10

Application of Pharmacokinetic Principles

Previous chapters have concerned basic pharmacokinetic principles, and have emphasized the development of pharmacokinetic theory. It is the purpose of this chapter to consider the application of these principles to drug utilization in the clinical setting. There will be little emphasis on the development of equations. Where appropriate, the practical utility of selected equations from previous chapters will be discussed.

MULTIPLE DOSING

The most common approach for the maintenance of therapeutic plasma concentrations is through the repetitive adminstration of oral doses at given time intervals. Although oral administration is the most frequently used route of administration, the basic principles of multiple dosing will apply regardless of the route of administration and the pharmacokinetic model used to describe the drug, as long as the kinetic behavior of the drug can be described by linear or first-order kinetics.

The general objective of drug treatment is to obtain quickly and to maintain drug plasma concentrations which fluctuate above some minimum effective concentration, and below those concentrations that have been associated with adverse effects (i.e., to maintain concentrations within the therapeutic range). The application of pharmacokinetic principles can have the greatest impact on therapy with drugs having a narrow therapeutic range. Frequently, a therapeutic range is perceived as being an absolute concentration range within which all patients will respond and no adverse effects will be observed. Unfortunately, this is not the case, and one must look at a therapeutic range as that concentration range within which there will be the greatest probability for a therapeutic response and the least probability for adverse effects. For example, 0.5 to 2 ng/ml is frequently

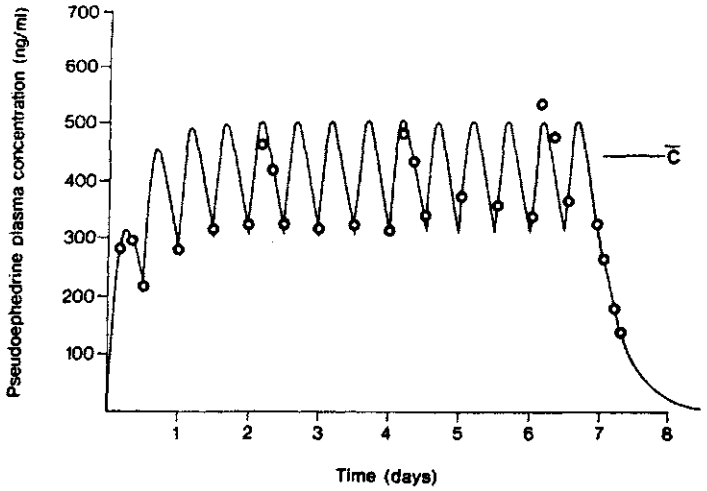

Fig. 10.1 Pseudoephedrine concentrations in plasma on twice-a-day oral administration of a slow-release product. The horizontal line, to the right of the curve, denotes the average steady-state drug concentration (see Ref. 1).

quoted as the therapeutic range for digoxin. However, there is about a 10% risk of seeing toxic symptoms at a concentration of 1.5 ng/ml. This risk increases with concentration and one sees about an 85% risk of adverse effects at concentrations greater than 2 ng/ml. Thus toxicity can be observed within a therapeutic range, and concentrations greater than the upper end of the therapeutic range may be found in patients demonstrating no adverse effects. Therefore, a therapeutic range can only be used as a guide to therapy.

When an oral multiple dosing regimen is initiated, plasma concentrations will increase, reach a maximum, and begin to decline (see Fig. 10.1). Generally, before all of the absorbed drug from the first dose is eliminated, a second dose will be administered. Consequently, plasma concentrations resulting from the second dose will be higher than those from the first dose. This increases in concentration with dose, or accumulation, will continue to occur until a steady state is reached. At steady state the rate of drug entry into the body will equal the rate of exit; hence the concentration at any time during a dosing interval should be the same from dose to dose. The extent to which a drug will accumulate relative to the first dose can be quantified by an accumulation factor R which is dependent on the relative magnitudes of the dosing interval τ and the half-life $t_{1/2}$ of a drug:

$$R = \frac{1}{1 - e^{-0.693\tau/t_{1/2}}} \qquad (10.1)$$

This relationship is depicted graphically in Fig. 10.2 and illustrates that the smaller the ratio $\tau/t_{1/2}$, the greater will be the extent of accumulation. Of interest is the fact that when the dosing interval equals the half-life of a drug, the average steady-state concentrations will be about twice the average concentration after the first dose.

Although the time to reach steady state will generally be a complex function of several pharmacokinetic parameters (see Chap. 3), it is usually found that regardless of the complexity of the pharmacokinetic

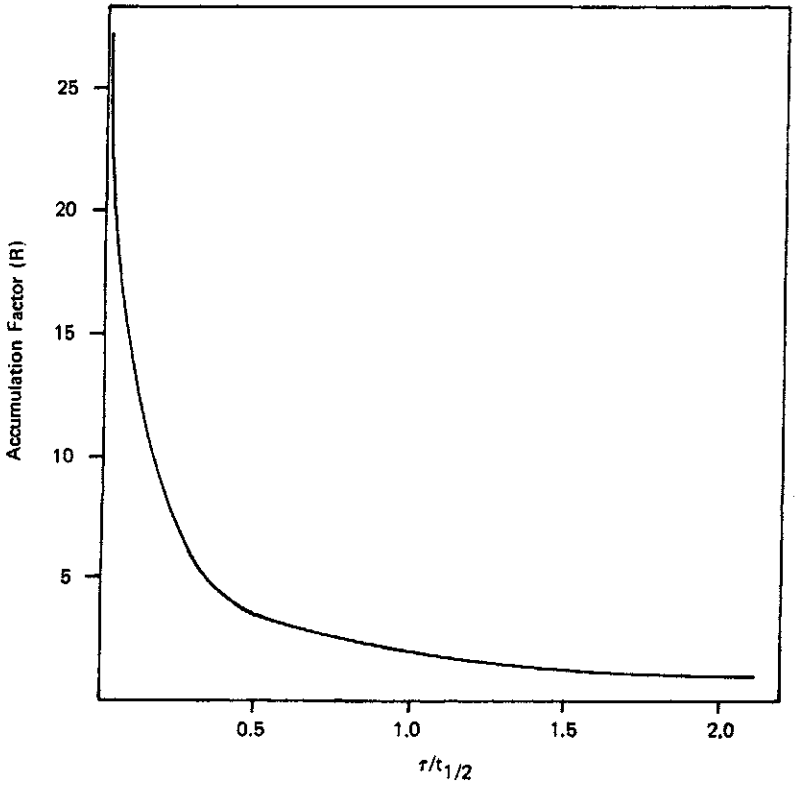

Fig. 10.2 Degree of drug accumulation at steady state relative to a single dose (expressed as an accumulation factor, R) as a function of the ratio of dosing interval to half-life of the drug, $\tau/t_{1/2}$. Administration of a fixed dose at a constant dosing interval equal to the half-life of the drug results in a twofold accumulation.

