

## Chapter 12 DRUG THERAPY

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### THE LABORATORY IN DRUG THERAPY

The objective of drug therapy is to administer drugs in such a way as to maximize the chances of achieving the desired therapeutic goals while minimizing the risk of or severity of unwanted side effects. This objective is met by the selection of the appropriate drug or drugs, the prescription of an appropriate dosing regimen, and the monitoring of the therapy. Laboratory studies can aid in all of these tasks. Laboratory methods used to direct the selection of appropriate drugs for antimicrobial and anticancer therapy have already been discussed in earlier chapters. Laboratory studies can also provide measures of organ function that can be used to individualize the initial dosing regimen and laboratory monitoring of plasma drug concentrations can be used to evaluate therapy and guide adjustment of the dosing regimen. The latter two uses of the laboratory are considered here.

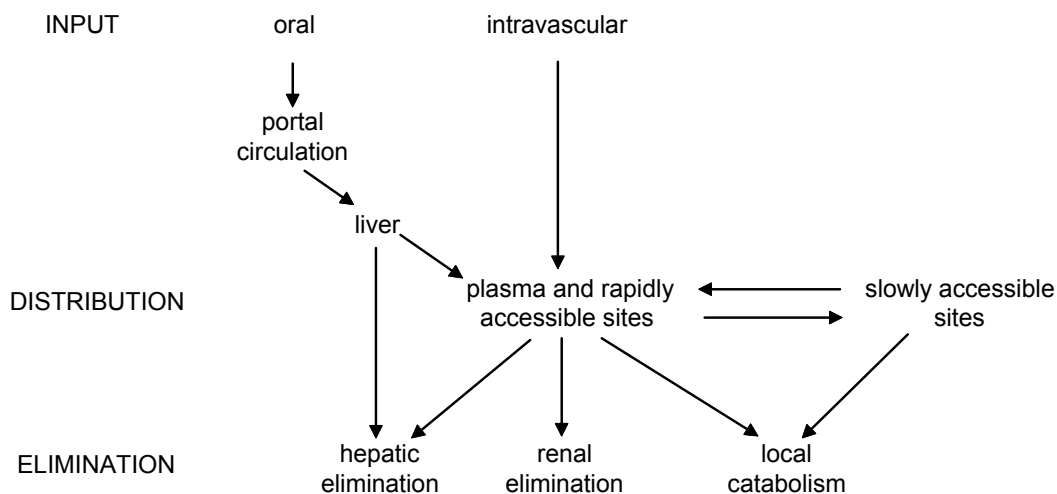
### DRUG DISPOSITION

The location in the body at which a drug has an effect, whether therapeutic or toxic, is referred to as a “site of action” or an “effect site” of the drug.

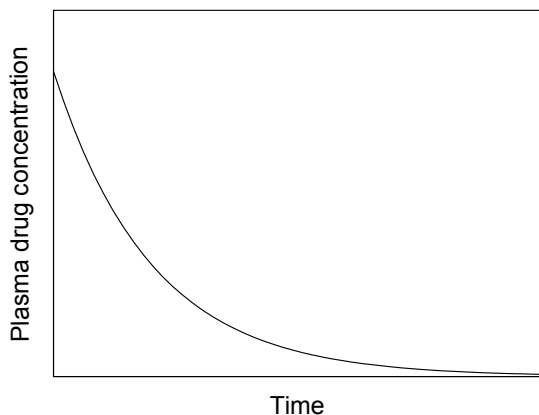
Occasionally a drug is delivered directly to its site of action but, in the majority of cases, the drug first enters the circulation and then distributes to the sites at which it will have its effects (Figure 12.1). In this way, the circulation serves as the source of supply of the drug with the plasma drug concentration being the driving force for drug entry into the effect site. Hence, the kinetics of drug disposition in the plasma determines the time course of the drug effects. It is not the only determinant—the kinetics of drug disposition within the effect site and the kinetics of cellular response to drug are also important—but it is the determinant that can most readily be evaluated and manipulated clinically.

The elements of drug disposition in the plasma are most clearly demonstrated following bolus intravascular injection of drug. Almost instantaneously, drug distributes into the various anatomic sites to which it has rapid access. The initial plasma drug concentration,  $C(0)$ , reflects the distribution of drug throughout the plasma and these rapidly accessible sites. The initial volume of distribution,  $V_o$ , quantifies the extent of rapid distribution of drug,

$$C(0) = \frac{\text{dose}}{V_o}$$



**Figure 12.1** A model of the disposition of drugs. The site of action of a drug may be the plasma, a rapidly accessible tissue site, or a slowly accessible tissue site. In addition, the liver and the kidneys may be sites of action as well as organs of elimination.



**Figure 12.2** Plasma disposition curve for a drug administered by bolus intravascular injection.

Note that the initial volume of distribution does not represent an anatomically defined volume or space but is instead simply a mathematical entity that defines the relationship between the drug dose and the resulting initial plasma drug concentration.

After its initial distribution, the plasma drug concentration progressively declines (Figure 12.2). For drugs that distribute rapidly into all accessible body sites, the decline is due to elimination of the drug. The plasma disposition curves of such drugs are monoexponential,

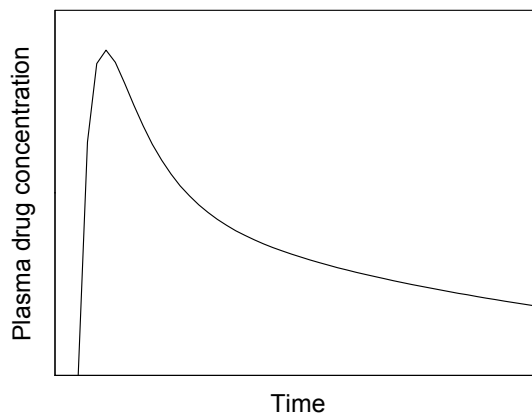
$$C(t) = \frac{\text{dose}}{V_0} e^{-kt}$$

where  $k$  is the disposition rate constant.

For drugs that distribute slowly into some accessible body sites, the decline is due to drug elimination and to drug distribution into and out of the slowly accessible sites. The plasma disposition curves of such drugs can usually be described using a biexponential equation,

$$C(t) = \frac{\text{dose}}{V_0} (C_\alpha e^{-\alpha t} + C_\beta e^{-\beta t}), \quad C_\alpha + C_\beta = 1$$

Because the plasma disposition curve of so many drugs can be described using a biexponential equation, terms specific for it have arisen and are common in clinical practice. The larger disposition rate constant is referred to as  $\alpha$  and that portion of the plasma disposition curve with a significant contribution from the alpha exponential term, i.e., the early part of the curve, is called the alpha phase. The alpha phase is also called the distribution phase because, for many drugs, the slow distribution process is more rapid than the drug elimination process, so the preponderant cause of the decline in plasma drug concentrations during this phase is drug



**Figure 12.3** Plasma disposition curve for a drug administered orally.

distribution. This is not always so, however. Some drugs are eliminated more rapidly than they distribute, so the initial fall in plasma drug concentrations is largely due to drug elimination. The smaller disposition rate constant in a biexponential curve is referred to as  $\beta$  and the late portion of the plasma drug disposition curve is called the beta phase. Using the same reasoning that leads to labeling the alpha phase as the distribution phase, the beta phase is often called the elimination phase. This designation is misleading because the late portion of the disposition curve always reflects drug redistribution as well as drug elimination.

Drug is usually delivered extravascularly in one of three ways: by internal reservoir (subcutaneous and intramuscular), by surface reservoir (buccal, rectal, and percutaneous), and orally, which is by far the most common way. The plasma drug kinetics following oral drug administration are characterized by a lag time, a concentration rise to a maximum value and a subsequent progressive decline in concentration (Figure 12.3). The lag time is the time it takes for drug to travel from the mouth to the gastrointestinal site of absorption. For solid drug formulations, the lag time depends largely upon the time spent in the stomach and the rate of dissolution of the tablet.

The rise in drug concentration occurs as long as the rate of drug absorption from the gastrointestinal tract exceeds the rate of elimination of drug from the plasma. The rate and magnitude of drug absorption are influenced by many factors including physicochemical properties of the drug (e.g., its  $pK_a$ ), physical properties of the drug formulation (e.g., its rate of dissolution), and physiologic factors (e.g., splanchnic blood flow at the site of absorption).

When the rate of drug absorption falls below the rate of drug elimination, the drug concentration begins to fall. Eventually drug uptake ceases and the drug concentrations depend only upon drug redistribution and elimination. This phase is sometimes called the post-absorptive phase.

The extent of uptake of a drug administered extravascularly is limited by presystemic drug elimination. For oral dosing, this means metabolism by intestinal cells and by hepatocytes during the trans-hepatic passage of the portal blood carrying the absorbed drug, the so-called first-pass effect. The completeness of gastrointestinal uptake is quantified by the parameter bioavailability. The bioavailable fraction,  $F$ , is defined as the fraction of a drug dose that reaches the systemic circulation after administration by an extravascular route.

