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Relationship between Dose and Plateau Levels of Drugs Eliminated by Parallel First-Order and Capacity-Limited Kinetics

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Abstract □ Repetitive administration at constant time intervals of fixed doses of drugs which are eliminated by apparent first-order kinetics will usually result in the eventual attainment of a drug level plateau in the body. If a drug is eliminated solely by capacity-limited (Michaelis–Menten) kinetics in the therapeutic dose range, it will accumulate in the body without limit when the dose exceeds a certain amount. Drugs eliminated by parallel apparent first-order and capacity-limited kinetics will attain a drug level plateau but, unlike drugs eliminated only by first-order kinetics, the ratio of plateau level–dose is not independent of dose but increases with increasing dose. The rate of this increase is particularly high in a certain dose range which, therefore, represents a "danger zone" in which an increase in dose causes a considerably more than proportional increase in plateau level. This may be the cause of some adverse and toxic effects of certain drugs, such as the salicylates, during chronic therapy.

Keyphrases □ Pharmacokinetics—dose–plateau levels relationship, parallel first-order and capacity-limited elimination kinetics □ Dose–plateau drug levels relationship—drugs eliminated by parallel first-order and capacity-limited kinetics □ Elimination kinetics, parallel first order and capacity limited—relationship between drug dose and plateau levels □ Toxicity, drugs—dose–plateau levels relationship, elimination kinetics

The most important reasons for elucidating the kinetics of absorption, distribution, and elimination of a drug are to be able to predict the time course of drug levels in the body as a function of dose and frequency of drug administration and to permit the design of safe and effective dosage regimens for long-term therapy. It is particularly important to be able to predict the plateau level of a drug in the body attained some time after repeated administration of a fixed dose at constant intervals. Many adverse reactions and intoxications are due to accumulation of drugs to excessive levels; lack of effectiveness is often the result of a dosage regimen that produces a plateau level lower than the therapeutic range.

The average amount of drug in the body ($\bar{A}_{pl}$) at the plateau is directly proportional to dose (D) provided that absorption, distribution, and elimination can be described by a set of *linear* differential equations (1). In Eq. 1, F is the fraction of the dose which is absorbed, τ is the dosing interval, and k_d is the elimination rate constant:

$$\bar{A}_{pl} = DF/\tau k_d \qquad \text{(Eq. 1)}$$

The equation holds for all linear systems, irrespective of the number of apparent compartments required to describe them (2, 3). The direct proportionality between dose and plateau level of drug in the body, represented by Eq. 1, makes it easy to adjust the plateau level by a corresponding adjustment of the maintenance dose.

It is now realized that the elimination of some important and widely used drugs cannot be described by a set of linear differential equations. Such drugs, of which salicylic acid and ethanol are prominent examples, exhibit dose-dependent kinetics (4). This dose dependence is most often due to the limited capacity of an enzyme system involved in the formation of a metabolite of the drug. In the case of salicylic acid, the formation of not one but two major metabolites is affected by the limited capacity of the respective enzyme systems, and this is evident in the therapeutic dose range in man (5). The elimination of such drugs proceeds relatively more slowly as the dose is increased (4, 6); for this reason, there is no direct, simple relationship between dose and plateau level as described by Eq. 1.

The purposes of this article are to identify the factors affecting the accumulation characteristics of drugs subject to capacity-limited elimination kinetics in the therapeutic dose range, to show the relationship between dose and plateau drug levels in the body, and to compare the nature of this relationship to that of drugs eliminated by linear processes.

