3

Multiple Dosing

Some drugs, for example, analgesics, hypnotics, neuromuscular blocking agents, bronchodilators, and antiemetics, may be used effectively as a single dose. More frequently, drugs are given on a continuous basis. Moreover, most drugs are administered with sufficient frequency that measurable and often pharmacologically significant levels of drug persist in the body when a subsequent dose is administered. For drugs administered in a fixed dose at a constant dosing interval (e.g., every 6 h or once a day), the peak plasma level following the second and succeeding doses of a drug is almost always higher than the peak level after the first dose, and therefore the drug accumulates in the body relative to the initial dose. However, under these conditions drug accumulation proceeds at a decreasing rate with increasing number of doses until a steady-state plasma level of drug is achieved. At steady state, the plasma concentration of drug at any time during any dosing interval should be identical to the concentration at the same time during any other dosing interval. As will be demonstrated, the rate and extent of accumulation of a drug is a function of the relative magnitudes of the dosing interval and the half-life of the drug. A model-independent approach to multiple dosing (i.e., superposition) is discussed in Appendix E.

INTRAVENOUS ADMINISTRATION

The following general equation can be used to describe the plasma concentration versus time curve resulting from the intravenous injection of a drug:

$$C = \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell t} \qquad (2.7)$$

where

$$A_\ell = \frac{X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.8}$$

In these equations X_0 is the intravenous dose, V_c is the volume of the central compartment, E_i is the sum of the exit rate constants from the ith compartment, λ_i and λ_ℓ are disposition rate constant, and n is the number of exponentials required to describe the curve adequately. The maximum plasma concentration resulting from the intravenous administration of the first bolus dose of a drug, $(C_1)_{max}$, would occur at t = 0. Therefore,

$$(C_1)_{max} = \sum_{\ell=1}^{n} A_\ell \tag{3.1}$$

The concentration of drug in the plasma at the end of the first dosing interval of length τ time units $(C_1)_{min}$ will be given by the relationship

$$(C_1)_{min} = \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell \tau} \tag{3.2}$$

which is obtained by setting t equal to τ in (2.7). Since there are usually measurable plasma concentrations of drug when a second dose is administered, administration of a second dose, equal in size to the first dose, will produce an immediate increase in plasma concentration of drug yielding a new maximum, $(C_2)_{max}$. This new maximum would be equal to the sum of the plasma concentration at the time of administration (i.e., at time $t = \tau$) and the maximum concentration resulting from the first dose [i.e., $(C_1)_{max}$]. Therefore,

$$(C_2)_{max} = (C_1)_{max} + (C_1)_{min} \tag{3.3}$$

Substitution for $(C_1)_{max}$ and $(C_1)_{min}$ according to (3.1) and (3.2), respectively, yields

$$(C_2)_{max} = \sum_{\ell=1}^{n} A_\ell + \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell \tau} = \sum_{\ell=1}^{n} A_\ell (1 + e^{-\lambda_\ell \tau}) \tag{3.4}$$

The minimum concentration of drug in the plasma after the second dose $(C_2)_{min}$ (assuming a constant dosing interval of τ) is given by

$$(C_2)_{min} = \sum_{\ell=1}^{n} A_\ell (1 + e^{-\lambda_\ell \tau}) e^{-\lambda_\ell \tau} \tag{3.5}$$

which can be modified to yield

$$(C_2)_{min} = \sum_{\ell=1}^{n} A_\ell (e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau}) \tag{3.6}$$

It follows that

$$(C_3)_{max} = \sum_{\ell=1}^{n} A_\ell + \sum_{\ell=1}^{n} A_\ell (e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau})$$

$$= \sum_{\ell=1}^{n} A_\ell (1 + e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau}) \tag{3.7}$$

and

$$(C_3)_{min} = \sum_{\ell=1}^{n} A_\ell (1 + e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau}) e^{-\lambda_\ell \tau}$$

$$= \sum_{\ell=1}^{n} A_\ell (e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau} + e^{-3\lambda_\ell \tau}) \tag{3.8}$$

where $(C_3)_{max}$ is the maximum plasma concentration following a third dose and $(C_3)_{min}$ is the minimum plasma concentration τ time units after the third dose.

On examination of (3.1), (3.4), and (3.7), it is readily apparent that a geometric series can be written for the maximum concentration of drug in the plasma following N doses, $(C_N)_{max}$:

$$(C_N)_{max} = \sum_{\ell=1}^{n} A_\ell (1 + e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau} + \cdots + e^{-(N-1)\lambda_\ell \tau}) \tag{3.9}$$

If we let

$$r = 1 + e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau} + \cdots + e^{-(N-1)\lambda_\ell \tau} \tag{3.10}$$

it follows that

$$(C_N)_{max} = \sum_{\ell=1}^{n} A_\ell r \tag{3.11}$$

Multiplication of (3.10) by $e^{-\lambda_\ell \tau}$ yields

$$re^{-\lambda_\ell \tau} = e^{-\lambda_\ell \tau} + e^{-2\lambda_\ell \tau} + \cdots + e^{-(N-1)\lambda_\ell \tau} + e^{-N\lambda_\ell \tau} \tag{3.12}$$

which when subtracted from (3.10) produces

$$r - re^{-\lambda_\ell \tau} = 1 - e^{-N\lambda_\ell \tau} \tag{3.13}$$

which can be solved for r to yield

$$r = \frac{1 - e^{-N\lambda_\ell \tau}}{1 - e^{-\lambda_\ell \tau}} \tag{3.14}$$

Substitution of this value of r in (3.11) yields the following general expression for the maximum concentration of drug in the plasma after intravenous administration of any number of doses:

$$(C_N)_{max} = \sum_{\ell=1}^{n} A_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{1 - e^{-\lambda_\ell \tau}} \tag{3.15}$$

From a comparison of previous equations [i.e., (3.1) and (3.2), (3.4) and (3.5), and (3.7) and (3.8)] it is equally clear that

$$(C_N)_{min} = (C_N)_{max} e^{-\lambda_\ell \tau} \tag{3.16}$$

and, therefore,

$$(C_N)_{min} = \sum_{\ell=1}^{n} A_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell \tau} \tag{3.17}$$

It is evident on examination of (3.15) and (3.17) that the concentration of drug in the plasma at any time during a dosing interval (i.e. C_N) is given by

$$C_N = \sum_{\ell=1}^{n} A_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell t} \tag{3.18}$$

where t is the time elapsed since dose N was administered. Therefore, by knowing the zero-time intercepts and disposition rate constants, A_ℓ and λ_ℓ, respectively (both of which can be obtained following a single intravenous dose), the plasma concentration of a drug at any time during a dosing interval can be predicted provided that a fixed dose is administered every τ time units.

Equation (3.18) may also be obtained by a method that does not rely on a detailed derivation of the type presented above, and consequently is significantly more convenient (see Appendix B). Any equa-

tion that describes the time course of a drug in a driving force compartment after a single dose may be directly converted to a multiple-dose equation by multiplying each exponential term containing t by the function

$$\frac{1 - e^{-Nk_i\tau}}{1 - e^{-k_i\tau}}$$

where N and τ are as defined previously and k_i is the apparent first-order rate constant in each exponential term. Therefore, multiplication of (2.7), $C = \sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell t}$, by the multiple-dosing function, and setting k_i equal to λ_ℓ [since λ_ℓ is the rate constant in the exponential term of (2.7)] permits (2.7) to be directly converted to (3.18).