model, about 90% of steady state will be reached within approximately four half-lives. Whereas the time to reach steady state depends primarily on the half-life of a drug, the average drug concentration at steady state, $\bar{C}$, is a function of the maintenance dose X_0, the fraction of the dose absorbed F, the dosing interval, and the clearance Cl_s of the drug. This relationship is

$$\bar{C} = \frac{FX_0}{Cl_s \tau} \tag{10.2}$$

or

$$\bar{C} = \frac{1.44FX_0 t_{1/2}}{V\tau} = \frac{AUC}{\tau} \tag{10.3}$$

where V is the apparent volume of distribution of a drug, and AUC is the area under the plasma concentration versus time curve from time zero to infinity following a single maintenance dose. These equations, although very useful, give no insight into the degree of fluctuation in steady-state plasma concentrations. For example, administration of a drug with a half-life of 12 h according to the following regimens: 600 mg daily, 300 mg twice a day, and 200 mg three times a day, will produce identical values for $\bar{C}$. However, 600 mg daily will result in greater fluctuations in steady-state concentrations than will 300 mg twice a day, which will in turn produce greater fluctuations than 200 mg three times a day. Although absorption rate will influence the degree of fluctuation in steady-state concentrations, the relative magnitude of τ and $t_{1/2}$ will be a major factor governing these fluctuations. This is illustrated by Fig. 10.3, which assumes a one-compartment system with intravenous bolus administration. As can be seen, the greater the ratio of $\tau/t_{1/2}$, the larger will be the ratio of $C_{max}/\bar{C}$ at steady state, and the smaller will be the ratio of $C_{min}/\bar{C}$ at steady state.

Equations (10.2) and (10.3) illustrate how the absorption, distribution, and elimination characteristics of a drug affect steady-state drug concentrations. The influence of such factors as disease states, drug interactions, and age on steady-state concentrations can also be readily appreciated from these equations by knowing which process is influenced by these factors. One can also utilize these relationships as tools to gain insight into a patient's therapy and to determine whether a patient's regimen may produce subtherapeutic or toxic concentrations of a drug. Equations (10.2) and (10.3) can also be rearranged to yield the following expression for maintenance dose:

$$X_0 = \frac{\bar{C}Cl_s \tau}{F} = \frac{\bar{C}V\tau}{1.44Ft_{1/2}} \tag{10.4}$$

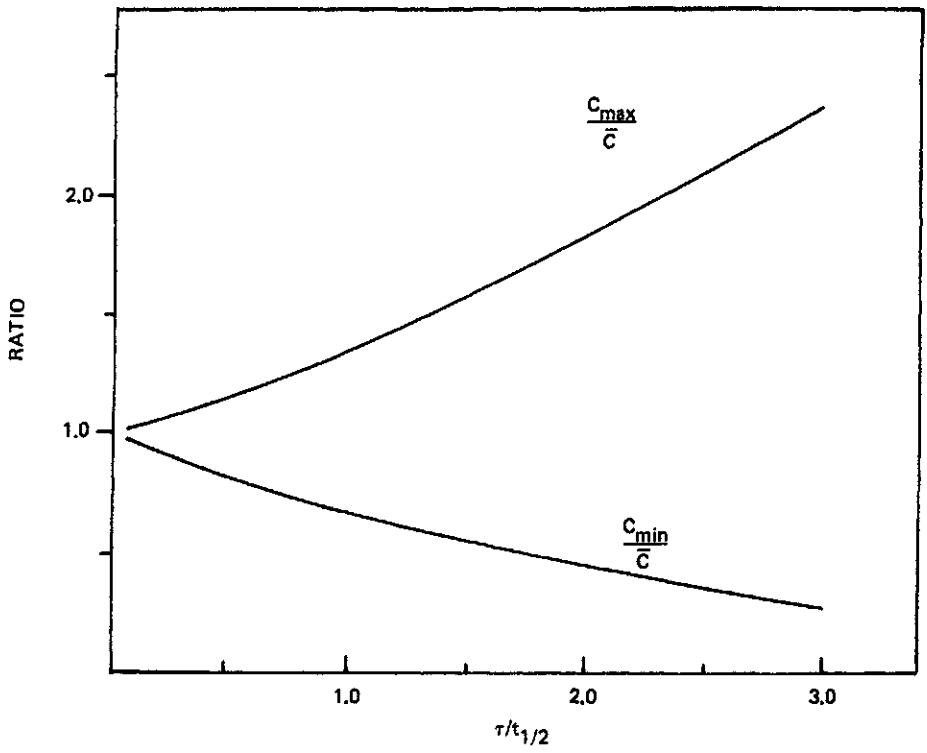

Fig. 10.3 Relationship between the ratio of C_{max} or C_{min} at steady state to the average drug concentration at steady state, $\bar{C}$ and the ratio of dosing interval to drug half-life, $\tau/t_{1/2}$. Assuming a fixed daily dose of drug, the larger the value of $\tau/1/2$, the greater the fluctuations of drug concentration in plasma at steady state.

