Note: Large images and tables on this page may necessitate printing in landscape mode.

CHAPTER 1

Frequently Asked Questions

1. Blood is composed of plasma and red blood cells (RBCs). Serum is the fluid obtained from blood after it is allowed to clot. Serum and plasma do not contain identical proteins. RBCs may be considered a cellular component of the body in which the drug concentration in the serum or plasma is in equilibrium, in the same way as with the other tissues in the body. Whole blood samples are generally harder to process and assay than serum or plasma samples.

2. Physiologic models are complex, and require more information for accurate prediction compared to compartment models. Missing information in the physiologic model will lead to bias or error in the model. Compartment models are more simplistic in that they assume that both arterial and venous drug concentrations are similar. The compartment model accounts for a rapid distribution phase and a slower elimination phase. Physiologic clearance models postulate that arterial blood drug levels are higher than venous blood drug levels. In practice, only venous blood samples are usually sampled. Organ drug clearance is useful in the treatment of cancers and in diagnosis of certain diseases involving arterial perfusion. Physiologic models are difficult to use for general application.

3. The exact site of drug action is generally unknown for most drugs. The time needed for the drug to reach the site of action, produce a pharmacodynamic effect, and reach equilibrium are deduced from studies on the relationship of the time course for the drug concentration and the pharmacodynamic effect. Often, the drug concentration is sampled during the elimination phase after the drug has been distributed and reached equilibrium. For multiple-dose studies, both the peak and trough drug concentrations are frequently taken.

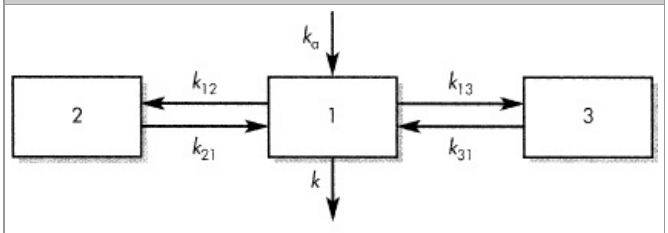
Learning Questions

1. The plasma drug level–time curve describes the pharmacokinetics of the systemically absorbed drug. Once a suitable pharmacokinetic model is obtained, plasma drug concentrations may be predicted following various dosage regimens such as single oral and IV bolus doses, multiple-dose regimens, IV infusion, etc. If the pharmacokinetics of the drug relate to its pharmacodynamic activity (or any adverse drug response or toxicity), then a drug regimen based on the drug's pharmacokinetics may be designed to provide optimum drug efficacy. In lieu of a direct pharmacokinetic–pharmacodynamic relationship, the drug's pharmacokinetics describe the bioavailability of the drug including inter- and intrasubject variability; this information allows for the development of drug products that consistently deliver the drug in a predictable manner.

2. The purpose of pharmacokinetic models is to relate the time course of the drug in the body to its pharmacodynamic and/or toxic effects. The pharmacokinetic model also provides a basis for drug product design, the design of dosage regimens, and a better understanding of the action of the body on the drug.

3. ()

Figure C-1



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

4. a. Nine parameters: V_1, V_2, V_3, k_{12}, k_{21}, k_e, k_b, k_m, k_u

b. Compartment 1 and compartment 3 may be sampled.

c. $k = k_b + k_m + k_e$

d. $$\frac{dC_1}{dt} = k_{21}C_2 - (k_{12} + k_m + k_e + k_b)C_1$$

6.

Compartment 1	Compartment 2
C_1	C_2

a. C_1 and C_2 are the *total* drug concentration in each compartment respectively. $C_1 > C_2$ may occur if the drug concentrates in compartment 1 due to protein binding (compartment 1 contains a high amount of protein or special protein binding), due to partitioning (compartment 1 has a high lipid content and the drug is poorly water soluble), if the pH is different in each compartment and the drug is a weak electrolyte (the drug may be more ionized in compartment 1), or if there is an active transport mechanism for the drug to be taken up into the cell (eg, purine drug). Other explanations for $C_1 > C_2$ may be possible.

b. Several different experimental conditions are needed to prove which of the above hypotheses is the most likely cause for $C_1 > C_2$. These experiments may use *in-vivo* or *in-vitro* methods, including intracellular electrodes to measure pH *in vivo*, protein binding studies *in vitro*, and partitioning of drug in chloroform/water *in vitro*, among others.

c. In the case of protein binding, the total concentration of drug in each compartment may be different (eg, $C_1 > C_2$) and, at the same time, the free (non-protein bound) drug concentration may be equal in each compartment—-assuming that the free or unbound drug is easily diffusable. Similarly, if $C_1 > C_2$ is due to differences in pH and the nonionized drug is easily diffusable, then the nonionized drug concentration may be the same in each compartment. The total drug concentrations will be $C_1 = C_2$ when there is similar affinity for the drug and similar conditions in each compartment.

d. The total amount of drug, A, in each compartment depends on the volume, V, of the compartment and the concentration, C, of the drug in the compartment. Since the amount of drug (A) = concentration (C) times volume (V), any condition that causes the product, $C_1V_1 \neq C_2V_2$, will result in $A_1 \neq A_2$. Thus, if $C_1 = C_2$ and $V_1 \neq V_2$, then $A_1 \neq A_2$.

CHAPTER 2

Frequently Asked Questions

1. A semilog plot spaces the data at logarithmic intervals on the y axis and rectangular (evenly spaced) intervals on the x axis. The paper comes in one or more cycles. Two-cycle semilog paper covers two logarithmic intervals (eg, 1 to 100). The semilog scale does not start with zero.

2. A common error in using logs is failing to remember that ln x = 2.3 log x. For the slope formula using a semilog plot,

$$\text{Slope} = \frac{\log y_2 - \log y_1}{x_2 - x_1} = \frac{-k}{2.3}$$

$$k = -\text{slope} \times 2.3 \qquad \text{(Did you forget the 2.3 factor?)}$$

Alternatively, if you determine the slope with natural logs,

$$\text{slope} = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} = -k$$

$$k = -\text{slope} \qquad \text{(You should not use the 2.3 factor in this case)}$$

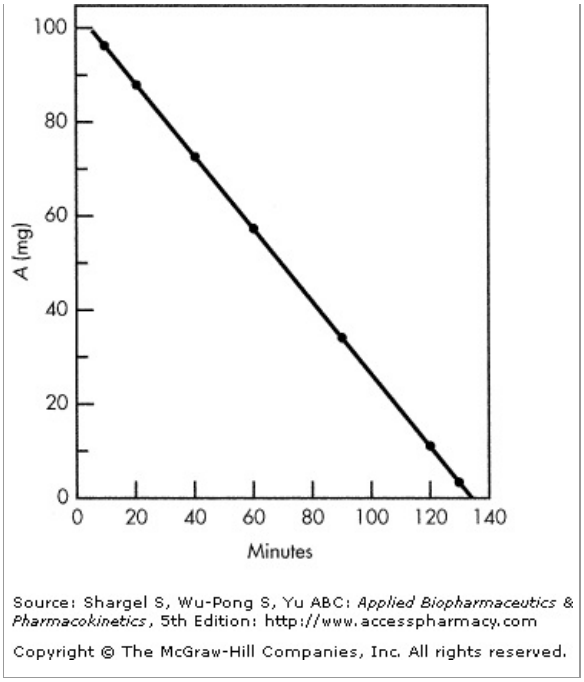
3. Use the natural antilog of the intercept, or the inverse of ln.

Learning Questions

1. a. Zero-order process ().

b. Rate constant, k_0:

Figure C-2



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Method 1

Values obtained from the graph ():

t **(min)**	***A*** **(mg)**
40	71
80	41

$$-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{y_2 - y_1}{x_2 - x_1}$$

$$-k_0 = \frac{41 - 71}{80 - 40} \qquad k_0 = 0.75 \text{ mg/min}$$

Notice that the negative sign shows that the slope is declining.

Method 2

By extrapolation:

$$A_0 = 103.5 \text{ at } t = 0;\ A = 71 \text{ at } t = 40 \text{ min}$$
$$A = k_0 t + A_0$$
$$71 = -40k_0 + 103.5$$
$$k_0 = 0.81 \text{ mg/min}$$

Notice that the answer differs in accordance with the method used.

c. $t_{1/2}$

For zero-order kinetics, the larger the initial amount of drug A_0, the longer the $t_{1/2}$.

Method 1

$$t_{1/2} = \frac{0.5\, A_0}{k_0}$$
$$t_{1/2} = \frac{0.5(103.5)}{0.78} = 66 \text{ min}$$

Method 2

The zero-order $t_{1/2}$ may be read directly from the graph ():

$$\text{At } t = 0,\ A_0 = 103.5 \text{ mg.}$$
$$\text{At } t_{1/2},\ A = 51.8 \text{ mg.}$$

Therefore, $t_{1/2}$ = 66 min.

d. The amount of drug *A* does extrapolate to zero on the *x* axis.

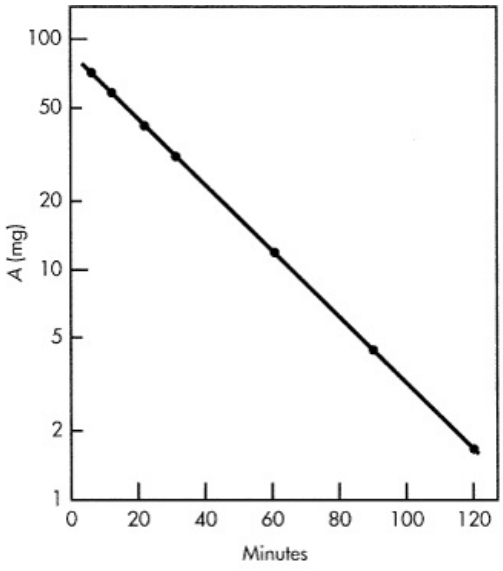
e. The equation of the line is

$$A = -k_0 t + A_0$$
$$A = -0.78t + 103.5$$

2. a. First-order process ().

b. Rate constant, *k*:

Figure C-3



Method 1

Obtain the first-order $t_{1/2}$ from the semilog graph ():

t **(min)**	***A*** **(mg)**
30	30
53	15

$$t_{1/2} = 23 \text{ min}$$
$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{23} = 0.03 \text{ min}^{-1}$$

Method 2

$$\text{Slope} = \frac{-k}{2.3} = \frac{\log Y_2 - \log Y_1}{X_2 - X_1}$$
$$k = \frac{-2.3(\log 15 - \log 30)}{53 - 30} = 0.03 \text{ min}^{-1}$$

c. $t_{1/2}$ = 23 min (see Method 1 above).

d. The amount of drug *A* does not extrapolate to zero on the *x* axis.

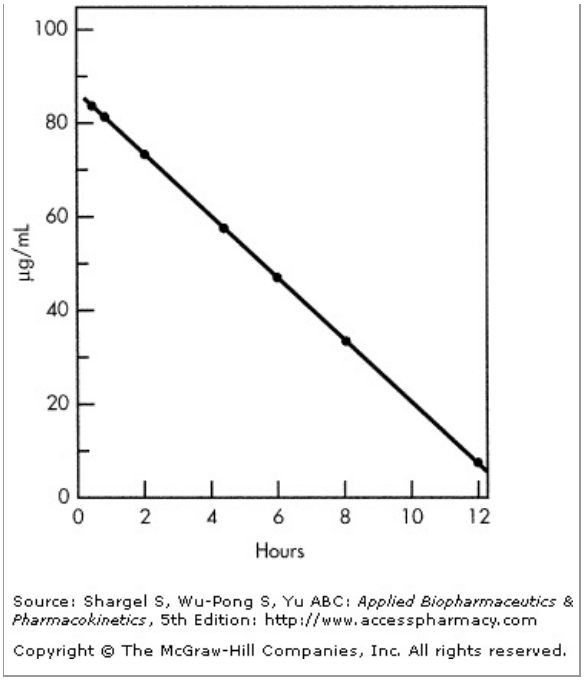
e. The equation of the line is

$$\log A = -\frac{kt}{2.3} + \log A_0$$
$$\log A = -\frac{0.03t}{2.3} + \log 78$$
$$A = 78e^{-0.03t}$$

On a rectangular plot, the same data shows a curve (not plotted).

3. a. Zero-order process ().

Figure C-4



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b. $k_0 = \text{slope} = \dfrac{\Delta Y}{\Delta X}$

Values obtained from the graph ():

***t* (hr)**	***C* (µg/mL)**
1.2	80
4.2	60

It is always best to plot the data. Obtain a regression line (ie, the line of best fit), then use points *C* and *t* from that line.

$$-k_0 = \frac{60 - 80}{4.2 - 1.2}$$

$$k_0 = 6.67\ \mu\text{g/mL hr}$$

c. By extrapolation:

$$\text{At } t_0,\ C_0 = 87.5\ \mu\text{g/mL}.$$

d. The equation (using a ruler only) is

$$A = -k_0 t + A_0 = -6.67t + 87.5$$

4. Given:

***C* (mg/mL)**	***t* (days)**
300	0
75	30

a. $\log C = \dfrac{-kt}{2.3} + \log C_0$

$$\log 75 = \frac{-30k}{2.3} + \log 300$$

$$k = 0.046\ \text{days}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.046} = 15\ \text{days}$$

b. Method 1

$$300\ \text{mg/mL} = C_0 \text{ at } t = 0$$

$$75\ \text{mg/mL} = C \text{ at } t = 30\ \text{days}$$

$$225\ \text{mg/mL} = \text{difference between initial and final drug concentration}$$

$$k_0 = \frac{225\ \text{mg/mL}}{30\ \text{days}} = 7.5\ \text{mg/mL/day}$$

The time, $t_{1/2}$, for the drug to decompose to ½ C_0 (from 300 to 150 mg/mL) is calculated by (assuming zero order)

$$t_{1/2} = \frac{150 \text{ mg/mL}}{7.5 \text{ mg/mL day}} = 20 \text{ days}$$

Method 2

$$C = -k_0 t + C_0$$
$$75 = -30k_0 + 300$$
$$k_0 = 7.5 \text{ mg/mL/day}$$

At $t_{1/2}$, $C = 150$ mg/mL

$$150 = -7.5t_{1/2} + 300$$
$$t_{1/2} = 20 \text{ days}$$

Method 3

A $t_{1/2}$ value of 20 days may be obtained directly from the graph by plotting C against t on rectangular coordinates.

