11

Multiple dosing: intravenous bolus administration

Objectives

Upon completion of this chapter, you will have the ability to:

- use the Dost ratio to transform a single dose equation into a multiple dose equation
- calculate plasma drug concentration at any time *t* following the *n*th intravenous bolus dose of a drug
- calculate peak, trough and average steady-state plasma drug concentrations
- explain the role of dose (X_0) and dosing interval (τ) in the determination of average steady-state drug concentration
- design a dosage regimen that will yield the target average steady-state plasma concentration in a particular patient
- explain and calculate the accumulation ratio (R)
- explain and calculate drug concentration fluctuation at steady state (Φ)
- calculate the number of doses, n, required to reach a given fraction of steady-state (f_{ss})
- calculate the number of elimination half lives (N) required to reach a given fraction of steady state
- calculate loading and maintenance intravenous bolus doses.

11.1 Introduction

Some drugs, such as analgesics, hypnotics and antiemetics, may be used effectively when administered as a single dose. More frequently, however, drugs are administered on a continual basis. In addition, most drugs are administered with sufficient frequency that measurable and, often, pharmacologically significant concentrations of drug remain in the body when a subsequent dose is administered.

For drugs administered in a fixed dose and at a constant dosing interval (e.g. 250 mg every 6 h), the peak plasma concentration following the second and succeeding doses of a drug is higher than the peak concentration following the administration of the first dose. This results in an accumulation of drug in the body relative to the first dose. Additionally, at steady state, the plasma concentration of drug during a dosing interval at any given time since the dose was administered will be identical.

When a drug is administered on a continual basis, the rate and extent of accumulation is a function of the relative magnitudes of the dosing interval and the half life of the drug.

A single intravenous bolus dose (one compartment)

Figure 11.1 illustrates a typical plasma concentration versus time profile following the administration of a single intravenous bolus dose of a drug that follows first-order elimination and one-compartment distribution.

Two equations, introduced in earlier chapters, describe the data points over time after an intravenous bolus dose:

$$X = X_0 e^{-Kt} \tag{11.1}$$

and

$$C_p = (C_p)_0 e^{-Kt} \tag{11.2}$$

At $t = 0$, $X = X_0$ and $C_p = (C_p)_0$ (i.e. highest or maximum or peak plasma concentration, or intercept of the concentration versus time plot) and, at $t = \infty$, $X = 0$ and $C_p = 0$.

Multiple dosing concepts

Under the condition illustrated in Fig. 11.2, plasma concentration of a drug at a given time will be identical following the administration of the first, second, third and all subsequent doses as long as the administered dose (X_0) remains unchanged and the time between subsequent doses is very long (greater than seven or eight elimination half lives). This is because there is essentially no drug accumulation in the body; in other words, there is no drug left in the body from previous doses.

In reality, however, most therapeutic agents (antihypertensive agents, antianxiety medications, antiepileptics and many more) are administered at finite time intervals. For drugs administered in a fixed dose and at a constant dosing interval (e.g. 250 mg every 6 h), the peak plasma level (highest plasma concentration), following the administration of second and each succeeding dose of a drug, is higher than the peak concentration following the administration of the first dose (Fig. 11.3). This phenomenon is the consequence of drug accumulation in the body relative to the first dose. Additionally, at steady state, the plasma concentration of drug at any given point in time during the dosing interval will be identical.

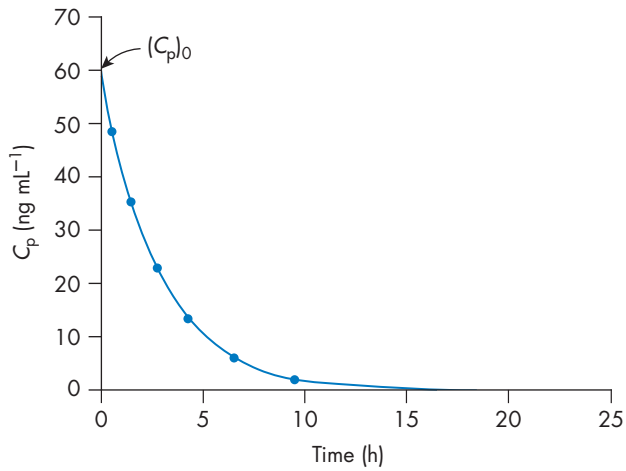

Figure 11.1 A typical plasma concentration (C_p) versus time profile for a single intravenous bolus dose of a drug that follows first-order elimination and has one compartment distribution. $(C_p)_0$: the initial and highest plasma concentration attained (the *y*-axis intercept of the concentration versus time plot).

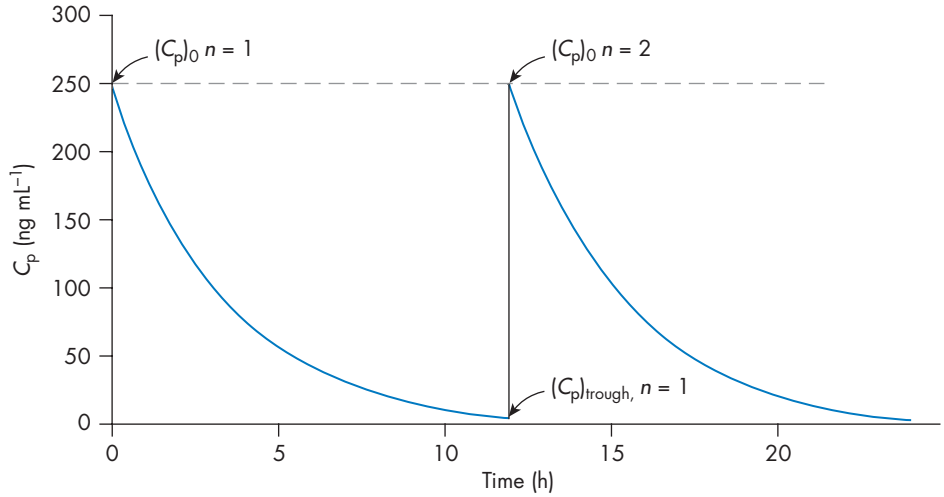

Figure 11.2 Plasma concentration (C_p) versus time profile following the administration of dose of a drug as an intravenous bolus ($n = 1$). Please note that the second identical dose ($n = 2$) was administered after a long interval. (It is assumed that the interval is > 10 half lives of drug and, therefore, there is an insignificant amount of drug left in the blood from the first dose.)

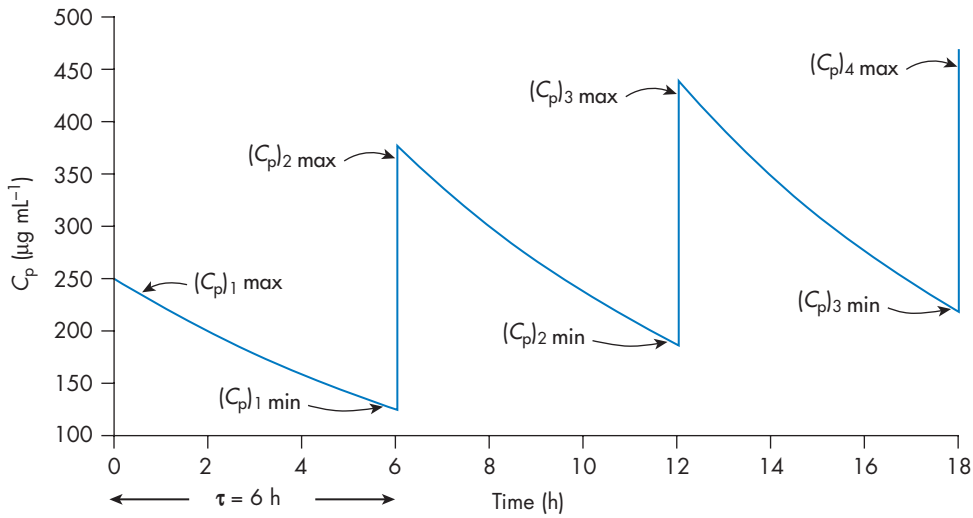

Figure 11.3 Plasma concentration (C_p) versus time profile following the administration by intravenous bolus of identical doses of a drug (1–4) at identical dosing intervals (τ). Please note that peak plasma concentration or, for that matter, the plasma concentration at any given time for the second, the third and subsequent doses are higher than for the first dose (because of drug accumulation). min, minimum; max, maximum.

