drugs with first-order elimination rates by their *elimination half-life*, the time required for half an administered drug dose to be eliminated. If drug elimination half-life can be estimated for a patient, it is often practical to continue therapy by administering half the loading dose at an interval of one elimination half-life. In this way, drug elimination can be balanced by drug administration and a steady state maintained from the onset of therapy. Because digoxin has an elimination half-life of 1.6 days in patients with normal renal function, it is inconvenient to administer digoxin at this interval. When renal function is normal, it is customary to maintain digoxin therapy by administering daily doses equal to one-third of the required loading dose.

Another consequence of first-order elimination kinetics is that a constant fraction of total body drug stores will be eliminated in a given time interval. Thus if there is no urgency in establishing a therapeutic effect, the loading dose of digoxin can be omitted and 90% of the eventual steady-state drug concentration will be reached after administering daily doses for a period of time equal to 3.3 elimination half-lives. This is referred to as the *Plateau Principle*. The classical derivation of this principle is provided later in this chapter, but for now brute force will suffice to illustrate this important concept. Suppose that we elect to omit the 0.375 mg digoxin loading dose shown in Fig. 2.5 and simply begin therapy with a 0.125 mg/day maintenance dose. If the patient has normal renal function, we can anticipate that one-third of the total amount of digoxin present in the body will be eliminated each day and that two-thirds will remain when the next daily dose is administered. As shown in Scheme 2.1, the patient will have digoxin body stores of 0.326 mg just after the fifth daily dose (3.3 × 1.6 day half-life = 5.3 days), and this is 87% of the total body stores that would have been provided by a 0.375 mg loading dose.

| | |
|---|---|
| .125 x 2/3 = .083 | Dose #1 |
| +.125 | Dose #2 |
| .208 x 2/3 = .139 | |
| +.125 | Dose #3 |
| .264 x 2/3 = .176 | |
| +.125 | Dose #4 |
| .301 x 2/3 = .201 | |
| +.125 | Dose #5 |
| .326 x 2/3 = .217 | |
| +.125 | Dose #6 |
| .342 x 2/3 = .228 | |
| +.125 | Dose #7 |
| .353 | |

**SCHEME 2.1** "Brute force" demonstration of drug cumulation when maintenance doses are administered repeatedly.

The solid line in Fig. 2.6 shows ideal matching of digoxin loading and maintenance doses. When the digoxin loading dose (called *digitalizing dose* in clinical practice) is omitted, or when the loading dose and maintenance dose are not matched appropriately, steady-state levels are reached only asymptotically. However, the most important concept that this figure

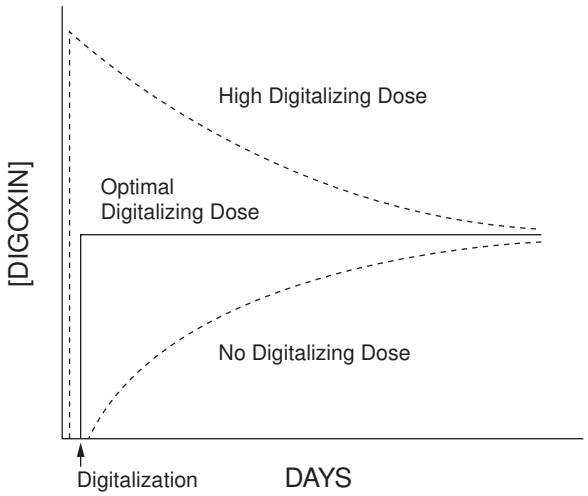



**FIG. 2.6** Expected digoxin plasma concentrations after administering perfectly matched loading and maintenance doses (*solid line*), no initial loading dose (*bottom dashed line*), or a high loading dose that is large in relation to the subsequent maintenance dose (*upper dashed line*).

demonstrates is that *the eventual steady state level is determined only by the maintenance dose*, regardless of the size of the loading dose. Selection of an inappropriately high digitalizing dose only exposes patients to an interval of added risk without achieving a permanent increase in the extent of digitalization. Conversely, when a high digitalizing dose is required to help control ventricular rate in patients with atrial fibrillation or flutter, a higher than usual maintenance dose also will be required.

### *Elimination clearance*

Just as creatinine clearance is used to quantitate the renal excretion of creatinine, the removal of drugs eliminated by first-order kinetics can be defined by an *elimination clearance* ($CL_E$). In fact, elimination clearance is the primary pharmacokinetic parameter that characterizes the removal of drugs that are eliminated by first-order kinetics. When drug administration is by intravenous infusion, the eventual steady-state concentration of drug in the body ($C_{ss}$) can be calculated from the following equation (note the similarity to Eq. 1.2), where the drug infusion rate is given by $I$:

$$C_{ss} = I/CL_E \tag{2.2}$$

When intermittent oral or parenteral doses are administered at a dosing interval, $\tau$, the corresponding equation is:

$$\overline{C}_{ss} = \frac{Dose/\tau}{CL_E} \tag{2.3}$$

where $\overline{C}_{ss}$ is the mean concentration during the dosing interval. Under conditions of intermittent administration, there is a continuing periodicity in maximum ("peak") and minimum ('trough") drug levels so that only a quasi-steady state is reached. However, unless particular attention is directed to these peak and trough levels, no distinction generally is made in clinical pharmacokinetics between the true steady state that is reached when an intravenous infusion is administered continuously and the quasi-steady state that results from intermittent administration.

Because there is a directly proportionate relationship between administered drug dose and steady-state plasma level, Eqs. (2.2), (2.3) provide a straightforward guide to dose adjustment for drugs that are eliminated by first-order kinetics. Thus, to double the plasma level, the dose simply should be doubled. Conversely, to halve the plasma level, the dose should be halved. It is for this reason that Eqs. (2.2), (2.3) are the most clinically important pharmacokinetic equations. Note that, as is apparent from Fig. 2.6, these equations also stipulate that the steady-state level is determined only by the maintenance dose and elimination clearance. The loading dose does not appear in the equations and does not influence the eventual steady-state level.

In contrast to elimination clearance, elimination half-life ($t_{1/2}$) is not a primary pharmacokinetic parameter because it is determined by distribution volume as well as by elimination clearance:

$$t_{1/2} = \frac{0.693\, V_{d(area)}}{CL_E} \tag{2.4}$$

The value of $V_d$ in this equation is not $V_{d(extrap)}$ but represents a second estimate of distribution volume, referred to as $V_{d(area)}$ or $V_{d(\beta)}$ that generally is estimated from measured elimination half-life and clearance. The similarity of these two estimates of distribution volume reflects the extent to which drug distribution is accurately described by a single-compartment model, and obviously varies from drug to drug [17].

Fig. 2.7 illustrates how differences in distribution volume affect elimination half-life and peak and trough plasma concentrations when the same drug dose is given to two patients with the same elimination clearance. If these two hypothetical patients were given the same nightly dose of a sedative-hypnotic drug for insomnia, $\overline{C}_{ss}$ would be the same for both. However, the patient with the larger distribution volume might not obtain sufficiently high plasma levels to fall asleep in the evening, and might have a plasma level that was high enough to cause drowsiness in the morning.

## Drugs not eliminated by first-order kinetics

Unfortunately, the elimination of some drugs does not follow first-order kinetics. For example, the primary pathway of phenytoin elimination entails initial metabolism to form 5-(parahydroxyphenyl)-5-phenylhydantoin (*p*-HPPH), followed by glucuronide conjugation (Fig. 2.8). The metabolism of this drug is not first order but follows *Michaelis-Menten* kinetics because the microsomal enzyme system that forms *p*-HPPH is partially saturated at phenytoin concentrations of 10–20 µg/mL that are therapeutically effective. The result is that phenytoin plasma concentrations rise hyperbolically as dosage is increased (Fig. 2.9).

