Digoxin is an inotropic agent primarily used to treat congestive heart failure (CHF) and atrial fibrillation. It is incompletely absorbed and once absorbed, a substantial fraction is cleared by the kidneys. In the acute care setting, historically digoxin loading doses of $\approx 1$ mg/70 kg were administered before the initiation of the usual maintenance dose of 0.125 to 0.25 mg/day. These loading and maintenance doses were from an era when target levels were 1 to 2 mcg/L and probably today doses of approximately one-half would be more common in patients with heart failure (see Therapeutic Plasma Concentrations, this chapter). Because it has a relatively long elimination half-life in adults, digoxin is given once daily. Dosage adjustments can be important for patients who are being converted from parenteral to oral therapy or vice versa; patients with renal impairment, CHF, or thyroid abnormalities; or patients who take amiodarone concurrently.

**THERAPEUTIC PLASMA CONCENTRATIONS**

Although there is considerable variation between patients, historically plasma digoxin concentrations of $\approx 1$ to 2 mcg/L (ng/mL) were generally considered to be within the therapeutic range.$^{1,2}$ Data now indicate that a therapeutic range of 0.5 to 0.9 mcg/L is indicated for patients with CHF.$^{3-6}$ This lower target range is based on the fact that most patients with left ventricular dysfunction do not demonstrate additional therapeutic benefits from higher digoxin concentrations and are at greater risk for toxicity with digoxin concentrations $\approx 1.2$ mcg/L.$^{7-9}$ For patients on digoxin for atrial fibrillation, the goal for digoxin is rate control.$^{10}$ Rate control is achieved by atrioventricular (AV) nodal blockade and may require higher digoxin concentrations. The use of pharmacokinetics to adjust the dosing regimen can reduce the incidence of digoxin toxicity.$^{2,11-13}$

**BIOAVAILABILITY (F)**

The bioavailability of digoxin tablets ranges from 0.5 to greater than 0.9. Many clinicians use a bioavailability of 0.7 to 0.8. A bioavailability of 0.7 will be used in this text as an estimate of the average bioavailability figures.
The elixir appears to have a bioavailability of approximately 0.8, and soft gelatin capsules of digoxin appear to be completely absorbed.\textsuperscript{16,17} The intravenous (IV) route of administration is also assumed to have 100% bioavailability.

St. John’s wort has been reported to reduce the bioavailability of digoxin by approximately 25%. It has been postulated that the interaction is with P-glycoprotein; however, other mechanisms (such as an induction of hepatic metabolism) have also been proposed.\textsuperscript{20–23} Similarly, various antibiotics have also been reported to alter the bioavailability of digoxin. In most cases the antibiotics appear to increase the bioavailability, supposedly by suppressing bacteria in the gastrointestinal tract that metabolize digoxin. Other mechanisms such as metabolism or renal excretion may reported in the literature.\textsuperscript{14,15}
also play a role in how some of the antibiotics increase the plasma concentrations of digoxin. The most common class of antibiotics that have been reported to increase digoxin concentrations are macrolides, but others such as itraconazole are not a surprise. Coadministration of cholestyramine has been reported to decrease the bioavailability of digoxin, and both cholestyramine and charcoal have been suggested as a treatment modality in patients who are digitalis toxic.

**VOLUME OF DISTRIBUTION (V)**

The average volume of distribution for digoxin is $\approx 7.3$ L/kg. This V is decreased in patients with renal disease (see Question 4).

\[
V_{\text{Digoxin}} (L) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(\text{Cl}_{\text{Cr}} \text{ in mL/min}) \quad [\text{Eq. 3.1}]
\]

In the above equation, the factors have been selected so that when creatinine clearance is in mL/min and weight is in kilograms, the unit of the calculated volume of distribution is L.

Digoxin V is also decreased in hypothyroid patients (see Question 12) and in patients who are taking quinidine (see Question 15). The volume of distribution is increased in hyperthyroid patients (see Question 12). In addition, the volume of distribution for digoxin in obese subjects appears to be more closely related to the non-obese or ideal body weight (IBW) than total body weight (TBW) (Table 3.1).

The manner in which digoxin is distributed in the body must be considered in the interpretation of plasma levels. The distribution of digoxin follows a two-compartment model (see Part I: Volume of Distribution: Two-Compartment Models). Digoxin first distributes into a small initial volume of distribution, $V_i$, consisting of plasma and other rapidly equilibrating tissues, and then distributes into a larger and more slowly equilibrating tissue compartment. The myocardium responds pharmacologically as though it were located in the larger more slowly equilibrating tissue compartment ($V_t$). Since plasma samples are obtained from $V_i$, plasma digoxin levels do not accurately reflect the drug's pharmacologic effects until the digoxin is completely distributed into both compartments. Serum concentrations of digoxin obtained before complete distribution are often misleading. Because the initial volume of distribution ($V_i$) of digoxin is relatively small ($\approx 1/10V_t$), high plasma concentrations are commonly reported immediately after a dose is administered. Because the heart behaves as though it were in the second or tissue compartment, the initial high serum concentrations that occur immediately after a dose are not reflective of either therapeutic or toxic potential of digoxin. Plasma concentrations are only meaningful when obtained after equilibration is complete (i.e., at least 4 hours after an IV dose or 6 hours after an oral dose). The
clinical effects of a dose, however, may be observed much sooner than 4 to 6 hours because the distribution half-life $t_{1/2}$ is only about 35 minutes.\(^{35}\) After approximately two $t_{1/2}$'s (i.e., 1 hour), the myocardium experiences the effects of 75% of an IV dose. However, a plasma sample taken at this time would be misleadingly high because the remaining 25% of the dose which is not yet distributed out of $V_i$ would produce a plasma concentration that is high relative to that which would be observed once equilibrium between the two compartments is complete (Fig. 3.1).