Following the administration of a number of doses (theoretically an infinite number of doses, and practically greater than seven or eight doses) of a suitable but identical size and at a suitable but identical dosing interval, the condition is reached where the administration of a chosen dose (X_0) and dosing interval (τ) will provide, at steady state, all concentrations within the therapeutic range of a drug (Fig. 11.4)

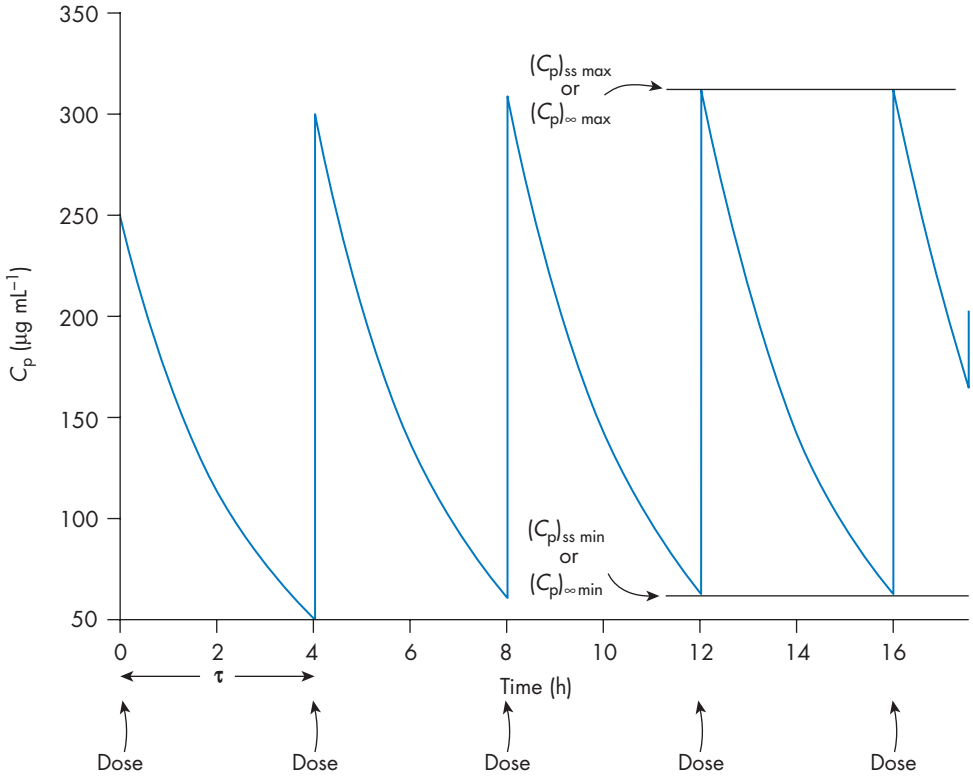

Figure 11.4 Plasma concentration (C_p) versus time profile following the administration of an identical intravenous bolus dose of a drug at an identical dosing interval (τ). Please note that the steady-state (ss) peak plasma concentrations are identical. Similarly, the steady-state plasma concentrations at any given time after the administration of a dose are identical. min, minimum; max, maximum.

Important definitions in multiple dosing

Dosage regimen. The systematized dosage schedule for a drug therapy, or the optimized dose (X_0) and dosing interval (τ) for a specific drug.

Drug accumulation (R). The build up of drug in the blood/body through sequential dosing.

Steady-state condition. Steady state is achieved at a time when, under a given dosage regimen, the mass (amount) of drug administered (for intravenous) or absorbed (for extravascular route), is equal to the mass (amount) of drug eliminated over a dosing interval.

Loading dose (D_L). A single intravenous bolus dose administered in order to reach steady-state condition instantly.

Maintenance dose (D_m). The dose administered every dosing interval to maintain the steady-state condition.

Multiple dosing assumptions

In obtaining expressions for multiple dosing, the following theoretical assumptions or suppositions are made, though they may not always be valid.

1. Linear pharmacokinetics applies; that is, the rate process obeys passive diffusion and first-order elimination kinetics (please review first-order process).
2. Tissues can take up an infinite amount of drug, if necessary.
3. The apparent volume of distribution (V), elimination half life ($t_{1/2}$) and the elimination rate

constant (K) are independent of the number of administered doses.
4. The time interval (τ [tau]) between dosing or successive doses is constant.
5. The administered dose (X_0) is equal at each successive time interval.

It should be noted that, in practice, some of the assumptions may not be valid for some drugs (e.g. salicylate, ethanol, phenytoin), for which capacity- limited kinetics (i.e. non-linear kinetics) may apply.

Before proceeding further on this important topic and for the purpose of simplifying complex-looking equations into more manageable and practical equations, we will reiterate the significance of the term e^{-Kt}, which has been so ubiquitous in this text. Please note that when $t=0$, $e^{-Kt}=1$ and when $t=\infty$, $e^{-Kt}=0$. Furthermore, it is of paramount importance to recognize that the size of the dose administered, dosing interval and the concept of measuring dosing interval in terms of the number of elimination half lives (N) of a drug play a pivotal role in assessing, computing, evaluating and examining numerous parameters that are salient features accompanying multiple-dosing pharmacokinetics.

It is also worth mentioning here that the pharmacokinetic parameters obtained following the administration of a single dose of a drug, intra- or extravascularly, may prove to be helpful while tackling some equations in multiple-dosing pharmacokinetics. This includes the intercepts of the plasma concentration versus time data, the systemic clearance and the absolute bioavailability of a drug, when applicable.

11.2 Useful pharmacokinetic parameters in multiple dosing

The following parameters are of importance.

1. The Dost ratio (r).
2. The (amount and) concentration of drug in the body at any time t during the dosing interval following administration of the nth (i.e. first dose, second dose, third dose, fourth dose, etc.) dose of a drug as an intravenous bolus or by an extravascular route.
3. The maximum and minimum (amount and) concentration

$$[(C_{p_n})_{max} \text{ and } (C_{p_n})_{min}]$$

of a drug in the body, following the administration of dose of a drug as an intravenous bolus or by an extravascular route.
4. The steady-state plasma concentrations $[(C_p)_\infty]$: attained only after administration of many doses (generally more than seven or eight).
5. The maximum and minimum plasma concentrations at steady state $[(C_p)_{\infty max}$ and $(C_p)_{\infty min}]$ following administration of a drug as an intravenous bolus or by an extravascular route.
6. The ''average'' steady-state plasma concentration, $(\overline{C}_p)_{ss}$, for an intravenous bolus dose and for an extravascular dose.
7. Drug accumulation (R), determined by different methods, for an intravenous bolus and extravascular route.
8. Fluctuation (Φ), determined following the administration of drug as an intravenous bolus.
9. Number of doses (n) required to attain a given fraction of steady state (f_{ss}), following the administration of drug as an intravenous bolus or by an extravascular route.
10. Calculation of loading (D_L) and maintenance dose (D_m) for both intravenous bolus and extravascular routes.

The Dost ratio (r)

The Dost ratio permits the determination of the amount and/or the plasma concentration of a drug in the body at any time t (range, $t=0$ to $t=\tau$) following the administration of the nth (i.e. second dose, third dose, fourth dose, etc.) dose by intravascular and/or extravascular routes. In other words, this ratio will transform a single dose equation into a multiple-dosing equation.

$$r = \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} \tag{11.3}$$

where r is the Dost ratio (named after a German scientist who developed this equation); n is the number of administered doses (range from 1 to ∞); K is the the first-order elimination rate constant; and τ is the the dosing interval (i.e. 4 h, 6 h, 8 h, etc.).

Use of the dost ratio for intravenous bolus administration (one compartment)

Inserting the Dost ratio (i.e. Eq. 11.3) between the terms X_0 and e^{-Kt} of Eq. 11.1 ($X = X_0e^{-Kt}$) or between $(C_p)_0$ and e^{-Kt} of Eq. 11.2 ($C_p = (C_p)_0e^{-Kt}$) yields equations that permit the determination of the amount and/or plasma concentration of a drug in the body at any time, t, following administration of the nth dose.

$$(X_n)_t = \frac{X_0(1 - e^{-n K\tau})}{(1 - e^{-K\tau})} e^{-Kt} \qquad (11.4)$$

Since $X/V = C_p$ and dose$/V = (C_p)_0$, following substitution for $(X_n)_t$ with the concentration term $(C_p)_n$ and X_0 with $(C_p)_0$, Eq. 11.4 becomes:

$$(C_{p_n})_t = \frac{(C_p)_0(1 - e^{-n K\tau})}{(1 - e^{-K\tau})} e^{-Kt} \qquad (11.5)$$

In Eqs 11.4 and 11.5, X_0 is the the administered dose; $(C_p)_0$ is the the initial plasma concentration (dose/V); n is the nth dose; K is the the elimination rate constant; τ is the the dosing interval; and t is the time since the nth dose was administered.

The following important comments will help in understanding the underlying assumptions and the practical uses of Eqs 11.4 and 11.5.

1. There are two terms in Eqs 11.4 and 11.5 that will simplify these two equations into more practical equations: $e^{-nK\tau}$ and e^{-Kt}.
2. When $n = 1$ (i.e. administration of the first dose), Eqs 11.4 and 11.5 will simplify or collapse into equations for a single dose (i.e. $X = X_0e^{-Kt}$ [Eq. 11.1] or $C_p = (C_p)_0e^{-Kt}$ [Eq. 11.2]).
3. When $n = \infty$ (i.e. administration of many doses; generally more than eight or nine), the term $1 - e^{-nK\tau}$ of Eqs 11.4 and 11.5 approaches a value of 1 and, therefore "vanishes" from these equations.
4. It is important to note that, in multiple-dosing kinetics, $t \geq 0$ and $t \leq \tau$ (a value between dosing interval) following the administration of the dose.

