Textbook of Therapeutics

Drug and Disease Management

EIGHTH EDITION

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Contents

Clinical Pharmacodynamics and Pharmacokinetics

1

Bernd Meibohm and William E. Evans

In applied pharmacotherapy, usage of medications is adjusted to the individual need of the patient to maximize efficacy and safety, i.e., to achieve the maximum therapeutic response with a minimum likelihood of adverse events. The rational use of drugs and the design of effective dosage regimens are facilitated by the appreciation of the relationships among the administered dose of a drug, the resulting drug concentrations in various body fluids and tissues, and the intensity of pharmacologic effects caused by these concentrations. These relationships and thus the dose of a drug required to achieve a certain effect are determined by the drug's pharmacokinetic and pharmacodynamic properties. Thus, pharmacokinetic (PK) and pharmacodynamic (PD) information form the scientific basis of modern pharmacotherapy.[1,2]

Pharmacokinetics describes the time course of the concentration of a drug in a body fluid, preferably plasma or blood that results from the administration of a certain dosage regimen. In simple terms, pharmacokinetics is "*what the body does to the drug.*" Pharmacodynamics describes the intensity of a drug effect in relation to its concentration in a body fluid, usually at the site of drug action. It can be simplified to "*what the drug does to the body.*"[3]

The plasma concentration-time profile resulting from drug administration is determined by pharmacokinetic parameters and the administered dosage regimen. While the pharmacokinetic parameters are characteristic for the disposition or handling of a drug in a specific patient and thus usually cannot be altered during pharmacotherapy, the dosage regimen is the clinician's tool to affect drug concentrations for maximum therapeutic benefit. For most drugs, therapeutic response and/or toxicity are related to free concentration of the drug at the site of action. However, drug concentrations at the site of action (e.g., heart tissue for β_1-blockers) often cannot be practically measured. Thus, drug concentrations in accessible body fluids such as plasma are often related to the observed effect under the assumption that the drug concentrations in the measured body fluid and at the site of action are in a constant relationship. Even though this assumption frequently is not accurate, it has proven to be a useful simplification that allows most drugs to achieve the desired effect levels via modulation of their plasma concentration, especially during prolonged pharmacotherapy with multiple dose regimens.

THERAPEUTIC RANGE

The relationship between dosage regimen and effects of a drug, also known as the dose–concentration–response relationship, or exposure–response relationship, is not identical for all patients. Biologic variability in pharmacokinetics and pharmacodynamics as well as their modification by physiologic, pathophysiologic, and environmental factors result in different effect intensities when the same dosage regimen of a drug is given to different patients. Thus, different patients may require different dosage regimens to achieve the same effect intensity. Factors that contribute to variability in the relationship between dose and effect intensity include age, weight, ethnicity and genetics, gender, disease type and severity, concomitant drug therapy, and environmental factors.

The variability in the relationship between dosage regimen and effect intensity is caused by pharmacokinetic variability, pharmacodynamic variability, or a combination of both. Knowledge about the variability in the plasma drug-concentration-effect relationship allows establishing a drug-specific *therapeutic range*. A therapeutic range is a range of drug concentrations within which the *probability* of desired clinical response in the considered patient population is relatively high and the probability of unacceptable toxicity is relatively low. The therapeutic range approach combines be-

tween-patient pharmacodynamic variability with the therapeutic as well as toxic effects of a drug. It is important to note that the therapeutic range should not be considered in absolute terms as the limits for this probability range are oftentimes chosen arbitrarily. In addition, the therapeutic range is not well defined for a large fraction of the drugs that are used clinically.

The left panel in Figure 1.1 *(see color insert)* shows a drug concentration-effect relationship. The probability of achieving the desired response is very low when drug concentrations are less than 5 mg per L, as is the chance of observing toxicity. As drug concentrations increase from 5 to 20 mg per L, the probability of desired response increases significantly, while the probability of toxicity increases more slowly. One could select a therapeutic range of 10 to 20 mg per L, where the minimum probability of a therapeutic response is at least 50% and the probability of toxicity is less than 10%. An optimal dosage regimen can be defined as one that maintains the plasma concentration of the drug within the therapeutic range. The right panel in Figure 1.1 demonstrates this concept by comparing two dosage regimens. The dosing interval (time between doses; in this case 8 hours) is the same, but the discrete doses given in regimen B are twice as large as those given in regimen A. As shown, drug accumulates in the body during multiple dosing. Regimen A keeps the concentration-time profile within the therapeutic range, which will result in the majority of patients with adequate therapeutic efficacy with only rare occurrence of undesired toxicity. Regimen B will likely result in most patients with only a marginal increase in efficacy compared to regimen A, but with a much larger likelihood of undesired toxicity. It should, however, be stressed, that despite having plasma concentrations within the therapeutic range at all times, some of the patients treated with regimen A may not experience an adequate drug response or may experience drug-related toxicity.

CLINICAL PHARMACOKINETICS

The utility of pharmacokinetics does not lie in diagnosing the disease or selecting the "drug of choice," but in deciding the best way to administer a given drug to achieve its therapeutic objective. The manner in which a drug is taken is referred to as the *dosage regimen.* The dosage regimen tells us "how much" and "how often" a drug must be taken to achieve the desired result. It is these two questions (how much?, how often?) that form the basis for the discipline of pharmacokinetics.[4,5]

Clinical pharmacokinetics is the application of pharmacokinetic principles in a patient care setting for the design of optimum dosage regimens for the individual patient. Probably the most difficult aspect of clinical pharmacokinetics is understanding the full potential and practical limitations and pitfalls of using specific pharmacokinetic models of drug disposition to attain target concentrations based on only a limited number (usually 1–2) of drug concentration measurements. Although a good understanding of common pharmacokinetic concepts is crucial, the competent clinician will have knowledge of not only the mathematics of these concepts, but also the principles, assumptions, and potential errors underlying their application in a clinical setting. Furthermore, a broad therapeutic knowledge is also necessary because measured drug concentrations must be interpreted with respect to the patient's clinical condition and the pharmacodynamic profile of the therapeutic agent.

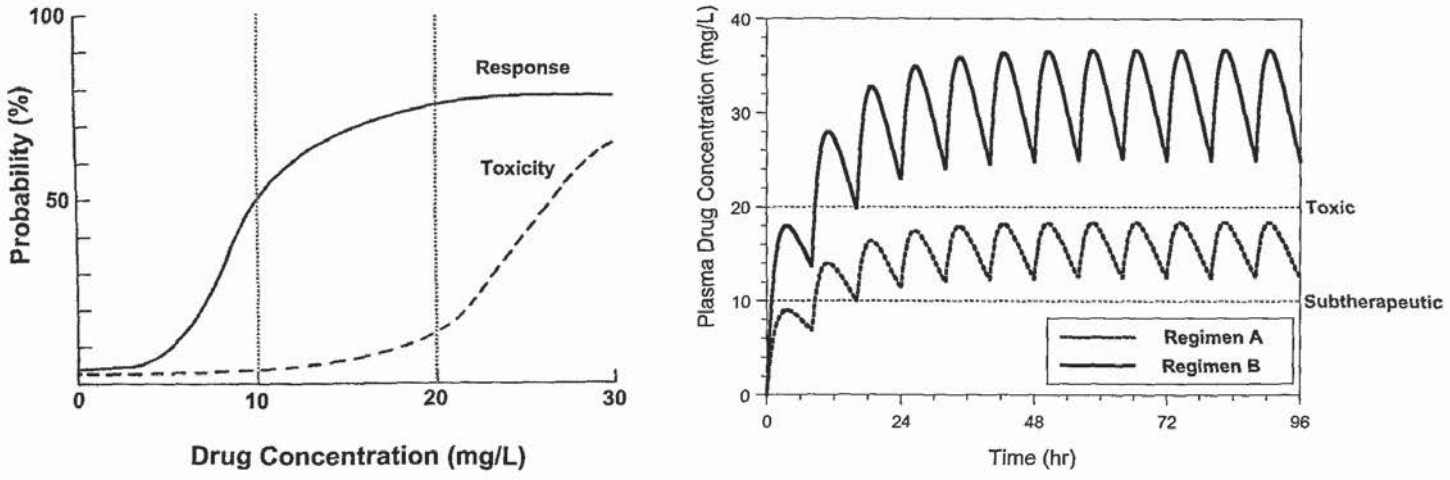

FIGURE 1.1 The concept of a therapeutic range. The **left panel** shows a relationship between the probability of achieving the desired response as well as the chance of observing toxicity in relation to drug concentration in plasma. A therapeutic range of 10 to 20 mg/L could be defined as a range of concentration with relatively high probability of a therapeutic response but low probability of drug-related toxicity. The **right panel** demonstrates the application of the therapeutic range concept in designing multiple dose regimens. In the concentration-time plot, regimen A keeps drug concentrations within the therapeutic range, whereas regimen B results in concentrations exceeding the therapeutic range. Regimen B will likely result in most patients with only a marginal increase in efficacy compared to regimen A, but with a much larger likelihood of drug-related toxicity.

PRIMARY PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters are characteristic for the disposition and uptake of drug into the body of one specific drug in a specific patient. Pharmacokinetic parameters are usually not accessible for therapeutic manipulation by the clinician, but may be modulated by physiologic or pathophysiologic processes in the patient as well as concomitant drug therapy (drug-drug interactions) and environmental factors.

The most important pharmacokinetic parameters are clearance (CL), volume of distribution (V), and bioavailability (F) (Fig. 1.2; *see color insert*). CL is reflective for the drug-eliminating capacity of the body, especially liver and kidneys, V refers to the distribution of drug within the body including uptake into specific organs and tissues as well as binding to proteins and other macromolecules. Based on these underlying physiologic processes, CL and V are independent of each other and are called *primary pharmacokinetic parameters*. Bioavailability (F) refers to the extent of drug uptake into the systemic circulation. Although being at least partially dependent on hepatic CL via the so-called first-pass effect, bioavailability may also be considered as a primary parameter.

Clearance. CL quantifies the elimination of a drug. It is the volume of body fluid, blood, or plasma that is cleared of the drug per time unit. Thus, it measures the removal of drug from the plasma or blood. For simplicity, only plasma CLs will be considered in the following. CL does not indicate how much drug is being removed, but it represents the volume of plasma from which the drug is completely removed, or cleared, in a given time period. The unit of CL is volume per time, e.g., liters per hour or milliliters per minute. It may also be normalized to body size, e.g., L/hr/kg. CL is an independent pharmacokinetic parameter, and is the most important pharmacokinetic parameter because it determines the dosing rate.

The overall total body CL is the sum of individual organ CLs that contribute to the elimination of a drug:

$$CL = CL_R + CL_H + CL_{Other} \qquad (1\text{-}1)$$

CL_R is the renal clearance representing elimination via the kidneys, CL_H hepatic clearance representing elimination via the liver, and CL_{other} the clearance of other elimination organs (e.g., gastrointestinal tract, lungs) that contribute to the elimination of a specific drug.

Organ CLs can be defined by a flow rate Q that represents the volume of plasma that flows through the organ per time unit and the extraction ratio E, a measure of the extraction efficiency of the organ. E provides the fraction of the volume of plasma that is completely cleared of drug per passage through the organ. The extraction ratio can be assessed as ratio of the difference between the drug concentration in the plasma entering (C_{in}) and leaving (C_{out}) the elimination organ compared to C_{in}. In other words, it gives the percent of Q that is completely cleared from the drug during passage through the organ.

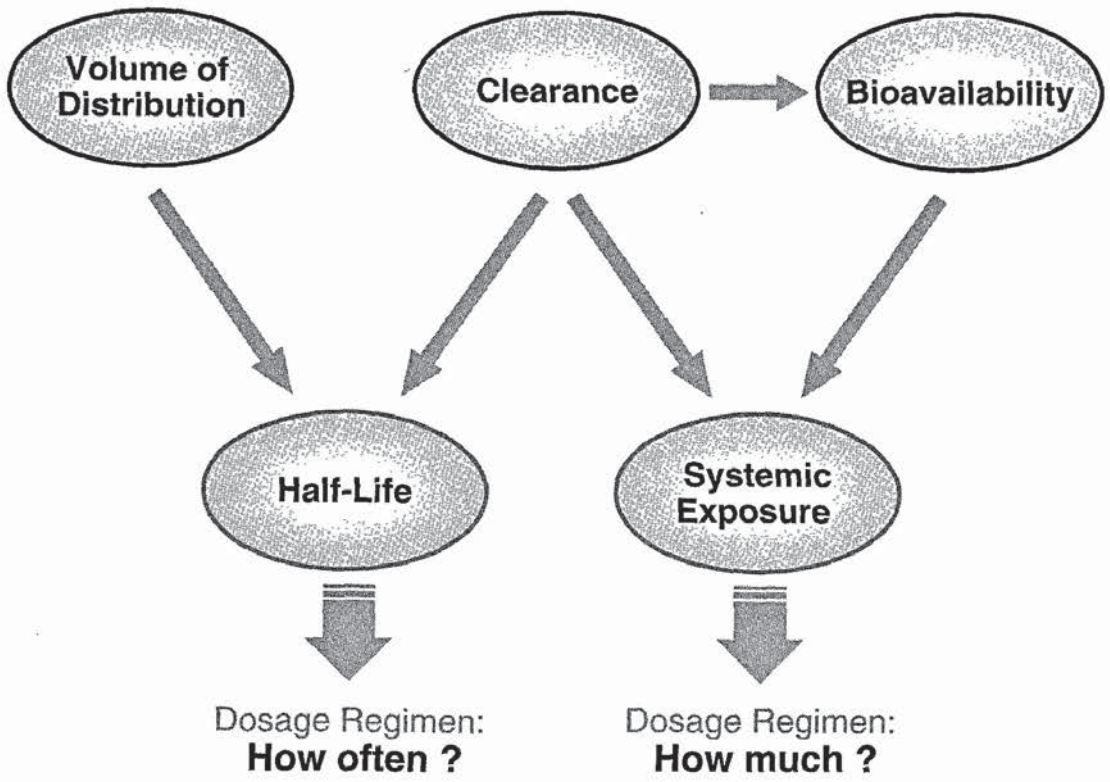

FIGURE 1.2 Interrelationship of primary pharmacokinetic parameters (clearance, volume of distribution, and bioavailability) and their relevance for determining dosage regimens. (Modified from van de Waterbeemd H, Gifford E. ADMET in silico modelling: towards prediction paradise? Nat Rev Drug Discov 2:192–204, 2003.)

Volume of Distribution. V quantifies the extent of distribution of a drug throughout the body. Drug distribution means the reversible transfer of drug from one location to another within the body. The concentration achieved in plasma after distribution depends on the dose and the extent of distribution. The V relates the amount of drug in the body to the plasma concentration. It is an apparent volume, which is calculated upon the simplifying assumption that the plasma concentration is present in all body compartments. The unit of V is volume, e.g., liter or milliliter. It may also be normalized to body size, e.g., liter per kilogram. The larger the V, the smaller the fraction of the dose that resides in the plasma.

Once drug has entered the vascular system, it becomes distributed throughout the various tissues and body fluids. However, most drugs do not distribute uniformly throughout the various organs and tissues of the body. This heterogeneous distribution is based on tissue-specific differences in rate and extent of drug uptake, including blood flow, i.e., the delivery of drug to the tissues, the ability for the drug to cross biomembranes, partitioning into the tissue, and drug binding to tissue elements including binding to proteins and other macromolecules. As a consequence, V is an apparent volume that acts as a proportionality factor between drug amount in the body and measured concentration in plasma and can range between 3 L for a typical 70-kg subject representing the plasma volume and up to values like 5,000 L for amiodarone, i.e., far in excess of the total body size.

For most drugs, distribution throughout the body is not instantaneous, but a time-consuming process. Thus, the initial drug distribution volume after intravenous (IV) bolus administration is frequently smaller than that after distribution equilibrium throughout the body has been reached. The initial V is frequently referred to as the volume of the central compartment V_C, representing well-perfused organs and tissues for which drug distribution for a specific drug is nearly instantaneous. Differentiation between the postequilibrium V and the volume of the central compartment V_C becomes especially important for loading dose calculations. Drugs with instantaneous and homogenous distribution are referred to in the following as having one-compartment distribution characteristics, those with differences between V_C and the postequilibrium V as having multicompartment distribution characteristics.

Bioavailability. Bioavailability commonly refers to the rate and extent of drug absorption into the systemic circulation. In the following, however, the term bioavailability (F) will be limited to the extent of absorption, i.e., the fraction of the administered dose that reaches the systemic circulation. By definition, F is 100% for intravascular administrations, e.g., IV dosing.

Absolute bioavailability is the fraction (or percent) of a dose administered extravascularly which is systemically available as compared to an IV dose. If given orally, absolute bioavailability (F) is:

$$F = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{D_{IV}}{D_{oral}} \tag{1-2}$$

where AUC is the area-under-the-plasma-concentration-time curve after oral or IV administration, respectively, and D is the administered dose (e.g., in milligrams) of the two respective administration routes.

Relative bioavailability does not compare an extravascular with an IV administration, but two formulations given via extravascular routes. It is the fraction of a dose administered as a test formulation that is systemically available as compared to a reference formulation:

$$F = \frac{AUC_{test\ formulation}}{AUC_{reference}} \times \frac{D_{reference}}{D_{test\ formulation}} \tag{1-3}$$

Bioavailability can be viewed as the result of a combination of processes that reduce the amount of extravascularly administered drug that reaches the systemic circulation. Components that describe these processes for an oral dose administration include the fraction of drug that is absorbed from the gastrointestinal tract (F_a), the fraction of drug that escaped presystemic gut wall metabolism (F_G), and the fraction of the drug that escaped hepatic first-pass metabolism (F_H).

$$F = F_a \times F_G \times F_H \tag{1-4}$$

First-pass metabolism refers to the phenomenon that drug absorbed in the gastrointestinal tract first undergoes transport through the portal vein, then passage through the capillary bed of the liver before it reaches the systemic circulation. Metabolism during this first liver passage may, depending on the drug, dramatically reduce the fraction of the administered dose that reaches the systemic circulation. F_H is interrelated with CL_H via the hepatic extraction ration E_H:

$$F_H = 1 - E_H = 1 - \frac{CL_H}{Q_H} \tag{1-5}$$

where Q_H is the hepatic flow rate of plasma.

INTERRELATIONSHIP BETWEEN PRIMARY PHARMACOKINETIC PARAMETERS AND THEIR EFFECT ON PLASMA CONCENTRATION-TIME PROFILES

The primary pharmacokinetic parameters CL, V, and F are major determinants for the plasma concentration-time profile resulting from administration of a dosage regimen. The clinically most useful characteristics of the resulting concentration-time profile are the elimination half-life $t_{½}$, as well as the average steady-state concentration $C_{ss,av}$ and the area under the plasma concentration-time curve AUC as measures of systemic exposure (Fig. 1.2).

