Biopharmaceutics

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Intravenous Infusion

Introduction: -

•Advantages for giving a drug by IV infusion are: |1| allows precise control of plasma drug concentrations to fit the individual needs of the patient, |2| drugs with a narrow therapeutic window (e.g.; heparin), IV infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration, |3| IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients, and |4| the duration of drug therapy may be maintained or terminated as needed using IV infusion.

•Drug level rises from zero drug concentration and gradually becomes constant, when the rate of drug leaving the body is equal to the rate of drug (infusion rate) entering the body at the steady state, where the rate of change in the plasma drug concentration dCp/dt = 0.

Rate of drug input = rate of drug output

(infusion rate) (elimination rate)

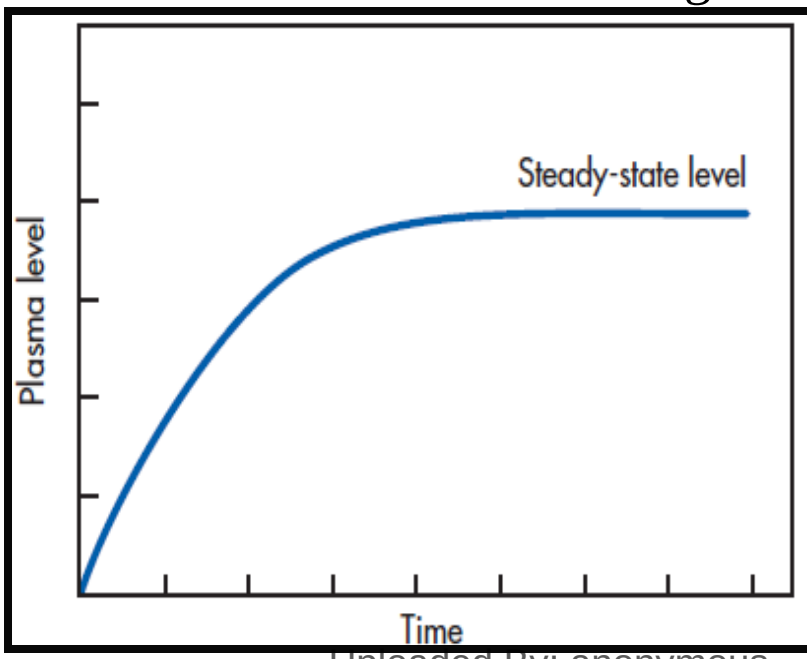


Figure 1: plasma level–time curve for constant IV infusion

One – Compartment Model Drugs: -

•A drug given by constant IV infusion follows a zero-order input and first-order output. The change in the amount of drug in the body at any time (dDB/dt) during the infusion is the rate of input minus the rate of output

$$\frac{dD_B}{dt} = R - kD_B \quad \text{.....(Eq. 1)}$$

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

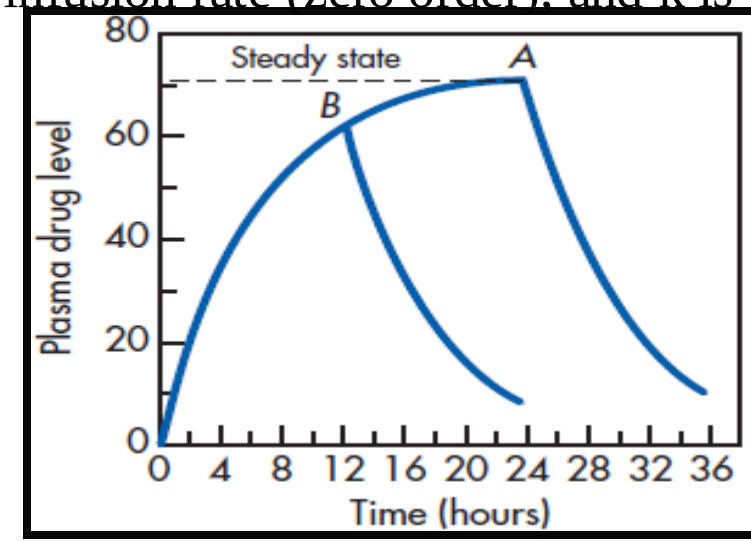


Figure 2: plasma drug concentrations–time profiles after IV infusion stopped at steady state (A) or prior to steady state (B). In both cases, plasma drug concentrations decline exponentially (first order) according to a similar slope

•Integration of equation 1 and substitution of $D_B = C_p V_D$ gives:

$$C_p = \frac{R}{V_D k}(1 - e^{-kt}) \quad \text{.....(Eq. 2)}$$

•At infinite time, t = ∞, e–kt approaches zero and equation 2 reduces to equation 4.

$$C_p = \frac{R}{V_D k}(1 - e^{-\infty}) \quad \text{.....(Eq. 3)}$$

$$C_{SS} = \frac{R}{V_D k} \quad \text{.....(Eq. 4)}$$

$$C_{SS} = \frac{R}{V_D k} = \frac{R}{Cl} \quad \text{.....(Eq. 5)}$$

Steady-State Drug Concentration (C_{ss}) and Time Needed to Reach C_{ss}:

•No net change in the amount of drug in the body, D_B, as a function of time during steady state, i.e.; the rate of drug leaving the body is equal to the rate of drug entering the body (infusion rate).

