7
Nonlinear Pharmacokinetics

At therapeutic or nontoxic plasma concentrations, the pharmacokinetics of most drugs can be adequately described by first-order or linear processes. However, there are a small number of well-documented examples of drugs which have nonlinear absorption or distribution characteristics [e.g., ascorbic acid [1] and naproxen [2,3], respectively], and several examples drugs that are eliminated from the body in a nonlinear fashion.

MICHAELIS-MENTEN KINETICS

Drug biotransformation, renal tubular secretion, and biliary secretion usually require enzyme or carrier systems. These systems are relatively specific with respect to substrate and have finite capacities (i.e., they are said to be capacity limited). Frequently, the kinetics of these capacity-limited processes can be described by the Michaelis-Menten equation:

$$-\frac{dC}{dt} = \frac{V_m C}{K_m + C} \tag{7.1}$$

where $-dC/dt$ is the rate of decline of drug concentration at time t, V_m the theoretical maximum rate of the process, and K_m the Michaelis constant. It is readily seen by determining C when $-dC/dt = (1/2)V_m$ that K_m is in fact equal to the drug concentration at which the rate of the process is equal to one-half its theoretical maximum rate. Equation (7.1) can be derived based on the following scheme (see Appendix G for derivation):

$$E + C \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} EC \xrightarrow{k_2} E + M$$

In this scheme C is the concentration of drug, E the concentration of enzyme, EC the concentration of the enzyme-drug complex, and M the concentration of metabolite. The constants k_2 and k_{-1} are first-order rate constants, and k_1 is a second-order rate constant. The Michaelis-Menten equation is of value for describing in vitro and in situ as well as certain in vivo rate processes. For in vivo systems the constants V_m and K_m are affected by distributional and other factors and therefore must be viewed as functional, model-dependent constants.

SOME PHARMACOKINETIC CHARACTERISTICS OF MICHAELIS-MENTEN PROCESSES

There are two limiting cases of the Michaelis-Menten equation. If K_m is much larger than C, (7.1) reduces to

$$-\frac{dC}{dt} = \frac{V_m}{K_m} C \tag{7.2}$$

This equation has the same form as that describing first-order elimination of a drug: (1) after intravenous administration in a one-compartment model, (2) in the postabsorptive phase after some other route of administration in a one-compartment model, or (3) in the postabsorptive, postdistributive phase in a multicompartment model. Assuming apparent first-order elimination of a drug which confers one-compartment characteristics to the body and which is eliminated by a single biotransformation process, the first-order rate constant K is actually V_m/K_m. As shown in (7.2), if treatment with an enzyme inducer causes an increase in the amount of enzyme (and therefore of V_m), the apparent first-order rate constant of the process will also be increased. Given the fact that drug elimination is so frequently observed to follow apparent first-order kinetics, one must conclude that the drug concentration in the body (or, more correctly, at the site of an active process) resulting from the usual therapeutic dosage regimens of most drugs is well below the Km of the processes involved in the disposition of these drugs.

There are some notable exceptions to this generalization and among them are ethanol [4], salicylate [5,6], and phenytoin [7]. The elimination kinetics of phenytoin [8] and ethanol [9] appear to be adequately described by a single Michaelis-Menten expression, while salicylate elimination [6] may be described by two capacity-limited and three linear processes. Marked deviations from apparent first-order drug elimination have also been noted frequently in cases of drug intoxications. In the latter situation there is often some ambiguity as to whether the deviations are due to capacity-limited biotransformation of the high drug levels in the body [described by (7.1)] or due to some toxicologic effect of the drug.

Another limiting case of the Michaelis-Menten equation is that which results when the drug concentration is considerably greater than K_m. Equation (7.1) then reduces to

$$-\frac{dC}{dt} = V_m \tag{7.3}$$

Under these conditions, the rate is independent of drug concentration, so that the process occurs at a constant rate V_m. The kinetics of biotransformation of ethanol [4] have been observed to approach the condition described by (7.3) even at drug levels in the body that are appreciably lower than those considered to be toxic.

Based on the discussion above, if $-dC/dt$ is plotted as a function of plasma concentration, $-dC/dt$ would initially increase linearly with concentration, indicating first-order kinetics (Fig. 7.1). As the concentration increases further, $-dC/dt$ would increase at a rate less than proportional to concentration, and eventually asymptote at a

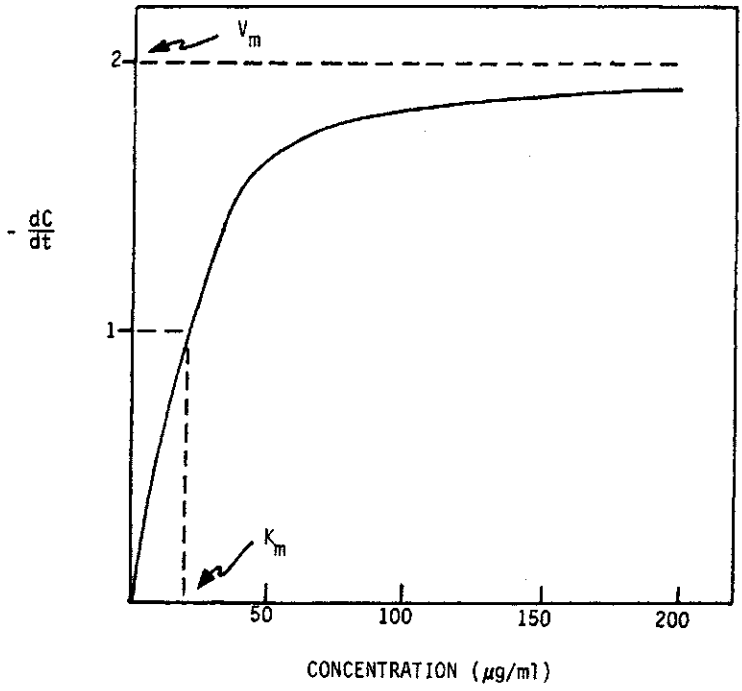


Fig. 7.1 Relationship between drug elimination rate $-dC/dt$ and drug concentration C for a Michaelis-Menten process. In this particular example the Michaelis constant K_m is equal to 10 μg/ml and the maximum rate V_m is equal to $2(\mu g/ml)h^{-1}$.

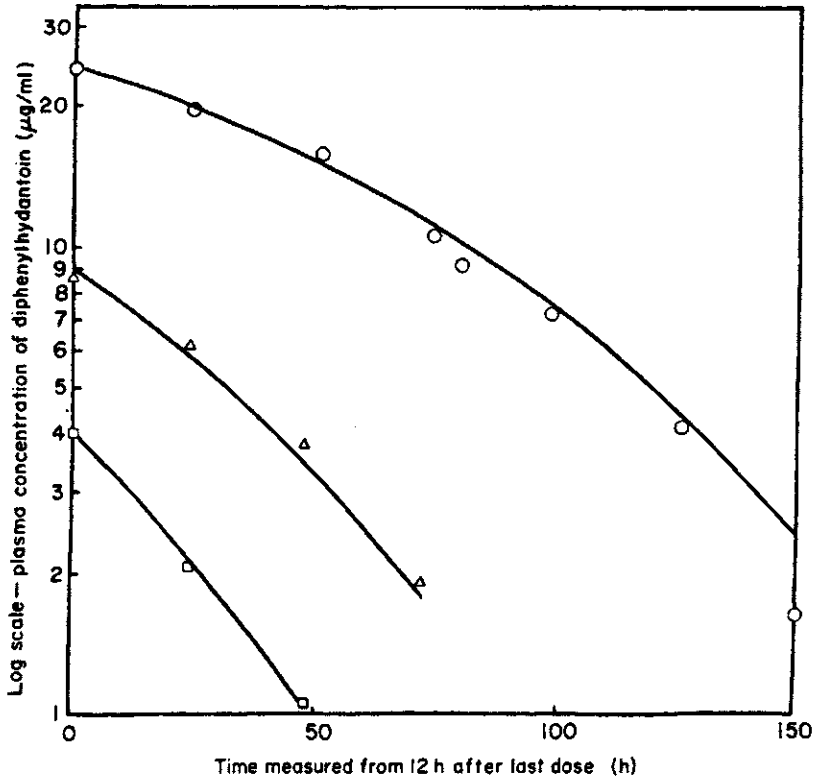


Fig. 7.2 Phenytoin (diphenylhydantoin) concentration in plasma 12 h after the last dose of a 3 day regimen of the drug at three different daily doses. The data are described by Eq. (7.9). ○: 7.9 mg/kg; △: 4.7 mg/kg; □: 2.3 mg/kg. (From Ref. 10, © 1972 PJD Publications Ltd., reprinted with permission.)

rate equal to V_m which would be independent of concentration (i.e., a zero-order rate).

The time course of drug plasma concentration after intravenous injection of a drug that is eliminated only by a single capacity-limited process can be described for a one-compartment system by the integrated form of the Michaelis-Menten equation. Rearrangement of (7.1) yields

$$-\frac{dC}{C}(C + K_m) = V_m\, dt \tag{7.4}$$

or

$$-dC - \frac{K_m dC}{C} = V_m\, dt \tag{7.5}$$

Integration of this equation gives the expression

$$-C - K_m \ln C = V_m t + i \tag{7.6}$$

where i is an integration constant. Evaluating i at t = 0, where $C = C_0$, yields

$$i = -C_0 - K_m \ln C_0 \tag{7.7}$$

Substituting this expression for i in (7.6) and rearranging terms gives

$$t = \frac{C_0 - C}{V_m} + \frac{K_m}{V_m} \ln \frac{C_0}{C} \tag{7.8}$$

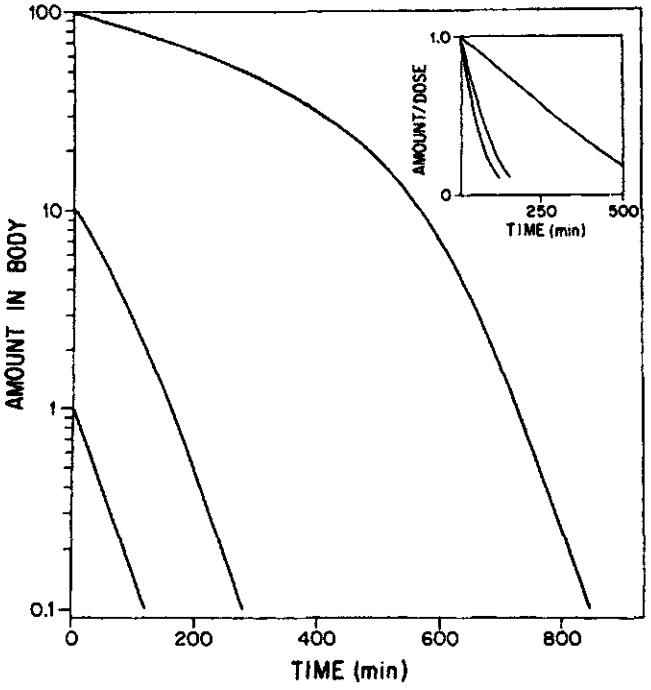


Fig. 7.3 Amount of drug in the body following intravenous administration of 1, 10, and 100 mg doses of a drug that is eliminated by a single Michaelis-Menten process. A one-compartment system is assumed; K_m = 10 mg and V_m = 0.2 mg/min. The inset shows a plot of amount of drug in the body divided by administered dose versus time to show that the principle of superposition does not apply.

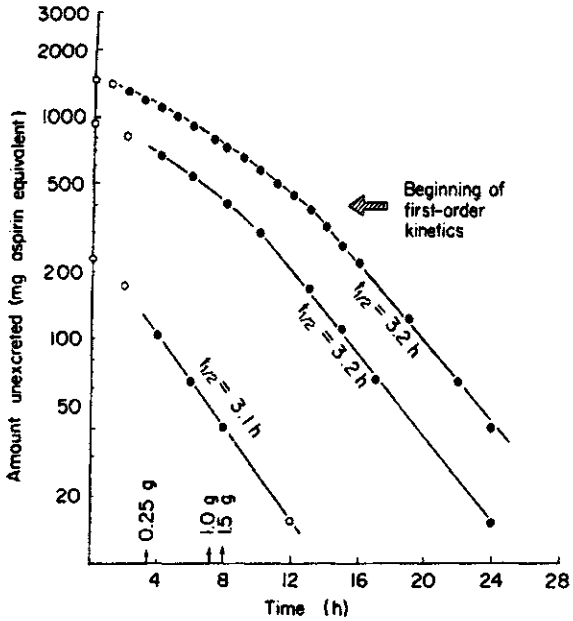


Fig. 7.4 Elimination of salicylate after oral administration of 0.25, 1.0, and 1.5 g doses of aspirin. Vertical arrows on the time axis indicate $t_{50\%}$, the time to eliminate 50% of the dose. (From Ref. 5, reprinted with permission.)

