Biopharmaceutics

Intravenous bolus administration

(one-compartment model)

Dr. Aymen Bash

- As discussed in the previous lecture , the differential equation for a first-order process:

$$-\frac{dY}{dt} = KY$$

- Applying this equation to the elimination of drug (X) in the body, gives:

$$-\frac{dX}{dt} = KX$$

- Integration of the previous equation will yield:

$$X = X_o e^{-kt}$$

$$or$$

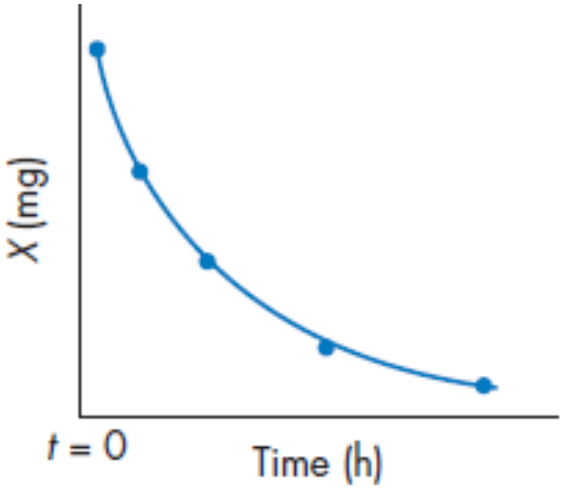
$$\ln X = \ln X_o - kt$$

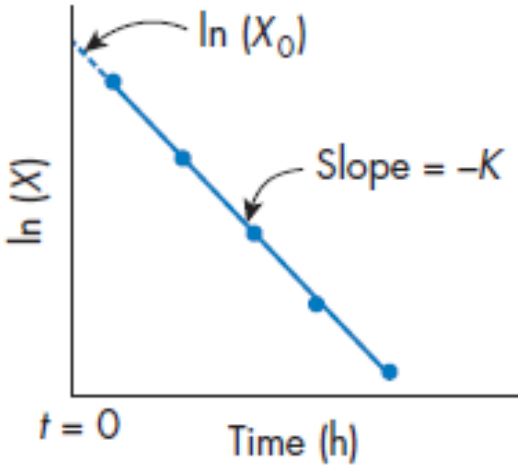
$$or$$

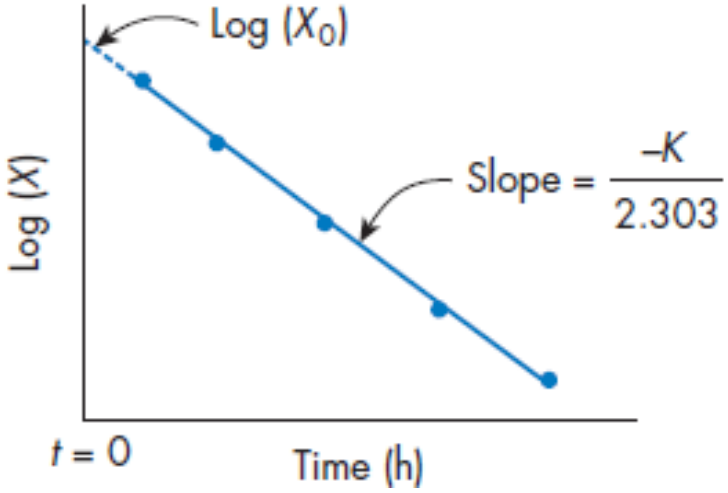
$$\log X = \log X_o - \frac{kt}{2.303}$$

where X_0 is the amount of unchanged drug in the body at time zero (t=0).

Please note that X_0 is the administered intravenous bolus dose (e.g. μg, mg, mg kg^{-1}) of the drug







Plots of the amount of drug remaining in the blood against time, following the intravenous administration of a drug (on a normal paper)