### CLEARANCE (Cl)

Digoxin clearance varies considerably among individuals and should be estimated for each patient. Total digoxin clearance ($Cl_t$) is the sum of its metabolic ($Cl_m$) and renal ($Cl_r$) clearances as illustrated by Equation 3.2:

$$Cl_t = Cl_m + Cl_r$$ \[Eq. 3.2\]
FIGURE 3.1  A theoretical two-compartment model for digoxin. The myocardium or target organ behaves as though it were in $V_i$ and therefore responds to the theoretical digoxin concentration in $V_i$. Following complete distribution, the concentrations in $V_i$ and $V_t$ are assumed to be equal and the pharmacologic effect maximal. Note that the initial volume of distribution ($V_i$) is much smaller than the tissue volume of distribution ($V_t$); therefore, the digoxin concentrations are very high following an initial IV dose. (A) depicts digoxin concentration immediately following an IV bolus. All of the drug is in $V_i$ and the plasma concentration is 10 mcg/L, but no digoxin is in the tissue compartment $V_t$; therefore, no effect is present. (E) depicts complete digoxin distribution. Note that the two compartments are in equilibrium and that the digoxin concentration in both $V_i$ and $V_t$ is assumed to be equal (i.e., 1 mcg/L). At this point, the plasma level accurately reflects the concentration in the tissue compartment and the potential for drug effect. (B–D) depict the relative digoxin concentrations in $V_i$ and $V_t$ after one, two, and three distribution half-lives ($t/H_1/2$). After three $t/H_1/2$s, 87.5% of the pharmacologic effect is achieved; however, it is still much too early to obtain a digoxin level, because the concentration in $V_i$ is more than 100% higher than the final equilibrated concentration.
In healthy individuals, the metabolic clearance of digoxin is \( \approx 0.57 \) to 0.86 mL/kg/min, and the renal clearance is approximately equal to or a little less than creatinine clearance. CHF reduces the metabolic clearance of digoxin to about one-half its usual value and may reduce the renal clearance slightly as well\(^{15,36–38}\) [also see Part I: Clearance (Cl)].

Using the data from Sheiner et al.,\(^36\) the total digoxin clearance in mL/kg/min can be calculated in patients with and without CHF as follows:

\[
\text{Total } Cl_{\text{digoxin}} \text{ (mL/min)} = \begin{cases} 
0.33 \text{ mL/kg/min} \times \text{Weight in kg} + 0.9 \times Cl_{\text{Cr}, \text{in mL/min}} & \text{(Patients with CHF)} \\
0.8 \text{ mL/kg/min} \times \text{Weight in kg} + Cl_{\text{Cr}, \text{in mL/min}} & \text{(Patients without CHF)}
\end{cases}
\]

Creatinine clearance can be estimated from the patient’s serum creatinine using Equations 3.5 and 3.6 below.

\[
Cl_{\text{Cr}}, \text{for males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCR}_{ss})} \quad \text{[Eq. 3.5]}
\]

\[
Cl_{\text{Cr}}, \text{for females (mL/min)} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCR}_{ss})} \quad \text{[Eq. 3.6]}
\]

Note that in the above equations the units do not cancel; however, the values of 140 in the numerator and 72 in the denominator result in a creatinine clearance that has a unit value of mL/min. Also, in obese subjects, creatinine clearance is normally calculated using IBW. The most common method of estimating IBW is as follows:

\[
\text{Ideal Body Weight for males in kg} = 50 + (2.3)(\text{Height in inches} - 60) \quad \text{[Eq. 3.7]}
\]

\[
\text{Ideal Body Weight for females in kg} = 45 + (2.3)(\text{Height in inches} - 60) \quad \text{[Eq. 3.8]}
\]

Similarly, IBW should also be used to estimate digoxin clearance (renal and metabolic) in obese patients. These and other methods for estimating digoxin clearance are illustrated in the questions later in this chapter. See Table 3.1 for common factors that alter digoxin clearance. It is the authors’ opinion that \( Cl_{\text{digoxin}} \) (Patients with CHF) equation is the more conservative approach and is recommended to use even in patients without a diagnosis of heart failure.
HALF-LIFE ($t_{1/2}$)

The half-life for digoxin is approximately 2 days in patients with normal renal function. In anephric patients, the half-life increases to approximately 4 to 6 days. This increase in the digoxin half-life is less than might be expected based on the reduction in clearance because the volume of distribution is also decreased in patients with diminished renal function (see Question 4 and Equations 3.1 and 3.17).

TIME TO SAMPLE

Plasma samples for routine digoxin level monitoring are ideally obtained 7 to 14 days after a maintenance regimen is initiated or changed. This delay in obtaining digoxin samples helps to ensure that steady state has been attained on the current dosing regimen. Samples may be obtained before steady state is achieved, but caution should be used in assessing the relationship between the current dosing regimen and the eventual steady-state concentration. In addition, in patients with end-stage renal disease it may take 15 to 20 days to achieve steady state because of the prolonged half-life.

Plasma samples obtained within 24 hours of an initial loading dose may help confirm the relationship between the digoxin plasma concentration and pharmacologic response or establish the apparent volume of distribution. When plasma samples are obtained this early, however, they are of little value in evaluating the maintenance regimen.

Once steady state has been achieved, routine plasma samples for digoxin monitoring should be drawn just before the next dose (trough levels); however, any sampling time that avoids the distribution phase (at least 4 hours following an IV dose or 6 hours following an oral dose) is acceptable.

Patients taking digoxin who are to be given amiodarone are likely to require digoxin plasma level monitoring to determine the extent to which the digoxin pharmacokinetics is altered (see Question 14). Although quinidine is rarely used, it is the classic digoxin drug–drug interaction. This interaction is especially troublesome since it results in a rapid rise in digoxin concentration (due to V) and sustained rise (due to Cl). With quinidine, there is the possibility that digoxin concentrations will fluctuate within a quinidine dosing interval. Consequently, in patients taking quinidine and digoxin, samples should be obtained at a time that corresponds to the trough of the quinidine dosing interval and that also avoids the distribution phase for digoxin. There have also been data suggesting fluctuations in digoxin concentrations with amiodarone.

