2

Compartmental and Noncompartmental Pharmacokinetics

The basic principles outlined in Chapter 1 are useful for many drugs but they do not apply to all drugs. When a drug distributes relatively slowly, the relationships that have been described do not strictly apply; rigorous pharmacokinetic analysis is much more complicated. The purpose of this chapter is to describe the difficulties encountered with drugs that impart multicompartmental characteristics to the body, and to introduce methods that permit noncompartmental pharmacokinetic analysis of drugs, irrespective of their distribution characteristics.

MULTICOMPARTMENTAL CHARACTERISTICS

On intravenous bolus administration, many drugs distribute sufficiently slowly so that a significant fraction of the dose is eliminated before distribution equilibrium is achieved. When this occurs, a semilogarithmic plot of drug concentration in plasma versus time looks like the curve shown in Figure 2–1. The data cannot be described by a single exponential expression (i.e., a single compartment). At the outset drug concentrations decline rapidly; ultimately, a linear relationship between log concentration and time is observed. The entire curve can usually be described by a mathematical expression that contains either two or three exponential terms [e.g., $C = A \exp(-\alpha t) + B \exp(-\beta t)$].

The mathematical models that apply to this situation are shown in Figure 2–2. In the simpler of the two models (the two-compartment model), the drug is assumed to distribute instantaneously into a space called the central compartment; the apparent volume of this space is usually larger than blood volume. The drug is simultaneously but more slowly distributed into a second space (the peripheral or tissue compartment) and eliminated. The three-compartment model assumes that there are two distinct spaces to which the drug distributes from the central compartment at measurably different rates. In either model, after administration, the apparent volume of the drug increases and the rate constant associated with the rate of decline of drug concentrations in plasma decreases until distribution equilibrium is achieved.

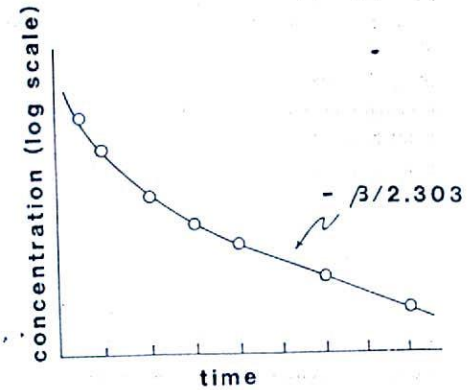

Fig. 2–1. Semilogarithmic plot of plasma concentration versus time after intravenous bolus administration of a drug with multicompartment pharmacokinetic characteristics. The slope of the terminal linear segment of the curve is indicated.

The kinetics of the situation might be better understood by considering the mathematical relationships that apply. For the two-compartment model,

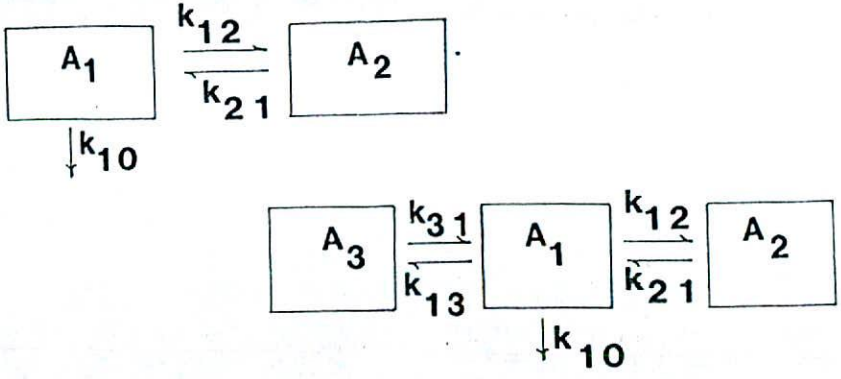

Fig. 2. Examples of a two- and three-compartment pharmacokinetic model. A_1 denotes the central compartment in each model and A_2 and A_3 are peripheral compartments. Immediately after an iv bolus injection, the central compartment contains an amount of drug equal to the dose. The general case for extravascular administration assumes that drug is transferred from the absorption site to the central compartment.

$$\text{Rate of loss of drug from central compartment} = \text{Rate of distribution} + \text{Rate of elimination} - \text{Rate of redistribution} \quad (2\text{–}1)$$

where

$$\text{Rate of loss of drug from central compartment} = -dA_1/dt \quad (2\text{–}2)$$

$$\text{Rate of distribution} = k_{12}A_1 \quad (2\text{–}3)$$

$$\text{Rate of elimination} = k_{10}A_1 \quad (2\text{–}4)$$

$$\text{Rate of redistribution} = \quad (2\text{–}5)$$

where A_1 and A_2 represent the amounts of drug in the central and peripheral compartments, respectively (see Fig. 2–2).