5. Assume the original concentration of drug to be 1000 mg/mL.

Method 1

mg/mL	No. of Half-Lives	mg/mL	No. of Half-Lives
1000	0	15.6	6
500	1	7.81	7
250	2	3.91	8
125	3	1.95	9
62.5	4	0.98	10
31.3	5		

$$99.9\% \text{ of } 1000 = 999$$

Concentration of drug remaining = 0.1% of 1000

$$1000 - 999 = 1 \text{ mg/mL}$$

It takes approximately 10 half-lives to eliminate all but 0.1% of the original concentration of drug.

Method 2

Assume any $t_{1/2}$ value:

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

Then

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

$$\log C = \frac{-kt}{2.3} + \log C_0$$

$$\log 1.0 = \frac{-kt}{2.3} + \log 1000$$

$$t = 9.96 t_{1/2}$$

Substituting $0.693/t_{1/2}$ for k:

$$\log 1.0 = \frac{-0.693t}{2.3 \times t_{1/2}} + \log 1000$$

$$t = 9.96\, t_{1/2}$$

6. $t_{1/2} = 12$ hr

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{12} = 0.058 \text{ hr}^{-1}$$

If 30% of the drug decomposes, 70% is left.

$$70\% \text{ of } 125 \text{ mg} = (0.70)\,(125) = 87.5 \text{ mg}$$

$$A_0 = 125 \text{ mg}$$

$$A = 87.5 \text{ mg}$$

$$k = 0.058 \text{ hr}^{-1}$$

$$\log A = -\frac{kt}{2.3} + \log A_0$$

$$\log 87.5 = -\frac{0.058t}{2.3} + \log 125$$

$$t = 6.1 \text{ hr}$$

7. Immediately after the drug dissolves, the drug degrades at a constant, or zero-order, rate. Since concentration is equal to mass divided by volume, it is necessary to calculate the initial drug concentration (at $t = 0$) to determine the original volume in which the drug was dissolved. From the data, calculate the zero-order rate constant, k_0:

$$-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{0.45 - 0.3}{2.0 - 0.5} \qquad k_0 = 0.1 \text{ mg/mL hr}$$

Then calculate the initial drug concentration, C_0, using the following equation:

$$C = -k_0 t + C_0$$

At $t = 2$ hours,

$$0.3 = -0.1(2) + C_0$$

$$C_0 = 0.5 \text{ mg/mL}$$

Alternatively, at $t = 0.5$ hour,

$$0.45 = -0.1(0.5) - C_0$$

$$C_0 = 0.5 \text{ mg/mL}$$

Since the initial mass of drug D_0 dissolved is 300 mg and the initial drug concentration C_0 is 0.5 mg/mL, the original volume may be calculated from the following relationship:

$$C_0 = \frac{D_0}{V}$$

$$0.5 \text{ mg/mL} = \frac{300 \text{ mg}}{V(\text{mL})}$$

$$V = 600 \text{ mL}$$

8. First order.

9. The volume of the culture tube is not important. In 8 hours (480 minutes), the culture tube is completely full. Because the doubling time for the cells is 2 minutes (ie, one $t_{1/2}$), then in 480 minutes less 2 minutes (478 minutes) the culture tube is half full of cells.

10. Data is often reported as the mean ± standard deviation or SD (see). One SD above and below the mean represents 95% of the population, assuming a normal distribution of the data. In this example,

$$\text{Mean} + 2\text{SD} = 9.8 \text{ L} + 8.4 \text{ L} = 18.2 \text{ L}$$

$$\text{Mean} - 2\text{SD} = 9.8 \text{ L} - 8.4 \text{ L} = 1.4 \text{ L}$$

Thus, 95% of the population would have a volume of distribution approximately ranging from 1.4 to 18.2 L.

11. The answer is **A.** Each of the equations are in the form of $y = Ae^{kt}$, where k is the slope of the line connecting the data points. A positive slope indicates that the direction of the line is slanted upward from left to right, whereas a negative slope

indicates that the line slants downward (declines) from left to right. Answer **C** would have a rising slope.

12. The answer is **C.** Recall that $e^{-kt} = 1/e^{kt}$, and that, as k or t gets larger, the fraction, $1/e^{kt}$ gets smaller (for both A and B). (Note: You may check the values using your calculator.)

13. The answer is **D.** You cannot obtain a log from a negative number.

14. The answer is **B.** Substitute the same value for t in each example and notice your answers.

CHAPTER 3

Frequently Asked Questions

1. 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/hr means the amount of drug is decreasing at 5 mg per hour. 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 = $-kD_B$, where k represents "the fraction" of the amount of drug in the body that is eliminated per hour. If $k = 0.1\ hr^{-1}$ and $D_B = 10$ mg, then the rate = $0.1\ hr^{-1} \times 10$ mg = 1 mg/hr. 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. 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. 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 V_D is larger than the physiologic vascular volume, the conclusion is that there is some drug outside the vascular pool, ie, in the tissues. If V_D 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. 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 $Cl = kV_D$ and is readily adapted to dosing since V_D is the volume of distribution. If the drug is eliminated solely by metabolism in the liver, then $Cl_H = Cl.Cl_H$ is usually estimated by the difference between $Cl - Cl_R$. Cl_H is directly estimated by the product of the hepatic blood flow and the extraction ratio.

5. 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 a RBC/plasma drug ratio much greater than 1, making the application of the physiologic model difficult without knowing the apparent volume of distribution.

Learning Questions

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

t (hr)	C_P (µg/mL)
2	1.2
5	0.3

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

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

$$k = 0.462\ hr^{-1}$$

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

$$t_{1/2} = 1.5\ hr$$

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

2. Dose (IV bolus) = 6 mg/kg x 50 kg = 300 mg

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

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

t (hr)	C_P (μg/mL)
2	6
6	3

(2) $t_{1/2}$ (from graph) $= 4$ hr $\qquad k = \dfrac{0.693}{4} = 0.173\ \text{hr}^{-1}$

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

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

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

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

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 $10t_{1/2}$

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

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

With 0.1% of drug remaining,

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

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

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

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

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

$$C_P^0 = 16.8\ \mu\text{g/mL} \qquad C_P = 2\ \mu\text{g/mL} \qquad k = 0.173\ \text{hr}^{-1}$$

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

$$t = 12.3\ \text{hr}$$

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

3. $D_0 = 200$ mg

$V_D = 10\%$ of body weight $= 0.1\ (80\ \text{kg}) = 8000\ \text{mL} = 8\ \text{L}$

At 6 hours:

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

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

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

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

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

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

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

4. $C_P = 78e^{-0.46t}$ (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, $k = 0.46\ \text{hr}^{-1}$, $C_P^0 = 78\ \mu\text{g/mL}$.

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

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) $C_P = 78e^{-0.46(4)} = 78e^{-1.84} = 78(0.165)$

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

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 = $(3.846\ \text{kg}/75\ \text{kg}) \times 100 = 5.1\%$

The apparent V_D approximates the plasma volume.

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

Find t.

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

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

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

Alternate Method

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

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

$$-3.7 = -0.46t$$

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

6. For first-order elimination kinetics, one-half of the initial quantity is lost each $t_{1/2}$. The following table may be developed:

Time (hr)	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 $t_{1/2}$ 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 $nt_{1/2}$
0	**100**

1	50	100 x 1/2
2	25	100 x 1/2 x 1/2
3	12.5	100 x 1/2 x 1/2 x 1/2
n		100 x $(1/2)^n$

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

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

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

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

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

t = 24 hr

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

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

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

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

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

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

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

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:

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

$$45 = -8t + 94.5$$

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

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

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

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

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

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

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

10.
$$\log D_B = \frac{-kt}{2.3} + \log D_B^0$$

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

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

$$\text{Percent drug lost} = \frac{600 - 74.9}{600} \times 100 = 87.5\%$$

C_P at t = 24 hours:

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

11. 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.

12. Set up the following table:

Time (hr)	D_u (mg)	D_u/t	mg/hr	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/hr versus t^*. The $t_{1/2}$ obtained graphically is approximately 2 hours.

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

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

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

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

CHAPTER 4

Frequently Asked Questions

1. *Mathematical* and *hypothetical* are indeed vague and uninformative terms. Mathematical equations are developed to calculate how much drug is in the vascular fluid, as well as outside the vascular fluid (ie, extravascular or in the tissue pool). *Hypothetical* refers to an unproven model. The assumptions in the compartmental models simply imply that the model simulates the mass transfer of drug between the circulatory system and the tissue pool. The mass balance of drug moving out of the plasma fluid is described even though we know the tissue pool is not real (the tissue pool represents the virtual tissue mass that receives drug from the blood). While the model is a less than perfect representation, we can interpret it, knowing its limitations. All pharmacokinetic models need interpretation. We use a model when there are no simple ways to obtain needed information. As long as we know the model limitations (ie, that the tissue compartment is not the brain, nor the muscle!) and stay within the

bounds of the model, we can extract useful information from it. For example, we may determine the amount of drug that is stored outside the plasma compartment at any desired time point. After an IV bolus drug injection, the drug distributes rapidly throughout the plasma fluid and more slowly into the fluid-filled tissue spaces. Drug distribution is initially rapid and confines to a fixed fluid volume known as the V_p or the initial volume. As drug distribution expands into other tissue regions, the volume of the penetrated spaces increases, until a critical point (steady state) is obtained when all penetrable tissue regions are equilibrated with the drug. Knowing that there is heterogenous drug distribution within and between tissues, the tissues are grouped into compartments to determine the amount of drugs in them. Mass balance, including drug inside and outside the vascular pool, accounts for all body drug storage ($D_B = D_t + D_p$). Assuming steady state, the tissue drug concentration equal to the plasma drug concentration, C_{PSS}, and one may determine size of the tissue volume using D_t/C_{PSS}. This volume is really a "numerical factor" that is used to describe the relationship of the tissue storage drug relative to the drug in the blood pool. The sum of the two volumes is the steady-state volume of distribution. The product of the steady-state concentration, C_{pSS}, and the (V_D)ss yields the amount of drug in the body at steady state. The amount of drug in the body at steady state is considered vital information in dosing drugs clinically. Students should realize that tissue drug concentrations are not predicted by the model. However, plasma drug concentration is fully predictable after any given dose once the parameters become known. Initial pharmacokinetic parameter estimation may be obtained from the literature using comparable age and weight for a specific individual.

2. Apparent volumes of distribution are not real tissue volumes, but rather reflect the volume in which the drug is contained. For example,

V_p = initial or plasma volume

V_t = tissue volume

$(V_D)_{SS}$ = steady-state volume of distribution (most often listed in the literature)

The steady-state drug concentration multiplied by $(V_D)_{SS}$ yields the amount of drug in the body. $(V_D)\beta$ is a volume usually determined from area under the curve (AUC), and differs from $(V_D)_{SS}$ somewhat in magnitude. $(V_D)\beta$ multiplied by b gives clearance of the drug.

3. A physiologic model is a detailed representation of drug disposition in the body. The model requires blood flow, extraction ratio, and specific tissue and organ size. This information is not often available for the individual. Thus, the less sophisticated compartment models are used more often.

4. Clearance is used to calculate the steady-state drug concentration and to calculate the maintenance dose. However, clearance alone is not useful in determining the maximum and minimum drug concentrations in a multiple-dosing regimen.

5. If the two-compartment model is ignored and the data are treated as a one-compartment model, the estimated values for the pharmacokinetic parameters are distorted. For example, during the distributive phase, the drug declines rapidly according to distribution α half-life, while in the elimination (terminal) part of the curve, the drug declines according to a β elimination half-life.

6. Compartment models have been used to develop dosage regimens and for the development of pharmacodynamic models. Compartment models have improved the dosing of drugs such as digoxin, gentamicin, lidocaine, and many others. The principal use of compartment models in dosing is to simulate a plasma drug concentration profile based on pharmacokinetic (PK) parameters. This information allows comparison of PK parameters in patients with only two or three points to a patient with full profiles using generated PK parameters.

Learning Questions

1. Equation for the curve:

$$C_p = 52e^{-1.39t} + 18e^{-0.135t}$$

$$k = 0.41\ \text{hr}^{-1} \qquad k_{12} = 0.657\ \text{hr}^{-1} \qquad k_{21} = 0.458\ \text{hr}^{-1}$$

2. Equation for the curve:

$$C_p = 28e^{-0.63t} + 10.5e^{-0.46t} + 14e^{-0.077t}$$

Note: When feathering curves by hand, a minimum of three points should be used to determine the line. Moreover, the rate constants and y intercepts may vary according to the individual's skill. Therefore, values for C_p should be checked by substitution of various times for t, using the derived equation. The theoretical curve should fit the observed data.

3. C_p = 11.14 μg/mL.

4. The initial decline in the plasma drug concentration is due mainly to uptake of drug into tissues. During the initial distribution of drug, some drug elimination also takes place. After the drug has equilibrated with the tissues, the drug declines at a slower rate because of drug elimination.

5. A third compartment may indicate that the drug has a slow elimination component. If the drug is eliminated by a very slow elimination component, then drug accumulation may occur with multiple drug doses or long IV drug infusions. Depending on the blood sampling, a third compartment may be missed. However, some data may fit both a two- and a three-compartment model. In this case, if the fit for each compartment model is very close statistically, the more simple compartment model should be used.

6. Because of the heterogeneity of the tissues, drug equilibrates into the tissues at different rates and the different drug

concentrations are usually observed in the different tissues. The drug concentration in the "tissue" compartment represents an "average" drug concentration and does not represent the drug concentration in any specific tissue.

7.

$$C_P = Ae^{-at} + Be^{-bt}$$

After substitution,

$$C_P = 4.62e^{-8.94t} + 0.64e^{-0.19t}$$

a. $$V_P = \frac{D_0}{A + B} = \frac{75{,}000}{4.62 + 0.64} = 14{,}259 \text{ mL}$$

b. $$V_t = \frac{V_P k_{12}}{k_{21}} = \frac{(14{,}259)\,(6.52)}{(1.25)} = 74{,}375 \text{ mL}$$

c. $$k_{12} = \frac{AB(b - a)^2}{(A + B)\,(Ab + Ba)}$$

$$k_{12} = \frac{(4.62)\,(0.64)\,(0.19 - 8.94)^2}{(4.62 + 0.64)\left[(4.62)\,(0.19) + (0.64)\,(8.94)\right]}$$

$$k_{12} = 6.52 \text{ hr}^{-1}$$

$$k_{21} = \frac{Ab + Ba}{A + B} = \frac{(4.62)\,(0.19) + (0.64)\,(8.94)}{4.62 + 0.64}$$

$$k_{21} = 1.25 \text{ hr}^{-1}$$

d. $$k = \frac{ab(A + B)}{Ab - Ba} = \frac{(8.94)\,(0.19)\,(4.62 + 0.64)}{(4.62)\,(0.19) + (0.64)\,(8.94)}$$

$$= 1.35 \text{ hr}^{-1}$$

8. The tissue compartments may not be sampled directly to obtain the drug concentration. Theoretical concentration, C_t, represents the average concentration in all the tissues outside the central compartment. The amount of drug in the tissue, D_t, represents the total amount of drug outside the central or plasma compartment. Occasionally C_t may be equal to a particular tissue drug concentration in an organ. However, this C_t may be equivalent by chance only.