The time course for the expected change in digoxin concentrations will depend on whether the drug interaction alters digoxin volume of distribution or clearance or both. In addition, the time required for the interacting drug to accumulate and effect a change in digoxin pharmacokinetic
parameter(s) should also be considered. When drugs are added to a patient’s therapy that can alter the disposition of digoxin, the nature of the drug interaction and expected change in half-life should provide some clues as to the time course and extent of the expected change in the digoxin concentration.

**QUESTION #1.** *Estimate a digoxin loading dose that will produce a plasma concentration of 0.8 mcg/L for a 50-year-old, 70-kg patient with a creatinine clearance of 80 mL/min being treated for CHF.*

Estimating a loading dose requires knowledge of the volume of distribution of the drug. Although one might consider using the average literature value for the V of digoxin (7.3 L/kg), a more conservative and/or logical approach would be to use patient-specific parameter estimates. Taking into consideration the patient’s renal function ($\text{Cl}_{\text{Cr}} = 80 \text{ mL/min}$), the patient’s volume can be calculated using Equation 3.1.

$$V_{\text{Digoxin}} (\text{L}) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(\text{Cl}_{\text{Cr}} \text{ in mL/min})$$
$$= (3.8 \text{ L/kg})(70 \text{ kg}) + (3.1)(80 \text{ mL/min})$$
$$= 266 \text{ L} + 248 \text{ L}$$
$$= 514 \text{ L}$$

Then using Equation 3.9, the loading dose can be calculated as follows:

$$\text{Loading Dose} = \frac{(V)(C)}{(S)(F)} \quad \text{[Eq. 3.9]}$$

$$= \frac{(514 \text{ L})(0.8 \text{ mcg/L})}{(1)(0.7)}$$
$$= \frac{411 \text{ mcg}}{0.7}$$
$$= 587 \text{ mcg or } \approx 500 \text{ mcg}$$

In this case, it was assumed that the loading dose was to be given orally as tablets; therefore, a bioavailability (F) of 0.7 was used. If the loading dose were to be given intravenously, F would have been 1 and the calculated loading dose would have been 411 mcg ($\approx 375 \text{ mcg}$). In both cases, S is 1 because digoxin is not administered as a salt.

Loading doses of digoxin are not usually given to patients with CHF in the ambulatory care setting. Loading doses may be used in the acute care
setting. The difference may be the level of acuity, the ability to closely monitor the patient during the loading process, and perhaps the economic pressures that force clinicians to achieve therapeutic goals as quickly as possible.

QUESTION #2. How should this loading dose be divided, and what would be an appropriate interval between doses?

Loading doses of digoxin are almost always administered in divided doses so that the patient can be evaluated for toxicity and efficacy in the course of receiving the total loading dose. If the patient appears to develop toxicity or is therapeutically controlled, the remainder of the calculated loading dose is withheld. The usual procedure is to give one-half of the calculated loading dose initially, followed by one-fourth in 6 hours; the remaining one-fourth is administered 6 hours after the second dose. However, doses are divided based on practically, taking into consideration that oral tablets are available as 125 and 250 mcg.

Six hours is the usual interval between doses because it is the approximate time to ensure that the oral dose of digoxin has been absorbed and distributed into the myocardium. Even following an IV injection, 2 to 4 hours are required for a single dose of digoxin to exhibit its full effect. In an emergency, when it is important to rapidly achieve pharmacologic effects, clinical decisions about efficacy/toxicity can be made 1 to 2 hours following an IV dose. This is because the majority of digoxin will have been distributed into the tissue compartment and ≈ 75% to 90% of the pharmacologic effect can be evaluated at this time. It would still be too soon, however, to evaluate plasma concentrations due to the distribution phase (see Fig. 3.1 and Part I: Volume of Distribution (V): Loading Dose). In this example, the loading dose of 500 mcg would be administered as 250 mcg and then two additional doses of 125 mcg each separated by 6 hours. It could also be given as two doses of 250 mcg separated by 6 hours. Again, the reason for dividing the dose is so that the patient can be evaluated for efficacy or toxicity before the next portion of the loading dose is administered.

QUESTION #3. R.J. is a 50-year-old, 70-kg man with CHF and has a serum creatinine of 1 mg/dL. Calculate a maintenance dose that will achieve an average plasma digoxin concentration of 0.8 mcg/L.

Since the objective is to achieve an average digoxin concentration of 0.8 mcg/L at steady state (Css ave), Equation 3.10 can be used to calculate the maintenance dose.

\[
\text{Maintenance Dose} = \frac{(Cl)(C_{\text{ss ave}})(\tau)}{(S)(F)} \\
\text{[Eq. 3.10]}
\]
When using Equation 3.10, it is important to ensure that the units will cancel properly and are easy to use. In the case of digoxin, the concentrations are usually reported as mcg/L, and, therefore, the digoxin dose should be expressed as mcg. Given that the dosing interval (\( t \)) is usually expressed in days, the clearance should be expressed as L/day. If the dosing interval is thought of as hours (e.g., 24 hours), then clearance would be in the units of L/hr. Therefore, assuming the dosing interval (\( t \)) to be 1 day, the bioavailability (F) 0.7 for oral tablets, and the fraction of the dose that is digoxin (S) to be 1, the digoxin clearance (Cl) is the only remaining parameter to be calculated.

The digoxin clearance for R.J. can be determined by use of Equation 3.4.

\[
\text{Total } \text{Cl}_{\text{Digoxin}} \text{ (mL/min)} = (0.33 \text{ mL/kg/min})(\text{Weight in kg}) + (0.9)(\text{Cl}_{\text{Cr}} \text{ in mL/min})
\]

Although the creatinine clearance (\( \text{Cl}_{\text{Cr}} \)) for R.J. is unknown, it can be estimated easily from his serum creatinine by use of Equation 3.5, assuming all the criteria for the use of this formula are met (i.e., serum creatinine is at steady state, and R.J.’s muscle mass is average for a 50-year-old man).

\[
\text{Cl}_{\text{Cr}} \text{ for males} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{Scr}_{ss})}
\]
\[
= \frac{(140 - 50 \text{ years})(70 \text{ kg})}{(72)(1 \text{ mg/dL})}
\]
\[
= 87.5 \text{ mL/min}
\]