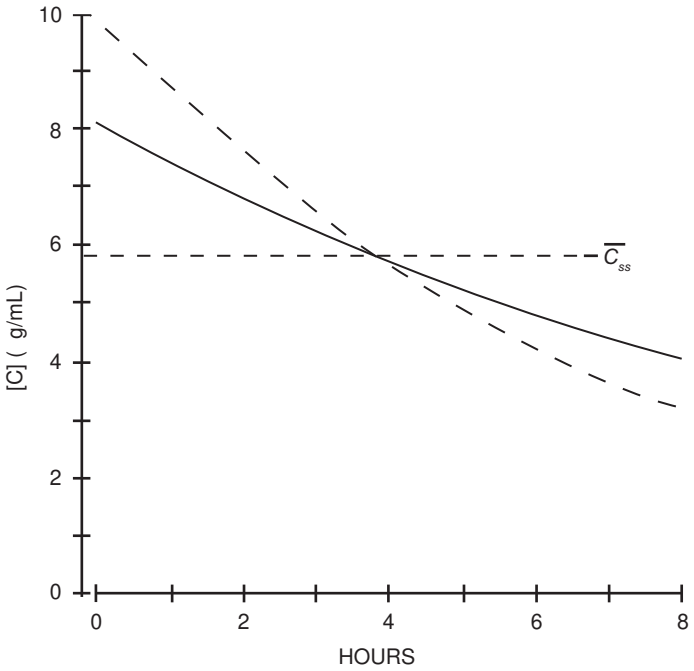



**FIG. 2.7** Plasma concentrations after repeated administration of the same drug dose to two hypothetical patients whose elimination clearance is the same but whose distribution volumes differ. The patients have the same $\overline{C}_{ss}$ but the larger distribution volume results in lower peak and higher trough plasma levels (*solid line*) than when the distribution volume is smaller (*dashed line*).

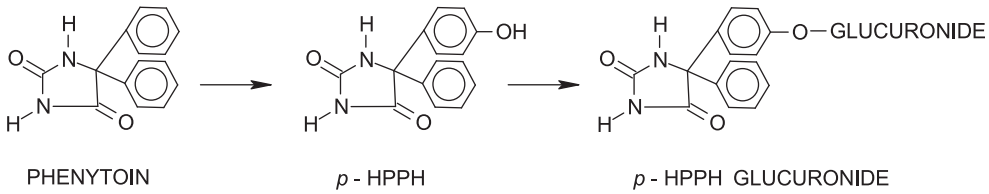



**FIG. 2.8** Metabolism of phenytoin to form *p*-HPPH and *p*-HPPH glucuronide. The first step in this enzymatic reaction sequence is rate limiting and follows Michaelis-Menten kinetics, showing progressive saturation as plasma concentrations rise within the range that is required for anticonvulsant therapy to be effective.

For drugs eliminated by first-order kinetics, the relationship between dosing rate and steady-state plasma concentration is given by rearranging Eq. (2.3) as follows:

$$Dose/\tau = CL_E \cdot \overline{C}_{ss} \tag{2.5}$$

The corresponding equation for phenytoin is:

$$Dose/\tau = \frac{V_{\max}}{K_m + \overline{C}_{ss}} \cdot \overline{C}_{ss} \tag{2.6}$$

where $V_{\max}$ is the maximum rate of drug metabolism and $K_m$ is the apparent Michaelis-Menten constant for the enzymatic metabolism of phenytoin.

Although phenytoin plasma concentrations show substantial interindividual variation when standard doses are administered, they average 10 µg/mL when adults are treated with a 300-mg total daily dose, but rise to an average of 20 µg/mL when the dose is increased to 400 mg [18]. This nonproportional relationship between phenytoin dose and plasma concentration complicates patient management and undoubtedly contributes to the many adverse reactions that are seen in patients treated with this drug. Although several pharmacokinetic approaches have been developed for estimating dose adjustments, it is safest to change phenytoin doses in small increments and to rely on careful monitoring of clinical response and phenytoin plasma levels. The pharmacokinetics of phenytoin were studied in both patients shown in Fig. 2.9 after they became toxic when treated with the 300 mg/day dose that is routinely prescribed as initial therapy for adults [19]. The figure demonstrates that the entire therapeutic range is traversed in these patients by a dose increment of less than 100 mg/day. This presents an obvious therapeutic challenge because the phenytoin oral formulation that is most commonly prescribed for adults is a 100 mg capsule.

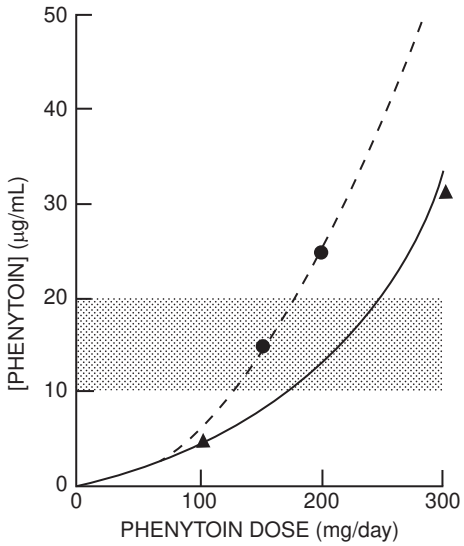



**FIG. 2.9** The *lines* show the relationship between dose and steady-state plasma phenytoin concentrations predicted for two patients who became toxic after initial treatment with 300 mg/day. Measured steady-state plasma concentrations are shown by the *solid circles* and *triangles*. The *shaded area* shows the usual range of therapeutically effective phenytoin plasma concentrations. *(Reproduced with permission from Atkinson AJ Jr. Individualization of anticonvulsant therapy. Med Clin North Am 1974;58:1037–1049.)*

Even though many drugs in common clinical use are eliminated by drug-metabolizing enzymes, relatively few of them have Michaelis-Menten elimination kinetics (e.g., aspirin and ethyl alcohol). The reason for this is that $K_m$ for most drugs is much greater than $\overline{C}_{ss}$. Hence for most drugs, $\overline{C}_{ss}$ can be ignored in the denominator of Eq. (2.6) and this equation reduces to:

$$Dose/\tau = \frac{V_{\max}}{K_m} \cdot \overline{C}_{ss}$$

where the ratio $V_{\max}/K_m$ is equivalent to $CL_E$ in Eq. (2.5). Thus, even for most metabolized drugs, a change in dose will change steady-state plasma concentrations proportionately, a property that is termed *dose proportionality*.

## Mathematical basis of clinical pharmacokinetics

In the following sections we will review the mathematical basis of some of the important relationships that are used when pharmacokinetic principles are applied to the care of patients. The reader also is referred to other literature sources that may be helpful [1, 17, 20].