Half-Life. Half-life ($t_{½}$) characterizes the monoexponential decline in drug concentration after drug input processes have been completed. Half-life is the time required for the plasma concentration to decrease by one-half. It is a transformation of the first-order elimination rate constant K that characterizes drug removal from the body if the elimination process follows first-order kinetics. Drug con-

centration C at any time t during a monoexponential decrease can be described by

$$C = C_0 \times e^{-K \times t} \tag{1-6}$$

where C_0 is the initial drug concentration at time t = 0 hours. Half-life is then given as

$$t_{1/2} = \frac{ln\ 2}{K} \tag{1-7a}$$

or

$$t_{1/2} = \frac{0.693}{K} \tag{1-7b}$$

The elimination rate constant K is the negative slope of the plasma concentration-time profile in a plot of the natural logarithm (*ln*) of the concentration versus time. Half-life can thus be calculated from two concentrations C_1 and C_2 during the monoexponential decline of drug concentration via the relationship

$$K = \frac{ln\left(\frac{C_1}{C_2}\right)}{t_2 - t_1} \tag{1-8}$$

Half-life is a secondary pharmacokinetic parameter that is defined by the primary parameters CL and V. The elimination rate constant K as a transform of half-life can be seen as a proportionality factor between CL and V:

$$CL = K \times V \tag{1-9A}$$

or

$$K = \frac{CL}{V} \tag{1-9B}$$

Thus, half-life is given by

$$t_{1/2} = \frac{0.693 \times V}{CL} \tag{1-10}$$

Because CL and V are determined by unrelated underlying physiologic processes as described earlier, they are independent of each other. If V, for example is increased due to a pathophysiologic process, then CL remains unaffected. According to Equation 1-9A, change in V would result in a compensatory change in the elimination rate constant K without affecting CL. Vice versa, an increase or decrease in CL will only result in a corresponding change in the elimination rate constant K, but V would remain unaffected.

Half-life provides important information about specific aspects of a drug's disposition, such as how long it will take to reach steady-state once maintenance dosing is started and how long it will take for "all" the drug to be eliminated from the body once dosing is stopped (usually considered five half-lives). Also, the relationship between half-life and dosing interval of a multiple dose regimen determines the fluctuation between peak and trough plasma concentration levels for this dosage regimen.

Systemic Exposure. Exposure to drug in the systemic circulation is a time-integrated or time-averaged measure of drug concentration that is secondary to the administered dosage regimen and the primary parameters CL and bioavailability (F).

The area-under-the-concentration-time curve (AUC) is the integrated concentration over time as a measure of overall exposure to a drug resulting from a specific dosage regimen. It is given by

$$AUC = \frac{F \times D}{CL} \tag{1-11}$$

where D is the administered dose.

The average steady-state concentration $C_{ss,av}$ is the average concentration over one dosing interval in a multiple dose regimen. It is related to CL and bioavailability (F) via

$$C_{ss,av} = \frac{F \times D}{\tau \times CL} = \frac{AUC}{\tau} \tag{1-12}$$

where τ is the dosing interval between two consecutive doses of the multiple dose regimen. The ratio D/τ is also referred to as *dosing rate*.

As indicated in Eqs. 1-11 and 1-12, systemic exposure assessed as AUC or $C_{ss,av}$ is only dependent on the bioavailable dose or dosing rate and CL, but not the extent of drug distribution as quantified by V. Table 1.1 summarizes the interrelationship between the primary pharmacokinetic parameters CL, V, and F and the secondary parameters half-life, AUC, and $C_{ss,av}$.

TABLE 1-1 Effect of Changes in Primary Pharmacokinetic Parameters on Secondary Parameters

Independent (primary) Parameters			Dependent (secondary) Parameters		
CL	V	F	$t_{1/2}$	C_{ssav}*	AUC
↑	↔	↔	↓	↓	↓
↓	↔	↔	↑	↑	↑
↔	↑	↔	↑	↔	↔
↔	↓	↔	↓	↔	↔
↔	↔	↑	↔	↑	↑
↔	↔	↓	↔	↓	↓
↑	↑	↔	*	↓	↓
↑	↓	↔	↓	↓	↓
↓	↑	↔	↑	↑	↑
↓	↓	↔	*	↑	↑

The '*' in the table indicates that the effect on the secondary parameter cannot be determined without knowing the extent of changes in CL, V, and F.

↑, increase; ↔, little or no change; ↓, decrease.

THERAPEUTIC DOSAGE REGIMENS

For a lot of drugs to be therapeutically effective, drug concentrations of a certain level have to be maintained within the therapeutic range for a prolonged period of time (e.g., β-lactam antibiotics, antiarrhythmics). To continuously maintain drug concentrations in a certain therapeutic range over a prolonged period of time, two basic approaches to administer the drug can be applied:

1. Drug administration at a constant input rate (i.e., a continuous, constant supply of drug; zero-order input)
2. Sequential administration of discrete single doses (multiple dose regimens)

Constant Input Rate Regimens. Administration of constant input rate regimens can be via intravascular or via extravascular administration. Intravascular administration is most frequently accomplished by IV infusion of drug via a drip or an infusion pump. Although IV drug administration provides a high level of control and precision, its major limitation is that it is restricted primarily to clinical settings. Extravascular administration with a constant input rate has become available only recently and is now widely used in constant release rate devices that deliver drug for an extended period of time at a constant rate. Best known examples for constant rate release devices are transdermal therapeutic systems in patch format and oral therapeutic systems in capsule form. Here, absorption is an additional prerequisite to attain effective plasma concentrations. An example for the resulting concentration-time profile of such a dosage form [oxybutynin chloride (OROS)] is given in Figure 1.3. For understanding the principles involved in constant rate regimens, administration by constant release rate devices in the following are assumed to be equivalent to constant rate IV infusions.

At any time during an infusion, the rate of change in the amount of drug in the body and subsequently the drug concentration is the difference between the input rate (infusion rate R_0) and the output rate (CL × concentration C). At time t = 0 hours, when the infusion is started, the concentration and the output rate are both zero. Thus, the rate of change in plasma concentration has its maximum value. With increasing time, the output rate increases as the plasma concentration C is rising while the input rate remains constant. Thus, the rate of change in drug concentration gets smaller with increasing time, but drug concentrations continue to increase as the rate of change is still positive. Finally, the plasma concentration has risen enough that the output rate is equal to the input rate. At this time, the so-called steady-state C_{ss} has been reached, where the rate of change in drug plasma concentration is zero and a constant steady-state concentration C_{ss} has been achieved. At steady-state, input rate is equal to output rate.

$$R_0 = CL \times C_{ss} \tag{1-13}$$

Hence, the steady-state concentration C_{ss} is only determined by the infusion rate R_0 and the CL.

$$C_{ss} = \frac{R_0}{CL} \tag{1-14}$$

An increase in the infusion rate will result in a proportional increase in the steady-state concentration C_{ss}, as shown in Figure 1.4. For therapeutic purposes, it is often of critical importance to know how long it will take after initiation of an infusion to finally reach a targeted steady-state concentration C_{ss}. The rise in drug concentration during a constant rate infusion before steady-state is exponential in nature and is determined by the elimination process (elimination rate constant K), *not* the infusion rate R_0:

$$C = \frac{R_0}{CL} \times \left(1 - e^{-K \times t}\right) \tag{1-15}$$

After initiation of a constant rate infusion, it takes one elimination half-life to reach 50% of C_{ss}, two elimination half-lives to reach 75% of C_{ss}, and three elimination half-

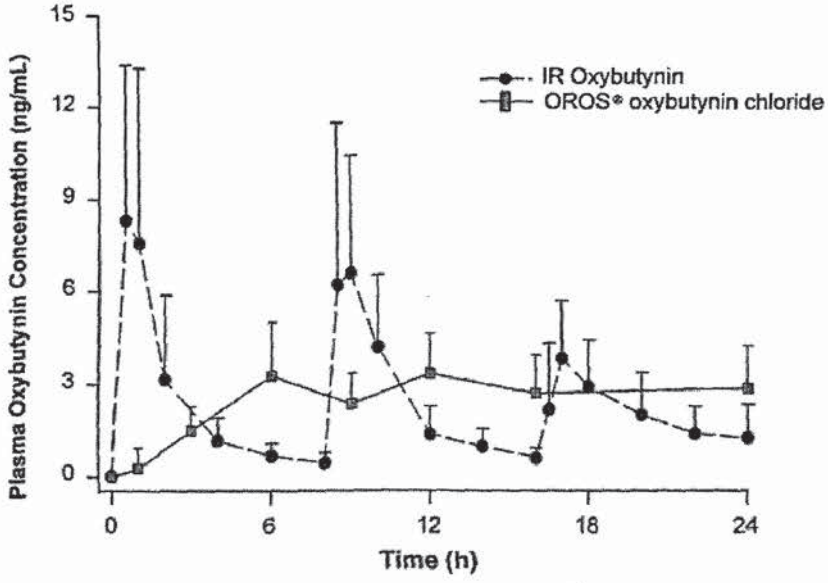

FIGURE 1.3 Oral dosage form with constant input rate. Mean (SD) oxybutynin plasma concentrations in 13 subjects after oral administration of either 15 mg OROS oxybutynin chloride once a day or 5 mg immediate release oxybutynin every 8 hours. OROS is an orally administered constant release rate dosage form. (From Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. J Clin Pharmacol 39: 289–296, 1999.)

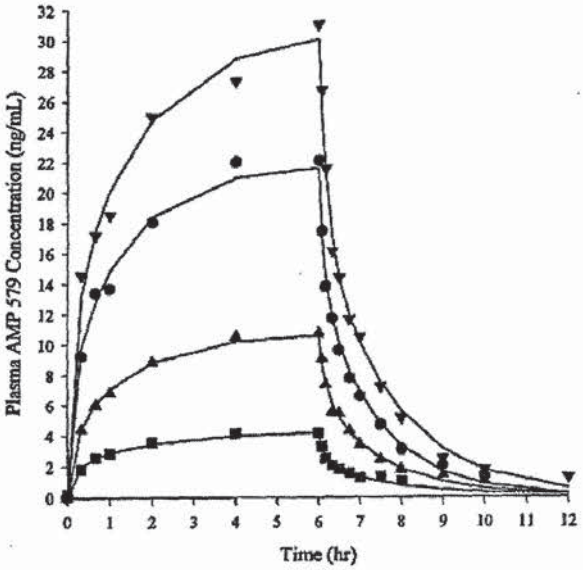

FIGURE 1.4 Linear relationship between steady-state concentration and infusion rate. Mean AMP 579 concentrations in six subjects after single intravenous infusions of 20, 50, 100, or 150 μg/kg AMP 579 administered as 6-hour constant rate infusions. AMP 579 is an investigational adenosine agonist for the treatment of paroxysmal supraventricular tachycardia. (From Zannikos PN, Baybutt RI, Boutouyrie BX, et al. Pharmacokinetics, safety, and tolerability of single intravenous infusions of an adenosine agonist, AMP 579, in healthy male volunteers. J Clin Pharmacol 39:1044–1052, 1999.)

lives to reach 87.5% of C_{ss}. Assuming for clinical purposes that a concentration of more than 95% of C_{ss} is therapeutically equivalent to the final steady-state concentration, it takes approximately five elimination half-lives ($t_{1/2}$) to reach steady-state after initiation of an infusion.

The decline in drug concentration after cessation of an infusion can be described by Equation 1-6 where C_0 is the concentration at the end of the infusion as determined by Equation 1-15 and t is the postinfusion time, the time increment between end of infusion and the time of the observed plasma concentration C.

During therapy it sometimes becomes necessary to change the input rate of a constant rate regimen, e.g., because of drug-related toxicity or inadequate therapeutic effect. After each change in the infusion rate it again takes five half-lives $t_{1/2}$ before more than 95% of the change in the steady-state concentration C_{ss} has occurred. An increase in the infusion rate R_0 is best imagined by the sum of two independent infusions. The first one has the same infusion rate as before the change in R_0. The second one has an infusion rate equal to the incremental increase in R_0. The resulting plasma concentration profile is the sum of the concentrations independently produced by the two infusions (Fig. 1.5). Similarly, a decrease in the infusion rate R_0 can be imagined as the result of two concomitant infusions of which one has been stopped.[4]

Loading Dose and Maintenance Dose. Because the time to reach steady-state concentrations after initiation of a constant rate infusion is determined by the elimination half-life of the drug, depending on the drug's half-life, it may

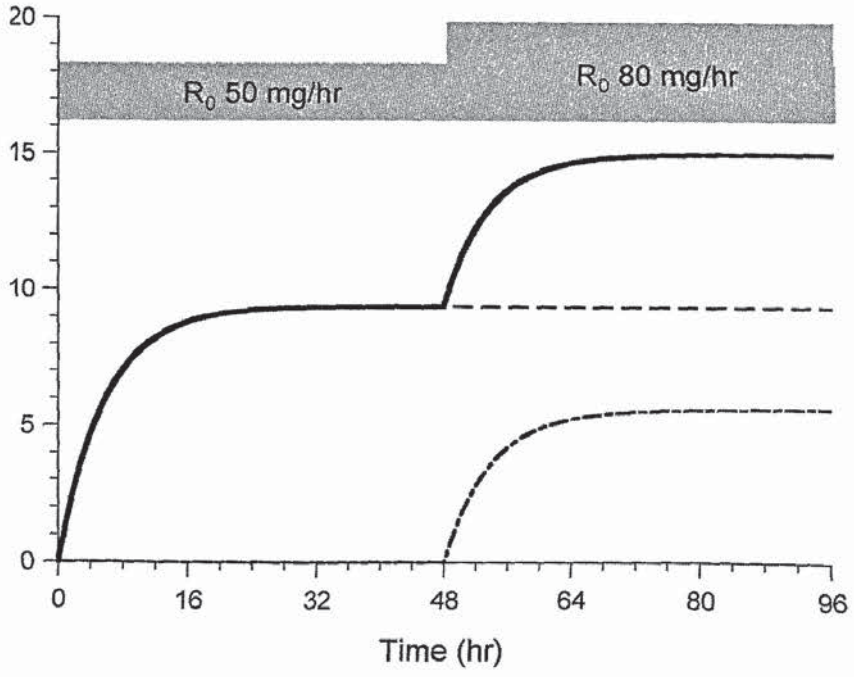

FIGURE 1.5 Increase in infusion rate. An increase in the infusion rate R_0 is best imagined by the sum of two independent infusions, where a second infusion with the incremental infusion rate (in this case 30 mg/hour) is initiated at the time of change in R_0. The resulting plasma concentrations (*bold line*) are the sum of the concentrations independently produced by the two infusions (*dashed lines*).

take a long time until the targeted steady-state concentration C_{target} is reached. For a drug with an elimination half-life of 8 hours, approximately 40 hours (5 × 8 hours) will be needed to reach more than 95% of C_{ss}. Clinical situations sometimes demand that the C_{target} is reached more rapidly.

A solution for this problem is to give a bolus dose and start an infusion at the same time. The resulting plasma concentration is additive from the two modes of administration. The loading dose (LD) is supposed to immediately reach the desired target concentration C_{target}. It is administered as an IV bolus injection or, more frequently, as a short-term infusion. The maintenance dose (MD) is intended to sustain C_{target}. It is administered as a constant rate infusion. When the LD and the MD are exactly matched, the concentrations of drug associated with LD and MD exactly complement each other (Fig. 1.6; *see color insert*). The gain in concentration of MD offsets the loss of the concentration that was initially achieved with LD. In clinical practice, IV dosage regimens are often performed as a sequential combination of LD and MD. But also oral constant rate release systems often contain a LD to facilitate a more rapid achievement of therapeutic concentrations.

The LD for a certain target concentration, C_{target} for a drug with one-compartment distribution characteristics is solely determined by V. It has the unit of an amount, e.g., milligrams.

$$LD = C_{target} \times V \qquad (1\text{-}16)$$

The MD necessary to sustain the target concentration C_{target} is solely determined by the CL. It has the unit of an amount per time, e.g., milligrams per hour:

$$MD = R_0 = C_{target} \times CL \qquad (1\text{-}17)$$

Multicompartment Characteristics and Loading Dose. When applying clinical pharmacokinetics to design and optimize dosage regimens for patients, it is generally assumed for practical purposes that the drug considered follows one-compartment characteristics. In reality, however, most drugs show at least after IV administration multicompartment characteristics. For those drugs, plasma concentrations resulting from an LD based on the postequilibrium V are initially always higher than predicted by a one-compartment model, which may lead to toxicity. The reason is that the volume of the central compartment V_C in which the drug is initially distributed is always smaller than postequilibrium V. Approaches to overcome this problem are to base the LD on V_C instead of V or to give a LD based on V as a short-term infusion rather than as bolus injection.

A patient shall be started on a combination dosing regimen consisting of a LD and a MD. A drug's postequilibrium V in a patient is V = 50 L. A LD of 500 mg was calculated to achieve a target plasma concentration of 10 mg per L. If the drug follows multicompartment characteristics and has a volume of the central compartment of V_C = 10 L, the concentration immediately after drug administration via bolus injection would be 50 mg per L—far beyond the target concentration and potentially toxic. If the LD of 500 mg, however, is slowly administered into the V_C of 10 L, the drug has time to distribute into peripheral tissues and high peak levels are avoided. Basing the LD calculation on V_C would give a LD of 50 mg. Although this LD would initially provide the target concentration, plasma concentrations would consequently drop temporarily below the target concentration because of concurrent distribution and elimination processes, for which only the elimination is offset by the MD.

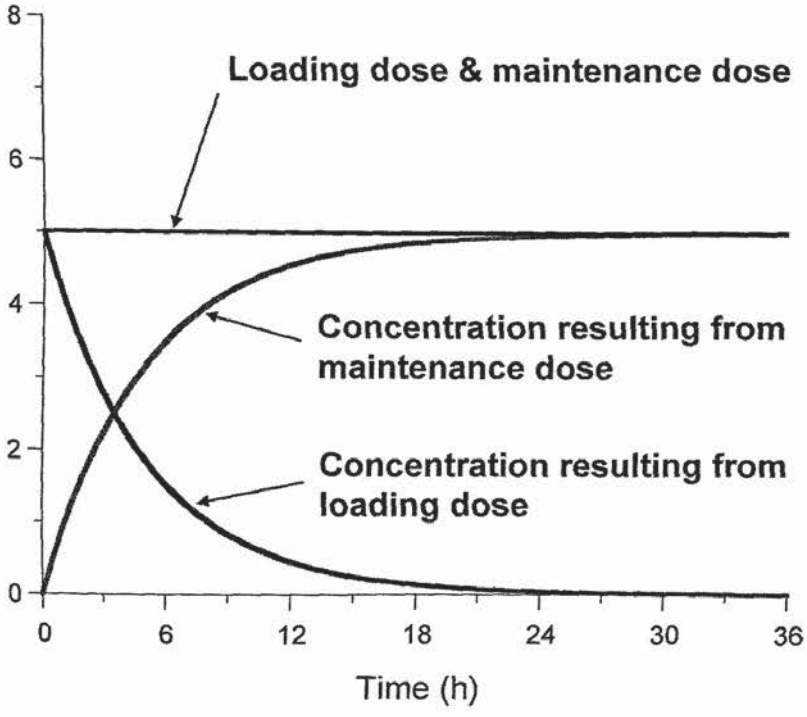

FIGURE 1.6 Loading dose and maintenance dose. When the loading dose and maintenance dose are exactly matched, the drug concentrations associated with the two modes of administration complement each other, maintaining a constant target concentration.