9. The data were analyzed using computer software called RSTRIP, and found to fit a two-compartment model:

$A(1) = 2.0049$ $A(2) = 6.0057$ (two preexponential values)

$k(1) = 0.15053$ $k(2) = 7.0217$ (two exponential values)

The equation that describes the data is

$$C_P = 2.0049e^{-0.15053t} + 6.0057e^{-7.0217t}$$

The coefficient of correlation = 0.999 (very good fit).

The model selection criterion = 11.27 (good model).

The sum of squared deviations = 9.3×10^{-5} (there is little deviation between the observed data and the theoretical value).

Alpha = 7.0217 hr^{-1}, beta = 0.15053 hr^{-1}.

10.a. Late-time samples were taken in some patients, yielding data that resulted in a monoexponential elimination profile. It is also possible that a patient's illness contributes to impaired drug distribution.

b. The range of distribution half-lives is 30–45 minutes.

c. None. Tissue concentrations are not generally well predicted from the two-compartment model. Only the amount of drug in the tissue compartment may be predicted.

d. No. At steady state, the rate in and the rate out of the tissues is the same, but the drug concentrations are not necessarily the same. The plasma and each tissue may have different drug binding.

e. None. Only the pooled tissue is simulated by the tissue compartment.

CHAPTER 5

Frequently Asked Questions

1. 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 rapidly IV into the body. The rate of infusion is particularly important in administering antiarrythmic 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.

2. 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.

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

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

b. $D_L = C_{SS}V_D = (10)(0.231)(65{,}000) = 150 \text{ mg}$

c. $R = C_{SS}V_Dk = (10)(15{,}000)(0.099) = 14.85 \text{ mg/hr}$

d. $Cl_T = V_Dk = (15{,}000)(0.099) = 1485 \text{ mL/hr}$

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:

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

2. 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:

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

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

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

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

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

$$t_{95\%_{ss}} = \frac{\ln 0.05}{-0.2} = 15 \text{ hr}$$

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

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

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

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^0_p. At the termination of the infusion, the drug level will decline by a first-order process.

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

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

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

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

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

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 was given and the drug is then infused at 0.2 mg/kg per hour, the plasma drug concentration will be 4.5 + 5.5 = 10 µg/mL.

3. Infusion rate R for a 75-kg patient:

$$R = (1 \text{ mg/kg hr})(75 \text{ kg}) = 75 \text{ mg/hr}$$

Sterile drug solution contains 25 mg/mL. Therefore, 3 mL contains (3 mL) x (25 mg/mL), or 75 mg. The patient should receive 3 mL (75 mg)/hr by IV infusion.

4. $C_{SS} = \frac{R}{V_D k} \qquad R = C_{SS} V_D k$

$$R = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg})\left(\frac{0.693}{3 \text{ hr}}\right) = 173.25 \text{ mg/hr}$$

Drug is supplied as 125 mg/mL. Therefore,

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

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

$$D_L = C_{SS} V_D = (20 \text{ mg/L})(0.5 \text{ L/kg})(75 \text{ kg}) = 750 \text{ mg}$$

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

a. $Cl_T = \frac{R}{C_{SS}} = \frac{5.3 \text{ mg/kg hr} \times 71.71 \text{ kg}}{17 \text{ mg/L}} = 22.4 \text{ L/hr}$

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

$$C_P = C_P^0 e^{-kt}$$
$$1.5 = 17e^{-k(2.5)}$$
$$0.0882 = e^{-2.5k}$$
$$\ln 0.0882 = -2.5\,k$$
$$-2.43 = -2.5\,k$$
$$k = 0.971 \text{ hr}^{-1}$$
$$t_{1/2} = \frac{0.693}{0.971} = 0.714 \text{ hr}$$

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

$$C_{SS} = \frac{R}{kV_D} \qquad kV_D = \frac{R}{C_{SS}}$$
$$\frac{R_{old}}{C_{SS,old}} = \frac{R_{new}}{C_{SS,new}}$$
$$\frac{30 \text{ mg/hr}}{20\ \mu\text{g/mL}} = \frac{40 \text{ mg/hr}}{C_{SS,new}}$$
$$C_{SS,new} = 26.7\ \mu\text{g/mL}$$

The new elimination rate will be 40 mg/hr.

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

$R = (20 \text{ mg/L})(0.693/8 \text{ hr})(1.5 \text{ L/kg})(75 \text{ kg}) = 194.9 \text{ mg/hr}$

$R \approx 195 \text{ mg/hr}$

b. $D_L = C_{SS} V_D = (20)(1.5)(75) = 2250$ 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/hr is equivalent to 225 mg/hr. 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.

CHAPTER 6

Frequently Asked Questions

1. Elimination half-life, $t_{1/2}$, is a concise and informative term that describes the time needed for half the dose to be removed from the body. Alternatively, the elimination half-life indicates the time for the plasma drug concentration to decline to one-half

from whatever concentration it started at. Classical pharmacokinetic models are based on $t_{1/2}$ (or k) and V_D. Some pharmacokineticists prefer Cl and V_D, and regard $t_{1/2}$ as a derived parameter.

2. A *parameter* is a model-based numerical constant estimated statistically from the data. Model parameters are used generally to make predictions about the behavior of the real process. A parameter is termed independent if the parameter is not dependent on other parameters of the model. In the classical one-compartment model, k and V_D are independent model parameters, and $t_{1/2}$ and Cl are regarded as derived parameters. In the physiologic model, Cl and V_D are regarded as independent model parameters, while k is a dependent parameter since k depends on Cl/V_D. In practice, both Cl and k are dependent on various physiologic factors, such as blood flow, drug metabolism, renal secretion, and drug reabsorption. Most biologic events are the result of many events that are described more aptly as mutually interacting rather than acting independently. Thus, the underlying elimination process may be adequately described as fraction of drug removed per minute (k) or as volume of fluid removed per minute (Cl).

3. With most drugs, total body clearance (often termed "clearance") is the sum of renal and nonrenal clearances. Creatinine is an endogenous marker that accumulates in the blood when renal function is impaired. Creatinine is excreted by glomerular filtration and is not reabsorbed. Creatinine clearance is a measure of glomerular filtration rate. Renal clearance is therefore proportional to creatinine clearance but not equal to it, since most drugs are reabsorbed to some extent, and some drugs are actively secreted.

Learning Questions

3. a. $$Cl_T = V_D k = V_D \frac{0.693}{t_{1/2}}$$

$$\text{Average } Cl_T = \frac{(30)(0.693)}{3.4} = 6.11 \text{ L/hr}$$

$$\text{Upper } Cl_T \text{ limit} = \frac{(30)(0.693)}{1.8} = 11.55 \text{ L/hr}$$

$$\text{Lower } Cl_T \text{ limit} = \frac{(30)(0.693)}{6.8} = 3.06 \text{ L/hr}$$

b. $Cl_R = k_e V_D = 0.36$ L/hr

$$k_e = \frac{0.36}{30} = 0.012 \text{ hr}^{-1}$$

$Cl_{nr} = Cl_T - Cl_r$

$Cl_{nr} = 6.11 - 0.36 = 5.75$ L/hr

$Cl_{nr} = k_m V_D$

$$k_m = \frac{5.75}{30} = 0.192 \text{ hr}^{-1}$$

4.

a. Apparent $V_D = (0.21)(78{,}000 \text{ mL})$

$= 16{,}380$ mL

$Cl_T = kV_D$

$$Cl_T = \left(\frac{0.693}{2}\right)(16{,}380)$$

$Cl_T = 5676$ mL/hr $= 94.6$ mL/min

b. $k_e = 70\%$ of the elimination constant

$$k_e = (0.7)\left(\frac{0.693}{2}\right) = 0.243 \text{ hr}^{-1}$$

$Cl_R = k_e V_D$

$Cl_R = (0.243)(16{,}380) = 3980$ mL/hr $= 66.3$ mL/min

c. Normal GFR = creatinine clearance = 122 mL/min

Cl_R of drug = 66.3 mL

Because the Cl_R of the drug is less than the creatinine clearance, the drug is filtered at the glomerulus and is partially reabsorbed.

5. a. During intravenous infusion, the drug levels will reach more than 99% of the plasma steady-state concentration after seven half-lives of the drug.

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

$$= \frac{300{,}000\ \mu g/hr}{11\ \mu g/mL} = 27{,}272\ mL/hr$$

b. $Cl_T = kV_D$

$$V_D = \frac{27{,}272}{0.693} = 39{,}354\ mL$$

c. Since $k_m = 0 \qquad k_e \approx k$

$$Cl_T = Cl_R = 27{,}272\ mL/hr$$

d. $Cl_R = 27{,}272\ mL/hr = 454\ mL/min$

Normal GFR is 100–130 mL/min. The drug is probably filtered and actively secreted in the kidney.

6. $$Cl_R = \frac{\text{excretion rate}}{C_P} = \frac{200\ mg/2\ hr}{2.5\ mg/100\ mL}$$

$$Cl_R = 4000\ mL/hr$$

7. $$Cl_T = \frac{R}{C_{SS}}$$

$$Cl_T = \frac{5.3\ mg/kg\ hr}{17\ mg/L} = 0.312\ L/kg\ hr$$

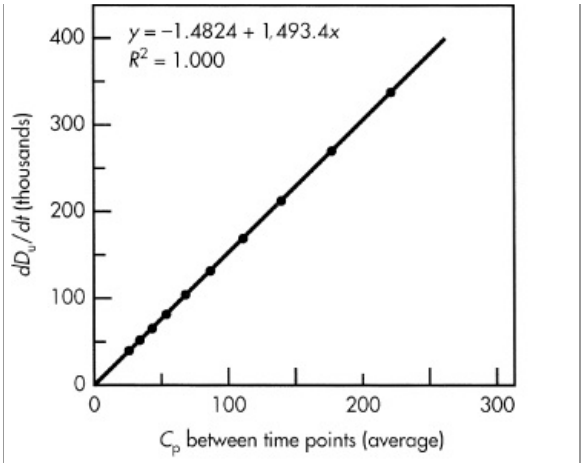
For a 71.7-kg adult,

$$Cl_T = (0.312\ L/kg\ hr)(71.7\ kg) = 22.4\ L/hr$$

11. From the data, determine urinary rate of drug excretion per time period by multiplying urinary volume by the urinary concentration for each point. Average C_p for each period by taking the mean of two consecutive points. Plot dD_u/dt versus C_p to determine renal clearance from slope. The renal clearance from slope is 1493.4 mL/hr ().

Time (hr)	Plasma Concentration (μg/mL)	Urinary Volume (mL)	Urinary Concentration (μg/mL)	Urinary Rate, dD_u/dt (μg/hr)	Average C_p
0	250.00	100.00	0.00	0.00	
1	198.63	125.00	2,680.00	334,999.56	224.32
2	157.82	140.00	1,901.20	266,168.41	178.23
3	125.39	100.00	2,114.80	211,479.74	141.61
4	99.63	80.00	2,100.35	168,027.76	112.51
5	79.16	250.00	534.01	133,503.70	89.39
6	62.89	170.00	623.96	106,073.18	71.03
7	49.97	160.00	526.74	84,278.70	56.43
8	39.70	90.00	744.03	66,962.26	44.84
9	31.55	400.00	133.01	53,203.77	35.63

Figure C-5



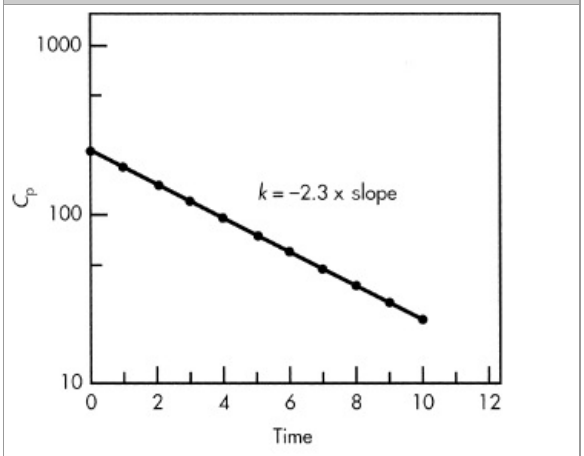
Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

To determine the total body clearance by the area method, the area under the plasma concentration curve [AUC] must be calculated and summed. The tailpiece is extrapolated because the data are not taken to the end. A plot of log C_p versus t () yields a slope of $k = 0.23\ hr^{-1}$. The tailpiece of area is extrapolated using the last data point divided by k or 31.55/0.23 = 137.17 μg/mL per hour.

Subtotal area	(0–9 hr)	953.97
Tailpiece	(9–∞ hr)	137.17
Total area	(0–∞)	1091.14

$$\text{Total clearance} = Cl_T = \frac{FD_0}{[AUC]_0^\infty} = \frac{2{,}500{,}000}{1091.14} = 2{,}291.2\ \text{mL/hr}$$

Figure C-6



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Because total body clearance is much larger than renal clearance, the drug is probably also excreted by a nonrenal route.

$$\text{Nonrenal clearance} = 2291.2 - 1493.4 = 797.8\ \text{mL/hr}$$

The easiest way to determine clearance by a compartmental approach is to estimate k and V_D from the graph. V_D is 10 L and k is $0.23\ hr^{-1}$. Total clearance is 2300 mL/min (a slightly different value when compared with the area method).

CHAPTER 7

Frequently Asked Questions

1. For drugs absorbed by a first-order process, the absorption half-life is $0.693/k_a$. Although drug absorption involves many stochastic (system based random) steps, the overall rate process is often approximated by a first-order process, especially with oral solutions and immediate-release drug products such as compressed tablets or capsules. The determination of the

absorption rate constant, k_a, is most often calculated by the Wagner–Nelson method for drugs, which follow a one-compartment model with first-order absorption and first-order elimination.

