Intravenous Infusion

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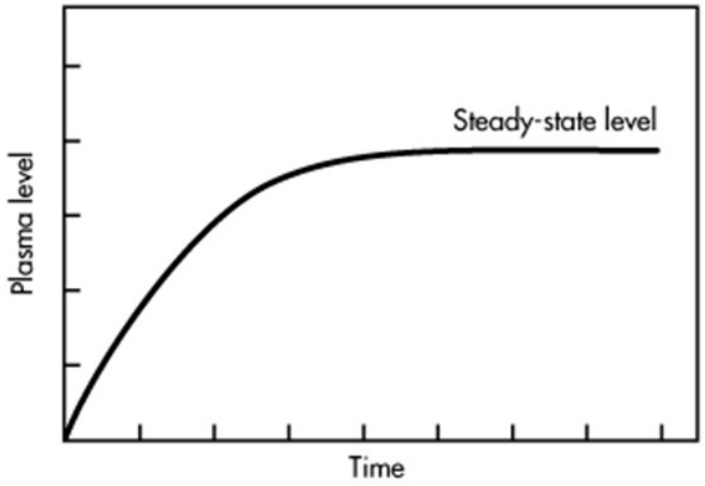
The plasma drug concentration-versus time curve of a drug given by constant IV infusion is shown in the right . Because no drug was present in the body at zero time, drug level rises from zero drug concentration and gradually becomes constant when a *plateau* or *steady-state* drug concentration is reached. At steady state, the rate of drug leaving the body is equal to the rate of drug(infusion rate) ente ring the body.

Therefore, at steady state, the rate of change in the plasma drug concentration, $dCp/dt = 0$, and:



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Plasma level–time curve for constant IV infusion.

$$\text{Rate of drug input} = \text{rate of drug output}$$
$$\text{(infusion rate)} \qquad \text{(elimination rate)}$$

One-Compartment Model Drugs

The pharmacokinetics of a drug given by constant IV infusion follows a zero-order input process in which the drug is infused directly into the systemic blood circulation. Equation (5.2) gives the plasma drug concentration at any time during the IV infusion, where t is the time for infusion. For most drugs, elimination of drug from the plasma is a first-order process. Therefore, in this one-compartment model, the infused drug follows zero-order input and first-order output. The change in the amount of drug in the body at any time (dD_B/dt) during the infusion is the rate of input minus the rate of output.

$$\frac{dD_B}{dt} = R - kD_B \qquad (5.1)$$

where D_B is the amount of drug in the body, R is the infusion rate (zero order), and k is the elimination rate constant (first order).

Integration of Equation 5.1 and substitution of $D_B = C_p V_D$ gives

$$C_p = \frac{R}{V_D k}(1 - e^{-kt}) \qquad (5.2)$$

As the drug is infused, the value for time (t) increases in Equation 5.2. At infinite time, $t = \infty$, e^{-kt} approaches zero, and Equation 5.2 reduces to Equation 5.4.

$$C_p = \frac{R}{V_D k}(1 - e^{-\infty}) \qquad (5.3)$$

$$C_{SS} = \frac{R}{V_D k} \qquad (5.4)$$

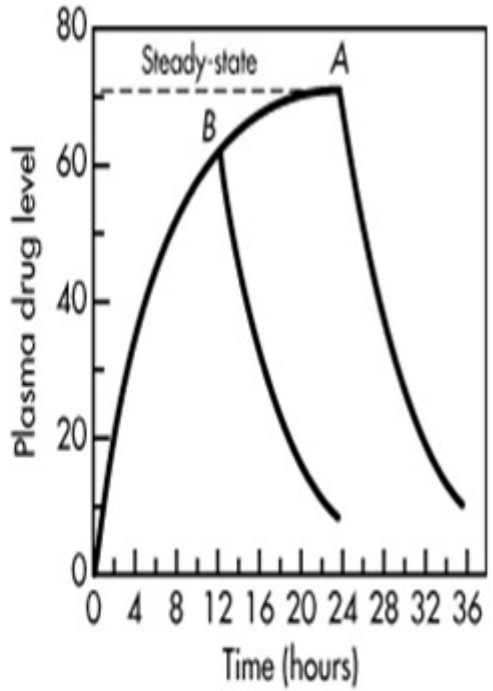
$$C_{SS} = \frac{R}{V_D k} = \frac{R}{Cl} \qquad (5.5)$$

Steady-State Drug Concentration (Css)and Time Needed to Reach Css

As stated earlier, the rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate) at steady state. In other words, there is no *net* change in the amount of drug in the body, D_B, as a function of time during steady state.

Drug elimination occur according to first - order elimination rate. Whenever the infusion stops either at steady state or before steady state is reached, the log drug concentration declines according to first-order kinetics with the slope of the elimination curve equal to -k/2.3.