Dosage Regimen Adjustment for Constant Rate Regimen. A 53-year-old male, 85-kg patient, was admitted to the coronary care unit with acute myocardial infarction. Besides other standard treatment, lidocaine therapy was started for the treatment of his symptomatic ventricular arrhythmia. He was given an IV LD of 85 mg and simultaneously started on a constant rate infusion of 2 mg per min (=120 mg/hour). As recurrent arrhythmia episodes occurred after several hours, a plasma level was drawn 10 hours after initiation of the therapy to determine whether lidocaine was underdosed or the ventricular arrhythmia was refractory to lidocaine treatment. The plasma drug concentration was 1.15 mg/L. The therapeutic concentration range for lidocaine is 1.5–5 mg per L. The population mean pharmacokinetic parameters for lidocaine are V = 1 L per kg and CL = 0.55 L/hr/kg. A LD and a MD shall be recommended to increase the patient's levels from 1.15 mg per L to a target concentration of 3 mg per L.

Based on the population pharmacokinetic parameters of lidocaine, the population estimate for half-life was calculated as 1.3 hours:

$$t_{1/2} = \frac{ln\ 2}{K} = \frac{ln\ 2 \times V}{CL} = \frac{0.693 \times 1\ L/kg}{0.55\ L/hr/kg} = 1.3\ hr \quad (1\text{-}18)$$

Because the time to reach steady-state after initiation of the infusion based on population estimates is approximately 5 × 1.3 hours = 6.5 hours, it can be expected that the plasma concentration measured 10 hours after initiation of the infusion was the steady-state concentration. Thus, the patient's individual CL can be calculated as

$$CL = \frac{R_0}{C_{ss}} = \frac{120\ mg/hr}{1.15\ mg/L} = 104\ L/hr \quad (1\text{-}19)$$

The new MD to reach the target concentration of 3 mg per L is then

$$\begin{aligned} MD &= CL \times C_{target} \\ &= 104\ L/hr \times 3\ mg/L \\ &= 312\ mg/hr \approx 300\ mg/hr \end{aligned} \quad (1\text{-}20)$$

The LD for the incremental increase in drug concentration from 1.15 to 3 mg/L is based on the population estimate of V as follows:

$$\begin{aligned} LD &= \left(C_{target} - C_{measured}\right) \times V \\ &= \left(3 - 1.15\right) mg/L \times 1\ L/kg \times 85\ kg \\ &= 157\ mg \approx 150\ mg \end{aligned} \quad (1\text{-}21)$$

Multiple Dose Regimens. As discussed in the previous section, steady drug concentrations for a prolonged therapy can be maintained by drug administration at a constant input rate or by sequential administration of discrete single doses via multiple dose regimens. The latter one is the more frequently used approach and can be applied for extravascular as well as intravascular routes of administration.

Multiple dose regimens are defined by two components, the *dose D* that is administered at each dosing occasion, and the *dosing interval* τ, the time period between the administrations of two consecutive doses. The ratio of dose and dosing interval can be summarized in the *dosing rate DR*. The dosing rate DR for multiple dose regimens can be seen as an analogue to the infusion rate R_0 for constant rate regimens. Multiple dose regimens are most commonly designed in such a way that a fixed dose is given in fixed time intervals, known as the dosing interval τ. In the following, the pharmacokinetic principles associated with such multiple dose regimens will be discussed.

When a drug is administered during multiple dosing before the previous dose has completely been eliminated, the doses are no longer independent from each other and accumulation takes place, i.e., the plasma concentration resulting after administration of the new dose is the sum of the drug concentrations produced by the new dose and the remainder of the previous doses that is still in the body at the time of administration of the new dose. Thus, the plasma concentration after administration of a dose during multiple dosing is not only dependent on that dose, but also on the dosing history. The drug accumulation observed during multiple dosing follows the *principle of superposition*, i.e., the observed drug concentration is the additive result of the concentration resulting from each individual dose administered (Fig. 1.7). This principle holds true for all drugs that follow linear PK, i.e., when primary PK parameters are constant and independent of dose and time. In this chapter, only cases of linear PK are considered.

On repeated drug administration, the plasma concentration will accumulate to finally reach a steady-state condition. Analogous to constant-rate regimens, at steady-state, the rate of drug input per dosing interval is equal to the rate of drug output. However, the drug concentration within each dosing interval is no longer constant, but is fluctuating between a

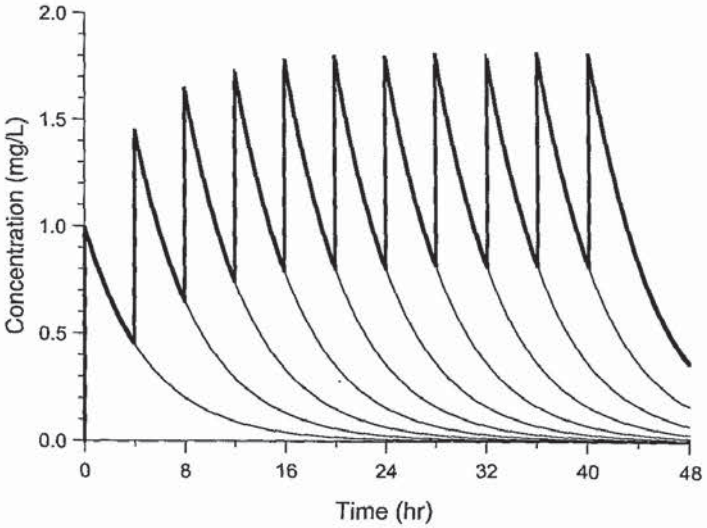

FIGURE 1.7 Principle of superposition. During multiple dose regimens, the resulting plasma concentration-time profile is the sum of the concentrations resulting from each individual dose administered during the dosing history of the regimen.

maximum or peak value $C_{ss,max}$ and a *minimum or through value* $C_{ss,min}$.

The plasma concentrations at any time point during a multiple dose regimen can be calculated as the sum of the plasma concentrations resulting from each individual dose at that time point. However, the calculation of this concentration might be very tedious work if numerous individual doses are involved. An easier way to calculate the drug concentrations during a fixed dose/fixed dosing interval multiple dose regimen (e.g., 300 mg every 8 hours) is to use the so-called accumulation factor (AF).

The AF can be used for calculating drug concentrations once steady-state has been reached:

$$AF = \frac{1}{1 - e^{-K\times\tau}} \qquad (1\text{-}22)$$

where K is the respective elimination rate constant of the drug and τ the dosing interval.

The concentration-time profile during each dosing interval of a multiple dose regimen at steady-state can now be calculated by using the equation that describes the concentration profile after a single dose and multiplying each exponential expression in the equation with the respective AF. Thus, the extent of accumulation during multiple dosing at steady-state is determined by the dosing interval τ and the half-life of the drug $t_{½}$ (or the elimination rate constant, *K*). Thus, the extent of accumulation is not only dependent on the pharmacokinetic properties of a drug, but also on the multiple dose regimen chosen.

Multiple Dose Regimens with Intravenous Input (IV Bolus). For the first dosing interval of an IV bolus multiple dose regimen, the peak $C_{1,max}$, trough $C_{1,min}$, and any concentration C are based on Equation 1-6 described by the following relationships:

$$C_{1,\max} = \frac{D}{V} \qquad (1\text{-}23a)$$

$$C_{1,\min} = \frac{D}{V} \times e^{-K\times\tau} \qquad (1\text{-}23b)$$

$$C = \frac{D}{V} \times e^{-K\times t} \qquad (1\text{-}23c)$$

Thus, peak and trough at steady-state can be expressed as the peak and trough after the first dose multiplied by the AF:

$$C_{ss,\max} = \frac{C_{1,\max}}{1 - e^{-K\times\tau}} = \frac{D}{V \times (1 - e^{-K\times\tau})} \qquad (1\text{-}24a)$$

$$C_{ss,\min} = \frac{C_{1,\min}}{1 - e^{-K\times\tau}} = \frac{D \times e^{-K\times\tau}}{V \times (1 - e^{-K\times\tau})} \qquad (1\text{-}24b)$$

Any other concentration during one dosing interval at steady-state is given by

$$C = \frac{D}{V} \times \frac{e^{-K\times t}}{1 - e^{-K\times\tau}} \qquad (1\text{-}25)$$

where t is the time elapsed within the dosing interval.

A less detailed, but also less computationally intensive view of accumulation is the calculation of the average concentration for a dosing interval τ. By definition, the average drug input rate is equal to the average drug output rate at steady-state. While the average input rate is the drug amount entering the systemic circulation per dosing interval, the average output rate is equal to the product of CL and the average plasma concentration within one dosing interval $C_{ss,av}$.

$$\frac{D}{\tau} = CL \times C_{ss,av} \qquad (1\text{-}26)$$

Thus, the average steady-state concentration $C_{ss,av}$ during multiple dosing is only determined by the dose, the dosing interval τ (or both together as dosing rate DR = D/τ), and the CL:

$$C_{ss,av} = \frac{D}{\tau \times CL} \qquad (1\text{-}27)$$

$C_{ss,av}$ is not the mean of $C_{ss,max}$ and $C_{ss,min}$. Due to the exponential decrease in plasma concentrations from peak to trough within each dosing interval, $C_{ss,av}$ is arithmetically closer to $C_{ss,min}$ than $C_{ss,max}$.

The average steady-state concentration $C_{ss,av}$ rises during multiple dosing just as it does following a constant-rate IV infusion. In contrast to a constant-rate infusion, however, concentrations are fluctuating within each dosing interval. Analogous to constant-rate infusions, the rate of drug accumulation is only determined by the elimination half-life of the drug. Thus, it takes one elimination half-life to reach 50% of $C_{ss,av}$, and two to reach 75% of $C_{ss,av}$.

Consequently, accumulation is complete after *five elimination half-lives* and more than 95% of the final average concentration at steady-state $C_{ss,av}$ is reached. In addition, the change in average concentration $C_{ss,av}$ after every change in dose rate, i.e., in dose D or dosing interval τ, also takes approximately five elimination half-lives. This is true for increases as well as decreases in τ or D, respectively.

The degree of fluctuation between peak and trough concentrations during one dosing interval, i.e., $C_{ss,max}$ and $C_{ss,min}$, can be expressed as

$$Fluctuation = \frac{C_{ss,\max} - C_{ss,\min}}{C_{ss,\min}} \qquad (1\text{-}28)$$

Fluctuation is determined by the relationship between elimination half-life $t_{½}$ and dosing interval τ. If the dosing interval τ is equal to the half-life $t_{½}$, then the trough concentration is exactly one half of the peak concentration and the degree of fluctuation is 100%. If $\tau > t_{½}$, the degree of fluctuation is more than 100%; if $\tau < t_{½}$, the degree of fluctuation is less than 100%. The same DR, i.e., the same amount of drug administered in a certain time period, always results in the same average steady-state concentration $C_{ss,av}$, independent of the number of doses into which it was divided. Dose frequency, however, determines the degree of fluctuation (Fig. 1.8).

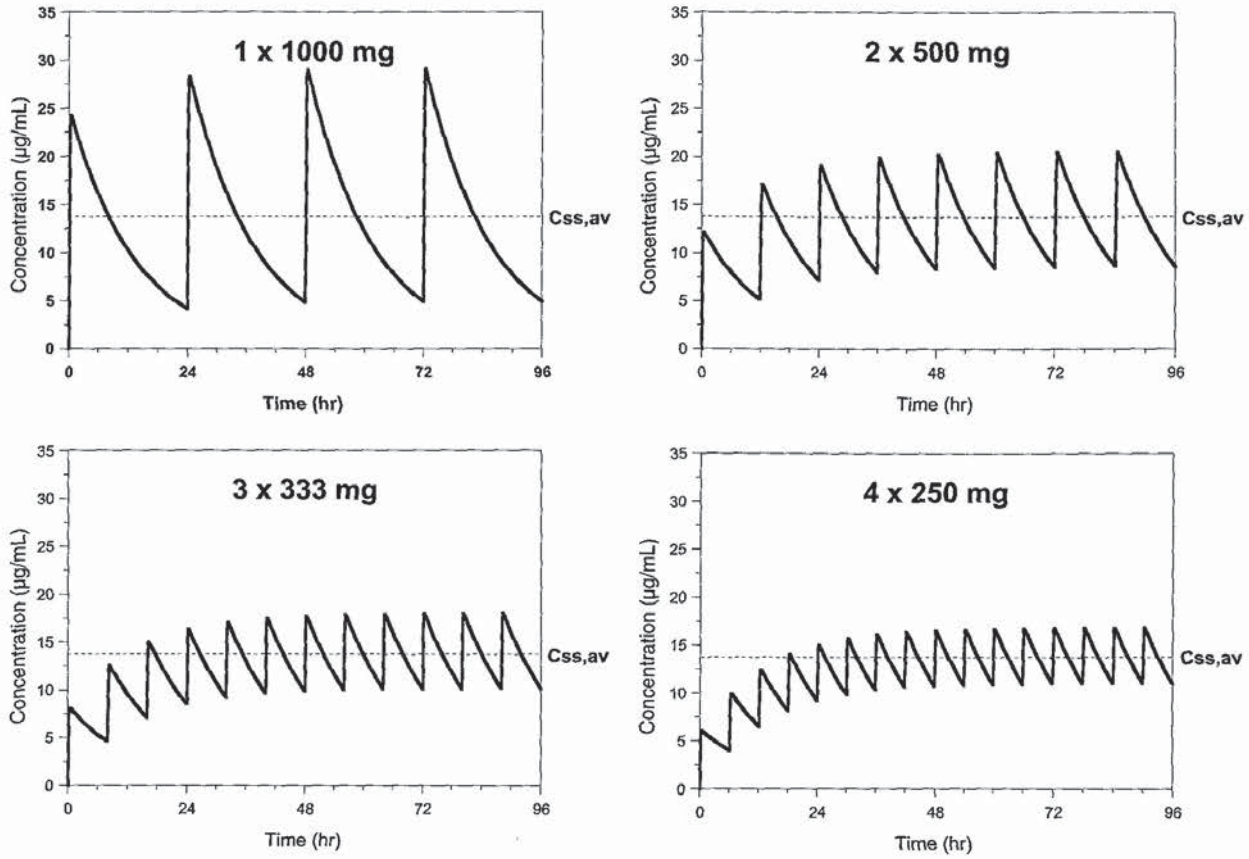

FIGURE 1.8 Fluctuation and dosing interval. In all four panels, a dosing rate of 1,000 mg daily or 41.7 mg/hour was given (CL = 3 L/hour, V = 40 L). This dosing rate is given once daily (1,000 mg QD), twice daily (500 mg BID), three times daily (333 mg TID), or four times daily (250 mg QID). The shorter the dosing interval, the less fluctuation is observed and the more $C_{ss,min}$ and $C_{ss,max}$ approximate $C_{ss,av}$.

Multiple Dose Regimens with First-Order Input (Oral Dosing). In clinical practice, most multiple dose regimens use dosage forms from which the drug enters the systemic circulation through a first-order or similar absorption process. Oral administration is the most predominant example for such multiple dose regimens, but other administration pathways also follow these principles, for example intramuscular (IM) administration.

The concepts of multiple dose regimens introduced for IV bolus multiple dosing are also applicable for multiple dose regimens of dosage forms with first-order drug input, e.g., oral dosage forms. It should be noted that the average steady-state concentration $C_{ss,av}$ is now determined by the bioavailable fraction F of the dose D administered per dosing interval τ and the CL:

$$C_{ss,av} = \frac{F \times D}{\tau \times CL} \qquad (1\text{-}29)$$

Given that absorption is virtually instantaneous, oral administration can be approximated more easily using IV bolus doses. The calculated peak and trough values at steady-state can then be used as reasonable approximations during oral multiple dosing at steady-state upper and lower limits for the expected peaks and troughs, respectively. This concept is shown in Figure 1.9 where the same dosage regimen is given as a multiple IV bolus dose regimen (equivalent to oral multiple dose regimens with very rapid absorption process; dotted line) or as dosage regimens with much slower absorption rate constants. Only the following differences have to be taken into account when dealing with multiple oral dosing compared to IV bolus dosing:

1. The dose has to be corrected for the extent of bioavailability F.
2. The rate of absorption affects the fluctuation of drug concentration, but not the value of the average steady-state concentration $C_{ss,av}$.
3. With increasing accumulation of drug, the concentration within one dosing interval at steady-state becomes relatively insensitive to variations in the rate of absorption.

Prediction of Concentration During a Multiple Dose Regimen. A patient is started on a therapy with 0.25 mg oral digoxin given once daily for the treatment of atrial fibrillation. Digoxin has a narrow therapeutic range (0.8–2 µg/L) and a long half-life (24–48 hours). Therefore, it is of particular interest to know early during therapy, whether the applied multiple dose regimen will ensure therapeutic plasma concentrations throughout the dosing interval at steady-state.

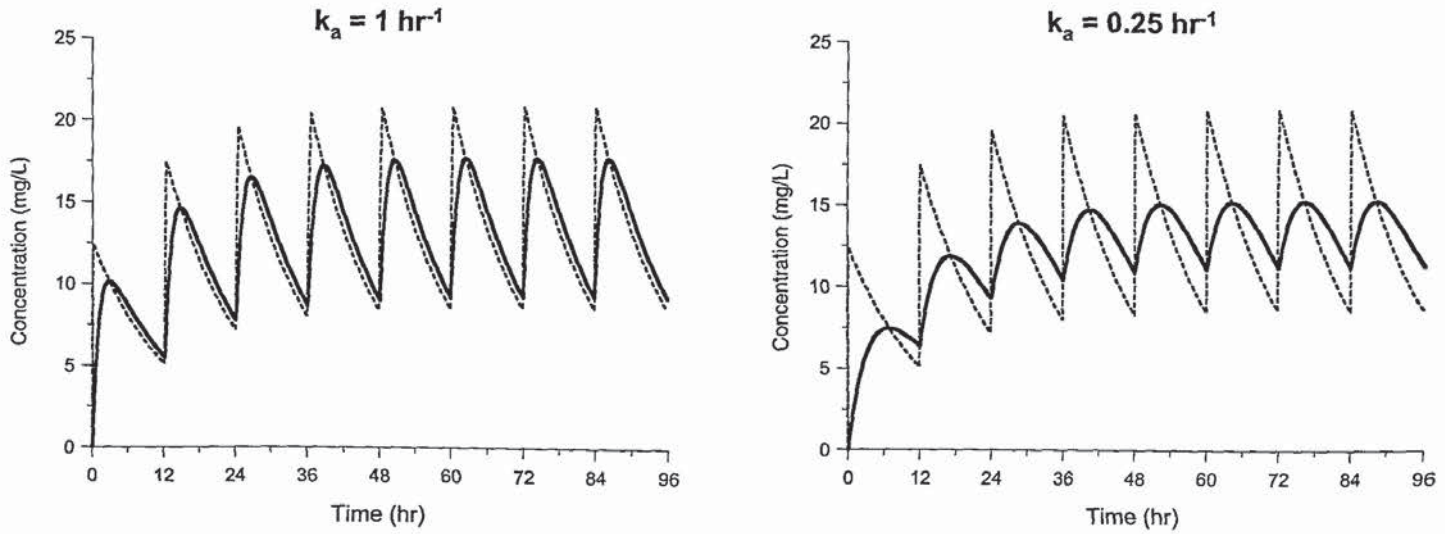

FIGURE 1.9 Comparison of IV and extravascular multiple dose regimens. The same multiple dose regimen is given by IV bolus dosing (*dashed line*) or by extravascular administration (*bold line*) with a fast (k_a = 1 hour^{-1}) and a slow (k_a = 0.25 hour^{-1}) first-order absorption rate constant (assuming F=1). The slower the absorption process, the less pronounced is the peak-to-trough fluctuation. Peak and trough concentrations after IV bolus dosing define the upper limit of peaks and the lower limit of troughs possible after multiple oral dosing.