The drug concentration in the plasma, at any time during a dosing interval, will increase and then approach a constant value as the number of doses increases (see Fig. 3.1). The equation describing the time course of drug at the plateau or steady state can be obtained by setting N in (3.18) to infinity (i.e., by recognizing that the term $e^{-N\lambda_\ell\tau}$ approaches zero with increasing number of doses). Thus

$$C_{ss} = \sum_{\ell=1}^{n} A_\ell \frac{1}{1 - e^{-\lambda_\ell\tau}} e^{-\lambda_\ell t} \tag{3.19}$$

where C_{ss} is the plasma concentration of drug at any time during a dosing interval at steady state. Similarly, the equations for the maximum and minimum concentrations of drug in the plasma during a dosing interval at steady state, $(C_{ss})_{max}$ and $(C_{ss})_{min}$, respectively, can be written as

$$(C_{ss})_{max} = \sum_{\ell=1}^{n} A_\ell \frac{1}{1 - e^{-\lambda_\ell\tau}} \tag{3.20}$$

and

$$(C_{ss})_{min} = \sum_{\ell=1}^{n} A_\ell \frac{1}{1 - e^{-\lambda_\ell\tau}} e^{-\lambda_\ell\tau} \tag{3.21}$$

If the dosing interval τ is much greater than the half-life of a drug (where $t_{1/2} = 0.693/\lambda_n$), $(C_{ss})_{min}$ approaches zero. Under these conditions no accumulation will occur and the plasma concentration versus time profile will be the result of the administration of a series of single doses.

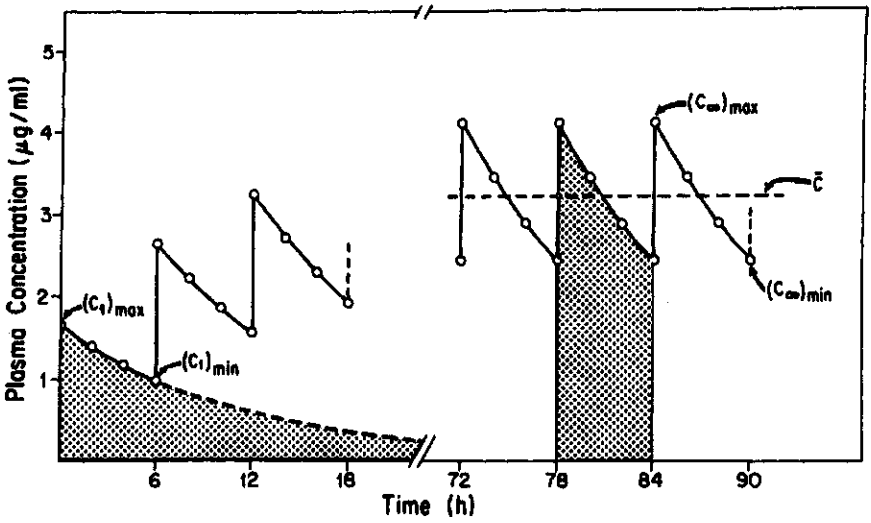

Fig. 3.1 Drug accumulation and attainment of steady state on multiple intravenous dosing of a fixed dose of drug every 6 h. Maximum and minimum drug concentrations after the first dose are denoted $(C_1)_{max}$ and $(C_1)_{min}$, respectively; those at steady state are denoted $(C_\infty)_{max}$ and $(C_\infty)_{min}$, respectively. The average drug concentration at steady state, $\bar{C}$, is also shown. The area under the drug concentration in plasma versus time curve during a dosing interval at steady state (shaded area) is the same as the total area under the curve after a single dose (shaded area bounded by solid and dashed lines).

As discussed in Chap. 2, one frequently finds in a two-compartment model that the larger the ratio of the zero-time intercepts A_1/A_2, the more readily one can discern the multicompartment characteristics of a drug. Equation (3.19) can be written as

$$C_{ss} = \sum_{\ell=1}^{n} U_\ell e^{-\lambda_\ell t} \tag{3.22}$$

where

$$U_\ell = A_\ell \frac{1}{1 - e^{-\lambda_\ell \tau}} \tag{3.23}$$

The ratio of U_1/U_2 would therefore be given by

$$\frac{U_1}{U_2} = \frac{A_1(1 - e^{-\lambda_2 \tau})}{A_2(1 - e^{-\lambda_1 \tau})} \tag{3.24}$$

and will always be less than the ratio A_1/A_2. Since λ_1 is by definition greater than λ_2, the ratio $(1 - e^{-\lambda_2 \tau})/(1 - e^{-\lambda_1 \tau})$ will always be less than 1. Consequently, following multiple dosing the ability to discern the multicompartment characteristics of a drug is usually decreased. On the other hand, analytical limitations may prevent one from observing more than one exponential phase after a single intravenous administration of a drug that has an exceptionally large ratio of A_1 to A_2. In this case, multiple dosing makes the multicompartment characteristic of the drug more obvious. For a more detailed discussion of this phenomenon, see Chap. 2.

Average Steady-State Concentration

A parameter that is very useful in multiple dosing is the "average" concentration of drug in the plasma at steady state, $\overline{C}$. This parameter can be defined as

$$\overline{C} = \frac{\int_0^\tau C_{ss} dt}{\tau} \tag{3.25}$$

where $\int_0^\tau C_{ss}\, dt$ is the area under the plasma concentration-time curve during a dosing interval at steady state (i.e., between time zero and τ) where τ is as defined previously. Integration of (3.19) from time zero to τ yields

$$\int_0^\tau C_{ss}\, dt = \sum_{\ell=1}^{n} \frac{A_\ell}{\lambda_\ell} \tag{3.26}$$

This expression for the area under the plasma concentration-time curve from time zero to τ during a dosing interval at steady state is equivalent to (2.40), the equation for the area under the plasma concentration-time curve from time zero to infinity following a single intravenous dose (see Fig. 3.1). Therefore, the average plasma concentration of drug at steady state can be predicted from a single-dose study by employing the following relationship:

$$\overline{C} = \frac{\int_0^\infty C\, dt}{\tau} \tag{3.27}$$

The area under the plasma concentration versus time curve, AUC or $\int_0^\infty C\,dt$, following a single intravenous dose, X_0, can be obtained by rearrangement of (2.214) to give

$$AUC = \frac{X_0}{V_\beta \lambda_n} \tag{3.28}$$

where V_β is the apparent volume of distribution and λ_n is the disposition rate constant associated with the terminal slope of a log plasma concentration-time curve and equals 0.693 divided by half-life (i.e., $0.693/t_{1/2}$) [Eq. (2.11)]. The relationship between these parameters and clearance Cl_s has also been presented previously:

$$Cl_s = V_\beta \lambda_n \tag{2.215}$$

Therefore, substituting $X_0/V_\beta\lambda_n$ for $\int_0^\infty C\,dt$ in (3.27) and setting $V_\beta\lambda_n$ equal to Cl_s yields

$$\bar{C} = \frac{X_0}{V_\beta \lambda_n \tau} = \frac{X_0}{Cl_s \tau} \tag{3.29}$$

which can also be written in terms of half-life, i.e.,

$$\bar{C} = \frac{1.44 X_0 t_{1/2}}{V_\beta \tau} \tag{3.30}$$

By knowing the AUC following a single dose, the clearance, or the half-life and volume of distribution of a drug, the average plasma concentration of a drug at steady state following the administration of a fixed dose X_0 at a constant time interval τ can be predicted. As can also be seen from (3.29) and (3.30), the size of the administered dose X_0 and the time interval at which this dose is administered, τ, can be adjusted to obtain a desired average steady-state plasma concentration. These equations assume that all parameters are constant over the entire dosing period.

The average plasma concentration of a drug at steady state as calculated employing (3.27), (3.29), or (3.30) is neither the arithmetic nor the geometric mean of $(C_{ss})_{max}$ and $(C_{ss})_{min}$. Rather, it is a plasma concentration value which when multiplied by τ equals the area under the plasma concentration-time curve over the time interval zero to τ at steady state. Therefore, from simple geometric considerations, $\bar{C}$ must represent a plasma concentration value between $(C_{ss})_{max}$ and $(C_{ss})_{min}$ (See Fig. 3.1). A limitation of the $\bar{C}$ approach is that it gives no information about the fluctuations in plasma levels [i.e., $\bar{C}$ gives no information as to the relative magnitudes of $(C_{ss})_{max}$ and $(C_{ss})_{min}$].

