

Chapter 8
MULTIPLE-DOSAGE
REGIMENS
Introduction

In earlier chapters of this book we have discussed single-dose drug administration. After single-dose drug administration, the plasma drug level rises above and then falls below the *minimum effective concentration* (MEC), resulting in a decline in therapeutic effect. **To maintain prolonged therapeutic activity, many drugs are given in a multiple-dosage regimen.** The plasma levels of drugs given in multiple doses must be maintained within the narrow limits of the therapeutic window (eg, plasma drug concentrations above the MEC but below the *minimum toxic concentration* or MTC) to achieve optimal clinical effectiveness. Among these drugs are **antibacterials, cardiotonics, anticonvulsants, and hormones.** Ideally, a dosage regimen is established for each drug to provide the correct plasma level without excessive fluctuation and drug accumulation outside the therapeutic window.

For certain drugs, such as antibiotics, a desirable MEC can be determined. Some drugs that have a narrow therapeutic range (eg, digoxin and phenytoin) require definition of the therapeutic minimum and maximum nontoxic plasma concentrations (MEC and MTC, respectively). In calculating a multiple-dose regimen, **the desired or *target* plasma drug concentration must be related to a therapeutic response, and the multiple-dose regimen must be designed to produce plasma concentrations within the therapeutic window.**

There are two main parameters that can be adjusted in developing a dosage regimen: (1) the size of the drug dose and (2) , the frequency of drug administration (ie, the time interval between doses).

DRUG ACCUMULATION

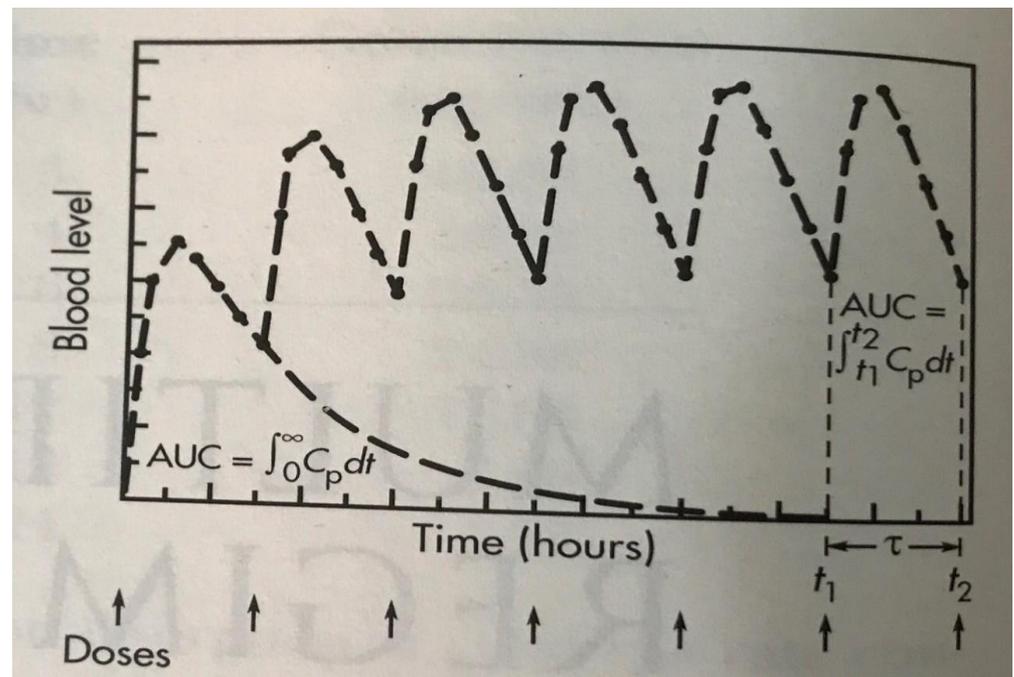
To calculate a multiple-dose regimen for a patient or patients, pharmacokinetic parameters are first obtained from the plasma level-time curve generated by single-dose drug studies.

With these pharmacokinetic parameters and knowledge of the size of the dose and dosage interval, the complete plasma level-time curve or the plasma level may be predicted at any time after the beginning of the dosage regimen.