The concentrations of digoxin 12 and 24 hours after administration of the first dose were measured and were 0.39 and 0.31 μg per L.

As the trough concentration is the lowest concentration during one dosing interval, the trough during multiple dosing at steady-state $C_{ss,min}$ should be higher than the lower limit of the therapeutic range.

Assuming that digoxin is rapidly absorbed and oral drug absorption has been completed by the time the first concentration was measured (12 hours), the elimination rate constant K can be estimated as

$$K = \frac{ln\left(\frac{0.39\ \mu g/L}{0.31\ \mu g/L}\right)}{24\ hr - 12\ hr} = 0.019\ hr^{-1} \qquad (1\text{-}30)$$

Thus, the accumulation factor for the multiple dose regimen is

$$AF = \frac{1}{1 - e^{-K\times\tau}} = \frac{1}{1 - e^{-0.019\ hr^{-1}\times 24\ hr}} = 2.7 \qquad (1\text{-}31)$$

$C_{ss,min}$ can then be predicted from the measured trough after the first dose (0.31 μg/L) and the accumulation factor:

$$\begin{aligned} C_{ss,min} &= C_{1,min} \times AF \\ &= 0.31\ \mu g/L \times 2.7 \\ &= 0.84\ \mu g/L \end{aligned} \qquad (1\text{-}32)$$

Dosage Regimen Adjustment for Multiple Dose Regimen. A patient with chronic obstructive pulmonary disease (COPD) will be started on a therapy with oral theophylline as part of the pharmacotherapeutic management of the disease. The recommended therapeutic range for theophylline in COPD is 8–12 mg per L. The population values for CL and V are CL = 2 L per hour and V = 35 L. The oral bioavailability of the immediate release tablet used was reported as 90%. A step-wise approach can be used to design a dosage regimen for achieving a target concentration of 10 mg per L.

Step 1: Necessary DR. In Step 1, the dose rate necessary to achieve the target concentration as $C_{ss,av}$ is determined based on the known values for bioavailability of the theophylline oral dosage form and the population average for theophylline CL:

$$\begin{aligned} DR_{necessary} &= \frac{C_{target} \times CL}{F} \\ &= \frac{10\ mg/L \times 2\ L/hr}{0.90} \\ &= 22.2\ mg/hr \\ &= 533\ mg/day \end{aligned} \qquad (1\text{-}33)$$

Step 2: Maximum dosing interval. In Step 2, a maximum dosing interval τ_{max} is calculated to keep the plasma drug concentrations within the therapeutic range of 8 to 12 mg per L, again using population averages for theophylline CL and V:

$$\tau_{max} = \frac{ln\left(\frac{C_{ss,max}}{C_{ss,min}}\right)}{K} = \frac{ln\left(\frac{C_{ss,max}}{C_{ss,min}}\right)\times V}{CL} = \frac{ln\left(\frac{12}{8}\right)\times 35\ L}{2\ L/hr} = 7.1\ hr \qquad (1\text{-}34)$$

Step 3: Practical dosage regimen. In Step 3, a clinically practical dosing interval smaller than τ_{max} is chosen and the dose per dosing interval is calculated based on the necessary dose rate:

Practical dosing interval $<\tau_{max}$: 6 hours

$$\begin{aligned} D &= DR_{necessary} \times \tau \\ &= 22.2\ mg/hr \times 6hr \\ &= 133.2\ mg \end{aligned} \quad (1\text{-}35)$$

Available dosage form: 125 mg
Recommended dosing regimen: 125 mg Q6hr
Step 4: Calculation of expected $C_{ss,max}$, $C_{ss,min}$, and $C_{ss,av}$. The optional Step 4 checks whether the dosage regimen chosen in Step 3 results in the desired peak, trough, and average concentrations at steady-state:

$$\begin{aligned} C_{ss,\max} &= \frac{D \times F}{V} \times \frac{1}{1-e^{-CL/V \times \tau}} \\ &= \frac{125\ mg \times 0.9}{35\ L} \times \frac{1}{1-e^{-2\ L/hr/35\ L \times 6hr}} \\ &= 11.1\ mg/L \end{aligned} \quad (1\text{-}36)$$

$$\begin{aligned} C_{ss,\min} &= C_{ss,\max} \times e^{-CL/V \times \tau} \\ &= 11.1\ mg/L \times e^{-2\ L/hr/35\ L \times 6hr} \\ &= 7.9\ mg/L \end{aligned} \quad (1\text{-}37)$$

$$\begin{aligned} C_{ss,av} &= \frac{D \times F}{\tau \times CL} = \frac{125\ mg \times 0.9}{6\ hr \times 2\ L/hr} \\ &= 9.4\ mg/L \end{aligned} \quad (1\text{-}38)$$

In clinical practice, oral sustained release dosage forms instead of immediate release dosage forms are frequently used in theophylline therapy to allow a longer dosing interval, i.e., less frequent dosing per day.

It should also be stressed that the calculated values for $C_{ss,max}$ and $C_{ss,min}$ are upper and lower limits, respectively, based on the assumption that absorption is instantaneous. Because absorption after oral administration of theophylline is likely to be a time-consuming process, actual peaks and troughs during multiple dosing at steady-state will be within the limits calculated. The slower the absorption process, the less fluctuation between $C_{ss,max}$ and $C_{ss,min}$ will be present.

Effect of Compliance on Multiple Dose Regimens. Because some medication regimens can be complex and many are self-administered by the patient, dosing errors can easily occur. The effect of dosing errors is different for drugs with similarly narrow therapeutic range dependent on their degree of accumulation. Generally, the more accumulation occurs, the less important compliance is. In other words, the smaller the ratio between dosing interval to half-life, the larger the degree of accumulation and the less impact a dosing error will have (Fig. 1.10).

PHYSIOLOGIC VARIABLES AFFECTING DRUG CLEARANCE

Clearance is one of the most important pharmacokinetic parameters for clinical pharmacokinetics as it determines the systemic exposure of a drug resulting from a therapeutic dosage regimen. Thus, any factors changing drug CL will also result in changes in the systemic exposure to the drug, which may ultimately be relevant for the efficacy and/or toxicity of the respective pharmacotherapeutic intervention.

As pointed out in Equation 1-1, total CL is the sum of individual organ CLs. The most important organs involved with drug elimination are the liver and the kidneys. The fractional contribution of excretion via the kidneys to overall drug CL can be expressed as f_e, the fraction of drug excreted unchanged into the urine. Thus, f_e is the fraction that renal CL contributes to overall CL:

$$CL_R = f_e \times CL \quad (1\text{-}39)$$

The parameter f_e can be used to describe the primary route of elimination for a drug and whether a change in the drug eliminating capacity of an elimination organ may likely affect the specific drug. Vancomycin is nearly exclusively eliminated by renal excretion ($f_e \sim 1$). Thus, any change in renal function is likely to affect vancomycin CL and thus systemic exposure. In contrast, nifedipine's route of elimination is nearly exclusively via hepatic metabolism ($f_e \sim 0$). Thus, nifedipine systemic exposure is likely to be affected by changes in hepatic function.

Protein Binding. Before further discussing the determinants and processes involved in the CL of drugs, the importance of free, unbound drug concentrations should be stressed. In therapeutic drug monitoring, drug concentrations in plasma are generally determined as total concentrations, i.e., bound and unbound drug. Drug molecules are to a variable extent bound to circulating proteins in plasma. Major binding proteins include albumin, α_1-acid glycoprotein (AAG), and lipoproteins. Drug bound in plasma, however, is not pharmacologically active, for some drugs is not accessible for metabolism and excretion, and is not able to pass biomembranes. In contrast, free drug is relevant for the pharmacologic effects, can be metabolized and excreted, and is able to pass biomembranes. Thus, only free drug concentrations are ultimately relevant in pharmacotherapy. Free drug concentrations are generally not measured by clinical laboratories, because their measurement involves advanced analytic techniques and is usually more expensive. Therapeutic ranges are therefore expressed as total concentration ranges. However, they can be related to therapeutic ranges for free, unbound concentrations.

Protein Binding and Therapeutic Range. The therapeutic range for total quinidine concentrations is 1 to 4 mg per L. As quinidine is approximately 90% bound to plasma proteins in normal patients, the corresponding therapeutic range for free quinidine concentrations is 0.1 to 0.4 mg per L.

Using total instead of the pharmacologically active free drug concentrations is valid as long as the degree of binding and thus the ratio between free and total drug concentrations remains constant. If the degree of binding changes, for example by drug-drug interactions or certain disease states, then the total drug concentration no longer provides a valid substitute for the free drug concentration. In these cases, measured total drug concentrations have to be carefully inter-

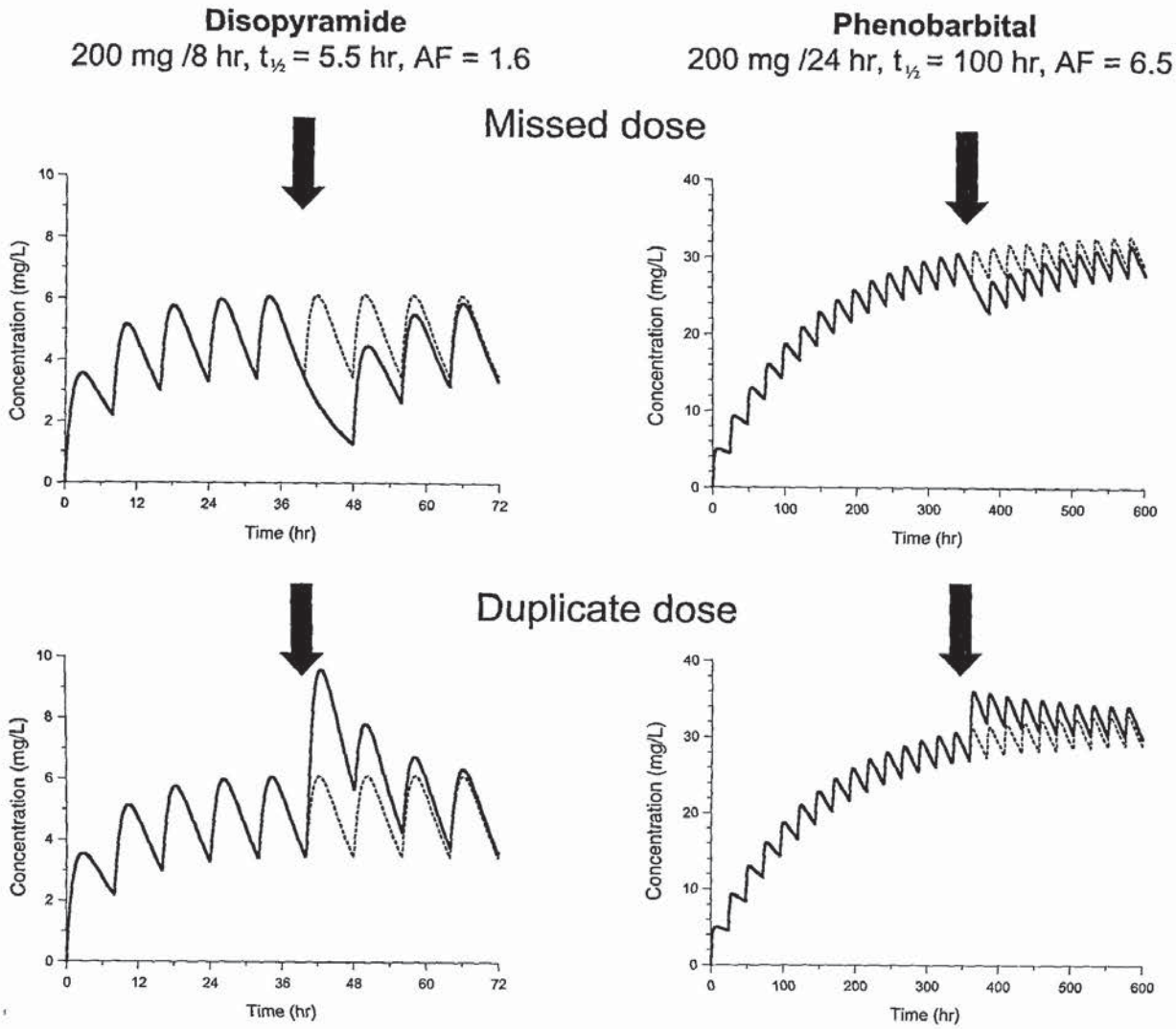

FIGURE 1.10 Effect of compliance on multiple dose regimens. Disopyramide and phenobarbital dosage regimens are used to compare the effect of compliance on multiple dose regimens with a small compared to a large ratio of half-life and dosing interval (disopyramide: 0.69; phenobarbital 4.2). The phenobarbital regimen results in substantial drug accumulation (AF 6.5), with only a small effect of each discrete dose on the plasma concentration-time profile. Thus, the effect of a duplicate of a missed dose on the average concentration is very limited and probably not clinically significant. The disopyramide regimen results only in relatively little accumulation (AF 1.6). Duplicate or missed doses have a substantial effect on the concentration-time profile and are likely to play a more important role than for phenobarbital.

preted and a different range of total drug concentrations may be therapeutically necessary.

In plasma, the total drug concentration C is the sum of the concentration of drug bound to plasma proteins C_b and the concentration of unbound, free drug C_u.

$$C = C_b + C_u \tag{1-40}$$

The degree of binding to plasma proteins is expressed as fraction unbound f_u. The fraction unbound f_u is a dimensionless number between 0 and 1, or 0% and 100%. It is defined as:

$$f_u = \frac{C_u}{C} \tag{1-41}$$

Thus, with the fraction unbound f_u, free drug concentrations can easily be assessed from total concentrations as

$$C_u = f_u \times C \tag{1-42}$$

Renal Clearance. Drug elimination of unchanged drug via the kidneys is the net result of three processes, glomerular filtration, tubular secretion, and tubular reabsorption. Renal CL is equal to the plasma volume that is cleared per minute by renal excretion. It is composed of the CLs related to glomerular filtration, tubular reabsorption, and tubular secretion:

$$CL_R = CL_{filtration} + CL_{secretion} - CL_{reabsorption} \tag{1-43}$$

Renal CL values can range from 0 mL/min for substances like glucose that are completely reabsorbed up to values approaching renal plasma flow for compounds like p-aminohippuric acid that are highly secreted.

Glomerular filtration is a passive process that removes all molecules of low molecular weight (MW <~20,000) out

of plasma. However glomerular filtration is limited to the fraction of drug not bound to plasma proteins. Thus, changes in plasma protein binding can modulate the glomerular filtration CL ($CL_{filtration}$) and thus CL_{ren} of a drug:

$$CL_{filtration} = f_u \times GFR \quad (1\text{-}44)$$

where GFR is the glomerular filtration rate, approximately 125 mL per min (7.5 L/hour) in a young, healthy individual, and f_u is the fraction of drug not bound to plasma proteins. Tubular secretion is an active secretion process that can occur against a concentration gradient and involves various drug transporters, specific membrane proteins that facilitate transport or actively transport drug molecules from one side of a biomembrane to the other. Tubular secretion is not limited by plasma protein binding. Tubular reabsorption may either occur by passive diffusion or by active transport.

For a drug that is only filtered and not reabsorbed or secreted, renal CL is only determined by plasma protein binding (f_u) and the glomerular filtration rate (GFR). GFR can clinically be estimated by measuring the CL of compounds that are not plasma protein bound ($f_u = 1$) and are exclusively eliminated via renal excretion ($f_e \sim 1$) with no contribution of tubular secretion and tubular reabsorption (e.g., creatinine, inulin, ^{51}Cr-EDTA).

Creatinine Clearance. Creatinine CL (CL_{cr}) is frequently used to estimate GFR in a clinical setting. Creatinine is an endogenous compound that is produced by muscle metabolism in the body with a production rate dependent on age, weight, and sex of the patient. It is predominantly excreted by glomerular filtration and shows only minor plasma protein binding, tubular secretion, or reabsorption. In stable patients, creatinine plasma concentration is determined by the equilibrium between creatinine formation controlled by muscle metabolism and creatinine excretion dependent on GFR. Under the assumption of constant muscle metabolism, creatinine concentrations (serum creatinine concentration S_{cr}) increase with decreasing renal function and vice versa.

$$CL_{cr} = \frac{Creatinine\ formation\ rate}{S_{cr}} \quad (1\text{-}45)$$

Creatinine CL can be estimated from various empirical relationships. The most frequently used is the equation of Cockcroft and Gault:

$$CL_{cr} = \frac{(140 - age) \times IBW}{72 \times S_{cr}} \quad (1\text{-}46)$$
$$(\times\ 0.85 \text{ for female patients})$$

The Cockcroft and Gault equation provides the CL_{cr} in mL per min. It requires using the ideal body weight (IBW) in kilograms, age in years, and creatinine plasma concentration in milligrams per deciliter. It is only valid for adult patients. IBW can be calculated by the following relationships:

$$\text{IBW (male)} = 50 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft} \quad (1\text{-}47)$$

$$\text{IBW (female)} = 45.5 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft} \quad (1\text{-}48)$$

Renal Impairment. Although creatinine CL is mechanistically only related to GFR, it is also often used clinically as a measure of global renal function. This approach assumes that only a fraction of the kidney's nephron population is affected by the impairment, and that the unaffected fraction is fully functional. The fraction of normal renal function RF is then determined as ratio of creatinine CL in a patient with impaired renal function compared to the normal creatinine CL. Because creatinine CL is body size dependent, is it usually corrected for body surface area to allow comparisons among different individuals. The creatinine CL of a normal adult is 125 mL/min/1.73 m^2. Renal function as a fraction of normal can then be determined as

$$RF = \frac{CL_{cr}^{impaired}}{125\ mL/min/1.73\ m^2 \times BSA} \quad (1\text{-}49)$$

where $CL_{Cr}^{impaired}$ is the creatinine CL in the individual with impaired renal function and BSA is the individual's body surface area. Body surface area can be estimated based on the individual's height and body weight via nomograms or empirical relationships such as the one by Dubois [$BSA = (Total\ body\ weight\ in\ kg)^{0.425} \times (Height\ in\ cm)^{0.725} \times 0.007184$].