This creatinine clearance can now be used in Equation 3.4 to estimate R.J.’s total digoxin clearance.

\[
\text{Total } \text{Cl}_{\text{Digoxin}} \text{ (mL/min)} = (0.33 \text{ mL/kg/min})(\text{Weight in kg}) + (0.9)(\text{Cl}_{\text{Cr}} \text{ in mL/min})
\]
\[
= (0.33 \text{ mL/kg/min})(70 \text{ kg}) + (0.9)(87.5 \text{ mL/min})
\]
\[
= 23.1 \text{ mL/min} + 78.8 \text{ mL/min}
\]
\[
= 101.9 \text{ mL/min}
\]

The digoxin clearance is then used to calculate the maintenance dose. Since the maintenance dose is commonly expressed in mcg/day, the clearance in mL/min can be converted to L/day by multiplying the value
by the number of minutes per day (1440 min/day) and dividing by the number of milliliters per liter (1000 mL/L) as shown below:

\[
\text{Cl (L/day)} = (\text{Cl as mL/min}) \times \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right)
\]

\[\text{Eq. 3.11}\]

\[
= (101.9 \text{ mL/min}) \times \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right)
\]

\[
= 146.7 \text{ L/day}
\]

The maintenance dose can now be calculated using Equation 3.10.

\[
\text{Maintenance Dose} = \frac{(\text{Cl})(\text{Css ave})(\tau)}{(S)(F)}
\]

\[
= \frac{(146.7 \text{ L/day})(0.8 \text{ mcg/L})(1 \text{ day})}{(1)(0.7)}
\]

\[
= \frac{117.4 \text{ mcg}}{0.7}
\]

\[
= 168 \text{ mcg}
\]

\[
= 0.168 \text{ mg}
\]

One could elect to give either 0.125 mg every day or 0.125 and 0.25 mg on alternate days for an average dose of 0.1875 mg/day. Given that the 0.168 mg/day dosing rate is only an estimate, most clinicians would probably give 0.125 mg/day since R.J. is being treated for CHF and a lower digoxin concentration would be desirable.

**QUESTION #4. If the patient in Question 1 had a serum creatinine of 5 mg/dL, would the estimated loading dose have been different?**

For a number of years it was assumed that renal function influenced only the clearance of digoxin. A number of studies have indicated, however, that patients with decreased creatinine clearance also have a decreased volume of distribution for digoxin.\textsuperscript{31,36,43}

The relationship between volume of distribution (V), plasma concentration (C), and amount of drug in the body is described by Equation 3.12 below.

\[
V = \frac{\text{Amount of drug in the body}}{C}
\]

\[\text{Eq. 3.12}\]
In uremic patients, it is assumed that digoxin is displaced from the tissue compartment. As a result, C is higher and V is smaller.

\[ \downarrow V = \frac{\text{Amount of drug in the body}}{\uparrow C} \]

There is some controversy about the significance of this tissue displacement of digoxin. Myocardial digoxin concentrations at any given plasma digoxin level are lower relative to their non-uremic counterparts. Consequently, some have suggested that no change in the loading dose is necessary. Almost all clinicians today assume that the higher the digoxin concentrations, the greater the drug effect, both therapeutic and toxic. Therefore, they generally target digoxin concentrations, in renal failure patients, that are similar to or lower than the concentrations for patients with normal renal function. Many clinicians, however, do not recognize that the volume of distribution is likely to be reduced in patients with significant renal dysfunction and therefore do not always make the appropriate initial reduction in digoxin loading doses.

Because very little digoxin is bound to plasma proteins, only about 10%, a change in the desired therapeutic plasma concentration is unlikely to result from plasma protein displacement [see Part I: Desired Plasma Concentration (C): Protein Binding].

There are a number of ways to estimate the volume of distribution for digoxin in a patient with decreased renal function; Equation 3.1 is most commonly used. It is the authors' opinion that this equation appears to be useful over a wider range of creatinine clearance values, especially in young adults with good renal function.

\[ V_{\text{Digoxin}} (L) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(\text{Cl}_{\text{Cr}} \text{ in mL/min}) \]

Equation 3.1 is for a specific patient; therefore, the estimated \( \text{Cl}_{\text{Cr}} \) should be expressed in mL/min for that patient. The volume of distribution for digoxin in uremic patients can vary considerably. For this reason, the values obtained from this equation and the calculated loading dose should be considered only rough estimates.

Using Equation 3.5, the patient's creatinine clearance is determined to be approximately 20 mL/min. Note that we are assuming the patient is not receiving any type of dialysis, as dialysis invalidates Equations 3.5 and 3.6.

\[ \text{Cl}_{\text{Cr}} \text{ for males} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCr}_{\text{ss}})} \]

\[ = \frac{(140 - 50 \text{ yrs})(70 \text{ kg})}{(72)(5 \text{ mg/dL})} \]

\[ = 17.5 \text{ mL/min or } \approx 20 \text{ mL/min} \]
Using this value in Equation 3.1, the estimated volume of distribution would be 328 L.

\[ V_{\text{Digoxin}}(L) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(\text{Cl}_{\text{Cr}} \text{ in mL/min}) \]
\[ = (3.8 \text{ L/kg})(70 \text{ kg}) + (3.1)(20 \text{ mL/min}) \]
\[ = (266 \text{ L}) + (62 \text{ L}) \]
\[ = 328 \text{ L} \]

If the volume of distribution is assumed to be approximately 330 L (as calculated from Equation 3.1), the estimated oral loading dose using Equation 3.9 would be approximately 375 mcg if a digoxin concentration of 0.8 mcg/L was desired.

\[
\text{Loading Dose} = \frac{(V)(C)}{(S)(F)}
\]
\[ = \frac{(330 \text{ L})(0.8 \text{ mcg/L})}{(1)(0.7)} \]
\[ = \frac{264 \text{ mcg}}{0.7} \]
\[ = 377 \text{ mcg} \quad \text{or} \quad \approx 375 \text{ mcg} \]

Again, as in Question 1, S and F are assumed to be 1 and 0.7, respectively. The total loading dose should be divided and administered as described in Question 2. Again, the loading dose is divided so that the patient’s response can be evaluated between each of the partial loading doses. This is to guard against the possibility that the patient’s volume of distribution is smaller than anticipated or that the patient is more sensitive to the pharmacologic effects than expected. One should also consider the possibility that the volume of distribution may be much larger than expected and additional doses may have to be administered to achieve the desired plasma concentration or pharmacologic effect.