Immediately after administration, $-dA_1/dt$ is at a maximum equal to the product of $(k_{12} + k_{10})$ and dose; since there is no drug in the tissue compartment, there is no redistribution. As drug levels (A_1) in the central compartment decline because of distribution and elimination, there is a corresponding fall in $-dA_1/dt$, but as drug levels build up in the tissue compartment and the rate of redistribution becomes significant, there is a braking effect on the rate of decline of A_1.

At distribution equilibrium a fixed relationship exists between A_1 and A_2 such that

$$A_2 = ZA_1 \quad (2\text{–}6)$$

where Z is a complex constant incorporating both distribution and elimination parameters. Under these conditions

$$-dA_1/dt = k_{12}A_1 + k_{10}A_1 - k_{21}ZA_1 \quad (2\text{–}7)$$

or

$$-dA_1/dt = (k_{12} + k_{10} - k_{21}Z)A_1 \quad (2\text{–}8)$$

Expressing Equation 2–8 in terms of drug concentrations rather than amounts yields

$$-dC/dt = (k_{12} + k_{10} - k_{21}Z)C = \beta C \quad (2\text{–}9)$$

where $\beta = k_{12} + k_{10} - k_{21}Z$. Equation 2–9 is a typical first-order rate expression. Thus, irrespective of the complexity of the model, drug concentrations in the plasma decline in a first-order manner once distribution equilibrium is achieved. The rate constant describing this first-order portion of the curve is usually termed β.

Data Analysis at Distribution Equilibrium

Integration of Equation 2–9 indicates that the log-linear region of the curve shown in Figure 2–1 will have a slope equal to $(-\beta/2.303)$. Therefore, for drugs that require multicompartmental description, a terminal half-life may be defined as

$$t_{1/2} = 0.693/\beta \qquad (2\text{–}10)$$

It is important to remember that this half-life reflects the persistence of only a fraction of the dose; the balance of the dose is eliminated more rapidly. It is also important to note that, irrespective of the model, the half-life of a drug always reflects both distribution and elimination. This is evident when Equation 2–9 is considered.

The mathematical relationships that apply when distribution equilibrium is reached also make it possible to calculate an apparent volume of distribution. This apparent volume, usually termed V_β, is given by

$$V_\beta = \frac{\text{iv dose}}{(\text{AUC})\beta} \qquad (2\text{–}11)$$

where AUC denotes the total area under the drug concentration-time profile and β is the terminal first-order elimination rate constant. V_β is a proportionality constant relating the amount of drug in the body to drug concentration in the plasma during the terminal (log-linear) phase of drug elimination (i.e., at distribution equilibrium).

An analogous expression that can be applied to drugs that distribute rapidly is

$$V = \frac{\text{iv dose}}{(\text{AUC})k} \qquad (2\text{–}12)$$

where k is the first-order elimination rate constant.

Equations 2–11 and 2–12 can usually be applied to data obtained after intramuscular administration of a drug; in this case, the term "iv dose" is replaced by "im dose." These equations should not ordinarily be applied to data obtained after oral administration. If they are, the term "iv dose" must be replaced by "amount absorbed" or, more precisely, by "amount of drug actually reaching the bloodstream."

Equation 2–12 is a mathematically rigorous and widely applied equation for the estimation of apparent volume of drugs that distribute rapidly once they reach the bloodstream. Equation 2–11 is a useful approximation of the volume of distribution of most drugs that require a multicompartmental description. However, V_β has several inherent problems not the least of which is that it reflects elimination as well as distribution. In all cases, V_β will overestimate the volume of distribution of a drug; in most cases, the overestimate is small and of little consequence, but it can be unacceptably large for drugs with pronounced multicompartmental characteristics. The dependence of V_β on drug elimination also means that changes in drug elimination may cause a change in V_β even though the perturbation has no effect on distribution per se.[1]

Sometimes it is also useful to calculate the apparent volume of the central compartment (V_1). This is usually done by curve-fitting the concentration-time data after iv bolus injection, by means of a computer-based nonlinear regression program, to an equation of the form

$$C = A\exp(-\alpha t) + B\exp(-\beta t) \qquad (2\text{–}13)$$

where $\alpha > \beta$. The iv dose divided by the sum of the coefficients is equal to the volume of the central compartment, i.e.

$$V_1 = \text{iv dose}/(A+B) \qquad (2\text{–}14)$$

V_1 is always smaller than the total volume of distribution (V). For this reason, high drug concentrations (i.e. dose/V_1) may occur immediately after a rapid iv injection. These levels fall quickly but could be dangerous. Good sense dictates that iv injections be given relatively slowly.