Unfortunately, it is not possible to solve this equation explicitly for C. Rather, one must determine the time t at which the initial concentration C_0 has decreased to C. A modified form of (7.8), that is,

$$t - t_0 = \frac{C_0 - C}{V_m} + \frac{K_m}{V_m} \ln \frac{C_0}{C} \tag{7.9}$$

has been used to fit phenytoin levels in the plasma as a function of time 12 h after administration of the last of several oral doses to human subjects (see Fig. 7.2). In this case C_0 represents the phenytoin plasma concentration at 12 h after the last dose, $t_0 = 12$ h, and C is the phenytoin plasma concentration at time t, where $t > t_0$.

Conversion of (7.8) to common logarithms ($\ln x = 2.303 \log x$) and solving for log C yields

$$\log C = \frac{C_0 - C}{2.303K_m} + \log C_0 - \frac{V_m}{2.303K_m} t \tag{7.10}$$

Figure 7.3 shows the time course of elimination, as described by (7.10), of three different doses of a drug that is eliminated by a process with Michaelis-Menten kinetics. The lowest dose represents the case where $K_m >> C$. At this dose the decline in plasma concentrations is first order with a slope of $-V_m/2.303K_m$. On the other hand, the highest dose yields initial concentrations which are considerably above K_m, so that drug levels decline initially at an essentially constant rate (see inset to Fig. 7.3). The curves show that the time required for an initial drug concentration to decrease by 50% is not independent of dose, but, in fact, increases with increasing dose. This particular pharmacokinetic property may present considerable clinical difficulty in the treatment of drug intoxications. Figure 7.3 also shows that regardless of the initial dose, when the plasma concentration becomes significantly less than K_m, elimination is describable by first-order kinetics and the slope of this linear portion of the curve is independent of dose. Semilogarithmic plots of plasma concentration or amount unexcreted versus time after administration of phenytoin (Fig. 7.2) or salicylate (Fig. 7.4) show characteristics that are remarkably similar to those described by the curves in Fig. 7.3.

To assess whether or not a drug possesses nonlinear kinetic properties, a series of single doses of varying size should be administered. If a plot of the resulting plasma concentrations divided by the administered dose are superimposable, the drug in question has linear kinetic properties over the concentration range examined. If, however, the resulting curves are not superimposable (see inset to Fig. 7.3), the drug behaves nonlinearly.

IN VIVO ESTIMATION OF K_m AND V_m

For a drug that is eliminated by a single capacity-limited process, there are a number of general methods which permit the initial estimation of apparent in vivo K_m and V_m values from plasma concentration-time data in the postabsorptive-postdistributive phase. Such estimates require the determination of the rate of change of the plasma concentration from one sampling time to the next, $\Delta C/\Delta t$, as a function of the plasma concentration C_m at the midpoint of the sampling interval (see Appendix F). The data are usually plotted according to one of the linearized forms of the Michaelis-Menten equation, such as the Lineweaver-Burk expression,

$$\frac{1}{\Delta C/\Delta t} = \frac{K_m}{V_m C_m} + \frac{1}{V_m} \tag{7.11}$$

so that a plot of the reciprocal of $\Delta C/\Delta t$ versus the reciprocal of C_m yields a straight line with intercept $1/V_m$ and slope K_m/V_m. Two sometimes more reliable [11,12] plots are the Hanes-Woolf plot [13] and

the Woolf-Augustinsson-Hofstee plot [13]. They are based on the relationships

$$\frac{C_m}{\Delta C/\Delta t} = \frac{K_m}{V_m} + \frac{C_m}{V_m} \tag{7.12}$$

and

$$\frac{\Delta C}{\Delta t} = V_m - \frac{(\Delta C/\Delta t)K_m}{C_m} \tag{7.13}$$

respectively. Based on (7.12), a plot of $C_m/(\Delta C/\Delta t)$ versus C_m should yield a straight line with a slope of $1/V_m$ and an intercept of K_m/V_m. Equation (7.13) indicates that a plot of $\Delta C/\Delta t$ versus $(\Delta C/\Delta t)/C_m$ gives a straight line with a slope of $-K_m$ and an intercept of V_m.

A method for estimating V_m and K_m directly from log C versus time data, obtained following the intravenous administration of a drug that can be adequately described by a one-compartment system, is also available [14]. Extrapolation of the terminal log-linear portion of the log C versus time plot, where the plot is described by (7.10), would yield a zero-time intercept of log C_0^* (see Fig. 7.5). The resulting straight line can be described by

$$\log C = \log C_0^* - \frac{V_m}{2.303K_m}t \tag{7.14}$$

At low plasma concentrations (7.10) and (7.14) are identical. By setting the right-hand sides of these two equations equal to each other, the following expression is obtained:

$$\frac{C_0 - C}{2.303K_m} + \log C_0 - \frac{V_m}{2.303K_m}\,t = \log C_0^* - \frac{V_m}{2.303K_m} \tag{7.15}$$

Cancellation of the common term, $V_m t/2.303K_m$, and rearrangement yields

$$\frac{C_0 - C}{2.303K_m} = \log \frac{C_0^*}{C_0} \tag{7.16}$$

Since the equality given by (7.15) is valid only at low concentrations, C_0 can be assumed to be significantly greater than C, and therefore $C_0 - C \simeq C_0$. Making this simplification in (7.16) and solving the resulting expression for K_m gives

$$K_m = \frac{C_0}{2.303 \log (C_0^*/C_0)} \tag{7.17}$$

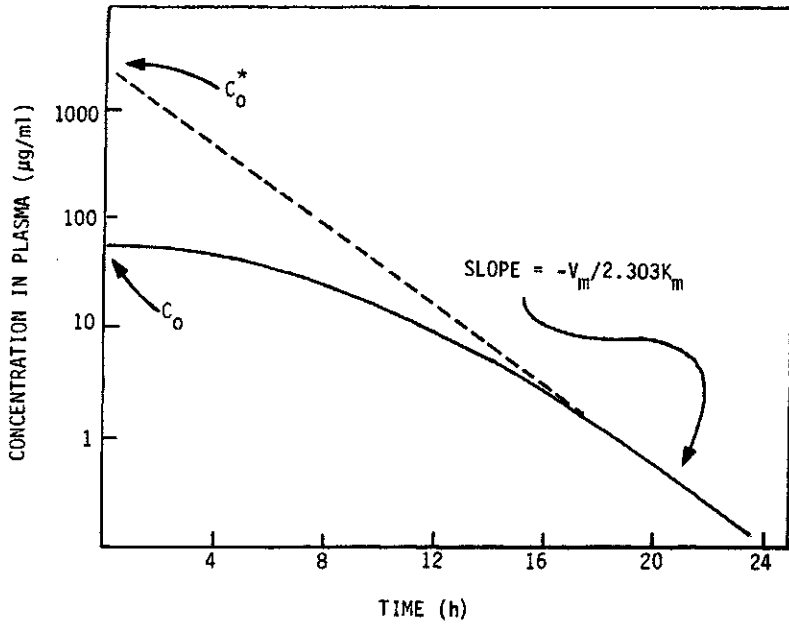


Fig. 7.5 Graphical method for estimating K_m and V_m after intravenous administration of a drug that is eliminated by a single Michaelis-Menten process. The solid line is described by Eq. (7.10). The terminal slope gives an estimate of the ratio of V_m to K_m, and the ratio of C_0^* to C_0 is used to estimate K_m [see Eq. (7.17)].

Since C_0^* and C_0 can be estimated from a log C versus time plot, an estimate of K_m is possible employing (7.17). V_m can be calculated from the slope of the terminal log-linear segment of the concentration versus time curve. Since slope = $-V_m/2.303K_m$, $V_m = -2.303(\text{slope})K_m$.

It is plausible to consider that drug elimination may involve a capacity-limited process in parallel with one or more first-order processes. Under these conditions, the foregoing methods for estimating V_m and K_m do not apply. When capacity-limited and first-order elimination occur in parallel, the rate of decline of drug levels in the plasma after intravenous administration in a one-compartment system is given by

$$-\frac{dC}{dt} = K'C + \frac{V_m C}{K_m + C} \tag{7.18}$$

where K' is the rate constant characterizing the various parallel first-order processes. The time course of drug levels under these conditions may be determined by integration of (7.18) as follows. Expansion of (7.18) yields

$$-\frac{dC}{dt} = \frac{K'C(K_m + C) + V_m C}{K_m + C} = \frac{K'K_m C + V_m C + K'C^2}{K_m + C} \tag{7.19}$$

Further simplification gives rise to

$$-\frac{dC}{dt} = \frac{C(K'K_m + KV_m + K'C)}{K_m + C} = \frac{C(a + K'C)}{K_m + C} \tag{7.20}$$

where $a = K'K_m + V_m$. Inversion and rearrangement of (7.20) yields

$$\frac{dt}{dC} = \frac{-(K_m + C)}{C(a + K'C)} = \frac{-K_m}{C(a + K'C)} - \frac{1}{a + K'C} \tag{7.21}$$

This equation is separable and can be rewritten as

$$dt = \frac{-K_m dC}{C(a + K'C)} - \frac{dC}{a + K'C} \tag{7.22}$$

The two terms in this equation are of the form $1/x(a + bx)$ and $1/(a + bx)$, respectively, the integrals of which are $(-1/a) \ln [(a + bx)/x]$ and $(1/b) \ln (a + bx)$ [15]. Therefore, integration of (7.22) gives

$$t = \frac{K_m}{a} \ln \frac{a + K'C}{C} - \frac{1}{K'} \ln (a + K'C) + i \tag{7.23}$$

Evaluating i at $t = 0$, where $C = C_0$, yields

$$i = -\frac{K_m}{a} \ln \frac{a + K'C_0}{C_0} + \frac{1}{K'} \ln (a + K'C_0) \tag{7.24}$$

Substituting this value of i in (7.23) and simplifying the resulting expression yields

$$at = K_m \ln \frac{C_0}{C} + \left(\frac{a}{K'} - K_m\right) \ln \frac{a + K'C_0}{a + K'C} \tag{7.25}$$

Since $a = K'K_m + V_m$,

$$(K'K_m + V_m)t = K_m \ln \frac{C_0}{C} + \left(\frac{K'K_m + V_m}{K'} - K_m\right) \ln \frac{K'K_m + V_m + K'C_0}{K'K_m + V_m + K'C} \tag{7.26}$$

or

$$t = \frac{1}{K'K_m + V_m}\left[K_m \ln \frac{C_0}{C} + \frac{V_m}{K'} \ln \frac{(C_0 + K_m)K' + V_m}{(C + K_m)K' + V_m}\right] \tag{7.27}$$

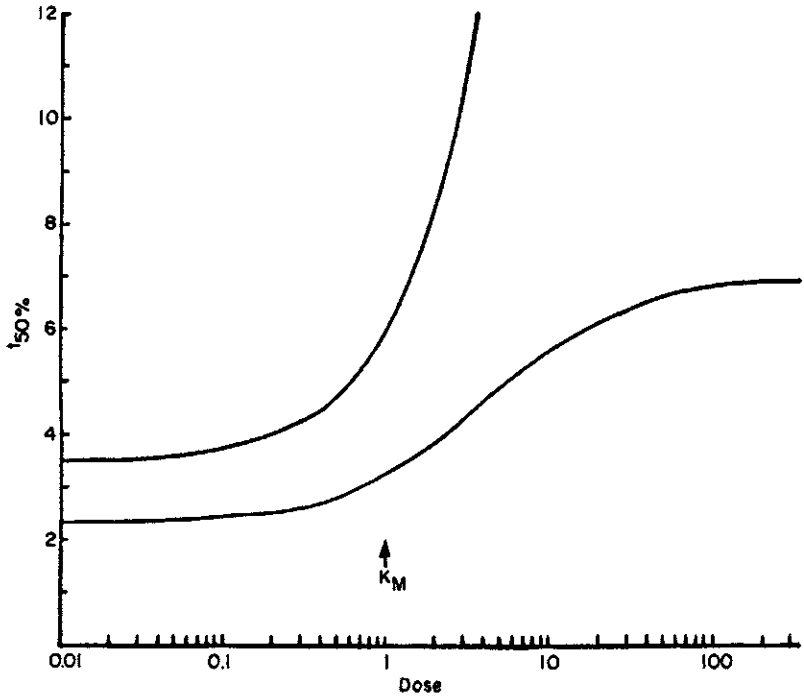


Fig. 7.6 Comparison of dose dependence of $t_{50\%}$ (time for elimination of 50% of the dose) after intravenous administration of a drug that is eliminated by a single Michaelis-Menten process (upper curve) or one that is eliminated by a single Michaelis-Menten process in parallel with a first-order process (lower curve). In each case, $K_m = 1.0$ and $V_m = 0.2$. The rate constant K' for the first-order process is equal to 0.1. (Data from Ref. 16.)

Equation (7.27), like (7.8), does not permit an explicit solution for C. Both (7.8) and (7.27) indicate that the time required to reduce an initial drug concentration by 50% is indeed dependent on the administered dose. Examples of this dependency are shown in Fig. 7.6.