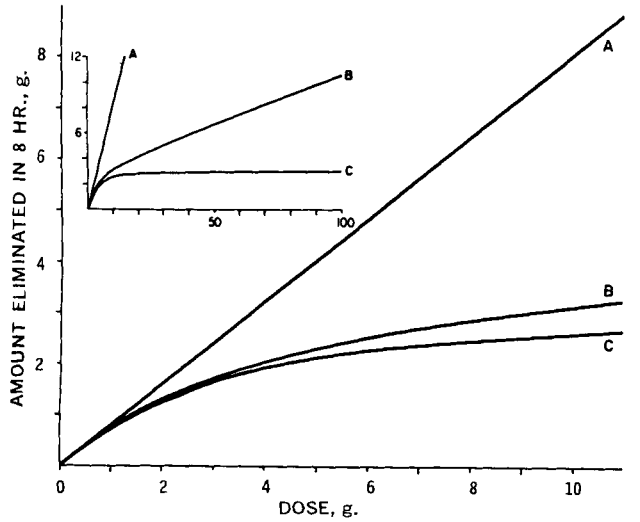

Figure 1—*Amount of drug eliminated in 8 hr. as a function of intravenous dose. Key: line A, first-order kinetics* (k = 0.2 $hr.^{-1}$)*; line B, parallel first-order and Michaelis-Menten kinetics* (k = 0.01 $hr.^{-1}$, V = 0.38 *g./hr.*, K_M = 2.0 *g.*)*; and line C, Michaelis-Menten kinetics only* (V = 0.4 *g./hr.*, K_M = 2.0 *g.*). *The inset shows the same curves over a wider dose range.*

THEORETICAL

When a fixed dose of drug (D) is administered repeatedly at a constant time interval (τ) such that there is always some drug remaining in the body when the next dose is given, a gradual accumulation of drug occurs in the body. This accumulation continues until the amount of drug eliminated from the body in time = τ exactly equals the amount entering the body during that time. This very simple concept leads to a correspondingly facile approach to the determination of drug plateau levels as a function of dose. Let it be assumed that the drug is administered intravenously and that it is distributed in the body very rapidly so that the body behaves as a single apparent compartment. If that drug is eliminated by one or more apparent first-order processes, then the amount of drug (A_t) in the body at time t after administration of a dose (A^0) is:

$$A_t = A^0 e^{-kt} \qquad \text{(Eq. 2)}$$

where k is the rate constant for elimination (and may be the sum of several constants for different biotransformation and excretion processes). The amount of drug eliminated from time = 0 to time = t is $A^0 - A_t$, or:

$$\text{amount eliminated} = A^0(1 - e^{-kt}) \qquad \text{(Eq. 3)}$$

It is only necessary to redefine terms to apply Eq. 3 to the problem of relating dose to plateau level of drug in the body. Since, at the plateau, the amount of drug eliminated during the dosing interval τ equals the intravenous dose, Eq. 3 may be restated in the following form:

$$D = A_{max.}(1 - e^{-k\tau}) \qquad \text{(Eq. 4)}$$

where D is the maintenance dose, and $A_{max.}$ is the maximum plateau level of drug (which occurs immediately after intravenous injection during the "steady state"); $A_{min.}$ is merely $A_{max.} - D$ and occurs immediately before administration of the next dose. The ratios $A_{max.}/D$ and $A_{min.}/D$ are independent of dose, characteristic of linear systems.

If a drug is eliminated *only* by Michaelis-Menten kinetics and therapeutic drug levels are not very much lower than the Michaelis constant (K_M), then the rate of elimination of the drug from the body may be described by the following equation (7):

$$\frac{A^0 - A_t}{t} = V - \frac{K_M}{t} \ln \frac{A^0}{A_t} \qquad \text{(Eq. 5)}$$

where V is the theoretical maximum rate of the process, and the other symbols are as defined previously. This equation may be redefined and rearranged for plateau calculations:

$$D = V\tau - K_M \ln \frac{A_{max.}}{A_{max.} - D} \qquad \text{(Eq. 6)}$$

The equation is only valid when D is smaller than $V\tau$. If D exceeds $V\tau$, no plateau will be reached and drug levels will accumulate without an upper limit.