### Clearance

Elimination is the irreversible removal of drug from the body by excretion or metabolism. Usually, the rate of elimination is proportional to the amount of drug in the plasma and rapidly accessible sites. The constant of proportionality for this first-order kinetic relationship is the elimination rate constant,  $k_{el}$ . Defining elimination in this form is not very useful because the amount of drug is not measurable. What is measurable is plasma drug concentration, so what is needed is the relationship between the elimination rate and the drug concentration. That relationship is

$$\text{drug elimination rate} = Cl C(t)$$

where  $Cl$  is the systemic clearance rate, the constant of proportionality for the relationship.

The irreversible removal of drug from the blood perfusing an organ is called organ clearance and is quantified as organ clearance rate. Just as the systemic clearance rate is the constant of proportionality between plasma drug concentration and the total drug elimination rate, organ clearance rate,  $Cl_{organ}$ , is the constant of proportionality between plasma drug concentration and the rate of drug elimination by the organ,

$$\text{drug elimination rate in organ} = Cl_{organ} C(t)$$

Because total drug elimination is the sum of the individual organ, or tissue, rates of drug elimination, the systemic clearance rate is the sum of the organ clearance rates. This makes it easy to calculate the change in systemic clearance rate that attends a

change in one or more organ clearance rate. This is extremely useful when adjusting drug dosages in the setting of dysfunction of an eliminating organ.

Another way to express the clearance of drug by an organ is the extraction fraction. The extraction fraction,  $E_{organ}$ , is the fraction of drug entering the organ that is removed in one pass through the organ. This fraction equals the drug elimination rate divided by the drug delivery rate,

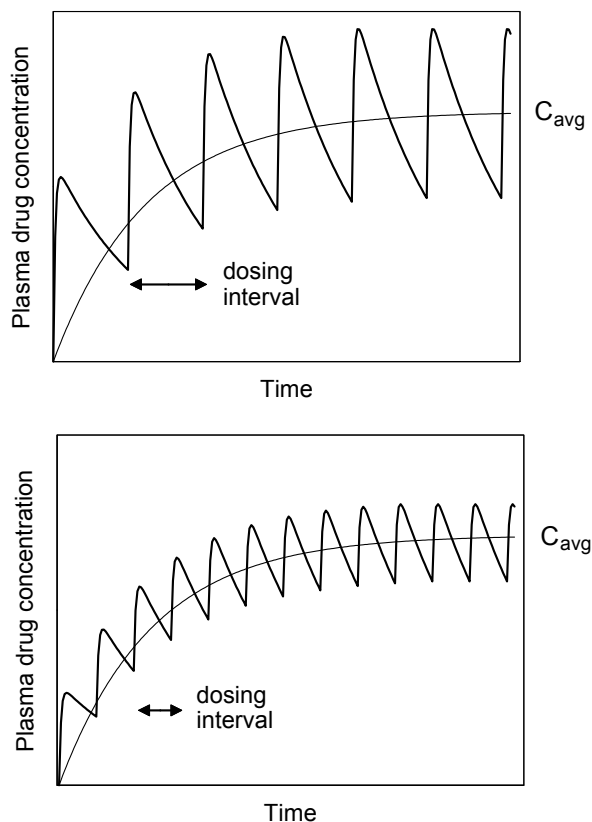
$$E_{organ} = \frac{\text{drug elimination rate in organ}}{\text{drug delivery rate to organ}}$$

Because the drug delivery rate is the product of the organ plasma flow rate,  $Q_{organ}$ , and the plasma drug concentration, the extraction fraction can also be calculated as,

$$E_{organ} = \frac{Cl_{organ}}{Q_{organ}}$$

**Organ clearance.** Two organs, the kidneys and the liver, are responsible for the elimination of most drugs. The elimination of drugs by the liver is accomplished by reversible uptake of drug by the hepatocytes followed by metabolic inactivation of the drug or excretion of unmetabolized drug in the bile. The latter process is a route of elimination only if there is minimal reabsorption of the drug (i.e., if there is little enterohepatic recirculation of drug). Over the usual pharmacologic ranges of plasma concentrations, the hepatic uptake and metabolism of most drugs show first-order kinetics, meaning that the rate of elimination of the drug is proportional to the concentration of the drug in the plasma. Enzyme-catalyzed hepatic metabolism is saturable, however, meaning that, at higher drug concentrations, the rate of metabolism is less than proportional to the concentration and, at very high concentrations, the rate of metabolism is constant.

The elimination of drugs by the kidney is accomplished by glomerular filtration and tubular secretion. These processes are opposed by passive back diffusion and tubular reabsorption. Approximately 20 percent of the plasma entering the glomerulus is ultrafiltered. The ultrafiltrate consists of water and low molecular weight solutes including smaller proteins; larger proteins are excluded by normal glomeruli. Nearly all of the water is reabsorbed, resulting in high tubular urine drug concentrations. This generates a considerable urine-to-plasma concentration gradient that causes passive back diffusion of drug into the plasma. The degree

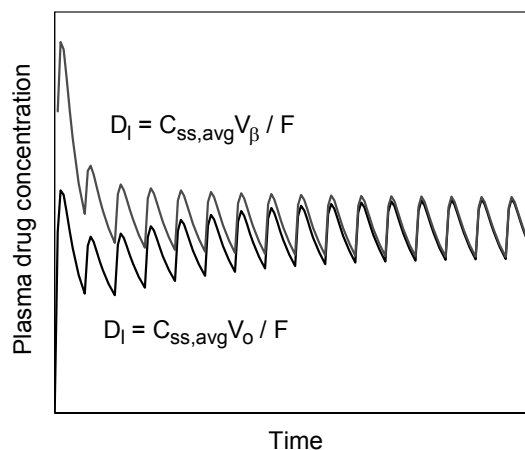


**Figure 12.4** Plasma disposition curves resulting from multiple dosing of an oral drug. The dosing interval and maintenance dose in the lower graph are half those in the upper graph.

of back diffusion depends upon the concentration gradient established, which is determined by the extent of water reabsorption, and upon the permeability of the drug, which relates to its lipophilicity. Drugs are secreted by the renal tubular organic anion or cation transport systems. Some drugs are actively reabsorbed from tubular urine, and others, such as aminoglycosides, are taken up from the tubular urine by tubular cell pinocytosis. Although tubular secretion and reabsorption usually display first-order kinetic behavior, they are saturable processes.

### Multiple dosing

In drug therapy the usual practice is to produce drug effects beyond the length of time that can be achieved by the administration of a single dose of the drug. Multiple dosing is then necessary. The characteristic plasma kinetics of a drug given on a regular schedule is shown for a hypothetical drug in Figure 12.4. For simplicity, the absorption kinetics of the drug are modeled as being very fast; consequently, the plasma drug concentration rapidly



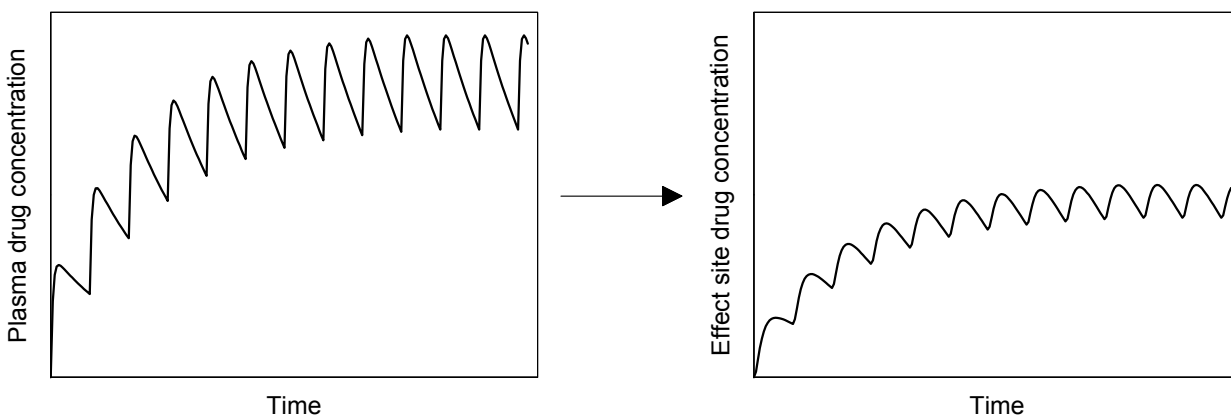
**Figure 12.5** Plasma disposition curves resulting from multiple dosing of an oral drug following a loading dose. The loading doses that apply to the curves are indicated. The maintenance doses are the same for both curves.

reaches its maximum value. The bottom graph shows the plasma kinetics that result if the dosing regimen shown in the top graph is changed by halving the dosing interval,  $\tau$ , and halving the maintenance dose,  $D_m$ , so that the dosing rate remains the same. The features to notice in the figure are: 1) within each dosing interval the plasma drug concentrations have a maximum (peak) value, a minimum (trough) value, and an average value; 2) the magnitude of the fluctuations in plasma drug concentration is directly related to the length of the dosing interval; 3) early on, the average concentration increases in magnitude with each dose (although, if the dosing interval is prolonged, the plasma concentrations at the end of the interval are negligible and the average concentration remains the same from dose to dose); 4) later on, the average concentration is the same for each dose, indicating that a steady state develops, wherein

$$C_{ss,avg} = \frac{\text{dosing rate}}{Cl} = \frac{F D_m}{\tau Cl}$$

where  $C_{ss,avg}$  is the average plasma drug concentration in the steady state; 5) the average plasma drug concentration in the steady state is the same regardless of the dosing interval, given constancy of the dosing rate; and 6) the time required to reach the steady state is the same regardless of the dosing interval.