It should be pointed out that dosing to a therapeutic endpoint is common in patients with atrial fibrillation in whom the therapeutic endpoint is increased AV nodal blockade and a decrease in ventricular rate. Patients with CHF, however, are more difficult to evaluate, and it is much less common to increase the loading dose beyond the initial targeted amount and in many cases with heart failure, loading doses of digoxin may not be appropriate. Of course, in either atrial fibrillation or CHF, if toxicity is observed, the process of administering the loading dose would be stopped.

**QUESTION #5.** Estimate the daily dose that would maintain the average digoxin concentration at 0.8 mcg/L in this same 70-kg, 50-year-old patient with a serum creatinine of 5 mg/dL.
As in Question 3, Equation 3.10 would be used to estimate the maintenance dose.

\[
\text{Maintenance Dose} = \frac{(Cl)(Css \ ave)(\tau)}{(S)(F)}
\]

Using the creatinine clearance estimate of 20 mL/min (see Question 4), the digoxin clearance can be estimated using Equation 3.4 (for CHF).

\[
\text{Total } Cl_{\text{digoxin}} (\text{mL/min}) = (0.33 \text{ mL/kg/min})(\text{Weight in kg}) + (0.9)(Cl_{\text{Cr}} \text{ in mL/min})
\]
\[
= (0.33 \text{ mL/kg/min})(70 \text{ kg}) + (0.9)(20 \text{ mL/min})
\]
\[
= 23.1 \text{ mL/min} + 18 \text{ mL/min}
\]
\[
= 41.1 \text{ mL/min}
\]

The digoxin clearance can be converted from mL/min to L/day as described in Question 3 using Equation 3.11.

\[
Cl (\text{L/day}) = (Cl \text{ as mL/min}) \left(\frac{1440 \text{ min/day}}{1000 \text{ mL/L}}\right)
\]
\[
= (41.1 \text{ mL/min}) \left(\frac{1440 \text{ min/day}}{1000 \text{ mL/L}}\right)
\]
\[
= 59.2 \text{ L/day}
\]

Again, assuming S to be 1 and F to be 0.7 for digoxin tablets, the approximate daily dose (calculated using Equation 3.10) would be 68 mcg/day or 0.068 mg/day.

\[
\text{Maintenance Dose} = \frac{(Cl)(Css \ ave)(\tau)}{(S)(F)}
\]
\[
= \frac{(59.2 \text{ L/day})(0.8 \text{ mcg/L})(1 \text{ day})}{(1)(0.7)}
\]
\[
= \frac{47.4 \text{ mcg}}{0.7}
\]
\[
= 67.7 \text{ mcg of digoxin each day}
\]

Again this dose is not convenient, and most clinicians would probably administer either 0.125 mg every other day or one-half of a 0.125-mg tablet.
(0.0625 mg) every day as digoxin comes in 0.125-mg tablets, and this is a reasonable dose for patients with significantly diminished renal function.

**QUESTION #6. Assume that the patient described above can take nothing by mouth and must be converted to daily intravenous doses of digoxin. Assume he was taking one-half of a 0.125-mg tablet (0.0625 mg) each day. Calculate an equivalent intravenous dose.**

If the bioavailability of digoxin is assumed to be 0.7, the equivalent IV dose would be 0.044 mg/day as calculated from Equations 3.13 and 3.14.

\[
\text{Amount of Drug Absorbed} = (F)(\text{Dose}) \quad [\text{Eq. 3.13}]
\]

\[
= (0.7)(0.0625 \text{ mg})
\]

\[
= 0.044 \text{ mg}
\]

\[
\frac{\text{Dose of New Dosage Form}}{\text{Dose of Old Dosage Form}} = \frac{\text{Amount of Drug Absorbed or Reaching the Systemic Circulation}}{F \text{ of New Dosage Form}} \quad [\text{Eq. 3.14}]
\]

\[
= \frac{0.044 \text{ mg}}{1}
\]

\[
= 0.044 \text{ mg} \quad \text{or} \quad 0.05 \text{ mg}
\]

If the dose is not adjusted to account for the increased bioavailability of the IV dose, higher steady-state digoxin concentrations would eventually be achieved [see Part I: Elimination Rate Constant (K) and Half-Life (t₁/₂) and Fig. 16]. Also note that the dose might be rounded to 0.05 mg, which would correspond to 0.4 mL of the injectable (0.125 mg/mL). The dose of 0.05 mg would be expected to achieve a Css ave of < 1 mcg/L. This could be further evaluated by calculating Css ave using Equation 3.20 (see Question 9) or by comparing the ratio of the old and new doses to the old Css ave.

\[
\frac{0.05 \text{ mg}}{0.044 \text{ mg}}(0.8 \text{ mcg/L}) = 0.91 \text{ mcg/L}
\]
B.G., a 62-year-old, 50-kg woman, with atrial fibrillation was admitted to the hospital for possible digoxin toxicity. Her serum creatinine was 3 mg/dL, and her dosing regimen at home had been 0.25 mg of digoxin daily for many months. The digoxin plasma concentration on admission was 3 mcg/L. How long will it take for the digoxin concentration to fall from 3 to 1.5 mcg/L?

The answer to this question requires knowledge of the digoxin half-life \( t_{1/2} \) or the elimination rate constant \( K \), both of which are dependent on the clearance and volume of distribution for digoxin in B.G. The relationship between these parameters is described by Equations 3.16 and 3.17.

\[
K = \frac{Cl}{V} \quad [\text{Eq. 3.16}]
\]

\[
t_{1/2} = \frac{(0.693)(V)}{Cl} \quad [\text{Eq. 3.17}]
\]

Three basic steps are required to solve this problem: (1) estimate digoxin clearance, (2) estimate the \( V \) for digoxin, and (3) calculate the half-life.