This equation can be used to predict an initial maintenance dose of a drug for a given patient. Knowledge of the therapeutic range will enable $\bar{C}$ and τ to be selected. It is generally appropriate to aim for a steady-state concentration which is safe (i.e., a concentration associated with a very low incidence of toxicity). A concentration midway between the limits of the therapeutic range or one just below this midpoint would generally be reasonable. Determination of τ requires information on a drug's half-life as well as its therapeutic range. If, for example, a drug has an optimum therapeutic range of 10 to 20 μg/ml, τ should probably be equal to or less than one half-life, since concentrations could fall from the upper to the lower end of the range in one half-life. If, however, the therapeutic range was between 2 and 20 μg/ml, it may be appropriate to use a dosing interval

equal to approximately three half-lives. For reasons of compliance, it is often desirable to have a dosing interval as long as possible, but it probably should not exceed one day. In addition, patients should not be expected to take a dose more frequently than four times a day. If a drug has a narrow therapeutic range and a short half-life (e.g., procainamide), it may be necessary to dose more frequently than four times a day for optimum effects. Sustained-release dosage forms are very desirable for such drugs.

Once $\bar{C}$ and τ are selected, one must usually rely on literature data for values of F, the availability of the dosage form being used, and clearance. Generally, average parameters are used even though we know that there is considerable interpatient variability in these parameters. Interpatient variability is a particular problem with estimates of F for poorly absorbed drugs and Cl_s for drugs eliminated predominantly by metabolism. Another problem frequently encountered is the fact that most pharmacokinetic studies are performed in young, healthy male populations rather in the patient population in which the drug is to be used, although this information is becoming more available. Although the use of Eq. (10.4) does have some pitfalls due to the limitation of not having individual patient parameters available, it does provide a rational basis for the initiation of therapy.

Because of the problem of interpatient variability, it would be desirable to be able to determine a maintenance dose based on one or more measurable parameters in the individual patient. From a practical point of view this is generally not feasible. Recently, however, publications have appeared which indicate that a maintenance dose producing therapeutic plasma concentrations can be estimated based on a single plasma concentration at a specific time t* following the oral administration of a test dose X_0^* [2–4]. The plasma concentration C* following the test dose, assuming that it is in the postabsorptive-postdistributive phase of a plasma concentration versus time curve, can be given by the following equation:

$$C^* = FX_0^* Z e^{-0.693t^*/t_{1/2}} \tag{10.5}$$

where Z is a constant dependent on the pharmacokinetic model and route of administration. Dividing Eq. (10.2) by (10.5) and solving for the reciprocal of the maintenance dose, $1/X_0$, yields

$$\frac{1}{X_0} = \frac{e^{0.693t^*/t_{1/2}}}{\bar{C}Cl_s \tau Z X_0^*} C^* \tag{10.6}$$

Plots of $1/X_0$ versus C* have resulted in a linear relationship, as illustrated in Figs. 10.4 and 10.5. Once data have been generated

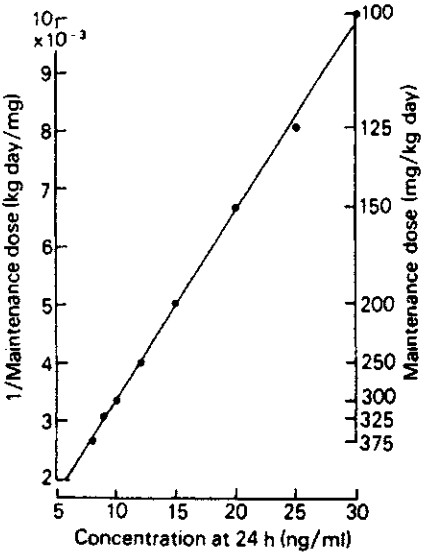

Fig. 10.4 Relationship between the reciprocal of the maintenance dose of imipramine needed to achieve a steady-state total tricyclics (imipramine and desipramine) concentration of 250 ng/ml and the concentration of total tricyclics 24 h after a single 50 mg oral test dose of imipramine (see Ref. 4).

such as those presented in Figs. 10.4 and 10.5, the administration of a test dose to a given patient followed by the measurement of C* should permit the prediction of a maintenance dose that would yield the desired $\overline{C}$. This method can be applied to a patient population with a relatively wide range of half-lives [4]. However, different $1/X_0$ versus C* data sets should be developed for the same drug in patient populations that have different ranges of half-lives. The optimum sampling time following the test dose equals the average half-life divided by 0.693 [5].

A more comprehensive single-point method has been described by Sheiner et al. [6]. This method requires a computer system with a large data base. In the case of digoxin, information concerning sex, age, height, weight, outpatient or inpatient status, presence or absence of moderate or severe heart failure, values of kidney function tests, as well as measured plasma concentration data must be available. The matching of patient characteristics and resulting plasma concentration(s) for a given patient to a typical member of a subgroup permits the forecasting of an individual's course of therapy based on known outcomes of this subgroup member. It has been

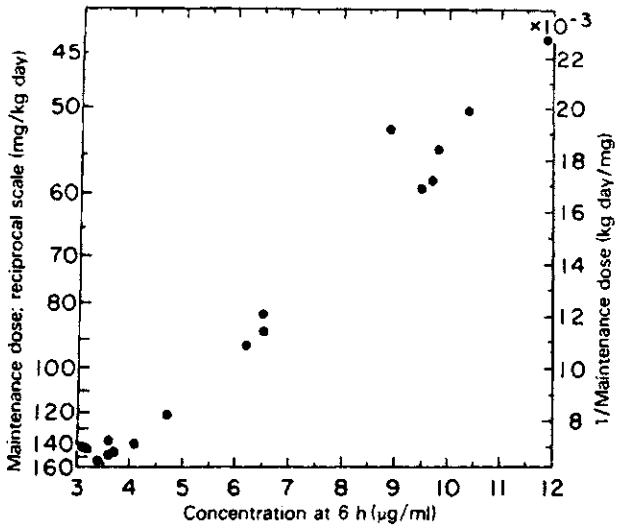

Fig. 10.5 Relationship between the reciprocal of the maintenance dose of chloramphenicol needed to achieve a steady-state concentration of 15 μg/ml and the concentration of chloramphenicol 6 h after a single 25 mg/kg test dose (see Ref. 4).

demonstrated that information from one plasma concentration is more valuable than all information on patient features, and if two plasma concentrations are available, forecast accuracy and precision are as good as theoretically possible.