**Loading dose.** It is frequently desirable to achieve plasma drug concentrations in the vicinity of the steady-state concentration early in drug therapy, sooner than would happen in the normal course of



**Figure 12.6** Plasma and effect site drug disposition curves for an oral drug with rapid effect site kinetics.

drug accumulation with multiple dosing. To do this a loading dose,  $D_l$ , which is larger than the maintenance dose, is administered. If the drug does not show a slow disposition phase, the following formula can be used to calculate the loading dose,

$$D_l = C_{ss,avg} \frac{V_o}{F}$$

This same formula should be used if the drug has a slow disposition phase and if, in addition, plasma drug concentrations higher than the steady-state values are to be avoided. With this loading dose, the steady-state drug concentrations are approached from the side of lesser concentrations, as shown in Figure 12.5. If plasma drug concentrations higher than the steady-state values can be safely tolerated, a larger loading dose can be used,

$$D_l = C_{ss,avg} \frac{V_o}{F} \frac{k_{el}}{\beta} = C_{ss,avg} \frac{V_\beta}{F}$$

With this dose, the steady-state drug concentrations are approached from the side of greater concentrations (Figure 12.5).  $V_\beta$  is referred to as the beta volume of distribution; it is the volume that is usually meant when referring to *the* volume of distribution.

### Drug effect

When drug is administered by multiple dosing, drug accumulates at its sites of action, eventually achieving local steady-state concentrations. If the kinetics at an effect site are rapid, the time it takes to reach the steady state at the site is essentially the same as that in the plasma. If the kinetics are slow, the steady state will be achieved later than in the plasma. Figure 12.6 depicts the effect site drug disposition curve for a drug with rapid effect site kinetics. The magnitude of drug accumulation at an

effect site depends upon the plasma drug concentrations and the effect site kinetic parameter values. The concentrations achieved may be less than, equal to, or greater than those in the plasma.

The kinetics of drug effect can be categorized as instantaneous or noninstantaneous. A drug has an instantaneous drug effect if the tissue effect evolves rapidly and reverses rapidly. For such drugs, the magnitude of the drug effect at any point in time is determined by the concentration of drug present at the site of drug action at that instant according to the (typically sigmoidal) drug concentration-drug effect relationship. For instance, for the drug considered in Figure 12.6, if the kinetics of its effect were instantaneous, the time course of the effect would follow the time course of its effect site concentration. There are drugs for which the magnitude of the drug effect is not determined by the instantaneous drug concentration at the site of action of the drug. This happens when there are time-consuming intermediate steps between the local drug effect and the observed clinical effect (delayed effect) and when the drug effects are not rapidly reversible so that the effect persists beyond the period of drug exposure (cumulative effect). These drugs show noninstantaneous drug effects.

### Pharmacologic variability

For most drugs, the appropriate dose, dosing interval, and length of treatment have been defined by clinical studies. However, due to interindividual variability in plasma drug kinetics and to variability in effect site kinetics and in the drug exposure-effect relationship, the response to a therapeutic agent varies when the agent is administered to different individuals. Consequently, to assure that the desired

clinical response is achieved in a patient, the practitioner will sometimes have to individualize the usual dosing regimen.

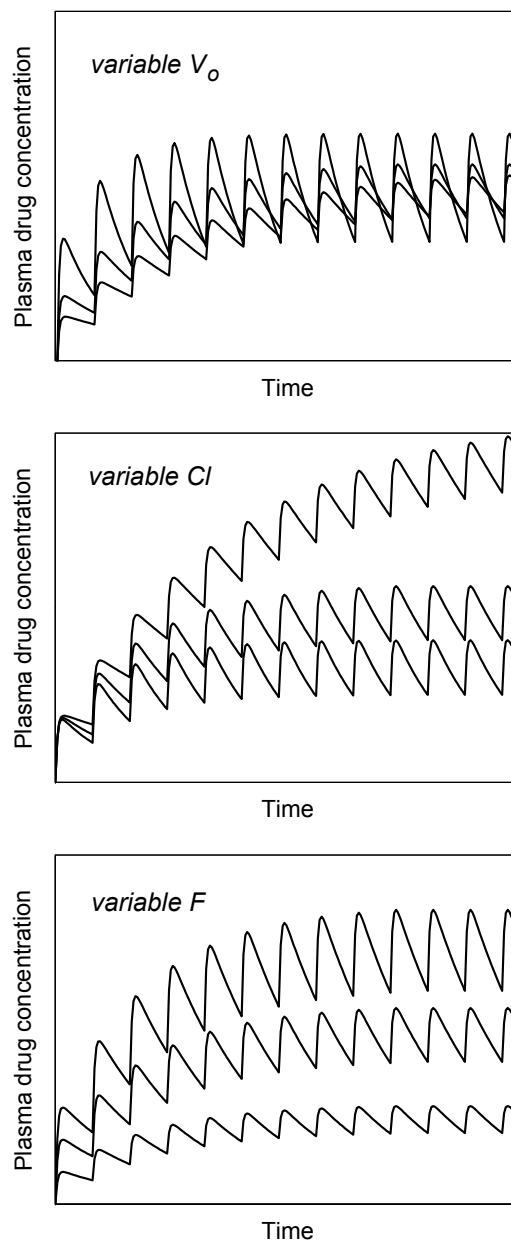
**Plasma kinetic variability.** Interindividual variability in plasma drug kinetics is usually large, with up to 5-fold ranges in the values of the kinetic parameters. Sources of normal interindividual variability include inheritance (Guttendorf and Wedlund 1992), sex (Harris *et al.* 1995), race (Johnson 1997), and age (Dawling and Crome 1989, Kinirons and Crome 1997). Body size can also be a source of interindividual variability. This is especially true in children in whom volume of distribution and clearance rate tend to vary in proportion to body size.

Inheritance is a particularly important source of interindividual variability. Indeed, genetic differences in drug clearance rate can be so large as to result in distinguishable subpopulations, called polymorphisms. The classic example of this are the slow and fast acetylators of isoniazid. Isoniazid clearance rate is determined by the activity of hepatic N-acetyltransferase. Slow acetylators are homozygous for the slow form of the enzyme while fast acetylators are either homozygous or heterozygous for the fast form of the enzyme.

Sources of intraindividual variability in plasma drug kinetics (i.e., variability over time in the same individual) include pregnancy (Loebstein *et al.* 1997), diet (Williams *et al.* 1996), biologic rhythms (Bruguerolle 1998, Kashuba and Nafziger 1998), and the intake of other drugs.

Inter- and intraindividual plasma kinetic variability also arise from the presence and variable severity of disease processes and as a result of combination drug therapy. The magnitude of the variability caused by disease is large, encompassing as it does the full range of kinetic parameter values that are physiologically possible. Liver disease may reduce hepatic drug clearance. Heart failure and severe illness usually result in a decline in hepatic drug clearance due to decreased hepatic perfusion. Renal drug clearance is decreased by kidney disease and by severe illness. Oral drug bioavailability is variably affected by gastrointestinal disease and is increased in liver disease due to a smaller first-pass effect.

The effects of plasma kinetic variability are illustrated in Figure 12.7 for multiple dosing of a drug administered orally. Variability in the initial volume of distribution (top graph) leads to differences in the peak and trough drug concentrations but, in the steady state, the average drug



**Figure 12.7** The effects of kinetic variability on the plasma disposition curve for multiple dosing of an oral drug. In each graph the kinetic parameter values vary in a 1:2:3 ratio. The top graph shows the effects of variation in initial volume of distribution, the middle graph the effects of variation in clearance rate, and the bottom graph the effects of variation in bioavailability.

concentrations are equal. Variability in clearance rate (middle graph) and variability in bioavailable fraction (bottom graph) produce drug concentration differences that increase over time reaching a maximum in the steady state. As dictated by the relationship,

$$C_{ss,avg} = \frac{F D_m}{\tau Cl}$$

in the steady state, the average drug concentration in the individual patient is directly proportional to the drug bioavailable fraction and inversely proportional to the clearance rate. Clearly, variability in drug clearance rate and bioavailable fraction are of paramount clinical importance in choosing the maintenance drug dose. Variability in initial drug volume of distribution is important in selecting the loading dose, if one is used.