### First-order elimination kinetics

For most drugs, the amount of drug eliminated from the body during any time interval is proportional to the total amount of drug present in the body. In pharmacokinetic terms, this is called *first-order* elimination and is described by the equation:

$$dX/dt = -kX \tag{2.7}$$

where $X$ is the total amount of drug present in the body at any time ($t$) and $k$ is the elimination rate constant for the drug. This equation can be solved by separating variables and direct integration to calculate the amount of drug remaining in the body at any time after an initial dose:

Separating variables:

$$dX/X = -kdt$$

Integrating from zero time to time $= t$:

$$\int_{X_0}^{X} dX/X = -k \int_{0}^{t} dt$$

$$\ln X \Big|_{X_0}^{X} = -kt \Big|_{0}^{t}$$

$$\ln \frac{X}{X_0} = -kt \tag{2.8}$$

$$X = X_0\, e^{-kt} \tag{2.9}$$

Although these equations deal with total amounts of drug in the body, the equation $C = X/V_d$ provides a general relationship between $X$ and drug concentration ($C$) at any time after the drug dose is administered. Therefore $C$ can be substituted for $X$ in Eqs. (2.7), (2.8) as follows:

$$\ln \frac{C}{C_0} = -kt \tag{2.10}$$

$$C = C_0\, e^{-kt} \tag{2.11}$$

Eq. (2.10) is particularly useful because it can be rearranged in the form of the equation for a straight line ($y = mx + b$) to give:

$$\ln C = -kt + \ln C_0 \tag{2.12}$$

Now when data are obtained after administration of a single drug dose and $C$ is plotted on base 10 semilogarithmic graph paper, a straight line is obtained with 0.434 times the slope equal to $k$ ($\log x/\ln x = 0.434$) and an intercept on the ordinate of $C_0$. In practice $C_0$ is never measured directly because some time is needed for the injected drug to distribute throughout body fluids. However, $C_0$ can be estimated by back-extrapolating the straight line given by Eq. (2.12) (Fig. 2.5).

## Concept of elimination half-life

If the rate of drug distribution is rapid compared with the rate of drug elimination, the terminal exponential phase of a semilogarithmic plot of drug concentrations vs. time can be used to estimate the elimination half-life of a drug, as shown in Fig. 2.10. Because Eq. (2.10) can be used to estimate $k$ from any two concentrations that are separated by an interval $t$, it can be seen from this equation that when $C_2 = ½\, C_1$:

$$\ln 1/2 = -kt_{1/2}$$

$$\ln 2 = kt_{1/2}$$

So:

$$t_{1/2} = \frac{0.693}{k}, \text{ and } k = \frac{0.693}{t_{1/2}} \tag{2.13}$$

For digoxin, $t_{1/2}$ is usually 1.6 days for patients with normal renal function and $k = 0.43\ \text{day}^{-1}$ ($0.693/1.6 = 0.43$). As a practical point, it is easier to estimate $t_{1/2}$ from a graph such as Fig. 2.10 and to then calculate $k$ from Eq. (2.13), than to estimate $k$ directly from the slope of the elimination-phase line.

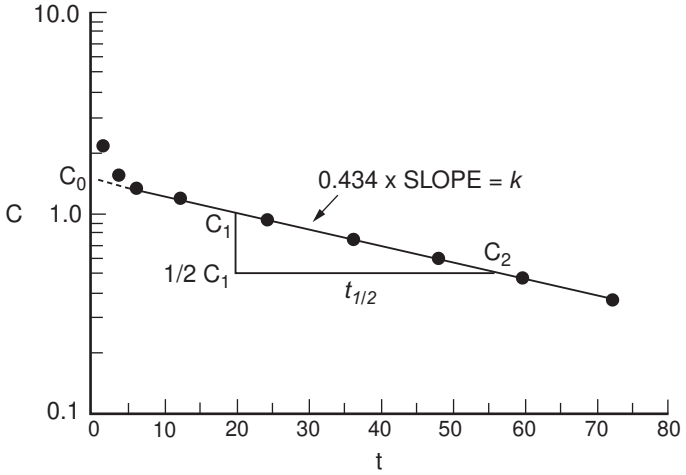



**FIG. 2.10** Plot of drug concentrations vs. time on semilogarithmic coordinates. Back extrapolation (*dashed line*) of the elimination phase slope (*solid line*) provides an estimate of $C_0$. The elimination half-life ($t_{1/2}$) can be estimated from the time required for concentrations to fall from some point on the elimination-phase line ($C_1$) to $C_2 = ½C_1$, as shown by the *dotted lines*.

## Relationship of *k* to elimination clearance

In Chapter 1, we pointed out that the creatinine clearance equation:

$$CL_{CR} = \frac{UV}{P}$$

could be rewritten in the form of the following first-order differential equation:

$$dX/dt = -CL_{CR} \cdot P$$

If this equation is generalized by substituting $CL_E$ for $CL_{CR}$, it can be seen from Eq. (2.7) that, since $P = X/V_d$:

$$k = \frac{CL_E}{V_d} \tag{2.14}$$

Eq. (2.4), that was previously cited, is derived by substituting $Cl_E/V_d$ for $k$ in Eq. (2.13). Although $V_d$ and $Cl_E$ are the two primary parameters of the single-compartment model, confusion arises because $k$ is initially calculated from experimental data. However, $k$ is influenced by changes in distribution volume as well as clearance and does not reflect just changes in drug elimination.

## Cumulation factor

In the steady-state condition, the rate of drug administration is exactly balanced by the rate of drug elimination. Gaddum [21] first demonstrated that the maximum and minimum drug levels that are expected at steady state (quasi-steady state) can be calculated for drugs that are eliminated by first-order kinetics. Assume that just maintenance doses of a drug are administered without a loading dose (Fig. 2.6, lowest curve). Starting with Eq. (2.9):

$$X = X_0\, e^{-kt}$$

where $X_0$ is the maintenance dose and $X$ is the amount of drug remaining in the body at time $t$. If $\tau$ is the dosing interval, let:

$$p = e^{-k\tau}$$

Therefore, just before the second dose:

$$X_{1(\min)} = X_0 p$$

Just after the second dose:

$$X_{2(\max)} = X_0 + X_0 p = X_0(1+p)$$

Similarly, after the third dose

$$X_{3(\max)} = X_0 + X_0 p + X_0 p^2 = X_0\left(1 + p + p^2\right)$$

and after the $n$th dose:

$$X_{n(\max)} = X_0\left(1 + p + \ldots\ldots p^{n-1}\right)$$

or,

$$X_{n(\max)} = X_0 \frac{(1-p^n)}{(1-p)}$$

Since $p < 1$, as $n \to \infty$, $p^n \to 0$. Therefore

$$X_{\infty(\max)} = X_0/(1-p)$$

or, substituting for $p$

$$X_{\infty(\max)} = \frac{X_0}{(1-e^{-k\tau})}$$

The value of $X_\infty$ is the maximum *total body content* of the drug that is reached during a dosing interval at steady state. The maximum *concentration* is determined by dividing this value by $V_d$. The *minimum* value is given by multiplying either of these maximum values by $e^{-k\tau}$.