•Whenever the infusion stops either at steady state, or before steady state is reached, the drug concentration declines exponentially, i.e.; first-order elimination kinetics with the slope of the elimination curve equal to –k/2.3, figure 2.

•The time required to reach the steady-state drug concentration in the plasma is dependent on the elimination rate constant of the drug for a constant volume of distribution as shown in equation 4.

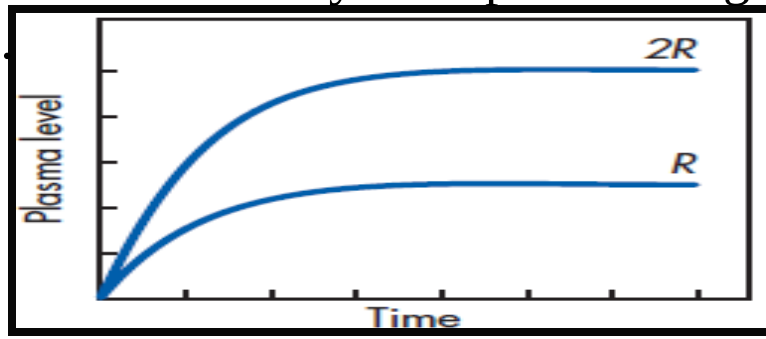
•For a zero-order elimination processes, if rate of input is greater than rate of elimination, plasma drug concentrations will keep increasing and no steady state will be reached. This is a potentially dangerous situation that will occur when saturation of metabolic process occurs.

•Drug solution is infused at constant zero-order rate, R, the C_p increases and the rate of drug elimination increases because it is concentration dependent (i.e.; rate of drug elimination = kC_p). Cp keeps increasing until steady state is reached at which rate of drug input (IV infusion rate) equals rate of drug output (elimination rate).

Table 1: number of $t_{1/2}$s 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

•The time for a drug whose $t_{1/2}$ is 6 hours to reach 95% of the steady-state plasma drug concentration will be 5 $t_{1/2}$, or 5 × 6 hours = 30 hours.



•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.

Figure 3: plasma level–time curve for IV infusions given at rates of R and 2R, respectively

•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.

•Equation 6 shows that the steady-state concentration (C_{ss}) is dependent on the volume of distribution, the elimination rate constant, and the infusion rate. Altering any one of these factors can affect steady-state concentration.

$$\frac{dC_p}{dt} = 0$$

$$\frac{dC_p}{dt} = \frac{R}{V_D} - kC_p = 0$$

$$(Rate_{in}) - (Rate_{out}) = 0$$

$$\frac{R}{V_D} = kC_p$$

$$C_{ss} = \frac{R}{V_D k} \qquad \text{(Eq. 6)}$$

Example 1 - An antibiotic has a volume of distribution of 10 L and a k of 0.2 h^{-1}. A steady-state plasma concentration of 10 μg/mL is desired. The infusion rate needed to maintain this concentration can be determined as follows: Equation 6 can be rewritten as: $R = C_{ss}V_Dk = (10\ \mu g/mL)\ (10)\ (1000\ mL)\ (0.2\ h^{-1}) = 20\ mg/h$

Assume the patient has a uremic condition and the elimination rate constant has decreased to 0.1 h^{-1}. To maintain the steady state concentration of 10 μg/mL, we must determine a new rate of infusion as follows. $R = (10\ mg/mL)\ (10)\ (1000\ mL)\ (0.1\ h^{-1}) = 10\ mg/h$

When the elimination rate constant decreases, then the infusion rate must decrease proportionately to maintain the same C_{ss}. However, because the elimination rate constant is smaller (i.e.; the elimination $t_{1/2}$ is longer), the time to reach C_{ss} will be longer.

Example 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} (i.e.; 99% steady-state level). Using equation 6, we know that the steady-state level is $C_{ss} = \frac{R}{V_D k}$ and 99% steady-state level would be equal to $99\%\ \frac{R}{V_D k}$

Substituting into equation 2 for C_p, we can find out the time needed to reach steady state by solving for t.

$$99\%\frac{R}{V_D k} = \frac{R}{V_D k}(1 - e^{-kt})$$

$$99\% = 1 - e^{-kt}$$

$$e^{-kt} = 1\%$$

Take the natural logarithm on both sides: $-kt = \ln 0.01$

$$t_{99\%ss} = \frac{\ln 0.01}{-k} = \frac{-4.61}{-k} = \frac{4.61}{k}$$

Substituting $(0.693/t_{1/2})$ for k,

$$t_{99\%ss} = \frac{4.61}{(0.693/t_{1/2})} = \frac{4.61}{0.693} t_{1/2}$$

$$t_{99\%ss} = 6.65\, t_{1/2}$$

Notice that in the equation directly above, the time needed to reach steady state is not dependent on the rate of infusion, but only on the elimination half-life. Using similar calculations, the time needed to reach any percentage of the steady-state drug concentration may be obtained, table 1.

IV infusion may be used to determine total body clearance if the infusion rate and steady-state level are known, as with equation 6 repeated here: $C_{ss} = \frac{R}{V_D k}$ …..(Eq. 6)

$$V_D k = \frac{R}{C_{ss}}$$

Because total body clearance, Cl_T, is equal to $V_D k$,

$$Cl_T = \frac{R}{C_{ss}} \quad \text{…..(Eq. 7)}$$

Example 3 - A patient was given an antibiotic ($t_{1/2}$ = 6 hours) by constant IV infusion at a rate of 2 mg/h. At the end of 2 days, the serum drug concentration was 10 mg/L. Calculate the total body clearance Cl_T for this antibiotic.