- However, When drugs are monitored in plasma or serum, it is concentration (not amount) that is measured $\Rightarrow$

$$Concentration\ (C_p) = \frac{\text{amount of drug (mg, } \mu\text{g, ng)}}{\text{unit volume (V) (ml, L)}}$$

$$C_p = \frac{X}{V}$$

The equation for a first order process is: $X = X_o e^{-kt}$

$\Rightarrow$ If we divide this equation by the volume term V, then

$$\frac{X}{V} = \frac{X}{V_o} e^{-kt} \qquad \text{and} \quad \frac{X}{V} = C_p$$

therfore,

$$C_p = (C_p)_o e^{-kt}$$

or

$$\ln C_p = \ln (C_p)_o - kt$$

or

$$\log C_p = \log (C_p)_o - \frac{kt}{2.303}$$

Useful pharmacokinetic parameters

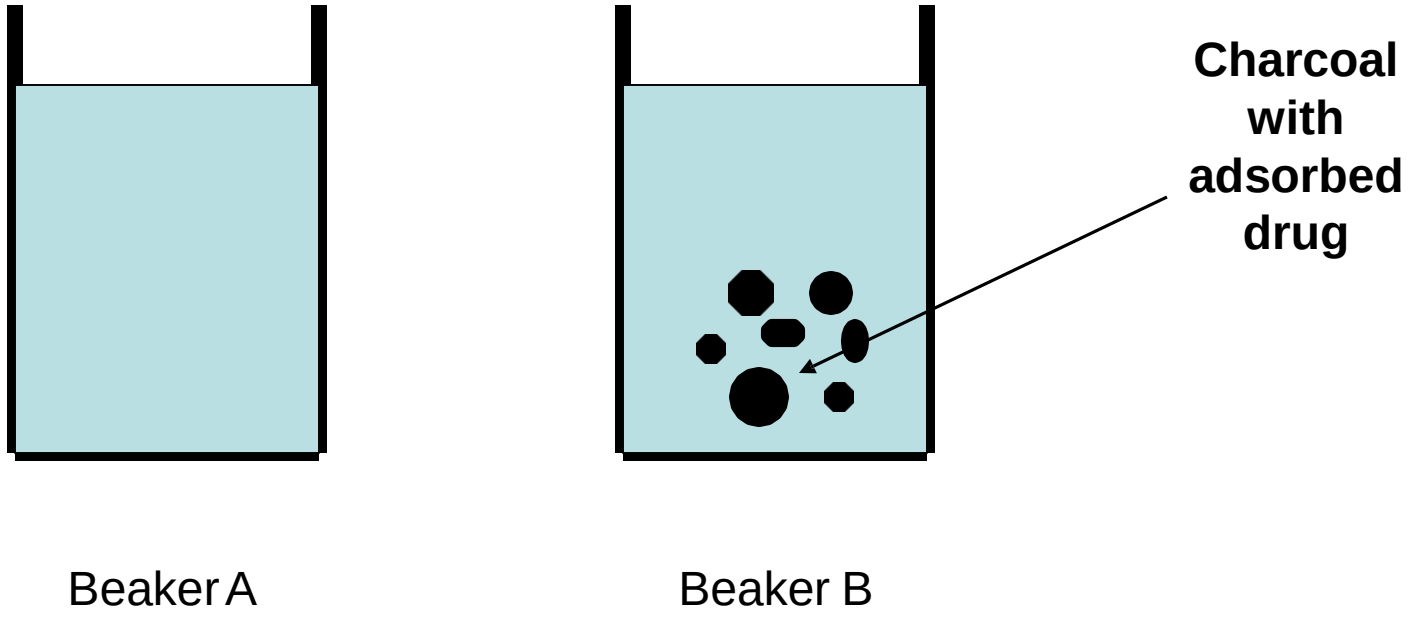
- The following are some of the most useful and fundamental pharmacokinetic parameters of a drug:
  - Apparent volume of distribution (V)
  - Elimination half life ($t_{1/2}$)
  - Elimination rate constant (K or K_el)
  - Systemic clearance $(Cl)_s$.

- The apparent volume of distribution (V)
  - Concentrations (amount per unit volume), are usually measured in plasma or serum (more often than blood).
  - Therefore, a term is needed to relate the measured concentration (C_p) at a time to the amount of drug (X) at that time.
    - This term is defined as the apparent volume of distribution (V).
  - The apparent volume of distribution is simply a proportionality constant for a given drug and is independent of the administered dose and route of drug administration.

    It is not a physiological volume.

The concept of the apparent volume of distribution

- Assume that we have two beakers:



- Beakers A and B contain equal but unknown volumes of water.
- Only beaker B contains a small quantity of charcoal (an adsorbing agent).
- Let us assume that we add 1 g of a drug that is soluble in water, to each beaker.
- Using a suitable analytical procedure, the concentration (μg/mL) of the drug in each beaker is determined.
- Finally: Let us assume that the drug concentration (μg/mL) in beakers A and B is determined to be
  - Beaker A: 100 μg/mL
  - Beaker B: 50 μg/mL

- Why the drug conc. is different although the volume of water in each beaker and drug added to each beaker is identical?