### Designing the initial dosing regimen

The formulas used to calculate the doses for a drug depend upon a number of kinetic parameters. It is much more likely that the target plasma drug concentrations will be achieved if an individual patient's actual kinetic parameter values are used in these formulas rather than the average parameters values of the clinical population. Although the parameter values for a patient cannot be known with absolute accuracy prior to instituting drug therapy, estimates of the values can be made based upon the clinical diagnosis and routine clinical and laboratory measurements. Dose calculations based upon these estimates, as rough as they sometimes seem, do increase therapeutic efficacy and, perhaps even more so, therapeutic safety. As an example of the safety benefit that can result from individualizing drug dosing, consider the findings of a study of asthma patients who had plasma theophylline concentrations in excess of the therapeutic range (Greenberger *et al.* 1991). Fully 80 percent of the patients had elevated concentrations as a result of the failure on the part of the patients' physicians to prescribe reduced doses of theophylline despite the presence in the patients of well recognized causes of decreased theophylline clearance rate such as congestive heart failure, and liver disease.

**Calculation of an individualized maintenance dose.** Modification of the maintenance dose is the primary method by which multiple dosing regimens are individualized. As discussed earlier,

$$C_{ss,avg} = \frac{D_m F}{\tau Cl}$$

For the general clinical population, the formula can be rewritten as

$$C_{ss,avg} = \frac{usual D_m F_{avg}}{\tau Cl_{avg}}$$

where  $F_{avg}$  and  $Cl_{avg}$  are the average drug bioavailability and drug clearance rate in the

population, respectively. Now consider the formula as it applies to an individual patient,

$$C_{ss,avg} = \frac{individualized D_m F_{indiv}}{\tau Cl_{indiv}}$$

where  $F_{indiv}$  and  $Cl_{indiv}$  are, respectively, the individual's drug bioavailable fraction and drug clearance rate. In order to attain the same value for  $C_{ss,avg}$  in the individual patient as in the population,

$$\frac{usual D_m F_{avg}}{\tau Cl_{avg}} = \frac{individualized D_m F_{indiv}}{\tau Cl_{indiv}}$$

Rearrangement yields,

$$individualized D_m = usual D_m \frac{F_{avg}}{F_{indiv}} \frac{Cl_{indiv}}{Cl_{avg}}$$

which is the maintenance dose individualization formula. The formula requires estimates of the bioavailable fraction and clearance rate of the drug in the individual and knowledge of the average values in the population. Means to obtain these numbers, or to estimate their ratio, are discussed in a subsequent section.

**Calculation of an individualized dosing interval.** Altering the maintenance dose so as to maintain a constant average plasma drug concentration leads to changes in the maximum and minimum drug concentrations. By individualizing the dosing interval, and not the maintenance dose, one can maintain the average plasma drug concentration while causing only slight changes in the maximum and minimum concentrations. Using logic similar to that employed for the derivation of the formula for maintenance dose individualization, the dosing interval individualization formula can be derived,

$$individualized \tau = usual \tau \frac{F_{indiv}}{F_{avg}} \frac{Cl_{avg}}{Cl_{indiv}}$$

**Calculation of an individualized loading dose.** Loading doses are calculated based on the initial volume of distribution or on the beta volume of distribution. If the drug has a single disposition phase, the initial volume of distribution is used,

$$D_l = C_{ss,avg} \frac{V_o}{F}$$

Manipulation of this equation yields the following formula for individualization of loading doses,

$$individualized D_l = usual D_l \frac{V_{o,indiv}}{V_{o,avg}} \frac{F_{avg}}{F_{indiv}}$$

where  $V_{o,indiv}$  and  $V_{o,avg}$  are individual and population average initial volumes of distribution, respectively.

If the drug has a slow disposition phase and plasma drug concentrations higher than the steady-state values are to be avoided, the loading dose is individualized based on the initial volume of distribution. If plasma drug concentrations higher than the steady-state values can be tolerated, the beta volume of distribution is used to calculate the loading dose,

$$D_l = C_{ss,avg} \frac{V_\beta}{F}$$

Utilizing the fact that

$$V_\beta = \frac{Cl}{\beta}$$

yields,

$$\frac{V_{\beta,indiv}}{V_{\beta,avg}} = \frac{Cl_{indiv}}{Cl_{avg}} \frac{\beta_{avg}}{\beta_{indiv}}$$

where  $\beta_{avg}$  and  $\beta_{indiv}$  are the population average and individual values of  $\beta$ , respectively.  $\beta$  is determined in part by the slow distribution process and in part by the clearance rate. Individualizing for clearance rate, the ratio  $\beta_{avg}/\beta_{indiv}$  will take on a value between  $Cl_{avg}/Cl_{indiv}$  and 1 depending upon the magnitude of the slow distribution process. Taking into account the maximum clearance rate effect gives,

$$\text{individualized } D_l = \text{usual } D_l \frac{F_{avg}}{F_{indiv}} \frac{Cl_{indiv}}{Cl_{avg}}$$

**Calculation of  $V_{o,indiv}/V_{o,avg}$ .** The only predictor of the initial volume of distribution routinely available clinically is body weight, so dose individualization is based on weight measurement. The usual clinical practice is to calculate the individualized dose as

$$\frac{\text{dose}}{\text{unit body weight}} \text{ individual body weight}$$

or

$$\text{target } C(0) V_{o,indiv}$$

rather than individualizing a usual dose.

As an example of the use of the target  $C(0)$  formula, consider the computation of a loading dose of coagulant factor VIII in a 15-year-old child with factor VIII deficiency who requires replacement therapy because of an uncomplicated hemarthrosis. Because it binds to von Willebrand factor, which is almost entirely intravascular, factor VIII rapidly distributes into a volume of distribution equal to the plasma volume. In nonobese individuals, the plasma

volume is approximately equal to 40 ml/kg body weight. If the patient weighs 60 kg, his volume of distribution is, therefore, estimated to be 2400 ml. For a target initial plasma factor VIII concentration of 0.4 U/ml,

$$\text{individualized } D_l = \frac{0.4 \text{ U}}{\text{ml}} \times 2400 \text{ ml} = 960 \text{ U}$$

**Calculation of  $Cl_{indiv}/Cl_{avg}$ .** For a drug eliminated predominantly by the kidneys, the ratio  $Cl_{indiv}/Cl_{avg}$  is well approximated by the ratio  $GFR_{indiv}/GFR_{avg}$  even if the drug is cleared by both glomerular and tubular mechanisms. An individual's GFR can be determined by measuring the urinary clearance rate of an endogenous substance eliminated solely by glomerular clearance. Then,

$$GFR_{indiv} = \frac{\text{urine excretion rate}}{\text{plasma concentration}}$$

Creatinine is the endogenous substance used clinically. It is not a perfect glomerular clearance marker substance in that a small fraction is eliminated extrarenally and some of its renal elimination is due to tubular secretion. However, extensive clinical experience has shown that the creatinine clearance rate is a reliable measure of GFR in both healthy individuals and in individuals with kidney disease (Giovanetti and Barsotti 1991).

The difficulty with the direct measurement of creatinine clearance rate is the necessity for an accurately timed and complete urine collection on which to base the measurement of the urine excretion rate. This problem can be circumvented by employing an alternative expression for clearance rate,

$$\text{clearance rate} = \frac{\text{synthesis rate}}{\text{plasma concentration}}$$

and using an estimate of the synthesis rate for creatinine based upon gender, body size, and age. Formulas for calculating creatinine clearance rate, and thereby GFR, based upon this clearance rate expression are presented in Table 12.1. There are numerous similar formulas and nomograms in the literature (Lam *et al.* 1997). The formulas given in Table 12.1 have been found to be clinically reliable (Schwartz *et al.* 1987, Luke *et al.* 1990).

Consider, for example, the calculation of an individualized maintenance dose of amikacin in a patient being treated for *E. coli* bacteremia. The patient is a 50 year old male who weighs 60 kg and has a plasma creatinine concentration of 2 mg/dl.