If the infusion is stopped before steady state is reached, the slope of the elimination curve remains the same .



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Plasma drug concentrations versus time profiles after IV infusion. IV infusion is stopped at steady state (*A*) or prior to steady state (*B*). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope.

Mathematically, the time to reach true steady-state drug concentration, *C*SS,
would take an infinite time.
The time required to reach the steady-state drug concentration in the plasma is dependent
on the elimination rate constant of the drug.

In clinical practice, the activity of the drug will be observed when the drug concentration is close to the desired plasma drug concentration, which is usually the target or desired steady-state drug concentration. The time to reach 90%, 95%, and 99% of the steady-state drug concentration, Css, may be calculated ().

In clinical practice, the activity of the drug will observed when the drug concentration is close to the desired plasma drug concentration, which is usually the *target* or *desired* steady-state drug concentration. The time to reach 90%, 95%, and 99% of the steady-state drug concentration, *C*ss, may be calculated .

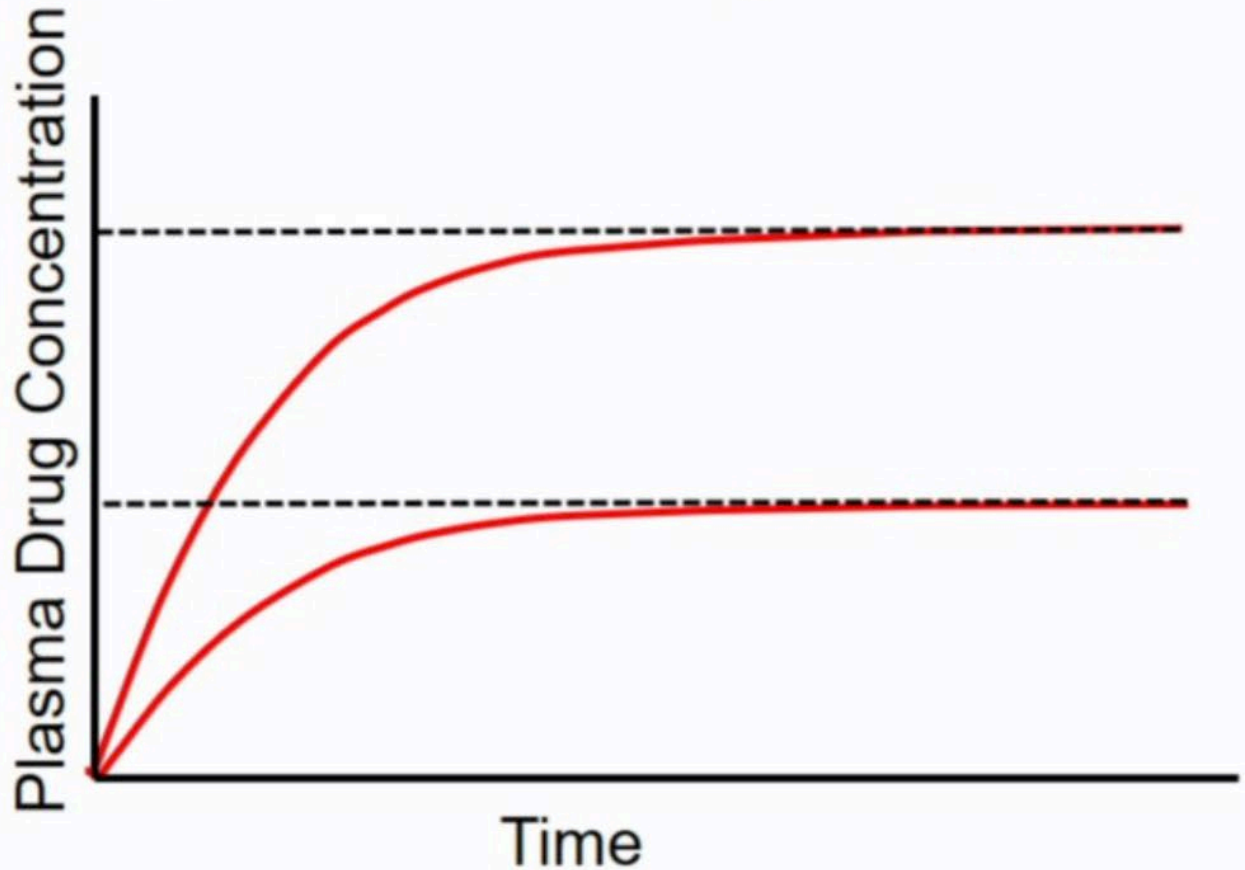
Table 5.1 Number of $t_{1/2}$ to Reach a Fraction of C_{SS}

Percent of C_{SS} Reached[a]	Number of Half-Lives
90	3.32
95	4.32
99	6.65

Thus, the time for a drug whose *t* 1/2 is 6 hours to reachat least 95% of the steady-state plasma drug concentration will be 5*t* 1/2, or 5 x 6 hours = 30 hours.