- But we stated at the start that each beaker contains an identical but unknown volume of water.
  - Why do we get a different volume of water in each beaker?

  10 L of water in beaker A and 20 L of water in beaker B
- The presence of a small amount of charcoal (adsorbing agent) is responsible for reducing the drug concentration in the available identical volume of water in beaker B.

- If one applies this concept to the animal or human body, one will observe similar outcomes $\Rightarrow$ instead of charcoal, we have tissues and organs

- The penetration of drug molecules into the organs and tissues play an important role in drug distribution and in assessment and determination of its extent.

- The more the drug molecules penetrate into tissues following the administration of the dose of a drug $\Rightarrow$

- - The smaller will be the plasma drug concentration.
  - Therefore the higher is the hypothetical volume into which the drug is distributed.

- The hydrophilic/lipophilic nature of the drug (the chemical structure of a compound) determines the extent to which the drug molecules penetrate into the tissues or the extent of drug distribution.

- It is important to recognize that the knowledge of this parameter is essential in **determining the dose of a drug required to attain the desired initial plasma concentration**.
- It is called an apparent volume because it is not a true volume.
- The apparent volume of distribution is a property of a drug rather than of a biological system.
- It describes the extent to which a particular drug is distributed in the body tissues.
- The magnitude of the volume of distribution usually does not correspond to plasma volume, extracellular or total body volume space.
- It may vary from a few liters (7 to 10 L) to several hundred liters (200 L and higher) in a 70 kg subject.

- The value of the apparent volume of distribution also reflects the lipophilicity of a drug.
  - The more lipophilic the nature of the drug, greater will be the value of the apparent volume of distribution and the smaller will be the initial plasma concentration.

- Conversely, if the drug is hydrophilic $\Rightarrow$ the drug will penetrate to a lesser extent into tissue $\Rightarrow$ its plasma concentration will be higher and its volume of distribution will be smaller.

Many acidic drugs, including salicylates, **sulfonamides, penicillins and anticoagulants**, are either **highly bound to plasma proteins** or too **water soluble**.

These drugs, therefore, have **low volumes of** distribution and **low tissue to plasma concentration ratios and a** given dose of these drugs will yield a relatively **high plasma concentration**.

Basic drugs, including **tricyclic antidepressants and antihistamines,** are extensively bound to extracellular tissues and are also taken up by adipose tissues.

- The apparent volumes of distribution of these drugs are large, often larger than the total body space.
- The relatively small doses and large volumes of distribution together produce low plasma concentrations, making quantitative detection in plasma a difficult task.

- How to calculate V_d?

➢ Then it is easy to determine the apparent volume of distribution from the knowledge of initial plasma concentration (mg/mL) and the administered dose (mg or mg/kg of body weight).

- Only applicable if the drug is administered as an intravenous bolus and exhibits the characteristics of a one-compartment model.

The elimination half life ($t_{1/2}$)