Table 12.1

Calculation of creatinine clearance rate (Schwartz *et al.* 1976, Cockcroft and Gault 1976) $P_{cr}$ , plasma creatinine concentration in mg/dl; L, length in cm; age, age in years; wt, weight in kg

	GFR <sub>indiv</sub>	GFR <sub>avg</sub>	Units
children 2—12 years	0.56 L / $P_{cr}$	135	ml/min/1.73 m <sup>2</sup>
children 13—21 years	M 0.73 L / $P_{cr}$	140	ml/min/1.73 m <sup>2</sup>
	F 0.56 L / $P_{cr}$	125	ml/min/1.73 m <sup>2</sup>
adults	M (1.95 - 0.014 age) wt / $P_{cr}$	115	ml/min
	F (1.65 - 0.012 age) wt / $P_{cr}$	100	ml/min

As with all the aminoglycoside antibiotics, amikacin is eliminated solely by renal excretion. The usual dose of amikacin is 5 mg/kg given every 8 h. The dose is scaled according to body weight to account for the effect of body size upon clearance rate. In this case, GFR can be estimated so the body weight scaling is redundant. Therefore, the scaled weight is multiplied by the average male body weight of 70 kg to obtain the unscaled usual dose, 350 mg given every 8 h. The patient's creatinine clearance rate is 37.5 ml/min using the formula of Cockcroft and Gault (Table 12.1) so,

$$\text{individualized } D_m = 350 \text{ mg} \frac{37.5}{115} = 114 \text{ mg}$$

For a drug cleared primarily by the liver, the ratio  $Cl_{indiv}/Cl_{avg}$  is approximately equal to the ratio  $Cl_{hepatic,indiv}/Cl_{hepatic,avg}$ . Unfortunately, there are no endogenous substances that can be used to estimate hepatic drug clearance rate reliably. The reason for this is that the drug elimination capacity of the liver depends not only upon the number of functioning hepatocytes but also upon the hepatocellular concentration of the specific enzyme(s) catalyzing the inactivation of the drug. Drugs are, for the most part, metabolized by enzyme systems that are not used to clear endogenous substances so the hepatocellular concentration of these enzymes are not reflected in the clearance rate of endogenous substances. For drugs that are metabolized by enzymes that show polymorphisms, it is desirable to know which of the polymorphic forms of the enzyme the patient has. A drug dose appropriate for members of that particular polymorphic population can then be prescribed. The polymorphic population to which a patient belongs can be characterized either by genotyping or by phenotyping (Gonzales and Idle 1994, Linder *et al.* 1997). Genotyping is

usually accomplished using restriction fragment length polymorphism analysis or allele-specific oligonucleotide hybridization. Phenotyping involves the administration of a probe drug that is metabolized only by the enzyme of interest. The activity of the enzyme, and thereby the phenotype, is quantified by measuring the rate of formation or extent of formation of drug metabolite. Phenotyping has a number of disadvantages compared to genotyping including the difficulty of performing the study, the risk of an adverse drug reaction to the probe drug, and a higher rate of misclassification due to the confounding effects of disease and of concurrent medications (Linder *et al.* 1997). So, for those enzymes for which genotyping is available, and that now includes most of the clinically relevant drug metabolizing enzymes that have significant polymorphisms, genotyping is preferred over phenotyping.

In patients with diseases of the liver, measurable reductions in hepatic drug clearance rate are found only when the disease is severe. Because of the substantial uncertainty in estimating the magnitude of the impairment in hepatic clearance rate, careful monitoring of drug therapy is necessary (Morgan and McLean 1995).

For a drug eliminated by the kidneys and the liver, the following formula can be used to calculate  $Cl_{indiv}/Cl_{avg}$ ,

$$\frac{Cl_{indiv}}{Cl_{avg}} = f_{renal} \frac{Cl_{renal,indiv}}{Cl_{renal,avg}} + f_{hepatic} \frac{Cl_{hepatic,indiv}}{Cl_{hepatic,avg}}$$

where  $f_{renal}$  is the fraction of drug clearance attributable to the kidneys and  $f_{hepatic}$  is the fraction contributed by the liver. Procainamide is a drug that is eliminated by both the kidneys ( $f_{renal}$ , 0.5) and the liver ( $f_{hepatic}$ , 0.5). Consider a patient receiving parenteral procainamide for atrial fibrillation following

cardiac surgery. The patient has chronic liver disease that is expected to result in about a 15 percent reduction in the hepatic clearance rate of the drug. His measured creatinine clearance rate is 85 ml/min. Individualization of his maintenance dose is based on,

$$\frac{Cl_{indiv}}{Cl_{avg}} = 0.5 \frac{85}{115} + 0.5 \times 0.85 = 0.79$$

**Calculation of  $F_{indiv}/F_{avg}$ .** For drugs administered orally (Noe 1997),

$$F = F_{form} \frac{F_{abs} (1 - E_{hepatic})}{1 - F_{abs} (1 - f_{noncycled}) E_{hepatic}}$$

where  $F_{form}$  is the fraction of drug released from the particular formulation,  $F_{abs}$  is the fraction of the released drug that enters the portal circulation, and  $f_{noncycled}$  is the fraction of the extracted drug that does not undergo enterohepatic recirculation. If enterohepatic recirculation is ignored,

$$F = F_{form} F_{abs} (1 - E_{hepatic})$$

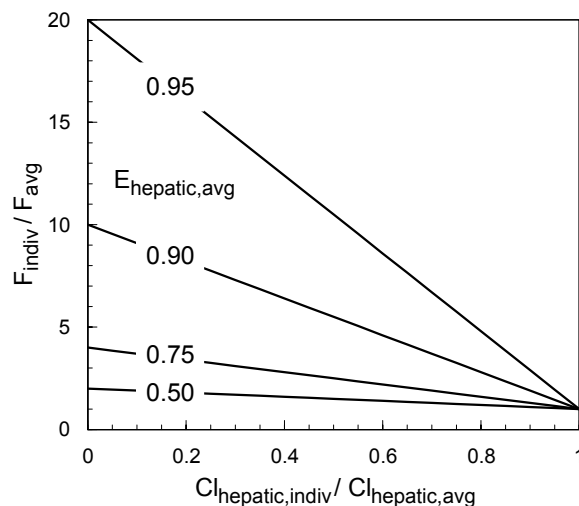
$F_{form}$  is generally assumed to be constant.  $F_{abs}$  is affected by gastrointestinal disease but not in a predictable way. Thus, individualization is based solely on hepatic extraction fraction,

$$\frac{F_{indiv}}{F_{avr}} = \frac{1 - E_{hepatic,indiv}}{1 - E_{hepatic,avg}}$$

where  $E_{hepatic,indiv}$  and  $E_{hepatic,avg}$  are the individual and population average values, respectively. If it is assumed that, in liver disease, the reduction in hepatic extraction fraction is proportional to the decline in hepatic clearance rate, then,

$$\frac{F_{indiv}}{F_{avr}} = \frac{1 - E_{hepatic,avg} \frac{Cl_{hepatic,indiv}}{Cl_{hepatic,avg}}}{1 - E_{hepatic,avg}}$$

This assumption is rarely strictly valid because the hepatic extraction fraction depends upon hepatic plasma flow rate as well as hepatic clearance rate, but it is a useful clinical simplification. The relationship is graphed for four values of the population average hepatic extraction fraction in Figure 12.8. The curves show that drugs with hepatic extraction fractions less than 0.5 (hepatic clearance rates less than 400 ml/min) require little or no individualization for bioavailable fraction except in severe liver disease. Drugs with larger hepatic extraction fractions should be individualized for bioavailable fraction whenever liver disease is present. The dose changes for drugs with very large hepatic extraction



**Figure 12.8**  $F_{indiv}/F_{avg}$  as a function of  $Cl_{indiv}/Cl_{avg}$  assuming that  $E_{hepatic,indiv}$  is proportional to  $Cl_{indiv}/Cl_{avg}$ .

fractions can be expected to be substantial. For instance, for a 15 percent reduction in the hepatic clearance rate of a drug with a hepatic extraction fraction of 0.90, the maintenance dose should be reduced by 0.85-fold based on individualization for clearance rate and by 0.43-fold based on individualization for bioavailable fraction, for a total of a 0.36-fold dose reduction.

**Determination of individual kinetic parameter values.** The foregoing approaches for calculating individual kinetic parameter values are based on measures that correlate with the individual parameter values. It would, of course, be preferable to actually determine the values of the parameters in the individual patient before beginning therapy. This is especially true when administering a drug that has a narrow therapeutic index. Accuracy in the individualization of therapy with such drugs is very important.

The most accurate way to obtain a patient's kinetic parameter values for a drug is to conduct a pharmacokinetic analysis of the plasma disposition curve that results from a small dose of the drug given to the patient. A drug dose administered for this purpose is called a test dose. To obtain the plasma disposition curve, blood specimens need to be obtained at specified times following administration of the drug. Typically, the blood sampling scheme needs to be fairly intensive; i.e., numerous blood specimens usually need to be taken. The kinetic parameter values can be derived from the plasma drug disposition using noncompartmental techniques (Noe 1997) or they can be calculated

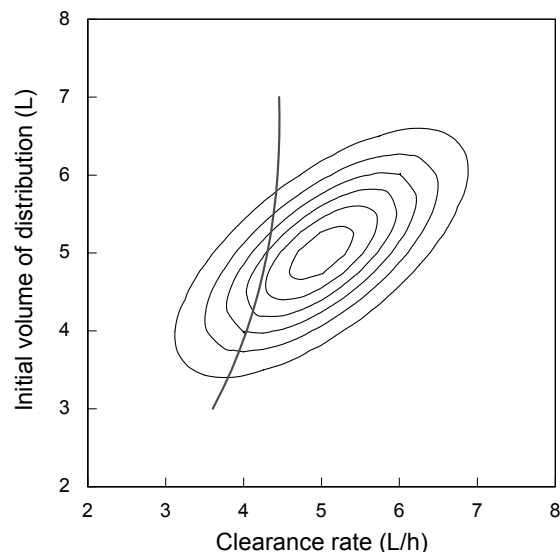
using the coefficients and exponents of a polyexponential equation fit to the disposition data (Wagner 1976). This can be done for oral drugs as well as drugs administered intravascularly because the plasma disposition curves of most oral drugs can be well described with a bi- or triexponential equation.