2. The fraction of drug absorbed, *F*, and the absorption rate constant, k_a, are independent parameters. A drug in an oral solution may have a more rapid rate of absorption compared to a solid drug product. If the drug is released from the drug product slowly or is formulated so that the drug is absorbed slowly, the drug may be subjected to first-pass effects, degraded in the gastrointestinal tract, or eliminated in the feces so that less drug (smaller *F*) may be absorbed systemically compared to the same drug formulated to be absorbed more rapidly from the drug product.

3. A drug with a rate of absorption slower than its rate of elimination will not be able to obtain optimal systemic drug concentrations to achieve efficacy. Such drugs are generally not developed into products.

4. Drug clearance is generally not affected by drug absorption from most absorption sites. In the gastrointestinal tract, a drug is absorbed via the hepatic portal vein to the liver and may be subject to hepatic clearance.

5. The fraction of drug absorbed may be less than 1 (ie, 100% bioavailable) after oral administration.

Learning Questions

1. a. The elimination rate constant is 0.1 hr^{-1} ($t_{1/2}$ = 6.93 hours).

b. The absorption rate constant, k_a, is 0.3 hr^{-1} (absorption half-life = 2.31 hours).

$$\text{The calculated } t_{max} = \frac{\ln(k_a/k)}{k_a - k} = 5.49 \text{ hr}$$

c. The *y* intercept was observed to be 60 ng/mL. Therefore the equation that fits the observed data is

$$C_P = 60(e^{-0.1t} - e^{-0.3t})$$

Note: Answers obtained by "hand" feathering the data on semilog graph paper may vary somewhat depending on graphing skills and skill in reading data from a graph.

2. By direct observation of the data, the t_{max} is 6 hours and the C_{max} is 23.01 ng/mL. The apparent volume of distribution, V_D, is obtained from the intercept, *I*, of the terminal elimination phase, and substituting *F* = 0.8, *D* = 10,000,000 ng, k_a = 0.3 hr^{-1}, *k* = 0.1 hr^{-1}:

$$I = \frac{Fk_aD_0}{V_D(k_a - k)} \qquad 60 = \frac{(0.8)(0.3)(10{,}000{,}000)}{V_D(0.3 - 0.1)}$$

$$V_D = 200 \text{ L}$$

3. The percent-of-drug-unabsorbed method is applicable to any model with first- order elimination, regardless of the process of drug input. If the drug is given by IV injection, the elimination rate constant, *k*, may be determined accurately. If the drug is administered orally, *k* and k_a may *flip-flop*, resulting in an error unless IV data are available to determine *k*. For a drug that follows a two-compartment model, an IV bolus injection is used to determine the rate constants for distribution and elimination.

4. After an IV bolus injection, a drug such as theophylline follows a two-compartment model with a rapid distribution phase. During oral absorption, the drug is distributed during the absorption phase, and no distribution phase is observed. Pharmacokinetic analysis of the plasma drug concentration data obtained after oral drug administration will show that the drug follows a one-compartment model.

5. The equations for a drug that follows the kinetics of a one-compartment model with first-order absorption and elimination are

$$C_P = \frac{FD_0}{V_D(k_a - k)}(e^{kt} - e^{-k_at}) \qquad t_{max} = \frac{\ln(k_a/k)}{k_a - k}$$

As shown by these equations:

a. t_{max} is influenced by k_a and *k* and not by *F*, D_0, or V_D.

b. C_p is influenced by *F*, D_0, V_D, k_a, and *k*.

6. A drug product that might provide a zero-order input is an oral controlled-release tablet or a transdermal drug delivery system (patch). An IV drug infusion will also provide a zero-order drug input.

7. The general equation for a one-compartment open model with oral absorption is

$$C_P = \frac{FD_0}{V_D(k_a - k)}(e^{-kt} - e^{-k_at})$$

From $C_p = 45(e^{-0.17t} - e^{-1.5t})$,

$$\frac{FD_0k_a}{V_D(k_a - k)} = 45$$

$$k = 0.17 \text{ hr}^{-1}$$

$$k_a = 1.5 \text{ hr}^{-1}$$

a. $t_{max} = \frac{\ln(k_a/k)}{k_a - k} = \frac{\ln(1.5/0.17)}{1.5 - 0.17} = 1.64 \text{ hr}$

b. $C_{max} = 45(e^{-(0.17)(1.64)} - e^{-(1.5)(1.64)})$

$= 30.2 \ \mu\text{g/mL}$

c. $t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.17} = 4.08 \text{ hr}$

8.

a. Drug A $t_{max} = \frac{\ln(1.0/0.2)}{1.0 - 0.2} = 2.01 \text{ hr}$

Drug B $t_{max} = \frac{\ln(0.2/1.0)}{0.2 - 1.0} = 2.01 \text{ hr}$

b. $C_{max} = \frac{FD_0k_a}{V_D(k_a - k)}(e^{-kt_{max}} - e^{-k_at_{max}})$

Drug A $C_{max} = \frac{(1)(500)(1)}{(10)(1 - 0.2)}(e^{-(0.2)(2)} - e^{-(1)(2)})$

$C_{max} = 33.4 \ \mu\text{g/mL}$

Drug B $C_{max} = \frac{(1)(500)(0.2)}{(20)(0.2 - 1.0)}(e^{-1(2)} - e^{-(0.2)(2)})$

$C_{max} = 3.34 \ \mu\text{g/mL}$

9. a. The method of residuals using manual graphing methods may give somewhat different answers depending on personal skill and the quality of the graph paper. Values obtained by the computer program ESTRIP gave the following estimates:

$k_a = 2.84 \text{ hr}^{-1}$ $k = 0.186 \text{ hr}^{-1}$ $t_{1/2} = 3.73 \text{ hr}$

b. A drug in an aqueous solution is in the most absorbable form compared to other oral dosage forms. The assumption that $k_a > k$ is generally true for drug solutions and immediate-release oral dosage forms such as compressed tablets and capsules. Drug absorption from extended-release dosage forms may have $k_a < k$. To demonstrate unequivocally which slope represents the true k, the drug must be given by IV bolus or IV infusion, and the slope of the elimination curve obtained.

c. The Loo–Riegelman method requires IV data. Therefore, only the method of Wagner and Nelson may be used on these data.

d. Observed t_{max} and C_{max} values are taken directly from the experimental data. In this example, C_{max} is 85.11 ng/mL, which occurred at a t_{max} of 1.0 hour. The theoretical t_{max} and C_{max} are obtained as follows:

$$t_{max} = \frac{2.3 \log(k_a/k)}{k_a - k} = \frac{2.3 \log(2.84/0.186)}{2.84 - 0.186} = 1.03 \text{ hr}$$

$$C_{max} = \frac{FD_0k_a}{V_D(k_a - k)}(e^{-kt_{max}} - e^{-k_at_{max}})$$

where $FD_0k_a/V_D(k_a - k)$ is the y intercept equal to 110 ng/mL and t_{max} = 1.03 hours.

$$C_{max} = (110)(e^{-(0.186)(1.0)} - e^{-(2.84)(1.03)})$$

$$C_{max} = 85 \text{ ng/mL}$$

e. A more complete model-fitting program, such as WIN NONLIN, is needed to fit the data statistically to a one-compartment model.

CHAPTER 8

Frequently Asked Questions

1. Some of the advantages of administering a drug by constant IV infusion include, the following. (1) A drug may be infused continuously for many hours without disturbing the patient. (2) Constant infusion provides a stable blood drug level for drugs that have a narrow therapeutic index. (3) Some drugs are better tolerated when infused slowly. (4) Some drugs may be infused simultaneously with electrolytes or other infusion media in an acute-care setting. Disadvantages of administering a drug by constant IV infusion include the following. (1) Some drugs are more suitable to be administered as a bolus IV injection. For example, some reports show that an aminoglycoside given once daily resulted in fewer side effects compared with dividing the dose into two or three doses daily. Due to drug accumulation in the kidney and adverse toxicity, aminoglycosides are generally

not given by prolonged IV infusions. In contrast, a prolonged period of low drug level for penicillins and tetracyclines may not be as efficacious and may result in a longer cure time for an infection. The pharmacodynamics of the individual drug must be studied to determine the best course of action. (2) Drugs such as nitroglycerin are less likely to produce tolerance when administered intermittently versus continuously.

2. A loading or priming dose is used to rapidly raise the plasma drug concentration to therapeutic drug levels to obtain a more rapid pharmacodynamic response. In addition, the loading dose along with the maintenance dose allows the drug to reach steady state concentration quickly, particularly for drugs with long elimination half-lives.

An alternative way of explaining the loading dose is based on clearance. After multiple IV dosing, the maintenance dose required is based on *Cl*, C_{SS}, and τ:

$$C_{SS} = \frac{\text{Dose}}{\tau Cl}$$

$$\text{Dose} = C_{SS}\tau Cl$$

If C_{SS} and τ are fixed, a drug with a smaller clearance requires a smaller maintenance dose. In practice, the dosing interval is adjustable and may be longer for drugs with a small *Cl* if the drug does not need to be dosed frequently. The steady-state drug level is generally determined by the desired therapeutic drug.

3.*Accumulation index, R,* is a ratio that indicates steady-state drug concentration to the drug concentration after the first dose. The accumulation index does not measure the absolute size of overdosing; it measures the amount of drug cumulation that can occur due to frequent drug administration. Factors that affect *R* are the elimination rate constant, *k,* and the dosing interval, τ. If the first dose is not chosen appropriately, the steady-state level may still be incorrect. Therefore, the first dose and the dosing interval must be determined correctly to avoid any significant drug accumulation. The accumulation index is a good indication of accumulation due to frequent drug dosing, applicable to any drug, regardless of whether the drug is bound to tissues.

4. The loading dose will affect only the initial drug concentrations in the body. Steady-state drug levels are obtained after several elimination half lives (eg, 4.32 $t_{1/2}$ for 95% steady-state level). Only 5% of the drug contributed by the loading dose will remain at 95% steady state. At 99% steady-state level, only 1% of the loading dose will remain.

5. Two possible examples are digoxin and amitriptyline.

6. After an IV bolus drug injection, the drug is well distributed within a few minutes. In practice, however, an IV bolus dose may be administered slowly over several minutes or the drug may have a slow distribution phase. Therefore, clinicians often prefer to take a blood sample 15 minutes or 30 minutes after IV bolus injection and refer to that drug concentration as the peak concentration. In some cases, a blood sample is taken an hour later to avoid the fluctuating concentration in the distributive phase. The error due to changing sampling time can be large for a drug with a short elimination half-life.

Learning Questions

1. $V_D = 0.20\,(50\text{ kg}) = 10{,}000\text{ mL}$

   a. $$D_{max} = \frac{D_0}{1 - f} = \frac{50\text{ mg}}{1 - e^{-(0.693/2)(8)}} = 53.3\text{ mg}$$

   $$C_{max} = \frac{D_{max}}{V_D} = \frac{53.3\text{ mg}}{10{,}000\text{ ml}} = 5.33\ \mu\text{g/mL}$$

   b. $$D_{min} = 53.3 - 50 = 3.3\text{ mg}$$

   $$C_{min} = \frac{3.3\text{ mg}}{10{,}000\text{ mL}} = 0.33\ \mu\text{g/mL}$$

   c. $$C_{av}^{\infty} = \frac{FD_0 1.44 t_{1/2}}{V_D \tau} = \frac{(50)\,(1.44)\,(2)}{(10{,}000)\,(8)} = 1.8\ \mu\text{g/mL}$$

2. a. $$D_0 = \frac{C_{av}^{\infty} V_D \tau}{1.44 t_{1/2}}$$

   $$= \frac{(10)\,(40{,}000)\,(6)}{(1.44)\,(5)} = 333\text{ mg every 6 hours}$$

   b. $$\tau = \frac{FD_0 1.44 t_{1/2}}{V_D C_{av}^{\infty}}$$

   $$= \frac{(225{,}000)\,(1.44)\,(5)}{(40{,}000)\,(10)} = 4.05\text{ hr}$$

6. Dose the patient with 200 mg every 3 hours.

$$D_L = \frac{D_0}{1 - e^{-k\tau}} = \frac{200}{1 - e^{-(0.23)(3)}} = 400\text{ mg}$$

Notice that D_L is twice the maintenance dose, because the drug is given at a dosage interval equal approximately to the $t_{1/2}$ of 3 hours.

8. The plasma drug concentration, C_p, may be calculated at any time after *n* doses by Equation 8.21 and proper substitution.

$$C_P = \frac{D_0}{V_D}\left(\frac{1 - e^{-n k \tau}}{1 - e^{-k\tau}}\right)e^{-kt}$$

$$C_P = \frac{200}{40}\left(\frac{1 - e^{-(3)(0.347)(4)}}{1 - e^{-(0.347)(4)}}\right)e^{-(0.347)(1)} = 4.63 \text{ mg/L}$$

Alternatively, one may conclude that for a drug whose elimination $t_{1/2}$ is 2 hours, the predicted plasma drug concentration is approximately at steady state after 3 doses or 12 hours. Therefore, the above calculation may be simplified to the following:

$$C_P = \frac{D_0}{V_D} = \left(\frac{1}{1 - e^{-k\tau}}\right)e^{-kt}$$

$$C_P = \left(\frac{200}{40}\right)\left(\frac{1}{1 - e^{-(0.347)(4)}}\right)e^{-(0.347)(1)} = 4.71 \text{ mg/L}$$

9. $C^{\infty}_{max} = \dfrac{D_0/V_D}{1 - e^{-k\tau}}$

where

$V_D = 20\%$ of 82 kg $= (0.2)(82) = 16.4$ L

$k = (0.693/3) = 0.231 \text{ hr}^{-1}$

$D_0 = V_D C^{\infty}_{max}(1 - e^{-k\tau}) = (16.4)(10)(1 - e^{-(0.231)(8)})$

a. $D_0 = 138.16$ mg to be given every 8 hours

b. $C^{\infty}_{min} = C^{\infty}_{max}(e^{-k\tau}) = (10)(e^{-(0.231)(8)}) = 1.58$ mg/L

c. $C^{\infty}_{av} = \dfrac{D_0}{kV_D\tau} = \dfrac{138.16}{(0.231)(16.4)(8)} = 4.56$ mg/L

d. In the above dosage regimen, the C^{∞}_{min} of 1.59 mg/L is below the desired C^{∞}_{min} of 2 mg/L. Alternatively, the dosage interval, τ, could be changed to 6 hours.