Expanding (7.27) and solving for ln C gives

$$\ln C = \ln C_0 + \frac{V_m}{K'K_m} \ln \frac{(C_0 + K_m)K' + V_m}{(C + K_m)K' + V_m} - \left(K' + \frac{V_m}{K_m}\right) t \qquad (7.28)$$

which in terms of common logarithms is

$$\log C = \log C_0 + \frac{V_m}{K'K_m} \log \frac{(C_0 + K_m)K' + V_m}{(C + K_m)K' + V_m} - \frac{K' + V_m/K_m}{2.303} t \qquad (7.29)$$

At low concentrations (i.e., $K_m >> C$), (7.29) becomes

$$\log C = \log C_0 + \frac{V_m}{K'K_m} \log \frac{(C_0 + K_m)K' + V_m}{K_mK' + V_m} - \frac{K' + V_m/K_m}{2.303} t \tag{7.30}$$

or

$$\log C = \log C_0^* - \frac{K' + V_m/K_m}{2.303} t \tag{7.31}$$

where

$$\log C_0^* = \log C_0 + \frac{V_m}{K'K_m} \log \frac{(C_0 + K_m)K' + V_m}{K_mK' + V_m} \tag{7.32}$$

As can be seen from (7.31), the slope of the terminal linear portion of a semilogrithmic plot of plasma concentration versus time at low plasma concentrations (i.e., $K_m >> C$) will yield an estimate of the first-order elimination rate constant of a drug, $K' + V_m/K_m$ (see Fig. 7.7). The extrapolated intercept of this terminal linear phase will be $\log C_0^*$.

For certain drugs that exhibit parallel capacity-limited and first-order elimination, it may be possible to administer sufficiently high doses intravenously so that initial drug concentrations are substantially larger than K_m. Under these conditions and where a one-compartment model applies, the initial segment of a semilogarithmic plot of plasma concentration versus time will be linear (see Fig. 7.7). The slope of this linear segment will be $-K'/2.303$ [14]. This can be demonstrated by assuming C to be much greater than K_m in (7.18) and solving for C. Therefore, estimates of both K' and $K' + V_m/K_m$ can be obtained directly from a semilogarithmic plot of plasma concentration versus time and the ratio V_m/K_m can be calculated for the case where there is one capacity-limited process in parallel with one or more first-order processes. The following approach can then be used to obtain initial estimates of K_m and V_m for this model. Expansion of the logarithmic term of (7.32) and rearrangement of this equation yields

$$\frac{K'K_m}{V_m} \log \frac{C_0^*}{C_0} = \log \left(1 + \frac{C_0K'}{K_mK' + V_m}\right) \tag{7.33}$$

Division of the numerator and denominator of this logarithmic term by K_m gives

$$\frac{K'K_m}{V_m} \log \frac{C_0^*}{C_0} = \log \left[1 + \frac{C_0K'}{K_m(K' + V_m/K_m)}\right] \tag{7.34}$$

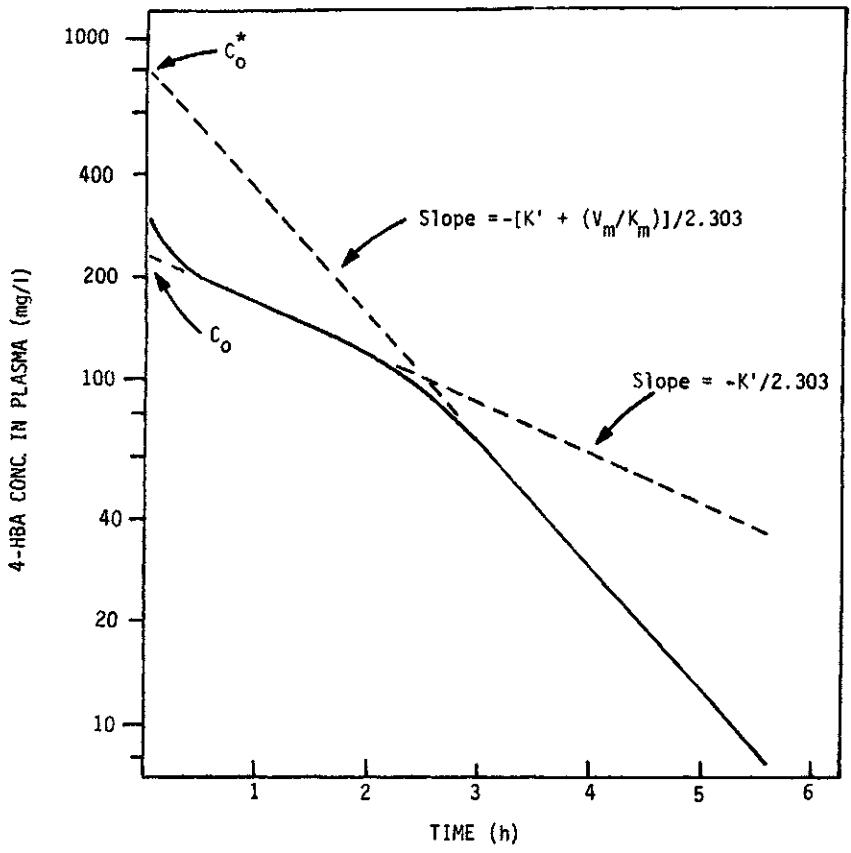


Fig. 7.7 4-Hydroxybutyric acid (4-HBA) concentration in plasma after intravenous administration. The compound appears to be eliminated by a Michaelis-Menten process in parallel with a first-order process. The initial slope gives an estimate of K' and the terminal slope provides an estimate of the ratio of V_m to K_m. K_m may be determined from Eq. (7.35). The deviation from theory for a short time after administration probably reflects drug distribution and the lack of strict adherence to a one-compartment model. (Data from Ref. 14.)

A solution for K_m based on this equation is

$$K_m = \frac{C_0 K'/(K' + V_m/K_m)}{(C_0^*/C_0)^{K'K_m/V_m} - 1} \qquad (7.35)$$

Since C_0 and C_0^* can be obtained directly from a semilogarithmic plasma concentration-time plot, and K' and V_m/K_m can be estimated as described above, an estimate of K_m is possible employing (7.35). Once K_m is known, V_m can be readily determined.

Although this is an interesting approach for the estimation of K', V_m, and K_m where there are parallel first-order and nonlinear elimination pathways, caution must be exercised. Initial plasma concentrations have to be sufficiently high (i.e., $C >> K_m$) to yield a semilogarithmic plasma concentration-time curve which is truly linear. If these con-

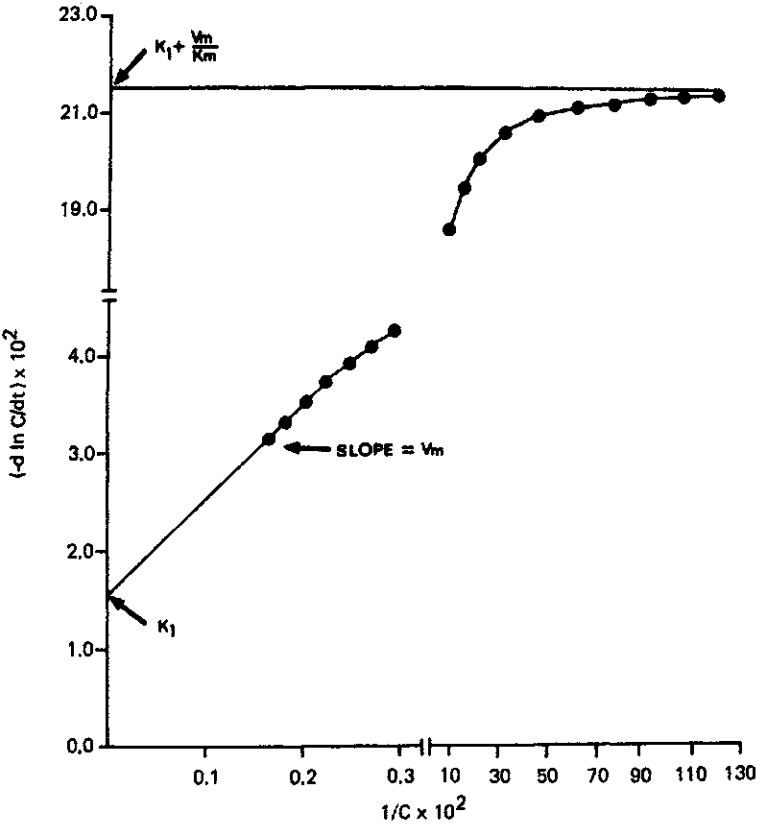


Fig. 7.8 Graphical method for estimating K' (designated K_1 in the plot), V_m and K_m based on Eqs. (7.36) to (7.39). At high concentrations, a plot of $-\Delta \ln C/\Delta t$ versus 1/C will be linear with a slope of V_m and an intercept equal to K' [see Eq. (7.38)], whereas at low concentrations the plot will asymptotically approach a limiting value equal to $K' + (V_m/K_m)$ [see Eq. (7.39)]. (From Ref. 17, © 1973 Plenum Publishing Corp.)

centrations are not attained, an overestimate of K' will result. This, in turn, will produce errors in the estimates of V_m and K_m.

A different approach can also be used for the estimation of K_m and V_m where nonlinear and linear processes of drug elimination occur in parallel. At high plasma concentrations (i.e., $C >> K_m$), (7.18) reduces to

$$-\frac{dC}{dt} = K'C + V_m \tag{7.36}$$

Division of both sides of (7.36) by C and recognition that $(-dC/dt)/C$ equals $-d \ln C/dt$ gives

$$-\frac{d \ln C}{dt} = K' + \frac{V_m}{C} \tag{7.37}$$

At low plasma concentrations (i.e., $K_m >> C$), (7.18) becomes

$$-\frac{dC}{dt} = K'C + \frac{V_m}{K_m} C \tag{7.38}$$

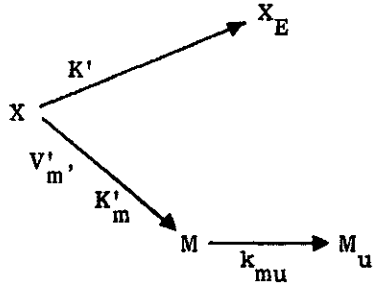
and, therefore, the analogous expression to (7.37) is

$$-\frac{d \ln C}{dt} = K' + \frac{V_m}{K_m} \tag{7.39}$$

A plot of $-\Delta \ln C/\Delta t$ versus $1/C$ will consequently be linear with a slope of V_m and an intercept of K' at high plasma concentrations [Eq. (7.37)], but will reach an asymptotic value of $K' + V_m/K_m$ at low concentrations [Eq. (7.39)] from which K_m can be calculated (see Fig. 7.8).

This method for estimating K', V_m, and K_m has limitations which are similar to those noted for the previous approach. Sufficiently high plasma concentrations are required to yield a straight line from the $-\Delta \ln C/\Delta t$ versus $1/C$ plot to permit accurate estimates of V_m and K'.

Urine data can also be used to estimate V_m and K_m. Consider the following scheme:



where X is the amount of drug in the body, X_E the amount of drug eliminated by the linear or first-order processes, M the amount of metabolite in the body which is formed by a capacity-limited process, and M_u the amount of this metabolite present in the urine. All of these amounts are time dependent. The constants K' and k_{mu} are first-order rate constants, V'_m is the maximum rate of metabolite formation in units of amount per time, and K'_m is the Michaelis constant in units of amount. Assuming that the urinary excretion rate of the metabolite ($\Delta M_u/\Delta t$) is rate limited by its formation, and therefore reflects the rate of formation, the following relationship for $\Delta M_u/\Delta t$ can be written:

$$\frac{\Delta M_u}{\Delta t} = \frac{V'_m X_m}{K'_m + X_m} \tag{7.40}$$

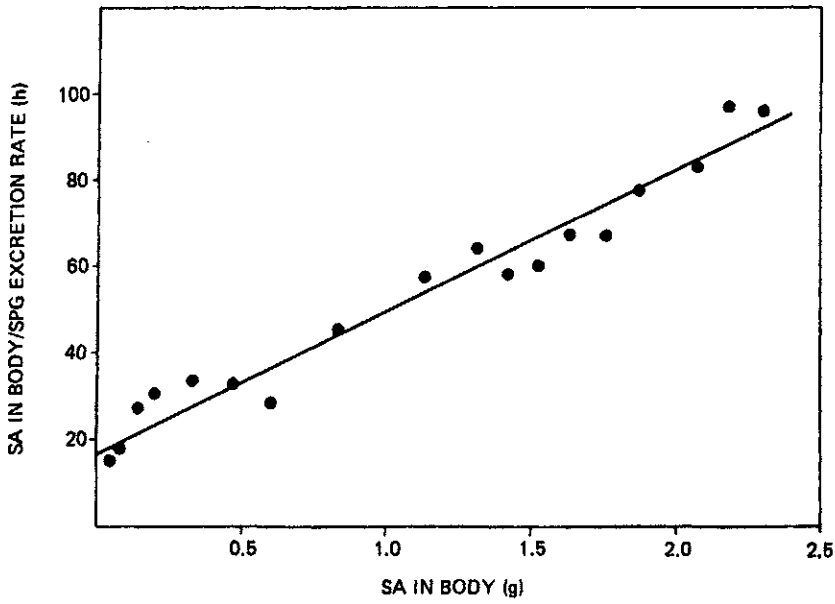


Fig. 7.9 Plot of linearized form of the Michaelis-Menten equation to describe the formation of salicyl phenolic glucuronide (SPG) after a single dose of salicylic acid (SA). According to Eq. (7.40) and the corresponding form of Eq. (7.12), a plot of SA in the body divided by the excretion rate of the metabolite (assuming that excretion of SPG is rate limited by its formation) versus SA in the body should be linear with slope equal to $1/V'_m$ and an intercept equal to K'_m. If the formation of SPG followed first-order kinetics, the slope of the line would be equal to zero. (From Ref. 23.)

where X_m is the amount of drug in the body at the midpoint of the urine collection interval. Division of the numerator and denominator by the apparent volume of distribution V yields

$$\frac{\Delta M_u}{\Delta t} = \frac{V'_m C_m}{K_m + C_m} \tag{7.41}$$

where K_m is as defined previously and equals K'_m/V, and C_m is the plasma concentration of drug at the midpoint of the collection interval. Equation (7.41) can be readily linearized [see Eqs. (7.11) to (7.13)] to yield estimates of V'_m and K_m. This approach has been used to evaluate the Michaelis-Menten parameters for two metabolites of salicylate, salicyl phenolic glucuronide, and salicyluric acid [6], and is illustrated in Fig. 7.9. The major limitation of this method is the assumption that the urinary excretion rate of the metabolite is rate limited by its formation. This situation certainly does not hold for all drugs and the assumption must be verified.

