Biopharmaceutics

Lec. 4 **Dr. AA Yas**

One-Compartment Open Model: Intravenous Bolus Administration

Introduction: -

•In order to develop pharmacokinetic models to describe and predict drug disposition kinetically, the model must account for both the route of administration and the pharmacokinetic behavior of the drug in the body, then dosing regimens for individuals or groups of patients can be calculated.

•The *one-compartment open model* is the simplest way to describe the process of drug distribution and elimination in the body, assuming that the drug can enter or leave the body (i.e.; the model is "open"), and the entire body acts like a single, uniform compartment.

•The simplest pharmacokinetic model that describes drug disposition in the body is the IV bolus model where the drug is injected all at once into a box (the human body) or compartment, and the drug distributes / equilibrates instantaneously and rapidly throughout the compartment. Drug elimination from the compartment also begins to occur immediately after the IV bolus injection.

•Uptake of drugs by various tissue organs will occur at varying rates and extents, depending on the blood flow to the tissue, the lipophilicity of the drug, the molecular weight of the drug, and the binding affinity of the drug for the tissue mass.

•Because of rapid drug equilibration between the blood and tissues, drug distribution and elimination occur via the kidney and / or by being metabolized in the liver as if the dose is all dissolved in a tank of uniform fluid (a single compartment) from which the drug is eliminated.

•The apparent volume of distribution, V_D assumes that the drug is theoretically rapidly and uniformly distributed in the body throughout the apparent volume and it is determined from the injected amount / dose and the plasma drug concentration C_p^0 immediately after injection.

•The elimination rate constant, k, which is proportional to the rate at which the drug concentration in the body declines over time.

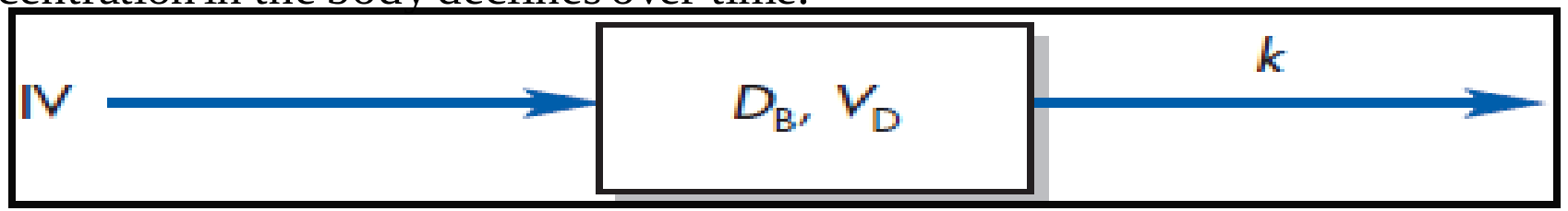


Figure 1: pharmacokinetic model for a drug administered by rapid intravenous injection. D_B = drug in body; V_D = apparent volume of distribution; k = elimination rate constant

Elimination Rate Constant: -

•The rate of elimination for most drugs from the body is a first-order process, i.e.; the rate of elimination at any point in time is dependent on the amount or concentration of drug present at that instant. Therefore, the elimination rate constant, k, is a first-order elimination rate constant with units of time^{-1} (e.g.; h^{-1} or 1/h).

•The elimination rate constant represents the sum of elimination of the parent drug by metabolism and excretion: $k = k_m + k_e$ …..(Eq. 1) where k_m = first-order rate process of metabolism and k_e = first-order rate process of excretion.

•A rate expression for figure 1 is: $\frac{dD_B}{dt} = -kD_B$ …..(Eq. 2) and by integration gives the following expression:

$$\log D_B = \frac{-kt}{2.3} + \log D_B^0$$ …..(Eq. 3)

where D_B = the drug in the body at time t and D_B^0 is the amount of drug in the body at t = 0.

•When log D_B is plotted against t for this equation, a straight line is obtained:

•In practice, instead of transforming values of D_B to their corresponding logs, each value of D_B is placed at log intervals on semilog paper. Equation 3 can also be expressed as:

$D_B = D_B^0 e^{-kt}$ …..(Eq. 4)