$D_0 = V_D C^{\infty}_{max}(1 - e^{-k\tau}) = (16.4)(10)(1 - e^{-(0.231)(6)})$

$D_0 = 123$ mg to be given every 6 hours

$C^{\infty}_{min} = C^{\infty}_{max}(e^{-k\tau}) = (10)(e^{-(0.231)(6)}) = 2.5$ mg/L

$C^{\infty}_{av} = \dfrac{D_0}{kV_D\tau} = \dfrac{123}{(0.231)(16.4)(6)} = 5.41$ mg/L

10. a. $C^{\infty}_{av} = \dfrac{FD_0}{kV_D\tau}$

Let $C^{\infty}_{av} = 27.5$ mg/L

$D_0 = \dfrac{C^{\infty}_{av} k V_D \tau}{F} = \dfrac{(27.5)(0.693/10.6)(0.5)(78)(6)}{0.77} = 546.3$ mg

$D_0 = 546.3$ mg every 6 hours

b. If a 500-mg capsule is given every 6 hours,

$C^{\infty}_{av} = \dfrac{FD_0}{kV_D\tau} = \dfrac{(0.77)(500)}{(0.693/10.6)(0.5)(78)(6)} = 25.2$ mg/L

c. $D_L = \dfrac{D_M}{1 - e^{-k\tau}} = \dfrac{500}{1 - e^{-(0.654)(6)}} = 1543$ mg

$D_L = 3 \times 500$ mg capsules $= 1500$ mg

CHAPTER 9

Frequently Asked Questions

1. A patient with concomitant hepatic disease may have decreased biotransformation enzyme activity. Infants and young subjects may have immature hepatic enzyme systems. Alcoholics may have liver cirrhosis and lack certain coenzymes. Other patients may experience enzyme saturation at normal doses due to genetic polymorphism. Pharmacokinetics provides a simple way to identify nonlinear kinetics in these patients and to estimate an appropriate dose. Finally, concomitant use of other drugs may cause nonlinear pharmacokinetics at lower drug doses due to enzyme inhibition.

2. A drug that follows linear pharmacokinetics generally has a constant elimination half-life and a constant clearance with an increase in the dose. The steady-state drug concentrations and AUC are proportional to the size of the dose. Nonlinear pharmacokinetics results in dose-dependent *Cl*, $t_{1/2}$, and AUC. Nonlinear pharmacokinetics are often described in terms of V_{max} and K_M.

3. The physiologic model based on organ drug clearance describes nonlinear drug metabolism in terms of blood flow and intrinsic hepatic clearance (). Drugs are extracted by the liver as they are presented by blood flow. The physiologic model accounts for the sigmoid profile with changing blood flow and extraction, whereas the Michaelis–Menten model simulates the metabolic profile based on V_{max} and K_M. The Michaelis–Menten model was applied mostly to describe *in-vitro* enzymatic reactions. When V_{max}

and K_M are estimated in patients, blood flow is not explicitly considered. This semiempirical method was found by many clinicians to be useful in dosing phenytoin. The organ clearance model was more useful in explaining clearance change due to impaired blood flow. In practice, the physiologic model has limited use in dosing patients because blood flow data for patients are not available.

4.*Chronopharmacokinetics* is the main cause of nonlinear pharmacokinetics that is not dose related. The time dependent or temporal process of drug elimination can be the result of rhythmic changes in the body. For example, nortriptyline and theophylline levels are higher when administered between 7 and 9 AM compared to between 7 and 9 PM after the same dose. Biological rhythmic differences in clearance cause a lower elimination rate in the morning compared to the evening. Other factors that cause nonlinear pharmacokinetics may result from enzyme induction (eg, carbamazepine) or enzyme inhibition after multiple doses of the drug. Furthermore, the drug or a metabolite may accumulate following multiple dosing and affect the metabolism or renal elimination of the drug.

Learning Questions

2. Capacity-limited processes for drugs include:

- Absorption
  - Active transport
  - Intestinal metabolism by microflora
- Distribution
  - Protein binding
- Elimination
  - Hepatic elimination
  - Biotransformation
  - Active biliary secretion
- Renal excretion
  - Active tubular secretion
  - Active tubular reabsorption

4. $$C_P^0 = \frac{\text{dose}}{V_D} = \frac{10{,}000\ \mu\text{g}}{20{,}000\ \text{mL}} = 0.5\ \mu\text{g/mL}$$

From Equation 9.1,

$$\text{Elimination rate} = -\frac{dC_P}{dt} = \frac{V_{max} C_P}{K_M + C_P}$$

Because K_M = 50 µg/mL, $C_p << K_M$ and the reaction rate is first order. Thus, the above equation reduces to Equation 9.3.

$$-\frac{dC_P}{dt} = \frac{V_{max} C_P}{K_M} = k' C_P$$

$$k' = \frac{V_{max}}{K_M} = \frac{20\ \mu\text{g/hr}}{50\ \mu\text{g}} = 0.4\ \text{hr}^{-1}$$

For first-order reactions,

$$t_{1/2} = \frac{0.693}{k'} = \frac{0.693}{0.4} = 1.73\ \text{hr}$$

The drug will be 50% metabolized in 1.73 hours.

7. When INH is coadminstered, plasma phenytoin concentration is increased due to a reduction in metabolic rate *v*. Equation 9.1 shows that *v* and K_M are inversely related (K_M in denominator). An increase in K_M will be accompanied by an increase in plasma drug concentration. shows that an increase in K_M is accompanied by an increase in amount of drug in the body at any time *t*. Equation 9.4 relates drug concentration to K_M, and it can be seen that the two are proportionally related, although they are not linearly proportional to each other due to the complexity of the equation. An actual study in the literature shows that *k* is increased severalfold in the presence of INH in the body.

8. The K_M has the unit of concentration. In laboratory studies, K_M is expressed in moles per liter, or micromoles per milliliter, because reactions are expressed in moles and not milligrams. In dosing, drugs are given in milligram and plasma drug concentrations are expressed as milligrams per liter or micrograms per milliliter. The units of K_M for pharmacokinetic models are estimated from *in-vivo* data. They are therefore commonly expressed as milligrams per liter, which is preferred over micrograms per milliliter because dose is usually expressed in milligrams. The two terms may be shown to be equivalent and convertible. Occasionally, when simulating amount of drug metabolized in the body as a function of time, the amount of drug in the body has been assumed to follow Michaelis–Menten kinetics, and K_M assumes the unit of D_0 (eg, mg). In this case, K_M takes on a very different meaning.

CHAPTER 10

Frequently Asked Questions

1. No. For some drugs, protein binding does not affect the overall distribution of other drugs. Typically, if a drug is highly bound, there is an increased chance of a significant change in the fraction of free drug when binding is altered.

2. Albumin, α_1-acid glycoprotein, and lipoprotein. For some drugs and hormones, there may be a specific binding protein.

3. Most drugs are assumed to be *restrictively bound,* and binding reduces drug clearance and elimination. However, some *nonrestrictively bound* drugs may be cleared easily. Changes in binding do not affect the rate of elimination of these drugs. Some drugs, such as some semisynthetic penicillins that are bound to plasma protein, may be actively secreted in the kidney. The elimination rates of these drugs are not affected by protein binding.

4.*Partitioning* refers to the relative distribution of a drug in the lipid and aqueous phases. Generally, a high partition coefficient ($P_{oil/water}$) favors tissue distribution and leads to a larger volume of distribution. Partitioning is a major factor that, along with protein binding of a drug, determines drug distribution.

5. It is important to examine why albumin level is reduced in the patient. For example, is the reduced albumin level due to uremia or hepatic dysfunction? In general, reduced protein binding will increase free drug concentration. Any change in drug clearance should be considered before reducing the dose, since the volume of distribution may be increased, partially offsetting the increase in free drug concentration.

6. In general, the early phase after an IV bolus dose is the distributive phase. The elimination phase occurs in the later phase, although distribution may continue for some drugs, especially for a drug with a long elimination half-life. The elimination phase is generally more gradual, since some drug may be returned to the blood from the tissues as drug is eliminated from the body.

7. Generally, the long distribution half-life is caused by a tissue/organ that has a high drug concentration, due either to intracellular drug binding or high affinity for tissue distribution. Alternatively, the drug may be metabolized slowly within the tissue.

8. The distribution half-life determines the time it takes for a tissue organ to be equilibrated. It takes 4.32 distribution half-lives for the tissue organ to be 95% equilibrated and one distribution half-life for the drug to be 50% equilibrated. The concept is analogous to reaching steady-state during drug infusion (see).

9. The answer is **False**. The free drug concentrations in the tissue and plasma are the same after equilibration, but the total drug concentration in the tissue is not the same as the total drug concentration in the plasma. The bound drug concentration may vary depending on local tissue binding or the lipid solubility of the drug. Many drugs have a long distributive phase due to tissue drug binding or lipid solubility. Drugs may equilibrate slowly into these tissues and then be slowly eliminated. Drugs with limited tissue affinity are easily equilibrated. Some examples of drugs with a long distributive phase are discussed in relation to the two-compartment model ().

10. The ratio, *r*, is defined as the ratio of the number of moles of drug bound to the number of moles of protein in the system. For a simple case of one binding site, *r* reflects the proportion of binding sites occupied; *r* is affected by (1) the association binding constant, (2) the free drug concentration, and (3) the number of binding sites per mole of protein. When [*D*], or free drug concentration, is equal to 1 (or the dissociation constant *K*), the protein is 50% occupied for a drug with 1:1 binding according to Equation 10.19. (This can be verified easily by substituting for [*D*] into the right side the equation and determining *r*.) For a drug with *n* similar binding sites, binding occurs at the extent of 1:2 of bound drug:protein when $[D] = 1/[K_a(2n - 1)]$. This equation, however, reflects binding *in vitro* when drug concentration is not changing; therefore, its conclusions are somewhat limited.

Learning Questions

1. The zone of inhibition for the antibiotic in serum is smaller due to drug–protein binding.

2. Calculate $r/(D)$ versus *r*, then graph the results on rectangular coordinates.

r	$r/(D \times 10^4)$
0.4	1.21
0.8	0.90
1.2	0.60
1.6	0.30

$$\text{The } y \text{ intercept} = nK_a = 1.5 \times 10^4$$
$$\text{The } x \text{ intercept} = n = 2$$

Therefore,

$$K_a = 1.5 \times 10^4/2 = 0.75 \times 10^4$$

K_a may also be found from the slope.

8. The liver is important for the synthesis of plasma proteins. In chronic alcoholic liver disease or cirrhosis, fewer plasma proteins are synthesized in the liver, resulting in a lower plasma protein concentration. Thus, for a given dose of naproxen, less drug is

bound to the plasma proteins, and the total plasma drug concentration is smaller.

10. Protein binding may become saturated at any drug concentration in patients with defective proteins or when binding sites are occupied by metabolic wastes generated during disease states (eg, renal disease). Diazoxide is an example of nonlinear binding at therapeutic dose.

11. The answer is **False**. The percent bound refers to the percent of total drug that is bound. The percent bound may be ≥99% bound for some drugs. Saturation may be better estimated using the Scatchard plot approach and by examining "*r*," which is the number of moles of drug bound divided by the number of moles of protein. When *r* is 0.99, most of the binding sites are occupied. The f_b, or fraction of bound drug, is useful for determining f_u, $f_u = 1 - f_b$.

12. Adenosine is extensively taken up by cells including the blood elements and the vascular endothelium. Adenosine is rapidly metabolized by deamination and/or is used as AMP in phosphorylation. Consequently, adenosine has a short elimination half-life.

CHAPTER 11

Frequently Asked Questions

1. Hepatic drug clearance describes drug metabolism in the liver and accounts for both the effect of blood flow and the intrinsic ability of the liver to metabolize a drug. Hepatic drug clearance is added to renal clearance and other clearances to obtain total (body) clearance, which is important in determining the maintenance dose of a drug. Hepatic drug clearance is often considered nonrenal clearance when it is measured as the difference between total clearance and renal clearance.

2. Most orally administered drugs pass through the liver prior to systemic absorption. The rate of blood flow can greatly affect the extent of drug that reaches the systemic circulation. Also, intrinsic metabolism may differ among individuals and may be genetically determined. These factors may cause drug levels to be more erratic for drugs that undergo extensive metabolism compared to drugs that are excreted renally.

3. Protein synthesis may be altered by liver dysfunction. In general, when drug protein binding is reduced, the free drug may be metabolized more easily. However, some drugs may be metabolized regardless of whether the drug is bound or free (for discussion of nonrestrictive binding, see). In such cases, there is little change in pharmacodynamic activity due to changes in drug protein binding.

4. Erythromycin, morphine, propranolol, various steroids, and other drugs have large metabolic clearance. In hepatic disease, highly potent drugs that have a narrow therapeutic index should be monitored carefully. Troglitazone (Rezulin), for example, is a drug that can cause severe side effects in patients with liver dysfunction; liver transaminase should be monitored in diabetic patients.

Learning Questions

1. a. $k = k_m + k_e + k_b = 0.20 + 0.25 + 0.15 = 0.60\ \text{hr}^{-1}$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.60} = 1.16\ \text{hr}$$

b. $k = k_m + k_e = 0.45\ \text{hr}^{-1}$

$t_{1/2} = 1.54\ \text{hr}$

c. $k = 0.35\ \text{hr}^{-1}$

$t_{1/2} = 1.98\ \text{hr}$

d. $k = 0.80\ \text{hr}^{-1}$

$t_{1/2} = 0.87\ \text{hr}$

2. a. $k = 0.347\ \text{hr}^{-1}$

$k_e = (0.9)\,(0.347) = 0.312\ \text{hr}^{-1}$

b. Renal excretion, 90% of the drug is excreted unchanged.

5. Normal hepatic clearance, Cl_H:

$$Cl_H = Q\left(\frac{Cl_{int}}{Q + Cl_{int}}\right) \qquad Q = 1.5\ \text{L/min} \qquad Cl_{int} = 0.040\ \text{L/min}$$

$$Cl_H = 1.5\left(\frac{0.040}{1.5 + 0.040}\right) = 0.039\ \text{L/min}$$

a. Congestive heart failure:

$$Cl_H = 1.0\left(\frac{0.040}{1.0 + 0.040}\right) = 0.038\ \text{L/min}$$

b. Enzyme induction:

$$Cl_H = 1.5\left(\frac{0.090}{1.5 + 0.090}\right) = 0.085\ \text{L/min}$$

Note: A change in blood flow, *Q*, did not markedly affect Cl_H for a drug with low Cl_{int}.

