MODULE 2.5

Drug Dosage

Downloads

The text's website has *OneCompartAspirin* and *OneCompartDilantin* files, which contain models for examples in this module, available for download in various system dynamics systems.

Introduction

Errors in the dispensing and administration of medications occur frequently. Although most do not result in great harm, some do. For instance, a Florida pharmacy dispensed 10 times the prescribed dose of a blood thinner to a mother of four, which resulted in her suffering a cerebral hemorrhage (Patel and Ross 2010). In other tragedies, a 10-mo-old infant died after receiving a 10-fold overdose of the chemotherapy agent Cisplatin (Fitzgerald and Wilson 1998), and three nurses were prosecuted for administering a 10-fold (fatal) overdose of penicillin to an infant (Ellis and Hartley 2004).

The National Quality Forum, a nonprofit whose mission involves enabling "private- and public-sector stakeholders to work together to craft and implement cross-cutting solutions to drive continuous quality improvement in the American healthcare system," has estimated that medication errors account for a conservative estimate of $21 billion in costs. This financial expenditure corresponds to serious preventable medication errors for 3.8 million hospital inpatients and 3.3 million outpatients per year (NQF 2010). These cases comprise an extraordinary amount of human suffering and, in some cases, death.

How do these errors occur? According to the Institute of Medicine, medication errors can be classified as errors in

ordering—incorrect drug or dosage;
transcribing—incorrect frequency of administration or missed dosages;
dispensing—incorrect drug, dosage, or timing;

administering—wrong dosage, technique;
monitoring—not observing effects of medication.

Whether these errors result from poor communication of orders, poor product labeling, or some other cause, the patients and their families suffer the consequences (IOM 2007).

It is not only health-care professionals who make mistakes in drug administration. On June 28, 2003, an Oklahoma teenager died from an overdose of Tylenol (acetaminophen). Suffering from a migraine headache, she took twenty 500-mg capsules, two and one-half times the maximum dosage recommended in 24 h. Apparently, the quantity was enough of the drug to cause liver and kidney failure. Assuming that an over-the-counter analgesic was safe, she apparently did not read the label and made a fatal dosage error (Robert 2004).

There are prescribed dosages for various drugs, but how do we determine what the correct/effective dosage is? There are quite a number of factors that are considered, including drug **absorption**, **distribution**, **metabolism**, and **elimination**. These factors are components of the quantitative science of **pharmacokinetics**.

One-Compartment Model of Single Dose

Metabolism of a drug in the human body is a complex system to represent in a model. Thus, in Step 2 of the modeling process, particularly for our first attempt, we should make simplifying assumptions about the drug and the body. A **one-compartment model** is a simplified representation of how a body processes a drug. In this model, we consider the body to be one homogeneous compartment, where distribution is instantaneous, the **concentration** of the drug in the system (amount of drug/volume of blood) is proportional to the drug dosage, and the rate of elimination is proportional to the amount of drug in the system. The concentration of a drug instead of the absolute quantity is important because a quantity that might be appropriate for a small child could be ineffective for a large adult. A drug has a **minimum effective concentration** (**MEC**), which is the least amount of drug that is helpful, and a **maximum therapeutic concentration**, or **minimum toxic concentration** (**MTC**), which is the largest amount that is helpful without having dangerous or intolerable side effects. The **therapeutic range** for a drug consists of concentrations between the MEC and MTC. A drug's **half-life**, or the amount of time for half the drug to be eliminated from the system, is useful for modeling as well as patient treatment. Often concentrations and half-life are expressed in relationship to the drug in the plasma or blood serum. The total amount of blood in an adult's body is approximately 5 liters (L), while the amount of **plasma**, or fluid that contains the blood cells, is about 3 L. Blood **serum** is the clear fluid that separates from blood when it clots, and an adult human has about 3 L of blood serum.

We begin by modeling the concentration in the body of aspirin (acetylsalicylic acid). For adults and children over the age of 12, the dosage for a headache is one or two 325-mg tablets every 4 h as necessary, up to 12 tablets/da. Analgesic effectiveness occurs at plasma levels of about 150 to 300 micrograms/milliliter (μg/mL), while toxicity may occur at plasma concentrations of 350 μg/mL. The plasma half-life of a dose from 300 to 650 mg is 3.1 to 3.2 h, with a larger dose having a longer half-life.