The total body clearance may be estimated from equation 7. The serum sample was taken after 2 days or 48 hours of infusion, which time represents 8 × $t_{1/2}$, therefore, this serum drug concentration approximates the C_{ss}.

$$Cl_T = \frac{R}{C_{ss}} = \frac{2\ \text{mg/h}}{10\ \text{mg/L}} = 200\ \text{mL/h}$$

Infusion Method for Calculating Patient Elimination Half – Life:

•Equation 2 is arranged to solve for k $C_p = \frac{R}{V_D k}(1 - e^{-kt})$ …..(Eq. 2). Since $C_{ss} = \frac{R}{V_D k}$,

substituting into equation 2: $C_p = C_{ss}(1 - e^{-kt})$ Rearranging and taking log on both sides:

$$\log\left(\frac{C_{ss} - C_p}{C_{ss}}\right) = -\frac{kt}{2.3} \text{ and}$$

$$k = \frac{-2.3}{t} \log\left(\frac{C_{ss} - C_p}{C_{ss}}\right)$$ …..(Eq. 8)

where C_p is the plasma drug concentration taken at time t, and C_{ss} is the approximate steady-state plasma drug concentration in the patient.

Example 4 - An antibiotic has an elimination half-life of 3 to 6 hours in the general population. A patient was given an IV infusion of an antibiotic at an infusion rate of 15 mg/h. 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.

Because the second plasma sample was taken at 24 hours, or 24/6 = 4 half-lives after infusion, the plasma drug concentration in this sample is approaching 95% of the true plasma steady-state drug concentration assuming the extreme case of $t_{1/2}$ = 6 hours. By substitution into equation 8: $\log\left(\frac{6.5 - 5.5}{6.5}\right) = -\frac{k(8)}{2.3}$

$k = 0.234\ h^{-1}$

$t_{1/2} = 0.693/0.234 = 2.96$ hours

•The elimination half-life calculated in this manner is not as accurate as the calculation of $t_{1/2}$ using multiple plasma drug concentration time points after a single IV bolus dose or after stopping the IV infusion.

•However, this method may be sufficient in clinical practice. As the second blood sample is taken closer to the time for steady state, the accuracy of this method improves.

•At the 30th hour, e.g.; the plasma concentration would be 99% of the true steady-state value (corresponding to 30/6 or 5 elimination half-lives), and less error would result in applying equation 8.

•When equation 8 was used in the example above to calculate the drug $t_{1/2}$ of the patient, the second plasma drug concentration was assumed to be the theoretical C_{ss}. As demonstrated below, when $t_{1/2}$ and the corresponding values are substituted,

$$\log\left(\frac{C_{ss}-5.5}{C_{ss}}\right)=-\frac{(0.231)(8)}{2.3}$$

$$\frac{C_{ss}-5.5}{C_{ss}}=0.157$$

C_{ss} = 6.5 mg/L

•(Note that C_{ss} is in fact the same as the concentration at 24 hours in the example above.)

Example 5 - If the desired therapeutic plasma concentration is 8 mg/L for the above patient (Example 4), what is the suitable infusion rate for the patient?

From example 4, the trial infusion rate was 15 mg/h. Assuming the second blood sample is the steady-state level, 6.5 mg/mL, the clearance of the patient is

$C_{ss} = R/Cl$

$Cl = R/C_{ss} = 15/6.5 = 2.31$ L/h

The new infusion rate should be $R = C_{ss} \times Cl = 8 \times 2.31 = 18.48$ mg/h

In this example, the $t_{1/2}$ of this patient is a little shorter, about 3 hours compared to 3 to 6 hours reported for the general population. Therefore, the infusion rate should be a little greater in order to maintain the desired steady-state level of 15 mg/L. Equation 7 or the steady-state clearance method has been applied to the clinical infusion of drugs.

Loading Dose Plus IV Infusion – One – Compartment Model: -

•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 $C_1 = C_0 e^{-kt} = \frac{D_L}{V_D} e^{-kt}$ ….(Eq. 9)

and concentration by infusion at the rate R is

$$C_2 = \frac{R}{V_D k}(1 - e^{-kt})$$ …..(Eq. 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 would be equal to $C_1 + C_2$ due to the sum contributions of bolus and infusion, or

$$C_p = C_1 + C_2$$

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

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

$$= \frac{R}{V_D k} + \left(\frac{D_L}{V_D} e^{-kt} - \frac{R}{V_D k} e^{-kt} \right) \quad \text{.....(Eq. 11)}$$

•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 4, $C_{ss} V_D = R/k$. Therefore,

$$D_L = R/k \text{ .....(Eq. 12)}$$

•Substituting $D_L = R/k$ in equation 11 makes the expression in parentheses in equation 11 cancel out. Equation 11 reduces to Equation 13, which is the same expression for C_{ss} or steady-state plasma concentrations: $C_p = \frac{R}{V_D k}$ .....(Eq. 13) $C_{ss} = \frac{R}{V_D k}$ .....(Eq. 14)

•Therefore, if an IV loading dose of R/k is given, followed by an IV infusion, steady-state plasma drug concentrations are obtained immediately and maintained, figure 4. In this situation, steady state is also achieved in a one-compartment model, since the rate in = rate out ($R = dD_B/dt$). The loading dose needed to get immediate steady-state drug levels can also be found by the following approach. Loading dose equation: $C_p = \frac{D_L}{V_D} e^{-kt}$