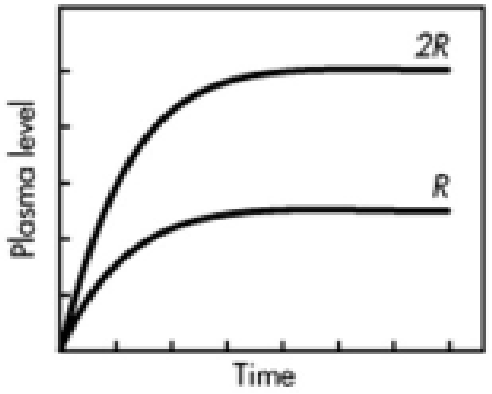
HALF-LIFE

- Doubling the infusion rate doubles the Css.
- But increasing the infusion rate does not influence the time required to reach C_{ss}.



An increase in the infusion rate will not shorten the time to reach the steady-state drug concentration. If the drug is given at a more rapid infusion rate, a higher steady-state drug level will be obtained, but the time to reach steady state is the same . This equation may also be obtained with the following approach. At steady state, the rate of infusion equals the rate of elimination. Therefore, the rate of change in the plasma drug concentration is equal to zero.

Figure 5-3.



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Plasma level–time curve for IV infusions given at rates of *R* and 2*R*, respectively.

$$\frac{dC_{\mathrm{P}}}{dt} = 0$$

$$\frac{dC_{\mathrm{P}}}{dt} = \frac{R}{V_{\mathrm{D}}} - kC_{\mathrm{P}} = 0$$

$$(Rate_{\mathrm{in}}) - (rate_{\mathrm{out}}) = 0$$

$$\frac{R}{V_{\mathrm{D}}} = kC_{\mathrm{P}}$$

$$C_{\mathrm{SS}} = \frac{R}{V_{\mathrm{D}}k}$$

$$C_P = \frac{R}{V_D k}\,(1 - e^{-kt}) \qquad (5.2)$$

Since

$$C_{SS} = \frac{R}{V_D K}$$

Substituting into Equation 5.2;

$$C_P = C_{SS}\,(1 - e^{-kt})$$

Rearranging and taking the log on both sides,

$$\log\left(\frac{C_{SS} - C_P}{C_{SS}}\right) = -\frac{kt}{2.3} \quad \text{and} \quad k = \frac{-2.3}{t}\log\left(\frac{C_{SS} - C_P}{C_{SS}}\right)$$

An antibiotic has an elimination half-life of 3- 6 hours in the general population.
A patient was given an IV infusion of an antibiotic at an infusion rate of 15 mg/hr.
Blood samples were taken at 8 and at 24 hours and plasma drug concentrations were 5.5 and 6.5 mg/L,respectively.
Estimate the elimination half-life of the drug in this patient.

$$\log\left(\frac{6.5 - 5.5}{6.5}\right) = -\frac{k(8)}{2.3}$$

$$k = 0.234 \text{ hr}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.234} = 2.96 \text{ hr}$$

The *loading dose*, D_L, or initial bolus dose of a drug, is used to obtain desired concentrations as rapidly as possible. The concentration of drug in the body for a one-compartment model after an IV bolus dose is described by

$$C_1 = C_0 e^{-kt} = \frac{D_L}{V_D} e^{-kt} \qquad (5.9)$$

and concentration by infusion at the rate R is

$$C_2 = \frac{R}{V_D k} = (1 - e^{-kt}) \qquad (5.10)$$

Assume that an IV bolus dose D_L of the drug is given and that an IV infusion is started at the same time. The total concentration C_p at t hours after the start of infusion is $C_1 + C_2$, due to the sum contributions of bolus and infusion, or

$$C_p = C_1 + C_2$$

$$C_P = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k}(1 - e^{-kt})$$

$$C_P = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k} - \frac{R}{V_D k} e^{-kt}$$

$$C_P = \frac{R}{V_D k} + \left(\frac{D_L}{V_D} e^{-kt} - \frac{R}{V_D k} e^{-kt} \right)$$