More realistic is the case where drug elimination involves one or several apparent first-order processes in parallel with a process showing Michaelis-Menten kinetics in the therapeutic dose range. The integrated form of the differential equation describing these combined processes is (7, 8):

$$t = \frac{1}{k \cdot K_M + V}\left[K_M \ln \frac{A^0}{A_t} + \frac{V}{k} \ln \frac{(A^0 + K_M)k + V}{(A_t + K_M)k + V}\right] \qquad \text{(Eq. 7)}$$

where k is the rate constant for one or several parallel apparent first-order processes, and the other symbols are as defined previously. For plateau level calculations, Eq. 7 may be redefined so that:

$$\tau = \frac{1}{k \cdot K_M + V}\left[K_M \ln \frac{A_{max.}}{A_{max.} - D} + \frac{V}{k} \ln \frac{(A_{max.} + K_M)k + V}{(A_{max.} - D + K_M)k + V}\right] \qquad \text{(Eq. 8)}$$

Unfortunately, it is not possible to obtain an expression that permits an explicit solution for A_t in Eq. 7 or for $A_{max.}$ in Eq. 8; these equations are, therefore, somewhat inconvenient to apply as such. It is easier to use the differential form of the equation directly in a suitable computer program. The Michaelis constant K_M, as used here, is the apparent *in vivo* constant (6) and is expressed in units of weight rather than concentration, with the body representing a system with a certain apparent volume of distribution with respect to the drug. It is recognized that even those elimination processes that appear to be apparent first order may actually be saturable *in theory*. As pointed out previously, apparent first-order kinetics is a limiting case of Michaelis-Menten kinetics when substrate concentration is very much lower than K_M (6).

METHODS

All calculations were carried out by means of the MIMIC analog digital computer program designed for the CDC 6400 digital computer (9). This program permits the introduction of the appropriate equations in differential form. Some randomly selected results were verified by direct use of Eq. 8 and by simulating with MIMIC repetitive dosing until the plateau was attained.

RESULTS AND DISCUSSION

Figure 1 shows the relationship between dose and the amount of drug eliminated at a fixed time after drug administration (8 hr.) for simple first-order elimination, mixed first-order and Michaelis-Menten kinetics, and Michaelis-Menten kinetics alone. The values of k, V, and K_M were chosen such that V/K_M for the Michaelis-Menten process, k for the first-order process, and $(V/K_M) + k$ for the combined first-order and Michaelis-Menten processes are equal. Consequently, the elimination of very small doses (<0.2 g.) proceeds at almost the same rate in all three cases. It can be seen that there is a linear relationship between dose and amount eliminated in the case of first-order elimination, while in the other two cases the fraction of a dose eliminated within the defined time decreases with increasing dose. The inset in Fig. 1 shows these relationships over a much wider dose range so that the saturation of the Michaelis-Menten process (Curve C) is clearly evident. Curve B, representing mixed first-order and Michaelis-Menten kinetics, becomes essentially linear in the high dose range where the contribution of the Michaelis-Menten process is negligible.

As explained in the preceding section, redefinition of the ordinate as the maintenance dose D and of the abscissa as the maximum plateau level $A_{max.}$ permits the use of Fig. 1 for illustrating drug accumulation problems. The data in Fig. 1 are shown in more informative form in Fig. 2. As predicted from theoretical considera-

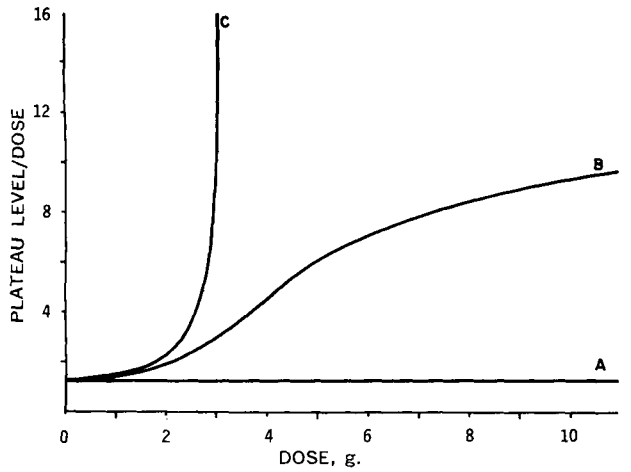

Figure 2—*Relationship between maximum plateau level and intravenous dose, given every 8 hr., assuming that drug elimination proceeds by first-order (A), parallel first-order and Michaelis–Menten (B), and Michaelis–Menten kinetics (C). Plotted are the ratios of the maximum amount of drug in the body divided by dose, as a function of dose. The pharmacokinetic constants are the same as in Fig. 1.*