Infusion equation: $$C_2 = \frac{R}{V_D k}(1 - e^{-kt})$$

•Adding up the two equations yields equation 15, an equation describing simultaneous infusion after a loading dose. $$C_2 = \frac{D_L}{V_D} e^{-kt} + \frac{R}{V_D k}(1 - e^{-kt}) \quad \text{.....(Eq. 15)}$$

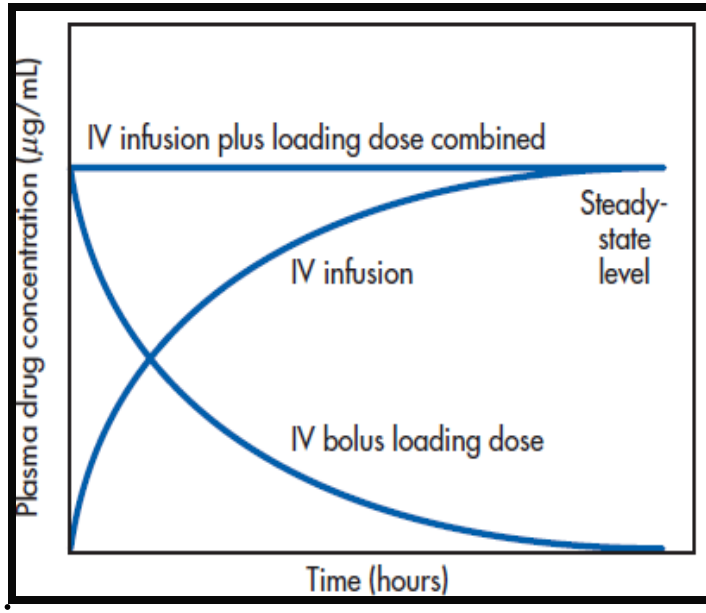


Figure 4: IV Infusion with loading dose D_L.
The loading dose is given by IV bolus injection at the start of the infusion. Plasma drug concentrations decline exponentially after D_L whereas they increase exponentially during the infusion. The resulting plasma drug concentration–time curve is a straight line due to the summation of the two curves.

•By differentiating this equation at steady state, we obtain:

$$\frac{dC_P}{dt} = 0 = \frac{-D_L k}{V_D} e^{-kt} + \frac{Rk}{V_D k} e^{-kt}$$

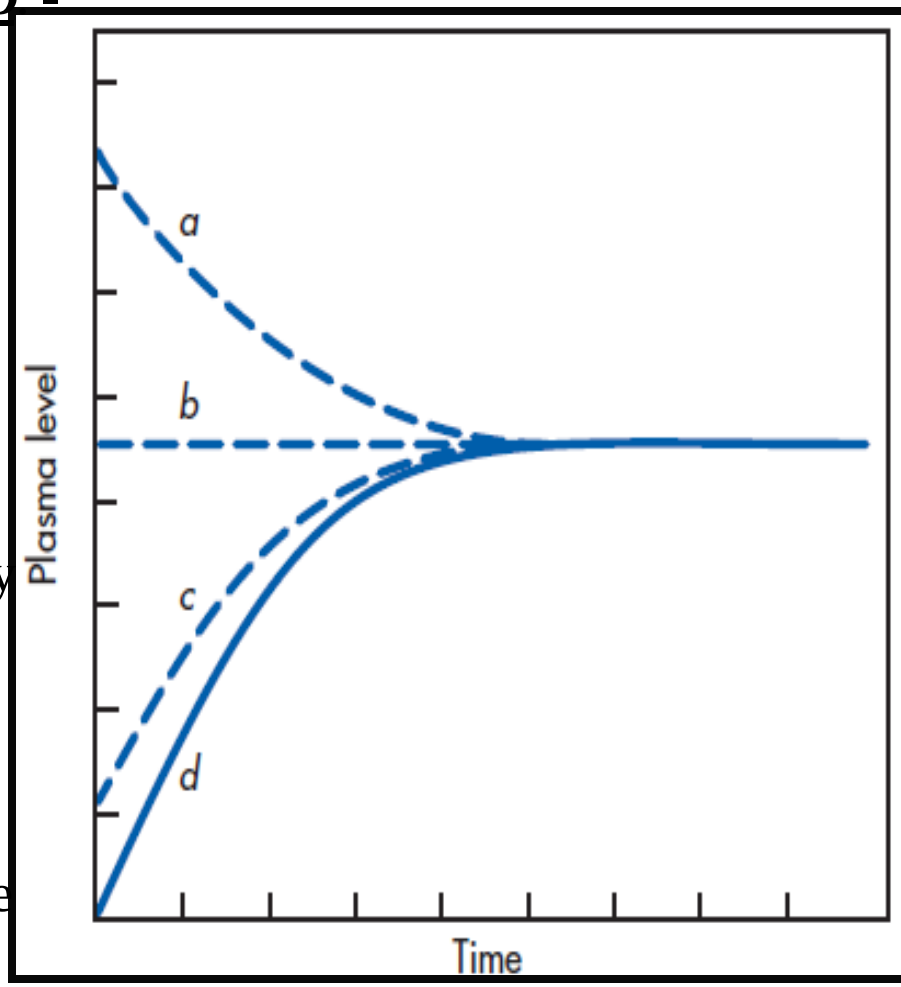
$$0 = e^{-kt}\left(\frac{-D_L k}{V_D} + \frac{R}{V_D}\right) \quad \text{.....(Eq. 16)}$$

$$\frac{D_L k}{V_D} = \frac{R}{V_D}$$

$$D_L = \frac{R}{k} = \text{loading dose} \quad \text{.....(Eq. 17)}$$

•In order to maintain instant steady-state level ($[dC_p/dt] = 0$), the loading dose should be equal to R/k.