To calculate **multiple-dose regimens**, it is necessary to decide whether successive doses of drug will have any effect on the previous dose. The principle of *superposition* assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses.

Therefore, the blood levels after the second, third, or n th dose will overlay or superimpose the blood level attained after the $(n - 1)$ th dose. **In addition, the AUC ($\int_0^\infty C_p dt$) following the administration of a single dose equals the AUC ($\int_{t_1}^{t_2} C_p dt$) during a dosing interval at steady state .**

Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.



The principle of ***superposition*** allows one to project the plasma drug concentration-time curve of a drug after **multiple consecutive doses** based on the plasma drug concentration-time curve obtained after a single dose. **The basic assumptions are that the drug is eliminated by first-order kinetics and that the pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.**

The plasma drug concentrations after multiple doses may be predicted from the plasma drug concentrations obtained after a single dose. The plasma drug concentrations from 0 to 24 hours are measured after a single dose. **A constant dose of drug is given every 4 hours and plasma drug concentrations after each dose are generated using the data after the first dose. Thus, the *predicted* plasma drug concentration in the patient is the total drug concentration obtained by adding the residual drug concentration obtained after each previous dose.** As shown in table below. The superposition principle may be used to predict drug concentrations after multiple doses of many drugs. Because the **superposition principle is an overlay method**, it may be used to **predict drug concentrations after multiple doses given at either *equal* or *unequal* dosage intervals.**

For example, the plasma drug concentrations may be predicted after a drug dose is given every 8 hours, or 3 times a day before meals at 8 AM, 12 noon, and 6 PM.

Dose Number	Time (hr)	Plasma Drug Concentration ($\mu\text{g}/\text{mL}$)						Total
		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	
1	0	0						0
	1	21.0						21.0
	2	22.3						22.3
2	3	19.8						19.8
	4	16.9	0					16.9
	5	14.3	21.0					35.3
	6	12.0	22.3					34.3
3	7	10.1	19.8					29.9
	8	8.50	16.9	0				25.4
	9	7.15	14.3	21.0				42.5
	10	6.01	12.0	22.3				40.3
4	11	5.06	10.1	19.8				35.0
	12	4.25	8.50	16.9	0			29.7
	13	3.58	7.15	14.3	21.0			46.0
	14	3.01	6.01	12.0	22.3			43.3
5	15	2.53	5.06	10.1	19.8			37.5
	16	2.13	4.25	8.50	16.9	0		31.8
	17	1.79	3.58	7.15	14.3	21.0		47.8
	18	1.51	3.01	6.01	12.0	22.3		44.8
6	19	1.27	2.53	5.06	10.1	19.8		38.8
	20	1.07	2.13	4.25	8.50	16.9	0	32.9
	21	0.90	1.79	3.58	7.15	14.3	21.0	48.7
	22	0.75	1.51	3.01	6.01	12.0	22.3	45.6
	23	0.63	1.27	2.53	5.06	10.1	19.8	39.4
	24	0.53	1.07	2.13	4.25	8.50	16.9	33.4