When estimating kinetic parameter values for oral drugs, values are derived for the hybrid parameters,  $V_o/F$  and  $Cl/F$ , not for the primary parameters,  $V_o$ ,  $Cl$ , and  $F$ . Fortunately, this is not a problem because  $V_o/F$  and  $Cl/F$  are the terms used in the dose individualization formulas.

There are two alternative approaches to estimating the values of individual kinetic parameters that are based on limited blood sampling schemes. The parameter values calculated by these approaches are somewhat less reliable than those derived from intensive blood sampling but the approaches are generally much more practicable in the clinical setting. In the first approach, the parameter values are calculated using multiple regression equations where the independent variable values are the plasma drug concentrations measured at a limited number of specific time points following the administration of drug. The equations are based on the statistical relationship between the parameter values and the stipulated plasma drug concentrations as found from the drug disposition curves of a large number of patients.

In the second approach, kinetic parameter values are estimated by Bayesian forecasting techniques (Grasela 1995). Bayesian forecasting involves the balancing of two sources of information regarding the parameter values in an individual. The first source is the frequency distribution of the parameter values in the clinical population to which the individual belongs, as derived from an in-depth pharmacokinetic study of that population. The second source is the set of plasma drug concentrations measured in the individual.

To see what is meant by “balancing” these sources of information, consider a patient in whom a plasma drug concentration of  $55 \mu\text{g/ml}$  is measured 1.5 h after the intravascular injection of a 1 g dose of the drug. If the drug does not have a slow distribution phase, its plasma kinetics can be described by the two parameters, the initial volume of distribution and the clearance rate. Paired values of these parameters that will yield the observed drug concentration are shown in Figure 12.9 as a curved line segment. Which of these pairs is most likely to



**Figure 12.9** Contour plot of the joint frequency distribution of clearance rate and initial volume of distribution for a hypothetical drug (concentric ellipses) and the plot of paired parameter values that yield an observed plasma drug concentration in an individual (curved line segment).

apply to the patient? That is determined by reference to the joint frequency distribution of the parameters, also shown in Figure 12.9. The pair of parameter pair values likely to apply to the patient is the pair that is most frequently found in the population. In this example, that parameter pair is identified as the point touching the second contour line: initial volume of distribution, 4.75 L and clearance rate, 4.25 L/h.

Continuing the example, if a second drug concentration is measured using a blood specimen taken soon after the injection of drug, the two concentrations will uniquely determine the values of the two kinetic parameters and the population information will not be contributory. Say the drug concentration is measured at 0.25 h as well as 1.5 h and its value is  $170 \mu\text{g/ml}$ . The single pair of parameter values, initial volume of distribution of 4.69 L and clearance rate of 4.24 L/h, yields the observed drug concentrations. Regardless of how frequent that parameter pair is in the population, it is the only one that fits the data.

This illustrates that the contribution of population information to the Bayesian forecast decreases as the number of drug concentration measurements increases. However, the contribution is never really zero, as in the example, because in real life there is always variability in the measurement of drug concentrations and therefore also in the calculation

of the individual parameter values. This variability is due to errors in the timing of drug administration, to variation introduced by blood specimen collection, and to variation in the process of assaying the drug concentration.

### **MONITORING THERAPY AND ADJUSTING THE DOSING REGIMEN**

The goal of individualizing the dosing regimen is to provide safe, efficacious drug treatment to the individual patient by targeting a steady-state plasma drug concentration within the range that has been found to be safe and efficacious in the usual patient. The initial dosing regimen may fail to achieve this goal because the steady-state drug concentration may not actually be within the target range. This can be due to poor or irregular patient compliance, to shortcomings in the dose individualization scheme (most notably, to the lack of a reliable quantitative measure of hepatic drug metabolism), or to unpredictable sources of interindividual pharmacokinetic variability. The regimen may also fail to attain its goal of safe and efficacious therapy even when the dosing regimen is a success in terms of achieving the target steady-state drug concentration. This can happen as a result of interindividual variability in effect site drug kinetics (Eichler and Müller 1998) or as a consequence of interindividual differences in the effect site drug concentration-drug effect relationship (Levy 1998).

Recognizing that the initial dose regimen may not yield the desired therapeutic results, drug therapy is monitored. Clinical observations and routine laboratory studies usually provide all of the information that is needed to assess the efficacy and toxicity of drug therapy, in which case a patient's dosing regimen can be incrementally adjusted to give the greatest therapeutic effect while maintaining acceptable levels of toxic effects. An example is the monitoring of the blood glucose concentration by patients with diabetes who are being treated with insulin. If the glucose concentration is within the target range, the insulin dose is not changed. If the glucose concentration is too high, and there is no other explanation for the lack of glycemic control, the insulin dose is increased or the dosing interval is shortened. The dose decreased or the dosing interval is lengthened if the glucose concentration is too low. Sometimes there are no clinical or routine laboratory findings that correlate in a timely fashion

with the effects of drug therapy. This is especially common for drugs with noninstantaneous drug effects and for drugs that are used to control episodic phenomena, such as anti-epileptic agents and anti-arrhythmic agents. For some these drugs, the relationship between plasma drug concentration and drug effect is obscured by interindividual variability in effect site drug kinetics and by interindividual variability in the effect site relationship between drug concentration and drug effect. For other drugs of this sort, however, plasma drug measurements have proven to be reliable predictors of drug effect. For these drugs therapy can be monitored using drug concentrations. This is called therapeutic drug monitoring (Brown et al. 1993, Murphy 1995).

#### **Therapeutic drug monitoring.**

The usual scheme for monitoring drug therapy is: (1) determine the value of the plasma drug concentration once steady-state conditions prevail, (2) compare the measured concentration to the therapeutic range for the drug, and, if indicated, (3) adjust the maintenance dose of the drug. After the attainment of the new steady state, the drug concentration is measured again to ascertain if the dose adjustment has brought the concentration into the therapeutic range. The process is repeated until the therapeutic range is achieved.

**Plasma drug concentration.** Most commonly, therapeutic drug monitoring is based upon the measurement of trough drug concentrations. The trough concentration is the concentration at the end of the dosing interval, immediately prior to the administration of the next maintenance dose. There are practical considerations that make this an attractive time to sample, especially fairly reliable timing of specimen collection. In addition, if the disposition kinetics at the drug's site of action are rapid, in the steady state, the trough plasma drug concentration is directly proportional to the minimum effect site drug concentration. The minimum effect site drug concentration is particularly important because it represents the proximate kinetic target for drugs whose effects are instantaneous and, therefore, depend upon the continuous maintenance of effect site concentrations at or above a minimum effective value.

When the effect site kinetics are slow, the steady-state effect site drug concentration curve is rather flat and the minimum effect site drug concentration is more nearly proportional to the average

plasma concentration. Therapeutic drug monitoring using the average drug concentration requires measurement of the area under the plasma drug disposition curve (AUC) during the dosing interval,

$$C_{ss,avg} = \frac{AUC \text{ dosing interval}}{\tau}$$

This means that obtaining a number of blood specimens during the interval, the optimal number and timing of which depend upon the plasma disposition of the drug and the level of reliability desired.

**The steady state.** It is generally accepted that the steady state is achieved 5 half-lives after the start of drug therapy. For drugs with a single disposition phase,

$$t_{1/2} = \frac{\ln(1/2)}{k}$$

and for drugs with a slow disposition phase,

$$t_{1/2} = \frac{\ln(1/2)}{\beta}$$

Individualization of the half-life estimate takes into account the maximum effect that variation in clearance rate has upon half-life,

$$\text{individualized } t_{1/2} = \text{usual } t_{1/2} \frac{Cl_{avg}}{Cl_{indiv}}$$

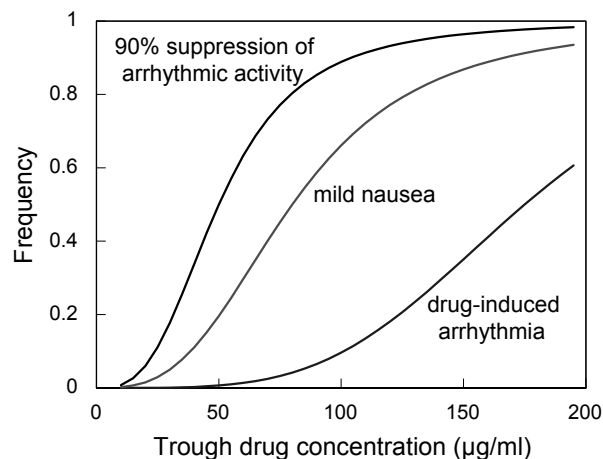
Consider the clinical application of this formula in a patient with a serious Gram-negative infection receiving gentamicin by short intravenous infusion on an every 8 h schedule. The patient is a 60 year old female who weighs 50 kg and has a stable plasma creatinine concentration of 1.4 mg/dl. The adequacy of the treatment can be monitored using the steady-state peak plasma drug concentration (defined as the concentration 0.5 h after following the end of drug infusion). The usual half-life of gentamicin is about 2 h. The patient's creatinine clearance rate is calculated to be 35.8 ml/min using the formula of Cockcroft and Gault (Table 12.1). Because gentamicin is eliminated solely by the kidneys,

$$\frac{Cl_{avg}}{Cl_{indiv}} = \frac{100}{35.8} = 2.8$$

and

$$\text{individualized } t_{1/2} = 2 \text{ h} \times 2.8 = 5.6 \text{ h}$$

Thus, it is necessary to wait 28 h (5 times the half-life) to obtain a steady-state specimen for therapeutic drug monitoring.