Note that the respective maximum and minimum drug concentrations after the first dose are:

$$\text{Maximum}: \quad C_0$$

$$\text{Minimum}: \quad C_0\, e^{-k\tau}$$

The expected steady-state counterparts of these initial concentration values can be estimated by multiplying them by the *cumulation factor* (CF):

$$CF = \frac{1}{1 - e^{-kt}} \tag{2.15}$$

## The plateau principle

Although the time required to reach steady state cannot be calculated explicitly, the time required to reach *any specified fraction (f) of the eventual steady state* can be estimated. In clinical practice, $f = 0.90$ is usually a reasonable approximation of the eventual steady state. For dosing regimens in which drugs are administered as a constant infusion, the pharmacokinetic counterpart of Eq. (1.1) in which both creatinine synthesis and elimination are considered is:

$$dX/dt = I - kX$$

Separation of variables and integration of this equation yields:

$$X = \frac{I}{k}\left(1 - e^{-kt}\right)$$

Because infinite time is required for $X$ to reach its steady state, $X_{ss} = I/k$ and

$$f_{.90} = \frac{X_{.90}}{X_{ss}} = \left(1 - e^{-kt_{.90}}\right)$$

By definition $X_{.90}/Xss = 0.90$, also $k = \ln 2/t_{1/2}$ (Eq. 2.13), so:

$$t_{.90} = 3.3 t_{1/2} \tag{2.16}$$

For dosing regimens in which drugs are administered at a constant dosing interval, Gaddum [21] showed that the number of drug doses ($n$) required to reach any fraction of the eventual steady-state amount of drug in the body can be calculated as follows:

$$f = \frac{X_n}{X_\infty} = \frac{X_0(1 - p^n)^0}{(1 - p)} \cdot \frac{(1 - p)}{X_0} = 1 - p^n \tag{2.17}$$

Once again, taking $f = 0.90$ as a reasonable approximation of eventual steady state, substituting this value into Eq. (2.17), and solving for $n$:

$$0.90 = 1 - e^{-nk\tau}$$

$$e^{-nk\tau} = 0.1$$

$$n = -\frac{\ln 0.1}{k\tau}$$

$$n = \frac{2.3}{k\tau}$$

Again from Eq. (2.13), $k = \ln 2/t_{1/2,}$ so the number of doses needed to reach 90% of steady state is:

$$n = 3.3\, t_{1/2}/\tau \tag{2.18}$$

and the corresponding time is:

$$n\tau = 3.3\, t_{1/2} \tag{2.19}$$

Not only are drug accumulation greater and steady-state drug levels higher in patients with a prolonged elimination half-life, but an important consequence of Eq. (2.18) is that it also takes these patients longer to reach steady state. For example, the elimination half-life of digoxin in patients with normal renal function is 1.6 days, so that 90% of the expected steady state is reached in 5 days when daily doses of this drug are administered. However, the elimination half-life of digoxin is approximately 4.3 days in functionally anephric patients, such as the one described in the illustrative case history, and 14 days would be required to reach 90% of the expected steady state. This explains why this patient's adverse reaction occurred 2 weeks after starting digoxin therapy.

## Application of Laplace transforms to pharmacokinetics

The Laplace transformation method of solving differential equations falls into the area of *operational calculus* that we will use in deriving several pharmacokinetic equations. Operational calculus was invented by an English engineer, Sir Oliver Heaviside (1850–1925), who had an intuitive grasp of mathematics [22]. Although Laplace provided the theoretical basis for the method, some of Sir Oliver's intuitive contributions remain (e.g., the Heaviside Expansion Theorem utilized in Chapter 3). The idea of operational mathematics and Laplace transforms perhaps is best understood by comparison with the use of logarithms to perform arithmetic operations. This comparison is diagrammed in the flow charts shown in Scheme 2.2.

Just as there are tables of logarithms, there are tables to aid the mathematical process of obtaining Laplace transforms ($\mathcal{L}$) and inverse Laplace transforms ($\mathcal{L}^{-1}$). Laplace transforms can also be calculated directly from the integral:

$$\mathcal{L}[F(t)] = f(s) = \int_0^\infty F(t)e^{-st}dt$$

We can illustrate the application of Laplace transforms by using them to solve the simple differential equation that we have used to describe the single-compartment model (Eq. 2.7) Starting with this equation:

$$dX/dt = -kX$$

we can use a table of Laplace transform operations (Appendix I) to take Laplace transforms of each side of this equation to create the *subsidiary equation*:

For $X$ on the right side of the equation:

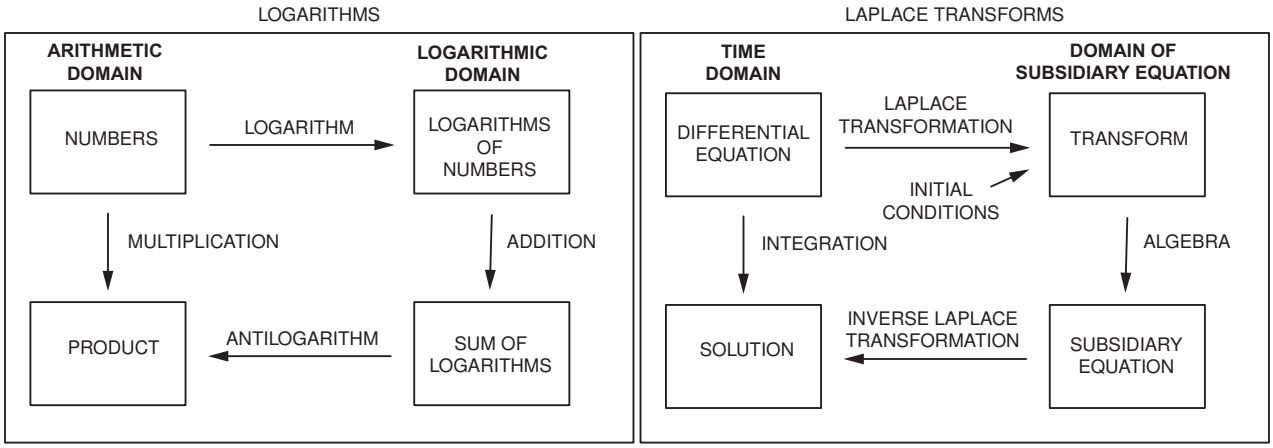
$$\mathcal{L}F(t) = f(s)$$

For $dX/dt$ on the left side of the equation:

$$\mathcal{L}F'(t) = sf(s) - F(0)$$

Since $F(0)$ represents the *initial condition*, in this case the amount of drug in the model compartment at time zero, $X_0$, the subsidiary equation can be written:

$$sf(s) - X_0 = -kf(s)$$




**SCHEME 2.2** Analogy between use of logarithms and Laplace transforms.

This can be rearranged to give:

$$(s+k)f(s)=X_0$$

Or,

$$f(s)=\frac{X_0}{s+k}$$

A table of *inverse Laplace transforms* indicates:

$$\mathcal{L}^{-1}\frac{1}{s-a}=e^{at}$$

Therefore the solution to the differential equation is:

$$X=X_0\,e^{-kt}$$

and this is the same result that we obtained as Eq. (2.9).

In other words, the Laplace operation transforms the differential equation from the time domain to another functional domain represented by the subsidiary equation. After algebraic simplification of this subsidiary equation, the inverse transformation is used to return the solved equation to the time domain. We have selected a simple example to illustrate the use of Laplace transform methods. A more advanced application is given in the next chapter in which equations are derived for a two-compartment model. It will be shown subsequently that Laplace transform methods also are helpful in pharmacokinetics when convolution/deconvolution methods are used to characterize drug absorption processes.

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## Study problems

Select the *one* lettered answer or statement completion that is BEST. It may be helpful to carry out dimensional analysis by including units in your calculations. Answers are provided in Appendix II.