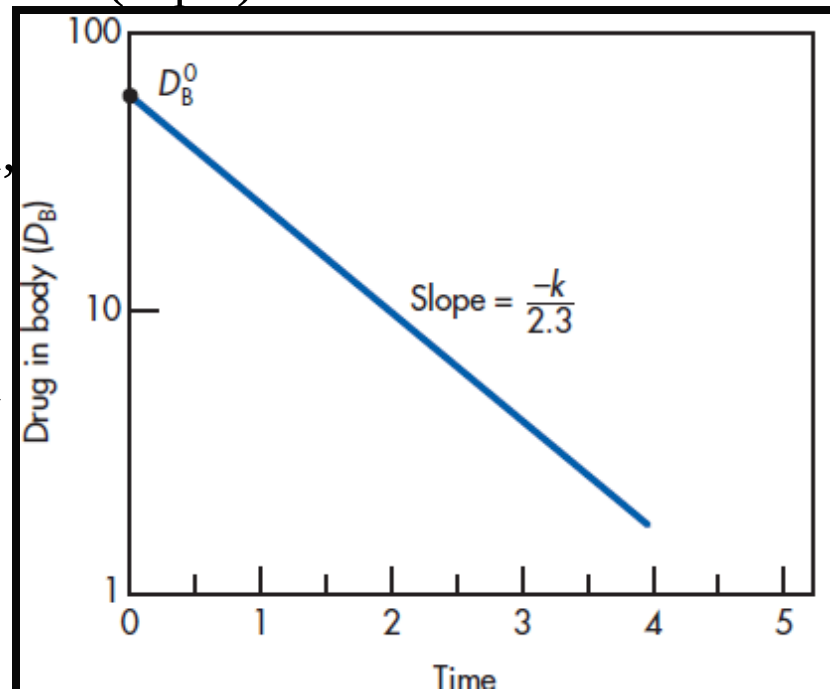


Figure 2: semilog graph of the rate of drug elimination in a one-compartment model

Apparent Volume of Distribution: -

•When plasma or any other biologic compartment is sampled and analyzed for drug content, the results are usually reported in units of concentration instead of amount.

•Each individual tissue in the body may contain a different concentration of drug due to differences in blood flow and drug affinity for that tissue.

•The volume of distribution represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment.

•The volume of distribution is the apparent volume (V_D) in which the drug is dissolved: $D_B = V_D C_p$ …..(Eq. 5) which relates the (V_D) to the concentration of drug in plasma (C_p) and the amount of drug in the body (D_B).

•Substituting equation 5 into equation 3, a similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

$$\log C_p = \frac{-kt}{2.3} + \log C_p^0 \quad \text{…..(Eq. 6)}$$

where C_p = concentration of drug in plasma at time t and C_p^0 = concentration of drug in plasma at t = 0. Equation 6 can also be expressed as: $C_p = C_p^0 e^{-kt}$ …..(Eq. 7)

Example 1: Exactly 1 g of a drug is dissolved in an unknown volume of water. Upon assay, the concentration of this solution is 1 mg/mL. What is the original volume of this solution?

•The original volume of the solution may be obtained by the following proportion,

$$\frac{1000\ \text{mg}}{x\ \text{mL}} = \frac{1\ \text{mg}}{\text{mL}} \quad x = 1000\ \text{mL}$$

•The volume of the solution is known to be 1 L, and the concentration of the solution is 1 mg/mL, then, to calculate the total amount of drug present,

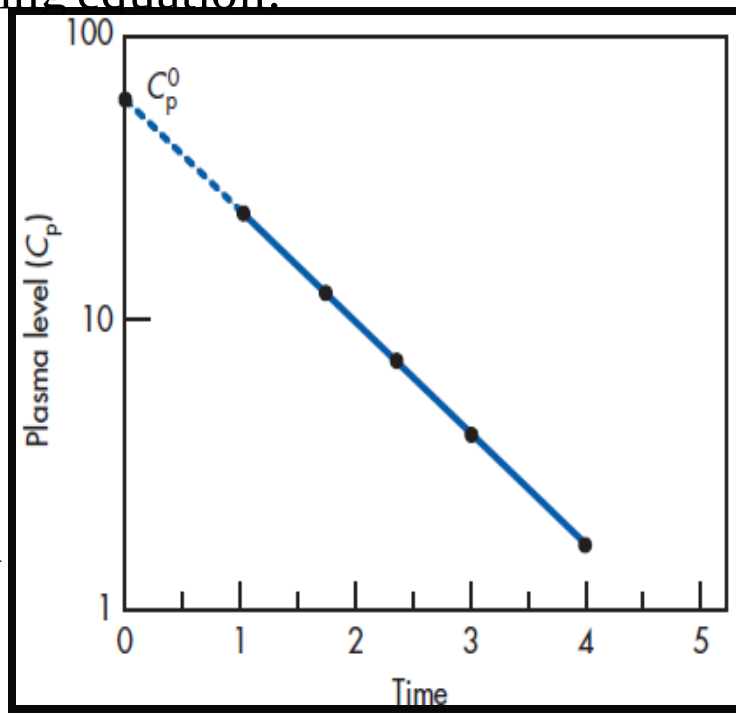
$$\frac{x\ \text{mg}}{1000\ \text{mL}} = \frac{1\ \text{mg}}{\text{mL}} \quad x = 1000\ \text{mg}$$

•This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

$$V_D = \frac{\text{Dose}}{C_p^0} = \frac{D_B^0}{C_p^0} \quad \text{.....(Eq. 8)}$$

Calculation of Volume of Distribution:

In a one-compartment model (IV administration), because both D_B^0 **[**The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, D_B^0, at t = 0**]** and C_p^0 **[**determined by extrapolation, C_p^0 represents the instantaneous drug concentration after drug equilibration in the body at t = 0 (figure 3)**]** are known, then the apparent volume of distribution, V_D, may be calculated from Equation 8 above.| Figure 3: semilog graph giving the value of C_p^0 by extrapolation



•From equation 2, the rate of drug elimination is $\frac{dD_B}{dt} = -kD_B$. Substituting equation 5, $D_B = V_D C_p$, into equation 2, the following expression is obtained:

$$\frac{dD_B}{dt} = -kV_D C_p \quad \text{..... (Eq. 9)}$$

•Rearrangement of equation 9 gives: $dD_B = -kV_D C_p dt$ ....(Eq. 10) As both k and VD are constants, equation 9 may be integrated as follows: $\int_0^{D_0} dD_B = -kV_D \int_0^{\infty} C_p dt$ .....(Eq. 11).