Figure 5: -



▪*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. If the D_L is not equal to R/k, then steady state will not occur immediately.

▪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*, but more quickly than without any loading dose.

Figure 5: intravenous infusion with loading doses a, b, and c | curve d represents an IV infusion without a loading dose

•Another method for the calculation of loading dose D_L is based on knowledge of the desired steady state drug concentration C_{ss} and the apparent volume of distribution V_D for the drug, as shown in: $D_L = C_{ss}V_D$…..(Eq. 18)

Estimation of Drug Clearance and Volume of Distribution from Infusion Data: -

•Equation 2 shows that the plasma concentration of a drug during constant infusion was described in terms of volume of distribution and elimination constant k. Then alternatively, the equation may be described in terms of clearance by substituting for k with $k = Cl/V_D$: $$C_p = \frac{R}{Cl}(1 - e^{-(Cl/V_D)t})$$ …..(Eq. 19)

Intravenous Infusion of Two – Compartment Model Drugs: -

•During a constant IV infusion, drug in the tissue compartment is in distribution equilibrium with the plasma; thus, constant C_{ss} levels also result in constant drug concentrations in the tissue, that is, no net change in the amount of drug in the tissue occurs during steady state. The time needed to reach a steady-state blood level depends entirely on the distribution half-life of the drug.

$$C_p = \frac{R}{V_p k}\left[1 - \left(\frac{k-b}{a-b}\right)e^{-at} - \left(\frac{a-k}{a-b}\right)e^{-bt}\right]$$ …..(Eq. 20)

where a and b are hybrid rate constants and R is the rate of infusion. At steady state (i.e.; $t = \infty$), equation 20 reduces to: $$C_{ss} = \frac{R}{V_p k}$$ …..(Eq. 21)

•By rearranging this equation, the infusion rate for a desired steady-state plasma drug concentration may be calculated: $R = C_{ss} V_p k$ …..(Eq. 22)

Loading Dose for Two-Compartment Model Drugs: the drug distributes slowly into extravascular tissues (compartment 2). Thus, drug equilibrium is not immediate. The plasma drug concentration of a drug that follows a two-compartment model after various loading doses is shown in figure 6.

•If a loading dose is given too rapidly, the drug may initially give excessively high concentrations in the plasma (central compartment), which then decreases as drug equilibrium is reached, figure 6. It is not possible to maintain an instantaneous, stable steady-state blood level for a two-compartment model drug with a zero- order rate of infusion.

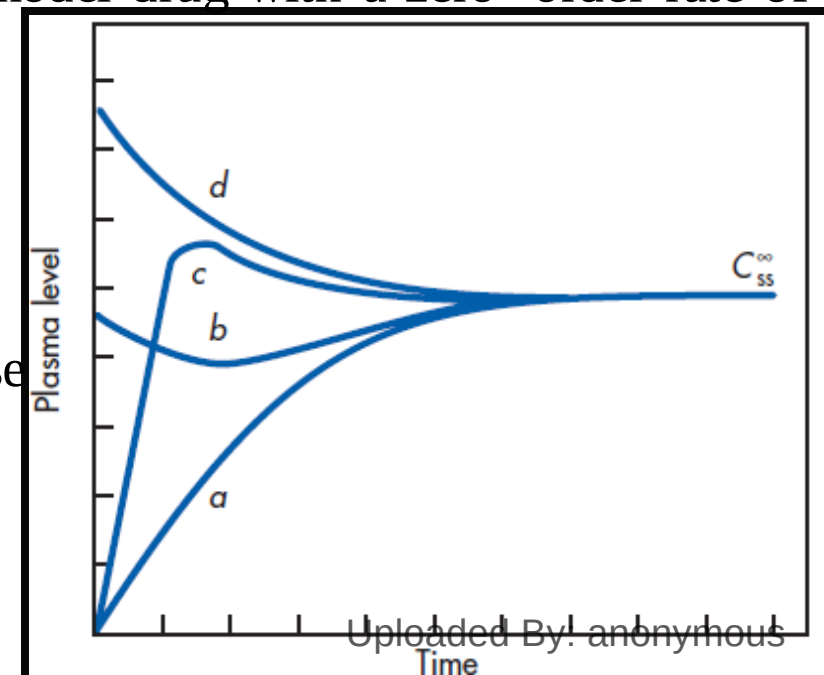


Figure 6: plasma drug level after various loading doses and rates of infusion for a drug that follows a two compartment model: a, no loading dose; b, loading dose = R/k (rapid infusion); c, loading dose = R/b (slow infusion); and d, loading dose = R/b (rapid infusion)

•Therefore, a loading dose produces an initial blood level either slightly higher or lower than the steady-state blood level. To overcome this problem, several IV bolus injections given as short intermittent IV infusions may be used as a method for administering a loading dose to the patient.