The time required to reach steady-state concentrations and obtain a maximum response from a given dosing regimen may be excessive because of the half-life of a given drug. This problem can be overcome by the administration of a loading dose followed by administration of maintenance doses. As discussed in Chap. 3, a loading dose X_0' can be estimated by multiplying the maintenance dose by the accumulation factor R, which is equal to $1/(1 - e^{-0.693\tau/t_{1/2}})$ [Eq. (10.1)]. Therefore,

$$X_0' = X_0 \frac{1}{1 - e^{-0.693\tau/t_{1/2}}} \tag{10.7}$$

Equation (10.7) assumes that each does is administered in the post-absorptive-postdistributive phase of each previous dose. For certain drugs it may be advisable not to administer the loading dose as a single dose, but rather to spread it over the first dosing inverval or even longer if necessary. For example, a 1 mg loading dose of digoxin should probably be given as three divided doses of 0.5, 0.25, and 0.25 mg at 4- to 8-h intervals.

Although consideration is given to the fluctuation in the steady-state plasma concentrations of a drug when the dosing interval τ is selected, more precise estimates may be obtained by utilizing Fig. 10.3. Once τ has been selected and $t_{1/2}$ has been estimated, the ratios $C_{max}/\bar{C}$ and $C_{min}/\bar{C}$ at steady state can be estimated from this figure using the $\tau/t_{1/2}$ ratio. Simply multiplying the chosen $\bar{C}$ by the $C_{max}/\bar{C}$ and $C_{min}/\bar{C}$ ratios will yield estimates of C_{max} and C_{min} at steady state. Since Fig. 10.3 is based on equations where instantaneous absorption is assumed, the measured C_{max} would be expected to be less than the predicted value, while the measured C_{min} should be greater than the predicted value.

DOSE ADJUSTMENTS IN RENAL FAILURE

There is generally a great deal of interpatient variability in the elimination rates of drugs which are predominantly eliminated by metabolism. Other than employing the method discussed above, which involves the administration of a test dose, there is no practical way to obtain a priori a measure of the ability of a given patient to eliminate such drugs. However, for drugs eliminated primarily by renal mechanisms, creatinine clearance and serum creatinine have been successfully employed to evaluate renal function in a given patient, thereby enabling estimates of the clearance or half-life of a drug. The use of serum creatinine measurements to determine renal function has been discussed by Bjornsson [7]. Creatinine is a useful marker of renal function since it is produced endogenously as an end product of muscle metabolism and is eliminated by the kidney at a rate that approximates glomerular filtration rate. It has been shown for a number of drugs that the elimination of creatinine directly reflects drug elimination.

The apparent first-order elimination rate constant of a drug, K, is equal to the sum of the rate constants for renal and nonrenal excretion, k_r and k_{nr}, respectively. That is,

$$K = k_r + k_{nr} \tag{10.8}$$

Assuming that renal elimination is directly related to creatinine clearance Cl_{cr} it follows that

$$K = aCl_{cr} + k_{nr} \tag{10.9}$$

where a is a proportionality constant. A plot of K versus Cl_{cr} will, therefore, be linear (see Fig. 10.6). Data relating K to creatinine clearance are available for many drugs, and summaries of such information appear in several publications [9–11]. Although the discussion above is concerned with adjusting an individual patient's K for changes in renal function, the same approach can be used to relate renal clearance or total body clearance of a drug to creatinine

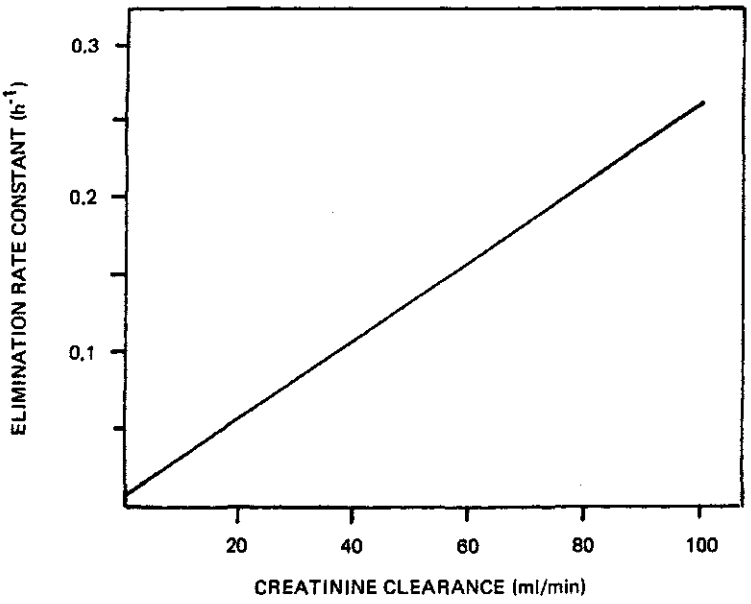

Fig. 10.6 Relationship between the elimination rate constants of 5-fluorocytosine and creatinine clearance, based on studies in patients with imparied renal function. The line intercepts the y axis at a value of 0.0067 h^{-1}. (Data from Ref. 8.)

clearance. Although these relationships have been established for digoxin [12], there are few data available for other drugs.

Because of the practical problem of obtaining a 24 h urine collection for the purpose of calculating creatinine clearance, serum creatinine is generally used as an index of renal function. Since serum creatinine C_c is inversely related to creatinine clearance by the relationship

$$C_c = \frac{PR}{Cl_{cr}} \tag{10.10}$$

where PR is endogenous production rate of creatinine, one would expect that a decrease in renal function would produce a corresponding increase in serum creatinine. Solving (10.10) for Cl_{cr} and substituting this value of creatinine clearance for Cl_{cr} in (10.9) yields

$$K = \frac{aPR}{C_c} + k_{nr} \tag{10.11}$$

which in terms of half-life $t_{1/2}$ is

$$\frac{1}{t_{1/2}} = \frac{aPR}{0.693}\frac{1}{C_c} + \frac{k_{nr}}{0.693} \qquad (10.12)$$

since $K = 0.693/t_{1/2}$ [Eq. (1.12)]. Therefore, a plot of K versus $1/C_c$, or $1/t_{1/2}$ versus $1/C_c$, will be linear (see Fig. 10.7).