Accumulation

As discussed previously, the administration of a drug on a multiple-dose regimen will usually result in its accumulation in the body. The extent of accumulation of a given drug may be quantified in several ways. One approach is to determine the ratio of the minimum plasma concentration of drug at steady state $(C_{ss})_{min}$ to the minimum plasma concentration following the first dose $(C_1)_{min}$. This ratio can be defined as the accumulation factor R. Therefore,

$$R = \frac{(C_{ss})_{min}}{(C_1)_{min}} \tag{3.31}$$

Substitution for $(C_{ss})_{min}$ and $(C_1)_{min}$ in (3.31) according to (3.21) and (3.2), respectively, yields

$$R = \frac{\sum_{\ell=1}^{n} A_\ell \dfrac{1}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell \tau}}{\sum_{\ell=1}^{n} A_\ell e^{-\lambda_\ell \tau}} \tag{3.32}$$

This relationship is rather complex. However, if all doses are administered in the postdistributive phase (i.e., $e^{-\lambda_1 \tau}$ to $e^{-\lambda_n - 1 \tau}$ approach zero) of a plasma concentration versus time curve, or if the plasma concentration versus time curve can be adequately described by a monoexponential equation [i.e., n = 1 in (3.32)], then (3.32) reduces to

$$R = \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.33}$$

Under these conditions the extent of accumulation can be predicted simply by knowing the terminal disposition rate constant of a drug, λ_n or K, or half-life $t_{1/2}$, since $t_{1/2} = 0.693/\lambda_n = 0.693/K$.

The ratio of $(C_{ss})_{max}$ to $(C_1)_{max}$ is also an appropriate expression of drug accumulation. According to Eqs. (3.20) and (3.1), this ratio is given by

$$\frac{(C_{ss})_{max}}{(C_1)_{max}} = \frac{\sum_{\ell=1}^{n} [A_\ell/(1 - e^{-\lambda_\ell \tau})]}{\sum_{\ell=1}^{n} A_\ell} \tag{3.34}$$

In the case of a drug that shows one-compartment model characteristics on intravenous administration, Eq. (3.34) may be simplified to Eq. (3.33) where K replaces λ_n.

Another expression that has been used to characterize drug accumulation is the ratio of $\bar{C}$, the average drug concentration at steady state, to $\bar{C}_1$, the average drug concentration during the first dosing interval. Consider that the average drug concentration during any dosing interval (i.e., $\bar{C}_N$) may be defined as

$$\bar{C}_N = \frac{\int_0^\tau C_N \, dt}{\tau} \tag{3.35}$$

where $\int_0^\tau C_N \, dt$ is the area under the plasma concentration-time curve during the Nth dosing interval. Integration of (3.18) from time zero to τ yields

$$\int_0^\tau C_N \, dt = \sum_{\ell=1}^{n} A_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{\lambda_\ell} \tag{3.36}$$

Substitution of this value of $\int_0^\tau C_N \, dt$ in (3.34) and substitution for $\int_0^\tau C_{ss} \, dt$ in (3.25) according to (3.26) yields

$$\bar{C}_N = \sum_{\ell=1}^{n} A_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{\lambda_\ell \tau} \tag{3.37}$$

and at steady state

$$\bar{C} = \sum_{\ell=1}^{n} A_\ell \frac{1}{\lambda_\ell \tau} \tag{3.38}$$

respectively. Taking the ratio of $\bar{C}_N$ to $\bar{C}$ and canceling the common term τ gives

$$\frac{\bar{C}_N}{\bar{C}} = \frac{\sum_{\ell=1}^{n} [A_\ell (1 - e^{-N\lambda_\ell \tau})/\lambda_\ell]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{3.39}$$

When N = 1, that is, for the first dose, (3.39) becomes

$$\frac{\bar{C}_1}{\bar{C}} = \frac{\sum_{\ell=1}^{n} [A_\ell (1 - e^{-\lambda_\ell \tau})/\lambda_\ell]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{3.40}$$

The inverse ratio $\overline{C}/\overline{C}_1$ may be used to express accumulation:

$$\frac{\overline{C}}{\overline{C}_1} = \frac{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)}{\sum_{\ell=1}^{n} [A_\ell(1 - e^{-\lambda_\ell \tau})/\lambda_\ell]} \tag{3.41}$$

In the case of a drug that can be described by a one-compartment model on intravenous administration, Eq. (3.41) reduces to (3.33) where K replaces λ_n.

Equation (3.33) indicates that the larger the ratio of $t_{1/2}/\tau$, the greater will be the extent of accumulation. For example, consider a drug with a half-life of 24 h (i.e., $\lambda_n = 0.029\ h^{-1}$). If this drug is administered every 24 h (i.e., $\tau = 24$ h), according to Eq. (3.33) R equals 2.0. However, administration of the same dose every 6 h results in much greater accumulation (R = 6.3). Consequently, when τ is equal to or greater than the half-life of a drug, the extent of accumulation is relatively modest (≤ 2). If the ratio $t_{1/2}/\tau$ is large, however, the extent of accumulation may be substantial.

Time to Reach Steady State

The ratio $\overline{C}_N/\overline{C}$ as given by (3.39) can be employed to calculate the time required to reach a certain fraction of the ultimate steady-state level, where the fraction of the steady-state level, f_{ss}, is defined in terms of average plasma levels:

$$f_{ss} = \frac{\overline{C}_N}{\overline{C}} \tag{3.42}$$

Substitution for $\overline{C}_N/\overline{C}$ in (3.42) according to (3.39) gives

$$f_{ss} = \frac{\sum_{\ell=1}^{n} [A_\ell(1 - e^{-N\lambda_\ell \tau})/\lambda_\ell]}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{3.43}$$

Equation (3.43) can be used to calculate the fraction of the ultimate steady state that is reached following the Nth dose. This equation cannot, however, be rearranged to obtain an expression for the time (i.e., $N\tau$) to reach a certain fraction of the steady-state level. The term $N\tau$ can only be estimated by numerical iteration. If the plasma concentration versus time profile of a drug can be adequately described by a monoexponential equation (i.e., n = 1), (3.43) reduces to

$$f_{ss} = 1 - e^{-NK\tau} \tag{3.44}$$

Rearrangement of (3.44) yields

$$e^{-NK\tau} = 1 - f_{ss} \tag{3.45}$$

the common logarithm of which is

$$-NK\tau = 2.303 \log (1 - f_{ss}) \tag{3.46}$$

Equation (3.46) can be further rearranged to obtain an expression for $N\tau$. Thus

$$N\tau = -\frac{2.303}{K} \log (1 - f_{ss}) \tag{3.47}$$

or

$$N\tau = -3.32\, t_{1/2} \log (1 - f_{ss}) \tag{3.48}$$

since K equals $0.693/t_{1/2}$ [Eq. (2.11)].

For a drug with one-compartment model characteristics the time required to reach a particular fraction of steady state is independent of the number of doses administered and the interval between administrations, but it is directly proportional to the half-life. From Eq. (3.48) it can be readily calculated that 3.32 and 6.64 half-lives would be required to reach 90 and 99%, respectively, of the steady-state plasma level of a drug. Since Eqs. (3.44) and (3.48) were derived based on a one-compartment system, they will be in error if used for a drug that demonstrates multicompartment characteristics.