Apparent Volume of Distribution at Steady State, Two-Compartment Model:

•After administration of any drug that follows two compartment kinetics, plasma drug levels will decline due to elimination, and some redistribution will occur as drug in tissue diffuses back into the plasma fluid. At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment:

$$D_t k_{21} = D_p k_{12} \quad \text{.....(Eq. 23)} \qquad \boxed{D_t = \frac{k_{12} D_p}{k_{21}}} \quad \text{.....(Eq. 24)}$$

•Because the amount of drug in the central compartment D_p is equal to $V_p C_p$, by substitution in the above equation, $\boxed{(V_D)_{SS} = \frac{D_p + D_t}{C_p}}$ .....(Eq. 25)

•The apparent volume of drug at steady state $(V_D)_{ss}$ may be calculated by dividing the total amount of drug in the body by the concentration of drug in the central compartment at steady state: $\boxed{D_t = \frac{k_{12} C_p V_p}{k_{21}}}$ .....(Eq. 26)

Frequently Asked Questions: -

1- How does one determine whether a patient has reached steady-state during an IV infusion?

2- What is the clinical relevance of steady-state?

3- How can the steady-state drug concentration be achieved more quickly?

4- What is the main reason for giving a drug by slow IV infusion?

Slow IV infusion may be used to avoid side effects due to rapid drug administration. For example, intravenous immune globulin (human) may cause a rapid fall in blood pressure and possible anaphylactic shock in some patients when infused rapidly. Some antisense drugs also cause a rapid fall in blood pressure when injected via rapid IV into the body. The rate of infusion is particularly important in administering antiarrhythmic agents in patients. The rapid IV bolus injection of many drugs (eg, lidocaine) that follow the pharmacokinetics of multiple-compartment models may cause an adverse response due to the initial high drug concentration in the central (plasma) compartment before slow equilibration with the tissues.

5- Why do we use a loading dose to rapidly achieve therapeutic concentration for a drug with a long elimination half-life instead of increasing the rate of drug infusion or increasing the size of the infusion dose?

The loading drug dose is used to rapidly attain the target drug concentration, which is approximately the steady-state drug concentration. However, the loading dose will not maintain the steady-state level unless an appropriate IV drug infusion rate or maintenance dose is also used. If a larger IV drug infusion rate or maintenance dose is given, the resulting steady-state drug concentration will be much higher and will remain sustained at the higher level. A higher infusion rate may be administered if the initial steady-state drug level is inadequate for the patient.

6- Explain why the application of a loading dose as a single IV bolus injection may cause an adverse event or drug toxicity in the patient if the drug follows a two-compartment model with a slow elimination phase.

7- What are some of the complications involved with IV infusion?

The common complications associated with intravenous infusion include phlebitis and infections at the infusion site caused by poor intravenous techniques or indwelling catheters.

Learning Questions: -

1- A female patient (35 years old, 65 kg) with normal renal function is to be given a drug by IV infusion. According to the literature, the elimination half-life of this drug is 7 hours and the apparent VD is 23.1% of body weight. The pharmacokinetics of this drug assumes a first-order process. The desired steady-state plasma level for this antibiotic is 10 μg/mL. a. Assuming no loading dose, how long after the start of the IV infusion would it take to reach 95% of the Css? b. What is the proper loading dose for this antibiotic? c. What is the proper infusion rate for this drug? d. What is the total body clearance? e. If the patient suddenly develops partial renal failure, how long would it take for a new steady-state plasma level to be established (assume that 95% of the Css is a reasonable approximation)? f. If the total body clearance declined 50% due to partial renal failure, what new infusion rate would you recommend to maintain the desired steady-state plasma level of 10 μg/mL.

a. To reach 95% of C_{SS}:

$$4.32t_{1/2} = (4.32)\,(7) = 30.2\text{ h}$$

b. $D_L = C_{SS}V_D$

$$= (10)\,(0.231)\,(65{,}000) = 150\text{ mg}$$

c. $R = C_{SS}V_D k = (10)\,(15{,}000)\,(0.099)$

$$= 14.85\text{ mg/h}$$

d. $Cl_T = V_D k = (15{,}000)\,(0.099) = 1485\text{ mL/h}$

e. To establish a new C_{SS} will still take $4.32t_{1/2}$. However, the $t_{1/2}$ will be longer in renal failure.

f. If Cl_T is decreased by 50%, then the infusion rate R should be decreased proportionately:

$$R = 10\,(0.50)\,(1485) = 7.425\text{ mg/h}$$

2- An anticonvulsant drug was given as (a) a single IV dose and (b) a constant IV infusion. The serum drug concentrations are as presented in table below, an IV bolus injection may be used at the start of an infusion to quickly achieve the desired steady-state plasma drug concentration. For drugs that follow a two-compartment model, multiple small loading doses or intermittent IV infusions may be needed to prevent plasma drug concentrations from becoming too high. Pharmacokinetic parameters may be calculated from samples taken during the IV infusion and after the infusion is stopped, regardless of whether steady state has been achieved. These calculated pharmacokinetic parameters are then used to optimize dosing for that patient when population estimates do not provide outcomes suitable for the patient.