tions, the relationship $A_{max.}/D$ is dose independent only in the case of first-order kinetics (line A). If elimination is only by Michaelis–Menten kinetics, $A_{max.}/D$ is almost dose independent when $D \ll K_M$ and the kinetics are apparent first order. There is a steep increase in the $A_{max.}/D$ ratio when D approaches K_M. When D is larger than V_T (here 0.4 g./hr. × 8 hr. or 3.2 g.), drug levels rise without limit and no plateau is attained.

It is unlikely that a drug is eliminated only by Michaelis–Menten kinetics. Even ethanol is eliminated in part by apparent first-order processes, including urinary and pulmonary excretion. Drugs eliminated by parallel first-order and Michaelis–Menten kinetics have a practically constant $A_{max.}/D$ ratio in the low dose range (when overall kinetics are apparent first order) and also in the very high dose range (where the contribution of the Michaelis–Menten process to drug elimination is negligible). However, the $A_{max.}/D$ ratio in the high dose range is considerably higher than in the low dose range (Fig. 2). Potential clinical hazards arise in the dose region where $A_{max.}/D$ shows a pronounced dose dependence, so that an increase in dose produces a much greater than anticipated increase in plateau drug level. In the example (Curve B in Fig. 2), doubling of the dose from 2.5 to 5 g. results in a fivefold increase in plateau level.

The induction of drug-metabolizing enzymes by such agents as the barbiturates results in an increase in the amount of enzyme and,

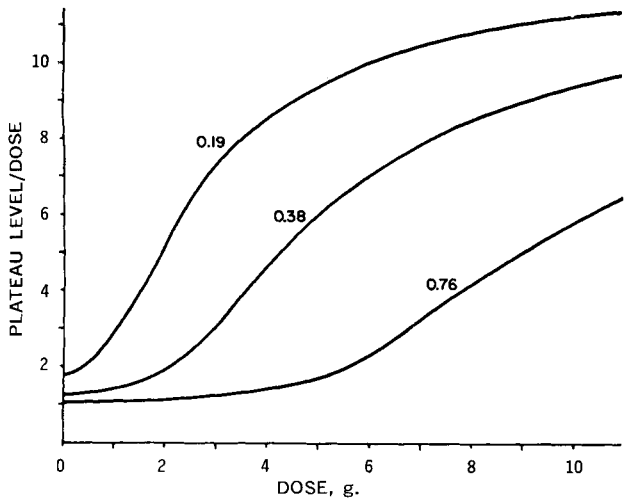

Figure 3—*Effect of a change in* V *on the relationship represented by Curve B in Fig. 2. The value of* V *in grams per hour is shown next to each curve.*

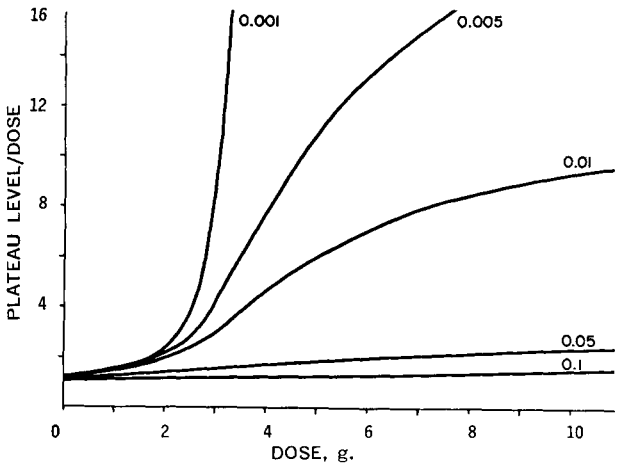

Figure 4—*Effect of a change in* k *on the relationship represented by Curve B in Fig. 2. The value of* k *in hr.*$^{-1}$ *is shown next to each curve.*