For example, if a dose is administered every 8 h, time values will be between 0 and 8 h; $t = 0$ represents the time at which the dose is administered and $t = 8$ h represent τ. For the second and subsequent doses, therefore, we start again from time 0 to 8 h. Therefore, t in multiple dose pharmacokinetics is the time since the latest (nth) dose was given.

Equations 11.4 and 11.5 permit us to determine the amount and the concentration of drug, respectively, at a time (from 0 to τ) following the administration of the nth dose (first, second, third dose, fourth, etc.).

We know from general mathematical principles and previous discussions that at $t = 0$, $e^{-Kt} = 1$, and the plasma concentration (C_p) at this time is the highest plasma concentration or maximum plasma concentration $(C_p)_{max}$. Therefore, Eqs 11.4 and 11.5 reduce to:

$$(X_n)_{max} = \frac{X_0(1 - e^{-n K\tau})}{(1 - e^{-K\tau})} \qquad (11.6)$$

$$(C_{p_n})_{max} = \frac{(C_p)_0(1 - e^{-n K\tau})}{(1 - e^{-K\tau})} \qquad (11.7)$$

In Eq. 11.6, the term $(X_n)_{max}$ represents the maximum amount of drug in the body following administration of the nth dose (or an intravenous bolus, this will always occur at $t = 0$).

In Eq. 11.7, the term $(C_{p_n})_{max}$ represents the maximum plasma concentration of a drug in the body following the administration of the nth dose. (Again, for an intravenous bolus this will always occur at $t = 0$.)

When time is equal to τ (i.e. $t = \tau$), the body will display the minimum amount,

$$(X_n)_{min},$$

and/or the minimum plasma concentration,

$$(C_{p_n})_{min},$$

of a drug. Therefore, Eqs 11.4 and 11.5 reduce to:

$$(X_n)_{\min} = \frac{X_0(1-e^{-n K\tau})}{(1-e^{-K\tau})} e^{-K\tau} \qquad (11.8)$$

$$(C_{p_n})_{\min} = \frac{(C_p)_0(1-e^{-nK\tau})}{1-e^{-K\tau}} e^{-k\tau} \qquad (11.9)$$

In Eq. 11.8, the term $(X_n)_{\min}$ represents the minimum amount of a drug in the body following administration of the *n*th dose. (This will always occur at $t=\tau$, regardless of the route of administration.)

In Eq. 11.9, the term $(C_{p_n})_{\min}$ represents the minimum plasma concentration of a drug in the body following administration of the *n*th dose (it will also always occur at time, $t=\tau$). Please note that this concentration is referred to, in clinical literature, as the ''trough'' plasma concentration. Please note that the only difference between Eqs 11.6 and 11.8 (for expressing the amount) and Eqs 11.7 and 11.9 (for expressing the concentration) is the term $e^{-K\tau}$. This simply reflects the time of occurrence of the maximum and minimum amount (or concentration) of drug in the body as illustrated in Fig. 11.5.

Steady-state plasma concentration

The steady-state condition is attained following the administration of many doses (when *n* is a high number) of a drug (i.e. $n \approx \infty$). When *n* approaches infinity, the value for the term $e^{-nK\tau}$ approaches 0; and therefore $1 - e^{-nK\tau} \approx 1.0$ in Eqs 11.4 and 11.5 and X_n and C_{p_n} become equal to X_∞ and $(C_p)_\infty$, respectively.

$$(X_\infty)_t = \frac{X_0}{(1-e^{-K\tau})} e^{-Kt} \qquad (11.10)$$

In Eq. 11.10, the term $(X_\infty)_t$ represents the amount of drug in the body at any time *t* (i.e. between $t>0$ and $t<\tau$) following the attainment of steady state. This will occur only after the administration of many doses.

$$(C_{p_\infty})_t = \frac{(C_p)_0}{(1-e^{-K\tau})} e^{-Kt} \qquad (11.11)$$

In Eq. 11.11, the term $(C_{p_\infty})_t$ represents the plasma concentration of drug in the body at any time *t* (i.e. between $t>0$ and $t<\tau$) following the

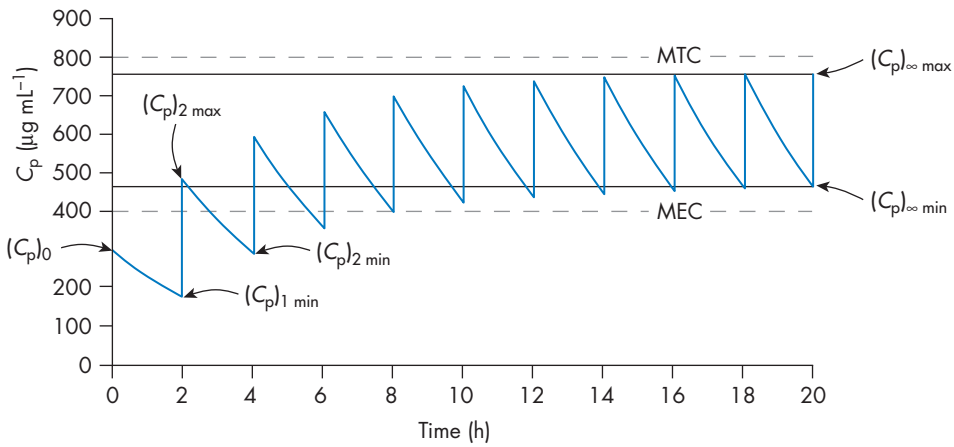

Figure 11.5 Maximum (max; peak) and minimum (min; ''trough'') plasma concentrations (C_p) following the administration of an identical intravenous bolus dose of a drug at an identical dosing interval. MTC, minimum toxic concentration; MEC, minimum effective concentration.

attainment of steady state. This will occur following the administration of many doses.

At this time, you are urged to consider the similarity between equations for a single intravenous bolus dose (Ch. 3) and multiple doses of intravenous bolus. You may notice an introduction of the term $1-e^{-nK\tau}$ in the denominator. Otherwise, everything else should appear to be identical.

Equation 11.11 permits the determination of plasma concentration at any time ($t=0$ to $t=\tau$), following the attainment of steady state. Please note that $(C_p)_0$ is the initial plasma concentration (dose/V) that can be obtained following the administration of a single dose. Therefore, if we know the dosing interval and the elimination half life of a drug, we can predict the steady-state plasma concentration at any time t (between 0 and τ) (Fig. 11.6).

The maximum and minimum plasma concentrations at steady state

For drugs administered intravenously, the maximum and minimum steady-state plasma concentrations will occur at $t=0$ and $t=\tau$, respectively, following the administration of many doses (i.e. n is large). Equation 11.11 may be used to determine the steady-state maximum and minimum plasma concentrations as follows:

$$(C_{p_\infty})_{max} \quad \text{or} \quad (C_{p_{ss}})_{max} = \frac{(C_p)_0}{(1-e^{-K\tau})} \tag{11.12}$$

In Eq. 11.12, the term $(C_{p_\infty})_{max}$ or $(C_{p_{ss}})_{max}$ represents the maximum plasma concentration of a drug in the body at the steady-state condition (i.e. following the administration of many doses). This maximum will occur only at $t=0$ (immediately after administration of the latest bolus dose) since $e^{-Kt}=1$, when $t=0$).

$$(C_{p_\infty})_{min} \quad \text{or} \quad (C_{p_{ss}})_{min} = \frac{(C_p)_0}{(1-e^{-K\tau})} e^{-K\tau} \tag{11.13}$$

In Eq. 11.13, the term $(C_{p_\infty})_{min}$ or $(C_{p_{ss}})_{min}$ represents the minimum or trough plasma concentration of a drug at steady-state condition (i.e. following the administration of many doses and when time since the latest dose, t, is equal to τ). Since Eq. 11.12,

$$\frac{(C_p)_0}{(1-e^{-K\tau})} = (C_{p_\infty})_{max}$$

substituting from Eq. 11.12 for the term $(C_{p_\infty})_{max}$ or $(C_{p_{ss}})_{max}$ in Eq. 11.13 yields the following equation:

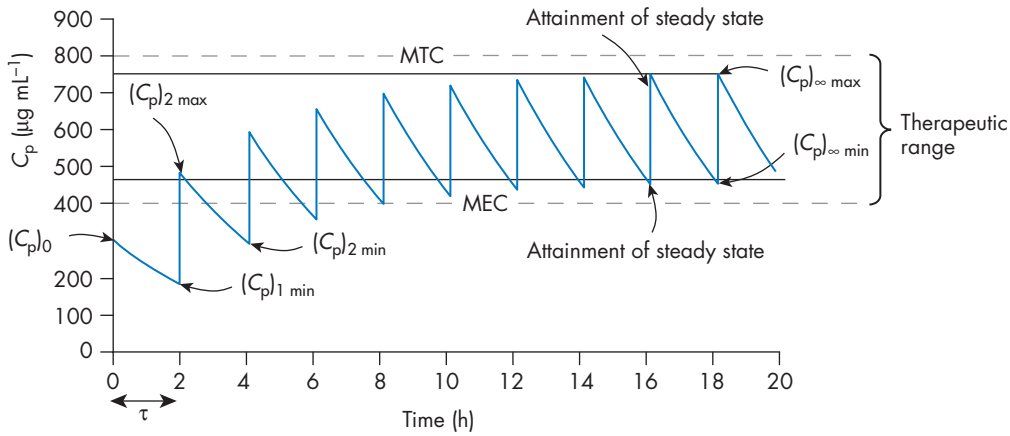

Figure 11.6 Plasma drug concentration (C_p) versus time profile following the intravenous bolus administration of many equal doses at an identical dosing interval (τ). In this representation, the dosing regimen has been designed so that the plasma drug concentrations will fall within the therapeutic range at steady state.

$$(C_{p_\infty})_{min} \quad \text{or} \quad (C_{p_{ss}})_{min} = (C_{p_\infty})_{max} e^{-K\tau} \tag{11.14}$$

Please note the importance of Eqs 11.12, 11.13 and 11.14 in multiple-dosing pharmacokinetics following the administration of drug as an intravenous bolus dose.

Equation 11.12 permits determination of maximum plasma concentration at steady state. A careful examination of Eq. 11.12 clearly suggests that peak steady-state concentration for a drug is influenced by the initial plasma concentration, the elimination rate constant and, more importantly, the dosing interval. And, since the administered dose is identical and the elimination rate constant is a constant for a given patient receiving a particular drug, the maximum plasma concentration at steady state is influenced only by the dosing interval. Therefore, more frequent administration (i.e. a smaller τ value) of an identical dose of a drug will yield a higher maximum plasma concentration at steady state. Conversely, less frequent administration (i.e. greater τ value) of an identical dose of a drug will yield a smaller maximum plasma concentration at steady state.

Equations 11.13 and 11.14 permit determination of the minimum or trough plasma concentration at steady state. A careful examination of the equation clearly suggests that the minimum or trough plasma concentration for a drug is influenced by the initial plasma concentration, the elimination rate constant and, more importantly, the dosing interval. Since the administered dose is identical and the elimination rate constant is a constant, the minimum plasma concentration at steady state is influenced only by the dosing interval.

Administration of an identical dose of a drug more frequently (i.e. a smaller τ value) will yield a higher minimum plasma concentration at steady state. Conversely, administration of the same dose of a drug less frequently (i.e. a greater τ value) will yield a smaller minimum plasma concentration at steady state.

If the dosing interval is very long (greater than seven or eight half lives of a drug, or infinity), what will be the maximum and minimum plasma concentrations at time infinity following the administration of an identical dose intravenously?

Please consider the following profiles:

1. Maximum or peak plasma concentration at steady state against the number of administered doses.
2. Minimum or trough plasma concentration at steady state against the number of administered doses.
3. Maximum or peak plasma concentration against the number of administered doses.
4. Minimum or trough plasma concentration against the number of administered doses.
5. Maximum or peak plasma concentration at steady state against the dosing interval.
6. Minimum or trough plasma concentration at steady state against the dosing interval.

Figure 11.7 shows the plasma concentration versus time profile following attainment of steady state for a drug administered by multiple intravenous bolus injections.

The "average" plasma concentration at steady state

A parameter that is very useful in multiple dosing is the "average" plasma concentration at steady state, $(\overline{C}_p)_{ss}$. Please note that the term average is in the quotation marks to signify that it does not carry the usual meaning (i.e. arithmetic mean). Although not an arithmetic average, this plasma concentration value will fall between the maximum and minimum steady-state plasma concentration values. This "average" concentration is the one desired therapeutically for patients on a regular dosage regimen. The parameter can be defined as:

$$(\overline{C}_p)_{ss} = \frac{\int_0^\tau C_{p_\infty} dt}{\tau} \tag{11.15}$$

where $\int_0^\tau C_{p_\infty} dt$ is the area under the plasma concentration time curve at steady state during dosing interval (τ). (i.e. between $t = 0$ and $t = \tau$).

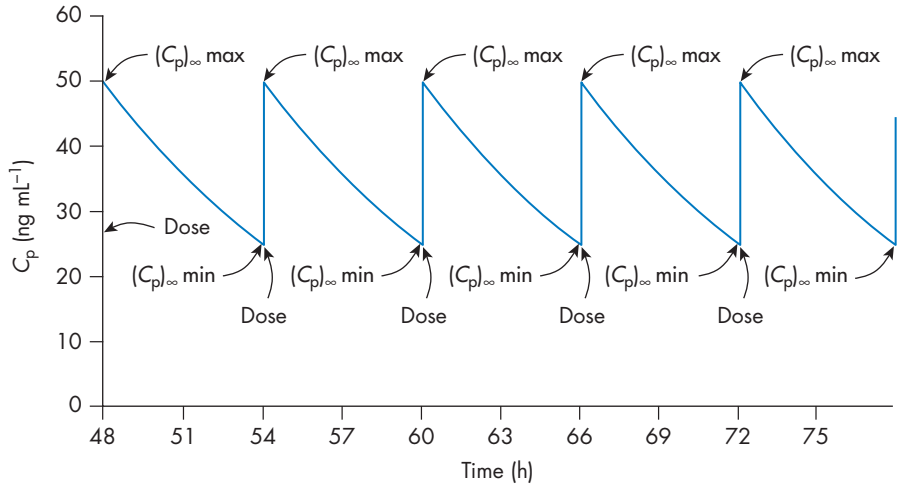

Figure 11.7 Plasma concentration (C_p) versus time profile following the attainment of steady-state condition for a drug administered by multiple intravenous bolus injections.

It may be shown that integration of Eq. 11.11, following substitution for $(C_p)_0$ with X_0/V, from $t=0$ to $t=\tau$ yields:

$$\frac{\int_0^\tau C_{p_\infty} dt}{\tau} = \frac{X_0}{VK} \tag{11.16}$$

Substitution of X_0/VK from Eq. 11.16 for the term $\int_0^\tau C_{p_\infty} dt$ in Eq. 11.15 yields:

$$(\overline{C}_p)_{ss} = \frac{X_0}{VK\tau} \tag{11.17}$$

where X_0 is the the administered dose; V is the the apparent volume of distribution; K is the the elimination rate constant; and τ is the the dosing interval.

Equation 11.17 indicates that knowing the apparent volume of distribution and the elimination rate constant of a drug, or the systemic clearance of a drug (all parameters obtained from a single intravenous bolus dose of a drug), the ''average'' plasma concentration of a drug at steady state following the intravenous administration of a fixed dose (X_0) at a constant dosing interval can be predicted. Furthermore, it should also be clear from Eq. 11.17 that only the size of the dose and the dosing interval need to be adjusted to obtain a desired ''average'' steady-state plasma concentration, since apparent volume of distribution, the elimination rate constant and systemic clearance are constant for a particular drug administered to an individual subject.

It should be noted that the ''average'' plasma concentration, obtained by employing Eqs 11.15 or 11.17, is neither the arithmetic nor the geometric mean of maximum and minimum plasma concentrations at infinity. Rather, it is the plasma concentration at steady state, which, when multiplied by the dosing interval, is equal to the area under the plasma concentration–time curve $(AUC)_0^\tau$ (i.e. from $t=0$ to $t=\tau$).

$$(\overline{C}_p)_{ss}\tau = \int_0^\tau C_{p_\infty} dt \tag{11.18}$$

Therefore, from geometric considerations, ''average'' concentration must represent some plasma concentration value between the maximum and the minimum plasma concentrations at infinity.

The proximity between the values of the ''average'' steady-state concentration and the arithmetic mean of the maximum and the minimum plasma concentrations at infinity is solely

influenced by the chosen dosing interval. The smaller the dosing interval (i.e. more frequent administration of a dose), the greater will be the proximity between the "average" steady-state concentration and the arithmetic mean of the maximum and the minimum plasma concentrations at infinity.

From Ch. 4, we know that:

$$\int_0^\infty C_p dt = (\text{AUC})_0^\infty \tag{11.19}$$

and

$$(\text{AUC})_0^\infty = \frac{Dose}{Cl_s} = \frac{Dose}{VK} \tag{11.20}$$

By substitution for $(\text{AUC})_0^\infty$ in Eq. 11.19, we obtain:

$$\int_0^\infty C_p dt = \frac{X_0}{VK} \tag{11.21}$$

Equation 11.21 and Eq. 11.16 both equal X_0/VK. Therefore, Eq. 11.21 for $(\text{AUC})_0^\infty$ (following the administration of a single intravenous bolus dose) is equivalent to Eq. 11.16, an equation for $(\text{AUC})_0^\tau$ during dosing interval at steady state. Therefore, $(\text{AUC})_0^\tau$ at steady state is equivalent to the total area under the curve following a single dose (Fig. 11.8 and 11.9).