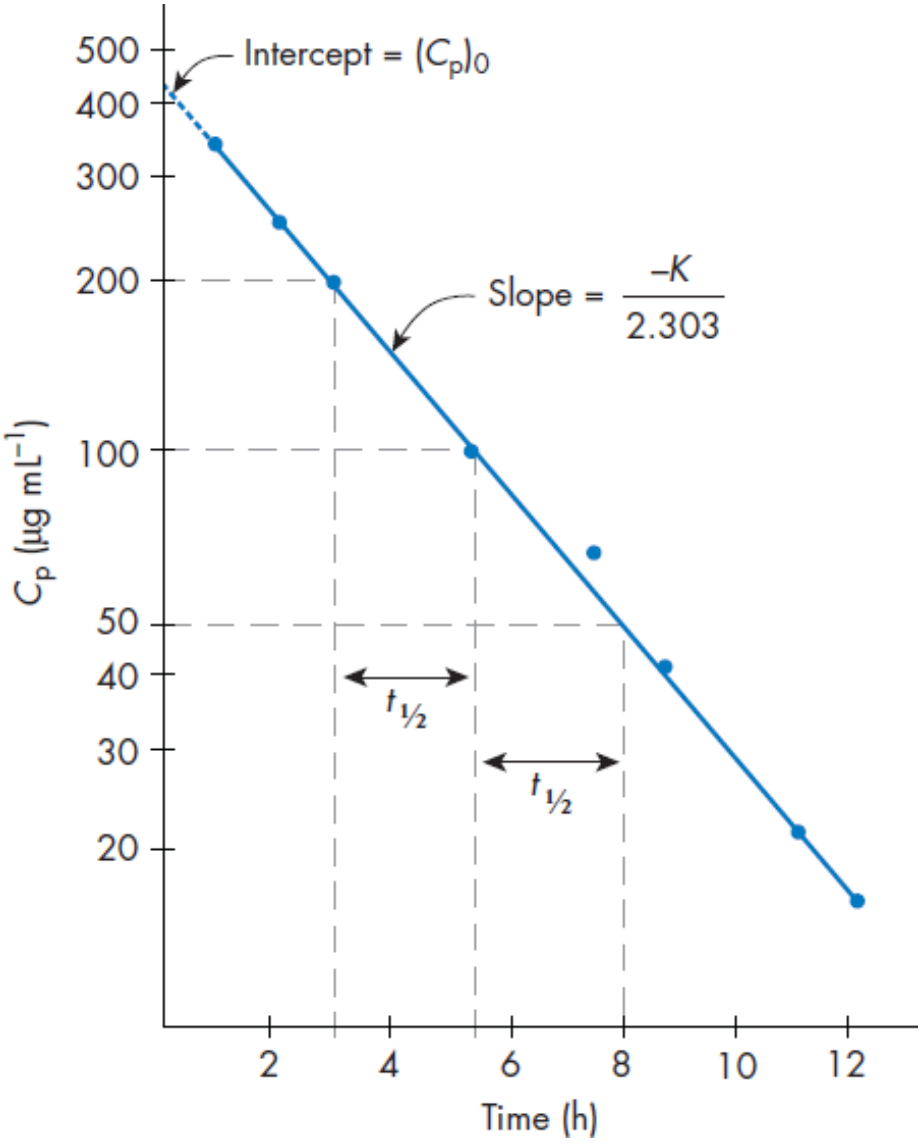
- The elimination half life is sometimes called "biological half-life" of a drug.
- The elimination half life may be defined as the time (h, min, day, etc.) at which the amount of unchanged drug becomes half (or 50%) of the initial amount of drug.
- As is the case for the parameter apparent volume of distribution, the elimination half life is also a constant for a drug and is independent of the administered dose and the route of drug administration.

❖ Determination of the elimination half life

– It can be calculated using the following equation provided that the value of the elimination rate constant is known

$$t_{1/2} = \frac{0.693}{K}$$

- Alternatively, the elimination half life may be obtained from the semilogarithmic plot of plasma concentration versus time data
  - By choosing any two concentration values (from the y-axis) that are one half of each other and the corresponding time values (from the x-axis).
  - The difference between the two time values represents the elimination half life of the drug.



Semilogarithmic plot of plasma concentration (C_p) versus time following administration of the drug prednisolone by intravenous bolus injection.

The elimination rate constant (K or K_{el})

- The elimination rate constant of a drug may be obtained by using the following methods:

1. Using the following equation provided that the value of the elimination half life is known

$$k = 0.693 / t_{1/2}$$

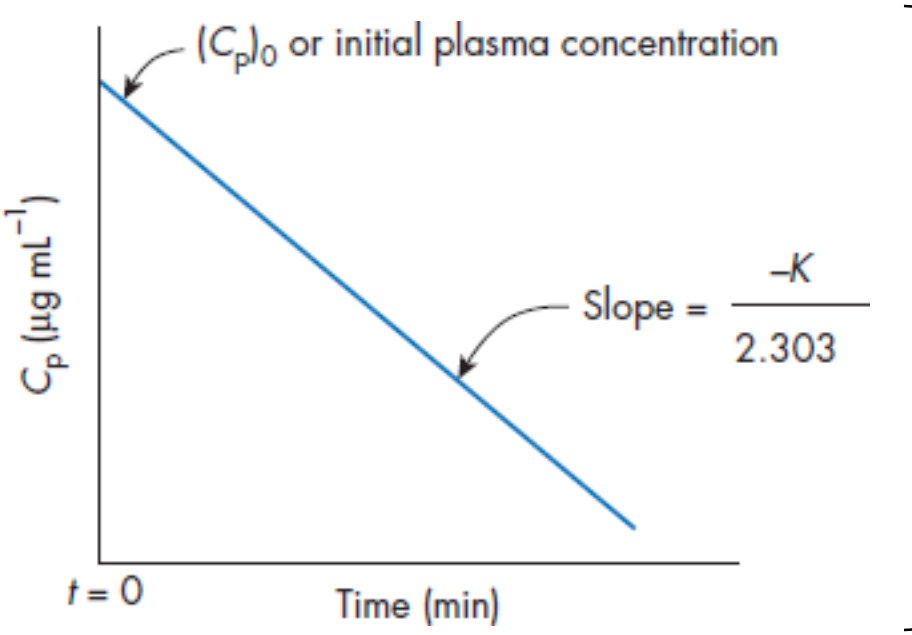
2. Using the following equation if the value of $(C_p)_o$ as well as any value of C_p at time t are known