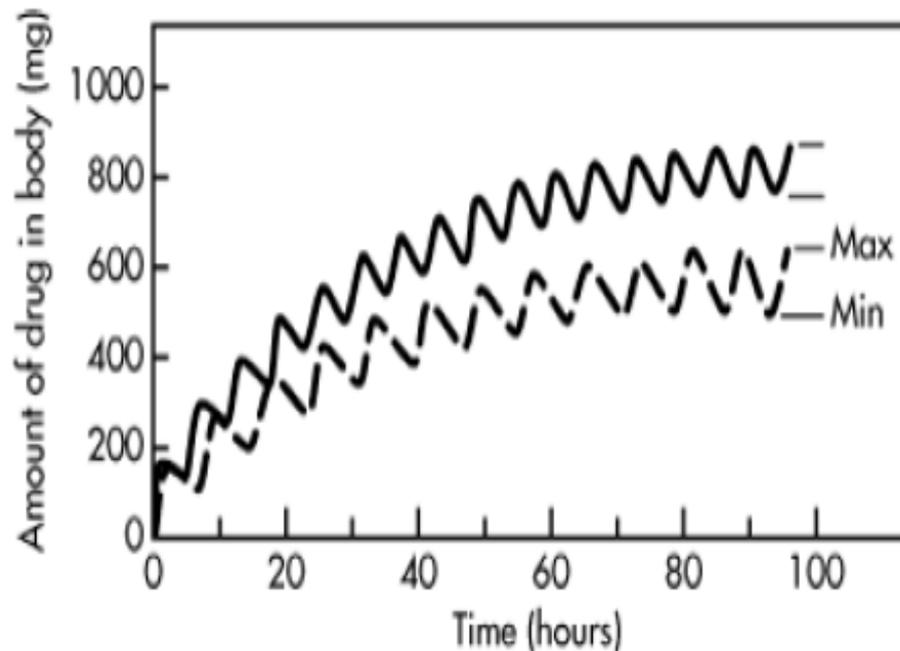
A single oral dose of 350 mg was given and the plasma drug concentrations were measured for 0-24 hr. The same plasma drug concentrations are assumed to occur after doses 2-6. The total plasma drug concentration is the sum of the plasma drug concentrations due to each dose. For this example, $V_D = 10 \text{ L}$, $t_{1/2} = 4 \text{ hr}$, and $k_a = 1.5 \text{ hr}^{-1}$. The drug is 100% bioavailable and follows the pharmacokinetics of a one-compartment open model.

There are situations, however, in which the superposition principle does not apply. In these cases, the pharmacokinetics of the drug change after multiple dosing due to various factors, including changing pathophysiology in the patient, saturation of a drug carrier system, enzyme induction, and enzyme inhibition.

Drugs that follow nonlinear pharmacokinetics, generally do not have predictable plasma drug concentrations after multiple doses using the superposition principle.

If the drug is administered at a **fixed dose and a fixed dosage interval**, as is the case with multiple-dose regimens, the amount of drug in the body will increase and then plateau to a mean plasma level higher than the peak C_p obtained from the initial dose. **When the second dose is given after a time interval shorter than the time required to "completely" eliminate the previous dose, *drug accumulation* will occur in the body. In other words, the plasma concentrations following the second dose will be higher than corresponding plasma concentrations immediately following the first dose.** However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, drug will not accumulate.

Figure 8-2.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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Amount of drug in the body as a function of time. Equal doses of drug were given every 6 hours (upper curve) and every 8 hours (lower curve). k_a and k remain constant.

As repetitive equal doses are given at a constant frequency, the plasma level-time curve plateaus and a steady state is obtained. At steady state, the plasma drug levels fluctuate between C_{\max}^{∞} and C_{\min}^{∞} .

Once steady state is obtained, C_{\max}^{∞} and C_{\min}^{∞} are constant and remain unchanged from dose to dose.

1-The C_{\max}^{∞} is important in determining drug safety. The C_{\max}^{∞} should always remain **below the minimum toxic concentration.** **2-The C_{\max}^{∞} is also a good indication of drug accumulation.** If a drug produces the same C_{\max}^{∞} at steady state, compared with the $(C_{n=1})_{\max}$ after the first dose, then there is no drug accumulation. If C_{\max}^{∞} is much larger than $(C_{n=1})_{\max}$, then there is significant accumulation during the multiple-dose regimen.

Accumulation is affected by the 1-elimination half-life of the drug and 2-the dosing interval.

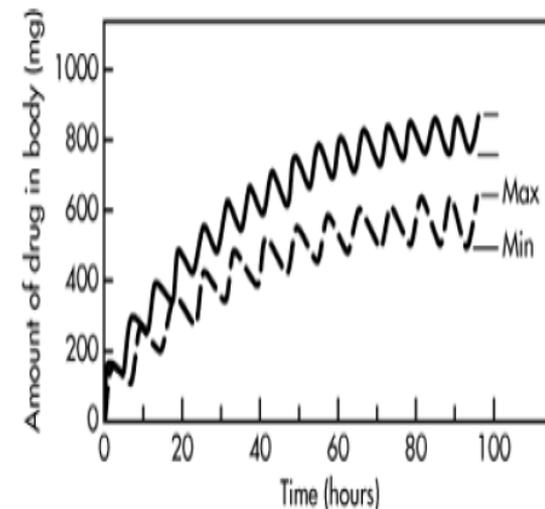
The index for measuring drug accumulation R is