For simplicity, we assume a one-compartment model with the aspirin immediately available in the plasma. A stock (box variable), *aspirin_in_plasma*, represents the mass of aspirin in the compartment, which is the person's system, and has an initial value of the mass of two aspirin, (2)(325 mg)(1000 μg/mg), where 1 milligram (mg) is equivalent to 1000 μg.

The flow from *aspirin_in_plasma* (*elimination*) is proportional to the amount present in the system, *aspirin_in_plasma*. Thus, the rate of change of the drug leaving the system is proportional to the quantity of drug in the system (*aspirin_in_plasma*, or Q in the following equation):

$$dQ/dt = -KQ$$

As Module 2.2, "Unconstrained Growth and Decay," shows, the solution to this differential equation is as follows:

$$Q = Q_0 e^{-Kt}$$

Using this solution, as Exercise 1 shows, the constant of proportionality K given earlier and *elimination_constant* in the system dynamics software model have the following relationship to the drug's half-life ($t_{1/2}$):

$$\boldsymbol{K = -\ln(0.5)/t_{1/2}}$$

Pharmaceutical sources widely report a drug's half-life.

Quick Review Question 1

Determine the elimination constant with units for aspirin, assuming a half-life of 3.2 h.

To compute aspirin's plasma concentration (*plasma_concentration*) in a converter (variable), we have another converter for the volume of the system (*plasma_volume*) with a value of 3000 mL and appropriate connectors and equation. Figure 2.5.1 contains a one-compartment model for one dose of a drug, where the initial value of *plasma_concentration* is the dosage; and Equation Set 2.5.1 gives the corresponding equations and values explicitly entered for the model of aspirin.

Quick Review Question 2

In terms of the variables in the model of Figure 2.5.1, give the equation for *plasma_concentration*.

Equation Set 2.5.1

Explicitly entered equations and values for one-compartment model of aspirin:

half_life = 3.2 h
plasma_volume = 3000 mL
aspirin_in_plasma(0) = 2 * 325 * 1000 μg
elimination_constant = –ln(0.5)/*half_life*

*elimination = elimination_constant * aspirin_in_plasma*
plasma_concentration = aspirin_in_plasma/plasma_volume

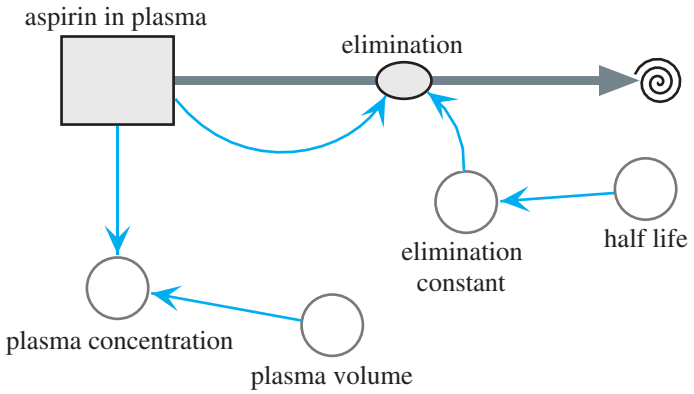

Figure 2.5.1 One-compartment model of aspirin

Running the simulation for 8 h and plotting *plasma_concentration*, the resulting graph in Figure 2.5.2 indicates that the concentration of the drug in the plasma is initially approximately 217 µg/mL, which is a safe, therapeutic dose. Subsequently, the concentration decreases exponentially.

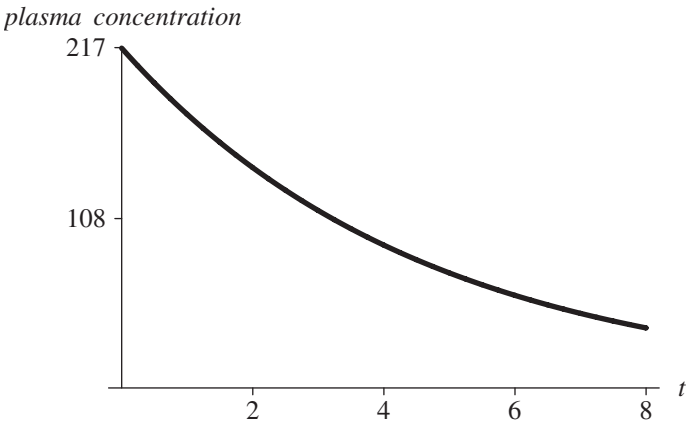

Figure 2.5.2 Graph of plasma_concentration (µg/mL) for aspirin versus time, t (h)