In the previous chapter, it was noted that the peak concentration of a drug is always smaller after iv infusion than after iv bolus. The difference in concentration for drugs that distribute immediately is a function of the infusion time and half-life of the drug. Strictly speaking, a drug must be infused over at least one half-life to see a 50% change in peak concentration. In practice, much shorter infusion times are almost always helpful because most drugs display a distributive phase and multicompartment characteristics on iv administration.

The initial rapid fall in drug levels after iv bolus injection, the distribution-elimination phase, is sometimes characterized by a half-life, the so-called alpha half-life (i.e., $0.693/\alpha$). The alpha half-life is usually much smaller than the beta half-life (i.e., $0.693/\beta$). Under these conditions, the difference in peak concentration after an iv bolus and an iv infusion is a function of the alpha half-life.

Consider a drug that shows two-compartment

characteristics after iv administration. Assume that the iv dose is 1 g, V_1 = 10 L, α half-life = 15 min, and β half-life = 6 hr. After an iv bolus, the initial drug concentration is 100 mg/L. In contrast, the peak concentration of the drug is only about 25 mg/L when it is infused over 30 minutes.

Other Problems with Multicompartmental Analysis

The number of exponentials and, therefore, the number of compartments required to describe the decline of drug concentration after intravenous bolus injection is not well defined, but depends on both the frequency and timing of blood samples. More frequent sampling right after administration tends to yield data that must be described by equations containing more exponential terms than would be required by less frequent sampling. Thus, the compartmental model required to describe the pharmacokinetics of a drug depends, in part, on the experimental design. In turn, estimates of half-life are dependent on the model selected.

Various statistical considerations are useful in minimizing the problems associated with model selection, but they do not overcome them. Studies with a single drug in a group of patients may result in some patients requiring a two-compartment model to describe the pharmacokinetics of the drug, whereas others require a three-compartment model. We frequently find that drugs requiring multicompartmental analysis after intravenous administration can be described by a one-compartment model after oral administration. Since pharmacokinetic analysis based on compartmental models can lead to unreconcilable difficulties, more and more investigators and clinicians who use pharmacokinetics are turning to noncompartmental approaches that can be applied to all drugs.

NONCOMPARTMENTAL METHODS

Noncompartmental methods for calculating absorption, distribution, and elimination parameters are based on the theory of statistical moments.[2,3] The zero moment of a drug concentration in plasma versus time curve is the total area under the curve from time zero to infinity (AUC), which has been described in Chapter 1. Estimates of AUC are not only useful for calculating bioavailability, but can also be used for calculating drug clearance, which is equal to the ratio of the intravenous dose to AUC.

The first moment of a plasma concentration-time profile is the total area under the curve resulting from a plot of the product of drug concentration and time versus time. Table 2–1 shows concentration data obtained after constant rate intravenous infusion of a drug. Also listed are the values of $C \cdot t$. These values are plotted versus time in Figure 2–3. The area under the $C \cdot t$ versus t plot from $t = 0$ to the last sampling time, t^*, can be calculated by means of the trapezoidal rule (see Appendix I). Provided that blood samples have been collected for a sufficiently long period of time so that the last sample may be considered in the post-absorptive and, where applicable, postdistributive

Table 2–1. Drug Concentration and Drug Concentration-Time Data, During and After a 1-hr Constant Rate Intravenous Infusion

Time (hr)	Concentration (μg/ml)	Concentration-Time (μg/ml)(hr)
0.5	3.2	1.6
1.0	5.9	5.9
2.0	4.2	8.4
3.0	3.0	9.0
4.0	2.1	8.4
5.0	1.5	7.5
6.0	1.1	6.6
8.0	0.5	4.0

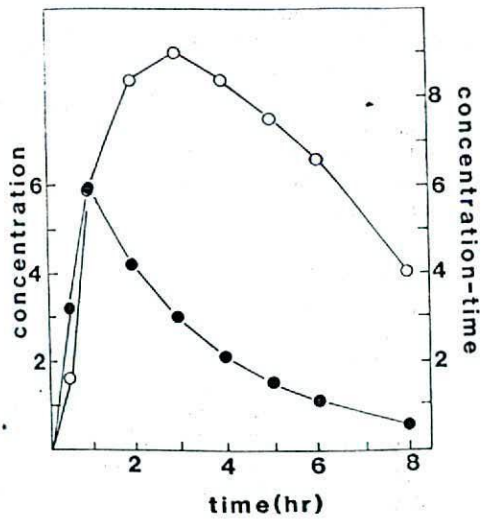

Fig. 2–3. Plots of drug concentration (μg/ml) (●) and drug concentration-time (μg-hr/ml) (○) versus time, during and after a 1-hr constant rate intravenous infusion. The area under the drug concentration versus time plot to infinity is AUC; the area under the drug concentration-time versus time plot to infinity is AUMC.