The effect of renal impairment on the CL of a drug undergoing renal excretion can then be estimated as

$$CL_{renal\ impairment} = CL \times \left[1 - f_e \times (1 - RF)\right] \quad (1\text{-}50)$$

where f_e is the fraction of drug excreted unchanged via the kidneys and CL is the drug's CL in the absence of renal impairment.

Dosage Adjustment in Renal Impairment. A female patient (61 years old; total body weight: 63.5 kg; height: 5′3″; BSA 1.66 m^2; serum creatinine 1.1 mg/dL) will be started on digoxin therapy. The therapeutic range of digoxin is 0.8–2.0 μg per L. The population value for CL is 2.7 mL/min/kg total body weight, f_e is 0.65, and the oral bioavailability of the dosage form is 72%. What dose rate is necessary to achieve an average steady-state concentration of 1.2 μg per L?

$$\text{IBW (female)} = 45.5 \text{ kg} + 2.3 \text{ kg} \times 3 = 52.4 \text{ kg}$$

$$CL_{cr} = \frac{(140 - 61) \times 52.4}{72 \times 1.1} \times 0.85 = 44.4\ mL/min \quad (1\text{-}51)$$

$$RF = \frac{44.4\ mL/min}{125\ mL/min/1.73\ m^2 \times 1.66\ m^2} = 0.37 \quad (1\text{-}52)$$

$$CL_{renal\ impairment} = 63.5\ kg \times 2.7\ mL/\min/kg \times [1-0.65\times(1-0.37)] = 101\ mL/\min = 6\ L/hr \quad (1\text{-}53)$$

$$DR = \frac{C_{target} \times CL_{renal\ impairment}}{F} = \frac{1.2\ \mu g/L \times 6\ L/hr}{0.72} = 10\ \mu g/hr \quad (1\text{-}54)$$

In clinical practice, a dose of 250 μg daily (10 μg/hour × 24 hours/day = 240 μg/day rounded off to 250 μg) can be given.

Hepatic Clearance

Hepatic Drug Elimination Processes. Hepatic drug elimination is mediated by two primary routes: biliary drug excretion, and hepatic drug metabolism. Drugs may be excreted into the bile either in unchanged form or after metabolism, especially by conjugation reactions such as glucuronidation. Biliary excretion is an active excretion process that is known to involve multiple drug transporters, including P-glycoprotein (MDR1, ABCB1), MRP2 (ABCC2), and BCRP (ABCG2).

Hepatic drug metabolism can be divided into two broad groups: phase I reactions, which involve chemical alteration of the drug structure (e.g., hydrolysis, reduction, or oxidation); and phase II reactions, in which the drug molecule is conjugated (e.g., by glucuronidation, sulfation, acetylation, etc.). Metabolism patterns generally consist of one or several phase I reactions and may be followed by phase II reactions. However, both reaction groups may also occur in isolation. An overview of the major phase I and phase II drug-metabolizing enzymes and their relative importance for drug disposition is described in Figure 1.11 *(see color insert)*.

The best-researched enzyme family, and perhaps the most important based on the proportion of drugs which are metabolized by it, is the cytochrome (CYP) P450-system, which is involved in the oxidative metabolism of many endogenous compounds, environmental chemicals, herbal components, and drugs. The family of CYP enzymes is divided into various subfamilies of enzymes that have different substrate specificity and may be involved in different chemical reactions. Major CYP enzymes that are relevant for drug metabolism include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and the CYP3A subfamily with CYP3A4, CYP3A5, and CYP3A7. The activity of CYP enzymes as well as other drug-metabolizing enzyme systems is dependent on genetic and environmental factors including nutrition, age, concomitant drug therapy (drug-drug interactions), and other host or environmental variables.

CYP enzymes demonstrate a high degree of substrate specificity, i.e., a drug is often a good substrate for one CYP enzyme but not others. Although many drugs rely heavily on a specific CYP enzyme for their metabolism, some drugs are metabolized by more than one CYP enzyme. The overall

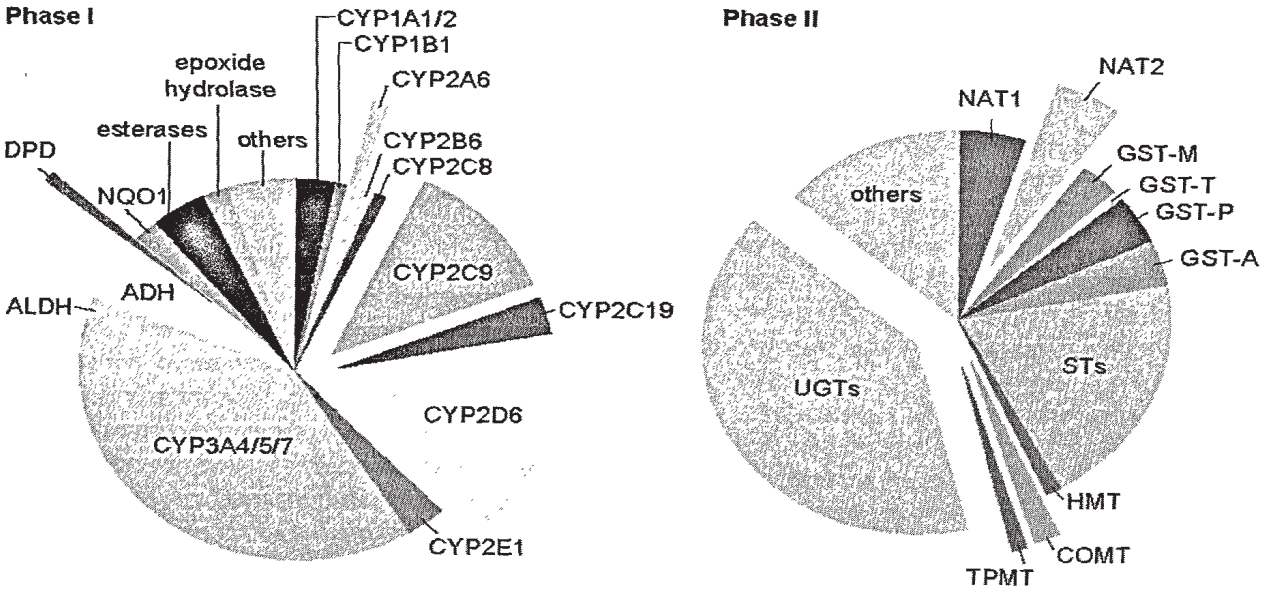

FIGURE 1.11 Major drug-metabolizing enzymes *(see color insert)*. The percentage of phase I and phase II metabolism of drugs that each enzyme contributes is estimated by the relative size of each section of the corresponding chart. Essentially all of the major human enzymes responsible for modification of functional groups [classified as phase I reactions **(left)**] or conjugation with endogenous substituents [classified as phase II reactions **(right)**] exhibit genetic polymorphisms; those enzyme polymorphisms that have already been associated with changes in drug effects are separated from the corresponding pie charts. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; NQO1, NADPH:quinone oxidoreductase or DT diaphorase; COMT, catechol O-methyltransferase; GST, glutathione S-transferase; HMT, histamine methyltransferase; NAT, N-acetyltransferase; STs, sulfotransferases; TPMT, thiopurine methyltransferase; UGTs, uridine 5′-triphosphate glucuronosyltransferases. (From Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 286:487–491, 1999.)

metabolism, and therefore metabolic CL, of a drug is the sum of all its metabolic pathways.

A frequently updated table that indicates which commonly used drugs are major substrates, inducers, and inhibitors for various CYP enzymes is available at: http://medicine.iupui.edu/flockhart/table.htm

Knowledge of the substrates, inhibitors, and inducers of individual CYP enzymes assists in predicting clinically significant drug interactions and allows part of the frequently observed interindividual variability in pharmacokinetics and thus drug response to be explained and predicted. Refer to Chapter 3 for a further discussion of drug-drug interactions.

Venous Equilibrium Model of Hepatic Clearance. Based on the previously discussed organ CL model, CL_H can be expressed by

$$CL_H = Q_H \times E_H \tag{1-55}$$

where Q_H is the liver flow rate (for blood: 1.5 L/min or 90 L/hour in a normal, 70 kg individual; for plasma: 0.825 L/min or 50 L/hour) and E_H is the hepatic extraction ratio. E_H is an indicator of the efficiency of the processes responsible (e.g., metabolism) for eliminating drug from the blood or plasma as it passes through the liver. E_H can range from 0 to 1. An E_H of 1 means 100% of the drug entering the liver is eliminated, and an E_H of 0 means none of the drug entering the liver is eliminated.

Based on the venous equilibrium model for hepatic CL,[6] the hepatic extraction ratio E_H is defined as

$$E_H = \frac{CL_{int} \times f_u}{Q_H + CL_{int} \times f_u} \tag{1-56}$$

where f_u is the unbound fraction as a measure of protein binding and CL_{int} is the intrinsic CL. CL_{int} is the theoretic value for a drug's CL by the liver if it were not protein bound, and it is an indication of the liver's enzymatic capacity to eliminate a drug if access is not impeded by protein binding or liver flow rate. Hepatic CL is then given as

$$CL_H = E_H \times Q_H = \frac{Q_H \times CL_{int} \times f_u}{Q_H + CL_{int} \times f_u} \tag{1-57}$$

and the fraction escaping hepatic first-pass metabolism F_H as

$$F_H = 1 - E_H = 1 - \frac{CL_{int} \times f_u}{Q_H + CL_{int} \times f_u} = \frac{Q_H}{Q_H + CL_{int} \times f_u} \tag{1-58}$$

Conceptually, two basic classes of drugs can be distinguished based on the venous equilibrium model, drugs with high hepatic extraction ratio and drugs with low hepatic extraction ratio. This approach has been useful to predict changes in hepatic CL or steady-state drug concentrations secondary to changes in protein binding (f_u), hemodynamics (Q_H), and drug-metabolizing activity (CL_{int}), for example by drug-drug interactions resulting in induction or inhibition of drug-metabolizing enzymes. Table 1.2 summarizes the effect of changes in f_u, Q_H, and CL_{int} on total and unbound steady-state concentration C_{ss} and $C_{ss,u}$.

High-Extraction Drugs. A high-extraction drug is one that has an extraction ratio greater than or equal to 0.7. In this case, the product of CL_{int} and f_u is much larger than Q_H as transport of drug to the liver is the limiting factor for hepatic CL. Thus, high-extraction drugs have a flow-limited hepatic CL. As $f_u \times CL_{int} >> Q_H$, the expressions for CL_H and F_H simplify to

$$CL_H \cong Q_H \tag{1-59}$$

$$F_H \cong \frac{Q_H}{CL_{int} \times f_u} \tag{1-60}$$

For the purpose of qualitative prediction of the effect of changes in f_u, CL_{int}, and Q_H on total and unbound steady-state concentrations (C_{ss} and $C_{ss,u}$), F_a and F_G are assumed to be 1 for extravascular administrations.

For IV administration with dose rate DR:

$$C_{ss} \cong \frac{DR}{Q_H} \tag{1-61a}$$

$$C_{ss,u} \cong \frac{f_u \times DR}{Q_H} \tag{1-61b}$$

For extravascular (oral) administration with dose rate DR:

$$C_{ss} \cong \frac{F_H \times DR}{Q_H} = \frac{Q_H \times DR}{CL_{int} \times f_u \times Q_H} = \frac{DR}{CL_{int} \times f_u} \tag{1-62a}$$

$$C_{ss,u} \cong \frac{f_u \times F_H \times DR}{Q_H} = \frac{DR}{CL_{int}} \tag{1-62b}$$

High-extraction drugs are characterized by route-dependent differences in the effect of f_u, Q_H, and CL_{int}. For a high-extraction drug given by the IV route, alterations in liver flow rate result in inverse changes in C_{ss} and $C_{ss,u}$. When given orally, changes in liver flow rate are offset by changes in bioavailability, resulting in no net change in C_{ss} or $C_{ss,u}$.

Changes in intrinsic clearance (CL_{int}) have no effect on C_{ss} and $C_{ss,u}$ after IV administration. When given orally, changes in CL_{int} result in inverse changes in C_{ss} and $C_{ss,u}$ due to changes in F_H.

Changes in protein binding do not affect C_{ss} after IV administration, but affect $C_{ss,u}$ proportionally. After oral administration, changes in f_u would be expected to result in changes in C_{ss} but not $C_{ss,u}$ based on changes in F_H. However, since high-extraction drugs are generally nonrestrictively cleared, i.e., protein binding is not a CL limiting factor, it might also be expected that hepatic first-pass metabolism is not affected by the degree of protein binding for high-extraction drugs.

TABLE 1-2 Predicted Effect of Perturbations on Free and Total Steady-State Concentrations Using the Venous Equilibrium Model for Hepatic Clearance

Perturbation	CL_H	F_H	C_{ss}	$C_{ss,u}$
High-Extraction Drugs – IV Administration				
$Q_H \uparrow$	↑	–	↓	↓
$Q_H \downarrow$	↓	–	↑	↑
$f_u \uparrow$	↔	–	↔	↑
$f_u \downarrow$	↔	–	↔	↓
$CL_{int} \uparrow$	↔	–	↔	↔
$CL_{int} \downarrow$	↔	–	↔	↔
High-Extraction Drugs – Oral Administration				
$Q_H \uparrow$	↑	↓	↔	↔
$Q_H \downarrow$	↓	↑	↔	↔
$f_u \uparrow$	↔	↔ (?)		
$f_u \downarrow$	↔	↔ (?)		
$CL_{int} \uparrow$	↔	↓	↓	↓
$CL_{int} \downarrow$	↔	↑	↑	↑
Low-Extraction Drugs – IV and Oral Administration				
$Q_H \uparrow$	↔	↔	↔	↔
$Q_H \downarrow$	↔	↔	↔	↔
$f_u \uparrow$	↑	↔	↓	↔
$f_u \downarrow$	↓	↔	↑	↔
$CL_{int} \uparrow$	↑	↔	↓	↓
$CL_{int} \downarrow$	↓	↔	↑	↑

↑, increase; ↔, little or no change; ↓, decrease.

High-Extraction Drug and Congestive Heart Failure. A 53-year-old patient recently developed congestive heart failure (CHF) due to a myocardial infarction. The patient has been on oral propranolol therapy for several years for the management of hypertension. Propranolol is almost exclusively eliminated by hepatic metabolism and can be classified as a high-extraction drug based on its high hepatic CL of 1,100 mL per min combined with its low oral bioavailability (25%). Mild-to-moderate CHF is known to reduce the hepatic flow rate, Q_H. Severe CHF may additionally result in liver damage, i.e., a reduction in CL_{int}. What are the expected effects on total and unbound propranolol concentrations C_{ss} and $C_{ss,u}$?

$$C_{ss} \cong \frac{DR}{CL_{\text{int}} \times f_u} \tag{1-63a}$$

$$C_{ss,u} \cong \frac{DR}{CL_{\text{int}}} \tag{1-63b}$$

The effect of Q_H on CL is predicted to be offset by its effect on bioavailability. Thus, C_{ss} and $C_{ss,u}$ would not be affected in mild-to-moderate CHF, but would increase if CL_{int} is reduced in more severe cases of CHF.

Low-Extraction Drugs. A low-extraction drug is one that has an extraction ratio less than or equal to 0.3. In this case, the product of CL_{int} and f_u is much smaller than Q_H as the capacity of drug-metabolizing enzymes is the limiting factor for hepatic CL. Thus, low-extraction drugs have a capacity-limited hepatic CL:

As $f_u \times CL_{\text{int}} << Q_H$, the expressions for CL_H and F_H simplify to

$$CL_H \cong f_u \times CL_{\text{int}} \tag{1-64}$$

$$F_H \cong 1 \tag{1-65}$$

For IV administration with dose rate DR:

$$C_{ss} \cong \frac{DR}{f_u \times CL_{\text{int}}} \tag{1-66a}$$

$$C_{ss,u} \cong \frac{f_u \times DR}{f_u \times CL_{\text{int}}} = \frac{DR}{CL_{\text{int}}} \tag{1-66b}$$

For extravascular (oral) administration with dose rate DR:

$$C_{ss} \cong \frac{F_H \times DR}{f_u \times CL_{int}} \cong \frac{DR}{f_u \times CL_{int}} \quad (1\text{-}67a)$$

$$C_{ss,u} \cong \frac{f_u \times F_H \times DR}{f_u \times CL_{int}} \cong \frac{DR}{CL_{int}} \quad (1\text{-}67b)$$

For low-extraction drugs, there are no route-dependent differences in the effect of alterations in CL_{int}, Q_H, or f_u. Changes in liver blood flow rate have no relevant effect on C_{ss} and $C_{ss,u}$. Changes in CL_{int} result in inversely proportional changes in both C_{ss}, and $C_{ss,u}$.

Changes in f_u have no effect on the pharmacologically active $C_{ss,u}$, but result in inversely proportional changes in C_{ss}. Acknowledging this change in the relationship between $C_{ss,u}$ and C_{ss} becomes especially important if concentration measurements for therapeutic drug monitoring are based on total rather than unbound drug. Although C_{ss} changes, no dosage adjustment is necessary as the pharmacologically active $C_{ss,u}$ remains unchanged. Misinterpretation of changes in total drug concentration under these conditions, especially if no unbound drug concentration is available, could result in unnecessary changes in the dosing regimen and subsequent toxicity or lack of efficacy. This is illustrated in Figure 1.12.

Low-Extraction Drug and Change in Plasma Protein Binding. The antiepileptic phenytoin is primarily eliminated via hepatic metabolism and is a low-extraction drug. It is 90% bound to plasma proteins ($f_u = 0.1$) with albumin as the major binding protein. The therapeutic range for phenytoin is 10–20 mg per L.

A patient with chronic renal failure has a steady-state phenytoin level of 8.4 mg per L and a serum albumin of 2.2 g per dL. One might be tempted to increase the daily dose of phenytoin to achieve a target concentration of 15 mg per L. However, this would likely result in toxicity.

When the patient developed chronic renal failure, renal loss of albumin resulted in a decrease in albumin concentrations from the normal value of approximately 4.3 g per dL to 2.2 g per dL. This led to an increase in f_u from 0.1 to 0.18. Because phenytoin is an orally administered low-extraction drug, the increase in f_u resulted in a decrease in C_{ss}, but $C_{ss,u}$ remained unchanged.

$$\downarrow C_{ss} \cong \frac{DR}{\uparrow f_u \times CL_{int}} \quad (1\text{-}68a)$$

$$\leftrightarrow C_{ss,u} \cong \frac{DR}{CL_{int}} \quad (1\text{-}68b)$$

This is the reason for the low total phenytoin concentration of 8.4 mg per L that was measured. It corresponds to an unbound concentration of

$$C_u = f_u \times C = 0.18 \times 8.4\ mg/L = 1.5\ mg/L \quad (1\text{-}69)$$

As the therapeutic range for total phenytoin concentrations is 10 to 20 mg per L and f_u is 0.1 in normal individuals, the therapeutic range for unbound concentrations is 1 to 2 mg per L. Thus, the patient's unbound phenytoin concentrations are within the therapeutic range and the dose rate of phenytoin in this patient should not be increased despite total phenytoin levels below the therapeutic range.