One-Compartment Model of Repeated Doses

As another example, we model the concentration in the body of the drug Dilantin, a treatment for epilepsy that the patient takes on a regular basis. Adult dosage is often one 100-mg capsule three times daily. The effective serum blood level is 10 to 20 µg/mL, which may take 7 to 10 da to achieve. Although individual variations occur,

serious side effects can appear at a serum level of 20 μg/mL. The half-life of Dilantin ranges from 7 to 42 h but averages 22 h.

For simplicity, we assume a one-compartment model with instantaneous absorption. A stock (box variable), *drug_in_system*, represents the mass of Dilantin in the compartment, which is the person's blood serum. A flow, *ingested*, into *drug_in_system* is for the drug absorbed into the system. Because of the periodic nature of the dosage, we employ a pulse function with converters/variables for the dose (*dosage*), time of the initial dose (*start*), and time interval between doses (*interval*). Presuming that only a fraction (*absorption_fraction*) actually enters the system, we multiply this constant (say, 0.12, from experimental evidence) and the pulse value together for the equation of *entering*. We can estimate the value of *absorption_fraction* by plotting actual data of drug concentration versus time and employing techniques of curve fitting, which Module 8.3, "Empirical Models," discusses.

Quick Review Question 3

Give the equation for *entering*.

The flow from *drug_in_system* (*elimination*) is proportional to the amount present in the system, *drug_in_system*. Thus, between doses of a drug, the rate of change of the drug leaving the system is proportional to the quantity of drug in the system. As for the preceding aspirin example, we use a constant of proportionality (*elimination_constant*) of $-\ln(0.5)/t_{1/2}$, where $t_{1/2}$ is Dilantin's half-life.

For comparison purposes, we have converters (variables) for *MEC*, *MTC*, and the concentration of the drug in the system (*concentration*). To compute the latter, we have a converter (variable) for the volume of the blood serum (*volume*) with a possible value of 3000 mL and appropriate connectors and equation. Figure 2.5.3 contains a one-compartment model, and Equation Set 2.5.2 gives the corresponding explicitly entered equations and constants for Dilantin. Note that, except for name

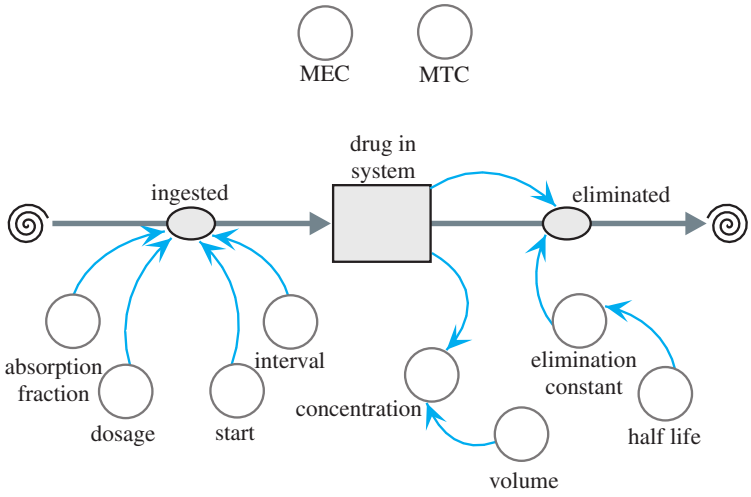

Figure 2.5.3 One-compartment model of Dilantin

changes, the middle and right side of the diagram agree with those of aspirin in Figure 2.5.1. The inflow for Figure 2.5.3 models the multiple doses of Dilantin, in contrast to no inflow for Figure 2.5.1 because of the assumption that exactly one dose of aspirin is immediately available in the plasma.

Equation Set 2.5.2

Explicitly entered equations and constants for one-compartment model of Dilantin:

half_life = 22 h; *interval* = 8 h; *MEC* = 10 µg/mL; *MTC* = 20 µg/mL; *start* = 0 h; *volume* = 3000 mL; *dosage* = 100 * 1000 µg; *absorption_fraction* = 0.12
elimination_constant = –ln(0.5)/*half_life*
drug_in_system(0) = 0
entering = *absorption_fraction* * (pulse of amount *dosage* beginning at *start* every *interval* hours)
elimination = *elimination_constant* * *drug_in_system*
concentration = *drug_in_system/volume*

Running the simulation and plotting the various concentrations that occur over 168 h (7 da), the resulting Figure 2.5.4 indicates that the concentration of the drug in the system between doses fluctuates. In less than 2 da, the concentration remains within the therapeutic range; and after about 5 da, the drug reaches a steady state.