phase of the curve, the area from t* to ∞ may be estimated from the following equation:[4]

$$\int_{t^*}^{\infty} t \cdot C = \frac{t^* C^*}{\beta} + \frac{C^*}{\beta^2} \qquad (2\text{–}15)$$

where the integral term on the left-hand side of the equation is the partial area under the curve, C* is drug concentration at the last sampling time, t*, and β is the terminal first-order elimination rate constant. This area is then added to the area from t = 0 to t = t*, determined by the trapezoidal rule, to estimate the total area. The total area under the C · t versus t plot is termed the AUMC or area under the first moment curve.

The ratio of AUMC to AUC for any drug is a measure of its mean residence time (MRT).[5,6] MRT calculated after intravenous administration is the statistical moment analogy to drug half-life; it provides a quantitative estimate of the persistence of a drug in the body. Like half-life, MRT is a function of both distribution and elimination.

Comparison of MRT values after intravenous bolus administration with the MRT after some other route of administration provides information regarding the mean absorption time.[7] Similar comparisons can be made between two dosage forms given orally to obtain relative absorption data.

One of the most useful properties of statistical moments is that they permit the estimation of a volume of distribution that is independent of drug elimination.[4,6] Using these methods, the volume of distribution of a drug is given by the product of the intravenous bolus dose and the ratio of AUMC to AUC squared.

Drug Clearance

Clearance is a function of both the intrinsic ability of certain organs, such as the kidneys and liver, to excrete or metabolize a drug and the blood flow rate to these organs. This concept is best illustrated by considering elimination in a single organ as depicted schematically in Figure 2–4. Under these conditions, the venous concentration of drug (C_V) will always be less than the arterial concentration (C_A) because some of the drug is eliminated or extracted during the passage of the blood through the organ. The rate at which drug enters the organ is equal to the product of blood flow (Q) and arterial concentration. The rate at which drug leaves the organ is equal to the product of blood flow and venous concentration. The difference between the input rate and the output rate is the rate of elimination of drug by the organ;

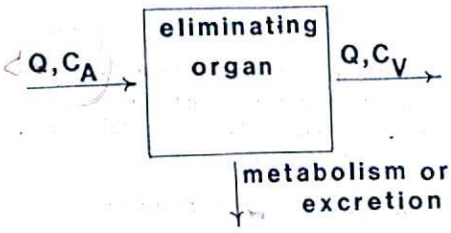

Fig. 2–4. Schematic representation of drug elimination by a single organ. Blood flows through the organ at a rate equal to Q. Drug concentration entering the organ is C_A; drug concentration leaving the organ is C_V; C_V is less than C_A.

$$\text{Elimination rate} = Q(C_A - C_V) \qquad (2\text{–}16)$$

The ratio of the elimination rate to the drug input rate (QC_A) is termed the extraction ratio (ER) and is given by

$$ER = \frac{C_A - C_V}{C_A} \qquad (2\text{–}17)$$

The extraction ratio of a drug ranges from 0 to 1 depending on how well the organ eliminates or extracts the drug from the blood flowing through it. If the organ does not eliminate the drug, then $C_V = C_A$ and ER = 0; if the organ avidly extracts the drug so that $C_V \cong 0$, then ER = 1.

By definition, the organ clearance (Cl) of a drug represents the volume of blood cleared per unit time. It may be viewed as a proportionality constant relating the elimination rate of a drug to the drug concentration in the blood, as expressed in the following equation:

$$Cl = \text{Elimination rate}/C_A \qquad (2\text{–}18)$$

It follows from Equation 2–16 that

$$Cl = Q(C_A - C_V)/C_A \qquad (2\text{–}19)$$

or, according to Equation 2–17

$$Cl = Q(ER) \qquad (2\text{–}20)$$

Thus, clearance is equal to the product of blood flow and extraction ratio. Since elimination rate is expressed in units of amount per unit time, and concentration is expressed in units of amount per unit volume, it follows that clearance has units of volume per unit time (e.g., ml/min or L/hr), the same as flow rate. If drug elimination is a first-order process, then clearance is independent of drug concentration.