CLEARANCE, HALF-LIFE, AND VOLUME OF DISTRIBUTION

As with linear kinetics, the total body clearance Cl_s of a drug can be defined for the nonlinear situation as being equal to the rate of drug elimination dX_E/dt divided by the plasma concentration of drug C:

$$Cl_s = \frac{dX_E/dt}{C} \tag{7.42}$$

The rate of elimination for a drug eliminated by only one capacity-limited process is given by

$$\frac{1}{V}\frac{dX_E}{dt} = \frac{V_m C}{K_m + C} \tag{7.43}$$

or

$$\frac{dX_E}{dt} = \frac{V_m VC}{K_m + C} \tag{7.44}$$

Division of both sides of (7.44) by C yields

$$\frac{dX_E/dt}{C} = \frac{V_m V}{K_m + C} \tag{7.45}$$

Substitution of $V_m V/(K_m + C)$ for $(dX_E/dt)/C$ in (7.42) gives the following concentration-dependent expression for clearance:

$$Cl_s = \frac{V_m V}{K_m + C} \tag{7.46}$$

At low plasma concentrations, where $K_m >> C$,

$$Cl_s = \frac{V_m}{K_m} V \tag{7.47}$$

whereas at high plasma concentrations, where $C >> K_m$,

$$Cl_s = \frac{V_m}{C} V \tag{7.48}$$

Therefore, clearance is independent of concentration at very low concentrations, but decreases with increasing concentration; that is, the higher the plasma concentration of a drug, the slower the drug will be cleared from the plasma. The influence of nonlinear clearance on a drug's half-life ($t_{1/2}$) can be readily illustrated by recognizing that

$$t_{1/2} = \frac{0.693V}{Cl_s} \tag{7.49}$$

Substituting the value of Cl_s given in (7.46) for Cl_s in (7.49) and canceling common terms yields

$$t_{1/2} = \frac{0.693(K_m + C)}{V_m} \tag{7.50}$$

It is readily apparent from this relationship that the half-life of a drug is independent of plasma concentration at low concentrations, whereas at high concentrations the half-life, or $t_{50\%}$, will increase with an increase in the plasma concentration of drug (see Fig. 7.6).

For the case where there are linear pathways of elimination in parallel with a nonlinear process, the rate of drug elimination is given by

$$\frac{1}{V}\frac{dX_E}{dt} = \frac{V_m C}{K_m + C} + K'C \tag{7.51}$$

Multiplication of both sides of (7.51) by V/C yields

$$\frac{dX_E/dt}{C} = \frac{V_m V}{K_m + C} + K'V \tag{7.52}$$

Therefore, clearance is given by the relationship

$$Cl_s = \frac{V_m V}{K_m + C} + K'V \tag{7.53}$$

Substitution of this value for Cl_s in (7.49) gives the following relationship between half-life and plasma concentration:

$$t_{1/2} = \frac{0.693}{[V_m/(K_m + C)] + K'} \tag{7.54}$$

At low drug concentrations both clearance and half-life are independent of concentration. As the concentration increases clearance decreases; at very high concentrations, clearance attains a limiting value of K'V. On the other hand, the half-life increases with concentration, ultimately reaching a limiting value of 0.693/K' (see Fig. 7.6).

A method for estimating the apparent volume of distribution of a drug eliminated *only* by Michaelis-Menten kinetics has been described [18]. This method was applied to ethanol in the cat and yielded an average value of 635 ml/kg, which is equivalent to total body water in this species.

DRUG CONCENTRATION AT STEADY STATE

The significance of a decrease in clearance with increasing plasma concentration of drug can be readily appreciated by considering chronic drug administration. The steady-state concentration C_{ss} of a drug is given by (see Chap. 3)

$$C_{ss} = \frac{DR}{Cl_s} \tag{7.55}$$

DR is the dose rate and equals infusion rate in the case of intravenous infusion and F dose/τ in the case of multiple oral dosing, where F is the systemic availability of the drug and τ is the dosing interval. As is illustrated in Fig. 7.10 and by Eq. (7.55), when Cl_s is given by (7.46) or (7.53), an increase in dose produces more than a proportional increase in steady-state concentration of a drug. The greater the contribution of the capacity-limited process to the overall elimination, the more dramatic is the increase in steady-state levels with increasing dose. This can be exemplified by salicylate where a twofold increase in the dose from 0.5 to 1.0 g every 8 h can result in a more than sixfold increase in steady-state salicylate body levels (Fig. 7.11). In addition, since half-life increases with concentration [see (7.50) and (7.54)], the time required to reach steady state will also increase with an increase in dose size. In the salicylate example cited above, the time to reach steady-state increased from 2 to 7 days.

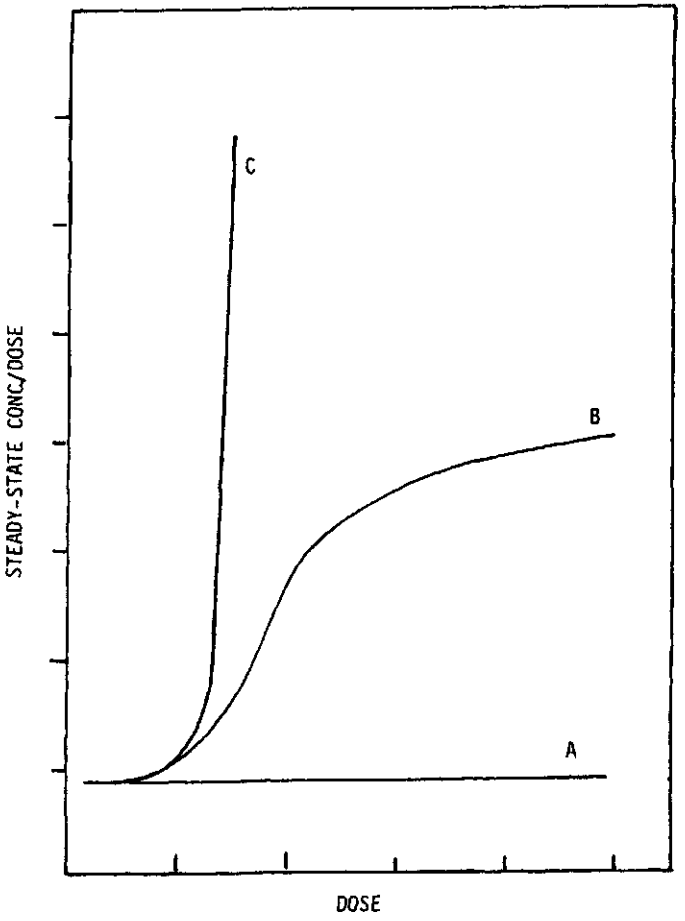


Fig. 7.10 Relationship between dose-adjusted steady-state concentrations and administered dose for drugs eliminated by first-order kinetics (A), parallel first-order and Michaelis-Menten kinetics (B), and Michaelis-Menten kinetics (C). (Data from Ref. 19.)

TIME TO STEADY STATE

The dependence in nonlinear systems of the time to reach steady state or some fraction thereof on the rate of drug administration can be demonstrated mathematically. If a drug is administered at a constant rate k_0 and is eliminated by a single pathway that is capacity limited, the following differential equation can be written:

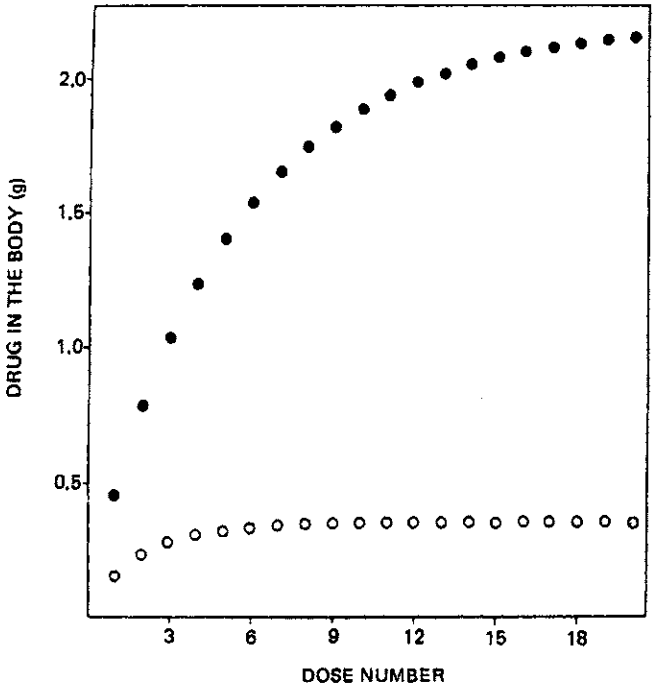


Fig. 7.11 Accumulation of salicylic acid in the body as a function of dose number when either 0.5 (○) or 1.0 (●) g doses are given every 8 h. (From Ref. 20, reprinted with permission.)

$$\frac{dC}{dt} = \frac{k_0}{V} - \frac{V_m C}{K_m + C} \tag{7.56}$$

Expansion of (7.56) and collection of common terms yields

$$\frac{dC}{dt} = \frac{(k_0 K_m/V) + [(k_0/V) - V_m]C}{K_m + C} \tag{7.57}$$

This equation is of the general form

$$\frac{dC}{dt} = \frac{x + yC}{z + C} \tag{7.58}$$

which can be rearranged to give

$$\frac{z}{x + yC}\,dC + \frac{C}{x + yC}\,dC = dt \tag{7.59}$$

The integral of (7.59) is [15]

$$\frac{z}{y} \ln (x + yC) + \frac{C}{y} - \frac{x}{y^2} \ln (x + yC) = t + i \tag{7.60}$$

which can be simplified to

$$\frac{C}{y} + \frac{zy - x}{y^2} \ln (x + yC) = t + i \tag{7.61}$$

At $t = 0$, $C = 0$ and

$$i = \frac{zy - x}{y^2} \ln x \tag{7.62}$$

Substitution for i in (7.61) and rearrangement yields

$$t = \frac{C}{y} + \frac{zy - x}{y^2} \ln \left(1 + \frac{y}{x} C\right) \tag{7.63}$$

Recognizing that $x = k_0K_m/V$, $y = (k_0/V) - V_m$ and $z = K_m$ [(7.57) and (7.58)],

$$t = \frac{C}{(k_0/V) - V_m} + \frac{K_m[(k_0/V) - V_m] - k_0K_m/V}{[(K_0/V) - V_m]^2}$$
$$\ln \left[1 + \frac{(k_0/V) - V_m}{k_0K_m/V} C\right] \tag{7.64}$$

Simplification gives the following:

$$t = \frac{C}{(k_0/V) - V_m} - \frac{K_mV_m}{[(k_0/V) - V_m]^2} \ln \left(1 + \frac{k_0 - VV_m}{k_0K_m} C\right) \tag{7.65}$$

The steady-state concentration C_{ss} of a drug that obeys the model above is given by

$$C_{ss} = \frac{k_0}{Cl_s} = \frac{k_0(K_m + C_{ss})}{VV_m} \tag{7.66}$$

where Cl_s at steady state is given by (7.46). Solving (7.66) for C_{ss} yields

$$-C_{ss} = \frac{k_0K_m}{k_0 - VV_m} \tag{7.67}$$

Substituting $-1/C_{ss}$ for $(k_0 - VV_m)/k_0K_m$ in (7.65) and setting C/C_{ss} equal to f_{ss}, the fraction of the steady-state concentration, and

C equal to $f_{ss}C_{ss}$ gives the following expression for the time to reach a given fraction of steady state:

$$t = \frac{f_{ss}C_{ss}}{(k_0/V) - V_m} - \frac{K_m V_m}{[(k_0/V) - V_m]^2} \ln (1 - f_{ss}) \tag{7.68}$$

The dependence of time to steady state on the rate of administration is clearly demonstrated. A relationship of the same form as (7.68) has been obtained from plasma concentration versus time data using numerical integration [21]. At a low administration rate (k_0 and $C_{ss} \to 0$), (7.68) reduces to

$$t = -\frac{1}{V_m/K_m} \ln (1 - f_{ss}) \tag{7.69}$$

and hence time to steady state is independent of the rate of administration, while at a high infusion rate (k_0 and $C_{ss} \to \infty$)

$$t = \frac{f_{ss}C_{ss}}{k_0/V} \tag{7.70}$$

and the time to steady state is independent of drug elimination.

