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concentration; in 3.3 half-lives, it will be 90 percent; and in five half-lives, it will be 97 percent of the plateau level.

Dosage recommendations for continuous infusions are designed to produce appropriate plasma concentrations at equilibrium. The phenomenon just described, which is often termed *drug accumulation,* entails a delay in achieving this concentration. The magnitude of the delay is related to the half-life of the drug, whereas the ultimate concentration is determined by the $V_d$, the half-life, and the rate of administration.

## Plasma Drug Clearance

The plasma clearance (Cl) of a drug is of primary importance in appreciating the relationship between rate of drug administration and consequent drug concentration. Drug clearance, like creatinine or inulin clearances, is determined by relating the rate of elimination (E) to the plasma concentration at equilibrium ($C_{ss}$):

$$Cl = \frac{E}{C_{ss}}$$

At equilibrium, E = R. Thus,

$$Cl = \frac{R}{C_{ss}}$$

or, with rearrangement,

$$C_{ss} = \frac{R}{Cl} \qquad (14.3)$$

$$R = Cl \times C_{ss} \qquad (14.3A)$$

where R = rate of administration.
Equation 14.3A emphasizes that it is drug clearance, rather than half-life, which determines the rate of administration (R) or dosage per interval (D/T) necessary to achieve a specific concentration. Ultimately, clearance is related to half-life and volume of distribution:

$$Cl = \frac{0.7 \times V_d \times Wt.}{t_{1/2}}$$

when $V_d$ is expressed in L/kg, half-life ($t_{1/2}$) in hours, and clearance (Cl) in L/hr.
With substitution into equation 14.3, this becomes:

$$C_{ss} = \frac{R \times t_{1/2}}{0.7 \times V_d \times Wt.} \qquad (14.4)$$

where R is expressed in mg/hr and $C_{ss}$ is expressed in mg/L.

Equation 14.4 indicates that equilibrium drug concentration is related to three variables: half-life ($t_{1/2}$), volume of distribution ($V_d$), and rate of administration (R, or D/T). Thus, doubling $V_d$ has the same effect upon steady state concentration as halving $t_{1/2}$. Either alteration will lead to a 50 percent reduction in drug concentration that can be exactly offset by doubling the dosage.

### *Multiple Dose Kinetics*

The reader has been introduced to the phenomenon of drug accumulation as it occurs during continuous infusion. Drug accumulation also occurs with intermittent dosage schedules.

Consider a drug that is given by intermittent IV injection. When the first dose is given, the concentration of drug is zero. Immediately after the dose, a peak concentration is recorded. The concentration then declines at a rate determined by the drug's half-life. If the next dose is given before the concentration has once again reached zero, the second peak will be higher than the first. As this process continues, the peak ($C_{max}$) and trough ($C_{min}$) levels rise toward plateau values, as will the average concentration, $C_{ave}$. This process is illustrated in Figure 14–4. Drug accumulation occurs during intermittent administration when a second, or nth, dose is administered before all the previous dose has been eliminated. For most clinical purposes, this condition is satisfied when the dosing interval is less than twice the half-life of the drug. As with continuous infusions, 50 percent of a plateau concentration is achieved in one half-life; 97 percent is achieved after five half-lives.

$C_{ave}$ is analogous to the equilibrium concentration ($C_{ss}$) that develops during continuous infusion. Thus, its value is determined only by the relationship between clearance (Cl) and rate of administration (R; see Equation 14.3). The peak ($C_{max}$) and trough ($C_{min}$) concentrations fluctuate around the $C_{ave}$ in a manner that is determined by the size of the dose and the length of the dosing interval. For example, theophylline may be administered by intermittent IV injection. In an adult, a standard regimen calls for 300 mg every 6 hours (1200