These equations, which have been developed for a single organ, can be extended to the elimination of a drug from the body. The total body clearance of a drug from the blood is equal to the ratio of the overall elimination rate of the drug to the drug concentration in blood, where the overall elimination rate is the sum of the elimination processes occurring in all organs.

By means of integral calculus, it can be shown that the ratio of the overall elimination rate of a drug to its concentration in the blood is equal to the ratio of the amount of drug ultimately eliminated to the total area under the drug concentration-time curve. Since, after intravenous administration, the amount eliminated is equal to the dose, clearance can be expressed as

$$Cl = \text{dose}/(AUC) \qquad (2\text{–}21)$$

Equation 2–21 provides the basis for the routine estimation of the total body clearance of a drug after a single dose. To estimate clearance, drug is ordinarily given intravenously, but Equation 2–21 usually applies as well to intramuscular administration. Clearance cannot be estimated after oral administration unless it can be assumed that the total dose reaches the bloodstream. Application of Equation 2–21 to data obtained after oral administration when bioavailability is incomplete results in an overestimate of clearance.

Clearance can also be estimated at steady state after prolonged constant rate intravenous infusion. Under these conditions

$$Cl = k_o/C_{ss} \qquad (2\text{–}22)$$

where k_o is the infusion rate and C_{ss} is the drug concentration at steady state.

It is sometimes useful to keep in mind that clearance can also be expressed as the product of V_β and β. For drugs that distribute rapidly and can be described by a single compartment, $Cl = Vk$.

Apparent Volume of Distribution

The most useful volume term in pharmacokinetics is the apparent volume of distribution at steady state or V_{ss}. It represents the proportionality constant relating the amount of drug in the body at steady state after prolonged constant rate intravenous infusion or repetitive administration to the drug concentration or average drug concentration at that time. V_{ss} is independent of drug elimination and reflects solely the anatomic space occupied by a drug and the relative degree of drug binding in the blood and extravascular space.

Estimation of V_{ss} does not require data obtained at steady state; this distribution parameter can be calculated after a single dose of a drug by means of the following equation:[4,6]

$$V_{ss} = \text{iv dose}(AUMC)/(AUC)^2 \qquad (2\text{–}23)$$

where AUMC is the total area under the first moment curve.

Although Equation 2–23 applies only to intravenous bolus administration, the relationship can be modified easily to accommodate the different ways drugs are administered. If a drug is given by a short-term constant rate intravenous infusion,[8] then

$$V_{ss} = \frac{\text{infused dose}(AUMC)}{(AUC)^2} - \frac{\text{infused dose}(T)}{2(AUC)} \qquad (2\text{–}24)$$

where T is the duration of infusion. Since the infused dose is equal to k_oT, we can also express Equation 2–24 as

$$V_{ss} = \frac{k_oT(AUMC)}{(AUC)^2} - \frac{k_oT^2}{2(AUC)} \qquad (2\text{–}25)$$

Relationship of Half-Life, Clearance, and Volume of Distribution

Earlier, we noted that clearance is equal to the product of V_β and β. This relationship does not imply, however, that clearance is dependent on volume of distribution and half-life. Both clearance and distribution volume are independent parameters, although both may be affected by a change in plasma protein binding. Half-life is a dependent parameter. For a multicompartment model, $t_{1/2} = 0.693\ V_\beta/Cl$.

This relationship shows that the larger is the distribution volume, the longer is the half-life. Independently, the larger is the clearance of a drug, the smaller is the half-life. An increase in half-life should not be interpreted as a decrease in drug elimination; it may merely reflect an increase in distribution volume. Changes in elimination are represented by changes in clearance.

Mean Residence Time

The mean residence time (MRT) of a drug after administration of a single dose is given by

$$MRT = (AUMC)/(AUC) \qquad (2\text{–}26)$$

The MRT of a drug after intravenous bolus administration provides a useful estimate of the persistence time in the body and in this sense is related to half-life. When applied to drugs that distribute rapidly it can be shown that

$$MRT_{iv} = 1/k \qquad (2\text{–}27)$$

where k is the first-order elimination rate constant. The half-life of a drug is equal to 0.693/k. Half-life tells us the time required to eliminate 50% of the dose; MRT_{iv} tells us the time required to eliminate 63.2% of the dose.

The MRT of a drug that distributes slowly and requires multicompartment characterization is a complex function of the model rate constants for distribution and elimination. However, in noncompartmental terms, the following relationship is useful:

$$MRT_{iv} = 1/\bar{k} \qquad (2\text{–}28)$$

where $\bar{k}$ is a rate constant equal to the ratio of clearance to V_{ss}. For drugs with multicompartment characteristics, $\bar{k} > \beta$. For drugs that distribute almost immediately, $\bar{k} = k$. In many cases, the ratio of 0.693 to $\bar{k}$ serves as the effective half-life of a drug.