$$R = \frac{(C^{\infty})_{\max}}{(C_{n=1})_{\max}} \quad (8.1)$$

Substituting for C_{\max} after the first dose and at steady state yields

$$R = \frac{D_0/V_D [1/(1 - e^{-k\tau})]}{D_0/V_D} \quad (8.2)$$

$$R = \frac{1}{1 - e^{-k\tau}}$$

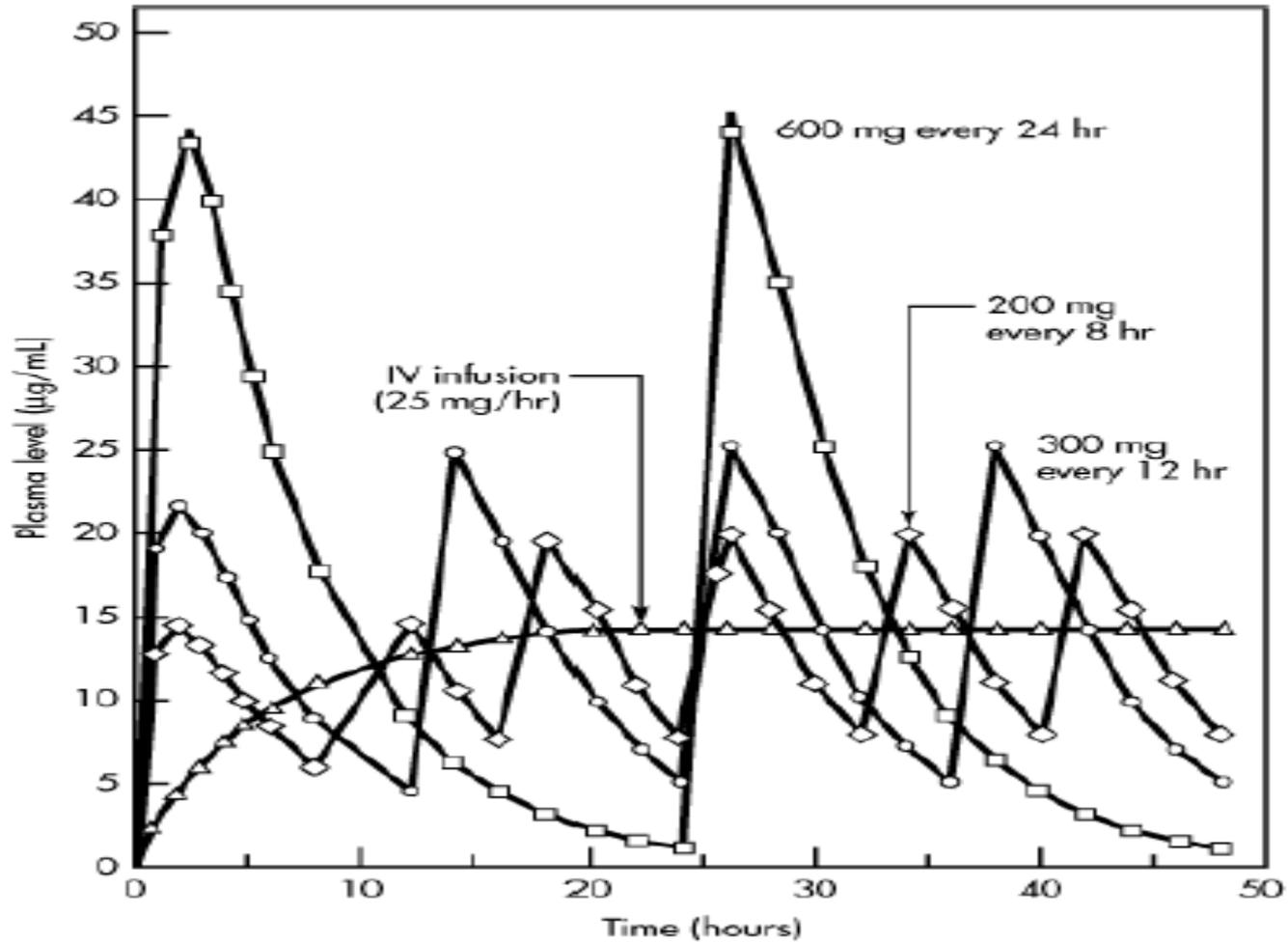


$$R = \frac{1}{1 - e^{-k\tau}}$$

Equation 8.2 shows that **drug accumulation** measured with the R index depends on the elimination constant and the dosing interval and is **independent** of the dose.