6. Normal hepatic clearance:

$$Cl_H = 1.5\left(\frac{12}{1.5 + 12}\right) = 1.33\ \text{L/min}$$

Congestive heart failure (CHF):

$$Cl_H = 1.0\left(\frac{12}{1.0 + 12}\right) = 0.923\ \text{L/min}$$

a. $$Cl_H = Q(\text{ER}) = Q\left(\frac{Cl_{int}}{Q + Cl_{int}}\right)$$

$$\text{ER} = \frac{Cl_{int}}{Q + Cl_{int}}$$

$$\text{Normal ER} = \frac{12}{1.5 + 12} = 0.89\ \text{L/min}$$

$$\text{CHF ER} = \frac{12}{1.0 + 12} = 0.92\ \text{L/min}$$

b. $F = 1 - \text{ER} = 1 - 0.89$

$F = 0.11$ *or* 11%

10. a. Because <0.5% of the unchanged drug is excreted in the urine, hepatic clearance nearly approximates total body clearance.

$$Cl_H \approx Cl_T = kV_D = \left(\frac{0.693}{3.9}\right)(4.3)\,(80) = 61.1\ \text{L/hr}$$

b. $Cl_H = Q\,\text{ER} \qquad Q = (1.5\ \text{L/min})\,(60\ \text{min}) = 90\ \text{L/hr}$

$\text{ER} = 61.1/90 = 0.68.$

11.

a. $$Cl_T = kV_D = \left(\frac{0.693}{1.6}\right)(0.78)\,(81) = 27.4\ \text{L/hr}$$

b. $Cl_R = k_e V_D$

$$k_e = 0.12k = (0.12)\left(\frac{0.693}{1.6}\right) = 0.052\ \text{hr}^{-1}$$

$$Cl_R = (0.052)\,(0.78)\,(81) = 3.29\ \text{L/hr}$$

Alternatively,

$Cl_R = f_e Cl_T$

$Cl_R = 0.12\ Cl_T = (0.12)\,(27.4) = 3.29\ \text{L/hr}$

c. $Cl_H = Cl_T - Cl_R = 27.4 - 3.29 = 24.11\ \text{L/hr}$

CHAPTER 13

Frequently Asked Questions

1. An *absorption window* refers to the segment of the gastrointestinal tract from which the drug is well absorbed and beyond which the drug is either poorly absorbed or not absorbed at all. After oral administration, most drugs are well absorbed in the duodenum and to a lesser extent in the jejunum. A small amount of drug absorption may occur from the ileum.

2. Food, particularly food with a high fat content, stimulates the production of bile, which is released into the duodenum. The bile helps to solubilize a lipid-soluble drug, thereby increasing drug absorption. Fatty food also slows gastrointestinal motility, resulting in a longer *residence time* for the drug to be absorbed from the small intestine.

3. After oral administration, the drug in solution may precipitate in the gastrointestinal tract. The precipitated drug needs to redissolve before it can be absorbed. Some drug solutions are prepared with a co-solvent, such as alcohol or glycerin, and form coarse crystals on precipitation that dissolve slowly, whereas other drugs precipitate into fine crystals that redissolve rapidly. The type of precipitate is influenced by the solvent, by the degree of agitation, and by the physical environment. *In-vitro* mixing and dilution of the drug solution in artificial gastric juice, artificial intestinal juice, or in other pH buffers may predict the type of drug precipitate that is formed.

In addition, drugs dissolved in a highly viscous solution (eg, simple syrup) may have slower absorption because of the viscosity of the solution. Furthermore, drugs that are readily absorbed across the gastrointestinal membrane may not be completely bioavailable (ie, 100% systemic absorption) due to *first-pass effects* (discussed in).

4. The major biologic factor that delays gastrointestinal drug absorption is a delay in gastric emptying time. Any factor that delays stomach emptying time, such as fatty food, will delay the drug entering into the duodenum from the stomach and, thereby, delay drug absorption.

Learning Questions

1. In the presence of food, undissolved aspirin granules larger than 1 mm are retained up to several hours longer in the

stomach. In the absence of food, aspirin granules are emptied from the stomach within 1–2 hours. When the aspirin granules empty into the duodenum slowly, drug absorption will be as slow as with a sustained-release drug product. Enteric-coated aspirin granules taken with an evening meal may provide relief of pain for arthritic patients late into the night.

2. The answer is b. A basic drug formulated as a suspension will depend on stomach acid for dissolution as the basic drug forms a hydrochloric acid (HCl) salt. If the drug is poorly soluble, adding milk may neutralize some acid so that the drug may not be completely dissolved. Making a HCl salt rather than a suspension of the base ensures that the drug is soluble without being dependent on stomach HCl for dissolution.

3. Protein drugs are generally digested by proteolytic enzymes present in the GI tract and therefore are not adequately absorbed by the oral route. Protein drugs are most commonly given parenterally. Other routes of administration, such as intranasal and rectal administration, have had some success or are under current investigation for the systemic absorption of protein drugs.

4. The answer is c. Raising the pH of an acid drug above its pK_a will increase the dissociation of the drug, thereby increasing its aqueous solubility.

5. The large intestine is most heavily populated by bacteria, yeasts, and other microflora. Some drugs which are not well absorbed in the small intestine are metabolized by the microflora to products that are absorbed in the large bowel. For example, drugs with an azo link (eg, sulfasalazine) are cleaved by bacteria in the bowel and the cleaved products (eg, 5-aminosalicylic acid and sulfapyridine) are absorbed. Other drugs, such as antibiotics (eg, tetracyclines), may destroy the bacteria in the large intestine, resulting in an overgrowth of yeast (eg, *Candida albicans*) and leading to a yeast infection. Destruction of the microflora in the lower bowel can also lead to cramps and diarrhea.

6. First-pass effects are discussed more fully in . Alternative routes of drug administration such as buccal, inhalation, sublingual, intranasal, and parenteral will bypass the first-pass effects observed after oral drug administration.

7. Although antacid statistically decreased the extent of systemic drug absorption ($p < 0.05$) as shown by an $AUC_{0-4\ hr}$ of 349 ± 108 pg hr/mL, compared to the control (fasting) $AUC_{0-4\ hr}$ value of 417 ± 135 pg hr/mL, the effect of antacid is not clinically significant. A high-fat diet decreased the rate of systemic drug absorption, as shown by a longer t_{max} value (64 minutes) and lower C_{max} value (303 pg/mL).

CHAPTER 14

Frequently Asked Questions

1. a. For optimal drug absorption after oral administration, the drug should be water soluble and highly permeable so it can be absorbed throughout the gastrointestinal tract. Ideally, the drug should not change into a polymorphic form that could affect its solubility. The drug should be stable in both gastric and intestinal pH and preferably should not be hygroscopic.

b. For parenteral administration, the drug should be water soluble and stable in solution, preferably at autoclave temperature. The drug should be nonhydroscopic and preferably should not change into another polymorphic form.

2. A lipid-soluble drug may be prepared in an oil-in-water (o/w) emulsion or dissolved in a nonaqueous solution in a soft gelatin capsule. A co-solvent may improve the solubility and dissolution of the drug.

3. The rate of hydrolysis (decomposition) of the ester drug may be reduced by formulating the drug in a co-solvent solution. A reduction in the percent of the aqueous vehicle will decrease the rate of hydrolysis. In addition, the drug should be formulated at the pH in which the drug is most stable.

4. Excipients are needed in a formulation to solubilize the drug, increase the dissolution rate, decrease gastrointestinal transit time, or improve oral absorption by complexation. Excipients can also decrease the rate of oral absorption in the gastrointestinal tract by reducing drug solubility, decreasing the dissolution rate, or forming a less soluble complex.

Learning Questions

1. The rate-limiting steps in the oral absorption of a solid drug product are the rate of drug dissolution within the gastrointestinal tract and the rate of permeation of the drug molecules across the intestinal mucosal cells. Generally, disintegration of the drug product is rapid and not rate limiting. Water-soluble drugs dissolve rapidly in the aqueous environment of the gastrointestinal tract, so the permeation of the intestinal mucosal cells may be the rate-limiting step. The drug absorption rate may be altered by a variety of methods, all of which depend on knowledge of the biopharmaceutic properties of the drug and the drug product and on the physiology of the gastrointestinal tract. Drug examples are described in detail in this chapter and in .

2. Most drugs are absorbed by passive diffusion. The duodenum area provides a large surface area and blood supply that maintains a large drug concentration gradient favorable for drug absorption from the duodenum into the systemic circulation.

3. If the initial drug absorption rate, dD_A/dt, was slower than the drug elimination rate, dD_E/dt, then therapeutic drug concentrations in the body would not be achieved. It should be noted that the rate of absorption is generally first order, $dD_A/dt = D_0 k_a$, where, D_0 is the drug dose which is great initially. Even if $k_a < k$, the initial drug absorption rate may be greater than the drug elimination rate. After the drug is absorbed from the absorption site, $dD_A/dt \leq dD_E/dt$.

4. A drug prepared as an oral aqueous drug solution is generally the most bioavailable. However, the same drug prepared as a well-designed immediate-release tablet or capsule may have similar bioavailability. In the case of an oral drug solution, there is no dissolution step; the drug molecules come into contact with intestinal membrane, and the drug is rapidly absorbed. As a result of first-pass effects (discussed in), a drug given in an oral drug solution may not be 100% bioavailable. If the drug

solution is formulated with a high solute concentration—-such as sorbitol solution, which yields a high osmotic pressure—-gastric motility may be slowed, thus slowing the rate of drug absorption.

5. Anticholinergic drugs prolong gastric emptying, which will delay the absorption of an enteric-coated drug product.

6. Erythromycin may be formulated as enteric-coated granules to protect the drug from degradation at the stomach pH. Enteric-coated granules are less affected by gastric emptying and food (which delays gastric emptying) compared to enteric-coated tablets.

CHAPTER 15

Frequently Asked Questions

1. Preclinical animal toxicology and clinical efficacy studies were performed on the marketed *brand* drug product as part of the New Drug Application (NDA) prior to FDA approval. These studies do not have to be repeated for the *generic* bio-equivalent drug product. The manufacturer of the generic drug product must submit an Abbreviated New Drug Application (ANDA) to the FDA, demonstrating that the generic drug product is a therapeutic equivalent (see definitions in) to the brand drug product.

2. The *sequence* is the order in which the drug products (ie, treatments) are given (eg, brand product followed by generic product or vice versa). Sequence is important to prevent any bias due to the order of the treatments in the study. The term *washout* refers to the time for total elimination of the dose. The time for washout is determined by the elimination half-life of the drug. *Period* refers to the drug-dosing day on which the drug is given to the subjects. For example, for Period One, half the subjects receive treatment A, brand product, and the other half of the subjects receive treatment B, generic product.

3. Manufacturers are required to perform a food-intervention bioavailability study on all drugs whose bioavailability is known to be affected by food. In addition, a food-intervention bioavailability study is required on all modified-release products since (1) the modified-release formulation (eg, enteric coating, sustained-release coating) may be affected by the presence of food and (2) modified-release products have a greater potential to be affected by food due to their longer residence time in the gastrointestinal tract and changes in gastrointestinal motility.

4. If the drug is not absorbed systemically from the drug product, a *surrogate marker* must be used as a measure of bioequivalence. This surrogate marker may be a pharmacodynamic effect or, as in the case of cholestyramine resin, the binding capacity for bile acids *in vitro.*

Learning Questions

3. a. Oral solution: the drug is in the most bioavailable form.

b. Oral solution: same reason as above.

c. $$\text{Absolute bioavailability} = \frac{[\text{AUC}]_{\text{oral solution}}/\text{dose}_{\text{soln}}}{[\text{AUC}]_{\text{IV}}/\text{dose}_{\text{IV}}} = \frac{145/10}{29/2} = 1.0$$

d. $$\text{Relative bioavailability} = \frac{[\text{AUC}]_{\text{tablet}}/\text{dose}_{\text{tab}}}{[\text{AUC}]_{\text{solution}}/\text{dose}_{\text{soln}}} = \frac{116/10}{145/10} = 0.80$$

e. (1) $C_P^0 = 6.67\ \mu\text{g/mL}$ (by extrapolation of IV curve)

$$V_D = \frac{2000\ \mu\text{g/kg}}{6.67\ \mu\text{g/mL}} = 300\ \text{mL/kg}$$

(2) $t_{1/2} = 3.01\ \text{hr}$

(3) $k = 0.23\ \text{hr}^{-1}$

(4) $Cl_T = kV_D = 69\ \text{mL/kg hr}$

4. Plot the data on both rectangular and semilog graph paper. The following answers were obtained from estimates from the plotted plasma level–time curves. More exact answers may be obtained mathematically by substitution into the proper formulas.

a. 1.37 hr

b. 13.6 hr

c. 8.75 hr

d. 5 hr

e. 4.21 µg/mL

f. 77.98 µg hr/mL

5.

Drug Product			
Subject	**Period 1**	**Period 2**	**Week 3**
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A

6	B	A	C

6. a. Absolute bioavailability $= \dfrac{D_{u,PO}^{\infty}/\text{dose}_{PO}}{D_{u,IV}^{\infty}/\text{dose}_{IV}}$

$= \dfrac{340/4}{20/0.2} = 0.85 \text{ or } 85\%$

b. Relative bioavailability $= \dfrac{D_{u}^{\infty} \text{ cap}/\text{dose cap}}{D_{u}^{\infty} \text{ sol}/\text{dose sol}}$

$= \dfrac{360/4}{380/4} = 0.947 \text{ or } 94.7\%$

7. The fraction of drug absorbed systemically is the absolute bioavailability.

$$\text{Fraction of drug absorbed} = \frac{\%\text{ of dose excreted after PO}}{\%\text{ of dose excreted after IV}}$$

$$= \frac{48\%}{75\%} = 0.64$$

CHAPTER 16

Frequently Asked Questions

1. Specifications provide a test and a quantitative limit (acceptance criteria) to a test (eg, the total content must be within ±5% or the amount of impurities in the drug substance must not be more than [NMT] 1%). Thus, one batch of nominally 200-mg ibuprofen tablets may contain an average content of 198 mg, whereas the average content for another batch of 200-mg ibuprofen tablets may have an average content of 202 mg. Both batches meet a specification of ±5% and would be considered to meet the label claim of 200 mg of ibuprofen per tablet.