A model-independent approach for the estimation of f_{ss} involves the use of areas under the plasma concentration versus time curve [1]. This approach is based on a simple extension of Eq. (3.43). Expansion of (3.43) yields

$$f_{ss} = \frac{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell) - \sum_{\ell=1}^{n} (A_\ell e^{-N\lambda_\ell \tau}/\lambda_\ell)}{\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)} \tag{3.49}$$

The total area under a plasma concentration versus time curve, AUC, following the intravenous administration of a single dose of drug equals $\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)$ [Eq. (2.40)]. Substitution of AUC for $\sum_{\ell=1}^{n} (A_\ell/\lambda_\ell)$ in (3.49) gives

$$f_{ss} = \frac{AUC - \sum_{\ell=1}^{n} (A_\ell e^{-N\lambda_\ell \tau}/\lambda_\ell)}{AUC} \tag{3.50}$$

The integral of (2.7) ($C = \Sigma_{\ell=1}^{n} A_\ell e^{-\lambda_\ell t}$) from time t to ∞ provides an expression for the area under a plasma concentration-time curve following a single intravenous bolus dose from time t to ∞, AUC_t^∞:

$$AUC_t^\infty = \sum_{\ell=1}^{n} \frac{A_\ell e^{-\lambda_\ell t}}{\lambda_\ell} \tag{3.51}$$

Since $N\tau$ in (3.50) equals the time since the beginning of dosing (i.e., t), AUC_t^∞ can be substituted for $\Sigma_{\ell=1}^{n} (A_\ell e^{-N\lambda_\ell \tau}/\lambda_\ell)$ in (3.50) to yield

$$f_{ss} = \frac{AUC - AUC_t^\infty}{AUC} = \frac{AUC_0^t}{AUC} \tag{3.52}$$

Therefore, the fraction of steady state reached at time t after initiation of a multiple-dosing regimen can be determined by knowing the areas, AUC and AUC_t^∞ or AUC_0^t obtained from a single bolus dose of the drug. No model has to be assumed to permit the use of (3.52) for determining f_{ss}.

Determination of a Loading Dose

As (3.48) indicates, a significant period of time may be required to attain steady-state plasma concentrations for drugs with long half-lives. A rational method to overcome the lapse in time before a steady-state concentration is reached would be to administer an initial loading dose. One approach to the calculation of a loading dose is as follows. It is often desirable to maintain plasma concentrations of drug greater than some minimum effective level. This level may be defined as $(C_{ss})_{min}$. Therefore, the first dose (i.e., the loading dose X_0^*) must be sufficiently high such that $(C_1)_{min}$ equals $(C_{ss})_{min}$, where $(C_1)_{min}$ and $(C_{ss})_{min}$ are given by (3.21) and (3.2), respectively. Substitution for A_ℓ according to (2.8), in (3.2) and (3.21), and substitution of X_0^* (the loading dose) for X_0 (the maintenance dose) in (3.2) yields

$$(C_1)_{min} = \sum_{\ell=1}^{n} \frac{X_0^*}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell \tau} \tag{3.53}$$

and

$$(C_{ss})_{min} = \sum_{\ell=1}^{n} \frac{X_0}{V_c} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{1}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell \tau} \tag{3.54}$$

respectively. Since $(C_1)_{min}$ as given by (3.53) must equal $(C_{ss})_{min}$,

$$\sum_{\ell=1}^{n} \frac{X_0^*}{V_c} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell \tau} = \sum_{\ell=1}^{n} \frac{X_0}{V_c} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{1}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell \tau} \tag{3.55}$$

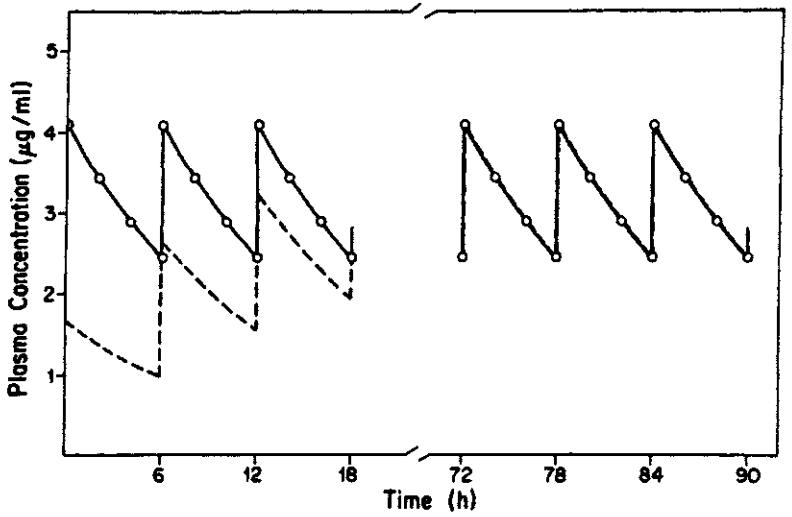

Fig. 3.2 Time course of drug concentration when a fixed dose of drug is given every 6 h (dashed line) and when the first dose of the regimen is replaced by an appropriately larger dose, a loading dose (solid line). Drug concentrations in plasma at steady state are identical, but steady state is attained much more quickly when a loading dose is used.

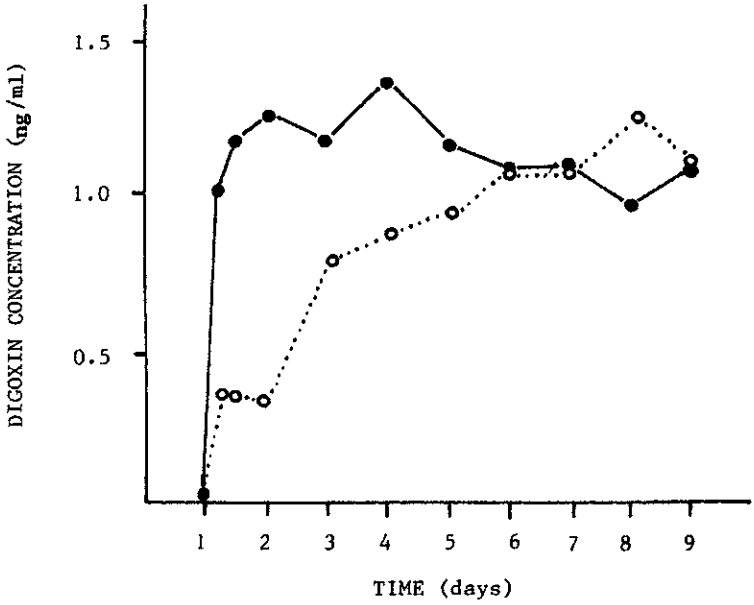

Fig. 3.3 Comparison of serum digoxin concentrations in human volunteers given a 2 mg loading dose followed by a 0.5 mg daily dose of the drug (●) and in those in whom the loading dose was omitted (○). (From Ref. 2.)

Solving (3.55) for X_0^* and canceling the common term V_c yields

$$X_0^* = X_0 \frac{\sum_{\ell=1}^{n} \left\{ \left[\prod_{i=2}^{n} (E_i - \lambda_\ell) \Big/ \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell) \right] [1/(1 - e^{-\lambda_\ell \tau})] e^{-\lambda_\ell \tau} \right\}}{\sum_{\ell=1}^{n} \left\{ \left[\prod_{i=2}^{n} (E_i - \lambda_\ell) \Big/ \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell) \right] e^{-\lambda_\ell \tau} \right\}} \tag{3.56}$$

In a one-compartment system (i.e., n = 1), or if all doses are administered in the postdistributive phase (i.e., $e^{-\lambda 1 \tau}$ to $e^{-\lambda n-1 \tau}$ approach zero), (3.56) reduces to

$$X_0^* = X_0 \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.57}$$

Therefore, the loading dose is equal to the product of the maintenance dose and the accumulation factor. Administration of a loading dose X_0^* as calculated by (3.57) followed by a maintenance dose X_0 every τ time units in the postdistributive phase should produce an immediate minimum steady-state plasma concentration of drug (Figs. 3.2 and 3.3). For example, administration of a loading dose twice the size of the maintenance dose for a drug where the dosing interval τ equals the half-life will yield immediate minimum steady-state concentrations. If a loading dose were not given, approximately four half-lives would have been required to reach 90% of the ultimate steady state.