For a drug given in repetitive oral doses, the time required to reach steady state is dependent on the elimination half-life of the drug and is independent of the size of the dose, the length of the dosing interval, and the number of doses.

For example, if the 1- dose or 2-dosage interval of the drug is altered as shown below , the time required for the drug to reach steady state is the same, but the final steady- state plasma level changes proportionately. Furthermore, if the drug is given at the same dosing rate but as an infusion (eg, 25 mg/hr), the average plasma drug concentrations (C_{av}^{∞}) will be the same but the fluctuations between C_{max}^{∞} and C_{min}^{∞} will vary . **An average steady-state plasma drug concentration is obtained by dividing the area under the curve (AUC) for a dosing period ($\int_{t_1}^{t_2} C_p dt$) by the dosing interval , at steady state.**



Simulated plasma drug concentration time curves after IV infusion and oral multiple doses for a drug with an elimination half-life of 4 hours and apparent V_D of 10 L. IV infusion given at a rate of 25 mg/hr, oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.

An equation for the estimation of the **time to reach one-half of the steady-state plasma levels or the accumulation half-life** has been described by .

$$\text{Accumulation } t_{1/2} = t_{1/2} \left(1 + 3.3 \log \frac{k_a}{k_a - k} \right) \quad (8.3)$$

For IV administration, k_a is very rapid (approaches ∞); k is very small in comparison to k_a and can be omitted in the denominator of Equation 8.3. Thus, Equation 8.3 reduces to

$$\text{Accumulation } t_{1/2} = t_{1/2} \left(1 + 3.3 \log \frac{k_a}{k_a} \right) \quad (8.4)$$

Because $k_a/k_a = 1$ and $\log 1 = 0$, the accumulation $t_{1/2}$ of a drug administered intravenously is the elimination $t_{1/2}$ of the drug. From this relationship, the time to reach 50% steady-state drug concentrations is dependent on the elimination $t_{1/2}$ and not on the dose or dosage interval.

As shown in Equation 8.4, the accumulation $t_{1/2}$ is directly proportional to the elimination $t_{1/2}$. gives the accumulation $t_{1/2}$ of drugs with various elimination half-lives given by multiple oral doses.

Table 8.2 Effect of Elimination Half-Life and Absorption Rate Constant on Accumulation Half-Life after Oral Administration^a

Elimination Half-Life (hr)	Elimination Rate Constant (1/hr)	Absorption Rate Constant (1/hr)	Accumulation Half-Life (hr)
4	0.173	1.50	4.70
8	0.0866	1.50	8.67
12	0.0578	1.50	12.8
24	0.0289	1.50	24.7
4	0.173	1.00	5.09
8	0.0866	1.00	8.99
12	0.0578	1.00	13.0
24	0.0289	1.00	25.0

^aAccumulation half-life is calculated by Equation 8.3, and is the half-time for accumulation of the drug to 90% of the steady-state plasma drug concentration.

From a clinical viewpoint, the time needed to reach 90% of the steady-state plasma concentration is 3.3 times the elimination half-life, whereas the time required to reach 99% of the steady-state plasma concentration is 6.6 times the elimination half-life. It should be noted from that at a constant dose size, the shorter the dosage interval, the larger the dosing rate (mg/hr), and the higher the steady-state drug level.