This allows us to calculate the "average"-plasma concentration of a drug at steady state from a single dose study by employing the following equation:

$$(\overline{C}_p)_{ss} = \frac{\int_0^\infty C_p dt}{\tau} \tag{11.22}$$

And since dose/$VK = (\text{AUC})_0^\infty$ following the administration of a single intravenous bolus dose, substituting for the term dose/VK in Eq. 11.17 with the term $(\text{AUC})_0^\infty$ yields the following equation:

$$(\overline{C}_p)_{ss} = \frac{(\text{AUC})_0^\infty}{\tau} \tag{11.23}$$

Please note, Eqs 11.22 and 11.23 do not require the calculation or the knowledge of the apparent volume of distribution, the elimination rate constant or the dose given every dosing interval. These equations, however, do assume that apparent volume of distribution, the elimination rate constant and the dose are constants over the entire dosing period. In Eq. 11.23, please note that the term $(\text{AUC})_0^\infty$ is the area under the plasma concentration time curve following the administration of a single dose. Therefore, the dosing

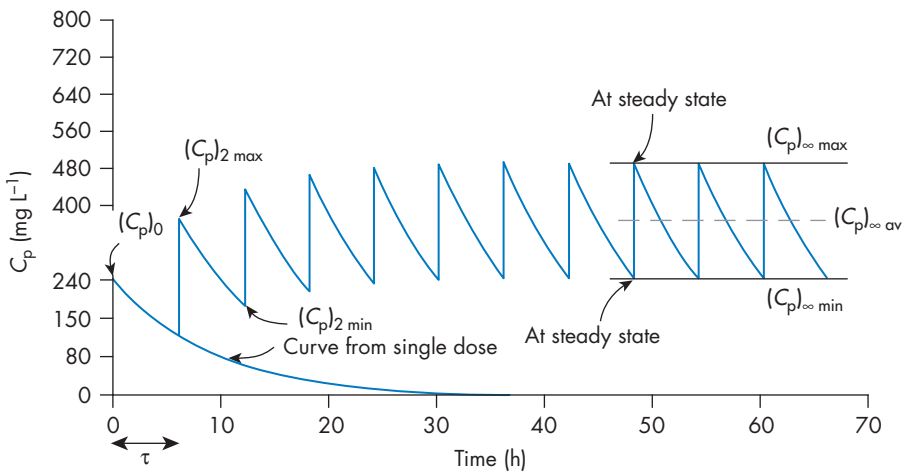

Figure 11.8 Plasma concentration (C_p) versus time profile following the administration of a single dose and multiple doses of a drug as intravenous bolus. min, minimum; max, maximum; av, average.

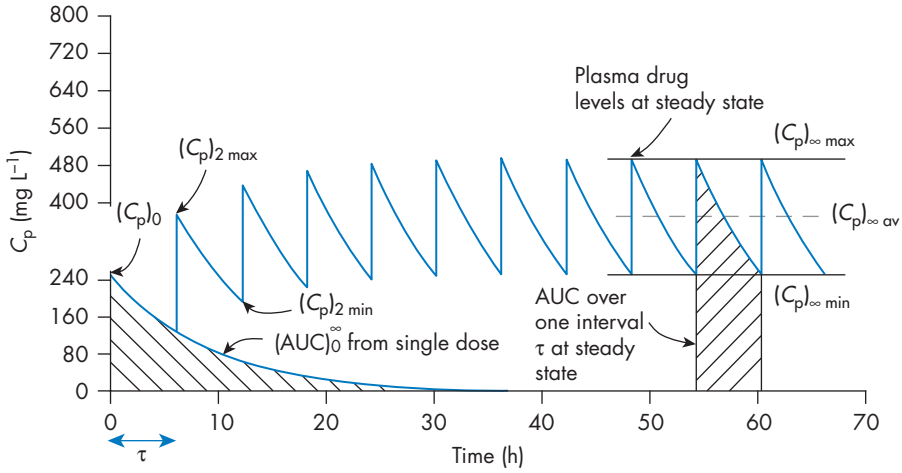

Figure 11.9 Plasma concentration (C_p) versus time profile following the administration of multiple intravenous bolus doses of a drug. min, minimum; max, maximum; av, average; τ, dosing interval.

interval is the only factor that influences the ''average'' steady-state concentration for a specified dose in a particular individual.

More frequent administration of an identical dose, therefore, will yield a higher ''average'' steady-state concentration.

Important comments on ''average'' steady state concentration

Regardless of the route of drug administration, the ''average'' plasma concentration at steady state is influenced by the dose administered, the fraction of the administered dose that reaches the general circulation (for extravascular routes), the systemic clearance of the drug and the chosen dosing interval.

In a normal subject, systemic clearance of a drug is constant and it is presumed to be independent of the dose administered and the route of administration; therefore, it will not play any role in influencing the ''average'' steady-state concentration. The ''average'' steady-state plasma concentration will be influenced by the three remaining parameters: the dose administered, the chosen dosing interval and the absolute bioavailability (F), when applicable.

The ''average'' plasma concentration is always directly proportional to the dose administered (linear pharmacokinetics). The term dosing interval is in the denominator of Eq. 11.17. Therefore, the larger the dosing interval, the lower will be the ''average'' steady-state plasma concentration (assuming, of course, the dose remains unchanged). If, however, the ratio of dose over dosing interval is maintained constant, the ''average''steady-state concentration will remain unchanged. For example, administration of a 400 mg dose of a drug at every 8 h (i.e. 50 mg h^{-1}) or the administration of 200 mg dose at every 4 h (i.e. 50 mg h^{-1}) will provide identical ''average'' steady-state plasma concentrations.

When a drug is administered by an extravascular route, it must be remembered that the fraction of the administered dose reaching the general circulation, or absolute bioavailability, plays an influential role (see Ch. 12). In addition, since the absolute bioavailability of a drug is influenced by the route of drug administration, the chosen dosage form and the formulation of a chosen dosage form, administration of the same dose of the same drug is likely to provide different ''average'' steady-state concentration. This, of course, assumes that the systemic clearance of a drug is not affected by any of these factors and the dosing interval is identical.

In renally impaired subjects, there will be a decrease in the systemic clearance of a drug eliminated by the kidneys; and, therefore, the normal dosage regimen of that drug will provide higher ''average'' steady-state concentration (Eq. 11.17).

This, therefore, requires adjustment in the dosage regimen. The dosage adjustment, in turn, can be accomplished by three approaches.

1. Administration of a smaller dose at a normal dosing interval.
2. Administration of a normal dose at a longer dosing interval (i.e. decreasing the frequency of drug administration).
3. A combination of both (i.e. administration of a smaller dose less frequently).

Please consider the following profiles.

1. "Average" concentration at steady state against the administered dose.
2. "Average" concentration at steady state against the systemic clearance (for a fixed dosage regimen).
3. "Average" concentration at steady state against the dosing interval.
4. "Average" concentration at steady state against the number of half-lives in a dosing interval.

11.3 Designing or establishing the dosage regimen for a drug

The following approach is recommended for the purpose of designing or establishing the dosage regimen for a drug:

1. Know the therapeutic range and/or the effective concentration range for the drug.
2. Select the desired or targeted "average" steady-state plasma concentration. It is a common practice to choose the mean of the therapeutic range of the drug as a starting desired "average" steady-state plasma concentration. For example, if the therapeutic range is 10–30 $mg\,L^{-1}$, choose 20 $mg\,L^{-1}$ as the targeted "average" steady-state concentration.
3. Use Eq. 11.17 (for an intravenous bolus administration):

$$(\overline{C}_p)_{ss} = \frac{X_0}{VK\tau}$$

Rearrange Eq. 11.17

$$(\overline{C}_p)_{ss} VK = \frac{X_0}{\tau}$$

4. Select the dosing interval (it is a safe and good practice to start with a dosing interval equal to the drug's elimination half life).
5. Using this dosing interval, and rearranging the equation in Step 3, calculate the dose (X_0) needed to attain the desired "average" steady-state concentration.

$$(\overline{C}_p)_{ss} VK\tau = X_0$$

$\mu g\,mL^{-1} \times mL\,h^{-1} \times h = dose$ (μg) or $\mu g\,mL^{-1} \times mL\,kg^{-1}\,h^{-1} \times h = dose$ ($\mu g\,kg^{-1}$).
6. Round off the number for the calculated dose and the chosen dosing interval. For example, a calculated dose of 109.25 mg may be rounded off to the nearest whole number of the commercially available product (i.e. 100 or 125 mg), whichever is more practical. The half life of 4.25 h may be rounded off to 4 h.
7. Using the rounded numbers for the dose and dosing interval, calculate the "average" steady-state concentration, peak steady-state concentration and trough steady-state concentration.
8. Make sure, by performing calculations, that the calculated peak steady-state concentration is below the minimum toxic concentration and calculated trough steady-state concentration is above the minimum effective concentration.
9. If necessary, make small adjustments (fine tuning) in the dose and dosing interval.