1. A 35-year-old woman is being treated with gentamicin for a urinary tract infection. The gentamicin plasma level is 4 μg/mL shortly after initial intravenous administration of an 80 mg dose of this drug. The distribution volume of gentamicin is:
   A. 5 L
   B. 8 L
   C. 10 L
   D. 16 L
   E. 20 L
2. A 58-year-old man is hospitalized in a cardiac intensive care unit following an acute myocardial infarction. He has had recurrent episodes of ventricular tachycardia that have not responded to lidocaine and an intravenous infusion of procainamide will now be administered. The patient weighs 80 kg and expected values for his procainamide distribution volume and elimination half-life are 2.0 L/kg and 3 h, respectively.
   What infusion rate will provide a steady-state plasma procainamide level of 4.0 μg/mL?
   A. 2.5 mg/min
   B. 5.0 mg/min
   C. 7.5 mg/min
   D. 10.0 mg/min
   E. 12.5 mg/min
3. A patient with peritonitis is treated with gentamicin 80 mg every 8 h. Plasma gentamicin levels are measured during the first dosing interval. The gentamicin plasma level is 10 μg/mL at its peak after initial intravenous administration of this drug, and is 5 μg/mL when measured 5 h later.
   The cumulation factor can be used to predict an expected steady-state peak level of:
   A. 10 μg/mL
   B. 12 μg/mL
   C. 15 μg/mL
   D. 18 μg/mL
   E. 20 μg/mL
4. A 20-year-old man is hospitalized after an asthmatic attack precipitated by an upper respiratory infection but fails to respond in the emergency room to two subcutaneously injected doses of epinephrine. The patient has not been taking theophylline-containing medications for the past 6 weeks. He weighs 60 kg and you estimate that his apparent volume of theophylline distribution is 0.45 L/kg. Bronchodilator therapy includes a 5.6 mg/kg loading dose of aminophylline, infused intravenously over 20 min, followed by a maintenance infusion of 0.63 mg/kg per hour (0.50 mg/kg per hour of theophylline). Forty-eight hours later, the patient's respiratory status has improved. However, he has nausea and tachycardia, and his plasma theophylline level is 24 μg/mL.
   For how long do you expect to suspend theophylline administration in order to reach a level of 12 μg/mL before restarting the aminophylline infusion at a rate of 0.31 mg/kg per hour?
   A. 5 h
   B. 10 h
   C. 15 h
   D. 20 h
   E. 25 h
5. Digitoxin has an elimination half-life of approximately 7 days and its elimination is relatively unaffected by decreased renal function. For this latter reason, the decision is made to use this drug to control ventricular rate in a 60-year-old man with atrial fibrillation and a creatinine clearance of 25 mL/min.
   If no loading dose is administered and a maintenance dose of 0.1 mg/day is prescribed, how many days would be required for digitoxin levels to reach 90% of their expected steady-state value?
   A. 17 days
   B. 19 days
   C. 21 days
   D. 23 days
   E. 24 days
6. A 75-year-old man comes to your office with anorexia and nausea. Five years ago he was found to have congestive heart failure that initially responded to treatment with a loop diuretic, a β-blocker, and an angiotensin-converting enzyme inhibitor. Three years ago his exercise tolerance was found to have deteriorated and digoxin was added to

the regimen in a dose of 0.25 mg/day. This morning he omitted his digoxin dose because of these symptoms and your office electrocardiogram showed frequent bigeminal extrasystoles. On hospitalization, the patient's serum creatinine and digoxin plasma digoxin levels were 1.4 mg/dL and 2.4 ng/mL, respectively. Twenty-four hours later, the digoxin level is 1.9 ng/mL. At that time you decide that it would be advisable to let the digoxin level fall to 0.6 ng/mL, within the current therapeutic range of 0.5–0.9 ng/mL, before restarting a daily digoxin dose of 0.0625 mg.

For how many *more* days do you anticipate having to withhold digoxin before your target level of 0.6 ng/mL is reached?

A. 2 days
B. 3 days
C. 4 days
D. 5 days
E. 6 days

**7.** A 50-year-old man is being treated empirically with gentamicin and a cephalosporin for pneumonia. The therapeutic goal is to provide a maximum gentamicin level of *more than* 8 μg/mL 1 h after intravenous infusion and a minimum concentration, just before dose administration, of *less than* 1 μg/mL. His estimated plasma gentamicin clearance and elimination half-life are 100 mL/min and 2 h, respectively. Which of the following dosing regimens is appropriate?

A. 35 mg every 2 h
B. 70 mg every 4 h
C. 90 mg every 5 h
D. 110 mg every 6 h
E. 140 mg every 8 h

**8.** You start a 19-year-old man on phenytoin in a dose of 300 mg/day to control generalized (grand mal) seizures. Ten days later, he is brought to an emergency room following a seizure. His phenytoin level is found to be 5 μg/mL and the phenytoin dose is increased to 600 mg/day. Two weeks later, he returns to your office complaining of drowsiness and ataxia. At that time his phenytoin level is 30 μg/mL.

Assuming patient compliance with previous therapy, which of the following dose regimens should provide a phenytoin plasma level of 15 μg/mL (therapeutic range: 10–20 μg/mL)?

A. 350 mg/day
B. 400 mg/day
C. 450 mg/day
D. 500 mg/day
E. 550 mg/day

Chapter 3

# Compartmental analysis of drug distribution

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*All models are wrong but some are useful.*

George E.P. Box, 1979 [1]

*Drug distribution* can be defined as the postabsorptive transfer of drug from one location in the body to another. Absorption after various routes of drug administration is not considered part of the distribution process and is dealt with separately. In most cases, the process of drug distribution is symmetrically reversible and requires no input of energy. However, there is increasing awareness that receptor-mediated endocytosis and carrier-mediated active transport also play important roles in either increasing or limiting the extent of drug distribution. The role of these processes in drug distribution will be considered in Chapter 13.

## Fit-for-purpose modeling of drug distribution

In the previous chapter we neglected distribution-phase data and considered drug distribution within the body to be represented by a single homogeneous compartment. Although both anatomically and physiologically wrong, this model nonetheless is useful for most clinical applications. In fact, most routine pharmacokinetic studies are performed using *noncompartmental* methods which provide useful estimates of drug elimination clearance and total distribution volume. This approach will be described in greater detail in Chapter 8.

A multicompartmental system was first used to model the kinetics of drug distribution in 1937 by Teorell [2]. The two body distribution compartments of this model consisted of a central compartment corresponding to intravascular space and a peripheral compartment representing nonmetabolizing body tissues. Drug elimination was modeled as proceeding from the central compartment. Since then, more complex physiologically based multicompartmental models have been developed using a *bottom-up* approach in which different anatomical organs or groups of organs are represented by separate compartments that are linked by blood flows in a model that incorporates *drug physical chemical* characteristics. Price [3] pioneered this approach in 1960 by analyzing thiopental distribution after intravenous dosing with a four-compartment model that combined previously published values for organ weight and blood flow with values for thiopental's tissue/blood partition ratio. Distribution was considered to be instantaneous in the intravascular space and then proceeded at different rates to visceral organ, lean tissue, and fat compartments. The brain, heart, splanchnic organs, and kidneys were lumped together into a single visceral compartment because their distribution characteristics were similar. Price used this model to compare measured thiopental concentrations in blood and fat with model-predicted values and to demonstrate that the termination of this drug's central nervous system pharmacologic effect was primarily due to redistribution from the brain to skeletal muscle and other lean tissues rather than to fat, as had previously been believed. Thiopental elimination from the body was considered to be relatively insignificant during the study period, so was not included in the model. This a priori approach was further extended by Bischoff and Dedrick [4] whose expanded model included parameters for drug metabolism, protein binding, and lipid solubility, while using a similar compartmental model structure. They compared their pharmacokinetic predictions with previously published human blood concentration results and with measured blood, visceral, lean tissue, and adipose concentrations in dogs.

This type of *physiologically based pharmacokinetics* has become increasingly popular in recent years and typical models now include 14 different tissues linked by arterial and venous blood compartments. They have been further

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modified to incorporate increasingly detailed information regarding drug physicochemical properties and drug interactions, and drug absorption, distribution, and eliminating organ function in specific patient populations [5, 6]. These models can now be implemented using commercially available software and, as described in Chapter 31, are playing an increasingly important role in drug development and regulatory review [7, 8].