Serum Drug Concentrations for a Hypothetical Anticonvulsant Drug

TIME (hour)	Single IV Dose (1 mg/kg)	Constant IV Infusion (0.2 mg/kg per hour)
0	10.0	0
2	6.7	3.3
4	4.5	5.5
6	3.0	7.0
8	2.0	8.0
10	1.35	8.6
12		9.1
18		9.7
24		9.9

a. What is the steady-state plasma drug level?
b. What is the time for 95% steady-state plasma drug level?
c. What is the drug clearance?
d. What is the plasma concentration of the drug 4 hours after stopping infusion (infusion was stopped after 24 hours)?
e. What is the infusion rate for a patient weighing 75 kg to maintain a steady-state drug level of 10 μg/mL?

f. What is the plasma drug concentration 4 hours after an IV dose of 1 mg/kg followed by a constant infusion of 0.2 mg/kg/h?

a. The steady-state level can be found by plotting the IV infusion data. The plasma drug–time curves plateau at 10 μg/mL. Alternatively, V_D and k can be found from the single IV dose data:

$$V_D = 100 \text{ mL/kg} \qquad k = 0.2 \text{ h}^{-1}$$

b. Using equations developed in Example 2 the first set of examples in Chapter 5:

$$0.95 \frac{R}{V_D k} = \frac{R}{V_D k}(1 - e^{-kt})$$

$$0.95 = 1 - e^{-0.2t}$$

$$0.05 = e^{-0.2t}$$

$$t_{95\%\,ss} = \frac{\text{In } 0.05}{-0.2} = 15 \text{ h}$$

c. $Cl_T = V_D k \qquad V_D = \dfrac{D_0}{C_P^0}$

$$Cl_T = 100 \times 0.2 \qquad V_D = \frac{1000}{10} = \frac{100 \text{ mL}}{\text{kg}}$$

$$Cl_T = 20 \text{ mL/kg h}$$

d. The drug level 4 hours after stopping the IV infusion can be found by considering the drug concentration at the termination of infusion as C_P^0. At the termination of the infusion, the drug level will decline by a first-order process.

$$C_P = C_P^0 e^{-kt}$$

$$C_P = 9.9 e^{-(0.2)(4)}$$

$$C_P = 4.5 \ \mu\text{g/mL}$$

e. The infusion rate to produce a C_{SS} of 10 μg/mL is 0.2 mg/kg/h. Therefore, the infusion rate needed for this patient is

$$0.2 \text{ mg/kg h} \times 75 \text{ kg} = 15 \text{ mg/h}$$

f. From the data shown, at 4 hours after the start of the IV infusion, the drug concentration is 5.5 μg/mL; the drug concentration after an IV bolus of 1 mg/kg is 4.5 μg/mL. Therefore, if a 1-mg dose is given and the drug is then infused at 0.2 mg/kg/h, the plasma drug concentration will be $4.5 + 5.5 = 10$ μg/mL.

3- An antibiotic is to be given by IV infusion. How many milliliters per hour should a sterile drug solution containing 25 mg/mL be given to a 75-kg adult male patient to achieve an infusion rate of 1 mg/kg/h?
Infusion rate R for a 75-kg patient: R = (1 mg/kg h)(75 kg) = 75 mg/h Sterile drug solution contains 25 mg/mL. Therefore, 3 mL contains (3 mL) × (25 mg/mL), or 75 mg. The patient should receive 3 mL (75 mg)/h by IV infusion.

4- An antibiotic drug is to be given to an adult male patient (75 kg, 58 years old) by IV infusion. The drug is supplied in sterile vials containing 30 mL of the antibiotic solution at a concentration of 125 mg/mL. What rate in milliliters per hour would you infuse this patient to obtain a steady-state concentration of 20 μg/ mL? What loading dose would you suggest? Assume the drug follows the pharmacokinetics of a one-compartment open model. The apparent volume of distribution of this drug is 0.5 L/kg and the elimination half-life is 3 hours.

$$C_{ss} = \frac{R}{V_D k} \qquad R = C_{ss} V_D k$$

$$R = (20\ \text{mg/L})\ (0.5\text{L/kg})\ (75\ \text{kg}) \left(\frac{0.693}{3\ \text{h}} \right)$$

$$= 173.25\ \text{mg/h}$$

Drug is supplied as 125 mg/mL. Therefore,

$$125\ \text{mg/mL} = \frac{173.25\ \text{mg}}{X}\ X = 1.386\ \text{mL}$$

$$R = 1.386\ \text{mL/h}$$

$$D_L = C_{ss} V_D = (20\ \text{mg/L})\ (0.5\ \text{L/kg})\ (75\ \text{kg})$$

$$= 750\ \text{mg}$$

5- According to the manufacturer, a steadystate serum concentration of 17 mg/mL was measured when the antibiotic, cephradine (Velosef, Bristol-Meyers, Squibb) was given by IV infusion to 9 adult male volunteers (average weight, 71.7 kg) at a rate of 5.3 mg/kg/h for 4 hours. a. Calculate the total body clearance for this drug. b. When the IV infusion was discontinued, the cephradine serum concentration decreased exponentially, declining to 1.5 mg/mL at 6.5 hours after the start of the infusion. Calculate the elimination half-life. c. From the information above, calculate the apparent volume of distribution. d. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for this interaction of probenecid with cephradine?

$$C_{SS} = \frac{R}{kV_D} = \frac{R}{Cl_T}$$

a. $$Cl_T = \frac{R}{C_{SS}} = \frac{5.3 \text{ mg/kg h} \times 71.71 \text{ kg}}{17 \text{ mg/L}}$$

$$= 22.4 \text{ L/h}$$

b. At the end of IV infusion, $C_p = 17\ \mu g/mL$. Assuming first-order elimination kinetics:

$$C_P = C_P^0 e^{-kt}$$

$$1.5 = 17e^{-k(2.5)}$$

$$0.0882 = e^{-2.5k}$$

$$\ln 0.0882 = -2.5\,k$$

$$-2.43 = -2.5\,k$$

$$k = 0.971 \text{ h}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.971} = 0.714 \text{ h}$$

c. $$Cl_T = kV_D \qquad V_D = \frac{Cl_T}{k}$$

$$V_D = \frac{22.4}{0.971} = 23.1 \text{ L}$$

d. Probenecid blocks active tubular secretion of cephradine.