•Equation 11 shows that a small change in time (dt) results in a small change in the amount of drug in the body, D_B. The integral $\int_0^{\infty} C_p\, dt$ represents the AUC_0^{∞} which is the summation of the area under the curve from t = 0 to t = ∞. Thus, the apparent V_D may also be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from t = 0 to t = ∞. After integration, equation 11 becomes: $D_0 = kV_D[\mathrm{AUC}]_0^{\infty}$ which upon rearrangement yields the following equation:

$$V_D = \frac{D_0}{k[\mathrm{AUC}]_0^{\infty}} \quad \text{.....(Eq. 12)}$$

Table 1: Fluid in the Body

Water Compartment	Percent of Body Weight	Percent of Total Body Water
Plasma	4.5	7.5
Total extracellular water	27.0	45.0
Total intracellular water	33.0	55.0
Total body water	60.0	100.0

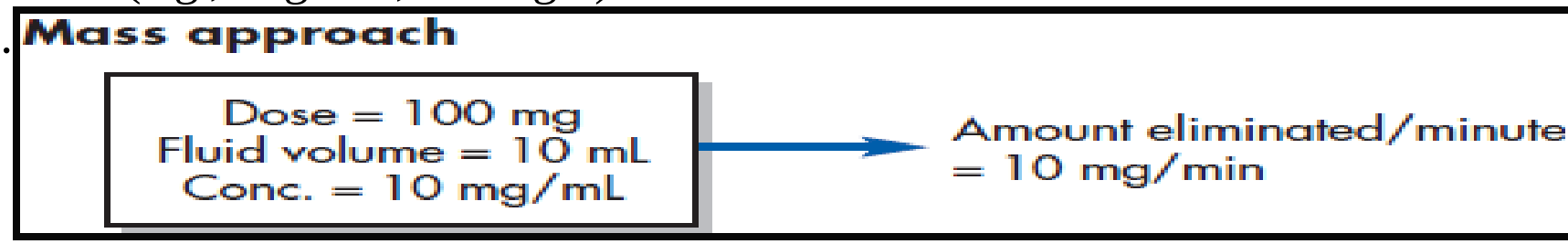
Clearance: -

Drug Clearance in the One-Compartment Model:

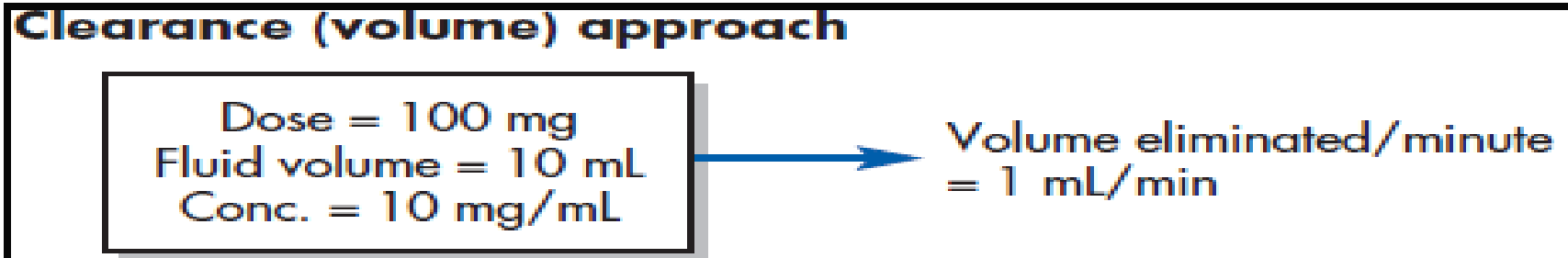
Drug elimination from the body is an ongoing process due to both metabolism (biotransformation) and drug excretion through the kidney and other routes. Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time or the fraction of drug removed per unit time.

Drug Elimination Expressed as Amount / Volume per Unit Time:

•For a zero-order elimination process, expressing the rate of drug elimination as mass per unit time (e.g.; mg/min, or mg/h) is convenient because the elimination rate is constant.



•For most drugs, the rate of drug elimination is a first-order elimination process, i.e.; the elimination rate is not constant and changes with respect to the drug concentration in the body, therefore; drug clearance expressed as volume per unit time (eg, L/h or mL/min) is convenient because it is a constant.



•Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time. Mathematically, the rate of drug elimination is similar to equations 2 & 9: $\frac{dD_B}{dt} = -kC_pV_D$ dividing this expression on both sides by C_p yields.

$$\frac{dD_B / dt}{C_p} = -kV_D = -Cl \quad \text{.....(Eq. 13)}$$

where dD_B/dt is the rate of drug elimination from the body (mg/h), C_p is the plasma drug concentration (mg/L), k is a first-order rate constant (h^{-1} or 1/h), and V_D is the apparent volume of distribution (L).

<u>Drug Elimination Expressed as Fraction Eliminated per Unit Time</u>:

•Consider a compartment volume, containing V_D liters. If Cl is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to Cl/V_D. Expressing drug elimination as the fraction of total drug eliminated is applicable regardless of whether one is dealing with an amount or a volume.

•Pharmacokineticists have incorporated this concept into the first-order equation (i.e.; k) that describes drug elimination from the one-compartment model.

Example 2: [*Clearance and Volume of Distribution Ratio, Cl/V_D*] Consider that 100 mg of drug is dissolved in 10 mL of fluid and 10 mg of drug is removed in the first minute.

The drug elimination process could be described as:

a. Number of mg of drug eliminated per minute (mg/min)

b. Number of mL of fluid cleared of drug per minute

c. Fraction of drug eliminated per minute

•If the drug concentration is C_p, the rate of drug elimination (in terms of rate of change in concentration, dC_p/dt) is: $\frac{dC_p}{dt} = -(Cl/V_D) \times C_p$ …..(Eq. 14)

•For a first-order process, $\frac{dC_p}{dt} = -kC_p = \text{rate of drug elimination}$ …..(Eq. 15)

•Equating the two expressions yields: $k = \frac{Cl}{V_D}$ …..(Eq. 16)

•Thus, a first-order rate constant is the fractional constant Cl/V_D. Some pharmacokineticists regard drug clearance and the volume of distribution as independent parameters that are necessary to describe the time course of drug elimination.

One-Compartment Model Equation in Terms of Cl and V_D:

•Equation 7 $C_p = C_p^0 e^{-kt}$ may be rewrite in terms of clearance and volume of distribution by substituting Cl / V_D for k: $C_p = D_0 / V_D e^{-(Cl/V_D)t}$ …..(Eq. 17)

Practical Focus: -

•The IV single dose equation 7 may be modified to calculate the elimination rate constant or half life of a drug in a patient when two plasma samples and their time of collection are known: $\ln C_p = \ln C_p^0 - kt$ …..(Eq. 18)

•If the first plasma sample is taken at t_1 instead of at 0 and corresponds to plasma drug concentration, then C_2 is the concentration at time t_2 and t is set to ($t_2 - t_1$).

$C_2 = C_1 e^{-k(t_2 - t_1)}$ $\ln C_2 = \ln C_1 - k\,(t_2 - t_1)$ …..(Eq. 19)

•Rearranging: $\ln C_2 - \ln C_1 = -k\,(t_2 - t_1)$ $k = \dfrac{\ln C_1 - \ln C_2}{(t_2 - t_1)}$ …..(Eq. 20)

where t_1 = time of first sample collection, C_1 = plasma drug concentration at t1, t_2 = time of second sample collection, C_2 = plasma drug concentration at t_2.

•The drug in the body is in the postabsorptive phase (i.e.; absorption is completed), this equation may be used to determine the half-life of the drug in the patient by taking two plasma samples far apart and recording the times of sampling.

Clearance from Drug-Eliminating Tissues:

•As long as first-order elimination processes are involved, clearance represents the sum of the clearances for both renal and non-renal clearance: $Cl_T = Cl_R + Cl_{NR}$ Cl_{NR} is assumed to be due primarily to hepatic clearance (Cl_H) in the absence of other significant drug clearances, such as elimination through the lung or the bile: $Cl_T = Cl_R + Cl_H$

•Cl_T is the rate of drug elimination divided by the plasma drug concentration. Thus, clearance is expressed in terms of the volume of plasma containing drug that is eliminated per unit time (e.g.; mL/min, L/h).

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration } (C_p)} \quad \text{.....(Eq. 21)}$$

$$Cl_T = \frac{(dD_E/dt)}{C_p} = (\mu g/\text{min})/(\mu g/\text{mL}) = \text{mL/min} \quad \text{....(Eq. 22)}$$

where D_E is the amount of drug eliminated and dD_E/dt is the rate of drug elimination.

•Rearrangement of equation 22 gives equation 23: $\text{Drug elimination } \frac{dD_E}{dt} = C_p Cl_T$ ....(Eq. 23)
Therefore Cl_T is a constant for a specific drug and represents the slope of the line obtained by plotting dD_E/dt versus C_p.

•For drugs that follow first-order elimination, the rate of drug elimination is dependent on the amount of drug remaining in the body: $\frac{dD_E}{dt} = kD_B = kC_pV_D$ .....(Eq. 24)

•Substituting the elimination rate in equation 23 for kC_pV_D in equation 24 and solving for Cl_T gives: $Cl_T \frac{kC_pV_D}{C_p} = kV_D$ .....(Eq. 25) $Cl_T = \frac{D_o}{[AUC]_o^\infty}$ .....(Eq. 26)

Frequently Asked Questions: -

1- What is the difference between a rate and a rate constant?