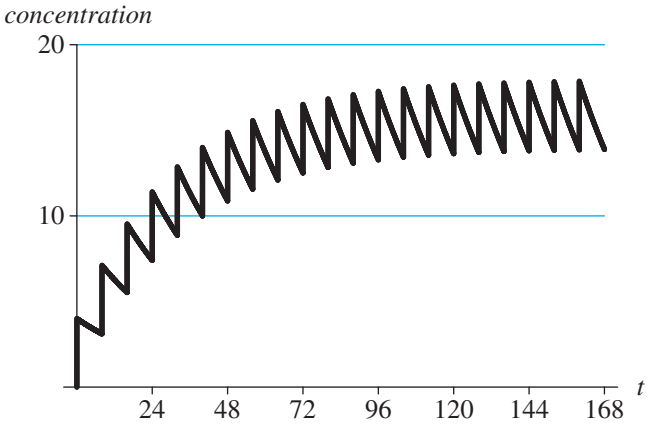

Figure 2.5.4 Graph of concentrations MEC = 10 µg/mL, MTC = 20 µg/mL, and concentration (µg/mL) versus time (h)

Mathematics of Repeated Doses

Let us show the mathematics of why the drug concentration in the Dilantin example tends to a fixed value, in this case about 12 µg/mL, immediately after a dose. Suppose that the patient takes a 100-mg tablet every 8 h. In the model, we assumed an absorption level of 0.12, so that the effective dosage is $Q_0 = (0.12)(100) = 12$ mg. With an elimination rate of –ln(0.5)/22, which is about 0.0315, the amount of drug

in the system after 8 h is $Q = Q_0 e^{-0.0315(8)} \approx (12)(0.7772) = 9.3264$ mg = 9326.4 μg. Thus, at the end of 8 h, about 77.72% of the drug remains in the system. The analytical value (9326.4 μg) for the mass of drug in the system is close to the simulated value (9327.91 μg) of *drug_in_system* at time 8.00 h (using a time step of 0.01 h and Runge-Kutta 4 numeric integration, which Module 6.4 discusses).

Suppose Q_n is the quantity (in mg) in the system immediately after the nth tablet. Thus, assuming 77.72% of the drug remains in the system at the end of an 8-h interval immediately before a dose, we have the following:

$$Q_1 = 12 \text{ mg}$$

$$Q_2 = \underbrace{(12 \text{ mg})(0.7772)}_{\text{remainder of tablet 1}} + \underbrace{12 \text{ mg}}_{\text{tablet 2}} = 21.3264 \text{ mg}$$

$$Q_3 = \underbrace{Q_2(0.7772)}_{\text{remainder of tablets 1 \& 2}} + \underbrace{12 \text{ mg}}_{\text{tablet 3}}$$

$$= (12(0.7772) + 12)(0.7772) + 12$$

$$= 12(0.7772)^2 + 12(0.7772) + 12 = 28.57488 \text{ mg}$$

$$Q_4 = \underbrace{Q_3(0.7772)}_{\text{remainder of tablets 1-3}} + \underbrace{12 \text{ mg}}_{\text{tablet 4}}$$

$$= (12(0.7772)^2 + 12(0.7772) + 12)(0.7772) + 12$$

$$= 12(0.7772)^3 + 12(0.7772)^2 + 12(0.7772) + 12 = 34.2084 \text{ mg}$$

Continuing in the same pattern, we determine that the general form of the quantity of the drug in the system immediately after the fifth tablet is as follows:

$$\begin{aligned} Q_5 &= 12(0.7772^4) + 12(0.7772^3) + 12(0.7772^2) + 12(0.7772) + 12 \\ &= 12(0.7772^4) + 12(0.7772^3) + 12(0.7772^2) + 12(0.7772^1) + 12(0.7772^0) \\ &= 12(0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 + 0.7772^0) \end{aligned}$$