Alterations in Plasma Protein Binding. The extent of plasma protein binding of a drug may be affected by several different mechanisms. Under numerous physiologic and

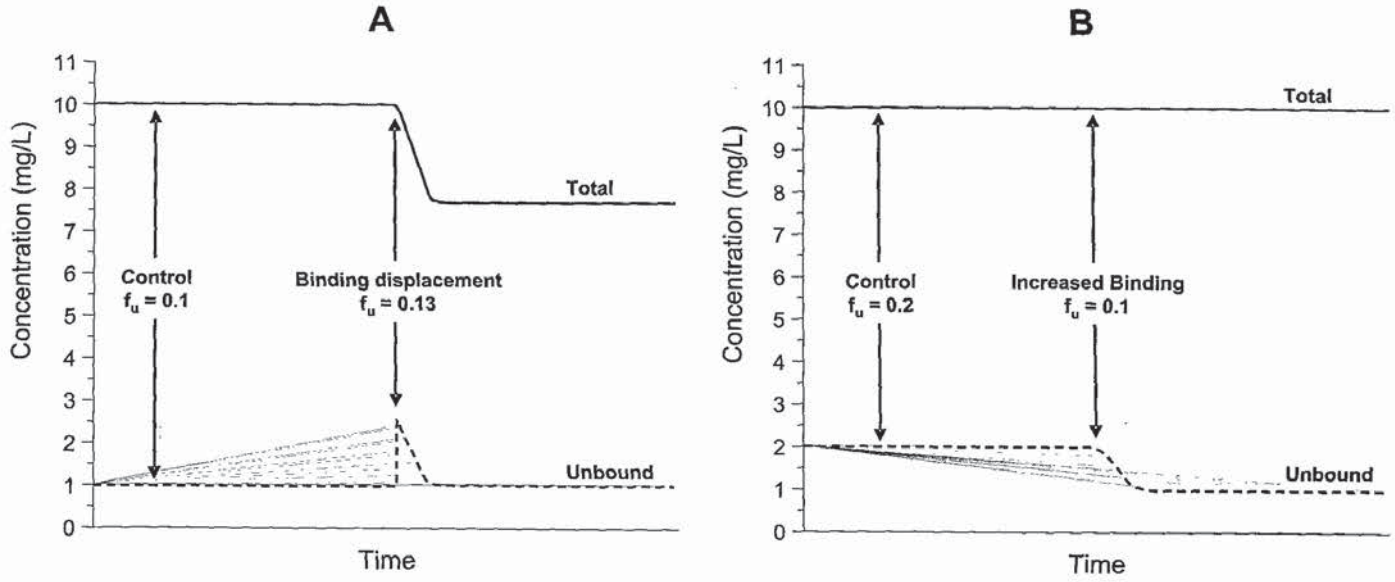

FIGURE 1.12 Effect of plasma protein binding displacement on steady-state plasma concentrations during a constant IV infusion. For a low extraction drug **(A)**, binding displacement has no effect on the unbound concentration $C_{ss,u}$ except for a transient increase, but total concentrations will be reduced. For a high extraction drug **(B)**, increase in binding results in a decrease in unbound concentration $C_{ss,u}$, but total concentrations C_{ss} remain unaffected. Solid lines, total drug concentrations; dashed lines,: unbound concentration. (From MacKichan JJ, Comstock TJ. General pharmacokinetic principles. In: Taylor WJ, Diers Cavinness M, eds. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX: Abbott Laboratories, 1986.)

pathologic conditions, synthesis or degradation of binding proteins is modified, thereby increasing or decreasing the binding capacity for the drug in plasma and thus changing the fraction unbound, f_u. In addition, binding displacements may occur either through endogenous substances competing for the same binding sites or exogenous compounds such as concomitantly administered drugs. The latter mechanism is the typical case of a drug-drug interaction via binding displacement.

One prerequisite for protein displacements to be clinically relevant is that the displaced drug must be extensively protein bound (i.e., >90% bound to plasma proteins), because only then will displacement result in a substantial increase in the fraction unbound.

Decreasing the binding of a drug that is 99% protein bound by 1% will result in doubling the fraction unbound (from 1% to 2%) and thus the unbound, pharmacologically active concentration of the drug. Decreasing the binding of a drug that is 60% protein bound by 1% will result in an increase of the fraction unbound from 40% to 41%, i.e., an increase in the unbound concentration of 2.5%.

The clinical importance of protein binding displacement interactions is frequently overstated.[7,8] Very specific conditions have to be fulfilled before protein displacement becomes therapeutically relevant. These are summarized in Figure 1.13. One can distinguish between long-term effects at steady-state and transient effects shortly after binding displacement.

Long-Term Effects of Displacement. The influence of displacement on the unbound concentration at steady-state $C_{ss,u}$ depends on the extraction ratio and the route of administration of the affected drug. As discussed in the previous section, $C_{ss,u}$ is unaffected by changes in f_u for low-extraction drugs. For high-extraction drugs given by IV administration, however, changes in f_u affect $C_{ss,u}$, but not total concentrations. These relationships are summarized in Figure 1.12.

Transient Effects of Displacement. Protein displacements for low-extraction drugs result in a transient increase in free concentration C_u while the body re-equilibrates. During this period, drug distribution and drug elimination will change to compensate for the increased C_u, but a relevant increase in C_u is only likely to occur for drugs with a small V (<10 L), for which most of the drug resides in the plasma. This transient increase in C_u becomes acutely relevant only if C_u increases above the corresponding therapeutic range, a situation that is relatively uncommon.

CLINICAL PHARMACODYNAMICS

This chapter has focused on the time course of drug concentrations in blood or plasma as a function of the administered dosage regimen, assuming that these concentrations are representative of or functionally related to the concentration at the sites of action for therapeutic as well as toxic effects. What is really of interest in clinical pharmacotherapy, however, is not the time course of concentrations, but the time course of therapeutic and toxic effects. Therefore, not only the PK of a drug have to be considered, but also its PD.

PHARMACOKINETIC VERSUS PHARMACODYNAMIC VARIABILITY

PK can be seen as the translator of dose to concentration over time, whereas PD links concentration to drug effects.

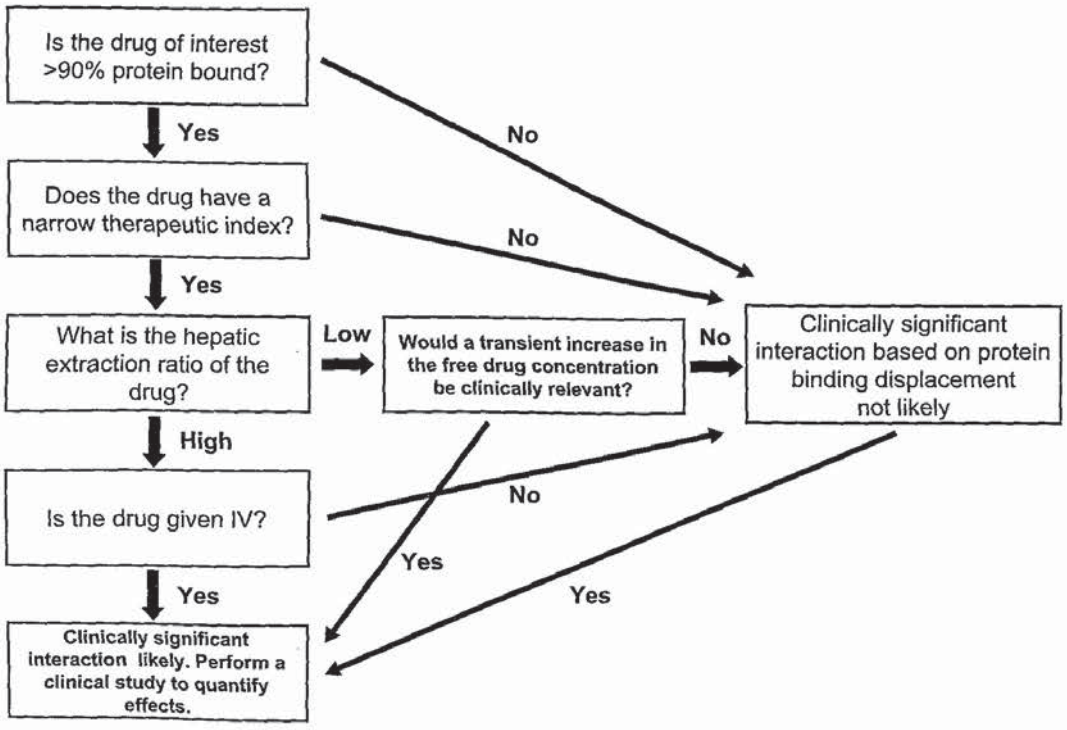

FIGURE 1.13 Algorithm for determining clinical significance of potential protein binding displacement interactions. (From Rolan PE. Plasma protein binding displacement interactions—why are they still regarded as clinically important? Br J Clin Pharmacol 37: 125–128, 1994.)

Together, they determine the time course of drug effects. Note that while PK and PD are essentially predetermined by the physiochemical properties of the drug and physiologic and/or pathophysiologic conditions of the body, manipulating the dose, route of administration, and frequency of dosing can result in optimized targeted effects by controlling concentrations.

Variability in response to the same dosage regimen of a drug given to different patients is the result of variability in PK and PD characteristics among patients. Empirical dosing without any knowledge about the PK and PD of individual patients leaves PK and PD variability uncontrolled. Thus, if PK and /or PD variability are high, the observed effect resulting from an administered dosage regimen is only poorly predictable in an individual patient.

Concentration-based dosing controls PK variability between different patients by determining individual PK based on plasma concentration measurements. Subsequent individualization of the dosage regimen allows a certain target concentration in all individuals to be maintained. However, the PD variability still is uncontrolled, which may lead to different magnitudes of effect in different patients despite the same target concentration. Concentration-based dosing is clinically used via therapeutic drug monitoring and is applicable for drugs for which PK variability is higher than PD variability. Thus, effectively controlling for PK variability may significantly reduce the variability in response to a drug therapy among patients.

For numerous drugs, however, PD variability is much higher than PK variability. In these cases, plasma concentration monitoring is of limited benefit, as the plasma concentration is a poor predictor for the patient's therapeutic response to the dosage regimen. Also, when drug concentrations required to achieve a desired therapeutic effect are much lower than concentrations that produce serious toxicity, then it may be feasible to treat all patients with a high enough dose so that essentially all patients achieve therapeutic drug concentrations, despite PK variability, without toxicity. These are among the major reasons why therapeutic drug monitoring is only performed for a limited number of drugs.

Theophylline and warfarin are drugs with a narrow therapeutic range and high interindividual variability in response. For theophylline, therapeutic drug monitoring by plasma level measurements is performed as theophylline plasma concentrations are a good predictor for its effects and PK variability is higher than PD variability. For warfarin, PD variability is higher than PK variability. Thus, warfarin plasma concentrations would only be a poor predictor for its effect and thus, patients are monitored for warfarin efficacy (prothrombin time or INR) instead of its plasma concentration.

PK/PD-based dosing would overcome the drawbacks of controlling only one component of pharmacologic variability by controlling for PK as well as PD variability. This would require determining the individual patient's PK parameters (i.e., CL and V) and the patient's PD parameters (i.e., E_{max} and EC_{50}). Individual assessment of pharmacodynamic parameters, however, currently is rarely performed in clinical settings. One example for clinically applied PK/PD-based dosing is antibiotic pharmacotherapy, for example with vancomycin, where the in vitro sensitivity of the pathogen is routinely assessed as minimum inhibitory concentration (MIC), a typical PD parameter characterizing the concentration-effect relationship. The MIC together with the site of infection is used to guide the selection of an appropriate target therapeutic range that can then be achieved by concentration-controlled dosing using plasma concentration measurements and therapeutic drug monitoring.

PHARMACODYNAMIC MODELS

PK relationships are linear for most drugs, i.e., follow the principle of superposition. In contrast, the relationship between plasma concentration and effect for most drugs is not linear, but follows a nonlinear relationship that levels off at a maximum effect being reached with a specific drug therapy.[9]

The most widely used pharmacodynamic model for concentration-dependent, reversible drug effects that are directly mediated is the E_{max}-model. The E_{max}-model is an empirically derived relationship that relates the effect (E) to the concentration (C) by the following relationship:

$$E = \frac{E_{max} \times C}{EC_{50} + C} \tag{1-70}$$

where E_{max} is the maximum effect possible with the specific drug and EC_{50} is the concentration that causes 50% of E_{max}, the half-maximum effect. E_{max} refers to the intrinsic activity of a drug, EC_{50} to its potency.

Although the E_{max}-model is an empiric relationship, its value lies in the fact that it can be related to the receptor theory of drug action. Under the assumption that the observed effect E is directly proportional to the number of occupied receptors, E_{max} is equivalent to the number of receptors available, and EC_{50} is equivalent to the affinity constant of the drug to the receptor, i.e., the concentration at which half of the receptor sites are occupied.

The E_{max}-model describes the concentration-effect relationship over a wide range of concentrations from zero effect in the absence of drug to the maximum effect at concentrations much higher than EC_{50} ($C >> EC_{50}$). The clear nonproportional concentration-effect relationship of the E_{max}-model is presented in Figure 1.14 *(see color insert)* in linear and semilogarithmic plots. Whereas small increases in concentration may result in significant increases of the effect for low concentrations, this is much less pronounced for higher concentrations where only small changes in effect will result from changes in concentration. From the semilogarithmic presentation, it is apparent that in the range from 20% to 80% of the maximum effect, the relationship between effect and the logarithm of the concentration is linear. This is consistent with a log-linear concentration-effect relationship

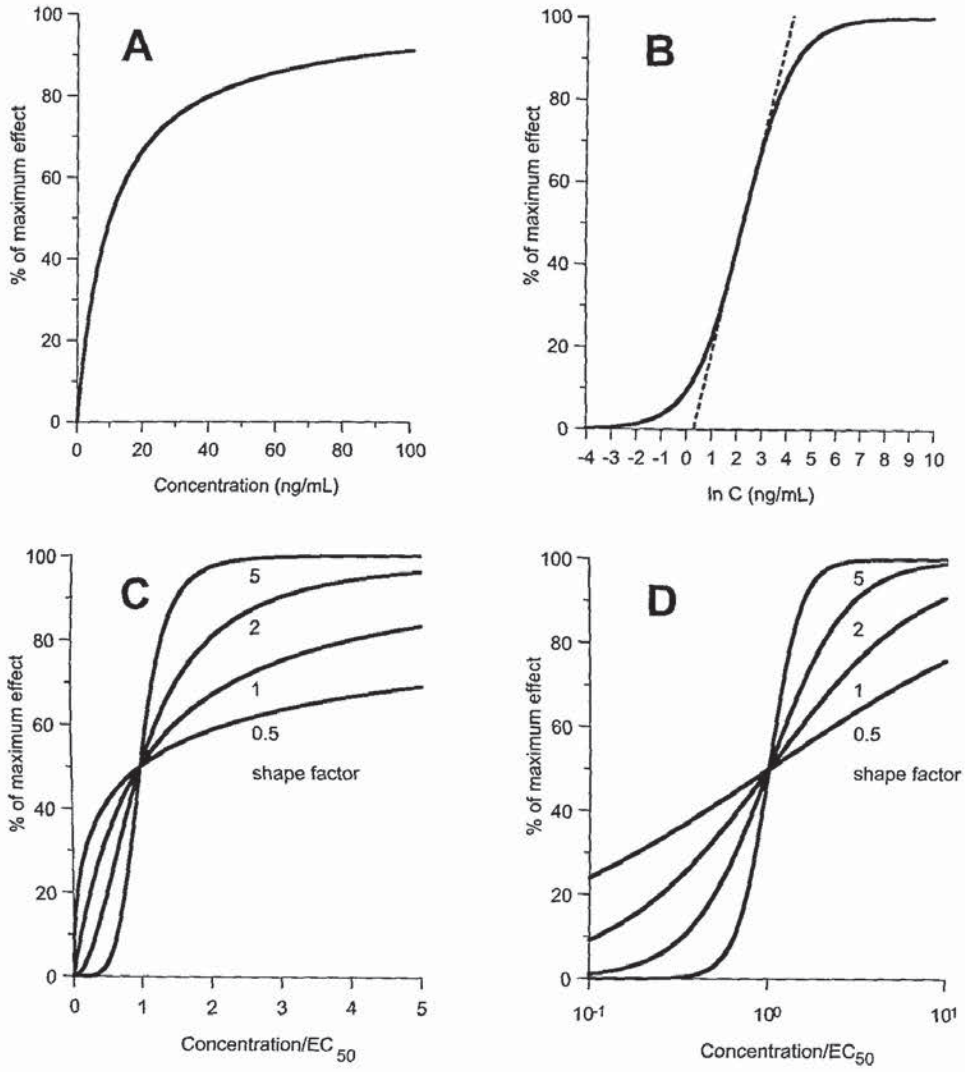

FIGURE 1.14 E_{max} and sigmoid E_{max}-model. Effect versus concentration (linear: **A,C**; and logarithmic: **B,D**) relationship defined by an E_{max}-model **(A,B)** and a sigmoid E_{max}-model **(C,D)**. The *dotted line* in **B** indicates the log-linear range of the concentration-effect relationship between 20% to 80% of the maximum effect. Numerals next to the curves in **C** and **D** indicate different values for the shape factor in the sigmoid E_{max}-model.

clinically observed for many drugs. Thus, in this range, the E_{max}-equation can be rewritten for a log-linear model as

$$E = \frac{E_{max}}{4} \times \ln C + \frac{E_{max}}{4} \times (\ln EC_{50} + 2) \quad (1\text{-}71)$$

where $E_{max}/4$ is the slope in the log-linear relationship. For concentrations much smaller than EC_{50} ($C << EC_{50}$), the E_{max}-model reduces to a linear relationship between concentration and effect with a slope of E_{max}/EC_{50}. Hence, both, a log-linear as well as the linear model for the concentration-effect relationship may be interpreted as special cases of the E_{max}-model.