For the case where there is one or more first-order processes of elimination in parallel with a saturable process, the expression for time to reach a given fraction of steady state becomes relatively complex (see Appendix G). This expression is

$$t = \frac{1}{\sqrt{-q}} \left(K_m + \frac{b}{2K'}\right) \ln \frac{-2K'C + b - \sqrt{-q}}{b - \sqrt{-q}} \frac{1}{1 - f_{ss}} - \frac{1}{2K'} \ln \frac{a + bC - K'C^2}{a} \tag{7.71}$$

where $a = k_0K_m/V$, $b = (k_0/V) - K'K_m - Vm$, and $-q = b^2 + 4k_0K_mK'/V$. When the rate of administration (i.e., k_0) is small, (7.71) simplifies to (see Appendix G)

$$t = \frac{-1}{K' + (V_m/K_m)} \ln (1 - f_{ss}) \tag{7.72}$$

This relationship is identical in form to (7.69), illustrating that the time to achieve a certain fraction of steady state is dependent only on the rate constant or half-life of elimination under linear conditions. However, when the rate of administration becomes large, (7.71) reduces to (see Appendix G)

$$t = -\frac{1}{K'} \ln (1 - f_{ss}) \tag{7.73}$$

Therefore, at high administration rates the time to steady state is dependent on the elimination rate constant for the first-order process.

AREA UNDER THE CURVE AND BIOAVAILABILITY

In theory, the area under the blood or plasma level versus time curve is proportional to the dose administered for drugs eliminated by first-order kinetics. However, for drugs that are eliminated by capacity-limited processes, area is not proportional to the administered dose. Rather, one finds that the area increases more than proportionally with an increase in dose. The total area under the drug level versus time curve ($\int_0^\infty C\ dt$) after the intravenous injection of a drug that is eliminated by a single capacity-limited process can be calculated for a one-compartment system as follows. Inversion of (7.1) and rearrangement of the resulting expression gives

$$C\ dt = -\frac{K_m + C}{V_m}\ dC \tag{7.74}$$

The expansion of (7.74) followed by integration over the limits $C = C_0$ at $t = 0$ and $C = 0$ at $t = \infty$ yields

$$\int_0^\infty C\ dt = -\int_{C_0}^{0} \frac{K_m}{V_m}\ dC - \int_{C_0}^{0} \frac{C}{V_m}\ dC \tag{7.75}$$

It follows that

$$\int_0^\infty C\ dt = -\frac{K_m}{V_m} C \Big|_{C_0}^{0} - \frac{C^2}{2V_m}\Big|_{C_0}^{0} \tag{7.76}$$

which when solved becomes

$$\int_0^\infty C\ dt = \frac{K_m}{V_m} C_0 + \frac{C_0^2}{2V_m} = \frac{C_0}{V_m}\left(K_m + \frac{C_0}{2}\right) \tag{7.77}$$

At sufficiently low doses such that $K_m >> C_0/2$, (7.77) reduces to

$$\int_0^\infty C\ dt = \frac{K_m}{V_m} C_0 = \frac{K_m X_0}{V_m V} \tag{7.78}$$

where $C_0 = X_0/V$ and V is the apparent volume of distribution. Under these conditions the area under the curve is simply proportional to the dose X_0. Inspection of (7.77) readily indicates for the nonlinear situation that as the dose is increased, the area shows a stronger dependence on the dose. At sufficiently high dosage levels where $C_0/2 >> K_m$, (7.77) reduces to

$$\int_0^\infty C\,dt = \frac{C_0^2}{2V_m} = \frac{X_0^2}{2V^2V_m} \tag{7.79}$$

which indicates that under these conditions the area is proportional to the square of the dose and a relatively modest increase in the dose may produce a dramatic increase in the total area under the drug level in the plasma versus time curve.

The area under the curve after administration of a fixed dose of a drug showing capacity-limited elimination may also vary with the rate of absorption. The more rapidly a given dose is absorbed, the more closely will the area approach that calculated by (7.77). In other words, the area calculated from (7.77) for a given dose is a maximum since it assumes that absorption is instantaneous. If absorption is sufficiently slow, the area will approach the minimum given by (7.78). Figure 7.12 illustrates the effect of dose and absorption rate on the area under the plasma concentration-time curve.

A nonlinear change in area with dose becomes important when attempting to assess the bioavailability of a drug, since this parameter is generally determined by comparing the area under the curve resulting from the administration of some test dosage form to the area under the curve from the administration of a standard. Bioavailability can be estimated for drugs eliminated by capacity-limited processes in the following manner [17]. Integration of the term $-dC/dt$ yields

$$\int_0^\infty -\frac{dC}{dt}dt = \int_0^\infty -dC = -C\,\Big|_0^\infty = C_0 \tag{7.80}$$

where C_0 is plasma concentration at time zero following intravenous drug administration. For a one-compartment system, C_0 equals the intravenous dose X_0 divided by the apparent volume of distribution V. Therefore,

$$\int_0^\infty -\frac{dC}{dt}\,dt = C_0 = \frac{X_0}{V} \tag{7.81}$$

From (7.81) it follows that a plot of $\int_0^\infty (-dC/dt)\,dt$ versus C_0 or X_0/V will be linear and pass through the origin regardless of whether or not the model is linear. The value of C_0 or X_0/V can be determined by numerical differentiation of intravenous plasma concentration versus time data, and measurement of the area under the curve resulting from a plot of $-dC/dt$ versus time.

After oral administration the rate of drug elimination from the body dX_E/dt, is given by

$$\frac{1}{V}\frac{dX_E}{dt} = K'C + \frac{V_m C}{K_m + C} \tag{7.82}$$

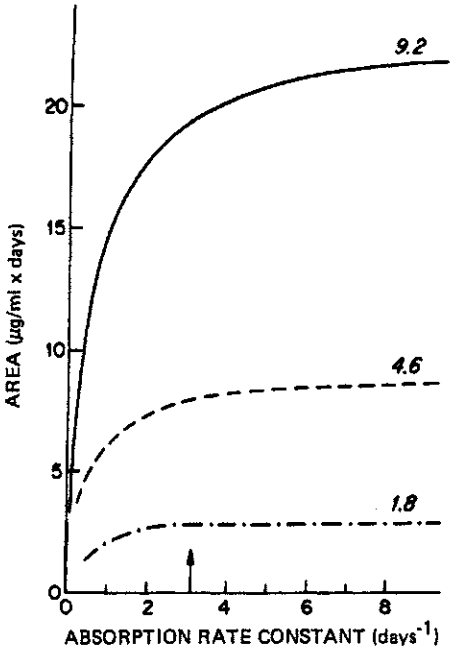


Fig. 7.12 Effect of absorption rate and dose on the area under the drug concentration in serum versus time curve after single doses of phenytoin. The curves reflect doses of 1.8, 4.6, and 9.2 mg/kg. The arrow marks the approximate absorption rate constant in a typical patient with the dosage form studied. (From Ref. 22, © 1976 Plenum Publishing Corp.)

where X_E is the amount eliminated to time t. If the amount ultimately eliminated is equal to the amount absorbed [i.e., $(X_E)_\infty = FX_0$, where F is the fraction of the orally administered dose absorbed], then

$$\frac{1}{V}\int_0^\infty \frac{dX_E}{dt}\,dt = \int_0^\infty \left(K'C + \frac{V_m C}{K_m + C}\right) dt = \frac{FX_0}{V} \tag{7.83}$$

since $\int_0^\infty (dX_E/dt)\,dt$ equals $(X_E)_\infty$. The bioavailability or fraction absorbed of an orally administered dose can be determined by dividing Eq. (7.83) by Eq. (7.81). This yields

$$\frac{FX_0/V}{X_0/V} = \frac{[(1/V)\int_0^\infty (dX_E/dt)]_{oral}}{[\int_0^\infty - (dC/dt)dt]_{i.v.}} \tag{7.84}$$

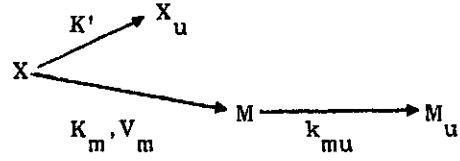
If equal doses are administered intravenously and orally, and it is assumed that volume of distribution remains constant,

$$F = \frac{[(1/V)\int_0^\infty (dX_E/dt)dt]_{oral}}{[\int_0^\infty -(dC/dt)dt]_{i.v.}} \tag{7.85}$$

Therefore, the absolute bioavailability of an oral dosage form can be determined by measuring the area under a $-dC/dt$ versus time plot using intravenous data, and generating values of $(dX_E/dt)/V$ from oral plasma concentration versus time data using (7.82). The latter determination requires K', V_m, and K_m, which can be obtained from the intravenous data by methods discussed previously in this chapter. Once the $(dX_E/dt)/V$ data are calculated, the area under a plot of $(dX_E/dt)/V$ versus time provides an estimate of the numerator of (7.85). This method has been applied to the determination of phenytoin bioavailability. It was demonstrated that the use of the nonlinear approach yielded a bioavailability estimate of 0.98 as compared to 0.87 when linear kinetics were assumed [22].

COMPOSITION OF URINARY EXCRETION PRODUCTS

For a drug eliminated from the body by multiple pathways, one of which is nonlinear, the composition of urinary excretion products will vary with dose. We illustrate this with the following scheme:



It is assumed that there are two pathways of elimination for the parent drug, a capacity-limited pathway for the formation of metabolite M and a first-order pathway for the urinary excretion of unchanged drug. X_u and M_u are the cumulative amounts of unchanged drug and metabolite in the urine at time t, and K' and k_{mu} are the first-order rate constants for urinary excretion of unchanged drug and metabolite, respectively. X is the amount of unchanged drug in the body at time t, and K_m and V_m are the Michaelis-Menten parameters for the capacity-limited formation of M. The rate of appearance of unchanged drug in the urine is given by the differential equation

$$\frac{dX_u}{dt} = K'X \tag{7.86}$$

or

$$\frac{dX_u}{dt} = K'VC \tag{7.87}$$

since the amount of drug in the body X equals the product of the volume of distribution and the plasma concentration. Integration of Eq. (7.87) from time zero to infinity yields

$$X_u^{\infty} = K'V \int_0^{\infty} C \, dt \tag{7.88}$$

where X_u^{∞} is the total amount of unchanged drug eliminated in the urine following the administration of a given dose, and $\int_0^{\infty} C \, dt$ is the area under the resulting plasma concentration versus time curve.