**Figure 12.10** Frequency plots of drug effects for a hypothetical anti-arrhythmic agent.

**The therapeutic range.** Simply put, the therapeutic range is the range of values of the monitoring marker that have been found to be associated with generally effective and safe therapy. Figure 12.10 illustrates how a therapeutic range is constructed. The figure shows plots derived from a hypothetical study of drug effect for an anti-arrhythmic agent. The plots show the relationship between the value of the monitoring marker, here the steady-state trough plasma drug concentration, and the percentage of patients who, at that trough concentration value, experience the stipulated effect. The therapeutic effect in this example is quantitative, 90 percent suppression of physiologic arrhythmic activity. The effect-marker relationships for two toxic effects are plotted; a nuisance effect, post-dose nausea, is semiquantitative, and a serious toxic effect, drug-induced arrhythmic activity, is categorical. The plots for each of these drug effects are sigmoidal which is an entirely typical shape. If a threshold of 50 percent is used, efficacious therapy is associated with trough concentrations greater than 50 µg/ml. Serious toxicity is seen in less than 5 percent of patients with trough concentrations less than 85 µg/ml. The therapeutic range, as defined by the stated thresholds, is, therefore, 50 to 85 µg/ml. Notice that the measurement of a trough drug concentration in this range does not assure that therapy will be effective in the individual patient nor does it guarantee that the therapy will not have a serious side effect. In addition, it provides no information concerning milder side effects. But it does provide some assurance that the therapy might be

efficacious and that it has only a low risk of serious toxicity.

The target value for the monitoring marker depends largely upon the seriousness of the illness being treated. The more serious the disease, in general, the higher the target value. The physician and patient both want a high probability of effective therapy and, usually, both are willing to accept a higher risk of adverse effects. For the drug depicted in Figure 12.10, a target value of 85  $\mu\text{g/ml}$ , the upper end of the therapeutic range, may be selected in the face of a life-threatening arrhythmia. Indeed, if the desired therapeutic effect is not achieved even when the monitoring marker is at the upper end of the therapeutic range, the drug dose may be increased until toxicity intervenes or until the risk of a serious adverse event is just too great.

**Dose adjustment.** Dose adjustments are based upon the assumption of linear drug kinetics. Linear kinetics means that plasma drug concentrations are directly proportional to drug dose. Using the target value selected for the monitoring marker,

$$\text{adjusted } D_m = \text{current } D_m \frac{\text{target marker value}}{\text{measured marker value}}$$

For example, if the steady-state trough plasma concentration for a drug is found to be 400 ng/ml and the target trough concentration is 700 ng/ml, a maintenance dose of 300 mg/day should be adjusted to 500 mg/day,

$$\text{adjusted dose} = 300 \text{ mg/day} \frac{700}{400} = 525 \text{ mg/day}$$

given that the drug formulation is available in 100 mg gradations. A conservative approach would be to increase the dose incrementally, first trying a dose of 400 mg/day then, if indicated, increasing the dose to 500 mg/day. In this way, if toxicity is experienced as a consequence of the increase in dose, it may manifest itself at the lower, less toxic, dose.

**The devil is in the details.** There are practical concerns that have a tremendous impact on the utility of therapeutic drug monitoring. First among these is patient compliance with the drug regimen. Rigorous adherence to a regular schedule of drug taking is impossible, even for the most well-intentioned patient. There are doses that are missed and doses that are taken at irregular times. If this happens in the period preceding the time of specimen collection for therapeutic drug monitoring, the value for the monitoring marker will not be the true steady-state for the marker and any adjustment made

in the dose will be ill-founded. To limit occurrences of this sort, it is highly desirable to have the patient keep a diary of his or her drug intake for the day or two before the monitoring specimen is obtained. For some patients it is even a good idea to witness the drug administration that precedes the monitoring specimen to confirm the timing of the specimen relative to that administration.

Practical considerations arise with inpatient drug therapeutic monitoring also. The most notable problem in this setting is spuriously high marker values that result from taking the monitoring specimen through the intravenous catheter being used for drug administration (Murphy 1995). The physician must always be vigilant for this and other potential sources of measurement error. The need for such vigilance is nicely demonstrated in the following vignette related by a clinical pharmacologist/laboratorian (Kumor 1985).

I recall another afternoon, . . . nice Dr. L.P. was on the phone with me. He was very upset. He was really angry. It seemed that my laboratory did not care about patient care and that nobody in the lab was doing his job.

He was taking care of a child recovering from *Haemophilus influenzae* meningitis. He had sent a sample for chloramphenicol determination and needed the result desperately because the previous levels had been low and the dose had been increased. The determination had not been done in the 3 days since sending the specimen, and as it was Friday, it would not be performed until Monday.

I was at a loss because the laboratory should get the results out much quicker than that. I apologized to Dr. L.P., normally a nice guy. I wandered into the laboratory and asked some casual questions, like "What the heck is going on with the chloro levels!" (Reader, please note: I was in error in being disrespectful to the technologists, but I must tell the story the way it occurred). The technologists explained the problem. The assay requires an enzyme and our batch was bad. The assay had been attempted on the Wednesday run, but the controls were out of acceptable limits. There was a problem again on Thursday. Friday they thawed some stored enzyme, but it didn't work either. We eventually decided to send the specimen to a reference laboratory.

The results received on the following Monday indicated low concentrations. This was followed by a second unpleasant phone call complaining about our poor service and the lousy assay (the good doctor wasn't aware we sent the specimen out). I asked him if he checked to see if there were other drugs that might change the clearance rate of chloramphenicol or whether he had checked other possibilities. He replied angrily that he knew what he was doing. Then I became angry. I went onto the ward and found the chart. The nursing notes were very interesting.

It happened that the child had been hospitalized for a long time. Her veins were very poor and keeping IV lines was very difficult. If the child's IV line came out near the time of her dose, the house officer ordered an oral dose and then put back in the IV line when he could. But in that hospital changing orders results in a significant delay in getting the drug to the floor. By the time the oral dose came, it was time for the next intravenous dose so the oral dose was dropped to avoid giving two doses together. And so for days the patient received only about half of her doses. The house officer and the attending physician were unaware of this persistent problem. The doses most often missed were those on the night shift when the delays in pharmacy service and in replacing the IV lines were greatest because the pharmacy and the house staff were on skeleton shifts. Thus, because the samples for analysis were drawn in the morning after rounds, the effect of missing the 2:00 a.m. dose was great, even if the 8:00 a.m. dose was given. The child's drug concentrations were consistently low because she consistently received less drug than she should have.

I wrote Dr. L.P. a controlled but angry letter informing him and we both decided not to bring the matter up again. We are still friendly and the child recovered uneventfully.

### **Molecular heterogeneity**

For some drugs, the molecules of drug in the body differ in their bioactivity, that is, in the magnitude of their physiologic effects. This molecular heterogeneity may arise because of differences in

molecular chirality, because of alterations in molecular structure due to metabolic processes, and because of reduced availability for diffusion and cellular uptake due to plasma protein binding.

**Chirality.** Chiral drugs are generally not produced as pure enantiomer preparations, which are expensive to manufacture, but are instead marketed as racemic mixtures. If the enantiomers of a drug have appreciable differences in their bioactivity, total drug effect will depend upon the fraction of drug in each of the enantiomeric forms. Differences in the pharmacokinetics of enantiomers further complicate matters because the fraction of drug present in each of the various enantiomeric forms will vary over time. It makes sense to employ enantiomer-specific drug assays in the therapeutic monitoring of such drugs (Lee and Williams 1990) but this is currently not done.