$$C_p = C_{p0}\, e^{-kt}$$

3. From the semilogarithmic plot of plasma concentration versus time:

- K = (slope) x 2.303

Where the slope is $$slope = \frac{\log Y_2 - \log Y_1}{t_2 - t_1}$$



Semilogarithmic plot

- The first-order rate constant (K) has a unit of reciprocal of time (e.g. h^{-1}).
- Over very small time segments, it approximates the fraction (%) of drug removed per unit time
  - for example: if K = 0.1 h^{-1} $\Rightarrow$ it means that approximately 10% of the remaining amount is removed per hour.

- Since drug is continuously removed from the body $\Rightarrow$ the remaining amount is continuously changing.

- The elimination rate constant represents overall drug elimination from the body, which includes
  - Renal excretion of unchanged drug (u), and/or
  - The formation of metabolites (m).

- Hence,

$$K = K_u + K_m$$

- If the drug has two metabolites for example, then

$$K = K_u + K_{m1} + K_{m2}$$

where K_u and K_m are excretion and metabolic rate constants, respectively.

- However, when the drug is removed in unchanged form only (i.e. no metabolite[s]), then $K = K_u$.
- Conversely, $K = K_m$ if the drug is completely metabolized.

Questions

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, that is, in the tissues. If VD is small, then there is little extravascular tissue drug storage, except perhaps in the lung, liver, kidney, and heart.

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

• Clearance is the volume of plasma fluid that is cleared of drug per unit time. Clearance may also be derived for the physiologic model as the fraction of drug that is eliminated by an organ as blood flows through it. The former definition is equivalent to Cl = kVD and is readily adapted to dosing since VD is the volume of distribution. If the drug is eliminated solely by metabolism in the liver, then ClH = Cl. ClH is usually estimated by the difference between Cl and ClR. ClH is directly estimated by the product of the hepatic blood flow and the extraction ratio.

Why does k always have the unit 1/time (eg, 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 cancelled when taking the log of the number

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 ug/mL, respectively. What is the biologic half-life for this drug, assuming first order elimination kinetics?

The C_p decreased from 1.2 to 0.3 μg/mL in 3 hours.

t (hours)	C_p (μg/mL)
2	1.2
5	0.3

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

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

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

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

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

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?

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

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

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

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

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?

$$D_0 = 200 \text{ mg}$$

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

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

At 6 hours:

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

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

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

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

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

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

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

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.)

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

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

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

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

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:

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

An intoxicated young man (75 kg, age 21 years) 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:

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

$$45 = -8t + 94.5$$

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

A single IV bolus injection containing 500 mg of cefamandole nafate 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 Cp0 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 mg/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. $$\log 0.5 = \frac{-(0.693/0.75)t}{2.3} + \log 90.0$$

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

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 (hours)	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 mg/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 (hours)	C_p (μg/mL)
2	6
6	3

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

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

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

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

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

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

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.

A new antibiotic drug was given in a single intravenous bolus of 4 mg/kg to 5 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 $Cp=78e^{-0.46t}$

− Determine the following (assume units of mg/mL for Cp and hours 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 mg/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. $V_D = \dfrac{\text{dose}}{C_p^0} = \dfrac{300{,}000\ \mu\text{g}}{78\ \mu\text{g/mL}} = 3846\ \text{mL}$

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

c.

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

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

(2) $C_p = 78e^{-0.46(4)} = 78e^{-18.4} = 78\,(0.165)$

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

d. At 4 hours:

$$D_B = C_p V_D = 12.4\ \mu g/mL \times 3846\ mL$$

$$= 47.69\ mg$$

e. $V_D = 3846\ mL$

Average weight $= 75\ kg$

Percent body wt $= (3.846\ kg/75\ kg) \times 100$

$$= 5.1\%$$

The apparent V_D approximates the plasma volume.

f. $C_p = 2\ \mu g/mL$

Find t.

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

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

$$t = 7.96\ h \approx 8\ h$$