While designing the optimum and practical dosage regimen for a drug administered extravascularly, the approach and steps involved are identical; however, it is important to take into consideration the absolute bioavailability of drug, which may vary depending upon the dosage form, route of drug administration and the formulation (see Ch. 12).

11.4 Concept of drug accumulation in the body (*R*)

As mentioned in the introduction to this chapter, the administration of a drug in a multiple dose

regimen will always result in the accumulation of drug in the body. The extent of accumulation (R) of a drug may be quantified in several ways.

Calculation of drug accumulation from the "average" plasma concentration

During any dosing interval, the "average" plasma concentration of a drug may be defined as:

$$(\overline{C}_p)_n = \frac{\int_0^{\tau} C_{p_n} dt}{\tau}$$

where $\int_0^{\tau} C_{p_n} dt$ is the area under the plasma concentration time curve during the nth dosing interval.

Integrating Equation 11.5 from $t=0$ to $t=\tau$, following substituting of dose/V for $(C_p)_0$, yields:

$$\int_0^{\tau} C_{p_n} dt = \frac{X_0}{VK}[1 - e^{-nK\tau}] \tag{11.24}$$

This is the same as:

$$(\overline{C}_p)_n = \frac{X_0}{VK\tau}[1 - e^{-nK\tau}] \tag{11.25}$$

However, Eq. 11.17

$$\frac{X_0}{VK\tau} = (\overline{C}_p)_{ss}$$

Substitution for the term $X_0/VK\tau$ (Eq. 11.17) into Eq. 11.25 gives:

$$(\overline{C}_p)_n = (\overline{C}_p)_{ss}[1 - e^{-nK\tau}] \tag{11.26}$$

Rearrangement of Eq. 11.26 yields:

$$\frac{(\overline{C}_p)_n}{(\overline{C}_p)_{ss}} = [1 - e^{-nK\tau}] \tag{11.27}$$

When $n=1$ (i.e. following the administration of the first dose), Eq. 11.27 becomes

$$\frac{(\overline{C}_p)_1}{(\overline{C}_p)_{ss}} = [1 - e^{-K\tau}] \tag{11.28}$$

The inverse ratio, $(C_p)_{ss}/(C_p)_1$, may be defined as an accumulation factor (R); hence,

$$\frac{(\overline{C}_p)_{ss}}{(\overline{C}_p)_1} = \frac{1}{1 - e^{-K\tau}} \tag{11.29}$$

From the knowledge of the elimination rate constant and/or the elimination half life of a drug and the dosing interval, the extent to which a drug would accumulate in the body following a fixed dosing regimen can be computed by employing Eq. 11.29.

Use of other ratios to calculate drug accumulation

We know that the minimum amount of drug in the body, following the administration of a first intravenous dose, can be obtained by using the equation below:

$$(X_1)_{min} = X_0 e^{-K\mathrm{T}} \tag{11.30}$$

In concentration terms (since $X = \mathrm{V}C_p$), Eq. 11.30 becomes:

$$(C_{p_1})_{min} = \frac{X_0}{V} e^{-K\tau} = (C_p)_0 e^{-K\tau} \tag{11.31}$$

We also know that $(X_1)_{max} = X_0 =$ dose.

$$(C_{p_1})_{max} = \frac{X_0}{V} = (C_p)_0 \tag{11.32}$$

We also know from Eqs 11.12 and 11.13 that

$$(C_{p_\infty})_{max} = \frac{(C_p)_0}{(1 - e^{-K\tau})}$$

and

$$(C_{p_\infty})_{min} = \frac{(C_p)_0}{(1 - e^{-K\tau})} e^{-K\tau}$$

The ratio of $(C_{p\infty})_{min}$ to $(C_{p1})_{min}$, (i.e. Eq. 11.13 to Eq. 11.31) and $(C_{p\infty})_{max}$ to $(C_{p1})_{max}$, (i.e. Eq. 11.12 to Eq. 11.32) yields an accumulation factor (R):

$$R = \frac{(C_{p_\infty})_{min}}{(C_{p_1})_{min}} = \frac{\frac{(C_p)_0}{(1-e^{-K\tau})}e^{-K\tau}}{(C_p)_0 e^{-K\tau}} = \frac{1}{1-e^{-K\tau}} \tag{11.33}$$

Analogously,

$$R = \frac{(C_{p_\infty})_{max}}{(C_{p_1})_{max}} = \frac{\frac{(C_p)_0}{(1-e^{-K\tau})}}{(C_p)_0} = \frac{1}{1-e^{-K\tau}} \tag{11.34}$$

Thus, a comparison of ''average'' concentration, minimum concentration and maximum plasma concentrations of a drug following the administration of the first dose and at steady state provides an insight into the extent to which a drug would be expected to accumulate upon multiple-dosing administrations.

Important comments on drug accumulation

As mentioned in the introduction, the administration of a drug on a multiple dose regimen will result in accumulation of drug in the body. The drug accumulation, indeed, is an indelible and salient feature of multiple-dosing pharmacokinetics.

It is important to understand that the numerical value for drug accumulation (i.e. for R), either calculated or reported, simply indicates how high the plasma concentration will be at steady state compared with the first dose of the drug at a comparable time within the dosage regimen.

For example, calculated or reported value of $R = 2$ simply suggests that the peak plasma concentration at steady state will be twice the peak plasma concentration for the first dose. Analogously, the minimum plasma concentration at steady state will be two times as high as the minimum plasma concentration for the first dose. An R value of 2 also means that the ''average'' plasma concentration at steady state will be twice the ''average'' plasma concentration for the first dose. This is applicable for an intravenous bolus of drug. Therefore, knowledge of the calculated or reported R value permits prediction of the peak, trough or ''average'' plasma concentrations at steady state from the knowledge of maximum, minimum or ''average'' plasma concentration for the first dose. Furthermore, knowledge of the R value may also provide useful information about the chosen dosing interval.

Careful examination of three equations (Eqs 11.29, 11.33 and 11.34) clearly indicates that, regardless of the method employed, drug accumulation solely depends on the dosing interval, since the elimination rate constant is a constant for a drug. Furthermore, Eqs 11.29, 11.33 and 11.34 suggest that the quantification of drug accumulation requires knowledge of the elimination rate constant of a drug and the dosing interval. The dosing interval can be measured in terms of the number of elimination half lives. Please attempt to find answers for the following questions:

- Will the administered dose of a drug affect drug accumulation? How will the profile (rectilinear paper) of drug accumulation against administered dose look?
- What will be the lowest value for drug accumulation? (Hint: if the dosing interval is equal to infinity, what will be value for R? Substitute for the term τ with ∞ in Eqs 11.29, 11.33 and 11.34.)
- What will the profile (rectilinear paper) of drug accumulation against dosing interval look like?
- What will the profile (rectilinear paper) of drug accumulation against dosing interval in terms of the number of half lives look like?
- If the subsequent doses are administered at a time equal to one half life of the drug, what will be the accumulation factor? In other words, if the dosing interval is equal to one half life of the drug, what will be the value of the accumulation factor? Will the drug accumulation be higher if the frequency of drug dosing is greater?

Calculation of drug accumulation

If the elimination half life of a drug is 24 h, for example,

$$K = 0.693/24 = 0.028875\ h^{-1} \approx 0.029\ h^{-1}$$

If a dose of this drug is administered every 24 h (i.e. $\tau = 24$ h or one half life of the drug), Eqs. 11.29, 11.33, and 11.34,

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

$$R = \frac{1}{1 - e^{-(0.029\ \mathrm{h}^{-1})(24\ \mathrm{h})}} = 2.0$$

If, however, a dose is administered more frequently (i.e. every 6 h, or $\tau = 6$ h or in this example, 25% of one half life of a drug), there will be greater accumulation of the drug, Eqs. 11.29, 11.33, and 11.34:

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

$$R = \frac{1}{1 - e^{-(0.029\ \mathrm{h}^{-1})(6\ \mathrm{h})}} = 6.25$$

Therefore, in this example, if the subsequent doses are administered at a 24 h interval (i.e. dosing interval equals one half life of the drug), the peak steady-state concentration, the trough steady-state concentration and the ''average'' steady-state concentration will be twice the corresponding plasma concentration for the first dose. Is it accurate to say that if the peak plasma concentration at steady state is twice the peak plasma concentration for the first dose then the dosing interval represents the half life of the drug?

If the subsequent doses are administered more frequently (every 6 h or $\tau = 0.25t_{1/2}$) the peak steady-state concentration, the trough steady-state concentration and the ''average'' steady-state concentration will be 6.25 times as high as the corresponding plasma concentration for the first dose. This is simply the consequence of the phenomenon of drug accumulation.