**Active metabolites.** Drug metabolism usually leads to drug inactivation, but not always. Metabolism may yield a product that has a reduced but still clinically significant degree of bioactivity. For example, the products of the hepatic metabolism of the tertiary amine cyclic antidepressants, such as imipramine and amitriptyline, include the corresponding secondary amines (desipramine and nortriptyline, respectively) which have antidepressant effects and which are themselves sometimes used as antidepressant agents. When monitoring therapy in patients taking tertiary amine cyclic antidepressants, the plasma concentrations of both the parent drug and the active metabolite are measured. Because the potencies of the secondary amine antidepressants effects are roughly comparable to those of the tertiary amines, the concentrations are interpreted by adding the two concentrations together and comparing the sum to the therapeutic range defined for the combined concentrations. For a metabolite that has a potency that is significantly different from the parent drug, one can scale the concentration of the metabolite by multiplying it by its potency relative to the parent drug and then add the concentration of the parent drug and the scaled concentration of the metabolite together.

A drug metabolite may also have drug effects that are different from those of the parent drug. These effects are often unwanted and may be seriously toxic. For instance, thiocyanate and cyanide are metabolites of nitroprusside. Treatment of a hypertensive crisis with nitroprusside can lead to the accumulation of these metabolites to

symptomatic concentrations, especially in the setting of renal insufficiency, so their concentrations are monitored during such therapy.

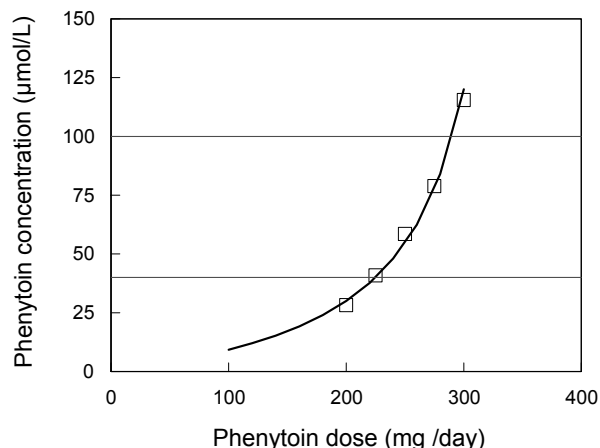
**Plasma protein binding.** Many drugs bind to plasma proteins. The most important of these binding proteins are albumin, which has three different drug binding sites per molecule, and  $\alpha_1$ -acid glycoprotein, the binding protein for lipophilic basic drugs (Hervé *et al.* 1994). Drugs that bind to plasma proteins circulate in two forms, as unbound drug and protein-bound drug. When blood passes through a tissue, unbound drug is removed from the plasma due to diffusion into the tissue and binding to tissue constituents. Other than in the liver and kidney, the amount of drug removed from the plasma is typically so small that there is little effect upon the plasma equilibrium between the unbound and protein-bound forms. Thus, tissue drug concentration at the sites of drug action is determined largely by the unbound drug concentration in the plasma. The physiologic effects of protein-bound drugs should, therefore, correlate better with the plasma concentration of unbound drug than with the plasma concentration of total drug. On the other hand, clinical experience has shown that, most of the time, total drug concentrations perform just as well as unbound drug concentrations as measures for therapeutic drug monitoring. The measurement of unbound drug concentration is more informative than the measurement of total drug concentration only for drugs that are highly protein-bound, that have narrow therapeutic indices, and that show considerable variability in their extent of binding and only in patients who have diseases likely to cause altered protein binding, who are taking drugs known to interact with the protein binding of the monitored drug, or who show clinical effects that are unexpected based upon measurement of total drug concentration (MacKichan 1992).

### Nonlinear plasma kinetics

Because hepatic metabolism is enzyme catalyzed, it is saturable, meaning that, with increasing plasma drug concentrations, the rate of metabolism is less than proportional to the concentration. It is natural to describe the saturability using the Michaelis-Menten model,

$$\text{elimination rate} = \frac{V_{\max}}{K_m + C(t)} C(t)$$

where  $V_{\max}$  is the maximum elimination rate, that attained at very high drug concentrations, and  $K_m$  is



**Figure 12.11** Steady-state trough serum phenytoin concentrations in a patient who received the drug at various dosing rates. The therapeutic range is indicated.

the Michaelis-Menten constant, the drug concentration at which the elimination rate is half maximal. According to this model, kinetic linearity implies that plasma drug concentrations are usually well below the  $K_m$  of the metabolizing enzymes, giving,

$$\text{elimination rate} = \frac{V_{\max}}{K_m} C(t)$$

Kinetic nonlinearity arises if the plasma drug concentrations approach or exceed the  $K_m$ . Rearrangement of the Michaelis-Menten model for the steady state, in which elimination rate equals dosing rate, gives,

$$C_{ss,avg} = \frac{K_m}{V_{\max} - \text{dosing rate}} \text{dosing rate}$$

This equation reveals that  $C_{ss,avg}$  is not proportional to dosing rate but, instead, increases more than proportionally with increases in the dosing rate.

An example of this form of kinetic nonlinearity is shown in Figure 12.11. The graph shows the steady-state trough plasma phenytoin concentrations for a patient who took the drug at each of several dosing levels (data from Richens and Dunlop 1975). The curve was generated by fitting the preceding equation to the subject's data (substituting trough concentration for average concentration). Notice how the kinetic nonlinearity of this drug produces extremely steep increases in steady-state plasma drug concentrations as the dosing rate is increased. The usual starting dosing rate for phenytoin is 200 to 300 mg/day so the kinetic behavior shown in the figure occurs at typical doses. For this reason, therapeutic drug monitoring is invaluable when treating a patient with phenytoin (Yukawa 1996).



## DRUG TOXICITY

The use of plasma drug concentrations in the clinical assessment of the risk of drug toxicity has been discussed in a number of places in the preceding sections. Plasma drug concentrations can also provide useful information in the diagnostic evaluation of drug toxicity.

Drug toxicity must be considered whenever a patient manifests symptoms or signs that could be attributable to a drug that the patient is taking. The question to be resolved is whether the clinical findings are due to the drug or from some other cause. As with other diagnostic queries, this question is answered in terms of probabilities. To calculate the probability of drug toxicity being the cause of the clinical findings, the following form of Bayes' formula is used,

$$P[\text{drug toxicity}] = \frac{P[\text{sick/drug}]}{P[\text{sick/drug}] + P[\text{sick/other}]}$$

where  $P[\text{sick/drug}]$  is the probability of developing the findings while receiving drug therapy (i.e., the risk of drug toxicity) and  $P[\text{sick/other}]$  is the probability of developing the findings for some other reason.

Referring to the frequency plot for toxic effect risk versus plasma drug concentration shown in Figure 12.10, for a measured drug concentration of 100  $\mu\text{g/ml}$ , the probability of developing mild nausea due to drug therapy is 0.66. For the sake of this example, the estimated probability of developing mild nausea as a result of the illness under treatment, as a result of intercurrent illness, or in response to a dietary indiscretion is 0.10. Therefore, the probability that drug toxicity explains the of clinical finding of mild nausea is,

$$P[\text{drug toxicity}] = \frac{0.66}{0.66 + 0.10} = 0.87$$

What if the clinical finding is a new arrhythmia? If the probability of the patient developing the arrhythmia for reasons other than drug toxicity is estimated to be low, say 0.02, then

$$P[\text{drug toxicity}] = \frac{0.10}{0.10 + 0.02} = 0.83$$

where 0.10 is the probability of developing an arrhythmia given a plasma drug concentration of 100  $\mu\text{g/ml}$ . For both these cases, precision in the characterization of the condition being evaluated is essential. For example, if the new arrhythmia were

of a different type, one less often associated with drug use (say, a probability of 0.02) and more often evolving from the arrhythmia under treatment (say, a probability of 0.20) then,

$$P[\text{drug toxicity}] = \frac{0.02}{0.02 + 0.20} = 0.09$$

making drug toxicity a much less likely cause of the finding.

These probabilities can also be generated using the posterior probability approach discussed in Chapter 3. For that purpose the prior probability must be calculated. This is done using the preceding form of Bayes' formula but here the probability of developing the clinical findings while receiving drug therapy is the probability as found in all patients receiving the drug at the dose given the patient; i.e., without reference to the plasma drug concentration. Say that probability is 0.025 in the case of a new arrhythmia. Then,

$$P[\text{pre}] = \frac{0.025}{0.025 + 0.02} = 0.56$$

Recall that the likelihood ratio from of Bayes' formula is,

$$P[\text{post}] = \frac{P[\text{pre}] \text{ likelihood ratio}}{P[\text{pre}] \text{ likelihood ratio} + (1 - P[\text{pre}])}$$

In this formula, the value of the likelihood ratio is equal to the ratio of the drug toxicity risk estimates. The risk estimate for a patient with a plasma drug concentration of 100  $\mu\text{g/ml}$  is 0.10 and the risk estimate without reference to the plasma drug concentration is 0.025, so the likelihood ratio is 4. Thus,

$$P[\text{post}] = \frac{0.56 \times 4}{0.56 \times 4 + 0.44} = 0.83$$

which is equal to the value calculated previously. In fact, the probability estimates will always be equal because the calculations are algebraically equivalent so it does not matter which approach is used.

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