Irrespective of the distribution characteristics of a drug, MRT represents the time required for 63.2% of an intravenous bolus dose to be eliminated. As such, it may be possible to determine MRT from urinary excretion data alone by determining the time required to excrete 63.2% of that amount which is ultimately excreted as unchanged drug.

Mean residence time is a function of how we give the drug. The MRT values for noninstantaneous administrations will always be greater than the MRT following intravenous bolus administration. However, the MRT_{iv} can be estimated following other modes of drug administration. For example, following a constant rate intravenous infusion

$$MRT_{iv} = MRT_{inf} - (T/2) \qquad (2\text{–}29)$$

where T is the duration of the infusion. MRT_{inf} is calculated according to Equation 2–26.

DRUG ABSORPTION

Noncompartmental methods for estimating the extent of absorption of a drug after oral or other extravascular routes of administration have been described in Chapter 1. Essentially, these methods require a comparison of areas under the curve. The fraction of an oral dose that actually reaches the bloodstream can be estimated from the ratio of AUC after oral administration to AUC after intravenous administration of equivalent doses of the drug. The extent of absorption of drug in a test dosage form relative to its absorption from a standard dosage form, such as an aqueous solution, can be estimated from the ratio of AUC after the test dose to AUC after the standard.

Noncompartmental methods for estimating the rate of absorption of a drug after extravascular administration are based on differences in MRT after different modes of administration. In general,[7]

$$MAT = MRT_{ni} - MRT_{iv} \qquad (2\text{–}30)$$

where MAT is the mean absorption time, MRT_{ni} is the mean residence time after administration of the drug in a noninstantaneous manner, such as orally, intramuscularly, or by iv infusion and MRT_{iv} is the mean residence time after intravenous bolus administration.

When absorption is a first-order process

$$MAT = (1/k_a) \qquad (2\text{–}31)$$

where k_a is the first-order absorption rate constant. Under these conditions, $k_a = 1/MAT$, and the absorption half-life is given by 0.693 (MAT). When absorption or input is a zero-order process

$$MAT = (T/2) \qquad (2\text{–}32)$$

where T is the time over which absorption or input takes place.

Moment analysis and the concept of MRT may also be useful for comparing the absorption characteristics of a drug from different formulations. This application is considered in Chapter 8.

A limitation of moment theory is seen when the difference between MRT_{ni} and MRT_{iv} is small. In this case, it may be difficult to estimate MAT with adequate accuracy.

A useful application of moment theory, to evaluate the pharmacokinetics of furosemide after iv and oral administration, has been reported.[9] The mean MRT after an iv dose of the loop diuretic to eight healthy subjects was less than 1 hr, suggesting an effective half-life of about 40 min. Absorption after oral administration, however, was slow and incomplete. Bioavailability was only about half the dose. The difference in MRT after oral and iv administration (MAT) was 84 min. The mean absorption time for furosemide was significantly

larger than the MRT_{iv}, suggesting absorption rate-limited elimination of the drug.

Predicting Steady-State Concentrations

When a drug is given continuously or intermittently for a sufficient period of time it accumulates and eventually reaches a steady state with respect to drug concentration in the blood (see Figs. 1–8 and 1–9). Drug concentration at steady state is solely a function of the effective rate of dosing and the total body clearance of the drug in the patient, both of which are noncompartmental parameters.

The steady-state concentration (C_{ss}) following constant rate intravenous infusion may be determined by rearranging Equation 2–22 which yields

$$C_{ss} = k_o/Cl \qquad (2–33)$$

where k_o is the infusion rate and Cl is the clearance of the drug.

A similar equation can be written to describe the average drug concentration at steady state ($\overline{C}$) following repetitive intermittent administration of a fixed dose (D) given at fixed intervals (τ) (see Fig. 1–9). Under these conditions,

$$\overline{C} = F(DR)/Cl \qquad (2–34)$$

where F is the fraction of the administered dose that actually reaches the bloodstream and DR is the average dosing rate; if a drug is given in a dose of 400 mg every 8 hr, then DR = 50 mg/hr.

If a drug is given at irregular intervals during the day (e.g., 3 times a day or after meals and at bedtime rather than every 8 hr or every 6 hr), one can use Equation 2–34 to calculate the average drug concentration over the day by setting DR equal to (total daily dose)/24 hr.