From calculations provided here, it is accurate to state that the failure to follow the dosage regimen (prescribed dose at a prescribed dosing interval) of a drug can result in serious consequences. Therefore, it is important that patients in your pharmacy, and/or a family member, follow the prescribed directions scrupulously, particularly for drugs that manifest a narrow therapeutic range and a long elimination half life. From your pharmacy experience, you may be aware that some patients tend to take selected therapeutic agents (generally controlled substances) more frequently than directed by a prescriber because of a ''feel good'' philosophy.

Please compare Eqs 11.29, 11.33 and 11.34, with Eqs 10.21 and 10.22 (intravenous infusion chapter) for a remarkable similarity.

By employing any one of the equations (i.e. Eqs 11.29, 11.33, and 11.34) and using dosing interval in terms of number of elimination half lives, one can construct a table (Table 11.1) illustrating the relationship between the dosing interval and drug accumulation.

Table 11.1 The relationship between drug accumulation (R) and the dosing interval (τ) in terms of number of elimination half life of a drug

No. elimination half lives in a dosing interval	Drug accumulation, or R value
0.25	6.24
0.5	3.41
1.0	2.00
2.0	1.33
3.0	1.14
4.0	1.07
∞	1.00

11.5 Determination of fluctuation (Φ): intravenous bolus administration

Fluctuation (Φ) is simply a measure of the magnitude of variation in, or the differences between, the peak and trough plasma concentrations at steady state or, by some definitions, the peak and ''average'' plasma concentrations at steady state.

Fluctuation, therefore, is simply a measure of the ratio of the steady-state peak or maximum plasma concentration to the steady-state minimum or trough plasma concentration of a drug or the ratio of the peak or maximum steady-state concentration to the ''average'' plasma concentration at steady state for the chosen dosage regimen.

The observed or calculated fluctuation for a dosage regimen of a drug also depends solely on the chosen dosing interval and, like drug accumulation, it is also expressed by using the concept of a numerical value.

A high fluctuation value indicates that the ratio of the steady-state peak or maximum concentration to the trough or minimum concentration is large. Conversely, a low fluctuation value suggests that the ratio of these concentrations is small. Ideally, it is preferable to have a smaller ratio (i.e. smaller Φ value) of maximum to minimum concentration at steady state, as illustrated in Fig. 11.10.

Calculation of fluctuation factor

By comparison of maximum concentration with minimum concentration at steady state

Eq. 11.12

$$(C_{p_\infty})_{max} \quad \text{or} \quad (C_{p_{ss}})_{max} = \frac{(C_p)_0}{(1 - e^{-K\tau})}$$

Eq. 11.13

$$(C_{p_\infty})_{min} \quad \text{or} \quad (C_{p_{ss}})_{min} = \frac{(C_p)_0}{(1 - e^{-K\tau})} e^{-K\tau}$$

Divide $(C_{p_{ss}})_{max}$ by $(C_{p_{ss}})_{min}$ (i.e. Eq. 11.12 by Eq. 11.13)

$$\frac{(C_{p_\infty})_{max} \text{ or } (C_{p_{ss}})_{max}}{(C_{p_\infty})_{min} \text{ or } (C_{p_{ss}})_{min}} = \frac{\frac{(C_p)_0}{(1 - e^{-K\tau})}}{\frac{(C_p)_0}{(1 - e^{-K\tau})} e^{-K\tau}} = \frac{1}{e^{-K\tau}} \tag{11.35}$$

If the dosing interval (τ) in Eq. 11.35 is expressed in terms of number (N) of elimination half lives ($t_{1/2}$), $N = \tau/t_{1/2}$ or $\tau = Nt_{1/2}$.

However, $K = 0.693/t_{1/2}$; therefore, $\tau = 0.693N/K$.

Substitute for τ and K in Eq. 11.35 gives:

$$\Phi = \frac{(C_{p_{ss}})_{max}}{(C_{p_{ss}})_{min}} = \frac{1}{e^{-\left(\frac{0.693}{t_{1/2}}\right)(N)(t_{1/2})}} = \frac{1}{e^{-(0.693)(N)}} \tag{11.36}$$

Equation 11.35 indicates that when N is small (i.e. dosing is more frequent), the range of drug concentrations is smaller (i.e. the difference between the maximum and minimum plasma concentrations, at steady state, will be smaller).

Hence, frequent dosing (smaller dose), if practical, is preferred over less-frequent larger doses in order to avoid a toxicity problem at steady state.

Table 11.2 shows that more frequent dosing (i.e. smaller N value) results in smaller ratio of maximum to minimum steady-state plasma concentrations.

Compare the accumulation and fluctuation values when the dosing interval is equal to one half life of the drug. Plot the graph of fluctuation against the dosing interval.

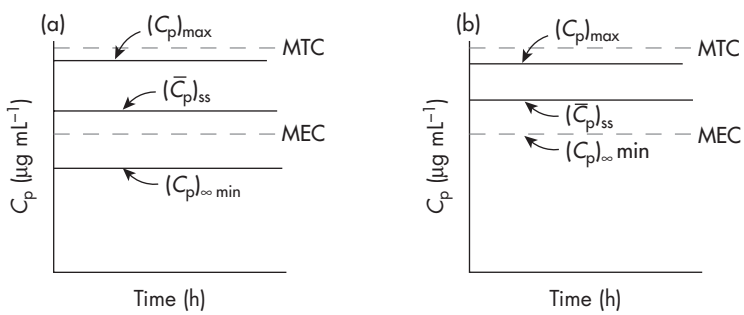

Figure 11.10 Plasma concentration (C_p) versus time plot illustrating high (a) and low (b) fluctuation (Φ) values following the attainment of the steady-state condition. min, minimum; max, maximum; MTC, minimum toxic concentration; MEC, minimum effective concentration.

By comparison of maximum concentration at steady state with "average" plasma concentration at steady state

Eq. 11.12

$$(C_{p_\infty})_{max} \quad \text{or} \quad (C_{p_{ss}})_{max} = \frac{(C_p)_0}{(1 - e^{-K\tau})}$$

and Eq. 11.17

$$(\overline{C}_p)_{ss} = \frac{X_0}{VK\tau}$$

Since dose/$V = (C_p)_0$,

$$\frac{(C_{p_{ss}})_{max}}{(\overline{C}_p)_{ss}} = \frac{\frac{(C_p)_0}{(1 - e^{-K\tau})}}{\frac{(C_p)_0}{K\tau}} = \frac{K\tau}{(1 - e^{-K\tau})}$$

However, since $\tau = Nt_{1/2}$ and $K = 0.693/t_{1/2}$, substitution for τ and K gives:

$$\frac{(C_{p_{ss}})_{max}}{(\overline{C}_p)_{ss}} = \frac{\left(\frac{0.693}{t_{1/2}}\right)(N)(t_{1/2})}{1 - e^{-\left(\frac{0.693}{t_{1/2}}\right)(N)(t_{1/2})}} = \frac{(0.693)(N)}{1 - e^{-(0.693)(N)}} \qquad (11.37)$$

Equation 11.37 gives the ratio of the maximum to "average" steady-state drug concentrations when there are N elimination half lives. The equation also indicates that the more frequent the dosing (N is smaller), the smaller is the ratio between the maximum and "average" drug concentration.

Important comments on drug fluctuation

It is clear from Eqs 11.36 and 11.37 and Table 11.2 that drug fluctuation, just as for drug accumulation, is simply a function of dosing interval and the elimination half life or elimination rate constant of a drug. Since the elimination half life and rate constant are constant for a particular drug administered to an individual patient, fluctuation is influenced only by the dosing interval. It should be clear from Table 11.2 that the more frequent the dosing of a drug, the smaller is the fluctuation (i.e. the smaller the difference between peak and trough concentrations at steady state and peak and "average" concentrations at steady state). Therefore, ideally and if practical and convenient for the patient, it is better to administer a smaller dose of a drug more frequently than a larger dose less frequently. In reality, however, convenience and practicality may prevail over what is ideal.

Table 11.2 Relationship between drug fluctuation (Φ)[a] and the dosing interval (τ) in terms of number of elimination half life of a drug

No. elimination half lives in a dosing interval	Drug fluctuation
0.5	1.41
1.0	2.0
2.0	4.0
3.0	8.0

[a] Drug fluctuation is the ratio of peak and trough plasma concentrations at steady state.

Let us take an example of metoprolol, a beta-blocker. It is better to administer 50 mg every 12 h rather than 100 mg every 24 h. If possible and practical, however, 25 mg every 6 h is even better.

The "average" steady-state plasma concentration of metoprolol from a 100 mg dose every 24 h, a 50 mg dose every 12 h or a 25 mg dose every 6 h will be identical; however, 25 mg every 6 h will provide peak, trough and "average" concentrations that are much closer to each other than can be achieved with 50 mg every 12 h or 100 mg every 24 h. By employing this more frequent dosing approach, one can optimize the dosage regimen in such a manner that, at steady state, all plasma concentration values will be in the therapeutic range of the drug; in other words, following the attainment of the steady-state condition, plasma concentration will remain in the therapeutic range as long as the patient follows the prescribed dosage regimen scrupulously.