**Step 1.** Estimate clearance. We can estimate digoxin clearance as illustrated in previous questions by first determining B.G.’s creatinine clearance through the use of Equation 3.6 for women.

\[
Cl_{Cr} \text{ for females} = (0.85) \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCR}_{ss})}
\]

\[
= (0.85) \frac{(140 - 62 \text{ yrs})(50 \text{ kg})}{(72)(3 \text{ mg/dL})}
\]

\[
= 15.3 \text{ mL/min}
\]

This estimation of \( Cl_{Cr} \) then can be used to determine the digoxin clearance by use of Equation 3.4 (for CHF), which is the more conservative approach.

\[
\text{Total } Cl_{\text{digoxin}} \text{ (mL/min)} = (0.33 \text{ mL/kg/min})(\text{Weight in kg}) + (0.9)(Cl_{Cr} \text{ in mL/min})
\]

\[
= (0.33 \text{ mL/kg/min})(50 \text{ kg}) + (0.9)(15.3 \text{ mL/min})
\]

\[
= 16.5 \text{ mL/min} + 13.8 \text{ mL/min}
\]

\[
= 30.3 \text{ mL/min}
\]
Converted to L/day by Equation 3.11, the digoxin clearance would be 43.6 L/day.

\[
Cl (L/day) = (Cl as mL/min) \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right) \\
= (30.3 \text{ mL/min}) \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right) \\
= 43.6 \text{ L/day}
\]

A more patient-specific approach would be to use the patient’s dosing history and the observed digoxin concentrations to derive a patient-specific digoxin clearance. If one assumes that the digoxin half-life is significantly longer than the dosing interval, the observed digoxin plasma concentration should closely reflect the average concentration at steady state; from this the digoxin clearance can be calculated [i.e., this level is relatively independent of the volume of distribution; see Part I: Elimination Rate Constant (K) and Half-Life (t\text{1/2}): Clinical Application of Elimination Rate Constant (K) and Half-life (t\text{1/2}): Dosing Interval \((\tau)\)]. Therefore, the observed digoxin concentration can be used in Equation 3.18 to estimate B.G.’s clearance.

\[Eq. 3.18\]

\[
Cl = \frac{(S)(F)(Dose/\tau)}{Css \text{ ave}}
\]

This higher-than-average digoxin clearance of 58.3 L/day calculated from B.G.’s dosing history and observed plasma level while different from population average is not unreasonable for this 50-kg, 62-year-old woman with a serum creatinine of 3 mg/dL. Given the usual uncertainty in predicting clearance, we would expect most of our patients to have an observed clearance that is between one-half to two times the predicted value. Actual clearance values outside of this range should be evaluated carefully to determine if the patient is substantially different from the assumed pharmacokinetic population. In most cases, it is more likely that we have made an error in our calculations or in our assumptions (see Question 9).

Step 2. Calculate B.G.’s digoxin volume of distribution. Because our only digoxin plasma concentration represents something approaching \(Css \text{ ave}\), we cannot derive a patient-specific volume and will have to rely on a literature estimate that we can calculate using Equation 3.1.

\[V_{\text{Digoxin}} (L) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(Cl_{Cr} \text{ in mL/min})\]

\[= (3.8 \text{ L/kg})(50 \text{ kg}) + (3.1)(15.3 \text{ mL/min})\]

\[= 190 \text{ L} + 47 \text{ L}\]

\[= 237 \text{ L}\]
Step 3. The digoxin elimination rate constant and half-life for B.G. can now be estimated from Equations 3.16 and 3.17 using our patient-specific digoxin clearance and the literature estimate of volume of digoxin.

\[
K = \frac{Cl}{V} = \frac{58.3 \text{ L/day}}{237 \text{ L}} = 0.246 \text{ day}^{-1}
\]

\[
t\frac{1}{2} = \frac{(0.693)(V)}{Cl} = \frac{(0.693)(237 \text{ L})}{58.3 \text{ L/day}} = 2.8 \text{ days}
\]

We now have the data necessary to answer the original question. The time required for B.G.’s plasma concentration of digoxin to fall from 3 to 1.5 mcg/L (one-half the original level) is one half-life, or 2.8 days.

In most situations the calculations are not this easy (i.e., one \(t\frac{1}{2}\)). When the time of decay is not obvious, the time required for the plasma concentration to fall to a predetermined level can be calculated using Equation 3.19.

\[
t = \frac{\ln\left(\frac{C_1}{C_2}\right)}{K}
\]

In the above equation, \(t\) represents the time required for \(C_1\), the initial higher concentration, to decay to \(C_2\), the lower concentration, for any given elimination rate constant \(K\). Of course, the equation assumes a first-order decay process (i.e., Cl and V are constants) and that no drug is administered or absorbed between the concentrations \(C_1\) and \(C_2\) [see Part I: Elimination Rate Constant (K) and Half-Life (\(t\frac{1}{2}\)): Elimination Rate Constant (K)].

\[
t = \frac{\ln\left(\frac{3 \text{ mcg/L}}{1.5 \text{ mcg/L}}\right)}{0.246 \text{ day}^{-1}} = \frac{\ln(2)}{0.246 \text{ day}^{-1}} = \frac{0.693}{0.246 \text{ day}^{-1}} = 2.8 \text{ days}
\]
QUESTION #8. Calculate a daily dose that will maintain B.G.’s average digoxin plasma concentration at 1.5 mcg/L.

Using the clearance value of 58.3 L/day calculated from B.G.’s data, and assuming S, F, and τ to be 1, 0.7, and 1 day, respectively, the new maintenance dose can be estimated using Equation 3.10.

\[
\text{Maintenance Dose} = \frac{(Cl)(Css_\text{ave})(\tau)}{(S)(F)}
\]

\[
= \frac{(58.3 \text{ L/day})(1.5 \text{ mcg/L})(1 \text{ day})}{(1)(0.7)}
\]

\[
= 87.5 \text{ mcg}
\]

\[
= 0.7
\]

\[
= 125 \text{ mcg}
\]

or 0.125 mg digoxin daily

Alternatively, the previous maintenance dose could be adjusted proportionately to the desired change in steady-state plasma level because clearance and other factors were assumed to be constant. Therefore, if the new steady-state level is to be one-half of the previous value, the new maintenance dose should be one-half the previous maintenance dose.