Essential to the appropriate use of serum creatinine as an index of renal function and drug elimination is that the production rate of creatinine must be relatively constant. Since production rate depends on the muscle mass in a given individual, one would expect sex, age, and body weight to influence the relationship between serum creatinine and creatinine clearance. Because of this, serum creatinine may be a relatively poor index of renal function. One such example is illustrated in Table 10.1. Renal function decreases with increasing age, whereas serum creatinine remains relatively constant; the decrease in creatinine clearance is associated with a corresponding increase in kanamycin half-life. Therefore, serum creatinine alone may have limited utility as an index of renal function and drug elimination under certain conditions. Serum creatinine can, however, be employed in conjunction with the age, sex, and weight of an individual to predict

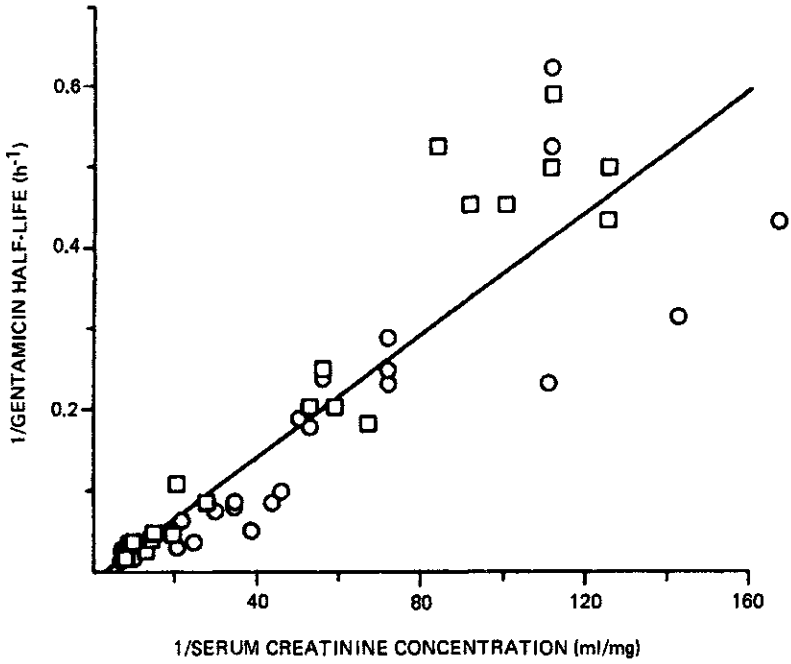

Fig. 10.7 Double reciprocal plot of gentamicin half-life versus serum creatinine concentration (see Ref. 13).

Table 10.1 Creatinine Clearance, Serum Creatinine, and Kanamycin Half-Life as a Function of Age in Healthy Humans

Age (yr)	n	Cl_{cr} (ml/min)	C_c (mg%)	$t_{1/2}$ (min)
20–50	13	94 ± 17[a]	0.97 ± 0.12	107 ± 27
50–70	21	75 ± 20	0.95 ± 0.23	149 ± 49
70–90	27	43 ± 12	0.98 ± 0.21	282 ± 99

[a]Mean ± SD.

Notes: The increase in kanamycin half-life $t_{1/2}$ with age is consistent with the decrease in creatinine clearance Cl_{cr}. Serum creatinine C_c appears to be independent of age. From Ref. 14.

a creatinine clearance. Although several approaches have been used for such a prediction [15,16], the following equation [17], based on the data of Kampmann et al. [18], is particularly useful:

$$Cl_{cr} = \frac{wt(144 - age)}{71C_c} \tag{10.13}$$

where age is in years, C_c is in mg%, Cl_{cr} is in ml/min, and wt is in kg. Since creatinine is an end product of muscle metabolism, total body weight should not be used in (10.13) for obese individuals. Rather, some weight between total and ideal body weight is appropriate [19]. Equation (10.13) is intended for use with males. For females the value obtained from (10.13) should be multiplied by 0.85 to correct for the average difference in creatinine production between males and females. As mentioned previously, (10.13) is only one of several approaches that has been used to predict creatinine clearance. A study correlating predictions using Eq. (10.13) to measure clearance has found a correlation coefficient of 0.84 [15], which is as high as any method to which it was compared.

Once a creatinine clearance has been either determined directly or predicted from a serum creatinine value using (10.13), an estimate of the elimination rate constant or clearance can be obtained for the patient from data such as those presented in Fig. 10.6. Once this elimination parameter has been determined, it can be used in Eqs. (10.4) and (10.7) to calculate a maintenance dose and a loading dose, respectively. The adjustment of doses of renally excreted drugs is most critical for those drugs that have a narrow therapeutic range, examples of which are digoxin and the aminoglycoside antibiotics. Drugs such as the penicillins and cephalosporins, which are also eliminated primarily by the kidneys, probably require dose adjust-

ments only when renal function is significantly compromised (i.e., a creatinine clearance less than 20 ml/min), since they have a much wider therapeutic range.

HEMODIALYSIS

Additional dose adjustments may be necessary in severe renal failure patients who require routine dialysis. Hemodialysis, peritoneal dialysis, or hemoperfusion may result in drug removal from the body and require replacement of this amount to maintain therapeutic concentrations. Hemodialysis is the most common method of removing endogenous waste material in chronic renal failure patients, although chronic ambulatory peritoneal dialysis is becoming more popular. Hemoperfusion appears to be used primarily to remove drugs from the body in cases of drug overdose.

A number of factors may influence the hemodialyzability of a drug [20–23]. Since hemodialysis membranes have discrete pores through which drug must diffuse to be dialyzed, one might expect that the larger the molecular size, the more poorly a drug will be dialyzed. However, the clinical significance of molecular weight has not been clearly established. Blood flow, dialysate flow, and aqueous solubility are also factors that will influence dialyzability. A decrease in each of these factors will tend to decrease the extent to which a drug is dialyzed, with the relative effect of each being governed by their influence on the concentration gradient between blood and dialysate.