therefore, in V. The effects of changes in V on the relationship between $A_{max.}/D$ and D are shown in Fig. 3. As V is increased, the ratio $A_{max.}/D$ decreases (except at very high doses relative to K_M) and the rapid change in the value of this ratio occurs at somewhat higher doses. Interestingly, a given magnitude of inductive effect (as reflected by a change in V) has a relatively more pronounced effect on $A_{max.}$ at higher than at lower doses of drug (Fig. 3) but has practically no effect when $A_{max.} \gg K_M$. It may be helpful to take this into consideration in the design of enzyme induction studies.

If a weak acid or weak base is eliminated partly by biotransformation and partly by excretion, the former process may show Michaelis–Menten characteristics in the therapeutic dose range while the latter may be apparent first order but highly sensitive to urine pH. Figure 4 illustrates the effect of changes in the first-order rate constant, such as might result from changes in urine pH, on the $A_{max.}/D$ *versus* D relationship for a drug eliminated by parallel first-order and Michaelis–Menten kinetics. An acidic drug may approach overall first-order characteristics (dose-independent $A_{max.}/D$) as urine pH is increased. Conversely, a basic drug which shows little evidence of capacity-limited kinetics at low urine pH may show pronounced dose-dependent characteristics at high urine pH where the excretion rate constant is much lower.

Figure 5 illustrates the effect of simultaneous changes in V and K_M such that the ratio V to K_M remains constant. Consistent with theory (4, 6), $A_{max.}/D$ is the same for all cases at very low doses. This ratio increases as V decreases, and the region of maximum

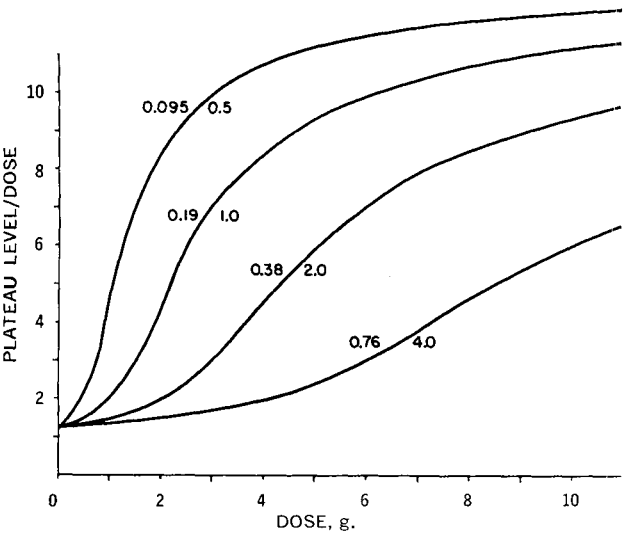

Figure 5—*Effect of a change in both* V *and* K_M *on the relationship represented by Curve B in Fig. 2. The value of* V *in grams per hour is on the left of each curve, that of* K_M *in grams is on the right. The ratio* V/K_M *is 0.19 in all of the simulations;* k *is constant at 0.01 hr.*$^{-1}$.