A still simpler method for estimating average drug concentration at steady state than that suggested by Equation 2–34 is also available. As may be seen in Figure 1–9, $\overline{C}$ is a concentration intermediate between the maximum and minimum drug concentrations at steady state. Specifically,

$$\overline{C} = AUC_{ss}/\tau \qquad (2–35)$$

where AUC_{ss} is the area under the curve from t = 0 to t = τ during a dosing interval at steady state. In other words, $\overline{C}$ is the height of a rectangle of width τ that has an area ($\overline{C} \times \tau$) equal to the area under the curve during a dosing interval at steady state. Steady-state bioavailability studies comparing AUC_{ss} for test product and reference standard are widely used for evaluating sustained-release

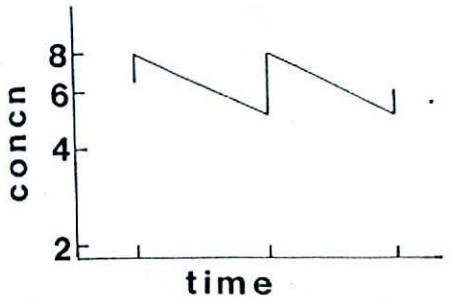

Fig. 2–5. Steady-state concentrations after repetitive administration of a rapidly distributing drug with a 12-hr half-life given every 8 hr. The ratio of C_{max} to C_{min} is 1.6.

dosage forms. By definition, AUC_{ss} is equal to AUC, the total area under the curve from t = 0 to t = ∞ after a single dose. Under these conditions

$$\overline{C} = AUC/\tau \qquad (2–36)$$

By merely knowing the AUC of a drug after a single dose administered in the same way that will be used for repetitive dosing, we can predict the average drug concentration at steady state.

Although $\overline{C}$ is a useful parameter and easy to calculate, we must remember that it tells us nothing about the time course of drug concentrations during a dosing interval. This limitation is of little consequence for drugs with long half-lives that distribute rapidly and are dosed relatively frequently (i.e., $\tau < t_{1/2}$). In this case, the steady-state ratio of C_{max} to C_{min} will be less than 2 and the drug concentration profile at steady state will be relatively flat (Fig. 2–5). On the other hand, large fluctuations may be seen with drugs having relatively short half-lives that are given less frequently than every half-life (Fig. 2–6) and with drugs that distribute slowly and display multicompartment characteristics (Fig. 2–7). In these cases, the steady-state ratio of C_{max} to C_{min} will exceed 2. For certain drugs, the attainment of an acceptable value of $\overline{C}$, well within the therapeutic concentration range, may belie the fact that C_{max} is too high and adverse effects may result or that C_{min} is too low and for some time during the dosing interval the patient may not be receiving the optimal benefit of the drug. Noncompartmental methods are generally not useful for describing the time course of drug in the blood. It is probably best to handle such considerations with the concept of half-life and the application of compartmental analysis. Questions

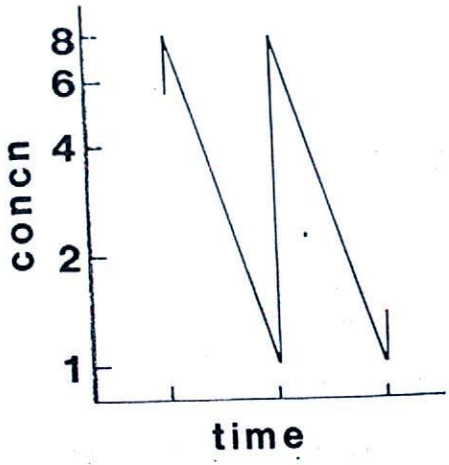

Fig. 2–6. Steady-state concentrations after repetitive administration of a rapidly distributing drug with a 2-hr half-life given every 6 hr. The ratio of C_{max} to C_{min} is 8.

regarding drug accumulation and loading dose may also be better answered by applying compartment theory, as described in Chapter 1. A noncompartmental alternative based on the principle of superposition is described in Appendix II.

Predicting the Time to Steady State

The time required to reach steady state on continuous constant rate intravenous infusion of a drug that distributes rapidly is a function of the half-life of the drug. After a period of infusion equal to 4 half-lives, the drug concentration in blood or plasma will be within 90% of the steady-state concentration; after a period equal to 7 half-lives, drug concentration is within 99% of the steady-state level. The same drug given as repetitive intravenous boluses of fixed doses at fixed intervals will show similar characteristics; after a period of dosing equal to 4 half-lives, the average drug concentration will be within 90% of the average steady-state concentration.