Because physiologically based pharmacokinetic models contain more parameters than can be identified from the analysis of experimental data, compartmental analysis of this data is usually made with systems that model drug distribution with only one, two, or three compartments [9]. Therefore this chapter will focus on the two- and three-compartment models that are most commonly used for this purpose. In most applications, these models retain Price's assumption that distribution within the intravascular space occurs instantaneously after intravenous administration. However, the onset of pharmacologic action of intravenously administered anesthetic agents occurs within seconds of administration and this necessitates consideration of the kinetics of intravascular mixing [10]. So, the appropriate selection of a given modeling approach and model type is very much dependent on the intended purpose of the analysis—what might be termed "fit-for-purpose pharmacokinetics."

Despite their varying complexity, all pharmacokinetic models represent parsimonious simplifications of real-world systems and, in the sense of the opening quote, are "wrong." However, after reaching that conclusion, Box [1] explained that parsimony is desirable because (i) when essential aspects of the system are simple, simplicity illuminates and complication obscures; (ii) parsimony typically results in increasingly precise model parameter estimates; and (iii) indiscriminate model elaboration is not practical because "the road is endless." Similarly, Cobelli et al. [11] pointed out that the validity of a model depends on its adequacy for a well-defined and limited set of objectives, rather than on whether it is a true representation of all facets of an underlying system. Berman [12] made the further distinction between mathematical models in which functions or differential equations are used without regard to the mechanistic aspects of a system, and physical models, which have features that have physiological, biochemical, or physical significance. Dollery [13] has referred to the former as "abstractions derived from curve fitting" that provide minimal mechanistic insight. So this chapter will focus on identifying mechanistic elements of the compartmental models most commonly used for pharmacokinetic data analysis that can be linked to underlying features of human physiology and drug physical chemistry. This can be conceptualized as a *top-down* approach to linking pharmacokinetics to physiology.

## Physiological significance of drug distribution volumes

The physiological concept of body compartments evolved slowly from desiccation of cadavers to measure total body water to exsanguination to measure intravascular space [14]. However, in the 20th century the dilution principle was introduced and various indicator compounds were used to measure physiologic spaces. This empirical approach also is taken when experimental data are used to analyze the pharmacokinetics of drug distribution. Unfortunately, digoxin is typical of most drugs in that its distribution volume, averaging 536 L in 70-kg subjects with normal renal function, is not readily interpreted by reference to physiologically defined fluid spaces. However, some drugs and other compounds appear to have distribution volumes that are physiologically identifiable. Thus the total distribution volumes of inulin, quaternary neuromuscular blocking drugs, and the initial distribution volumes of aminoglycoside antibiotics approximate expected values for extracellular fluid space (ECF). The distribution volumes of urea, antipyrine, ethyl alcohol, and caffeine also can be used to estimate total body water (TBW) [9].

Binding to plasma proteins affects drug distribution volume estimates. Initial attempts to explain the effects of protein binding on drug distribution were based on the assumption that the distribution of these proteins was confined to the intravascular space. However, "plasma" proteins distribute throughout ECF, so the distribution volume of even highly protein bound drugs exceeds plasma volume and approximates ECF in many cases [9]. For example, thyroxine is 99.97% protein bound and its distribution volume of 0.15 L/kg [15] approximates ECF estimates of $0.16 \pm 0.01$ L/kg made with inulin [16]. Distribution volumes are usually larger than ECF for uncharged drugs that are less tightly protein bound to plasma proteins. Theophylline is a methylxanthine, similar to caffeine, and its nonprotein bound, or free fraction is like caffeine in that it distributes throughout TBW. The fact that theophylline is normally 40% bound to plasma proteins accounts for the finding that its 0.5 L/kg apparent volume of distribution is intermediate between expected values for ECF and TBW (Fig. 3.1). The impact on distribution volume ($V_d$) of changes in the extent of theophylline binding to plasma proteins can be estimated from the following equation:

$$V_d = \text{ECF} + f_U\,(\text{TBW} - \text{ECF}) \tag{3.1}$$

where $f_U$ is the unbound fraction of theophylline that can be measured in plasma samples [17]. An additional correction has been proposed to account for the fact that interstitial fluid protein concentrations are less than those in plasma [18].

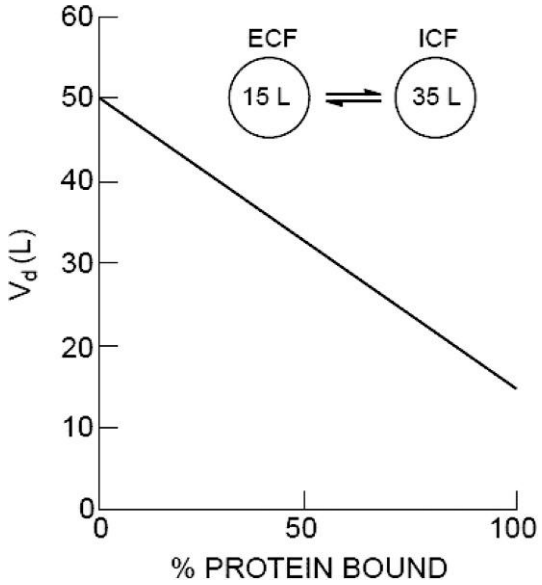


**FIG. 3.1** Analysis of theophylline $V_d$ in terms of protein binding, ECF, and intracellular fluid (ICF) components of TBW in a hypothetical 70-kg subject. Theophylline is normally 40% bound, so its $V_d$ approximates 35 L or 0.5 L/kg. *(Reproduced with permission from Atkinson AJ Jr, Ruo TI, Frederiksen MC. Physiological basis of multicompartmental models of drug distribution. Trends Pharmacol Sci 1991;12:96–101.)*

However, this correction does not account for the heterogeneous nature of interstitial fluid composition and entails additional complexity that may not be warranted [9].

Many drugs have distribution volumes that exceed expected values for TBW or are considerably larger than ECF despite extensive binding to plasma proteins. The extensive tissue binding of these drugs increases the apparent distribution volume that is calculated by reference to drug concentrations measured in plasma water. By modifying Eq. (3.1) as follows:

$$V_d = \mathrm{ECF} + \Phi f_U\,(\mathrm{TBW} - \mathrm{ECF}) \tag{3.2}$$

published kinetic data can be used to estimate the tissue-binding affinity ($\Phi$) of these drugs.

For many drugs, the extent of tissue binding is related to their lipophilicity. Although the octanol/water partition coefficient ($P_{oct}$) measured at pH 7.4 is the in vitro parameter traditionally used to characterize lipophilicity and is appropriate for neutral compounds, this coefficient fails to take into account the fact that many acidic and basic drugs are ionized at physiological pH. Because only unionized drug generally partitions into tissues, a distribution coefficient ($D_{oct}$) is thought to provide a better correlation with the extent to which a drug distributes into tissues [19]. Thus for drugs that are monoprotic bases:

$$\log D_{oct} = \log P_{oct} + \left[1/\left(1 + 10^{\mathrm{pK}_a - \mathrm{pH}}\right)\right]$$

where $\mathrm{p}K_a$ is the dissociation constant of the drug. For monoprotic acids, the exponent in this equation becomes $\mathrm{pH} - \mathrm{p}K_a$. In Fig. 3.2, published experimentally determined values for $\log D_{oct}$ are compared with estimates of $\log \Phi$. Eq. (3.2) was rearranged to calculate $\Phi$ from literature values for $f_u$ and distribution volume [20, 21], and estimates of ECF (0.16 L/kg) and TBW (0.65 L/kg) were obtained from a study of inulin and urea distribution kinetics [16].