INTRAVENOUS INFUSION

Some drugs are administered as an intravenous infusion rather than an intravenous bolus injection. The relationship describing the rise in drug concentration in the plasma during infusion is

$$C = \frac{k_0}{V_c}\left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t}\right] \tag{2.55}$$

where k_0 is the zero-order infusion rate, and all other parameters are as defined previously. Administration of a second dose as an infusion, τ time units after administration of the first dose, where τ is in the postdistribution phase of the previous dose, would yield the following equation for plasma concentration (C_2) as a function of time

$$C_2 = (C_1)_{min} e^{-\lambda_n (t-\tau)} + \frac{k_0}{V_c}\left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{\substack{i=2 \\ i\neq\ell}}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell (t-\tau)}\right] \tag{3.58}$$

If a third infusion is given τ time units after the second infusion, plasma concentrations resulting from this infusion would be given by the following equation:

$$C_3 = (C_2)_{min} e^{-\lambda_n (t-2\tau)} + \frac{k_0}{V_c} \left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell (t-2\tau)} \right] \tag{3.59}$$

On examination of Eqs. (2.55), (3.58), and (3.59), it is readily apparent that a general equation can be written for the plasma concentration of drug following N doses, C_N, that is

$$C_N = (C_{N-1})_{min} e^{-\lambda_n (t-(N-1)\tau)} + \frac{k_0}{V_c} \left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell (t-(N-1)\tau)} \right] \tag{3.60}$$

Since $t = (N-1)\tau + t_i$ where t_i is some time during infusion (i.e., $0 \leq t_i \leq T$, where T is the infusion time), Eq. (3.60) can be written as follows:

$$C_N = (C_{N-1})_{min} e^{-\lambda_n t_i} + \frac{k_0}{V_c} \left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t_i} \right] \tag{3.61}$$

The maximum plasma concentration following the Nth infusion will occur when $t_i = T$ and is therefore given by the relationship

$$(C_N)_{max} = (C_{N-1})_{min} e^{-\lambda_n T} + \frac{k_0}{V_c} \left[\frac{\prod_{i=2}^{n} E_i}{\prod_{i=1}^{n} \lambda_i} - \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell T} \right] \tag{3.62}$$

The plasma concentration of a drug as a function of time following the cessation of infusion is given by

$$C = \sum_{\ell = 1}^{n} R_\ell e^{-\lambda_\ell t'} \tag{2.66}$$

where

$$R_\ell = \frac{k_0}{V_c} \frac{(e^{-\lambda_\ell T} - 1) \prod_{i=2}^{n} (E_i - \lambda_\ell)}{-\lambda_\ell \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \tag{2.67}$$

and t' is the time postinfusion. Equation (2.66) can be readily converted to a multiple-dosing equation by multiplying it by the multiple-dosing function and setting k_i equal to λ_ℓ, yielding

$$C_N = \sum_{\ell = 1}^{n} R_\ell \frac{1 - e^{-N\lambda_\ell \tau}}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell t'}$$

The minimum postinfusion concentration will occur when t' equals $\tau - T$. If each dose is administered in the postdistribution phase of the previous dose, $\ell = n$. Therefore, $(C_{N-1})_{min}$, a value necessary to determine C_N and $(C_N)_{max}$ from Eqs. (3.61) and (3.62), is given by

$$(C_{N-1})_{min} = R_n \frac{1 - e^{-(N-1)\lambda_n \tau}}{1 - e^{-\lambda_n \tau}} e^{-\lambda_n(\tau - T)} \tag{3.63}$$

R_n is given by 2.67 when $\ell = n$.

At steady state, that is, when $e^{-(N-1)\lambda_n \tau}$ approaches zero

$$(C_{ss})_{min} = R_n \frac{1}{1 - e^{-\lambda_n \tau}} e^{-\lambda_n(\tau - T)} \tag{3.64}$$

The maximum concentration of drug at steady state, and the concentration of drug at steady state during infusion can be determined by setting $(C_{N-1})_{min}$ in Eqs. (3.61) and (3.62) equal to $(C_{ss})_{min}$; the latter is given by (3.64).

The average concentration of drug in the plasma at steady state, $\overline{C}$, resulting from multiple intravenous infusions can be determined from

the same basic relationship used for the intravenous bolus case, namely $\overline{C} = \int_0^\tau C_{ss}\, dt/\tau$ [Eq. (3.25)]. It can be demonstrated that

$$\int_0^\tau C_{ss}\, dt = \int_0^\infty C\, dt \tag{3.65}$$

Therefore,

$$\overline{C} = \frac{k_0 T}{V_c k_{10} \tau} \tag{3.66}$$

since $\int_0^\infty C\, dt$ following an intravenous infusion equals k_0T/V_ck_{10} [see Eq. (2.212)]. The product k_0T equals the intravenous dose X_0, and $V_ck_{10} = V_\beta\lambda_n = Cl_s$ [Eq. (2.21)]. Therefore, the average plasma concentration of drug at steady state resulting from intravenous infusions can also be determined using Eqs. (3.27), (3.29), or (3.30).

Provided that the same underlying assumptions are met, an accumulation factor R, the time to reach a certain fraction of steady state $N\tau$, and a loading dose X_0^* can be determined for intravenous infusion data using the same relationships as used for intravenous bolus data:

$$R = \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.33}$$

$$N\tau = -3.32 t_{1/2} \log (1 - f_{ss}) \tag{3.48}$$

and

$$X_0^* = X_0 \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.57}$$

respectively. Equation (3.48) applies only to a one-compartment model. In (3.57) X_0^* would equal the product of the loading infusion rate k_0^* and the loading infusion time T* for the loading dose, and X_0 would equal the product of the infusion rate k_0 and infusion time T for the maintenance dose. Therefore,

$$k_0^* T^* = k_0 T \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.67}$$

Assuming that the infusion times for the loading and maintenance doses are the same (i.e., T* = T), (3.67) can be simplified to

$$k_0^* = k_0 \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.68}$$

FIRST-ORDER ABSORPTION

The vast majority of drugs administered on a continuous basis are given orally. The equation describing the plasma concentration versus time curve following multiple dosing of a drug that is absorbed by an apparent first-order process can be arrived at directly. Multiplication of the exponential terms in (2.93), which describes the time course of drug in the plasma following first-order input, by the multiple-dosing function and setting k_i in each function equal to the rate constant in each exponential term (see Appendix B) yields

$$C_N = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} \frac{1 - e^{-Nk_a\tau}}{1 - e^{-k_a\tau}} e^{-k_a t}$$

$$+ \frac{k_a F X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{1 - e^{-N\lambda_\ell\tau}}{1 - e^{-\lambda_\ell\tau}} e^{-\lambda_\ell t} \qquad (3.69)$$

where $0 \leq t \leq \tau$, k_a is an apparent first-order absorption rate constant, and F is the fraction of the orally administered drug that reaches the systemic circulation. All other parameters are as defined previously in this chapter. Equation (3.69) can be employed to predict the plasma concentration of drug at any time during any dosing interval. However, information that is often difficult to obtain, such as estimates of F/V_c and k_a, is required for such predictions. In such cases superposition (Appendix E) is an attractive alternative.

At steady state the time course of drug in the plasma during a dosing interval can be described by the equation

$$C_{ss} = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} \frac{1}{1 - e^{-k_a\tau}} e^{-k_a t}$$

$$+\frac{k_a F X_0}{V_c}\sum_{\ell=1}^{n}\frac{\prod_{i=2}^{n}(E_i-\lambda_\ell)}{(k_a-\lambda_\ell)\prod_{\substack{i=1\\ i\neq\ell}}^{n}(\lambda_i-\lambda_\ell)}\frac{1}{1-e^{-\lambda_\ell\tau}}e^{-\lambda_\ell t} \tag{3.70}$$

which is obtained by setting N equal to a sufficiently large number in (3.69) and realizing that the terms $e^{-Nk_a\tau}$ and $e^{-N\lambda_\ell\tau}$ then approach zero.