Equation (7.18) is the differential equation for plasma concentration for the model above. Factoring out C and expanding (7.18) gives

$$\frac{dC}{dt} = -C \frac{K'K_m + V_m + K'C}{K_m + C} \tag{7.89}$$

which when inverted and rearranged becomes

$$C \, dt = -\frac{K_m + C}{K'K_m + V_m + K'C} \, dC \tag{7.90}$$

By expanding (7.90) and taking the integral over the limits $C = C_0$ at $t = 0$ and $C = 0$ at $t = \infty$, the following is obtained:

$$\int_0^{\infty} C \, dt = \int_{C_0}^{0} \frac{K_m}{K'K_m + V_m + K'C} \, dC - \int_{C_0}^{0} \frac{C}{K'K_m + V_m + K'C} \, dC \tag{7.91}$$

The two terms to be integrated are of the general forms $dx/(a + bx)$ and $x \, dx/(a + bx)$, respectively, the integrals of which are $(1/b) \ln (a + bx)$ and $(x/b) - (a/b^2) \ln (a + bx)$ [15]. Therefore, (7.91) when integrated becomes

$$\int_0^{\infty} C \, dt = -\frac{K_m}{K'} \ln (K'K_m + V_m + K'C) \Big|_{C_0}^{0} - \frac{C}{K'} \Big|_{C_0}^{0} + \frac{K'K_m + V_m}{(K')^2} \ln (K'K_m + V_m + K'C) \Big|_{C_0}^{0} \tag{7.92}$$

Collecting common terms and simplifying provides

$$\int_0^{\infty} C \, dt = -\frac{C}{K'} \Big|_{C_0}^{0} + \frac{V_m}{(K')^2} \ln (K'K_m + V_m + K'C) \Big|_{C_0}^{0} \tag{7.93}$$

Solving (7.93) gives the following expression for the area under the curve:

$$\int_0^\infty C\,dt = \frac{C_0}{K'} - \frac{V_m}{(K')^2} \ln\left(\frac{K'C_0}{K'K_m + V_m} + 1\right) \tag{7.94}$$

By substituting this value of $\int_0^\infty C\,dt$ for $\int_0^\infty C\,dt$ in (7.88), the following expression for X_u^∞ is obtained:

$$X_u^\infty = C_0V - \frac{VV_m}{K'} \ln\left(\frac{K'C_0}{K'K_m + V_m} + 1\right) \tag{7.95}$$

At very low plasma concentrations the natural log term becomes approximately equal to $K'C_0/(K'K_m + V_m)$ since for very small numbers $\ln(1 + x)$ becomes approximately equal to x [15]. Therefore, at low concentrations, (7.95) becomes

$$X_u^\infty = C_0V - \frac{VV_m}{K'} \frac{K'C_0}{K'K_m + V_m} = C_0V - \frac{C_0VV_m}{K'K_m + V_m} = C_0V \frac{K'K_m}{K'K_m + V_m} \tag{7.96}$$

Recognizing that C_0V equals the dose X_0 and dividing the numerator and denominator by K_m yields

$$X_u^\infty = X_0 \frac{K'}{K' + V_m/K_m} \tag{7.97}$$

This illustrates that at low doses the amount of unchanged drug in the urine is directly proportional to the administered dose. As the dose is increased and the capacity of the enzyme system becomes limited, the amount of unchanged drug appearing in the urine will increase more than proportionally to the increase in dose as illustrated by (7.95).

According to the scheme above, at time infinity

$$X_u^\infty + M_u^\infty = X_0 \tag{7.98}$$

where M_u^∞ is the total amount of metabolite in the urine at time infinity. Solving (7.98) for M_u^∞ and substituting the value of X_u^∞ in (7.95) yields

$$M_u^\infty = X_0 - C_0V + \frac{VV_m}{K'} \ln\left(\frac{K'C_0}{K'K_m + V_m} + 1\right) = \frac{VV_m}{K'} \ln\left(\frac{K'C_0}{K'K_m + V_m} + 1\right) \tag{7.99}$$

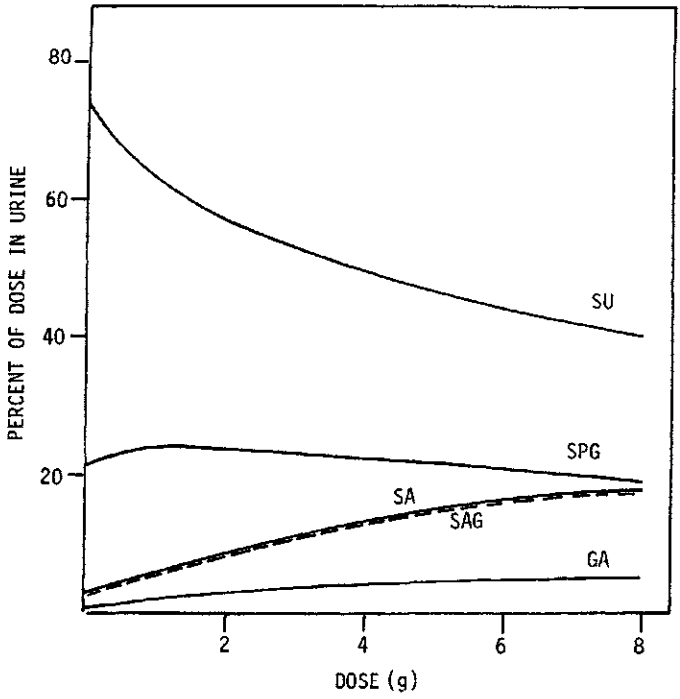


Fig. 7.13 Effect of dose on metabolic fate of salicylic acid in humans. The curves are based on urinary excretion data from four healthy subjects. SU is salicyluric acid, SPG is salicyl phenolic glucuronide, SA is salicylic acid, SAG is salicyl acyl glucuronide (dashed line), and GA is gentisic acid. (Data from Ref. 23.)

This equation indicates that M_u^∞ will increase less than proportionally with an increase in dose. At low doses (7.99) reduces to

$$M_u^\infty = \frac{VV_m}{K'} \frac{K'C_0}{K'K_m + V_m} = \frac{C_0VV_m}{K'K_m + V_m} \tag{7.100}$$

Substituting X_0 for C_0V and dividing the numerator and denominator by K_m gives

$$M_u^\infty = X_0 \frac{V_m/K_m}{K' + V_m/K_m} \tag{7.101}$$

As is evident from (7.101), at low doses M_u^∞ is directly proportional to dose.

The influence of dose on excretion patterns is readily demonstrated with salicylate. As can be seen in Fig. 7.13, the fraction of the dose

eliminated as salicyluric acid, SU, a metabolite formed by a capacity-limited process, decreases with dose. For those excretion products formed or eliminated by first-order kinetics, the fraction of the dose eliminated as such increases with dose (see SA, SAG, and GA). The enzyme system responsible for the formation of the phenolic glucuronide is capacity limited but has a higher capacity than the system responsible for the formation of salicyluric acid. Consequently, the fraction eliminated as this metabolite initially increases with dose, and then decreases with dose as this enzyme system becomes saturated.

The composition of excretion products will also be dependent on the rate of drug absorption when the drug is subject to capacity-limited metabolism. The more rapid the absorption, the higher the drug level in the body and the lower the fraction of the dose converted to the metabolite formed by capacity-limited metabolism. This phenomenon has been demonstrated in humans with p-aminobenzoic acid, which is eliminated by capacity-limited acetylation as well as excreted unchanged [24]. When 55 μmoles/kg was given at once, 56% of the dose was acetylated, whereas when 10 consecutive 5.5 μmoles/kg doses were administered at 30 min intervals, 91% of the dose was acetylated. After administration of 110 μmoles/kg to fasted subjects, which should result in rapid absorption, 51% of the dose was acetylated. However, when the same dose was administered to subjects after a high-fat meal, which is known to reduce gastric emptying and the absorption rate of many drugs, 90% of the dose was acetylated.

OTHER NONLINEAR ELIMINATION PROCESSES

Dose-dependent elimination kinetics may be due to effects other than a limited capacity of biotransformation or excretion processes. If a drug is partly reabsorbed from renal tubules by a capacity-limited process, the elimination (urinary excretion) of large doses proceeds more rapidly than the elimination of smaller doses. Capacity-limited reabsorption has been demonstrated for several compounds, including riboflavin [25], bethanidine [26], cephapirin [27], and cephaloridine [27]. There is evidence to suggest that some drug metabolites can inhibit their own metabolism [28,29]. This process of product inhibition can also cause dose-dependent effects, with large doses being relatively more slowly eliminated than small doses [30]. However, whereas the rate of decline of drug concentrations in the postdistributive phase at any given concentration of drug in the body will be independent of dose in the case of simple Michaelis-Menten kinetics [see (7.1)], this rate will tend to decrease with increasing dose in the case of product inhibition. Moreover, drug elimination may appear to be first order but with half-lives increasing with increasing dose provided that the initial drug levels (i.e., the intravenous doses) are lower than K_m and elimination of the inhibiting metabolite is relatively slow (see Fig. 7.14). These obser-

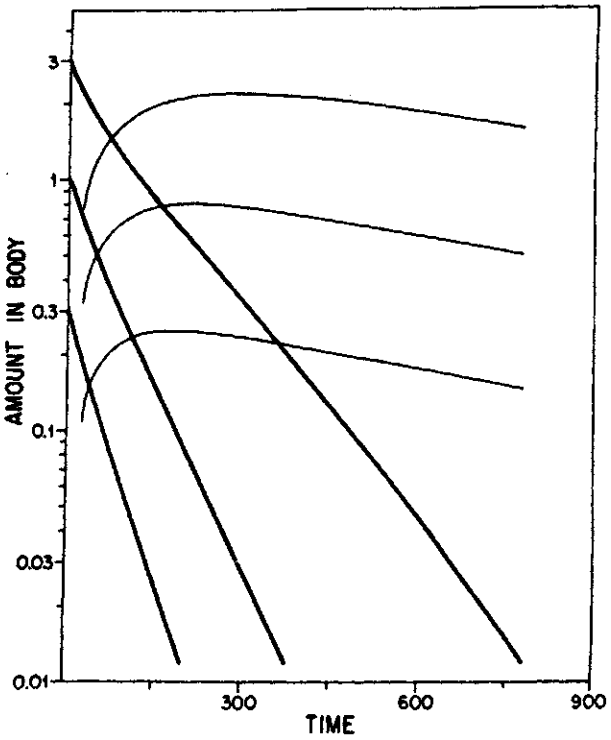


Fig. 7.14 Effect of competitive inhibition by a metabolite (light lines) on the time course of parent drug (heavy lines) after intravenous administration of different doses of the drug. Although the semilogarithmic plots of amount of drug in the body are apparently linear, the half-life increases with dose. (From Ref. 31, © 1973 Plenum Publishing Corp.)

vations can be explained by the following relationship, which describes the rate of change in plasma concentrations for a drug with one pathway of elimination that is subject to competitive product inhibition [13]:

$$-\frac{dC}{dt} = \frac{V_m C}{K_m(1 + C_m/K_p) + C} \qquad (7.102)$$

where C_m is the concentration of inhibiting metabolite and K_p is the equilibrium constant for the enzyme-metabolite (product) complex. Dose dependence with similar characteristics has been observed in humans with dicumarol [32] (see Fig. 7.15) and in dogs with phenytoin [33].

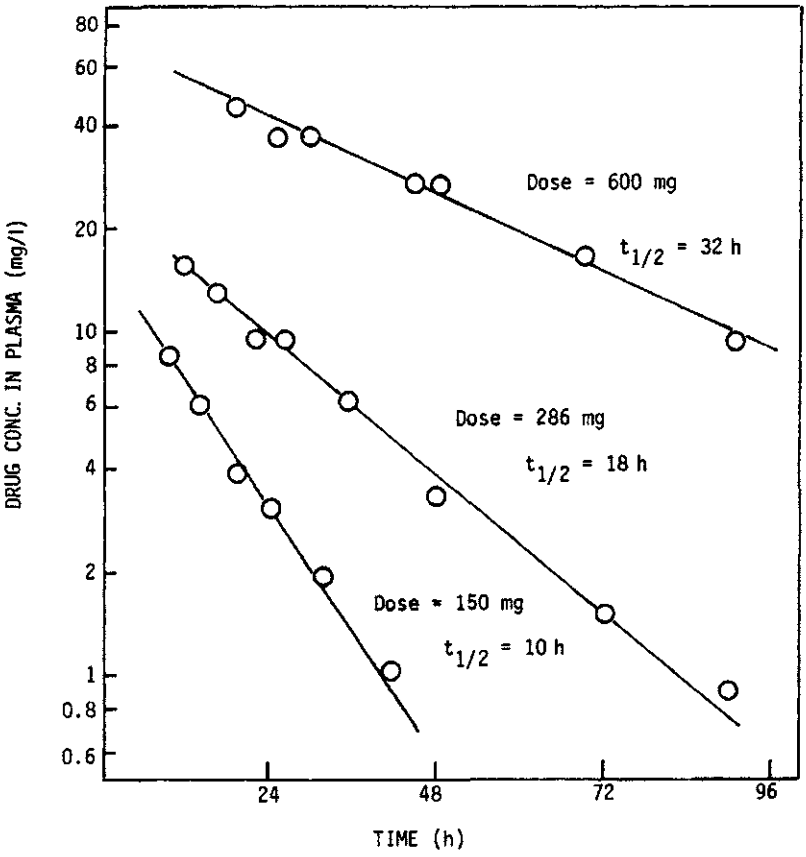


Fig. 7.15 Dicumarol concentration in plasma after intravenous administration of different doses. (Data from Ref. 32.)