Since the parameters $f_u$ and $D_{oct}$ can be obtained by in vitro measurements, Lombardo et al. [21] have used the reverse of this approach to predict drug distribution volume in humans in order to facilitate compound optimization and selection during the early stages of drug development. Although this type of approach would not be expected to provide an accurate prediction of the distribution volume of drugs that bind to specific subcellular components, this is not necessarily the case. For example, digoxin incorporates a steroid molecule (aglycone) but is relatively polar because three glycoside (sugar) groups are attached to it. It is a neutral compound and has an octanol/water partition coefficient of 18 ($\log = 1.25$), but also binds very tightly to the enzyme Na/K-ATPase that is present in most body tissues. Since digoxin is only 25% bound to plasma proteins ($f_U = 0.75$), Eq. (3.2) can be used to estimate that a 536-L distribution volume of this drug corresponds to a $\Phi$ value of 20.4 ($\log = 1.31$), consistent with the relationship between lipophilicity and tissue partitioning shown in Fig. 3.2. However, an important consequence of its binding to Na/K-ATPase is that digoxin can be displaced from its binding sites on this enzyme by concurrent administration of quinidine, causing a decrease in digoxin distribution volume [22]. As discussed in Chapter 5, Sheiner et al. [23] showed that elevations in serum creatinine concentration, resulting from impaired renal function, also are associated with

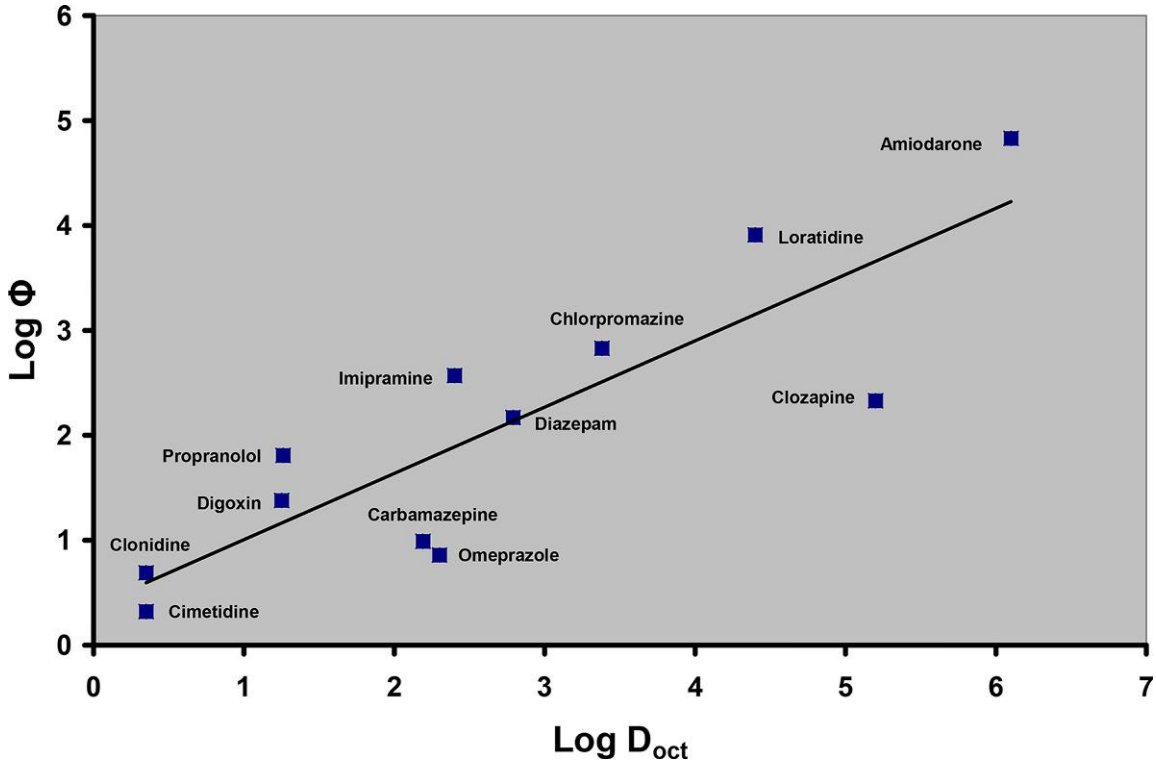


**FIG. 3.2** Relationship between lipophilicity, estimated from $D_{oct}$, and tissue/plasma partition ratio ($\Phi$) for several commonly used drugs.

decreases in digoxin distribution volume. This presumably parallels the impairment in Na/K-ATPase activity that makes these patients more susceptible to toxicity when digoxin levels are $\geq$3.0 ng/mL [24].

## Physiological basis of multicompartmental models of drug distribution

### Formulation of multicompartmental models

The construction of multicompartmental models for data analysis entails consideration of the *identifiability*, the structural *uniqueness*, and, for physiologically relevant models, the biological *plausibility* of the model. Identifiability of model parameters is problematic when there is a mismatch between the limited data provided by a pharmacokinetic study and the complexity of the proposed model structure [11]. However, a plot of plasma concentration data vs. time from a pharmacokinetic experiment can be resolved in many cases into a number of discrete exponential phases and characterized by a *sum of exponentials* data equation, such as described later in this chapter. This provides a guide to allowable model complexity in that the minimal number of exponential terms in the data equation corresponds to the number of compartments that can be specified in the model [12]. In addition, the total number of independently identifiable model parameters can not exceed the number of parameters in the data equation. Because of this restriction, drug elimination is usually modeled as proceeding only from the central compartment rather than from several model compartments. Drug transfer between model compartments is best characterized by *intercompartmental clearance*, a term coined by Sapirstein et al. [25] to describe the volume-independent parameter that quantifies the rate of analyte transfer between the compartments of a kinetic model. Thus elimination clearance and intercompartmental clearance are primary pharmacokinetic parameters because they share the property of volume independence and are not affected by changes in compartment volume. However, a number of compartment and parameter configurations are compatible with the data equation in most cases and additional information about the underlying system may be required to arrive at a unique model structure.

### Basis of multicompartmental structure

In contrast to Teorell's model, the central compartment of most two-compartment models often exceeds expected values for intravascular space, and three-compartment models are required to model the kinetics of many other drugs. The situation

has been further complicated by the fact that some drugs have been analyzed with two-compartment models on some occasions and with three-compartment models on others. To some extent, these discrepancies reflect differences in experimental design. Particularly for rapidly distributing drugs, a tri-exponential plasma-level-vs.-time curve is likely to be observed only when the drug is administered by rapid intravenous injection and blood samples are obtained frequently in the immediate postinjection period.

The central compartment of a pharmacokinetic model usually is the only one that is directly accessible to sampling. When attempting to identify this compartment as intravascular space, the erythrocyte/plasma partition ratio must be incorporated in comparisons of central compartment volume with expected blood volume if plasma levels, rather than whole blood levels, are used for pharmacokinetic analysis. Models in which the central compartment corresponds to intravascular space are of particular physiological interest because the process of distribution from the central compartment then can be identified as transcapillary exchange (Fig. 3.3). In three-compartment models of this type, it might be tempting to conclude that the two peripheral compartments are connected in series (*catenary* model) and represent interstitial fluid space and intracellular water. Urea is a marker of TBW and the kinetics of its distribution could be analyzed with a three-compartment catenary model of this type. On the other hand, a three-compartment model is also required to model distribution of inulin from a central compartment that corresponds to plasma volume. Since inulin distributes only within ECF, this implies that interstitial fluid is kinetically heterogeneous and suggests that the *mammillary* system shown in Fig. 3.3 is the proper unique configuration for models of both inulin and urea distribution kinetics [9, 16].