The average plasma concentration of drug at steady state, $\bar{C}$, as defined by (3.25) ($\bar{C} = \int_0^\tau C_{ss}\,dt/\tau$), can be calculated either by employing (3.25) directly, or by employing (3.27) ($\bar{C} = \int_0^\infty C\,dt/\tau$) or equations analogous to (3.29) ($\bar{C} = X_0/V_\beta\lambda_n\tau = X_0/Cl_s\tau$) or (3.30) ($\bar{C} = 1.44X_0t_{1/2}/V_\beta\tau$). Integration of (3.70) from time zero to τ yields

$$\int_0^\tau C_{ss}dt = \frac{k_a F X_0}{V_c}\frac{\prod_{i=2}^{n}(E_i-k_a)}{k_a\prod_{i=1}^{n}(\lambda_i-k_a)} + \frac{k_a F X_0}{V_c}\sum_{\ell=1}^{n}\frac{\prod_{i=2}^{n}(E_i-\lambda_\ell)}{\lambda_\ell(k_a-\lambda_\ell)\prod_{\substack{i=1\\ i\neq\ell}}^{n}(\lambda_i-\lambda_\ell)} \tag{3.71}$$

This equation can be further simplified to

$$\int_0^\tau C_{ss}\,dt = \frac{FX_0}{V_c}\left[\frac{\prod_{i=2}^{n}(E_i-k_a)}{\prod_{i=1}^{n}(\lambda_i-k_a)} + \sum_{\ell=1}^{n}\frac{k_a\prod_{i=2}^{n}(E_i-\lambda_\ell)}{\lambda_\ell(k_a-\lambda_\ell)\prod_{\substack{i=1\\ i\neq\ell}}^{n}(\lambda_i-\lambda_\ell)}\right] \tag{3.72}$$

Expanding the term within the brackets for a given n, canceling common terms, and recognizing that $\prod_{i=2}^{n}E_i/\prod_{i=1}^{n}\lambda_i = 1/k_{10}$ [see (2.107) and (2.169)], where k_{10} is the first-order elimination rate constant from the central compartment, gives

$$\int_0^{\tau} C_{ss}\, dt = \frac{FX_0}{V_c k_{10}} \tag{3.73}$$

Since

$$V_c k_{10} = V_\beta \lambda_n = Cl_s \tag{2.215}$$

(3.73) can also be written as follows:

$$\int_0^{\tau} C_{ss}\, dt = \frac{FX_0}{V_\beta \lambda_n} = \frac{FX_0}{Cl_s} \tag{3.74}$$

It can also be demonstrated that

$$\int_0^{\tau} C_{ss}\, dt = \int_0^{\infty} C\, dt \tag{3.75}$$

where $\int_0^{\infty} C\, dt$ is the area under the plasma concentration-time curve from time zero to infinity following first-order input of a single dose.

Substituting $FX_0/V_\beta \lambda_n$ and/or FX_0/Cl_s for $\int_0^{\tau} C_{ss}\, dt$ in (3.25) and recognizing that $\lambda_n = 0.693/t_{1/2}$ [Eq. (2.11)] yields

$$\overline{C} = \frac{FX_0}{V_\beta \lambda_n \tau} = \frac{FX_0}{Cl_s \tau} = \frac{1.44 FX_0 t_{1/2}}{V_\beta \tau} \tag{3.76}$$

As is evident from (3.76), $\overline{C}$ is dependent on the size of dose administered, the extent to which it is absorbed, and the dosing interval. However, $\overline{C}$ is independent of the rate of absorption and all other disposition rate constants, as evidenced by the absence of k_a and λ terms from (3.76). The same average plasma concentration of drug will be obtained whether the dose X_0 is administered as a single dose every τ time units, or is subdivided and administered at different times within τ time units; that is, 600 mg once a day is equivalent to 300 mg every 12 h, is equivalent to 150 mg every 6 h, and so on (see Figs. 3.4 and 3.5). However, upon subdividing the dose, the difference between the minimum and maximum plasma concentration will usually decrease.

Although Eq. (3.76) permits the estimation of average drug concentration at steady state based on the pharmacokinetic parameters of the drug, it is rarely used as such; a much simpler approach is available. Since $\overline{C} = \int_0^{\tau} C_{ss}\, dt/\tau$ and $\int_0^{\tau} C_{ss}\, dt = \int_0^{\infty} C\, dt$, $\overline{C}$ may be estimated directly from the ratio of total area under the drug concentration in plasma versus time curve after a single oral dose, to the dosing interval τ (see Fig. 3.6). This approach assumes that systemic availability and clearance are constants from dose to dose.

Accumulation can be determined by comparing the minimum plasma concentrations of drug at steady state and following the first dose,

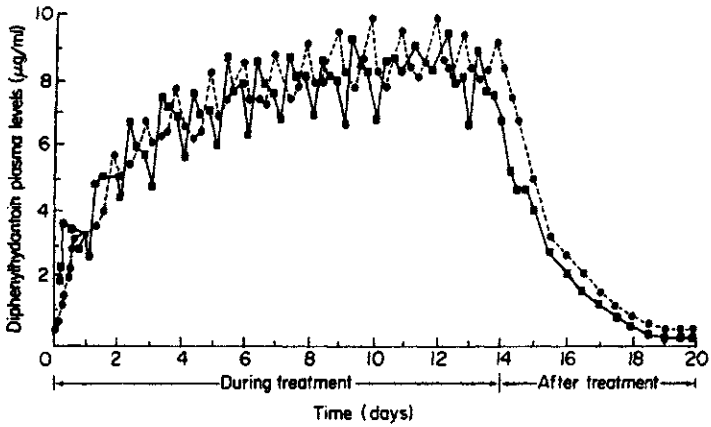

Fig. 3.4 Mean concentrations of phenytoin (diphenylhydantoin) in normal adult volunteers who received either 300 mg once a day (single-dose group: ■——■) or 100 mg three times a day (divided-dose group: ●---●). The average drug concentration at steady state is a function of the total daily dose (see Ref. 3).

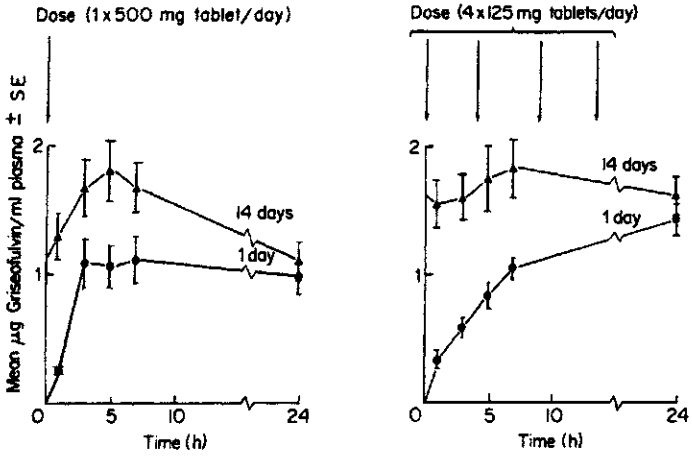

Fig. 3.5 Average concentrations of griseofulvin during the first and fourteenth day of drug administration in human volunteers who received 500 mg once a day or 125 mg four times a day. Theory predicts that the average drug concentration at steady state will be the same for both regimens but that the steady-state peak-to-trough ratio will be larger for the once-a-day regimen. (From Ref. 4.)

$R = (C_{ss})_{min}/(C_1)_{min}$ [Eq. (3.31)]. However, this method is relatively simple only when one is dealing with a situation in which each dose is administered in the postabsorptive-postdistributive phase of the preceding dose. This situation probably exists for a large number of drugs, although it may not be valid for sustained-release products and for drugs that are absorbed very slowly.