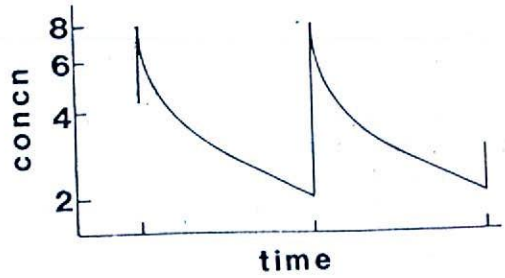

Fig. 2–7. Steady-state concentrations after repetitive administration of a slowly distributing drug with a 12-hr half-life given every 12 hr. The ratio of C_{max} to C_{min} is 4.

In practice, the time after the start of dosing to attain a certain fraction (e.g., 90%) of the steady-state concentration is not only a function of half-life, but also of the way we give the drug and of the distribution characteristics of the drug. Repetitive extravascular or noninstantaneous administration of a drug requires a longer period to attain steady state than we would predict from its half-life. On the other hand, repetitive administration of a drug that distributes slowly and shows multicompartment characteristics requires a shorter period to reach steady state in the plasma than we would predict from its terminal half-life. Exact equations to solve for the time after starting dosing at which a certain percentage of steady state is reached for different drugs under different conditions of use are both complex and difficult to solve.

Moment analysis provides a unique solution to this problem. Chiou has shown that by means of AUC analysis one can calculate the time to steady state for any drug after a single dose given in the same way that will be used for repetitive dosing.[10] In essence, the time required after giving the dose for the partial area under the curve (AUC_0^t) to be equal to a certain fraction of the total area under the curve (AUC) is the same as the time required to reach the same fraction of steady state on repetitive dosing of the drug.[11] This idea is expressed in the following equation:

$$f_{ss} = AUC_0^t/AUC \qquad (2\text{–}37)$$

where f_{ss} is the fraction of the steady-state concentration reached at time t on repetitive dosing and the area terms refer to a single dose.

When using Equation 2–37, one does not explicitly solve for time. Rather, one selects a time after giving the dose and carries out an area analysis to calculate f_{ss}. The time required to reach a desired f_{ss} (e.g., 90%) is estimated by trial and error. Usually two trials followed by interpolation should be sufficient to provide a useful estimate of the required time.

Parameters Based on Free Drug Concentration

The noncompartmental methods described in this chapter are based on total drug concentrations in blood or plasma. Most drugs are bound to some extent to plasma proteins and formed elements in

the blood. Therefore, we can speak of a free drug concentration and a total drug concentration (free plus bound) in blood or plasma.

The usual analytic methods determine total drug concentration in plasma (C). Total drug concentration in blood (C_b) can be estimated by the following equation:

$$C_b = C_{rbc} \cdot HCT + C(1 - HCT) \quad (2–38)$$

where C_{rbc} is drug concentration in the red blood cell and HCT is hematocrit.

The ratio of free (C_f) to total drug concentration in blood or plasma is termed the free fraction (f). Free fraction is usually determined in plasma (f_p) by means of equilibrium dialysis or ultrafiltration. Free fraction in blood is calculated by the following equation:

$$f_b = f_p C/C_b \quad (2–39)$$

The plasma or blood binding of most drugs given in usual doses is independent of drug concentration. Therefore, by determining total drug concentration and by determining free fraction at a given concentration, we can calculate free drug concentration.

In theory, free rather than total drug concentration in blood or plasma is more closely related to pharmacologic effects. There is some experimental and clinical data to support this idea. In the absence of inter- or intrasubject differences in binding, a given total drug concentration always reflects the same free drug concentration. However, some patients bind a drug much more or much less effectively than average because of disease-related factors. During a course of therapy, there may be a change in binding because of concomitant drug therapy. Therefore, an undesirably low or high total drug concentration may not reflect a corresponding low or high free drug concentration.

Total drug concentration at steady state is a function of clearance (see Eq. 2–34). The clearance of drugs with a low hepatic or renal extraction ratio depends on binding as well as the efficiency of the eliminating organs. The clearance of total drug may increase or decrease simply because of a change in binding. In this case, there will be a change in the steady-state concentration of total drug but not of free drug. Since free drug concentration at steady state is unchanged, an unusually high or low total drug concentration may not require a change in dosing rate.

Under these conditions, it may be desirable to determine the clearance of free drug (Cl_f) as well as the clearance of total drug. Free drug clearance from plasma is given by the following equation:

$$Cl_f = Cl/f_p \quad (2–40)$$

CONCLUSIONS

The noncompartmental methods described in this chapter permit a comprehensive pharmacokinetic analysis without resort to curve-fitting, computers, or tedious mathematical equations. Although these methods cannot be applied to all pharmacokinetic problems, they are useful for most problems and are particularly useful for the clinical application of pharmacokinetics. In the following pages, you will find many of these relationships used to answer important clinical questions.

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