ENZYME INDUCTION

Another type of nonlinear kinetics is seen when a drug induces its own metabolism. It has been suggested that enzyme induction is a result of new protein synthesis and not a change in substrate affinity [34]. Based on this premise, a model to describe the change in enzyme concentration following induction has been described by Berlin and Schimke [35]. Prior to induction the rate of change of enzyme levels, dE/dt, is a function of the rate of synthesis and rate of degradation of the enzyme; that is,

$$\frac{dE}{dt} = S - kE \tag{7.103}$$

where S is the rate of enzyme synthesis and is assumed to be zero order and k is the first-order rate constant for enzyme degradation. Assuming that a steady state for the enzyme exists prior to induction (i.e., $dE/dt = 0$), it follows that

$$E = \frac{S}{k} \tag{7.104}$$

Following induction, a new steady-state enzyme level, E', will be determined by the new ratio S'/k'; that is,

$$E' = \frac{S'}{k'} \tag{7.105}$$

The rate at which E approaches E' can be given by the differential equation

$$\frac{dE}{dt} = S' - k'E \tag{7.106}$$

Rearrangement of (7.106) yields

$$\frac{dE}{S' - k'E} = dt \tag{7.107}$$

which when integrated becomes

$$-\frac{1}{k'} \ln (S' - k'E_t) = t + i \tag{7.108}$$

where E_t is the concentration of enzyme at some time t after the start of administration of the drug. At $t = 0$, $E_t = E_0$, the enzyme level prior to induction, and therefore

$$i = -\frac{1}{k'} \ln (S' - k'E_0) \tag{7.109}$$

Substitution for i in (7.108) according to (7.109) and rearrangement gives

$$\ln \frac{S' - k'E_t}{S' - k'E_0} = -k't \tag{7.110}$$

which in exponential terms becomes

$$\frac{S' - k'E_t}{S' - k'E_0} = e^{-k't} \tag{7.111}$$

Solving (7.111) for E_t yields

$$E_t = \frac{S'}{k'} - \frac{S' - k'E_0}{k'} e^{-k't} \tag{7.112}$$

Substitution of S/k for E_0 according to (7.104) and further simplification produces the following expression for E_t:

$$E_t = \frac{S'}{k'} - \left(\frac{S'}{k'} - \frac{S}{k}\right) e^{-k't} \tag{7.113}$$

Therefore, the enzyme level during induction is dependent on the preinduction and induced steady-state enzyme concentrations, S/k and S'/k', respectively, and the first-order rate constant for enzyme degradation, k'.

An expression similar to (7.113) can be obtained to describe the change in maximum velocity V_{m_t} during induction. V_m is equal to k_2E [see Appendix G, Eq. (G.8)] prior to induction, while at steady state after induction $V'_m = k_2E'$, where k_2 is the rate constant for the formation of metabolite. Substitution of S/k for E and S'/k' for E' according to (7.104) and (7.105), respectively, yields the expressions

$$\frac{S}{k} = \frac{V_m}{k_2} \tag{7.114}$$

and

$$\frac{S'}{k'} = \frac{V'_m}{k_2} \tag{7.115}$$

Further, substitution for S/k and S'/k', according to (7.114) and (7.115), as well as substitution of V_{m_t}/k_2 for E_t in (7.113) and cancelation of common terms yields

$$V_{m_t} = V'_m - (V'_m - V_m)e^{-k't} \tag{7.116}$$

The time course of the change in the systemic clearance Cl_{s_t} of a drug following self-induction can be given by a similar expression,

$$Cl_{s_t} = Cl'_s - (Cl'_s - Cl_s)e^{-k't} \tag{7.117}$$

where Cl_s is the preinduction clearance and Cl'_s is the clearance at steady-state postinduction. Equation (7.117) can be obtained from (7.116) by recognizing that clearance equals the sum of the clearance of the inducible Cl_{s_i} and noninducible Cl_{s_n} pathways, and that

$$Cl_{s_i} = Vk_i = V\frac{V_m}{K_m} \tag{7.118}$$

where k_i is the first-order rate constant for elimination by the inducible pathway.

Of interest is the plasma concentration-time course of a drug that is subject to self-induction. In a one-compartment system where a drug is administered at a constant rate DR and is eliminated by first-order processes,

$$C = \frac{DR}{Cl_s}\left[1 - e^{-(Cl_s/V)t}\right] \qquad (7.119)$$

where Cl_s and V are as defined previously. Once self-induction begins, Cl_s will become time dependent and will be given by (7.117). Therefore, substitution of Cl_{s_t}, according to (7.117), for Cl_s in (7.119) will yield an expression that describes the plasma concentration as a function of time for a drug that is subject to self-induction. If there is a time delay between drug administration and the beginning of the self-induction, t in (7.117) should be replaced by $t - t_0$, where t_0 is the time at which induction began. The kinetic properties of carbamazepine appear to behave in a nonlinear manner as a result of self-induction (see Fig. 7.16) [36].

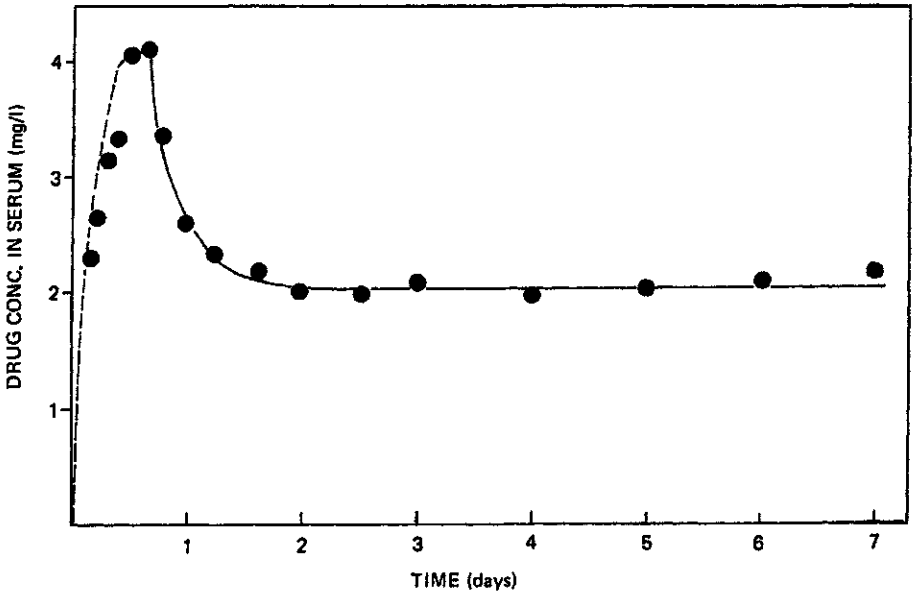


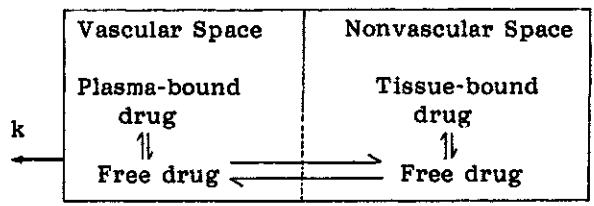
Fig. 7.16 Carbamazepine concentration in serum during continuous constant rate intravenous infusion of the drug for 7 days to a monkey. The data suggest pronounced autoinduction of carbamazepine metabolism. The continuous line corresponds to the following equation: $C = 2.04 + 2.06 \exp[-0.693/5.8(t - t_0)]$, where $t_0 = 16$ h. (Data from Ref. 36.)

Enzyme induction has been cited as an example of time-dependent rather than dose-dependent or concentration-dependent pharmacokinetics. The reason for this is that the changes in clearance one observes are not obviously related to drug concentration or dose but may be described as a function of time [see Eq. (7.117)]. Levy [37], in a comprehensive discussion of time-dependent pharmacokinetics, has noted the following: "A major distinguishing feature between dose and time dependency is that the latter involves an actual physiological or biochemical change in the organ(s) of the body associated with the drug disposition parameters in question. For example, in time dependence of the auto- or heteroinduction type, the increase in drug intrinsic clearance results from an increase in amount of enzyme (in protein synthesis). However, in a typical Michaelis-Menten dose-dependency, drug clearance changes with concentration and such a system should not be considered time-dependent simply because the values of pharmacokinetic parameters also change with time." Other examples of time-dependent pharmacokinetics are circadian rhythms in drug absorption, distribution, and elimination.

NONLINEAR BINDING

In discussions of nonlinear pharmacokinetics, capacity-limited elimination generally receives greatest attention because it is the most common and best understood. Although it is recognized that drugs are reversibly bound to proteins in the vascular space and to proteins and other materials in the "tissues," it is generally assumed that the fraction bound is essentially constant and independent of the drug concentration at the site of binding. However, it is obvious that there is a finite amount of each tissue which can bind a given drug and that the amount of drug which can be taken up per gram of given tissue will be related to the number of available binding sites and to some type of affinity constant. Accordingly, at sufficiently high concentrations of drug, one may find that the fraction bound decreases with increasing concentration. This will result in an alteration in the kinetics of a drug.

The following model will serve as a basis for considering the effect of nonlinear vascular protein and tissue binding on drug plasma concentration versus time profiles, and on the resultant pharmacokinetic parameters derived from such profiles:



The parameter k is the first-order elimination rate constant. In the vascular compartment, drug will interact with protein to form a drug-protein complex according to the scheme

$$C_f + P_f \underset{k_1}{\overset{k_2}{\rightleftharpoons}} C_b$$

where C_f and C_b are the molar concentrations of free and bound drug in the vascular space, respectively. C_b is equal to the concentration of occupied protein binding sites. P_f is the molar concentration of free protein binding sites, and the parameters k_2 and k_1 are rate constants. From the scheme it follows that

$$\frac{dC_f}{dt} = k_2 C_b - k_1 C_f P_f \tag{7.120}$$

Based on the steady-state assumption (i.e., $dC_f/dt = 0$),

$$\frac{k_2}{k_1} = \frac{C_f P_f}{C_b} \tag{7.121}$$

The total concentration of vascular protein binding sites, nP, where n is the number of binding sites per protein molecule and P is the molar concentration of protein, is given by

$$nP = P_f + C_b \tag{7.122}$$

Solving (7.122) for P_f, substituting this value for P_f in (7.121), and recognizing that k_2/k_1 is equal to the dissociation constant for the drug-protein complex, K_d, yields

$$K_d = \frac{C_f(nP - C_b)}{C_b} \tag{7.123}$$

which when solved for C_b becomes

$$C_b = \frac{C_f nP}{K_d + C_f} \tag{7.124}$$

The total concentration of drug in the vascular space, C_t, is equal to the sum of the concentrations of free and bound drug:

$$C_t = C_f + C_b \tag{7.125}$$

Substitution for C_b according to (7.124) gives

$$C_t = C_f + \frac{C_f nP}{K_d + C_f} \tag{7.126}$$

An expression for the total drug concentration in the tissues, C_t^T, which includes everything but the vascular space, can be obtained in an analogous manner. The resulting equation is given by

$$C_t^T = C_f + \frac{C_f A}{K_d^T + C_f} \tag{7.127}$$

where K_d^T is the dissociation constant for the drug tissue complex and A is a constant similar to nP. When the binding to vascular protein or tissue is linear, total drug concentrations in the vascular space and tissue are given by

$$C_t = \frac{C_f}{f_B} \tag{7.128}$$

and

$$C_t^T = \frac{C_f}{f_T} \tag{7.129}$$

respectively, where f_B is the fraction free in the vascular space and f_T is the fraction free in the tissues.

Expansion followed by differentiation of (7.126) and (7.127) and collection of common terms yields

$$\frac{dC_t}{dt} = \frac{(dC_f/dt)\{(K_d + C_f)(2C_f + K_d + nP) - [C_f^2 + (K_d + nP)C_f]\}}{(K_d + C_f)^2} \tag{7.130}$$

and

$$\frac{dC_t^T}{dt} = \frac{(dC_f/dt)\{(K_d^T + C_f)(2C_f + K_d^T + A) - [C_f^2 + (K_d^T + A)C_f]\}}{(K_d^T + C_f)^2} \tag{7.131}$$

These equations can be further simplified to give

$$\frac{dC_t}{dt} = \frac{(dC_f/dt)(C_f^2 + 2C_f K_d + nPK_d + K_d^2)}{(K_d + C_f)^2} \tag{7.132}$$

and

$$\frac{dC_t^T}{dt} = \frac{(dC_f/dt)[C_f^2 + 2C_fK_d^T + AK_d^T + (K_d^T)^2]}{(K_d^T + C_f)^2} \tag{7.133}$$

When there is linear binding, differentiation of (7.128) and (7.129) results in the following two equations:

$$\frac{dC_t}{dt} = \frac{dC_f/dt}{f_B} \tag{7.134}$$

and

$$\frac{dC_t^T}{dt} = \frac{dC_f/dt}{f_T} \tag{7.135}$$

respectively. When a dose D of a drug is given, the following mass balance can be written:

$$X_B + X_T + X_E = D \tag{7.136}$$

where X_B and X_T are the amounts of drug in the vascular space and tissue, respectively, and X_E is the amount of drug eliminated from the body by all routes of elimination. Differentiation of (7.136) yields

$$\frac{dX_B}{dt} + \frac{dX_T}{dt} + \frac{dX_E}{dt} = 0 \tag{7.137}$$

The rate of elimination, dX_E/dt, is given by

$$\frac{dX_E}{dt} = kV_BC_t \tag{7.138}$$

where V_B is intravascular volume. Recognizing that $X_B = V_BC_t$ and $X_T = V_TC_t^T$, where V_T is the tissue volume, (7.137) may be written as

$$V_B\frac{dC_t}{dt} + V_T\frac{dC_t^T}{dt} + \frac{dX_E}{dt} = 0 \tag{7.139}$$

where dX_E/dt is given by (7.138). To evaluate the influence of linear or nonlinear vascular protein and/or tissue binding on drug disposition, the appropriate expressions for dX_E/dt, dC_t/dt, and dC_t^T/dt as given by (7.138) and (7.132) to (7.135) can be substituted into (7.139). Numerical analysis of the resulting equation will provide insight into the influence of nonlinear binding to vascular protein and/or tissue protein on drug disposition [38].