By setting N equal to 1 and t equal to τ in (3.69), an expression for the minimum plasma concentration following the first dose $(C_1)_{min}$ can be obtained:

$$(C_1)_{min} = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} e^{-k_a \tau} + \frac{k_a F X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell \tau} \quad (3.77)$$

Similarly, by setting t equal to τ in (3.70), the following expression for the minimum plasma concentration at steady state $(C_{ss})_{min}$ results:

$$(C_{ss})_{min} = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} \frac{1}{1 - e^{-k_a \tau}} e^{-k_a \tau} + \frac{k_a F X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{1}{1 - e^{-\lambda_\ell \tau}} e^{-\lambda_\ell \tau} \quad (3.78)$$

Assuming that each dose is administered in the postabsorptive-postdistributive phase [i.e., as $e^{-k_a \tau}$ and $e^{-\lambda_1 \tau}$ to $e^{-\lambda_{n-1} \tau}$ approach zero], (3.77) and (3.78) become

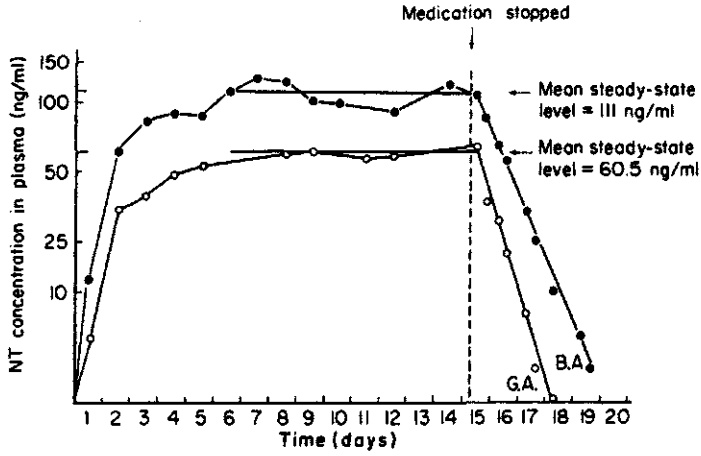

Fig. 3.6 Time course of plasma nortriptyline concentrations in two normal subjects, G. A. (○) and B. A. (●), who received 0.4 mg/kg three times a day for 2 weeks. The average drug concentrations predicted from the total area under the curve after a single dose were 53 and 116 ng/ml for G. A. and B. A., respectively. (From Ref. 5.)

$$(C_1)_{min} = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_n)}{(k_a - \lambda_n) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_n)} e^{-\lambda_n \tau} \tag{3.79}$$

and

$$(C_{ss})_{min} = \frac{k_a F X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - \lambda_n)}{(k_a - \lambda_n) \prod_{\substack{i=1 \\ i \neq \ell}}^{n} (\lambda_i - \lambda_n)} \frac{1}{1 - e^{-\lambda_n \tau}} e^{-\lambda_n \tau} \tag{3.80}$$

respectively. Therefore, the accumulation factor R, which is defined as $(C_{ss})_{min}/(C_1)_{min}$, equals $1/(1 - e^{-\lambda_n \tau})$ [Eq. (3.33)]. This expression can readily be employed to determine the extent of accumulation following first-order input every τ time units, since only an estimate of the terminal disposition rate constant is required. However, if each dose is not administered in the postabsorptive-post-

distributive phase, a rather complex function would result for the accumulation factor. R would then be equal to the ratio of Eq. (3.78) to Eq. (3.77).

The time required to reach a certain fraction of the ultimate steady state following first-order input can also be estimated where the fraction of the steady-state concentration f_{ss} is as defined by (3.42), that is, $f_{ss} = \overline{C}_N/\overline{C}$, where $\overline{C}_N = \int_0^\tau C_N\,dt/\tau$ [Eq. (3.34)] and $\overline{C} = FX_0/Cl_s\tau = FX_0/V_\beta\lambda_n\tau$ [Eq. (3.76)]. Integration of (3.69) is relatively complex. However, the concentration-time profile following the oral administration of many if not most drugs can be adequately characterized by a one-compartment model with first-order input. Under these conditions, appropriate redefinition of the terms and integration of Eq. (3.69) from 0 to τ yields

$$\int_0^\tau C_N\,dt = \frac{k_a FX_0}{V(k_a - K)}\left(\frac{1 - e^{-Nk_a\tau}}{1 - e^{-k_a\tau}}\,\frac{e^{-k_a\tau}}{k_a} - \frac{1 - e^{-NK\tau}}{1 - e^{-K\tau}}\,\frac{e^{-K\tau}}{K} + \frac{1 - e^{-NK\tau}}{1 - e^{-K\tau}}\,\frac{1}{K} - \frac{1 - e^{-Nk_a\tau}}{1 - e^{-k_a\tau}}\,\frac{1}{k_a}\right) \tag{3.81}$$

which on rearrangement and simplification becomes

$$\int_0^\tau C_N\,dt = \frac{FX_0}{VK}\left(1 + \frac{Ke^{-Nk_a\tau}}{k_a - K} - \frac{k_a e^{-NK\tau}}{k_a - K}\right) \tag{3.82}$$

Substitution of the value of $\int_0^\tau C_N\,dt$, as given in (3.82), into (3.34) yields the following expression for the average plasma concentration of drug during the Nth dosing interval:

$$\overline{C}_N = \frac{FX_0}{VK\tau}\left(1 + \frac{Ke^{-Nk_a\tau}}{k_a - K} - \frac{k_a e^{-NK\tau}}{k_a - K}\right) \tag{3.83}$$

By substituting $\overline{C}$ for $FX_0/VK\tau$ according to (3.76) in (3.83) and dividing both sides of the equation by $\overline{C}$, one obtains

$$f_{ss} = \frac{\overline{C}_N}{\overline{C}} = 1 + \frac{Ke^{-Nk_a\tau}}{k_a - K} - \frac{k_a e^{-NK\tau}}{k_a - K} \tag{3.84}$$

From (3.84) it is readily apparent that the time required to reach a certain fraction of the steady-state level is a complex function of the absorption and elimination rate constants. The larger the value of k_a relative to K, the less dependent on k_a is the time required to

reach a given fraction of steady state [6]. At very large values of k_a relative to K (i.e., $k_a/K \geq 10$), Eq. (3.84) approaches

$$f_{ss} = 1 - e^{-NK\tau} \tag{3.44}$$

Therefore,

$$N\tau = -3.32t_{1/2}\log (1 - f_{ss}) \tag{3.48}$$

Hence, when the absorption rate constant is significantly larger than the terminal disposition rate constant, the time required, $N\tau$, to reach a certain fraction of the steady-state level is a function only of the half-life of the drug. If this is not the case, then f_{ss} is also dependent on k_a. The smaller the value of k_a, the longer the time required to attain steady state or some fraction thereof.

Estimation of the time to steady state for a drug that shows multicompartment characteristics on oral administration is a task particularly well handled by the method of Chiou [1] [see Eq. (3.52)].

As discussed in the section on multiple dosing by intravenous administration, an initial loading dose may be desirable, since for drugs with long half-lives, a long period of time is required to reach steady state. The loading dose X_0^* required to achieve steady-state levels on the first dose may be determined by letting X_0 equal X_0^* in Eq. (3.77) [the equation for $(C_1)_{min}$] and setting this equal to the equation for $(C_{ss})_{min}$ [Eq. (3.78)]:

$$\frac{k_a FX_0^*}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} e^{-k_a\tau} + \frac{k_a FX_0^*}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell\tau}$$

$$= \frac{k_a FX_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} \frac{1}{1 - e^{-k_a\tau}} e^{-k_a\tau}$$

$$+ \frac{k_a FX_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_a - \lambda_\ell) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{1}{1 - e^{-\lambda_\ell\tau}} e^{-\lambda_\ell\tau} \tag{3.85}$$

Solving for X_0^* results in a relatively complex equation. However, by administration of the maintenance dose in the postabsorptive-post-distributive phase of the loading dose plasma concentration-time curve (i.e., $e^{-k_a\tau}$ and $e^{-\lambda 1\tau}$ to $e^{-\lambda n-1\tau}$ approach zero), the following equation is obtained for X_0^*:

$$X_0^* = X_0 \frac{1}{1 - e^{-\lambda_n \tau}} \tag{3.57}$$

from which it is relatively simple to estimate a loading dose. This equation was employed to calculate a loading dose for drugs administered by the intravenous route. Irrespective of the size of the initial dose the steady-state plasma concentration of drug ultimately reached will be the same since the steady-state level is governed by the size of the maintenance dose (Fig. 3.7).