The pharmacokinetic characteristics of a drug will also have a significant impact on the ability of a drug to be dialyzed. Those drugs that have a large volume of distribution and/or are highly plasma protein bound tend to be poorly dialyzed. When the ratio of percent unbound/volume of distribution (in liters/kg) is less than 20, a small and probably insignificant amount (i.e., less than 10%) of drug will be removed from the body by a 6 h dialysis, while a value greater than 80 suggests that between 20 and 50% of the amount of drug in the body will be removed by dialysis (see Fig. 10.8).

The use of binding and distribution data will give one a general appreciation of the dialyzability of a given drug, but more precise estimates of the amount removed may be desirable for the purpose of dose adjustments. One approach involves the use of the half-lives of drug during dialysis, $(t_{1/2})_d$, and when dialysis is not being performed, $t_{1/2}$. The fraction of drug in the body removed by dialysis, f, can be given by [24]

$$f = \frac{t_{1/2} - (t_{1/2})_d}{t_{1/2}} \left(1 - e^{-0.693t/(t_{1/2})_d}\right) \qquad (10.14)$$

where t is the duration of dialysis. The half-lives $t_{1/2}$ and $(t_{1/2})_d$ can be obtained from the literature for a number of drugs, some of

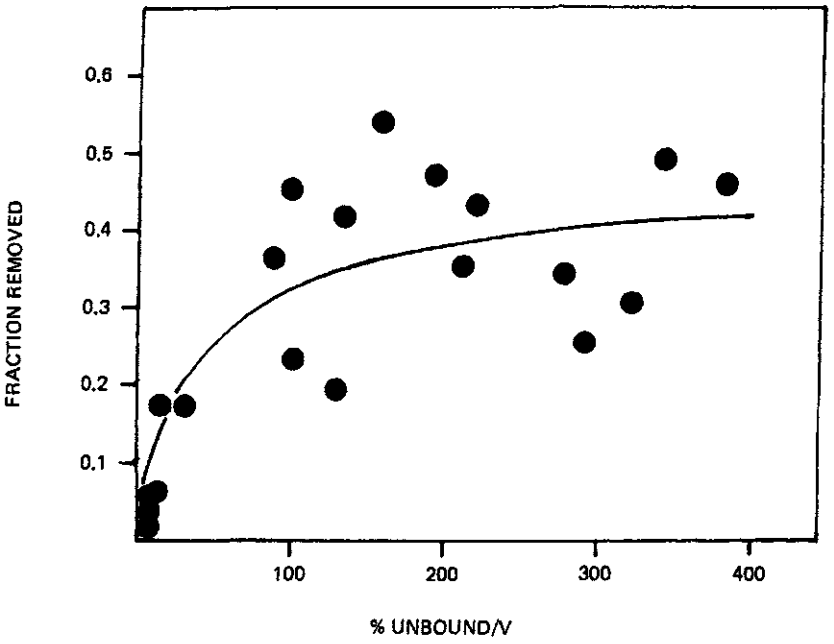

Fig. 10.8 Plot of the fraction of drug in the body removed by a 6 h hemodialysis treatment versus the ratio of the percentage of drug in the plasma unbound to plasma proteins to the apparent volume of distribution V of the drug expressed in liters/kg. (From Ref. 24.)

which have been tabulated [24]. A predialysis concentration C and the volume of distribution V of the drug must also be known. This information then enables the amount of drug that will be removed from the body by dialysis, X_d, to be estimated. The relationship is

$$X_d = fCV \tag{10.15}$$

This amount of drug can then be administered at the end of the dialysis.

Another approach for estimating the amount of drug removed during dialysis involves the use of dialysis clearance. The rate of appearance of drug in the dialysate, dX_d/dt, is given by

$$\frac{dX_d}{dt} = k_d X \tag{10.16}$$

where k_d is the first-order rate constant for appearance of drug in the dialysate, and X is the amount of drug in the body. Over a finite

period of time (e.g., dialysis time), dX_d/dt can be replaced by $\Delta X_d/\Delta t$. The amount of drug in the body is equal to the product of the plasma concentration C_p and volume of distribution V. Since dX_d/dt is replaced by $\Delta X_d/\Delta t$, plasma concentration must be measured at the midpoint (i.e., C_{pm}). Equation (10.16) can therefore be written as

$$\frac{\Delta X_d}{\Delta t} = k_d V C_{pm} \tag{10.17}$$

The product $k_d V$ will equal dialysis clearance Cl_d; therefore,

$$\frac{\Delta X_d}{\Delta t} = Cl_d C_{pm} \tag{10.18}$$

Equation (10.18) can be solved for the amount of drug appearing in the dialysate, ΔX_d or X_d, during a given dialysis time Δt or t:

$$\Delta X_d = Cl_d \Delta t C_{pm} \tag{10.19}$$

or

$$X_d = Cl_d t C_{pm} \tag{10.20}$$

To determine the amount of drug in the dialysate, one must know the duration of dialysis, the plasma concentration at the midpoint of the dialysis interval, and dialysis clearance. A value for dialysis clearance must be obtained from the literature and should have been determined based on plasma concentration-time rather than blood concentration-time data.

Dialysis clearance measured in terms of plasma $(Cl_d)_p$ is given by

$$(Cl_d)_p = Q_p \frac{C_{ap} - C_{vp}}{C_{ap}} \tag{10.21}$$

and

$$(Cl_d)_p = Q_d \frac{C_{do}}{C_{vp}} \tag{10.22}$$

where Q_p is plasma flow through the dialyzer, Q_d is dialysate flow, C_{ap} and C_{vp} are arterial and venous plasma concentrations of drug (i.e., the plasma concentrations entering and leaving the dialyzer), and C_{do} is the dialysate concentration leaving the dialyzer. Equation (10.22) can be readily applied if dialysate concentrations can be measured. This may be a problem because of the low concentrations frequently encountered and the inconvenience of collecting the large volume of dialysate.