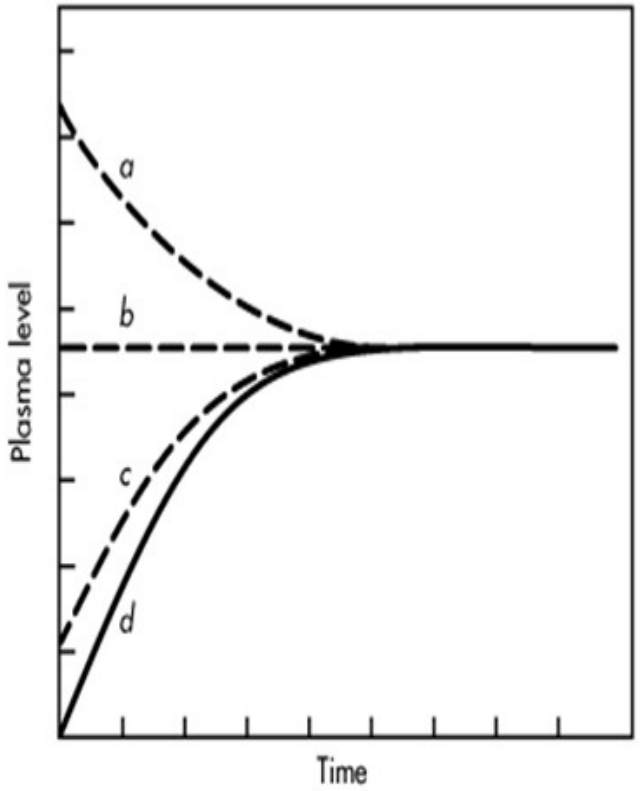
Let the loading dose (D_L) equal the amount of drug in the body at steady state:

$$D_L = C_{ss} V_D$$

From Equation 5.4, $C_{ss} V_D = R/k$. Therefore,

$$D_L = \frac{R}{k} \qquad (5.12)$$

If the loading dose given is larger than *R/k*, the plasma drug concentration takes longer to decline to the concentration desired at steady state (curve *a*).
If the loading dose is lower than *R/k*, the plasma drug concentrations will increase slowly to desired drug levels (curve *c*).
Curve *b* shows the blood level after a single loading dose of *R/k* plus infusion from which the concentration desired at steady state is obtained.



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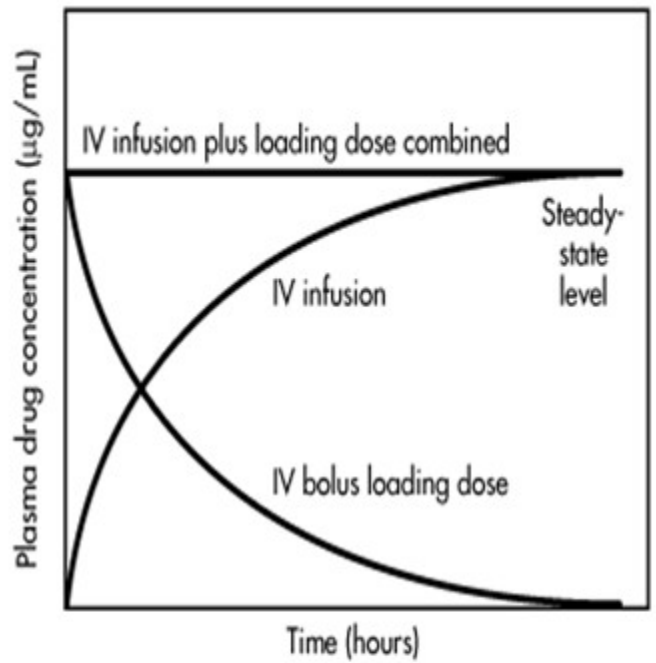
Intravenous infusion with loading doses *a*, *b*, and *c*. Curve *d* represents an IV infusion without a loading dose.



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IV Infusion with loading dose D_L. The loading dose is given by IV bolus injection at the start of the infusion. Plasma drug concentrations decline exponentially after D_L whereas they increase exponentially during the infusion. The resulting plasma drug concentration-versus-time curve is a straight line due to the summation of the two curves.

$$C_p = \frac{R}{V_p k}\left[1 - \left(\frac{k-b}{a-b}\right)e^{-at} - \left(\frac{a-k}{a-b}\right)e^{-bt}\right] \qquad (5.22)$$

where a and b are hybrid rate constants and R is the rate of infusion. At steady state (ie, $t = \infty$), Equation 5.22 reduces to

$$C_{SS} = \frac{R}{V_p k} \qquad (5.23)$$

By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated.

$$R = C_{SS} V_p k \qquad (5.24)$$

1. An antibiotic has a volume of distribution of 10 L and a *k* of 0.2 hr^{-1}. A steady-state plasma concentration of 10g/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows.

2. An infinitely long period of time is needed to reach steady-state drug levels. However, in practice it is quite acceptable to reach 99% *C* SS (ie, 99%steady-state level). Calculate the time required to reach 99% CSS.

3. A patient was given an antibiotic (*t* 1/2 =6 hr) by constant IV infusion at a rate of 2mg/hr. At the end of 2 days, the serum drug concentration was 10 mg/L. Calculate the total body clearance *Cl* T for this antibiotic.