The drug concentration in plasma versus time curve after oral administration of many drugs can be adequately described by a one-compartment model. Setting n equal to 1 in (3.85) and canceling the common term k_aF/V_c yields

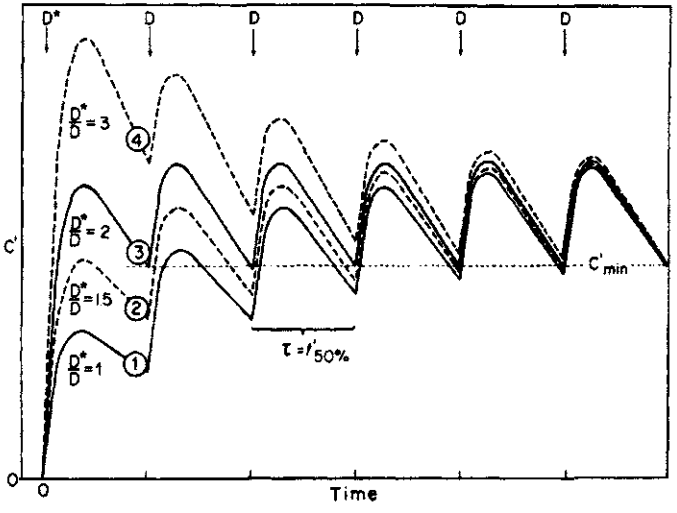

Fig. 3.7 Influence of the first dose of a multiple dose regimen on the time course of drug concentrations, C', in plasma. D* denotes the first dose (loading dose) and D denotes all subseqeunt doses (maintenance dose). The dosing interval was selected to equal the half-life of the drug (i.e., $\tau = t_{50\%}$). The ratio of D* to D varies from 1 to 3. (From Ref. 7.)

$$X_0^* \frac{e^{-k_a\tau}}{K - k_a} - X_0^* \frac{e^{-K\tau}}{K - k_a} = X^0 \frac{e^{-k_a\tau}}{(K - k_a)(1 - e^{-k_a\tau})} - X^0 \frac{e^{-K\tau}}{(K - k_a)(1 - e^{-K\tau})} \tag{3.86}$$

By canceling the common term, $K - k_a$, bringing the right side of the equation to a common denominator, and solving for X_0^* gives

$$X_0^* = X^0 \frac{e^{-k_a\tau} - e^{-(k_a+K)\tau} - e^{-K\tau} + e^{-(k_a+K)\tau}}{(1 - e^{-k_a\tau})(1 - e^{-K\tau})(e^{-k_a\tau} - e^{-K\tau})} \tag{3.87}$$

Further simplification results in the following expression for X_0^*:

$$X_0^* = X^0 \frac{1}{(1 - e^{-k_a\tau})(1 - e^{-K\tau})} \tag{3.88}$$

If the maintenance dose is administered in the postabsorptive phase, (3.88) can be further simplified to yield (3.57) since the term $e^{-k_a\tau}$ approaches zero.

Assuming that the fraction F of each dose absorbed is constant during a multiple-dosing regimen, the time at which a maximum plasma concentration of drug at steady state occurs (t'_{max}) may be arrived at by differentiating (3.70) with respect to time and setting the resultant equal to zero. Doing this and canceling the common term k_aFX_0/V_c yields

$$\frac{\prod_{i=2}^{n} (E_i - k_a)}{\prod_{i=1}^{n} (\lambda_i - k_a)} \frac{k_a}{1 - e^{-k_a\tau}} e^{-k_a t'_{max}} = \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(\lambda_\ell - k_a) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} \frac{\lambda_\ell}{1 - e^{-\lambda_\ell\tau}} e^{-\lambda_\ell t'_{max}} \tag{3.89}$$

As is evident from examining (3.89) t'_{max} cannot be readily solved for. As discussed previously, plasma concentration versus time

curves following oral drug administration can frequently be described by a one-compartment model. Under these conditions we may write that

$$\frac{1}{K - k_a} \frac{k_a}{1 - e^{-k_a \tau}} e^{-k_a t'_{max}} = \frac{1}{K - k_a} \frac{K}{1 - e^{-K\tau}} e^{-Kt'_{max}} \tag{3.90}$$

Canceling common terms and rearranging (3.90) gives

$$e^{(k_a - K)t'_{max}} = \frac{k_a(1 - e^{-K\tau})}{K(1 - e^{-k_a \tau})} \tag{3.91}$$

By taking the common logarithm of both sides of (3.91) and dividing by $k_a - K$, the following expression is obtained for the time at which the maximum plasma concentration at steady state occurs:

$$t'_{max} = \frac{2.303}{k_a - K} \log \frac{k_a(1 - e^{-K\tau})}{K(1 - e^{-k_a \tau})} \tag{3.92}$$

The time t_{max} at which a maximum plasma concentration occurs following a single dose is given by

$$t_{max} = \frac{2.303}{k_a - K} \log \frac{k_a}{K} \tag{1.106}$$

Subtraction of (3.92) from (1.106) yields

$$t_{max} - t'_{max} = \frac{2.303}{k_a - K} \log \frac{1 - e^{-k_a \tau}}{1 - e^{-K\tau}} \tag{3.93}$$

Since the right side of this equation is always positive, it is apparent that the maximum plasma concentration occurs at an earlier time at steady state than following a single dose. Frequently, the time at which the maximum plasma concentration is observed after the first dose, t_{max}, is the time at which the plasma is sampled after administration of subsequent doses to assess C_{max}. Based on mathematical principles this would not be a sound practice, since the time at which a maximum plasma concentration occurs is not constant until steady state is achieved.

DETERMINATION OF PHARMACOKINETIC PARAMETERS FROM MULTIPLE-DOSING DATA

Estimates of all pharmacokinetic parameters can be made from steady-state intravenous plasma concentration-time data if τ is sufficiently large to permit an accurate determination of the intercept and disposition rate constant associated with the terminal phase of the concentration-time curve. Even if the dosing interval is too small to permit this, one can still estimate clearance Cl_s since only the area under the plasma concentration versus time curve at steady state, $\int_0^\tau C_{ss}\,dt$ or AUC, is required. Once AUC is known, Cl_s can be determined using (2.43) ($Cl_s = X_0/AUC$). Assuming that λ_n can be accurately determined, $t_{1/2}$ and V_β can be obtained employing (2.11) ($t_{1/2} = 0.693/\lambda_n$) and (2.216) ($V_\beta = Cl_s/\lambda_n$), respectively. Steady-state plasma concentrations can be described by

$$C_{ss} = \sum_{\ell=1}^{n} U_\ell e^{-\lambda_\ell t} \tag{3.22}$$

The method of residuals (Appendix C) can be applied to the data, generating the coefficients and disposition rate constants, U_ℓ and λ_ℓ, respectively. Once these parameters are obtained, values of A_ℓ, the coefficients generated from intravenous single-dose data, can be calculated from

$$A_\ell = U_\ell(1 - e^{-\lambda_\ell \tau}) \tag{3.94}$$

which is a rearrangement of (3.23). This then permits the volume of the central compartment V_c, and the steady-state volume of distribution V_{ss}, to be determined using (2.15) ($V_c = X_0/\Sigma_{\ell=1}^{n} A_\ell$) and (2.234) [$V_{ss} = X_0\,\Sigma_{\ell=1}^{n}(A_\ell/\lambda_\ell^2)/\Sigma_{\ell=1}^{n}(A_\ell/\lambda_\ell)^2$]. The constants k_{10} [Eqs. (2.107) and (2.169)], k_{12} [Eqs. (2.108) and (2.172)], k_{21} [Eqs. (2.106) and (2.168)], k_{31} [Eq. (2.167)], and k_{13} [Eq. (2.173)] can also be determined from multiple-dose data once the values for A_ℓ and λ_ℓ are known.

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