The effect of nonlinear binding can be illustrated by the following relationships:

$$V = V_B + \frac{f_B}{f_T} V_T \tag{5.49}$$

and

$$Cl = Q \frac{f_B Cl_I'}{Q + f_B Cl_I'} \tag{8.27}$$

where V_B, V_T, f_B, and f_T are defined above, and V is the apparent volume of distribution. Cl and Cl_I' are clearance and intrinsic clearance of free drug from the blood, respectively, and Q is blood flow to the eliminating organ. The influence of nonlinear binding on the shape of a log plasma concentration versus time can be illustrated by recognizing that half-life ($t_{1/2}$) equals 0.693V/Cl [Eq. (2.217)], and that if half-life increases or decreases with time, a concave or convex curve will result. For drugs with a low intrinsic clearance (i.e., $Q >> f_B Cl_I'$), where nonlinear binding occurs in the vascular space, a decrease in volume of distribution and clearance should be observed as a function of time after an intravenous bolus dose because of the decrease in free fraction as drug concentration in the vascular space decreases. Under the conditions noted above, the log plasma concentration versus time curve may appear curved even when a one-compartment model with first-order elimination is extant. The effect of binding on clearance will tend to make the curves concave, whereas the effect of binding on volume of distribution will tend to make the curves convex (see Fig. 7.17). As linear tissue binding increases, there is a general tendency to straighten the concave log plasma concentration-time curves resulting from nonlinear protein binding in the vascular space. Nonlinear tissue binding with linear protein binding in the vascular space will result in no net change in clearance with time, but will result in an increase in volume of distribution with time. This becomes readily apparent by considering Eqs. (5.49) and (8.27). The consequence will be a concave log plasma concentration versus time curve even though a single compartment is extant.

Nonlinear protein binding in the vascular space or nonlinear tissue binding will have the same effect on volume of distribution of drugs with a high clearance as they do on drugs with a low clearance. However, changes in protein binding in the vascular space should have little if any effect on the clearance of highly cleared drugs (i.e., $f_B Cl_I' >> Q$), and the total area under a plasma concentration versus time curve should be a simple linear function of dose or amount absorbed. This lack of dependence of clearance on binding can be readily appreciated by considering (8.27). Therefore, the shape of log plasma concentra-

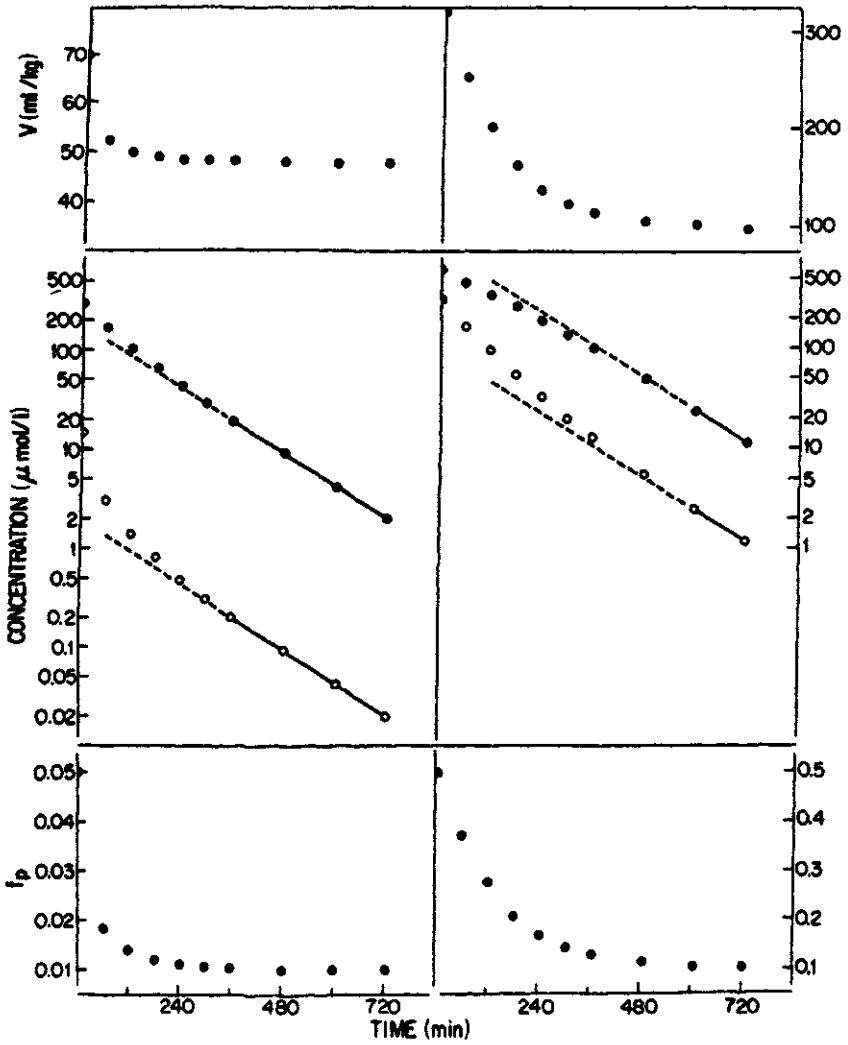


Fig. 7.17 Effect of concentration-dependent plasma protein binding (assuming no tissue binding) on the time course of free (O) and total (●) drug concentration in the plasma. Also shown are the instantaneous apparent volume of distribution V and the free fraction in the plasma f_p. In the panel on the left, the effect of plasma protein binding on clearance predominates and the total drug concentration in plasma curve is concave, whereas in the panel on the right, the effect of binding on volume of distribution predominates and the curve describing total drug concentration in plasma is convex. (From Ref. 38, © 1979 Plenum Publising Corp.)

tion versus time curves will appear convex since the effect of protein binding in the vascular space on volume of distribution will be the primary factor influencing this shape. Such curves may be interpreted incorrectly as indicating nonlinear or Michaelis-Menten drug elimination.

SOME PROBLEMS IN QUANTIFYING NONLINEAR PHARMACOKINETICS

Because of the possible effects of nonlinear binding on log plasma concentration versus time profiles, it is simplistic always to interpret log plasma concentration times curves on the basis of multicompartment pharmacokinetic models or to simply assume nonlinear elimination. Interpretation is complicated by the fact that tissue binding is difficult to characterize since tissue represents such an heterogeneous phase. Whether or not a multiexponential plasma concentration versus time curve is a consequence of the distribution characteristics of a drug or a result of nonlinear binding in the vascular or extravascular space can be evaluated by giving an intravenous bolus dose and an intravenous infusion of a drug such that drug concentrations immediately after the bolus dose and upon termination of the infusion are equal. If the drug does in fact confer multiexponential characteristics on the body as a result of its distribution properties, the distribution phase postinfusion will be less pronounced than that after the intravenous bolus dose. However, if the multiexponential characteristics are a result of nonlinear binding, the distributive phases postinfusion and postbolus will be equivalent (see Fig. 7.18) [39].

Although the equations developed in previous sections of this chapter have been based on a one-compartment system, the principles discussed apply regardless of the compartmental characteristics of the drug. However, in the case of capacity-limited elimination, errors do occur in the estimation of K_m and V_m if a one-compartment system is assumed when in fact a multicompartment system is more appropriate. This can be readily appreciated by considering that in a multicompartment system, the ratio V_m/K_m equals k_{10}, the elimination rate constant, not the smallest exponent (typically β). If data are incorrectly assumed to obey a one-compartment system, the estimate of V_m/K_m will approximate β, the terminal disposition rate constant, rather than approximating k_{10}.

As would be expected, V_m/K_m estimated assuming a one-compartment system will always be less than the value obtained when the data are analyzed according to the appropriate multicompartment system. In addition, the value of V_m obtained by one-compartment analysis will always be less than the V_m of a multicompartment system, while K_m may be overestimated or underestimated when multicompartment data are analyzed assuming a one-compartment system [40]. Therefore, V_m

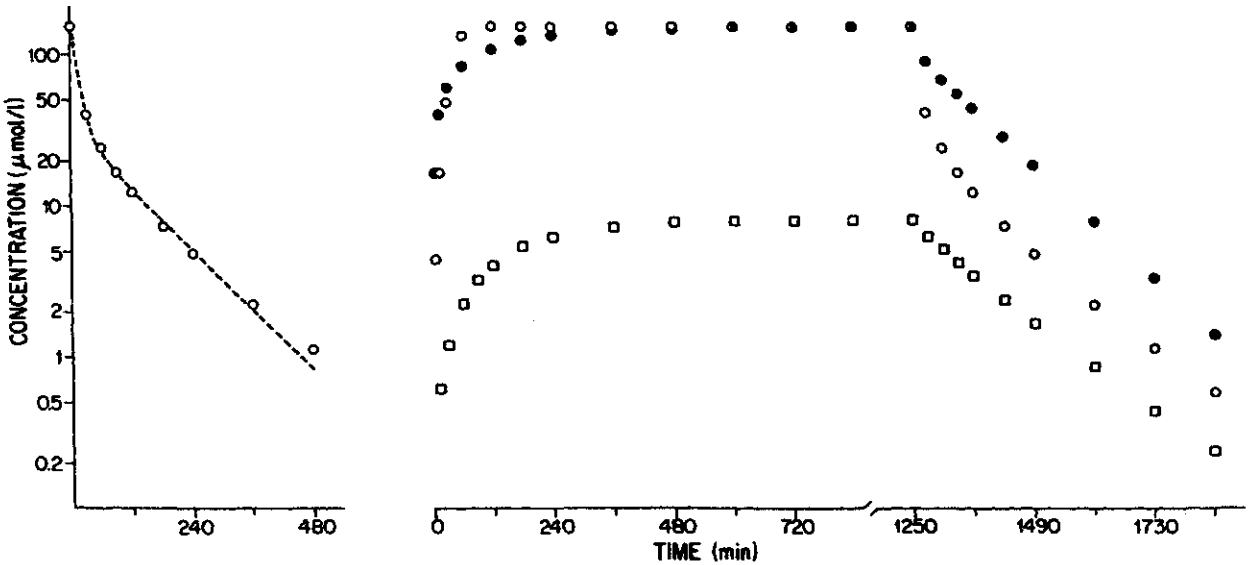


Fig. 7.18 Time course of drug concentration in plasma (○) following a single intravenous dose (panel on left), and during and after constant rate intravenous infusion (panel on right) of drug with nonlinear tissue binding in a one-compartment system. Drug concentrations after the bolus and upon cessation of the infusion are superimposable. Infusion at a lower rate yields proportionately lower steady-state concentrations (□), but the time required to reach steady state is longer than during the higher rate infusion. Drug concentrations in plasma (●), predicted by incorrectly assuming that the data after intravenous bolus administration could be described by a linear biexponential model, take longer to reach steady state and have a much less pronounced postinfusion distribution phase. (From Ref. 39, © 1979 Plenum Publishing Corp.)

and K_m values obtained assuming an incorrect model must be interpreted and used with caution.

Another problem is encountered when a drug is eliminated by more than one capacity-limited pathway. In linear models, first-order elimination rate constants for parallel pathways can be summed as a means of simplifying the model. It would be advantageous if data described by parallel Michaelis-Menten equations could be approximated over several orders of magnitude by a single Michaelis-Menten equation with constants V_m and K_m insensitive to large changes in dose. Approximation of data by a single Michaelis-Menten equation appears reasonable when values of K_m for parallel pathways are within a factor of 3 of each other [41]. The constants obtained, however, are generally not characteristic of any one enzyme system. When values of K_m are separated by a factor of 5 or more, data cannot be well represented over several orders of magnitude by a single Michaelis-Menten equation, and therefore, simplification of such a system is inappropriate. In this case V_m and K_m increase markedly with dose. To determine whether a system can be adequately described by a single Michaelis-Menten equation requires that the parameters V_m and K_m be relatively constant over the extremes of the dose range of interest.

A final point to consider is that some drugs exert dose-dependent effects on blood circulation, urine pH, and on other physiologic processes that may affect drug disposition. For example, it is well known that the elimination of certain drugs is influenced largely by the rate of hepatic blood flow. Some of these drugs may actually reduce hepatic blood flow either directly or indirectly via an effect on cardiac index. In such cases one may observe a decrease in the half-life and/or clearance of the drug with increasing dose.

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