A rate represents the change in amount or concentration of drug in the body per time unit. For example, a rate equal to –5 mg/h means the amount of drug is decreasing at 5 mg/h. A positive or negative sign indicates that the rate is increasing or decreasing, respectively. Rates may be zero order, first order, or higher orders. For a first-order rate, the rate of change of drug in the body is determined by the product of the elimination rate constant, k, and by the amount of drug remaining in the body, ie, rate = –kDB, where k represents "the fraction" of the amount of drug in the body that is eliminated per hour. If k = 0.1 h–1 and DB = 10 mg, then the rate = 0.1 h–1 × 10 mg = 1 mg/h. The rate constant in this example shows that one-tenth of the drug is eliminated per hour, whatever amount of drug is present in the body. For a first-order rate, the rate states the absolute amount eliminated per unit time (which changes with the amount of drug in the body), whereas the first-order rate constant, k, gives a constant fraction of drug that is eliminated per unit time (which does not change with the amount of drug in the body).

2- Why does k always have the unit 1/time (e.g.; h^{-1}), regardless of what concentration unit is plotted?

The first-order rate constant k has no concentration or mass units. In the calculation of the slope, k, the unit for mass or concentration is canceled when taking the log of the number:

$$\text{Slope} = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} = \frac{\ln (y_2/y_1)}{x_2 - x_1}$$

3- If a drug is distributed in the one-compartment model, does it mean that there is no drug in the tissue?

The one-compartment model uses a single homogeneous compartment to represent the fluid and the vascular tissues. This model ignores the heterogeneity of the tissues in the body, so there is no merit in predicting precise tissue drug levels. However, the model provides useful insight into the mass balance of drug distribution in and out of the plasma fluid in the body. If *VD is larger* than the physiologic vascular volume, the conclusion is that there is some drug outside the vascular pool, ie, in the tissues. If *VD is small,* then there is little extravascular tissue drug storage, except perhaps in the lung, liver, kidney, and heart. With some knowledge about the lipophilicity of the drug and an understanding of blood flow and perfusion within the body, a postulation may be made as to which organs are involved in storing the extravascular drug. The concentration of a biopsy sample may support or refute the postulation.

4- How is clearance related to the volume of distribution and k?

5- If we use a physiologic model, are we dealing with actual volumes of blood and tissues? Why do volumes of distribution emerge for drugs that often are greater than the real physical volume?

Since mass balance (ie, relating dose to plasma drug concentration) is based on volume of distribution rather than blood volume, the compartment model is used in determining dose. Generally, the total blood concentrations of most drugs are not known, since only the plasma or serum concentration is assayed. Some drugs have an RBC/plasma drug ratio much greater than 1, making the application of the physiologic model difficult without knowing the apparent volume of distribution.

6- Define the term apparent volume of distribution. What criteria are necessary for the measurement of the apparent volume of distribution to be useful in pharmacokinetic calculations?

7- For drugs that follow the kinetics of a one compartment open model, must the tissues and plasma have the same drug concentration? Why?

The total drug concentration in the plasma is not usually equal to the total drug concentration in the tissues. A one-compartment model implies that the drug is rapidly equilibrated in the body (in plasma and tissues). At equilibrium, the drug concentration in the tissues may differ from the drug concentration in the body because of drug protein binding, partitioning of drug into fat, differences in pH in different regions of the body causing a different degree of ionization for a weakly dissociated electrolyte drug, an active tissue uptake process, etc.

Learning Questions: -

1- A 70-kg volunteer is given an intravenous dose of an antibiotic, and serum drug concentrations were determined at 2 hours and 5 hours after administration. The drug concentrations were 1.2 and 0.3 μg/mL, respectively. What is the biologic half-life for this drug, assuming first-order elimination kinetics?

t (h)	C_P (μg/mL)
2	1.2
5	0.3

$$\log C_P = -\frac{kt}{2.3} + \log C_P^0$$

$$\log 0.3 = -\frac{k(3)}{2.3} + \log 1.2$$

$$k = 0.462\ \text{h}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.462}$$

$$t_{1/2} = 1.5\ \text{h}$$

These data may also be plotted on a semilog graph and $t_{1/2}$ obtained from the graph.

2- A 50-kg woman was given a single IV dose of an antibacterial drug at a dose level of 6 mg/kg. Blood samples were taken at various time intervals. The concentration of the drug (Cp) was determined in the plasma fraction of each blood sample and the following data were obtained:

t (hour)	C_p (μg/mL)
0.25	8.21
0.50	7.87
1.00	7.23
3.00	5.15
6.00	3.09
12.0	1.11
18.0	0.40

a. What are the values for VD, k, and t1/2 for this drug?

b. This antibacterial agent is not effective at a plasma concentration of less than 2 μg/mL. What is the duration of activity for this drug?

c. How long would it take for 99.9% of this drug to be eliminated?

d. If the dose of the antibiotic was doubled exactly, what would be the increase in duration of activity?