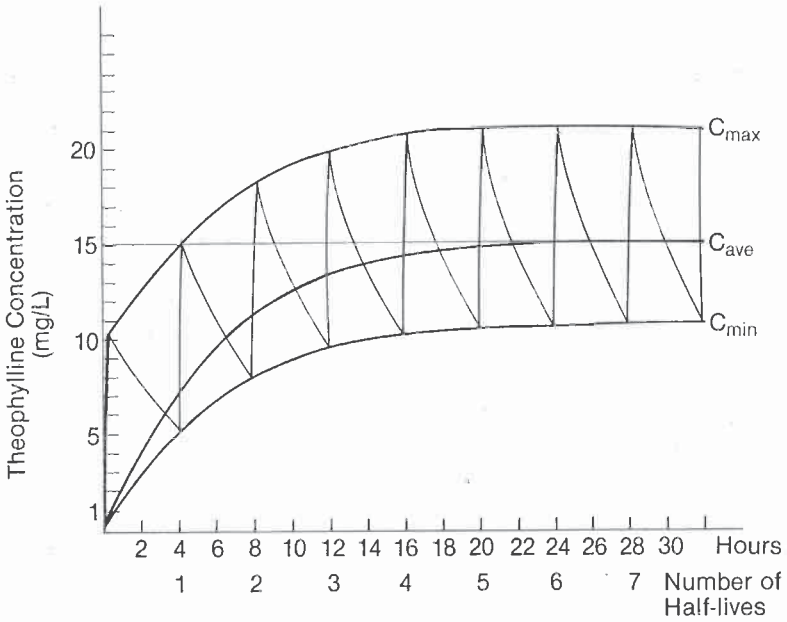


**Figure 14–4.** Concentration of theophylline during intermittent IV administration. Note that $C_{max}$, $C_{min}$, and $C_{ave}$ increase to equilibrium values. $C_{ave} = C_{ss}$ that obtains during continuous administration if the total daily dosages are identical.

mg/day). Alternatively, one may administer 150 mg every 3 hours (1200 mg/day). Finally, some physicians administer a continuous infusion of 50 mg/hr (1200 mg/day). Both intermittent regimens produce the same ($C_{ave}$), which is equal to the $C_{ss}$ during the continuous infusion. This does not mean that the regimens are equivalent. The 6-hour schedule produces much greater fluctuation around $C_{ave}$ than the 3-hour schedule. With the 3-hour regimen, the peaks and troughs lie closer to $C_{ave}$. This increases the likelihood of remaining within the therapeutic range throughout the dosing interval (Fig. 14–5).

In this regard, the half-life of a drug is a watershed. When a drug is given at an interval that is equal to its half-life ($T = t_{½}$), $C_{max}/C_{min}$ is approximately 2. During more frequent administration ($T < t_{½}$), $C_{max}/C_{min}$ is less than 2, and during less frequent administration ($T > t_{½}$), $C_{max}/C_{min}$ is greater than 2.

Thus, drugs with a long half-life, such as digoxin or phenobarbital, are often given once daily, because even with this schedule, T is less than $t_{½}$ and the plasma concentration remains within the relatively narrow therapeutic range of these agents. Conversely, theophylline and quinidine have relatively short half-lives (3 to 6 hours in children). When conventional formulations of these agents are administered, they require relatively frequent dosing (every 3 to 6 hours) if the plasma concentration is to remain within the respective therapeutic ranges throughout the dosing interval.

### *Nonlinear Kinetics*

To this point, the discussion has concerned *first-order* kinetic behavior in which a *fixed proportion* of drug is eliminated per unit time. *Zero-order* kinetics occurs under some conditions, notably when plasma drug concentrations are rel-

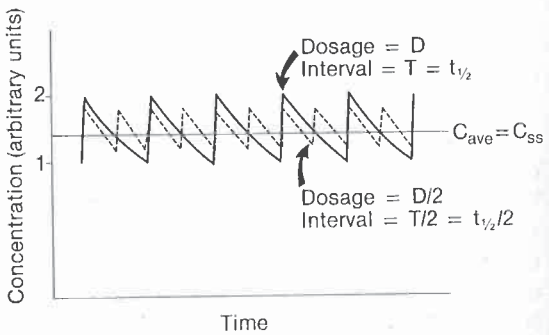


**Figure 14–5.** Effect of varying both dosage and dose interval upon peak ($C_{max}$) and trough ($C_{min}$) concentrations during steady state. The solid saw tooth line indicates the time concentration curve that results with intermittent IV administration of dosage D at an interval T equal to the drug t½. Note that $C_{max}/C_{min} = 2$. The interrupted line indicates the curve that results when dosage (D/2) and interval (T/2) are halved. $C_{max}/C_{min} = 1.5$. The straight solid line indicates $C_{ave}$, which is the same during both conditions, and is equal to $C_{ss}$, which results when the same total daily dosage is administered by continuous IV infusion.

atively large. With zero order or nonlinear kinetics, a fixed *amount* of drug is eliminated per unit time. Ethanol is an extreme example, because the usual dosage is large (gm amounts) relative to other drugs (mg amounts). Within the usual range of blood ethanol concentrations, humans eliminate about 120 mg per kg per hr of the substance. Because the volume of distribution of ethanol is about 0.5 L per kg, blood ethanol levels decline at a fixed rate of 20 to 25 mg/dl per hr. The rate of elimination does not change with increases in concentration. Consequently, increments in dosage produce much greater changes in concentration than would be the case for a drug eliminated in accordance with first-order kinetics.