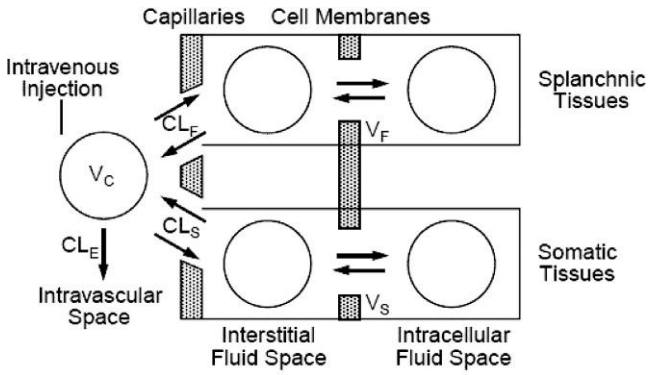


**FIG. 3.3** Multicompartmental model of the kinetics of inulin and urea distribution and elimination. After injection into a central compartment corresponding to intravascular space ($V_C$), both compounds distribute to rapidly ($V_F$) and slowly ($V_S$) equilibrating peripheral compartments (*rectangles*), at rates of transcapillary exchange that are characterized by intercompartmental clearances $CL_F$ and $CL_S$. These peripheral compartments contain both interstitial and intracellular fluid components but transfer of urea between them is too rapid to be distinguished kinetically. Inulin is limited in its distribution to the interstitial fluid components of the peripheral compartments. *(Reproduced with permission from Odeh YK, Wang Z, Ruo TI, Wang T, Frederiksen MC, Pospisil PA, Atkinson AJ Jr. Simultaneous analysis of inulin and $^{15}N_2$-urea kinetics in humans. Clin Pharmacol Ther 1993:53:419–425.)*

The proposed physiological basis for this model is that transfer of relatively small polar compounds, like urea and inulin, occurs rapidly across fenestrated and discontinuous capillaries that are located primarily in the splanchnic vascular bed, but proceeds more slowly through the interendothelial cell junctions of less porous capillaries that have a continuous basement membrane and are located primarily in skeletal muscle and other somatic tissues. Direct evidence to support this proposal has been provided by kinetic studies in which the volume of the rapidly equilibrating compartment was found to be reduced in animals whose spleen and lower intestine had been removed [26]. Indirect evidence also has been provided by a study of the distribution and pharmacologic effects of *insulin*, a compound with molecular weight and extracellular distribution characteristics similar to *inulin*. As shown in Fig. 3.4, insulin distribution kinetics were analyzed together with the rate of glucose utilization needed to stabilize plasma glucose concentrations (glucose clamp) [27]. Since changes in the rate of glucose infusion paralleled the rise and fall of insulin concentrations in the slowly equilibrating peripheral compartment, it was inferred that this compartment is largely composed of skeletal muscle. This *pharmacokinetic-pharmacodynamic* (PK-PD) study is also of interest because it illustrates one of the few examples in which a distribution compartment can be plausibly identified as the site of drug action or *biophase*.

## Mechanisms of transcapillary exchange

At this time, the physiological basis for the transfer of drugs and other compounds between compartments can only be inferred for mammillary systems in which the central compartment represents intravascular space and intercompartmental

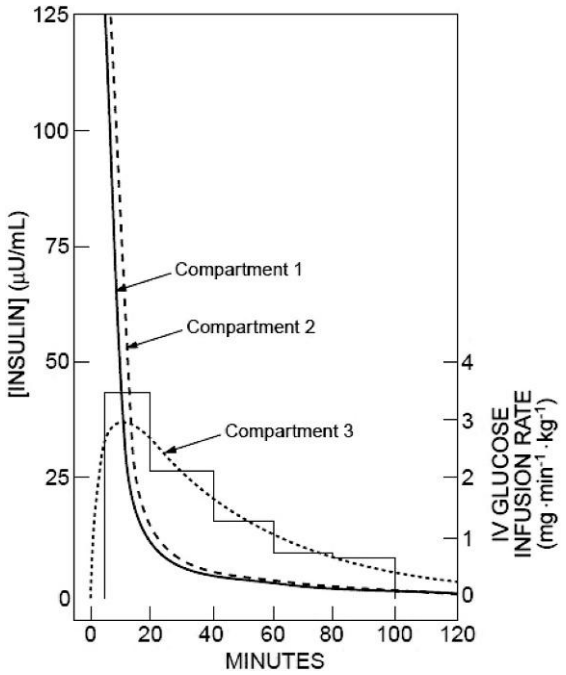


**FIG. 3.4** Measured plasma concentrations of insulin in compartment 1 (intravascular space) after intravenous injection of a 25-mU/kg dose and computer-derived estimates of insulin concentration in presumed splanchnic (compartment 2) and somatic (compartment 3) components of interstitial fluid space. The bar graph indicates the glucose infusion rate needed to maintain blood glucose concentrations at the basal level. *(Reproduced with permission from Sherwin RS, Kramer KJ, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R. A model of the kinetics of insulin in man. J Clin Invest 1974;53:1481–1492.)*

clearance can be equated with transcapillary exchange. In the case of inulin and urea, intercompartmental clearance ($CL_I$) can be analyzed in terms of the rate of blood flow ($Q$) through exchanging capillary beds and the permeability coefficient-surface area product ($P \bullet S$) characterizing diffusion through capillary fenestrae (primarily in splanchnic capillary beds) or small pores (primarily in somatic capillary beds). The following permeability-flow equation has a long developmental history [28] but was first used by Renkin [29] for analyzing transcapillary exchange of nongaseous solutes in an isolated perfused hind limb preparation before being incorporated in multicompartmental pharmacokinetic models [30],

$$CL_I = Q\left(1 - e^{-P \cdot S/Q}\right) \tag{3.3}$$

In order to estimate both $Q$ and $P \bullet S$ from measured values of $CL_I$ it was necessary to study both inulin and urea kinetics simultaneously. The additional assumption needed to be made that the ratio of urea/inulin $P \bullet S$ values for each compartment was the same as the ratio of their free water diffusion coefficients. Calculations based on this assumption yielded estimates of the sum of blood flows to the peripheral compartments that were in close agreement with independently measured cardiac output when studies were conducted in both dogs [31] and humans [16]. We will see in Chapter 6 that this modeling approach has been particularly useful in characterizing the physiological basis of the pharmacokinetic changes that occur during hemodialysis.

Although there have been few studies designed to interpret actual drug distribution results in physiological terms, one approach has been to administer the drug under investigation along with reference compounds such as inulin and urea. In one study, it was found that the molecular charge of gallamine retards its transcapillary exchange to the ECF [32]. In a second study, it was found that the intercompartmental clearances of theophylline to its two peripheral compartments corresponded to the compartmental blood flow components of urea and inulin transcapillary exchange [33]. Given that the free water diffusion coefficient of theophylline is less (slower) than that of urea, yet its intercompartmental clearances were more rapid than the corresponding urea clearances, its transcapillary exchange presumably occurs by carrier-mediated facilitated diffusion. Very lipid soluble compounds also appear to pass directly though capillary walls at rates limited only by blood flow (i.e., $P \bullet S \gg Q$ in Eq. 3.3). On the other hand, large molecular size retards transcapillary exchange and molecules considerably larger than inulin are probably transported through small-pore capillaries by convection rather than diffusion (Fig. 3.5) [34]. These observations lead to the classification of transcapillary exchange mechanisms presented in Table 3.1.