Dose (IV bolus) = 6 mg/kg × 50 kg = 300 mg

a. $V_D = \frac{\text{dose}}{C_p^0} = \frac{300 \text{ mg}}{8.4 \ \mu\text{g/mL}} = \frac{300 \text{ mg}}{8.4 \text{ mg/L}} = 35.7 \text{ L}$

(1) Plot the data on semilog graph paper and use two points from the line of best fit.

t (h)	C_p (μg/mL)
2	6
6	3

(2) $t_{1/2}$ (from graph) = 4 h

$$k = \frac{0.693}{4} = 0.173 \text{ h}^{-1}$$

b. $C_p^0 = 8.4 \ \mu\text{g / mL} \quad C_p = 2 \ \mu\text{g/mL} \quad k = 0.173 \text{ h}^{-1}$

$$\log C_p = -\frac{kt}{2.3} + \log C_p^0$$

$$\log 2 = -\frac{0.173t}{2.3} + \log 8.4$$

$$t = 8.29 \text{ h}$$

Alternatively, time t may be found from a graph of C_p versus t.

c. Time required for 99.9% of the drug to be eliminated:

(1) Approximately 10 $t_{1/2}$

$$t = 10(4) = 40 \text{ h}$$

(2) $C_p^0 = 8.4 \ \mu\text{g/mL}$

With 0.1% of drug remaining,

$$C_p = 0.001 \ (8.4 \ \mu\text{g/mL}) = 0.0084 \ \mu\text{g/mL}$$

$$k = 0.173 \text{ h}^{-1}$$

$$\log 0.0084 = \frac{-0.173t}{2.3} + \log 8.4$$

$$t = 39.9 \text{ h}$$

d. If the dose is doubled, then C_p^0 will also double. However, the elimination half-life or first-order rate constant will remain the same. Therefore,

$$C_p^0 = 16.8\ \mu\text{g/mL} \quad C_p = 2\ \mu\text{g/mL} \quad k = 0.173\ \text{h}^{-1}$$

$$\log 2 = \frac{0.173t}{2.3} + \log 16.8$$

$$t = 12.3\ \text{h}^{-1}$$

Notice that doubling the dose does not double the duration of activity.

3- A new drug was given in a single intravenous dose of 200 mg to an 80-kg adult male patient. After 6 hours, the plasma drug concentration of drug was 1.5 mg/100 mL of plasma. Assuming that the apparent VD is 10% of body weight, compute the total amount of drug in the body fluids after 6 hours. What is the half-life of this drug?

- $D_0 = 200$ mg

  $V_D = 10\%$ of body weight $= 0.1\ (80\ \text{kg})$

  $= 8000\ \text{mL} = 8\ \text{L}$

  At 6 hours:

$$C_p = 1.5\ \text{mg} / 100\ \text{mL}$$

$$V_D = \frac{\text{drug in body } (D_B)}{C_p}$$

$$D_B = C_p V_D = \frac{1.5}{100\ \text{mL}}(8000\ \text{mL}) = 120\ \text{mg}$$

$$\log D_B = -\frac{kt}{2.3} + \log D_B^0$$

$$\log 120 = -\frac{k(6)}{2.3} + \log 200$$

$$k = 0.085\ \text{h}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.085} = 8.1\ \text{h}$$

4- A new antibiotic drug was given in a single intravenous bolus of 4 mg/kg to five healthy male adults ranging in age from 23 to 38 years (average weight 75 kg). The pharmacokinetics of the plasma drug concentration–time curve for this drug fits a one-compartment model. The equation of the curve that best fits the data is $C_p = 78e^{-0.46t}$

Determine the following (assume units of μg/mL for Cp and hour for t):

a. What is the t1/2?

b. What is the VD?

c. What is the plasma level of the drug after 4 hours?

d. How much drug is left in the body after 4 hours?

e. Predict what body water compartment this drug might occupy and explain why you made this prediction.

f. Assuming the drug is no longer effective when levels decline to less than 2 μg/mL, when should you administer the next dose?

$C_p = 78e^{-0.46t}$ (the equation is in the form $C_p = C_p^0 e^{-kt}$)

$$\ln C_p = \ln 78 - 0.46t$$

$$\log C_p = -\frac{0.46t}{2.3} + \log 78$$

Thus, $k = 0.46\ \text{h}^{-1}$, $C_p^0 = 78\ \mu\text{g/mL}$.

a. $t_{1/2} = \dfrac{0.693}{k} = \dfrac{0.693}{0.46} = 1.5 \text{ h}$

b. $V_D = \dfrac{\text{dose}}{C_p^0} = \dfrac{300{,}000\ \mu g}{78\ \mu g/\text{mL}} = 3846 \text{ mL}$