Similarly, the quantity of the drug immediately after the nth tablet, Q_n, follows:

$$Q_n = 12(0.7772^{n-1} + \cdots + 0.7772^2 + 0.7772^1 + 0.7772^0)$$

Quick Review Question 4

Suppose a patient takes a 200-mg tablet once a day, and within 24 h, 75% of the drug is eliminated from the body. With Q_n being the quantity of the drug in the body after the nth dose, determine the following:

a. Q_1

b. Q_2 expressed as a sum
c. Q_3 expressed as a sum
d. Q_4 expressed as a sum
e. Q_n expressed as a sum

We would like to determine what happens to the quantity of the drug in the system over a long period of time. To do so, we need a formula for the sum $0.7772^{n-1} + \cdots + 0.7772^2 + 0.7772^1 + 0.7772^0$ for positive integer n. This sum is a **finite geometric series**, and its general form is as follows:

$$a^{n-1} + \cdots + a^2 + a^1 + a^0 \text{ for } a \neq 1 \text{ and positive integer } n$$

As we verify in the next section, this sum is the following ratio:

$$a^{n-1} + \cdots + a^2 + a^1 + a^0 = \frac{\left(1 - a^n\right)}{\left(1 - a\right)} \text{ for } a \neq 1$$

Thus, for $a = 0.7772$ and $n = 5$, we can compute the value of Q_5:

$$Q_5 = 12(0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 + 0.7772^0)$$
$$= 12 \cdot \frac{1 - 0.7772^5}{1 - 0.7772} = 38.5868 \text{ mg} = 38{,}586.8 \text{ µg}$$

Within simulation error, this value agrees with *drug_in_system* (38,580.92) after the fifth dose, at time 32.01 h. In general, the quantity of the drug immediately after the nth tablet, Q_n, is as follows:

$$Q_n = 12(0.7772^{n-1} + \cdots + 0.7772^2 + 0.7772^1 + 0.7772^0)$$
$$= 12 \cdot \frac{1 - \left(0.7772\right)^n}{1 - 0.7772}$$

Definition $a^{n-1} + \cdots + a^2 + a^1 + a^0$ for $a \neq 1$ and positive integer n is a **finite geometric series** with **base** a.

Quick Review Question 5

Using the drug of Quick Review Question 4 and the formula for the sum of a finite geometric series, evaluate the following:

a. Q_{10}
b. Q_n

Using the formula for the sum of a finite geometric series, we can compute the quantity of drug after the nth tablet. To determine the long-range affect, we let n go to infinity and see that Q_n approaches 53.8599 mg, as follows:

$$Q_n = 12 \cdot \frac{1-(0.7772)^n}{1-0.7772} \to 12 \cdot \frac{1-0}{1-0.7772} \approx 53.8599 \text{ mg}$$

Thus, the serum concentration is about (53.8599 mg)/(3000 mL) = 0.0179533 mg/mL = 17.95 μg/mL, which agrees closely with the peak value of the concentration in Figure 2.5.4.

Quick Review Question 6

Using the drug of Quick Review Questions 4 and 5, determine the quantity of drug after the *n*th tablet when the patient has been taking the drug for a long time.

Sum of Finite Geometric Series

To derive the formula for the sum of a finite geometric series, we start by considering a particular example, Q_5 as before. Let s be equal to the sum of the powers from 0 through 4 of 0.7772, as follows:

$$s = 0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 + 0.7772^0 \quad (1)$$

Multiplying both sides by 0.7772, we have the following:

$$0.7772s = (0.7772)\,(0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 + 0.7772^0)$$
$$0.7772s = 0.7772^5 + 0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 \quad (2)$$

Subtracting Equation 2 from Equation 1, we subtract off all but two terms on the right:

$$\begin{array}{rl} s = & 0.7772^4 + 0.7772^3 + 0.7772^2 + 0.7772^1 + 0.7772^0 \\ -0.7772s = & -0.7772^5 - 0.7772^4 - 0.7772^3 - 0.7772^2 - 0.7772^1 \\ \hline s - 0.7772s = & -0.7772^5 \qquad\qquad\qquad\qquad\qquad\qquad + 0.7772^0 \end{array}$$

With 0.7772^0 being 1, we factor out s on the left as follows:

$$s(1 - 0.7772) = -0.7772^5 + 1$$

or

$$s(1 - 0.7772) = 1 - 0.7772^5$$

Dividing both sides by the factor (1 – 0.7772), we obtain the following formula:

$$s = \frac{1-0.7772^5}{1-0.7772}$$

By the same reasoning, we have the general formula for the sum of a finite geometric series.