Often, the effect of a drug therapy is the change in a physiologic parameter, e.g., mean arterial blood pressure. In these cases, a baseline value E_0, i.e., a measure for the physiologic response variable in the absence of drug dosing, has to be considered in the E_{max}-relationship:

$$\text{For stimulating effects: } E = E_0 + \frac{E_{max} \times C}{EC_{50} + C} \quad (1\text{-}72)$$

$$\text{For inhibitory effects: } E = E_0 - \frac{E_{max} \times C}{EC_{50} + C} \quad (1\text{-}73)$$

The sigmoid E_{max}-model is an expansion of the E_{max}-model, including a so-called shape factor or Hill-coefficient n.

$$E = \frac{E_{max} \times C^n}{EC_{50}^n + C^n} \quad (1\text{-}74)$$

Addition of the shape factor n increases the versatility of the model to describe concentration-effect relationships. The simple E_{max}-model can be seen as a special case of the sigmoid E_{max}-model with $n = 1$. The effect of different values of n on the concentration-effect curves for a sigmoid E_{max}-model are shown in Figure 1.14. The larger n, the steeper the curve in the log-linear phase from 20% to 80% of the maximum effect, with the respective slope given by $n \times E_{max}/4$.

Figure 1.15 shows the use of an inhibitory sigmoid E_{max}-model in relating the antiarrhythmic activity of tocainide measured as reduction of premature ventricular heart contractions (PVCs) per hour in relation to its plasma concentration. The range of slope factor in individual subjects was $n = 2.3–20.6$. As the maximum effect is total suppression of PVCs, $E_{max} = E_0$, the resulting model can be simplified as

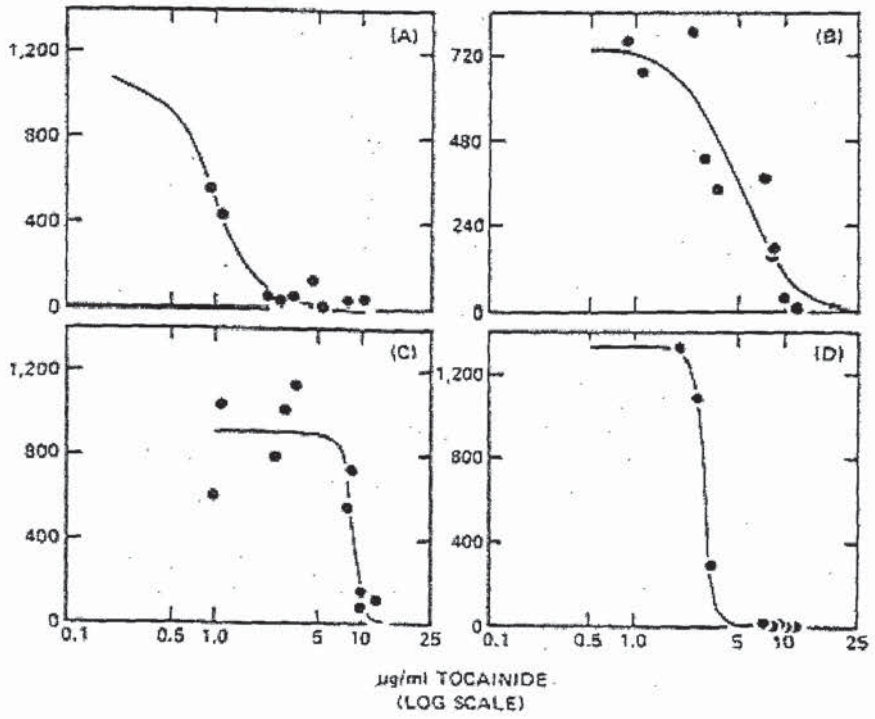

FIGURE 1.15 Inhibitory sigmoid E_{max}-model. Antiarrhythmic activity of tocainide measured as reduction of premature ventricular heart contractions (PVCs) per hour in relation to its plasma concentration. Shown are the concentration-effect relationships of four representative patients (measured data as dots), modeled with an inhibitory sigmoid E_{max}-model (solid lines). (From Meffin PJ, Winkle RA, Blaschke TF, et al. Response optimization of drug dosage: antiarrhythmic studies with tocainide. Clin Pharmacol Ther 22:42–57, 1977.)

$$E = E_0 - \frac{E_{max} \times C^n}{EC_{50}^n + C^n} \qquad (1\text{-}75)$$
$$= E_0 \times \left(1 - \frac{C^n}{EC_{50}^n + C^n}\right)$$

DOSING BASED ON PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

PK/PD modeling combines both approaches, PK and PD, and establishes models to describe the time course of the effect directly resulting from the administration of a certain dosage regimen. Thus, a so-called integrated PK/PD model consists of a PK model component that describes the time course of drug in plasma and a PD model component that relates the plasma concentration to the drug effect (Fig. 1.16).

Two simple, characteristic parameters can be used to translate PK and PD data into dosage recommendations. Both parameters, D_{50} and DR_{50} assume equilibrium between plasma and effect-site concentrations and can be based on $EC_{50,u}$ for free drug concentrations or EC_{50} for total drug concentrations.[10]

D_{50} is the amount of drug that has to be in the body to produce 50% of the maximum effect. It is the LD to be given to achieve 50% of E_{max}:

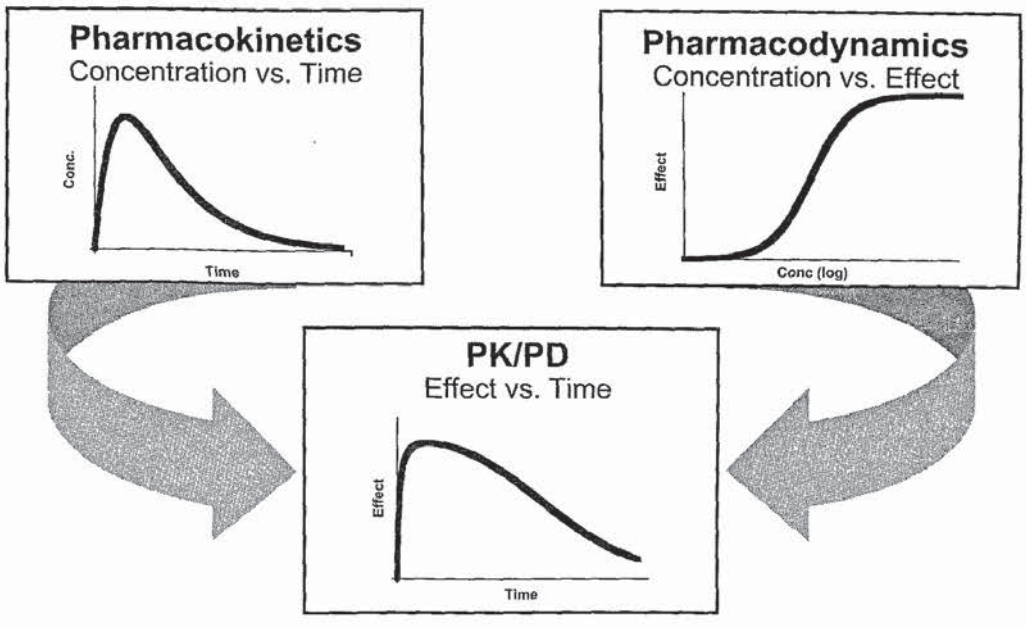

FIGURE 1.16 General concept of PK/PD-modeling. Pharmacokinetic/pharmacodynamic (PK/PD) modeling combines a PK model component that describes the time course of drug in plasma and a PD model component that relates the plasma concentration to the drug effect in order to describe the time course of the effect intensity resulting from the administration of a certain dosage regimen. (From Derendorf H, Meibohm B. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharm Res 16:176–185, 1999.)

$$D_{50} = EC_{50} \times V \quad (1\text{-}76a)$$

or

$$D_{50} = \frac{EC_{50,u} \times V}{f_u} \quad (1\text{-}76b)$$

The second, more important parameter is DR_{50}, the dose rate that produces 50% of the maximum effect. It is the MD to be given to maintain 50% of E_{max}:

$$DR_{50} = EC_{50} \times CL \quad (1\text{-}77a)$$

or

$$DR_{50} = \frac{EC_{50,u} \times CL}{f_u} \quad (1\text{-}77b)$$

The dosing rate DR_{50} (as well as D_{50}) can easily be converted to a dosing rate for any other fraction (x%) of E_{max} as:

$$DR_x = \frac{x}{100 - x} \times DR_{50} \quad (1\text{-}78)$$

A patient (53 years old, female, 5'4", 66 kg) will be started on an oral theophylline dosage regimen with an immediate release dosage form to control her asthma. The effect of theophylline on respiratory function was reported as an improvement in peak expiratory flow rate from baseline (PEFR) using an E_{max}-model. The reported population average parameters are E_{max} = 344 L per min and EC_{50} = 11 mg per L. For the pharmacokinetic parameters of theophylline, a CL of 0.04 L/hr/kg, a V_{ss} of 0.5 L/kg, and an oral bioavailability of F = 1 are assumed. If PEFR improvement of at least 200 L/min from baseline is targeted, the corresponding LD and MD to achieve this target can be calculated:

Step 1: Determine the D_{50} and DR_{50} for the PEFR improvement by theophylline:

$$D_{50} = EC_{50} \times V_{ss} = 11\ mg/L \times 0.5\ L/kg \times 66\ kg = 363\ mg \quad (1\text{-}79)$$

$$DR_{50} = EC_{50} \times CL = 11\ mg/L \times 0.04\ L/hr/kg \times 66\ kg = 29\ mg/hr \quad (1\text{-}80)$$

Step 2: Determine the $\%E_{max}$ for the targeted effect level:

$$\%E_{max} = \frac{E}{E_{max}} = \frac{200\ L/min}{344\ L/min} = 58\% \quad (1\text{-}81)$$

Step 3: Convert D_{50} and DR_{50} to the targeted effect level:

$$D_{58} = \frac{58}{100 - 58} \times D_{50} = \frac{58}{42} \times 363\ mg = 501\ mg \quad (1\text{-}82)$$

$$DR_{58} = \frac{58}{100 - 58} \times DR_{50} = \frac{58}{42} \times 29\ mg/hr = 40\ mg/hr \quad (1\text{-}83)$$

HYSTERESIS

For the previously discussed PK/PD models, the drug concentrations were directly linked to the observed effect. That means that the same drug concentration will always cause the same effect intensity. For some drugs, however, the relationship between concentration and effect is also dependent on the time point after drug administration. For these drugs, the relationship between concentration and effect is not defined by a curve like in the sigmoid E_{max}-model, but by a hysteresis loop (Fig. 1.17). Hysteresis in the concentration-effect relationship means that the same drug concentration

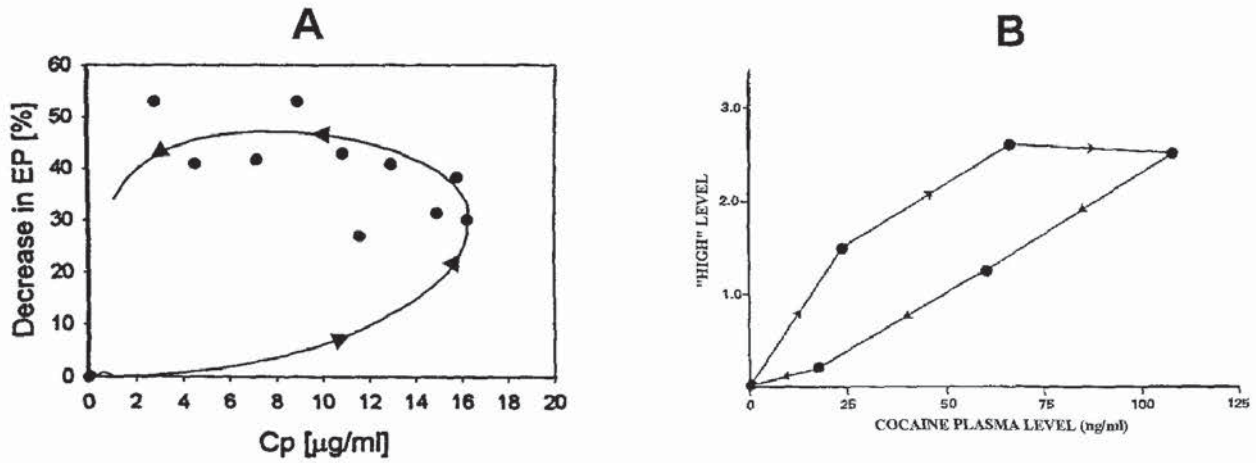

FIGURE 1.17 Hysteresis in the concentration-effect relationships. **(A)** Counterclockwise hysteresis loop for the relationship between plasma concentration of S-ibuprofen and its analgesic effect quantified as a decrease in evoked potential amplitudes (EP) attributed to a distributional delay between plasma and effect site concentration. **(B)** Clockwise hysteresis loop for the subjective psychologic effect ("high" levels) versus plasma concentrations after 1.5 mg/kg cocaine intranasally attributed to development of functional tolerance. (From Suri A, Grundy BL, Derendorf H. Pharmacokinetics and pharmacodynamics of enantiomers of ibuprofen and flurbiprofen after oral administration. Int J Clin Pharmacol Ther 35:1–8, 1997; Van Dyke C, Ungerer J, Jatlow P, et al. Intranasal cocaine: dose relationships of psychological effects and plasma levels. Int J Psychiatry Med 12:1–13, 1982.)

in plasma will result in different effect levels at different time points after drug administration. A hysteresis loop may be clockwise or counterclockwise, depending on the mechanisms involved in the temporal dissociation between plasma concentration and effect profile.

The major reasons for counterclockwise hysteresis loops include a distributional delay to the effect site, a time-consuming indirect response mechanism, agonistically acting active metabolites of a drug that are not quantified, or sensitization, i.e., an increase in effect over time despite constant drug concentration. Major reasons for clockwise hysteresis loops include functional tolerance and antagonistically acting active metabolites of a drug that are not quantified. Some of these causes of hysteresis will be discussed in detail.

Distributional Delay to the Effect Site. While the measurement of drug concentrations is usually performed in plasma, the input in the response system mediating the effect is provided by the concentration at the effect site, the site of action. For the previously described PK/PD models, the measured concentration in plasma is directly related to the effect site concentration. Equilibrium between concentrations is assumed to be rapidly achieved, and thus their ratio is constant, under PK steady-state as well as non-steady–state conditions. Hence, the measured concentrations can be directly linked to the observed effect. In that case, concentration and effect maxima would occur at the same time and effect versus concentration plots would lack any hysteresis. An example for this kind of concentration-effect relationship is the effect of tocainide measured on premature ventricular heart contractions (Fig. 1.15).

The equilibration between the plasma and the effect site concentrations, however, may be slow for some drugs due to time-consuming distribution processes involved. As a consequence of such a distributional delay, the ratio between plasma and effect site concentration would change with time resulting in a temporal dissociation between the time courses of measured plasma concentration and observed effect. For example, concentration maxima would occur before effect maxima, effect intensity might increase despite decreasing plasma concentrations and may persist beyond the time drug concentrations in plasma are no longer detectable. A counterclockwise hysteresis loop would be the consequence in an effect versus concentration plot. The muscle relaxant effect of d-tubocurarine is an example of a temporal dissociation between the concentration and effect-time courses (Fig. 1.18).

Tolerance. Development of tolerance to a drug therapy is characterized by diminishing effects in response to repeated administration of the same drug dose. Two major categories of tolerance can be distinguished based on the underlying causal mechanisms:

Metabolic tolerance, also called PK tolerance, is characterized by decreasing drug concentrations after repeated administration of the same dose, which consequently results in diminishing drug effects in response to these doses. The mechanistic basis for metabolic tolerance is a time-dependent change in PK parameters of the drug, most frequently caused by induction of the capacity of drug-metabolizing enzymes (i.e., an increase in CL_{int}).

Functional tolerance, also called PD tolerance, is characterized by a reduction in effect intensity at concentrations that earlier produced a greater effect or a decrease in drug effect over time despite constant drug concentrations at the effect site. The mechanistic basis for functional tolerance is a time-dependent change in

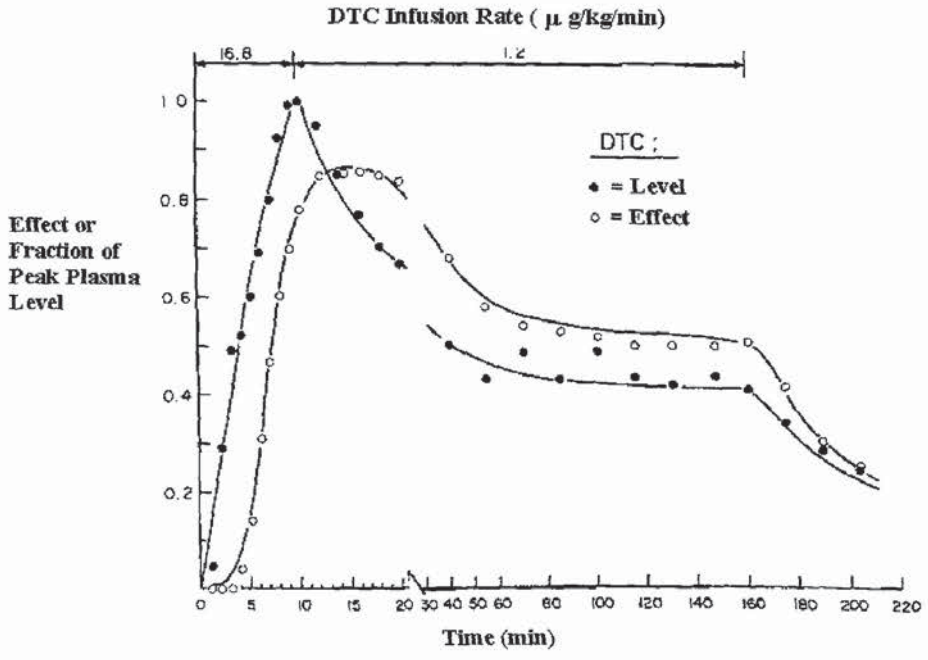

FIGURE 1.18 Temporal dissociation between the concentration and effect-time courses. Muscle relaxant effect of d-tubocurarine (DTC) after infusion of 16.8 μg/kg/min for 10 min followed by 1.2 μg/kg/min for 150 min. Shown are plasma concentration and effect versus time courses for one patient (lines are modeled). The temporal dissociation between concentration and effect is the result of a distributional delay between the concentrations in plasma and at the effect site. (From Sheiner LB, Stanski DR, Vozeh S, et al. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979.)

one or several pharmacodynamic parameters, e.g., E_{max} and EC_{50}. The diminishing response with rechallenging stimulus (i.e., concentrations) may be caused, for example, by downregulation of the number of receptors or a decrease in the receptor binding affinity for the drug. Functional tolerance results in a clockwise hysteresis loop in a plot of effect versus concentration (Fig. 1.17).

PHARMACOGENOMICS

Differences in efficacy as well as toxicity between patients in response to a medication are frequently much greater than the variations in efficacy and toxicity within the same person at different times. This discrepancy between large differences among members of a population and small intraindividual variability is consistent with inheritance as a major determinant of drug response. It is estimated that, depending on the drug, genetics can account for 20% to 95% of variability in drug disposition and effect. The phenotype, or clinically observable characteristics of a drug response, however, is a function of genetics (i.e., genotype), as well as nongenetic factors. Nongenetic factors include age, organ function, concomitant therapy, drug interactions, and nature and severity of the patient's disease. Unlike other factors influencing drug response, however, inherited determinants generally remain stable throughout a person's lifetime.[11]

Pharmacogenomics aims to identify the inherited basis for interindividual differences in drug response, and to translate this knowledge into molecular diagnostics that can be used to individualize drug therapy. While classic pharmacogenetics addresses the effect of polymorphic expression of a single gene on a drug's response profile, pharmacogenomics is a polygenic approach that assesses the effect of the concurrent interplay of multiple polymorphically expressed genes on an individual's response to a specific drug. Most drug effects are determined by multiple genes encoding drug-metabolizing enzymes, drug transporters, and drug targets (e.g., receptors).