$\text{Dose} = 4 \text{ mg/kg} \times 75 \text{ kg} = 300 \text{ mg}$

c. (1) $\log C_p = \dfrac{0.46(4)}{2.3} + \log 78 = 1.092$

$C_p = 12.4\ \mu\text{g/mL}$

(2) $C_p = 78e^{-0.46(4)} = 78e^{-1.84} = 78\,(0.165)$

$C_p = 12.9\ \mu\text{g/mL}$

d. At 4 hours:

$D_B = C_P V_D = 12.4\ \mu\text{g / mL} \times 3846 \text{ mL}$

$= 47.69 \text{ mg}$

e. $V_D = 3846 \text{ mL}$

Average weight = 75 kg
Percent body wt = (3.846 kg/75 kg) × 100
= 5.1%
The apparent V_D approximates the plasma volume.

f. $C_P = 2\ \mu\text{g/mL}$
Find t.

$$\log 2 = -\frac{0.46t}{2.3} + \log 78$$

$$t = -\frac{2.3\,(\log 2 - \log 78)}{0.46}$$

$$t = 7.96 \text{ h} \approx 8 \text{ h}$$

Alternate Method

$$2 = 78e^{-0.46t}$$

$$\frac{2}{78} = 0.0256 = e^{-0.46t}$$

$$-3.7 = -0.46t$$

$$t = \frac{3.7}{0.46} = 8 \text{ h}$$

5- A drug has an elimination t1/2 of 6 hours and follows first-order kinetics. If a single 200-mg dose is given to an adult male patient (68 kg) by IV bolus injection, what percent of the dose is lost in 24 hours?

For first-order elimination kinetics, one-half of the initial quantity is lost each t1/2. The following table may be developed:

Time (h)	Number of $t_{1/2}$	Amount of Drug in Body (mg)	Percent of Drug in Body	Percent of Drug Lost
0	0	200	100	0
6	1	100	50	50
12	2	50	25	75
18	3	25	12.5	87.5
24	4	12.5	6.25	93.75

Method 1

From the above table the percent of drug remaining in the body after each t1/2 is equal to 100% times (1/2)n, where n is the number of half-lives, as shown below:

Number of $t_{1/2}$	Percent of Drug in Body	Percent of Drug Remaining in Body after n $t_{1/2}$
0	100	
1	50	$100 \times 1/2$
2	25	$100 \times 1/2 \times 1/2$
3	12.5	$100 \times 1/2 \times 1/2 \times 1/2$
n		$100 \times (1/2)^n$

Percent of drug remaining $\frac{100}{2^n}$, where n = number of $t_{1/2}$

$$\text{Percent of drug excreted} = 100 - \frac{100}{2^n}$$

At 24 hours, $n = 4$, since $t_{1/2} = 6$ h.

$$\text{Percent of drug lost} = 100 - \frac{100}{16} = 93.75\%$$

Method 2

The equation for a first-order elimination after IV bolus injection is

$$\log D_B = \frac{-kt}{2.3} + \log D_0$$

where

D_B = amount of drug remaining in the body

D_0 = dose = 200 mg

k = elimination rate constant

$$= \frac{0.693}{t_{1/2}} = 0.1155\ \text{h}^{-1}$$

$t = 24$ h

$$\log D_B = \frac{-0.1155(24)}{2.3} + \log 200$$

$$D_B = 12.47\ \text{mg} \approx 12.5\ \text{mg}$$

$$\%\ \text{of drug lost} = \frac{200 - 12.5}{200} \times 100 = 93.75\%$$

6- A rather intoxicated young man (75 kg, age 21) was admitted to a rehabilitation center. His blood alcohol content was found to be 210 mg%. Assuming the average elimination rate of alcohol is 10 mL of ethanol per hour, how long would it take for his blood alcohol concentration to decline to less than the legal blood alcohol concentration of 100 mg%? (Hint: Alcohol is eliminated by zero-order kinetics.) The specific gravity of alcohol is 0.8. The apparent volume of distribution for alcohol is 60% of body weight.

The zero-order rate constant for alcohol is 10 mL/h. Since the specific gravity for alcohol is 0.8,

$$0.8 \text{ g/mL} = \frac{x(g)}{10 \text{ mL}}$$

$$x = 8 \text{ g}$$

Therefore, the zero-order rate constant, k_0, is 8 g/h.

Drug in body at $t = 0$:

$$D_B^0 = C_P V_D = \frac{210 \text{ mg}}{0.100 \text{ L}} \times (0.60)(75 \text{ L}) = 94.5 \text{ g}$$

Drug in body at time t:

$$D_B = C_P V_D = \frac{100 \text{ mg}}{0.100 \text{ L}} \times (0.60)(75 \text{ L}) = 45.0 \text{ g}$$