The formula for the sum of a finite geometric series is as follows:

$$a^{n-1} + \cdots + a^2 + a^1 + a^0 = \frac{(1 - a^n)}{(1 - a)} \text{ for } a \neq 1$$

Two-Compartment Model

The one-compartment model is more appropriate for an injection of a drug into the system than for a pill, which takes time to dissolve, be absorbed, and be distributed within the system. In such cases, a **two-compartment model** might yield better results. The first compartment represents the digestive system (stomach and/or intestines), while the second might indicate the blood, plasma, serum, or a particular organ that the drug targets. A flow pumps the drug from one compartment to the other in the model. One option for modeling the rate of change of absorption from the intestines to blood serum has the rate proportional to the amount of drug in the intestines. Probably a more accurate representation has the rate of change of absorption from the intestines to blood serum be proportional to the volume of the intestines and to the difference of the drug concentrations in the intestines and serum.

Although the one- or two-compartment model is appropriate for most situations, a drug dosage problem could benefit from more compartments in a **multicompartment model**. Various projects employ more than one compartment.

Quick Review Question 7

This question applies to the rate of change of absorption of a drug from the intestines to blood serum in a two-compartment model. Suppose k is a constant of proportionality; i and b are the masses of the drug in the intestines and blood serum, respectively; v_i and v_b are the volumes of the intestines and blood serum, respectively; c_i and c_b are the drug concentrations in the stomach and blood serum, respectively; and time t is in hours.

a. Give the differential equation for this rate if the rate of absorption is proportional to the mass of drug in the intestines.
b. In this case, give the units of k.
c. Give the differential equation for this rate if the rate of absorption is proportional to the volume of the intestines and to the difference of the drug concentrations in the intestines and blood serum.
d. In this case, give the units of k.

Exercises

1. Assuming that a quantity of a drug (Q) is $Q = Q_0e^{Kt}$, show that $K = -\ln(0.5)/t_{1/2}$, where $t_{1/2}$ is the drug's half-life.
2. a. In Figure 2.5.4, what are the units for *MEC* and *MTC*?

b. What are the units for *dosage*?
c. With a dosage of Dilantin being 100 mg, why is the value of *dosage* 100 * 1000?

3. Prove the general formula for the sum of a finite geometric series.

4. a. In Dilantin example, describe the effect a longer half-life has on *elimination_constant*.
b. Evaluate *elimination_constant* for $t_{1/2} = 7$ h.
c. Evaluate *elimination_constant* for $t_{1/2} = 22$ h.
d. Evaluate *elimination_constant* for $t_{1/2} = 42$ h.

5. a. Suppose a patient taking Dilantin decides for convenience to take 300 mg once a day instead of 100 mg every 8 h. Adjusting the model in *OneCompartDilantin*, determine the results of such a decision. Is the decision advisable?
b. Mathematically, determine the long-term value of Q_n, the quantity of Dilantin in the system immediately after the *n*th dose, assuming absorption of only (0.09)(300 mg).

6. a. Determine mathematically the quantity of Dilantin in the system immediately before the fifth dose. Use the same assumptions as in the section "Mathematics of Repeated Doses."
b. Determine mathematically the long-term value of the quantity of Dilantin in the system immediately before the *n*th dose.
c. Compare your answers to the values in *OneCompartDilantin*.

7. How should the one-dose aspirin example be adjusted to incorporate the weight of a male patient? About 65% to 70% of a male's body is liquid. Assume that 1 kilogram (kg) of body liquid has a volume of 1 L. Assume the patient has a mass of 90 kg (comparable to about 198 lb).

Projects

For additional projects, see Module 7.7, "Cardiovascular System—A Pressure-Filled Model."

1. Develop a two-compartment model for one dose of aspirin.

2. Develop a two-compartment model for aspirin, where someone with a headache takes three aspirin tablets and 2 h later takes two more aspirin tablets.

3. In attempt to raise the concentration of a drug in the system to the minimum effective concentration quickly, sometimes doctors give a patient a **loading dose**, which is an initial dosage that is much higher than the maintenance dosage. A loading dose for Dilantin is three doses—400 mg, 300 mg, and 300 mg 2 h apart. Twenty-four hours after the loading dose, normal dosage of 100 mg every 8 h begins. Develop a model for this dosage regime.