PHARMACOGENETICS AFFECTING PHARMACOKINETIC PROCESSES

Genetic variations affecting functional activity have been identified for several drug-metabolizing enzymes and drug transporters. Functionally relevant polymorphisms have been described for genes encoding for multiple phase I and phase II enzymes including *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, and *CYP3A5* as well as *NAT2*, *COMT*, and *TPMT* (see Fig. 1.11). For drug transporters, the effect of genetic variants has been described most extensively for *MDR1* (*ABCB1*), the gene encoding for the exsorption transporter P-glycoprotein.

CYP2D6. Metabolism via CYP2D6 is the major elimination pathway for numerous widely used medications, including beta-blockers such as carvedilol, metoprolol, and propranolol; antidepressants such as amitriptyline, desipramine, imipramine, and fluoxetine; and antipsychotics such as haloperidol and risperidone. *CYP2D6* is a highly polymorphic gene for which more than 70 variant alleles have been described. A series of genetic variants is responsible for low levels of CYP2D6 activity or no activity. Carriers of these variant alleles are characterized by impaired metabolism for CYP2D6 substrates, which is referred to as a "poor metabolizer" status. In comparison, "extensive metabolizer" status refers to normal CYP2D6 activity. Approximately 5% to 10% of the white population has a relative deficiency in their CYP2D6-mediated metabolism, i.e., are poor metabolizers with regard to CYP2D6. These patients are likely to experience high levels of systemic exposure after standard doses of CYP2D6 substrates, which depending on the drug may lead to an increased likelihood of drug-induced toxicity. In addition, some subjects have multiple copies of the *CYP2D6* gene, resulting in ultrarapid metabolism. These patients are likely to have inadequate therapeutic response to standard doses of drugs that are metabolized by CYP2D6. The frequency of genetic variants in *CYP2D6* is ethnically diverse. Ultrarapid metabolizers are relatively rare in Northern European populations (1% to 3%), but more frequent in Mediterranean (7% to 10%) and African populations (20% to 30%).[12]

The effect of the variable number of *CYP2D6* functional alleles is shown in Figure 1.19 for the systemic exposure of nortriptyline. The higher the number of functional *CYP2D6* alleles, the lower the systemic exposure that was observed after administration of the same 25-mg nortriptyline dose to groups of subjects with different genotypes. Correspondingly, systemic exposure to 10-hydroxynortriptyline, the metabolite formed from nortriptyline via CYP2D6, was highest in the group with the highest number of functional *CYP2D6* alleles.[13]

TPMT. The genetic polymorphism of thiopurine-S-methyltransferase (TPMT) is a prime example for genetic variations used to adjust pharmacotherapy in individual patients. TPMT is the predominant inactivation mechanism for thiopurine drugs like mercaptopurine and azathioprine in hematopoietic tissues, two drugs that are clinically used as antineoplastic and immunosuppressant agents, respectively. TPMT activity is highly variable and polymorphic: approximately 90% of individuals have high activity, 10% have intermediate activity, and 0.3% (1 in 300) have low or undetectable enzyme activity. Patients with inherited TPMT deficiency accumulate excessive amounts of the active thioguanine nucleotides in blood cells when treated with thiopurines, resulting in potentially fatal hematopoietic toxicity. TPMT-deficient patients can be treated successfully with much lower doses of thiopurines (5% to 10% of the conventional dose), thereby avoiding the hematopoietic toxicity. Molecular diagnostic tests have recently become clinically available to detect the inactivating genetic variations in the *TPMT* gene before treatment initiation to adjust dosing a priori to the TPMT activity status of the patient. This approach of dosage individualization based on a genetic test is cost-effective in avoiding serious drug-associated toxicity.[14]

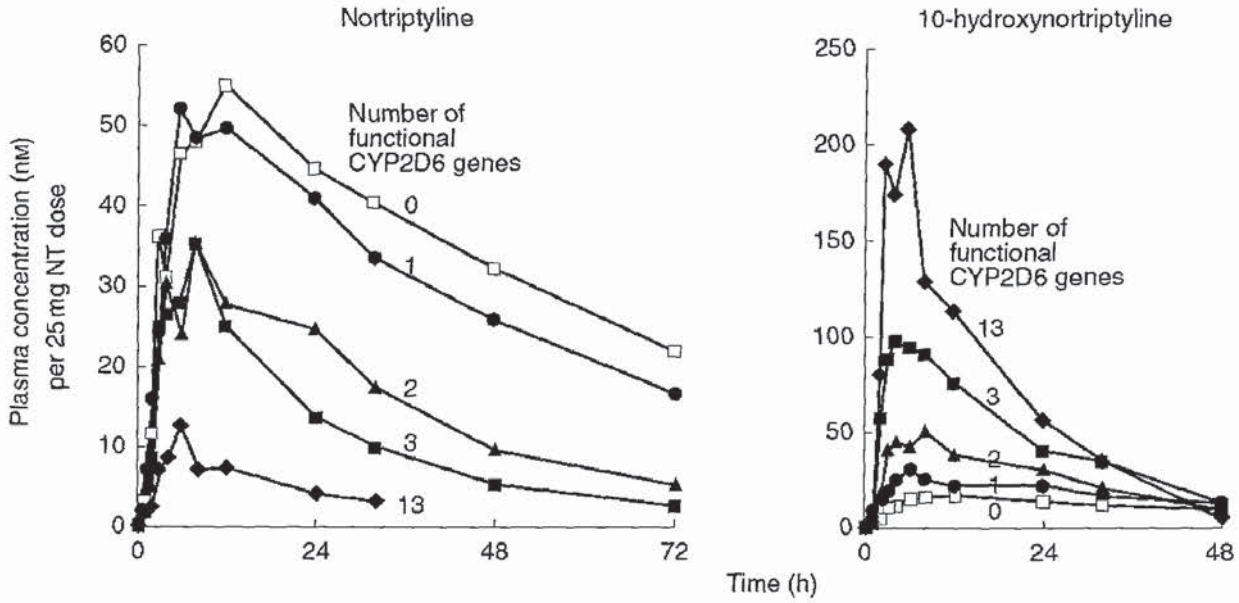

FIGURE 1.19 Effect of the variable number of *CYP2D6* functional alleles on the systemic exposure of nortriptyline. Mean plasma concentration of nortriptyline **(left)** and 10-hydroxynortriptyline **(right)** in different *CYP2D6* genotype groups after a single oral dose of nortriptyline. The numerals close to the curves represent the number of functional *CYP2D6* genes in each genotype group. In groups with 0–3 functional genes, there were five subjects in each group while there was only one subject with 13 functional genes. (From Dalen P, Dahl ML, Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 63:444–452, 1998.)

PHARMACOGENETICS AFFECTING PHARMACODYNAMIC PROCESSES

Genetic variations leading to polymorphisms may not be limited to drug-metabolizing enzymes and drug transporters affecting the PK of a drug. They might also affect drug targets such as receptors, enzymes, ion channels, or other endogenous proteins, thereby altering the concentration-effect relationship for a drug, i.e., its PD. Therapeutically relevant polymorphisms have been described for numerous drug targets, including angiotensin-converting enzymes (ACE inhibitors), arachidonate 5-lipoxygenase (leukotriene inhibitors), dopamine receptors (antipsychotics), estrogen receptor-α (estrogen hormone replacement therapy), and the serotonin transporter (antidepressants).

Polymorphisms for the β_2-adrenergic receptor (*ADRB2*) are a well-investigated example of the effect of genetic variations on a drug's PD. Single nucleotide polymorphisms (SNPs) leading to sequence changes in the ADRB2 protein

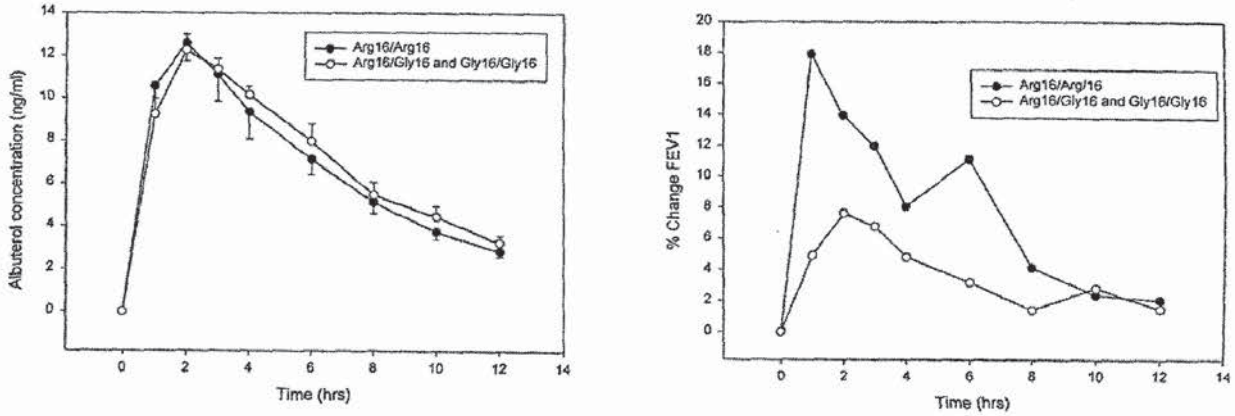

FIGURE 1.20 Effect of genetic polymorphism in the β_2-adrenergic receptor (*ADRB2*) on bronchodilator response to albuterol in asthmatics. Comparison of median FEV_1 **(right)** and mean ± SE albuterol plasma concentrations **(left)** versus time after administration of a single 8-mg oral dose of albuterol in Arg16 homozygotes (solid circles) and in heterozygotes and Gly16 homozygotes (open circles). (From Lima JJ, Thomason DB, Mohamed MH, et al. Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther 65:519–525, 1999.)

at amino acid positions 16, 27, and 164 have been found to significantly alter receptor function. In in vitro experiments, the Thr-to-Ile amino acid change at position 164 displays altered coupling to adenyl cyclase, the Arg-to-Gly change at position 16 results in enhanced agonist-promoted downregulation of *ADRB2* expression, and the form with the Gln-to-Glu change at position 27 is resistant to downregulation.

Therapeutic relevance of the genetic variations in *ADRB2* has been shown for the response to β_2-agonists in asthma. The frequencies of these various *ADRB2* genetic variants are not different in asthmatics compared to normal individuals, but albuterol-evoked FEV_1 (forced expiratory volume in one second) was higher and the bronchodilatory response was more rapid in Arg16 homozygotes than in a group of carriers of the Gly16 variant. In addition, an association has been demonstrated between the Arg16Gly variant and susceptibility to bronchodilator desensitization in moderately severe, stable asthmatics. Figure 1.20 shows the time courses of albuterol plasma concentrations and change in FEV_1 in subjects that are homozygous wild-type or a carrier of at least one variant allele with respect to codon 16 of the *ADRB2* gene. Although there is no pharmacokinetic difference between the two groups as indicated by the superimposable concentration-time profiles for albuterol, the Arg16Gly

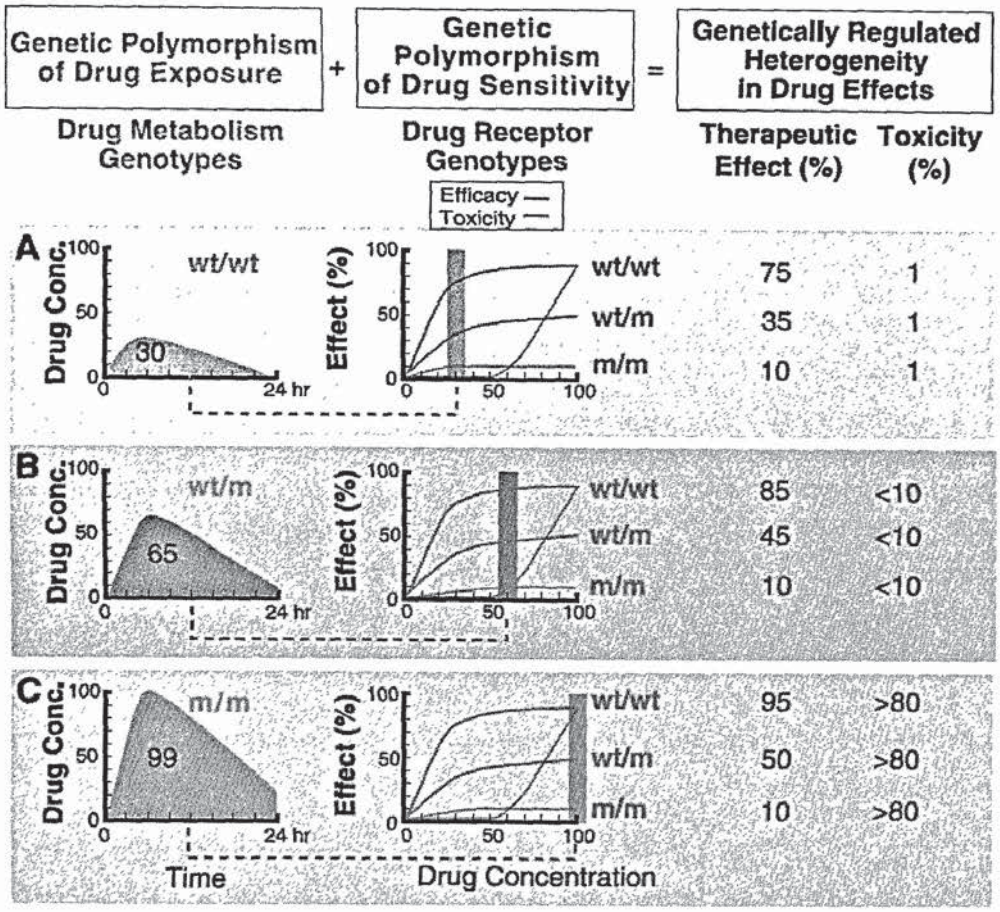

FIGURE 1.21 Polygenic determinants of drug effects *(see color insert)*. The potential consequences of administering the same dose of a medication to individuals with different drug metabolism genotypes and different drug-receptor genotypes is illustrated. Active drug concentrations in systemic circulation are determined by the individual's drug-metabolism genotype (green lettering), with **(A)** homozygous wild type (wt/wt) patients converting 70% of a dose to the inactive metabolite, leaving 30% to exert an effect on the target receptor. **(B)** For the patient with heterozygous (wt/m) drug-metabolism genotype, 35% is inactivated, whereas **(C)** the patient with homozygous mutant (m/m) drug metabolism inactivates only 1% of the dose by the polymorphic pathway, yielding the three drug concentration-time curves. Pharmacologic effects are further influenced by different genotypes of the drug receptor (blue lettering), which have different sensitivity to the medication, as depicted by the curves of drug concentration versus effects (middle). Patients with a wt/wt receptor genotype exhibit a greater effect at any given drug concentration in comparison to those with a wt/m receptor genotype, whereas those with m/m receptor genotypes are relatively refractory to drug effects at any plasma drug concentration. These two genetic polymorphisms (in drug metabolism and drug receptors) yield nine different theoretical patterns of drug effects **(right)**. The therapeutic ratio (efficacy: toxicity) ranges from a favorable 75 in the patient with wt/wt genotypes for drug metabolism and drug receptors to <0.13 in the patient with m/m genotypes for drug metabolism and drug receptors. (From Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 286:487–491, 1999.)

variant was associated with a difference in the concentration-effect relationship, i.e., a pharmacodynamic difference, between the groups: Asthmatics who were homozygous for the Arg 16 allele (Arg16/Arg16) showed more rapid increases in response and a higher bronchodilator response ($\%\Delta FEV_1$) 1 hour after drug administration than asthmatics that carried at least one variant allele (Arg16/Gly16 or Gly16/Gly). These results suggest that the genetic variation at codon 16 of the *ADRB2* gene is a major determinant of bronchodilator response to albuterol in asthmatics.

POLYGENIC EFFECTS ON PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacogenetics influences the pharmacologic response to drug therapy by determining both the dose-concentration relationship (i.e., PK) as well as the concentration-effect relationship (i.e., PD). Most genetic effects on pharmacotherapy and drug response that have been described are monogenic and highly penetrant, with clearly recognizable drug-induced phenotypes. A more likely frequent situation, however, is a scenario in which several polymorphisms influence simultaneously the pharmacologic response observed after administration of a therapeutic dosage regimen. The simplest case of such a polygenic effect on pharmacotherapy with only two polymorphic genes involved is exemplified in a hypothetical example in Figure 1.21 *(see color insert)*. Here, PK and PD of a drug are influenced by one polymorphism each, including high, intermediate, and low activity for each polymorphism for homozygous wild-type, heterozygous, and homozygous variant (nonfunctional or low-activity/sensitivity) individuals, respectively. The resulting nine different genotype combinations from only two polymorphisms illustrate the multitude of effect levels that may be expected from a polygenic modulation of pharmacotherapy. A future challenge will be to define these genetic determinants of drug response when 6 or 12 or even more genes are involved.

CONCLUSION

This chapter highlights some basic concepts in PK and PD as well as some pharmacogenetic aspects that are relevant to applied pharmacotherapy and determine the selection of an optimum dosage regimen for the individual patient. These concepts also provide the basis for the clinically applied interpretation of drug concentration measurements in patients and for therapeutic drug monitoring. It should be viewed as the starting point toward acquiring the skills and knowledge needed to become a competent clinical pharmacist with regard to clinical PK and PD.

KEY POINTS

- The systemic exposure to a drug is only determined by dose, bioavailability, and CL.
- Dosing regimens, i.e., how much and how often a dose needs to be administered, are determined by half-life and the targeted systemic exposure.
- If half-life changes, it is because CL or V changed.
- The therapeutic range is a range of concentrations with high probability of the desired therapeutic success and low probability of unacceptable toxicity.
- Loading dose is determined by the target concentration and the V, MD by the target concentration and the CL of the drug.
- The extent of drug accumulation is a function of drug properties and dosing regimen, namely the half-life of the drug and the dosing interval of the dosage regimen.
- Free, unbound drug concentrations need to be considered in dosing adjustments if the degree of plasma protein binding is changed.
- Renal and hepatic CL models can be used to guide dosage adjustments in case of changes in physiologic variables affecting the systemic exposure to a drug.
- Pharmacodynamic responses usually follow a nonlinear relationship with concentration, which levels off at high concentrations.
- Pharmacodynamic parameters like EC_{50} can be used together with pharmacokinetic parameters to guide dosage selection.
- Pharmacogenomics may explain between-subject variability in drug effects on the level of drug disposition (PK) and/or drug response (PD).

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