For a zero-order reaction:

$$D_B = -k_0 t + D_B^0$$

$$45 = -8t + 94.5$$

$$t = 6.19 \text{ h}$$

7- A single IV bolus injection containing 500 mg of cefamandole nafate (Mandol, Lilly) is given to an adult female patient (63 years, 55 kg) for a septicemic infection. The apparent volume of distribution is 0.1 L/kg and the elimination half-life is 0.75 hour. Assuming the drug is eliminated by first-order kinetics and may be described by a one-compartment model, calculate the following:

a. The C_p^0

b. The amount of drug in the body 4 hours after the dose is given

c. The time for the drug to decline to 0.5 μg/mL, the minimum inhibitory concentration for streptococci

a. $$C_P^0 = \frac{\text{dose}}{V_D} = \frac{500\ \text{mg}}{(0.1\ \text{L/kg})(55\ \text{kg})} = 90.9\ \text{mg/L}$$

b. $$\log D_B = \frac{-kt}{2.3} + \log D_B^0$$

$$\log D_B = \frac{(0.693/0.75)(4)}{2.3} + \log 500$$

$$D_B = 12.3\ \text{mg}$$

c. $$\log 0.5 = \frac{-(0.693/0.75)t}{2.3} + \log 90.0$$

$$t = 5.62\ \text{h}$$

8- If the amount of drug in the body declines from 100% of the dose (IV bolus injection) to 25% of the dose in 8 hours, what is the elimination half-life for this drug? (Assume first-order kinetics.)

$$\log D_B = \frac{-kt}{2.3} + \log D_B^0$$

$$\log 25 = \frac{-k(8)}{2.3} + \log 100$$

$$k = 0.173\ \text{h}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.173} = 4\ \text{h}$$

9- A drug has an elimination half-life of 8 hours and follows first-order elimination kinetics. If a single 600-mg dose is given to an adult female patient (62 kg) by rapid IV injection, what percent of the dose is eliminated (lost) in 24 hours assuming the apparent VD is 400 mL/ kg? What is the expected plasma drug concentration (Cp) at 24 hours postdose?

$$\log D_B = \frac{-kt}{2.3} + \log D_B^0$$

$$= \frac{(-0.693/8)(24)}{2.3} + \log 600$$

$$D_B = 74.9\ \text{mg}$$

$$\text{Percent drug lost} = \frac{600 - 74.9}{600} \times 100$$

$$= 87.5\%$$

C_P at $t = 24$ hours:

$$C_P = \frac{74.9\ \text{mg}}{(0.4\ \text{L/kg})(62\ \text{kg})} = 3.02\ \text{mg/L}$$

10- An adult male patient (age 35 years, weight 72 kg) with a urinary tract infection was given a single intravenous bolus of an antibiotic (dose = 300 mg). The patient was instructed to empty his bladder prior to being medicated. After dose administration, the patient saved his urine specimens for drug analysis. The urine specimens were analyzed for both drug content and sterility (lack of bacteriuria). The drug assays gave the following results:

t (hour)	Amount of Drug in Urine (mg)
0	0
4	100
8	26

a. Assuming first-order elimination, calculate the elimination half-life for the antibiotic in this patient. b. What are the practical problems in obtaining valid urinary drug excretion data for the determination of the drug elimination half-life?

Time (h)	D_u (mg)	dD_u/t	mg/h	t^*
0	0			
4	100	100/4	25	2
8	26	26/4	6.5	6

The elimination half-life may be obtained graphically after plotting mg/h versus t^*. The $t_{1/2}$ obtained graphically is approximately 2 hours.

$$\log \frac{dD_u}{dt} = \frac{-kt}{2.3} + \log k_e D_B^0$$

$$\text{Slope} = \frac{-k}{2.3} = \frac{\log Y_2 - \log Y_1}{X_2 - X_1} = \frac{\log 6.5 - \log 25}{6 - 2}$$

$$k = 0.336 \text{ h}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.336} = 2.06 \text{ h}$$

Encircle the Correct Answer Only: -

1- The simplest pharmacokinetic model that describes drug disposition in the body is the ----------.

[a. *IV bolus*] b. oral absorption c. IV infusion d. nebulization

2- The apparent volume of distribution determined from ---------- immediately after drug injection.

b. D^0 [b. D^0 / C_P^0] c. C_p^0 d. C_p^0 / D^0

3- The rate of elimination for most drugs from the body is a first-order process, because it is ---------- dependent of drug present at that instant.

a. amount b. concentration [c. *amount / concentration*] d. V_D

4- The elimination rate constant, k, is a first-order elimination rate constant, unit of -----.

a. concentration b. volume / time c. time [d. time $^{-1}$]

5- The volume of distribution represents a volume that must be considered in estimating the ---------- of drug in the body from the concentration of drug found in the sampling compartment.

[a. *amount*] b. volume cleared c. unbound ratio d. bound ratio

6- Integration form $\int_0^{D_0} dD_B = -kV_D \int_0^{\infty} C_p dt$ represents of ----------.

a. $\frac{dD_B}{dt} = -kD_B$ [b $\frac{dD_B}{dt} = -kV_D C_p$] c. $\frac{dD_E}{dt} = kD_B = kC_p V_D$ d $D_0 = kV_D[\mathrm{AUC}]_0^{\infty}$

7- Cl_T = ----------.

a. Ke C_p b. C_p / Ke [c. Ke / C_p] d. $e^{-ke / Cp}$