QUESTION #9. N.W., a female who has been taking the same dose of digoxin for 15 days, is seen in the clinic and is found to be doing well clinically. A digoxin plasma level drawn on the morning of her visit is 2.4 mcg/L. What are the possible explanations for this elevated serum digoxin concentration?

Because this serum digoxin concentration theoretically represents an average steady-state concentration (Css ave), one must evaluate each of the factors that could alter steady state. The relationship of each of these factors to the average steady-state concentration may be seen by studying Equation 3.20.

\[
\text{Css ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl}
\]  \[\text{[Eq. 3.20]}\]

1. (S)(F). N.W. may be absorbing more than 70% (average bioavailability) from the oral dosage form. Since there are no salt forms of digoxin, S should be 1. Whereas an increase in F could account for some of the elevated digoxin concentration, F alone could only increase the digoxin by a factor of 1.4 (i.e., 1/0.7).

2. Dose. N.W. may be taking more than the prescribed dose, although taking less than the prescribed dose is more common. Of course,
each tablet may not contain the labeled amount. In some cases, the tablets may be larger than normal and on physical inspection may show that, however, if the tablet is standard size but contains more drug, this would be impossible to tell. While given current manufacturing standards this is not high on the list of possibilities, clinicians need to watch for US Food and Drug Administration (FDA) and manufacturer alerts for this type of information.

3. N.W. may be taking the proper dose more often than prescribed.
4. Cl. N.W.’s clearance or ability to eliminate the drug may be less than we estimated. We expect most patients to be within the range of one-half to two times the expected clearance values (i.e., two times to one-half the expected Css ave).
5. Css ave. The assay could be in error. Interfering substances may be present, or the plasma level may have been drawn during the distribution phase of the drug.

Plasma levels obtained during the distribution phase of digoxin are higher than anticipated because digoxin is absorbed from the gastrointestinal tract into the plasma and \( V_i \) faster than it is distributed into the tissues or \( V_t \). Since the myocardium responds to digoxin as though it were in the tissue compartment (\( V_t \)), plasma levels obtained before distribution is complete do not correlate with pharmacologic effects of the drug.\(^{12,34}\) Digoxin plasma levels should be obtained just before the next dose is given, or at least 6 hours after the oral digoxin dose\(^ {34} \) (see the discussion on Digoxin Volume of Distribution (V) and Time to Sample, this chapter).

**QUESTION #10. Outline a reasonable plan to determine the cause of N.W.’s higher-than-predicted digoxin level.**

1. Ask N.W. when that day’s digoxin dose was taken relative to when the blood sample was obtained.
2. Determine N.W.’s adherence to the digoxin regimen. This is difficult but must be attempted through a history or pill count.
3. Determine whether any drugs interfered with the digoxin assay. Literature reports of interference by drugs having a steroid nucleus are applicable only to the antibody assay used in the particular report and to the assay techniques and may not apply to the assay used to determine N.W.’s digoxin plasma level. Therefore, the laboratory measuring the serum level would have to be contacted about the possibility of assay interference.\(^ {38,50–54} \) While falsely elevated digoxin concentrations are most commonly reported and should be considered in N.W.’s case, interfering substances may also result in a falsely decreased assay measurement.\(^ {53} \)

Patients with poor renal function and newborn infants accumulate an endogenous digoxin-like compound that can produce a
falsely elevated or false-positive digoxin assay result. The usual range of the false-positive reaction is from 0.1 to > 1 mcg/L, with an average of ∼0.1 to 0.4 mcg/L. This interference does not appear to represent a cross-reactivity with digoxin metabolites, since it has been observed in patients who have never received digoxin. The assay interference in these patients with apparent renal dysfunction is assay-specific and is much more significant for some assays than for others. Assays continue to change so clinicians need to check on which assays are used at their site and what can affect assay accuracy and specificity.

4. Reschedule a second digoxin plasma level, but be certain that it is drawn at least 6 hours after a dose. Preferably, obtain the sample in the morning before the daily dose is taken.

5. Evaluating N.W.’s CI and F is difficult and costly because such evaluation would require hospitalization. Furthermore, it would only result in the obvious conclusion that the dose should be reduced if, in fact, the dosage level was too high. This approach would only be used under the most unusual circumstances. In addition, F could only increase from the assumed 0.7 to a maximum of 1 and could not, by itself, account for the observed elevation in Css ave.

**QUESTION #11.** T.S., a female receiving digoxin 0.25 mg/day for several months, has a reported digoxin plasma concentration of 0.3 mcg/L. Her CHF is poorly controlled. What is the most probable explanation?

The answer to this question is essentially the same as that to Question 9; the same factors should be considered. T.S. should be asked if she is receiving the same brand or dosage form of digoxin because bioavailability may vary between products, however, with today’s standards, not likely an issue. Also check if T.S. has conditions that accelerate intestinal transit time (e.g., small bowel resection), which can decrease digoxin absorption. T.S. also could be one of the very rare patients who has a large metabolic and renal clearance for digoxin. As indicated in Question 10, there are some drugs that result in a falsely decreased digoxin assay result and that possibility should also be considered. The most likely explanation for the subtherapeutic digoxin concentrations is noncompliance with the prescribed regimen.

**QUESTION #12.** In 1966, Doherty and Perkins evaluated the pharmacokinetics of digoxin in hyperthyroid, hypothyroid, and euthyroid patients. Figure 3.2 is a representation of one of the graphs from this study. Using the graph, discuss the implications of thyroid disease on the loading dose, maintenance dose, and the time required to reach
steady state relative to the euthyroid state. Assume that the sameCss
ave is desired in all patients.