6- Calculate the excretion rate at steady state for a drug given by IV infusion at a rate of 30 mg/h. The Css is 20 μg/mL. If the rate of infusion were increased to 40 mg/h, what would be the new steady-state drug concentration, Css? Would the excretion rate for the drug at the new steady state be the same? Assume first-order elimination kinetics and a one-compartment model.

At steady state, the rate of elimination should equal the rate of absorption. Therefore, the rate of elimination would be 30 mg/h. The C_{SS} is directly proportional to the rate of infusion R, as shown by

$$C_{SS} = \frac{R}{kV_D} \qquad kV_D = \frac{R}{C_{SS}}$$

$$\frac{R_{old}}{C_{SS,old}} = \frac{R_{new}}{C_{SS,\,new}}$$

$$\frac{30\ \text{mg/h}}{20\ \mu\text{g/mL}} = \frac{40\ \text{mg/h}}{C_{SS,new}}$$

$$C_{SS,new} = 26.7\ \mu\text{g/mL}$$

The new elimination rate will be 40 mg/h.

7- An antibiotic is to be given to an adult male patient (58 years, 75 kg) by IV infusion. The elimination half-life is 8 hours and the apparent volume of distribution is 1.5 L/kg. The drug is supplied in 60-mL ampules at a drug concentration of 15 mg/mL. The desired steady-state drug concentration is 20 μg/mL. a. What infusion rate in mg/h would you recommend for this patient? b. What loading dose would you recommend for this patient? By what route of administration would you give the loading dose? When? c. Why should a loading dose be recommended? d. According to the manufacturer, the recommended starting infusion rate is 15 mL/h. Do you agree with this recommended infusion rate for your patient? Give a reason for your answer. e. If you were to monitor the patient's serum drug concentration, when would you request a blood sample? Give a reason for your answer. f. The observed serum drug concentration is higher than anticipated. Give two possible reasons based on sound pharmacokinetic principles that would account for this observation.

a. $R = C_{SS} k V_D$

$R = (20\ \text{mg/L})(0.693/8\ \text{h})(1.5\ \text{L/kg})(75\ \text{kg})$

$= 194.9\ \text{mg/h}$

$R = 195\ \text{mg/h} / 15\ \text{mg/mL} = 13\ \text{mL/h}$

b. $D_L = C_{SS} V_D = (20)\ (1.5)\ (75) = 2250\ \text{mg}$ given by IV bolus injection

c. The loading dose is given to obtain steady-state drug concentrations as rapidly as possible.

d. 15 mL of the antibiotic solution contains 225 mg of drug. Thus, an IV infusion rate of 15 mL/h is equivalent to 225 mg/h. The C_{SS} achieved by the manufacturer's recommendation is

$$C_{SS} = \frac{R}{kV_D} = \frac{225}{(0.0866)(112.5)} = 23.1\ \text{mg/L}$$

The theoretical C_{SS} of 23.1 mg/L is close to the desired C_{SS} of 20 mg/L. Assuming a reasonable therapeutic window, the manufacturer's suggested starting infusion rate is satisfactory.

Encircle the Correct Answer Only: -

1- IV infusion provide all but; ----------.

[a. C_{ss} *control*] b. reduce ↓TI drugs C_p fluctuations

c. antibiotics IV fluids d. maintain/terminate IV infusion

2- The time required to reach the steady-state drug concentration in the plasma is dependent on the ---------- of the drug.

a. $t_{0.5}$ [b. K_e] c. Cl d. V_D

3- For a zero-order elimination processes, ----------, plasma drug concentrations will keep increasing and no steady state will be reached.

a. $R = KD_B$ b. $R < KD_B$ [c. $R > KD_B$] d. $R - KD_B$

4- The time for a drug whose $t_{1/2}$ is 6 hours to reach 95% of the steady-state plasma drug concentration will be ---------- hours.

a. 15 b. 20 c. 25 [d. *30*]

5- IV infused drug at 2R, will reach steady state ---------- time in comparison when infused at R.

[a. *at same*] b. half the c. double the d. one – tenth the

6- As the elimination rate constant is smaller, i.e.; the elimination $t_{1/2}$ is longer and hence the time to reach C_{ss} will be ----------.

a. shorter [b. *longer*] c. short d. long

7- In order to maintain instant C_{ss} level, the D_L should be equal to ----------.

a. R b. K_e [c. R/k_e] d. K_e/R

8- IV infusion of two – compartment model drug, the time needed to reach a steady-state blood level depends entirely on the ---------- of the drug.

a. K_e b. elimination $to_{0.5}$ c. K_d [d. *distribution* $t_{0.5}$]