2. The manufacturer must consider whether the excipient is critical or not critical to drug release. If the excipient (eg, starch) is not critical to drug release (ie, a non-release-controlling excipient), then small changes in the starch concentration, generally less than 3% of the total target dosage form weight, is unlikely to affect the formulation quality and performance. A qualitative change in the excipient may affect drug release and thus will have significant effect on the formulation performance.

CHAPTER 17

Frequently Asked Questions

1. Extended-release drug products have many advantages compared to immediate-release drug products, as discussed in . However, a extended-release drug product of a drug that has a long elimination half-life (eg, chlorpheniramine maleate, digoxin, levothyroxine) has no advantage over the same drug given in an immediate-release (conventional) drug product. For some drugs, the clinical rationale for an extended-release drug product that provides a long-sustained drug level is not established. Nitroglycerin, for example, is less likely to produce tolerance with intermittent dosing compared with dosing by a continuous-release product. For some antibiotics there is also a specific duration of postantibiotic effect, during which bactericidal activity continues even when the plasma drug level is depleted. Some drugs are better tolerated with a "pulse" type of drug input into the body.

2. A zero-order rate for drug absorption will give more constant plasma drug concentrations with minimal fluctuations between peak and trough levels compared to first-order drug absorption. Depending on the therapeutic window for the drug and the relationship between the pharmacokinetics and pharmacodynamics of the drug, zero-order drug absorption may not always be more efficacious than first-order absorption.

Learning Questions

1. a. For many drugs, the plasma drug concentration is proportional to the drug concentration at the receptor site and the pharmacodynamic effect. By maintaining a prolonged, constant plasma drug concentration, the pharmacodynamic effect is also maintained.

b. A drug that releases at a zero-order rate and is absorbed at a zero-order rate provides a more constant plasma drug concentration compared to a first-order drug release.

2. a. Both *A* and *B* release drug at a zero-order rate (straight line). Curve *B* shows that 100% of drug is released in 12 hours, or about 8.3% per hour.

b. Product *C*.

c. Product *C* initially releases drug at a zero-order rate (first 3 hours).

d. Drug release usually slows down toward the end of dissolution because most tablets get smaller as dissolution proceeds, resulting in a smaller surface for water penetration inward and drug diffusion outward. Also, as drug dissolution occurs, the concentration gradient (Fick's law) gets progressively smaller due to the buildup of drug in the bulk solution.

e. As the surface drug of a sustained-release product is dissolved, the interior drug has to traverse a longer or a more tortuous path to reach the outside, resulting in the slowing rate of dissolution.

3. a. A drug given 10 mg 4 times daily would be equivalent to 40 mg/day or 20 mg/12 hr at the rate of 1.67 mg/hr.

b. 0.5 mL/hr should deliver 1.67 mg of drug. Therefore, the concentration should be

$$\frac{1.67\ \text{mg}}{0.5\ \text{mL}} = 3.34\ \text{mg/mL}$$

4. Using the infusion equation,

$$k = \frac{0.693}{3.5} = 0.198\ \text{hr}^{-1}$$

$$V_D = 10\ \text{L} \qquad C_p = 20\ \text{mg/L}$$

$$R = C_p V_D k = (20)\,(10)\,(0.198) = 39.6\ \text{mg/hr}$$

$$\text{Total drug needed} = R \times 12\ \text{hr} = (39.6)\,(12) = 475.2\ \text{mg}$$

CHAPTER 18

Frequently Asked Questions

1. The most frequent route of administration for biologic compounds is parenteral (eg, IM or IV). For example, β-interferon for multiple sclerosis is given IM to allow gradual drug release into the systemic circulation.

2. Glycosylation is the addition of a carbohydrate group to the molecule. For example, Betaseron (interferon beta-1A) is not glycosylated, whereas Avonex (interferon β-1B) is glycosylated. Glycosylation will increase the water solubility and the molecular weight of the drug. Although both drugs are β-interferons, glycosylation affects the pharmacokinetics, the stability, and the efficacy of these drugs.

3. The distribution of a biotechnology compound depends on its physicochemical characteristics. Many peptides, proteins, and nucleotides have polar chains so that a major portion of the drug is distributed in the extracellular fluid with a volume of 7–15 L. Drugs that easily penetrate into the cell have higher volumes of distribution, about 15–45 L, due to the larger volume of intracellular fluid.

Learning Questions

None

CHAPTER 19

Frequently Asked Questions

1. Doubling a dose does not double the drug response (or the pharmacodynamic effect). The pharmacodynamic effect of a drug is proportional to the log of the plasma drug concentration—-usually within 20% to 80% of the maximal response. Near the maximal pharmacodynamic effect, doubling the dose may only cause a very small increase in effect. No further increase in pharmacodynamic effect is achieved by an increase in dose once the maximum pharmacodynamic effect, E_{max}, is obtained.

2. For many drugs, the drug responses over time plotted versus plasma drug concentrations produces a loop-shaped (*hysteresis loop*) profile. The hysteresis loop shows that the plasma drug concentration is not always a good indicator of drug response. A *clockwise* hysteresis loop shows that response decreases with time and may be the result of drug tolerance or formation of an antagonistic metabolite.

3. The *effect compartment* is postulated to describe the pharmacodynamics of drugs that are not well described by drug concentration in the plasma compartment. The effect compartment is assumed to be the receptor site in the body for drug response. Drug concentration in this site is referred to as drug concentration in the effect compartment. The amount of drug in the effect compartment is relatively small and is insignificant compared to the amount of drug in other tissues. Drug elimination from the effect compartment is governed by k_{eo}, a first-order rate constant that is estimated from the pharmacodynamic data. Drug concentration in the effect compartment may be equilibrated with the central compartment when a steady-state plasma drug concentration is reached.

Learning Questions

1. a. True. Drug concentration is more precise because an identical dose may result in different plasma drug concentration in different subjects due to individual differences in pharmacokinetics.

b. True. The kinetic relationship between drug response and drug concentration is such that the response is proportional to log concentration of the drug.

c. True. The data show that after IV bolus dose, the response begins at the same point indicating that the initial plasma drug concentration is the same. In uremic patients, the volume of distribution may be affected by changes in protein binding and electrolyte levels, which may range from little or no effect to strongly affecting the V_D.

d. False. The drug is likely to be excreted through the kidney, since the slope (elimination) is reduced in uremic patients.

e. True. Assuming that the volume of distribution is unchanged, the starting pharmacologic response should be the same if the receptor sensitivity is unchanged. In a few cases, receptor sensitivity to the drug can be altered in uremic patients. For example, the effect of digoxin will be more intense if the serum potassium level is depleted.

2. These antibiotics inhibit β-lactamase by irreversible binding to the enzyme protein via an acylation reaction, similar to antibiotic binding to the protein in the cell wall. β-lactamase breaks the cyclic amide bond of the antibiotics.

3. Several answers are possible.

a. Pharmacokinetic considerations: Subsequent doses induce the hepatic drug metabolizing enzymes (auto-induction),

thereby decreasing the elimination half-life resulting in lower steady-state drug concentrations.

b. Pharmacodynamic considerations: The patient develops tolerance to the drug, resulting in the need for a higher dose to produce the same effect.

5. CNS drugs.

6. An allergic response to a drug may be unpredictable and does not generally follow a dose–response relationship.

7. PAT (postantibiotic time) is the time for continued antibacterial activity even though the plasma antibiotic concentration has fallen below MEC, or minimum effective concentration.

8. AUC/MIC or AUIC is a pharmacokinetic parameter incorporating MIC together in order to provide better prediction of antibiotic response (cure percent). An example is ciprofloxacin. AUIC is a good predictor of percent cure in infection treated at various dose regimens.

CHAPTER 20

Frequently Asked Questions

1. Therapeutic drug monitoring (TDM) may be performed by sampling other biologic fluids, such as saliva or, when available, tissue or ear fluids. However, the sample must be correlated to blood or special tissue level. Urinary drug concentrations generally are not reliable. Saliva is considered an ultrafiltrate of plasma and does not contain significant albumin. Saliva drug concentrations represent free plasma drug levels and have been used with limited success to monitor some drugs.

Pharmacodynamic end points such as prothrombin clotting time for warfarin, blood glucose concentrations for antidiabetic drugs, blood pressure for antihypertensive drugs, and other clinical observations are useful indications that the drug is dosed correctly.

2. Most pharmacokinetic models require well-controlled studies in which many blood samples are taken from each subject and the pharmacokinetic parameters estimated. In patient care situations, only a limited number of blood samples is collected, which does not allow for the complete determination of the drug's pharmacokinetic profile in the individual patient. However, the data from blood samples taken from a large demographic sector are more reflective of the disease states and pharmacogenetics of the patients treated. Population pharmacokinetics allow data from previous patients to be used in addition to the limited blood sample from the individual patient. The type of information obtained is less constrained and is sometimes dependent on the model and algorithm used for analysis. However, many successful examples have been reported in the literature.

3. The major considerations in TDM include the pathophysiology of the patient, the blood sample collection, and the data analysis. Clinical assessment of patient history, drug interaction, and demographic factors are all part of a successful program for therapeutic drug monitoring.

4. With the Bayesian approach, the estimates of patient parameters are constrained more narrowly, to allow easier parameter estimation based on information provided from the population. The information is then combined with one or more serum concentrations from the patient to obtain a set of final patient parameters (generally Cl and V_D). When no serum sample is taken, the Bayesian approach is reduced to an *apriori* model using only population parameters.

5. Pharmacokinetics provides a means of studying whether an unusual drug action is related to pharmacokinetic factors, such as drug disposition, distribution, or binding, or is related to pharmacodynamic interaction, such as a difference in receptor sensitivity, drug tolerance, or some other reason. Many drug interactions involving enzyme inhibition, stimulation, and protein binding were discovered as a result of pharmacokinetic, pharmacogenetic, and pharmacodynamic investigations.

Learning Questions

1. Steady-state drug concentrations are achieved in approximately 5 half-lives. For a drug with a half-life of 36 hours, steady-state drug concentrations are achieved in approximately 180 hours (or 7.5 days). Thus, dose adjustment in patients is difficult for drugs with very long half-lives. In contrast, steady-state drug concentrations are achieved in approximately 20–30 hours (or 1 day) for drugs whose half-lives are 4–6 hours.

2. $$C_{\max}^{\infty} = \frac{D_0}{V_D}\left(\frac{1}{1 - e^{-k\tau}}\right)$$

$$C_{\max}^{\infty} = \frac{250{,}000}{42{,}000}\left(\frac{1}{1 - e^{-(6)(1.034)}}\right)$$

$$C_{\max}^{\infty} = \frac{250{,}000}{42{,}000}\left(\frac{1}{0.998}\right) = 5.96\ \mu g/mL$$

At steady state, the peak concentration of penicillin G will be 5.96 μg/mL.

3. $$C_{av}^{\infty} = \frac{D}{kV_D\tau} = \frac{250{,}000}{(0.99)(20{,}000)(6)} = 2.10\ \mu g/mL$$

Free drug concentration at steady state = $2.10(1 - 0.97) = 0.063\ \mu g/mL$.

4. $C_{av}^{\infty} = \dfrac{1.44 D_0 F t_{1/2}}{V_D \tau}$

For the Normal Patient:

$$V_D = (0.392)(1)(1000) = 392 \text{ mL/kg}$$

$$C_{av}^{\infty} = \frac{(1.44)(D_0)(1)(1.49)}{(392)(6)} = 2 \ \mu\text{g/mL}$$

$$D_0 = \frac{(392)(6)(2)}{(1.44)(1.49)} = 2192 \ \mu\text{g/kg} = 2.2 \text{ mg/kg}$$

For the Uremic Patient:

$$V_D = (23.75)(1)(1000) = 237.5 \text{ mL/kg}$$

$$C_{av}^{\infty} = \frac{(1.44)(D_0)(1)(6.03)}{(237.5)(6)} = 2 \ \mu\text{g/mL}$$

$$D_0 = \frac{(2)(237.5)(6)}{(1.44)(6.03)} = 328.2 \ \mu\text{g/kg} = 0.3 \text{ mg/kg}$$

5. **a.** $V_D = 306{,}000 \text{ mL}$

$$\text{Dose} = 0.5 \times 10^6 \text{ ng}$$

$$C_{av}^{\infty} = \frac{(1.44)(DFt_{1/2})}{V_D \tau} = \frac{(1.44)(0.5 \times 10^6)(0.56)(0.95)}{(306{,}000)(1)} = 1.25 \text{ ng/mL}$$

b. The patient is adequately dosed.

c. $F = 1$; using the above equation, the C^{∞}_{av} is 2.2 ng/mL; although still effective, the C^{∞}_{av} will be closer to the toxic serum concentration of 3 ng/mL.

6. The Cl_{Cr} for this patient shows normal kidney function.

$$t_{1/2} = 2 \text{ hr} \qquad k = 0.693/2 = 0.3465 \text{ hr}^{-1}$$

$$V_D = 0.2 \text{ L/kg} \times 80 \text{ kg} = 16 \text{ L}$$

a. $$C_{max}^{\infty} = \frac{D_0 / V_D}{1 - e^{-k\tau}} = \frac{250/16}{1 - e^{-(0.3465)(8)}} = 16.68 \text{ mg/L}$$

$$C_{min}^{\infty} = C_{max}^{\infty} e^{-k\tau} = 16.68 e^{-(0.3465)(8)} = 1.04 \text{ mg/L}$$

The dosage regimen of 250 mg every 8 hours gives a C^{∞}_{max} above 16 mg/L and a C^{∞}_{min} below 2 mg/L. Therefore, this dosage regimen is not correct.

b. Several trials might be necessary to obtain a more optimal dosing regimen. One approach is to change the dosage interval, τ, to 6 hours and to calculate the dose, D_0:

$$D_0 = C_{max}^{\infty} V_D (1 - e^{-k\tau}) = (16)(16)(1 - e^{-(0.3465)(6)}) = 224 \text{ mg}$$

$$C_{min}^{\infty} = C_{max}^{\infty} e^{-k\tau} = 16 e^{-(0.3465)(6)} = 2 \text{ mg/L}$$

A dose of approximately 224 mg given every 6 hours should achieve the desired drug concentrations.