The use of (10.21) requires an estimate of plasma flow through the dialyzer. This can be calculated from blood flow, which is quite readily measured. Blood concentration C_{vb} is related to plasma concentration C_{vp} by the relationship

$$C_b = C_p\left(1 - H + \frac{C_{vrbc}}{C_{vp}} H\right) \tag{10.23}$$

where H is hematocrit and C_{vrbc} is the drug concentration in the red blood cells. Since drug removal rates will be equal no matter whether clearance is expressed in terms of blood or plasma, it follows that [25]

$$(Cl_d)_b C_{vb} = (Cl_d)_p C_{vp} \tag{10.24}$$

where $(Cl_d)_b$ is dialysis clearance based on blood concentrations. Solving Eqs. (10.23) and (10.24) for the ratio of blood to plasma concentrations and setting the right sides of the resulting equations equal to each other yields

$$\frac{(Cl_d)_p}{(Cl_d)_b} = 1 - H + \frac{C_{vrbc}}{C_{vp}} H \tag{10.25}$$

An equation analogous to (10.21) can be written in terms of blood concentrations C_{ab} and C_{vb}, flow Q_b, and clearance $(Cl_d)_b$:

$$(Cl_d)_b = Q_b \frac{C_{ab} - C_{vb}}{C_{ab}} \tag{10.26}$$

The extraction ratios $(C_{ap} - C_{vp})/ C_{ap}$ and $(C_{ab} - C_{vb})/C_{ab}$ in (10.21) and (10.26) are equal if the red blood cell-to-plasma concentration ratio is constant on both sides of the dialyzer. Therefore, the ratio of (10.21) to (10.26) is given by

$$\frac{(Cl_d)_p}{(Cl_d)_b} = \frac{Q_p}{Q_b} \tag{10.27}$$

Substituting for $(Cl_d)_p/(Cl_d)_b$ according to (10.25) and solving for Q_p yields

$$Q_p = Q_b\left(1 - H + \frac{C_{vrbc}}{C_{vp}} H\right) \tag{10.28}$$

Therefore, to calculate dialysis clearance based on (10.21), plasma flow should be calculated using (10.28). As can be seen, red blood cell concentration and hematocrit in addition to plasma concentration must be measured to permit this calculation.

The plasma flow calculated by (10.28) is actually an apparent plasma flow and will only equal real plasma flow as given by

$$Q_p = Q_b(1 - H) \tag{10.29}$$

if no drug distributes into the red blood cells. The use of (10.29) instead of (10.28) will result in an underestimate of the true dialysis clearance if the drug partitions to any significant degree into red blood cells. It is also readily apparent from (10.28) that plasma flow equals blood flow if the concentrations of drug in the red blood cells and plasma are equal.

Utilizing a correctly determined dialysis clearance [i.e., one calculated using (10.21) or (10.22)] will permit an estimate of the amount of drug removed during dialysis. This amount can then be replaced at the end of the dialysis to permit the maintenance of therapeutic plasma concentrations.

In general, the same principles apply to the dialyzability of a drug by peritoneal dialysis as were mentioned for hemodialysis, the primary difference being the properties of the membrane to be traversed by the drug, the peritoneal membrane versus the synthetic membrane in hemodialysis. It has been suggested that the peritoneal membrane appears more permeable to larger molecules (e.g., molecular weights of 5000 or more) than does a hemodialysis membrane [26]. Also, the characteristics of the peritoneal membrane would require that to be dialyzable a drug must have a certain degree of lipid solubility. Overall peritoneal dialysis tends to be much less efficient than hemodialysis in removing drugs. Although there is much less quantitative information available on peritoneal dialysis, it would seem reasonable that the amount of drug removed from the body due to peritoneal dialysis, and hence the amount of additional drug necessary to maintain therapeutic plasma concentrations, could be determined using either (10.14), or (10.20) and (10.22).

METHODS FOR DETERMINATION OF INDIVIDUAL PATIENT PARAMETERS

Most individualized drug dosing and/or dose adjustment methods have relied on population data and individual patient characteristics. A more precise approach would be to assess the pharmacokinetics of a drug directly in the patient receiving the drug. The single-point method [2–5] described earlier in this chapter is one such approach to estimate clearance in individuals within a defined population. The method described by Sheiner et al. [6] is a more general approach. Other methods which require several blood samples after administration of test doses have been applied to gentamicin [27,28] and phenytoin [29,30]. These methods may be used for drugs with similar pharmacokinetic properties.

If the half-life $t_{1/2}$ or elimination rate constant K and volume of distribution V can be determined in a patient for a drug that obeys first-order kinetics and essentially confers on the body the pharmacokinetic characteristics of a one-compartment model, a total dosing regimen can be designed. This has been demonstrated with gentamicin [27,28]. Following a 1 h intravenous infusion of gentamicin the maximum plasma concentration of gentamicin, C_{max}, is given by (see Chap. 1)

$$C_{max} = \frac{k_0}{VK}(1 - e^{-KT}) + C_0 e^{-KT} \tag{10.30}$$

where k_0 is the zero-order infusion rate, T the infusion time, and C_0 the preinfusion drug concentration, which will be zero if the patient has not recently received drug prior to this dose. Collection of blood samples prior to the infusion and at 1, 2, and 4 h after the start of the infusion will yield a value for C_{max} (i.e., the 1 h concentration), C_0, and K. The rate constant is obtained by applying linear regression to the logarithms of the 1, 2, and 4 h concentrations plotted against time.