Many substances follow a first-order model at low plasma concentrations but a zero-order model at higher concentrations. When the transition from first- to zero-order elimination occurs at concentrations appreciably higher than the usual therapeutic range, the pharmacokinetic treatment of the drug is uncomplicated and a first-order kinetic model will be sufficiently accurate for most clinical purposes.

Unfortunately, a few commonly used drugs, such as phenytoin and salicylate, exhibit this transition at concentrations within the therapeutic range.

A change from first- to zero-order kinetics as concentration increases is typical of an enzyme-mediated process. This change is due to saturation of the enzyme system that is responsible for metabolic transformation of the drug. There is a limited amount of enzyme at the metabolic site; therefore, there is a maximum rate at which transformation can occur ($V_{max}$). At concentrations that are low relative to $V_{max}$, first-order behavior predominates. As concentration increases, $V_{max}$ is approached. After $V_{max}$ has been achieved, further increases in concentration cannot augment the metabolic rate. Thus, a fixed amount of drug is metabolized per unit time. This amount, of course, is equal to $V_{max}$. Mathematically, this process is described by the Michaelis–Menton equation:

$$E = \frac{V_{max} \times C}{K_m + C} \qquad (14.5)$$

where E is the rate of elimination or metabolism; $V_{max}$ is the maximum rate of metabolism; $K_m$ is the Michaelis–Menton constant, which defines the affinity of the enzyme for the drug; and C is plasma drug concentration.

Note that when C is much less than $K_m$, E varies directly with C. This resembles a first-approaches $V_{max}$, and zero-order behavior occurs.

There are two important consequences of this kinetic behavior. The first is that an increase in dosage produces an *exponential*, rather than a linear rise in concentration. This occurs very often when treating patients with phenytoin (Fig. 14–6); on occasion, this phenomenon is recognized during treatment with theophylline. It requires that dosage adjustments must be made cautiously and in small amounts. The second major consequence of Michaelis–Menton kinetics is that the *apparent* plasma half-life increases with the plasma concentration. The greater the plasma concentration, the slower is the relative rate of elimination. Using representative values of $K_m$ and $V_{max}$ for phenytoin, one can estimate that at a concentration of 10 mg per L, the apparent $t_{½}$ of phenytoin is 24 hours; at a concentration of 25 mg per L, the apparent $t_{½}$ is 42 hours. This means: 1) increases in dosage cause lengthening of the apparent $t_{½}$ (thus, Michaelis–Menton kinetics is sometimes referred to as *dose dependent* kinetics), 2) small increments in dosage can produce huge increases in drug concentration, and 3) intoxication with phenytoin will be prolonged, because, at high concentrations, elimination is extremely slow relative to the amount of drug in the body.

## MAINTENANCE DOSE

The maintenance dose (MD) is the amount of drug (R for continuous infusion, D/T for an intermittent schedule) that is administered during equilibrium. Thus, from Equation 14.3A, maintenance dose, MD, is equal to the product of clearance, Cl, and desired steady state plasma concentration, $C_{ss}$, ($MD = Cl \times C_{ss}$). The maintenance dose is often determined by consulting standard reference material. In patients

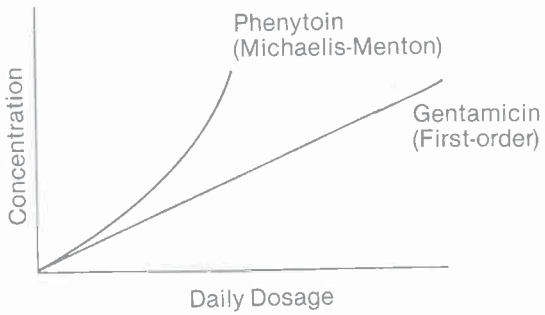


**Figure 14–6.** Effect of dosage upon plasma concentration for drugs following first-order vs. Michaelis-Menton

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