11.6 Number of doses required to reach a fraction of the steady-state condition

The number of doses required to attain a given fraction of the steady-state condition may be calculated as follows, Eq. 11.5:

$$(C_{p_n})_t = \frac{(C_p)_0(1-e^{-nK\tau})}{(1-e^{-K\tau})}e^{-Kt}$$

where $(C_{p_n})_t$ is the plasma concentration at time t after the nth dose.

For steady state (i.e. after administration of many doses), Equation 11.5 becomes Eq. 11.11:

$$(C_{p_\infty})_t = \frac{(C_p)_0}{(1-e^{-K\tau})}e^{-Kt}$$

where $(C_{p_\infty})_t$ is the steady-state plasma concentration at time t.

Take the ratio of $(C_{p_n})_t$ to $(C_{p_\infty})_t$:

$$\frac{(C_{p_n})_t}{(C_{p_\infty})_t} = \frac{\frac{(C_p)_0(1-e^{-nK\tau})}{(1-e^{-K\tau})}e^{-Kt}}{\frac{(C_p)_0}{(1-e^{-K\tau})}e^{-Kt}} = f_{ss} = 1-e^{-nK\tau} \qquad (11.38)$$

where f_{ss} is the fraction of the steady state.

As $N=\tau/t_{1/2}$ or $\tau=Nt_{1/2}$, and $K=0.693/t_{1/2}$, τ and K in Eq. 11.38 can be substituted:

$$\frac{(C_{p_n})_t}{(C_{p_\infty})_t} = f_{ss} = 1-e^{-\frac{(n)(0.693)(N)(t_{1/2})}{t_{1/2}}}$$

$$f_{ss} = 1-e^{-0.693nN}$$

$$\ln(f_{ss}-1) = -0.693nN$$

or

$$n = -\ln(1-f_{ss})/0.693N \qquad (11.39)$$

where n is the number of doses required to reach a given fraction of the steady-state (f_{ss}) condition and N is the number of elimination half lives in the dosing interval.

Using Eq. 11.39, one can calculate the number of doses required to attain a fraction of steady-state concentration (Table 11.3).

Table 11.3 indicates that the more frequent the dosing (smaller N value or smaller dosing interval), the greater the number of doses required to reach a given fraction of steady-state condition.

11.7 Calculation of loading and maintenance doses

It may take a long time and the administration of many doses (over seven or eight) before the desired "average" steady-state drug concentration is attained. Therefore, an intravenous bolus loading dose (D_L) may be administered to obtain an instant steady-state condition. The calculated loading dose should be such that that, at time τ after its administration, the plasma concentration of drug is the desired minimum plasma concentration at steady state, that is:

Table 11.3 Relationship between the numbers (n) of doses required to attain a desired fraction of steady state (f_{ss}) and the dosing interval in terms of number of elimination half lives (N)

f_{ss}	n				
	$N=0.5$	$N=1.0$	$N=2.0$	$N=3.0$	$N\neq n$
0.50	2.00	1.00	0.50	0.33	1.00
0.90	6.64	3.32	1.66	1.11	3.32
0.95	8.64	4.32	2.16	1.44	4.32
0.99	13.29	6.64	3.32	2.21	6.64

$$(C_{p_{ss}})_{min} = \frac{D_L}{V} e^{-K\tau} \quad (11.40)$$

From Eq. 11.13 we know that:

$$(C_{p_{ss}})_{min} = \frac{X_0}{V} \frac{e^{-K\tau}}{(1 - e^{-K\tau})}$$

where X_0 is the intravenous bolus maintenance dose (D_m).

Equating Eqs 11.40 and 11.13, therefore, yields:

$$\frac{D_L}{V} e^{-K\tau} = \frac{D_M}{V} \frac{e^{-K\tau}}{(1 - e^{-K\tau})}$$

Upon simplification and rearrangement,

$$\frac{D_L}{D_M} = \frac{V e^{-K\tau}}{V(1 - e^{-K\tau}) e^{-K\tau}} = \frac{1}{1 - e^{-K\tau}} \quad (11.41)$$

Substituting for τ and K using $\tau = Nt_{1/2}$ and $K = 0.693/t_{1/2}$ gives:

$$\frac{D_L}{D_M} = \frac{1}{1 - e^{-\left(\frac{0.693}{t_{1/2}}\right)(N)(t_{1/2})}} = \frac{1}{1 - e^{-(0.693)(N)}} \quad (11.42)$$

Equations 11.41 and 11.42 provide the ratio of loading dose to maintenance dose required to attain the steady-state condition instantaneously when there are N elimination half lives in a dosing interval (τ). Furthermore, Eq. 11.42 indicates that the more frequent the dosing (i.e. smaller N value or τ), the larger is the loading dose required compared with the maintenance dose (i.e. the greater is the ratio of D_L/D_m) in order to attain the instantaneous steady-state condition.

From Table 11.4, it is clear that if we wish to attain immediately the desired steady-state concentration for a drug dosed at an interval equal to half the elimination half life of the drug, the loading dose required will be 3.41 times the maintenance dose of the drug. If the dosing interval is equal to the half life of the drug, the loading dose will be twice the maintenance dose.

Figure 11.11 illustrates a typical plasma concentration versus time profile following the administration of a series of single maintenance doses and administration of a loading dose followed by a series of maintenance doses.

Table 11.4 Relationship between the ratios of loading dose to maintenance dose required to attain the steady-state condition and the dosing interval in terms of number of elimination half lives (N)

N	Ratio loading dose/maintenance
0.5	3.41
1.0	2.00
2.0	1.33
3.0	1.14

11.8 Maximum and minimum drug concentration at steady state

For an intravenous bolus, the maximum drug concentration occurs at $t = 0$ after a dose at steady state, and the minimum drug concentration occurs at $t = \tau$ (i.e. one dosing interval after the dose is given).

At time t after a dose is given at steady state:

$$(C_{p_\infty})_t = \frac{X_0}{V} \frac{e^{-Kt}}{(1 - e^{-K\tau})}$$

When $t = 0$, $e^{-Kt} = 1.0$ and:

$$(C_{p_\infty})_{max} = (C_{p_{ss}})_{max} = \frac{X_0}{V(1 - e^{-K\tau})} \quad (11.43)$$

When $t = \tau$,

$$(C_{p_\infty})_{min} = (C_{p_{ss}})_{min} = \frac{X_0 e^{-K\tau}}{V(1 - e^{-K\tau})} \quad (11.44)$$

Subtracting $(C_{p_{ss}})_{min}$ from $(C_{p_{ss}})_{max}$ (i.e. Eq. 11.44 from Eq. 11.43) gives:

$$(C_{p_{ss}})_{max} - (C_{p_{ss}})_{min} = \frac{X_0}{V(1 - e^{-K\tau})} - \frac{X_0 e^{-K\tau}}{V(1 - e^{-K\tau})} = \frac{X_0 - X_0 e^{-K\tau}}{V(1 - e^{-K\tau})}$$

$$= \frac{X_0(1 - e^{-K\tau})}{V(1 - e^{-K\tau})} = \frac{\text{dose}}{V} = (C_p)_0 \quad (11.45)$$

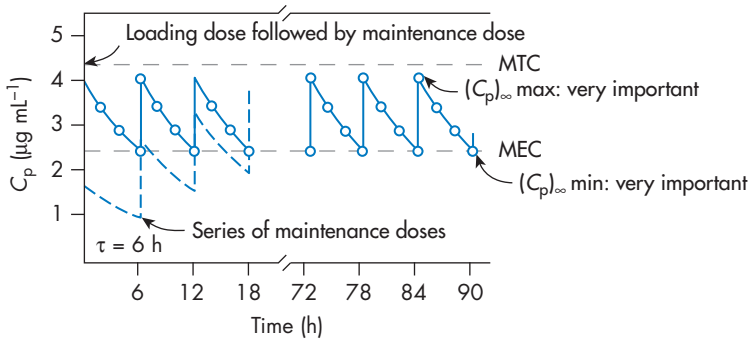

Figure 11.11 A plot of plasma concentration (C_p) versus time following repetitive intravenous bolus administration of a drug. The figure demonstrates the plasma level resulting from either a series of maintenance doses (dashed line) or an initial loading dose followed by a series of maintenance doses (continuous line). min, minimum; max, maximum; MTC, minimum toxic concentration; MEC, minimum effective concentration; τ, dosing interval.

where $(C_p)_0$ is the peak concentration from the initial intravenous bolus dose.

However, VC_p is the mass of drug in the body, X. Hence,

$$(X_{ss})_{max} - (X_{ss})_{min} = \text{dose} = X_0 \qquad (11.46)$$

Equations 11.45 and 11.46 clearly indicate that, at steady state, the difference between maximum and minimum concentrations or peak and trough concentrations is equal to the initial plasma concentration or maximum plasma concentration following the administration of the first dose. Furthermore, this confirms that, at steady state, the amount or the mass of drug leaving the body during one dosing interval is equal to the administered dose.