Solving (10.30) for volume of distribution yields

$$V = \frac{k_0(1 - e^{-KT})}{K(C_{max} - C_0 e^{-KT})} \tag{10.31}$$

Since all of the terms are known, V can be readily calculated. The estimated values of V and K can then be used to calculate the amount of gentamicin to be infused over 1 h to provide the desired maximum or minimum steady-state concentrations, $(C_{ss})_{max}$ and $(C_{ss})_{min}$. $(C_{ss})_{max}$ is given by [27]

$$(C_{ss})_{max} = \frac{k_0(1 - e^{-KT})}{VK(1 - e^{-K\tau})} \tag{10.32}$$

where τ is the dosing interval. Equation (10.32) can be solved for the infusion rate required to obtain the desired maximum steady-state concentration, that is

$$k_0 = \frac{VK(C_{ss})_{max}(1 - e^{-K\tau})}{1 - e^{-KT}} \tag{10.33}$$

The predicted minimum steady-state concentration will be given by the following equation:

$$(C_{ss})_{min} = (C_{ss})_{max} e^{-K(\tau - T)} \tag{10.34}$$

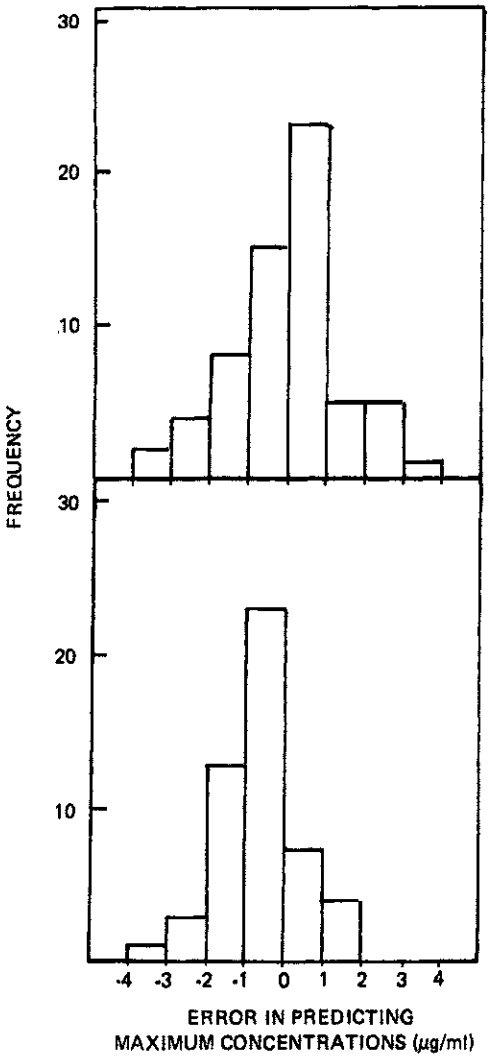

Fig. 10.9 Distribution of differences between predicted and observed peak (upper panel) and nadir (lower panel) concentrations of gentamicin in serum at steady state. (From Ref. 28.)

This method was evaluated in 63 patients for whom it was desirable to produce maximum and minimum gentamicin concentrations ranging from 6 to 10 μg/ml and 0.5 to 2 μg/ml, respectively [28]. The results are presented in Fig. 10.9. Sixty percent of the maximum values and 56% of the minimum values were within 1 μg/ml of those predicted.

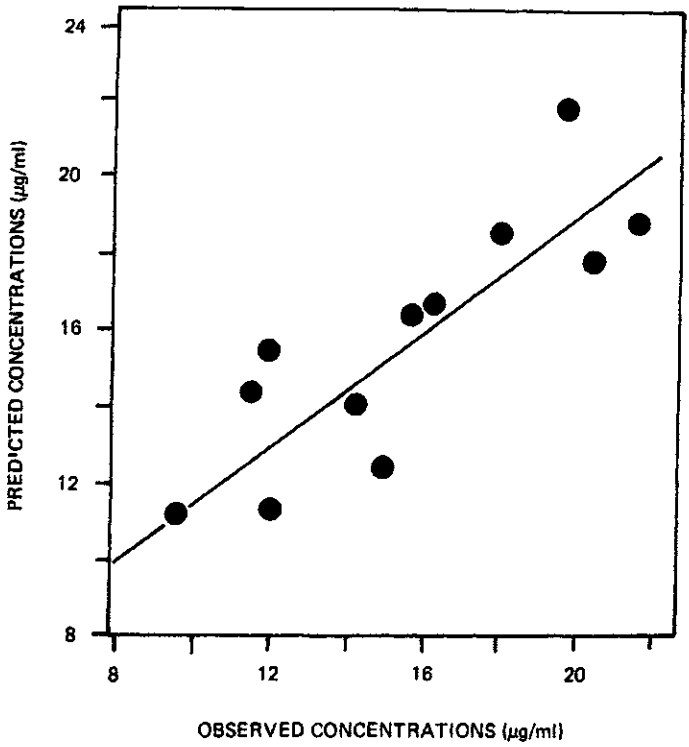

Fig. 10.10 Correlation of predicted and observed concentrations of phenytoin in serum. (From Ref. 29.)

Other methods have been recommended for the dosing of the anticonvulsant phenytoin based on its pharmacokinetic parameters in the patient receiving the drug. Since phenytoin is eliminated by a nonlinear process, the assessment of the necessary parameters becomes somewhat demanding. The elimination rate dX_e/dt of phenytoin can be adequately described by the equation (see Chap. 7)

$$\frac{dX_e}{dt} = \frac{V_m C}{K_m + C} \tag{10.35}$$

where C is plasma concentration, V_m the maximum rate of elimination, and K_m the concentration at which dX_e/dt equals one-half V_m. At steady state the rate of drug administration RA in mg/day equals the rate of elimination, and concentration will then be the steady-state concentration. Therefore,

$$RA = \frac{V_m C_{ss}}{K_m + C_{ss}} \tag{10.36}$$

This relationship can be rearranged to yield

$$RA = -K_m \frac{RA}{C_{ss}} + V_m \tag{10.37}$$

Therefore, a plot of dose rate versus dose rate divided by steady-state concentration (i.e., RA versus RA/C_{ss}) will yield a straight line with a slope of $-K_m$ and an intercept of V_m. Thus this method requires that the phenytoin be dosed to at least two steady states. Once estimates of these parameters are obtained, the daily dose required to produce a desired steady-state concentration can be calculated from (10.36). The predictive ability of this approach is illustrated in Fig. 10.10.

Although this method is sufficiently accurate for clinical purposes, it is simply too time consuming to be of much value in routine practice. Simpler methods have been described [30,31] but are probably less accurate. Thus far, no widely accepted method has been proposed for individualized dosing with drugs having nonlinear pharmacokinetics.

In conclusion, we wish to reiterate that this chapter does nothing more than provide a few examples of the potential usefulness of pharmacokinetics in the clinical setting. There is general agreement that such applications have permitted us to use certain drugs more safely and more sensibly.

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