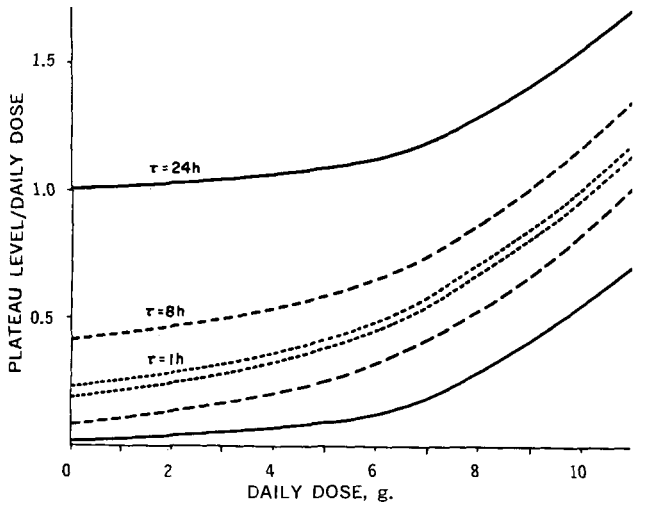

Figure 6—*Effect of a change in dosing interval (τ) on the relationship represented by Curve B in Fig. 2. The daily dose is given in 1, 3, or 24 increments. Both maximum and minimum plateau levels are shown for each case. (Note that the denominator on the ordinate of this figure differs from that of Fig. 2.)*

change in $A_{max.}/D$ moves to a higher dose range. The $A_{max.}/D$ ratio again approaches a constant value for all cases at very high doses where this ratio is primarily a function of the first-order kinetic process.

It is of interest to consider the effect of a change in dosing interval τ. As shown in Fig. 6, the range between $A_{max.}$ and $A_{min.}$ increases greatly when τ is increased. As τ is increased, $A_{max.}$ is increased also and capacity-limited kinetic effects are more pronounced. Conversely, $A_{min.}$ decreases with increasing τ so that capacity-limited effects in the lower drug level range of the plateau level are less pronounced as τ is increased. The net result of these opposing effects is shown in Table I in terms of the area under the amount of drug in the body *versus* time curve during steady state, *i.e.*, when drug levels are at a plateau. This area is independent of dosing pattern in the case of drugs eliminated by first-order kinetics. Thus, a similar situation is approached at very low and very high doses of a drug that is eliminated by parallel first-order and Michaelis–Menten kinetics. In the intermediate dose range, the average amount of drug in the body decreases as the dosing frequency increases.

The results of this study serve to identify a very significant and potentially hazardous characteristic of drugs that are subject to capacity-limited kinetics in the therapeutic dose range. Repetitive administration of fixed doses of such drugs at constant time intervals will lead to eventual attainment of a drug level plateau in the body. However, the magnitude of this plateau is not directly proportional to dose but increases more than proportionately. This dose dependence is particularly evident in a certain, definable dose region in which pronounced and unanticipated drug accumulation effects are most likely to occur. Salicylate has the typical pharmacokinetic characteristics discussed here in that it is eliminated by parallel apparent first-order and Michaelis–Menten processes (5). Significantly, most fatal salicylate intoxications in infants and young children are due to the therapeutic use of this drug and not to accidental ingestion of single large doses (10, 11). The kinetics of salicylate accumulation and the clinical implications will be described elsewhere.

This study has focused on the effect of Michaelis–Menten elimination kinetics on drug accumulation during repetitive dosing. Factors that can complicate the relationships described here or that could by themselves account for unusual drug accumulation characteristics include nonlinear distribution phenomena, product or substrate inhibition of biotransformation processes, induction by a drug of the enzyme system involved in the biotransformation of that drug, competitive effects of other drugs or dietary constituents, and dose-dependent pharmacologic effects of a drug which will affect the elimination of that drug (*i.e.*, changes in urine pH or organ perfusion rates). It is essential, therefore, to verify directly the accumulation characteristics predicted mathematically on the basis of pharmacokinetic constants obtained from single-dose studies of drug elimination kinetics.

Table I—Effect of Dosing Interval on the Area under the Amount of Drug in the Body–Time Curve during "Steady State" for a Drug which is Eliminated by Parallel First-Order and Michaelis–Menten Kinetics[a]

Dose, g./Day	—Area under Curve[b], g. × hr.— Administered in Hourly Increments	Administered as a Single Daily Dose	Ratio of Areas, 1:24 hr.
0.375	1.95	2.04	0.956
1.5	8.80	10.2	0.863
3.0	21.1	25.9	0.815
6.0	67.4	78.1	0.863
12.0	388.0	391.0	0.992

[a] k = 0.01 hr.$^{-1}$, V = 0.38 g./hr., and K_M = 2.0 g. [b] Over 24 hr.

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