4. Develop a two-compartment model for Dilantin, where the rate of change of absorption from the stomach to the blood serum is proportional to the amount of drug in the stomach.

5. Develop a two-compartment model for Dilantin, where the rate of change of absorption from the stomach to the blood serum is proportional to the

volume of the stomach and to the difference of the drug concentrations in the stomach and serum. Assume the volume of the stomach is 500 mL.

6. Develop a two-compartment model for a pediatric dosage of Dilantin that includes the mass of the patient. The initial dose is 5 mg/kg per day in two or three equally divided doses. The maintenance dosage is usually 4 to 8 mg/kg per day.
7. Develop a model for vancomycin HCI, which is a treatment for serious infections by susceptible strains of methicillin-resistant staphylococci in penicillin-allergic patients. The drug is administered by IV infusion. The intravenous dose is usually 2 g divided either as 500 mg every 6 h or 1 g every 12 h, and the rate is no more than 10 mg/min or over a period of at least 50 min, whichever is longer. When kidney function is normal, multiple intravenous dosing of 1 g results in mean plasma concentrations of about 63 μg/mL immediately after infusion, 23 μg/mL in 2 h, and 8 μg/mL 11 h after infusion. In such patients, the mean elimination half-life from plasma is 4 to 6 h. The mean plasma clearance is approximately 0.058 L/kg/h (liter of drug per kilogram of patient mass each hour), while the mean renal clearance is about 0.048 L/kg/h (Hospira 2010). Thus, include the mass of the patient in the model.
8. Repeat Project 7 for patients with renal dysfunction in which the average half-life of elimination is 7.5 da (Hospira 2010).
9. Develop a model for Vancocin HCI in which the patient initially has normal kidney function (see Project 7). However, at the start of the third day, one of the patient's kidneys stops functioning; and the elimination rate becomes half its previous value. Consider using a step function.
10. Do Project 7 for children, where the dosage is 10 mg/kg every 6 h, and the rate of administration is over a period of at least 60 min (Hospira 2010).
11. Do Project 7 for neonates and young infants. The initial dose is 15 mg/kg. Thereafter, the dosage is 10 mg/kg every 12 h for neonates in their first week of life and afterward, up to age of 1 mo, every 8 h. Administration is more than 60 min (Hospira 2010).
12. Model drug dosage of aspirin for arthritis, where the initial dose is 3 g/da in divided doses. The dosage can be increased. Relief usually occurs at plasma levels of 20 to 30 mg per 100 mL. The plasma half-life of aspirin increases with dosage, so that a dose of 1 g has a half-life of about 5 h and a dose of 2 g has a half-life of about 9 h.
13. Considering the information about mass in Project 7, do any of the previous projects except one involving children or infants, accounting for the mass of a male patient.
14. By consulting a pharmacy reference or website, such as http://www.nlm.nih.gov/medlineplus/druginformation.html, obtain relevant information about some drug. Model the dosage of this drug.

Answers to Quick Review Questions

1. $K = -\ln(0.5)/3.2$ per hour = 0.22/h
2. *plasma_concentration* = *aspirin_in_plasma* / *plasma_volume*

3. *absorption_fraction* * (pulse of amount *dosage* beginning at *start* every *interval* hours), where the pulse function depends on the particular system dynamics tool
4. **a.** 200 mg
   b. (200 mg)(0.25) + 200 mg
   c. (200 mg)$(0.25)^2$ + (200 mg)(0.25) + 200 mg
   d. (200 mg)$(0.25)^3$ + (200 mg)$(0.25)^2$ + (200 mg)(0.25) + 200 mg
   e. (200 mg)$(0.25)^{n-1}$ + · · · + (200 mg)$(0.25)^2$ + (200 mg)(0.25) + 200 mg
5. **a.** (200 mg)$(1 - (0.25)^{10})/(1 - 0.25)$ = 266.67 mg
   b. (200 mg)$(1 - (0.25)^n)/(1 - 0.25)$ = (200 mg)$(1 - (0.25)^n)/(0.75)$
6. (200 mg)(1 – 0)/(0.75) = 266.67 mg
7. **a.** $db/dt = ki$
   b. 1/h
   c. $db/dt = k(v_i)(c_i - c_b)$
   d. 1/h

References

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