REPETITIVE INTRAVENOUS INJECTIONS

The maximum amount of drug in the body following a single rapid IV injection is equal to the dose of the drug. For a one-compartment open model, the drug will be eliminated according to first-order kinetics.

$$D_B = D_0 e^{-kt}$$

If T is equal to the dosage interval (ie, the time between the first dose and the next dose), then the amount of drug remaining in the body after several hours can be determined with

$$D_B = D_0 e^{-kT} \quad (8.6)$$

The fraction (f) of the dose remaining in the body is related to the elimination constant (k) and the dosage interval as follows:

$$f = \frac{D_B}{D_0} = e^{-kT} \quad (8.7)$$

With any given dose, f depends on k and T . If T is large, f will be smaller because D_B (the amount of drug remaining in the body) is smaller.

a. The fraction of drug remaining in the body is estimated by Equation 8.7. The concentration of the drug declines to one-half after 3 hours ($t_{1/2} = 3$ hr), after which the amount of drug will again decline by one-half at the end of the next 3 hours. Therefore, at the end of 6 hours only one-quarter, or 0.25, of the original dose remains in the body. Thus f is equal to 0.25.

To use Equation 8.7, we must first find the value of k from the $t_{1/2}$. $f = \frac{D_B}{D_0} = e^{-kr}$ (8.7)

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{3} = 0.231 \text{ hr}^{-1}$$

The time interval τ is equal to 6 hours. From Equation 8.7,

$$f = e^{-(0.231)(6)}$$
$$f = 0.25$$

In this example, 1000 mg of drug is given intravenously, so the amount of drug in the body is immediately increased by 1000 mg. At the end of the dosage interval (ie, before the next dose), the amount of drug remaining in the body is 25% of the amount of drug present just after the previous dose, because $f = 0.25$. Thus, if the value of f is known, a table can be constructed relating the fraction of the dose in the body before and after rapid IV injection (f).

Table 8.4 Fraction of the Dose in the Body before and after Intravenous Injections of a 1000-mg Dose^a

Number of Doses	Amount of Drug in Body	
	Before Dose	After Dose
1	0	1000
2	250	1250
3	312	1312
4	328	1328
5	332	1332
6	333	1333
7	333	1333
\hat{a}	333	1333

^a $f = 0.25$.

From the maximum amount of drug in the body is 1333 mg and the minimum amount of drug in the body is 333 mg. The difference between the maximum and minimum values, D_0 , will always equal the injected dose.

$$D_{\max} - D_{\min} = D_0 \quad (8.8)$$

In this example,

$$1333 - 333 = 1000 \text{ mg}$$

D_{\max}^{∞} can also be calculated directly by the relationship

$$D_{\max}^{\infty} = \frac{D_0}{1 - f} \quad (8.9)$$

Substituting known data, we obtain

$$D_{\max}^{\infty} = \frac{1000}{1 - 0.25} = 1333 \text{ mg}$$

then, from Equation 8.8,

$$D_{\min}^{\infty} = 1333 - 1000 = 333 \text{ mg}$$

The average amount of drug in the body at steady state, D_{av}^{∞} , can be found by Equation 8.10 or Equation 8.11. F is the fraction of dose absorbed. For an IV injection, F is equal to 1.0.

$$D_{\text{av}}^{\infty} = \frac{FD_0}{k\tau} \quad (8.10)$$

$$D_{\text{av}}^{\infty} = \frac{FD_0 1.44t_{1/2}}{\tau} \quad (8.11)$$

Equations 8.10 and 8.11 can be used for repetitive dosing at constant time intervals and **for any route of administration as long as elimination occurs from the central compartment.**

To determine the concentration of drug in the body after multiple doses, divide the amount of drug in the body by the volume in which it is dissolved. **For a one-compartment model, the maximum, minimum, and steady-state concentrations of drug in the plasma are found by the following equations:**

$$C_{\max}^{\infty} = \frac{D_{\max}^{\infty}}{V_D} \quad (8.12)$$

$$C_{\min}^{\infty} = \frac{D_{\min}^{\infty}}{V_D} \quad (8.13)$$

$$C_{\text{av}}^{\infty} = \frac{D_{\text{av}}^{\infty}}{V_D} \quad (8.14)$$

$$C_{\max}^{\infty} = \frac{C_p^0}{1 - e^{-k\tau}} \quad (8.15)$$

$$C_{\min}^{\infty} = \frac{C_p^0 e^{-k\tau}}{1 - e^{-k\tau}} \quad (8.16)$$

$$C_{\text{av}}^{\infty} = \frac{FD_0}{V_D k\tau} \quad (8.17)$$

$$D_{\text{av}}^{\infty} = \frac{FD_0}{k\tau} \quad (8.10)$$

As mentioned, C_{av}^{∞} is not the arithmetic mean of C_{max}^{∞} and C_{min}^{∞} because plasma drug concentration declines exponentially. The C_{av}^{∞} is equal to the AUC $\int_{t_1}^{t_2} C_p dt$ for a dosage interval at steady state divided by the dosage interval .