10. Assume desired C^{∞}_{av} = 0.0015 µg/mL and τ + 24 hours.

$$C_{av}^{\infty} = \frac{F D_0 \, 1.44 t_{1/2}}{V_D \tau}$$

$$D_0 = \frac{C_{av}^{\infty} V_D \tau}{F \, 1.44 t_{1/2}}$$

$$D_0 = \frac{(0.0015)(4)(68)(24)}{(0.80)(1.44)(30)} = 0.283 \text{ mg}$$

Give 0.283 mg every 24 hours.

a. For a dosage regimen of one 0.30-mg tablet daily,

$$C_{av}^{\infty} = \frac{(0.80)(0.3)(1.44)(30)}{(4)(68)(24)} = 0.0016 \ \mu\text{g/mL}$$

which is within the therapeutic window.

b. A dosage regimen of 0.15 mg every 12 hours would provide smaller fluctuations between C^{∞}_{max} and C^{∞}_{min} compared to a dosage regimen of 0.30 mg every 24 hours.

c. Since the elimination half-life is long (30 hours), a loading dose is advisable.

$$D_L = D_m\left(\frac{1}{1 - e^{-k\tau}}\right)$$

$$D_L = 0.30\left(\frac{1}{1 - e^{-(0.693/30)(24)}}\right) = 0.70 \text{ mg}$$

For cardiotonic drugs related to the digitalis glycosides, it is recommended that the loading dose be administered in several portions with approximately half the total as the first dose. Additional fractions may be given at 6- to 8-hour intervals, with careful assessment of the clinical response before each additional dose.

d. There is no rationale for a controlled-release drug product because of the long elimination half-life of 30 hours inherent in the drug.

11. a. $C_{av}^{\infty} = \dfrac{FD_0\,1.44t_{1/2}}{V_D\tau}$

$$C_{av}^{\infty} = \frac{(1500)\,(1.44)\,(6)}{(1.3)\,(63)\,(4)} = 39.6\ \mu\text{g/mL}$$

b. $D_L = D_M\left(\dfrac{1}{1 - e^{-k\tau}}\right)$

c. A D_L of 4.05 g is needed, which is equivalent to 8 tablets containing 0.5 g each.

d. The time to achieve 95–99% of steady state is, approximately, $5t_{1/2}$ without a loading dose. Therefore,

$$5 \times 6 = 30 \text{ hr}$$

12. a. $C_{ss} = \dfrac{R}{kV_D} \qquad R = C_{ss}kV_D$

$$R = (5)\left(\frac{0.693}{2}\right)(0.173)\,(75) = 22.479 \text{ mg/hr}$$

$$D_L = C_{ss}V_D = (5)\,(0.173)\,(75) = 64.875 \text{ mg}$$

b. $\dfrac{R_{old}}{C_{SS,old}} = \dfrac{R_{new}}{C_{SS,new}}$

$$\frac{22.479}{2} = \frac{R_{new}}{5} \qquad R_{new} = 56.2 \text{ mg/hr}$$

c. $4.32t_{1/2} = 4.32(2) = 8.64 \text{ hr}$

13. $t_{1/2} = 8 \text{ hr} \qquad k = 0.693/8 = 0.0866 \text{ hr}^{-1}$

$V_D = (1.5 \text{ L/kg})\,(75 \text{ kg}) = 112.5 \text{ L} \qquad C_{SS} = 20\ \mu\text{g/mL}$

a. $R = C_{SS}V_D = (20)\,(0.0866)\,(112.5) = 194.85 \text{ mg/hr}$

b. $D_L = C_{SS}V_D = (20)\,(112.5) = 2250 \text{ mg}$

Alternatively, $D_L = R/k = 194.85/0.0866 = 2250 \text{ mg}$

c. 0.2 mL of a 15-mg/mL solution contains 3 mg.

$$R = 3 \text{ mg/hr/kg} \times 75 \text{ kg} = 225 \text{ mg/hr}$$

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

The proposed starting infusion rate given by the manufacturer should provide adequate drug concentrations.

CHAPTER 21

Frequently Asked Questions

1. Renal disease can cause profound changes in the body that must be evaluated by assessing the patient's condition and medical history. Renal dysfunction is often accompanied by reduced protein drug binding and by reduced glomerular filtration rate in the kidney. Some changes in hepatic clearance may also occur. While there is no accurate method for predicting the resulting *in-vivo* changes, a decrease in albumin may increase f_u, or the fraction of free plasma drug concentration in the body. The f_u is estimated from $f_u = 1 - f_b$, where f_b is the fraction of bound plasma drug. For the uremic patient, the fraction of drug bound f_b' is affected by a change in plasma protein: $f_b'/f_b = p'/4.4$, where p is the normal plasma protein concentration (4.4 g/dL assuming albumin is the protein involved) and p' is the uremic plasma protein concentration; f_b' is the fraction of drug bound in the uremic patient. Since f_u' or fraction of unbound drug, is increased in the uremic patient, the free drug concentration may be increased and sometimes lead to more frequent side effects. On the other hand, an increase in plasma free drug in the uremic patient is offset somewhat by a corresponding increase in the volume of distribution as plasma protein drug binding is reduced. Reduction in GFR is more definite; it is invariably accompanied by a reduction in drug clearance and by an increase in the elimination half-life of the drug.

2. Two approaches to dose adjustment in renal disease are the clearance method and the elimination rate constant method. The methods are based on estimating either the uremic Cl_R or uremic k_R after the creatinine clearance is obtained in the uremic patient.

3. Aminoglycosides are given as a larger dose spaced farther apart (once daily). Keeping the same total daily dose of the aminoglycoside improves the response (efficacy) and possibly lessens side effects in many patients. Model simulation shows reduced exposure (AUC) to the effect compartment (toxicity), while the activity is not altered. The higher drug dose produces a higher peak drug concentration. In the case of gentamicin, the marketed drug is chemically composed of three related, but distinctly different, chemical components, which may distribute differently in the body.

4. Hepatic disease may reduce albumin and α_1-acid glycoprotein (AAG) concentrations resulting in decreased drug protein binding. Blood flow to the liver may also be affected. Generally, for a drug with linear binding, f_u may be increased as discussed in FAQ #1. Consult also for a discussion of restrictive clearance of drugs. Examples of binding to AAG are the protease inhibitors for AIDS.

5. Congestive heart failure (CHF) can reduce renal or hepatic blood flow and decrease hepatic and renal drug clearance. In CHF, less blood flow is available in the splanchnic circulation to the small intestine and may result in less systemic drug bioavailability after oral drug administration. Severe disturbances to blood flow will affect the pharmacokinetics of many drugs. Myocardiac infarction (MI) is a clinical example which often causes drug clearance to be greatly reduced, especially for drugs with large hepatic extraction.

Learning Questions

1. The normal dose of tetracycline is 250 mg PO every 6 hours. The dose of tetracycline for the uremic patient is determined by the k_u/k_N ratio, which is determined by the kidney function, as in . From line H in the figure, at Cl_{Cr} of 20 mL, k_u/k_N = 40%. In order to maintain the average concentration of tetracycline at the same level as in normal patients, the dose of tetracycline must be reduced.

$$\frac{D_u}{D_N} = \frac{k_u}{k_N} = 40\%$$

$$D_u = (250)(0.40) = 100 \text{ mg}$$

Therefore, 100 mg of tetracycline should be given PO every 6 hours.

2. The drug in this patient is eliminated by the kidneys and the dialysis machine. Therefore,

$$\text{Total drug clearance} = Cl_T + Cl_D$$

Using Equation 21.33,

Using Equation 21.33,

$$Cl_D = \frac{Q(C_a - C_v)}{C_a}$$

$$Cl_D = \frac{50(5 - 2.4)}{5} = 26 \text{ mL/min}$$

Total drug clearance = 10 + 26 = 36 mL/min

Since the drug clearance is increased from 10 to 36 mL/min, the dose should be increased if dialysis is going to continue. Since dose is directly proportional to clearance,

$$\frac{D_u}{D_N} = \frac{36}{10} = 3.6$$

The new dose should be 3.6 times the dose given before dialysis if the same level of antibiotics is to be maintained.

4. The creatinine clearance of a patient is determined experimentally by using Equation 21.11,

$$Cl_{Cr} = \frac{C_u V 100}{C_{Cr} 1440}$$

$$Cl_{Cr} = \frac{(0.1)(1800)(100)}{(2.2)(1440)} = 5.68 \text{ mL/min}$$

Assuming that the normal Cl_{Cr} in this patient is 100 mL/min, the uremic dose should be 5.7% of the normal dose, since kidney function is drastically reduced:

$$(0.057)(20 \text{ mg/kg}) = 1.14 \text{ mg/kg given every 6 hours}$$

5. From , line F, at a Cl_{Cr} of 5 mL/min,

$$\frac{k_u}{k_N} = 45\%$$

a. The dose given should be as follows:

$$(0.45)(600 \text{ mg}) = 270 \text{ mg every 12 hours}$$

b. Alternatively, the dose of 600 mg should be given every

$$12 \times \frac{100}{45} = 26.7 \text{ hr}$$

c. Since it may be desirable to give the drug once every 24 hours, both dose and dosing interval may be adjusted so that the patient will still maintain an average therapeutic blood level of the drug, which can then be given at a convenient time. Using the equation for C^{∞}_{av},

$$C^{\infty}_{av} = \frac{D_0}{kV_D\tau}$$
$$D_0 = 600 \text{ mg}$$
$$\tau = 26.7 \text{ hr}$$
$$C^{\infty}_{av} = \frac{600}{kV_D \times 26.7}$$

To maintain C^{∞}_{av} the same, calculate a new dose, D_N, with a new dosing interval, τ_N, of 24 hours.

$$C^{\infty}_{av} = \frac{D_N}{kV_D 24}$$

Thus,

$$\frac{600}{26.7} = \frac{D_N}{24}$$

Therefore,

$$D_N = \frac{24}{26.7} \times 600 = 539 \text{ mg}$$

The drug can also be given at 540 mg daily.

6. For females, use 85% of the Cl_{Cr} value obtained in males.

$$Cl_{Cr} = \frac{0.85[140 - \text{age (yr)}]\,\text{body weight (kg)}}{72\ (Cl_{Cr})}$$

$$Cl_{Cr} = \frac{0.85[140 - 38]62}{(72)\,(1.8)} = 41.5 \text{ mL/min}$$

9. Gentamycin is listed in group K (). From the nomogram in ,

$$Cl_{Cr} = 20 \text{ mL/min} \qquad \frac{k_u}{k_n} = 25\%$$

Uremic dose = 25% of normal dose = (0.25) (1 mg/kg) = 0.25 mg/kg

For a 72-kg Patient:

$$\text{Uremic dose} = (0.25)\,(75) = 18.8 \text{ mg}$$

The patient should receive 18.8 mg every 8 hours by multiple IV bolus injections.

10. a. During the first 48 hours postdose, $t_{1/2}$ = 16 hours. For IV bolus injection, assuming first-order elimination:

$$D_B = D_0 e^{-kt}$$
$$D_B = 1000 e^{-(0.693/16)(48)}$$
$$D_B = 125 \text{ mg remaining in body just before dialysis}$$

During dialysis, $t_{1/2} = 4$ hours, and

$$D_B = 125 e^{-(0.693/4)(8)} = 31.3 \text{ mg after dialysis}$$

b. $V_D = (0.5 \text{ L/kg})\,(75 \text{ kg}) = 37.5 \text{ L}$

Drug concentration just before dialysis:

$$C_p = 125 \text{ mg}/37.5 \text{ L} = 3.33 \text{ mg/L}$$

Drug concentration just after dialysis:

$$C_p = 31.3 \text{ mg}/3.75 \text{ L} = 0.83 \text{ mg/L}$$

CHAPTER 22

Frequently Asked Questions

1. Differential equations are used to describe the rate of drug transfer between different tissues and the blood. Differential equations have the advantage of being very adaptable to computer simulation without a lot of mathematical manipulations.

2. After an IV bolus drug injection, a drug is diluted rapidly in the venous pool. The venous blood is oxygenated in the lung and

becomes arterial blood. The arterial blood containing the diluted drug then perfuses all the body organs through the systemic circulation. Some drug diffuses into the tissue and others are eliminated. In cycling through the body, the blood leaving a tissue (venous) generally has a lower drug concentration than the perfusing blood (arterial). In practice, only venous blood is sampled and assayed. Drug concentration in the venous blood rapidly equilibrates with the tissue and will become arterial blood in the next perfusion cycle (seconds later) through the body. In pharmacokinetics, the drug concentration is assumed to decline smoothly and continuously. The difference in drug concentration between arterial and venous blood reflects drug uptake by the tissue, and this difference may have important consequences in drug therapy, such as tumor treatment.

3. Statistical moment is adaptable to mean residence time calculation and is widely used in pharmacokinetics.

4.*Mean residence time* (MRT) represents the average staying time of the drug in a body organ or compartment as the molecules diffuse in and out. MRT is an alternative concept used to describe how long a drug stays in the body. The main advantage of MRT is that it is based on probability and is consistent with how drug molecules behave in the physical world.

Learning Questions

1. a. $$\text{MRT} = \frac{[\text{AUMC}]_0^\infty}{[\text{AUC}]_0^\infty} = \frac{100\ (\text{mg/L})\ \text{hr}^2}{25\ (\text{mg/L})\ \text{hr}} = 4\ \text{hr}$$

b. $$Cl_T = \frac{D_0}{[\text{AUC}]_0^\infty} = \frac{500\ \text{mg}}{20\ (\text{mg/L})\ \text{hr}} = 25\ \text{L/hr}$$

c. V_{SS} may be calculated using Equation 22.49:

$$\text{MRT} = Cl_T/V_{SS}$$

Therefore,

$$V_{SS} = \frac{Cl_T}{\text{MRT}} = \frac{25}{4} = 6.25\ \text{L}$$

2. MRT is not calculated directly based on its definition (AUC/C_0), because it is not possible to determine C_0 except with simple data involving a one-compartment model. Based on rigorous derivation, C_0 is not C^0_p except in a one-compartment IV bolus dose; rather, it is the concentration D_0/V_D which is equal to $C_p = C^0_p$ in the simple IV bolus dose. With oral absorption data, it is not possible to determine D_0/V_D without using a model.

3. If the data in Problem 1 are fitted to obtain k, and $k = 0.25\ \text{hr}^{-1}$,

$$\text{MRT} = \frac{1}{k} = \frac{1}{0.25} = 4\ \text{hr}$$

Although the answer agrees with the result calculated above using a noncompartmental approach, the calculation now uses an equation with assumptions of the one-compartment model for IV bolus.

4. The principal considerations in interspecies scaling are size, protein–drug binding, and maximum lifespan potential (MLP) of the species.

5. The model assumptions should be consistent with known information about the system. The number of model parameters should not exceed the available data, and an adequate degree of freedom should be present to test for lack of fit. The law of parsimony should apply at all times.