$$C_{av}^{\infty} = \frac{[AUC]_{t_1}^{t_2}}{\tau} \quad (8.18)$$

The AUC is related to the amount of drug absorbed divided by total body clearance (Cl), as shown in the following equation.

$$[AUC]_{t_1}^{t_2} = \frac{FD_0}{Cl_{\tau}} = \frac{FD_0}{kV_D} \quad (8.19)$$

Substitution of FD_0/kV_D for AUC in Equation 8.18 gives Equation 8.17. Equation 8.17 or 8.18 can be used to obtain C_{av}^{∞} after a multiple-dose regimen regardless of the route of administration.

It is sometimes desirable to know the plasma drug **concentration at any time** after the administration of **n doses of drug**. The general expression for calculating this plasma drug concentration is

$$C_P = \frac{D_0}{V_D} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right) e^{-kt} \quad (8.20)$$

where n is the number of doses given and t is the time after the n th dose. At steady state, $e^{-nk\tau}$ approaches zero and Equation 8.20 reduces to

$$C_P^\infty = \frac{D_0}{V_D} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-kt} \quad (8.21)$$

MULTIPLE-ORAL-DOSE REGIMEN

and present typical cumulation curves for the concentration of drug in the body after multiple oral doses given at a constant dosage interval. The plasma concentration at any time during an oral or extravascular multipledose regimen, **assuming a one-compartment model and constant doses and dose interval, can be determined as follows:**

$$C_P = \frac{Fk_a D_0}{V_D (k - k_a)} \left[\left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}} \right) e^{-k_a t} - \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right) e^{-kt} \right] \quad (8.34)$$

where n = number of doses, τ = dosage interval, F = fraction of dose absorbed, and t = time after administration of n doses.

LOADING DOSE

Since extravascular doses require time for absorption into the plasma to occur, therapeutic effects are delayed until sufficient plasma concentrations are achieved. To reduce the onset time of the drug—that is, **the time it takes to achieve the minimum effective concentration (assumed to be equivalent to the C_{av}^{∞} -a loading (priming) or initial dose of drug is given.**

The main objective of the loading dose is to achieve desired plasma concentrations, C_{av}^{∞} as quickly as possible. If the drug follows one-compartment pharmacokinetics, then, steady state is also achieved immediately following the loading dose.

Thereafter, a maintenance dose is given to maintain C_{av}^{∞} and steady state so that the therapeutic effect is also maintained. In practice, a loading dose may be given as a bolus dose or a short-term loading IV infusion.

As discussed earlier, the time required for the drug to accumulate to a steady-state plasma level is dependent mainly on its elimination half-life. The time needed to reach 90% of C_{av}^{∞} is approximately 3.3 half-lives, and the time required to reach 99% of C_{av}^{∞} is equal to approximately 6.6 half-lives. For a drug with a half-life of 4 hours, it will take approximately 13 and 26 hours to reach 90% and 99% of C_{av}^{∞} , respectively.

For drugs absorbed rapidly in relation to elimination ($k_a \gg k$) and are distributed rapidly, the loading dose DL can be calculated as follows:

$$\frac{D_L}{D_0} = \frac{1}{(1 - e^{-k_a\tau})(1 - e^{-k\tau})} \quad (8.42)$$

For extremely rapid absorption, as when the product of kaT is large or in the case of IV infusion, e^{-kaT} becomes approximately zero and Equation 8.42 reduces to

$$\frac{D_L}{D_0} = \frac{1}{1 - e^{-k\tau}} \quad (8.43)$$

The loading dose should approximate the amount of drug contained in the body at steady state. The dose ratio is equal to the loading dose divided by the maintenance dose.

$$\text{Dose ratio} = \frac{D_L}{D_0} \quad (8.44)$$

As a general rule, the dose ratio should be equal to 2.0 if the selected dosage interval is equal to the elimination half-life.

Figure 8-5.