Loading Dose. Since hypothyroid patients have higher plasma levels
following a single loading dose, they must have a decreased apparent vol-
ume of distribution. Therefore, a decrease in the loading dose may be ap-
propriate. Hyperthyroid patients have lower plasma levels and would be
expected to require larger loading doses because of a larger volume of dis-
tribution. In addition, atrial fibrillation is one of the common cardiac ar-
rhythmias in hyperthyroid patients. In these patients, higher-than-average
digoxin concentrations are often necessary to achieve adequate AV nodal
blockade and ventricular rate control.

Time to Reach Steady State. The slope of all the decay curves is the
same. Therefore, the half-lives and elimination rate constants are equal,
and the time required to reach steady state will be the same for hyperthy-
roid, hypothyroid, and euthyroid patients receiving digoxin.

Maintenance Dose. Since K is the same in all patients, the clearance
and volume of distribution must both be changed by the same proportion
and in the same direction. See Equation 3.16 below.

\[ K = \frac{C_l}{V} \]

\[ K \text{ (Same in All Patients Studied)} = \frac{C_l \text{ (Variable)}}{V \text{ (Variable)}} \]

Hypothyroid patients must have a decreased clearance, since the vol-
ume of distribution is decreased. This reduction in Cl would necessitate a
reduction in maintenance doses. Similarly, the larger V in the hyperthyroid patients is consistent with an increased clearance; therefore, an increase in maintenance dose would be indicated ifCss ave is to remain the same as that used for euthyroid patients.

It is important to reemphasize, however, that although K and V were used to estimate clearance, V is an independent variable, which, like clearance, is affected by thyroid disease. As both Cl and V were affected in the same direction and to the same degree, the half-life (and K) did not change (see Table 3.1).

Two other studies\textsuperscript{63,64} have examined the pharmacokinetics of digoxin in patients with thyroid disease. Both of these suggest that the changes in the digoxin clearance result from an increased glomerular filtration rate associated with hyperthyroidism. If this increased renal function is the primary factor responsible for the altered digoxin clearance observed in hyperthyroid patients, it would be possible to encounter such patients with decreased digoxin clearance if they also had intrinsic renal dysfunction.

**QUESTION #13. Do patients receiving hemodialysis require additional digoxin following dialysis?**

One should first determine if digoxin is expected to be significantly removed by dialysis. To evaluate digoxin’s unbound volume in a dialysis patient, we need to calculate digoxin’s volume. Assuming a Cl\textsubscript{Cr} of 5 mL/min and a weight of 70 kg, and using Equation 3.1, the volume we would expect is 281.5 L.

\[
V\text{digoxin (L)} = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(\text{Cl\textsubscript{Cr} in mL/min})
\]
\[
= (3.8 \text{ L/kg})(70 \text{ kg}) + (3.1)(5 \text{ mL/min})
\]
\[
= 266 \text{ L} + 15.5 \text{ L}
\]
\[
= 281.5 \text{ L}
\]

Now using Equation 3.21, we can calculate digoxin’s unbound volume.

\[
\text{Unbound Volume of Distribution} = \frac{V}{f\text{u}} \quad \text{[Eq. 3.21]}
\]
\[
= \frac{281.5 \text{ L}}{0.9}
\]
\[
= 313 \text{ L}
\]

Based on the unbound volume of 313 L for this 70-kg patient or 4.5 L/kg, we would not expect digoxin to be significantly removed by dialysis (see Part I: Dialysis of Drugs: Estimating Drug Dialyzability).
This assessment of digoxin not being significantly removed by dialysis is further supported by the literature. Digoxin has a molecular weight of about 500 Da and will pass through the dialysis membrane; however, most of the digoxin is in the deeper, more slowly equilibrating tissue compartment and is difficult to remove by any intermittent hemofiltration process. The dialysis clearance for digoxin is only 10 mL/min using dialysis membranes having a molecular weight cutoff of about 1000 Da. Therefore, <3% of the total amount of drug in the body is removed during hemodialysis. This dialysis clearance of 10 mL/min may seem significant when compared with the metabolic clearance of 23 mL/min/70 kg for patients with CHF, but the dialysis takes place for only 3 to 4 hours every few days, while the metabolic clearance is continuous. High-efficiency or high-flux membranes will have higher digoxin clearance values and be more efficient in clearing plasma digoxin, but the digoxin in the deep compartment is slowly equilibrating and unlikely to be effectively eliminated in the usual 3- or 4-hour dialysis run. Continuous renal replacement therapy (CRRT) may be more effective over several days in removing digoxin because it is continuous. However, given the long $t_{1/2}$ of digoxin, even with the increased clearance, changes in concentration are likely to be over several days, and any necessary dose adjustments can be made as needed.

It is important to note that dialysis can induce digitalis toxicity by altering serum electrolyte concentrations and acid–base balance. For example, a decrease in serum potassium or other electrolytes may occur during dialysis and result in digoxin toxicity during or just following dialysis. If digoxin plasma samples are to be obtained around the time of dialysis, it would be wise to sample before dialysis is started or to wait at least 4 hours following the end of dialysis to ensure that the vascular and deep tissue concentrations of digoxin have had sufficient time to re-equilibrate.

**QUESTION #14.** C.B. is a patient with atrial fibrillation who was given digoxin for ventricular rate control. He is taking a maintenance dose of 0.25 mg/day of digoxin. Now, however, amiodarone will be added to C.B.’s drug regimen in an attempt to further control his ventricular response and, it is hoped, to convert him to normal sinus rhythm. What are the pharmacokinetic considerations with regard to the amiodarone–digoxin drug interaction?

Amiodarone is well recognized to decrease both the metabolic and renal clearance of digoxin. Although estimates vary, most patients have about a 50% reduction in digoxin clearance when amiodarone is added to their regimen. While the digoxin volume of distribution may also decrease slightly, the change is small. In addition, amiodarone has a very long $t_{1/2}$ of approximately 40 days and accumulates slowly in the body. As a result, following the initiation of amiodarone, digoxin concentrations rise slowly over a 1- to 2-week period (Fig. 3.3, Line C).
Given that the change in digoxin disposition is primarily a 50% reduction in clearance, we would expect to reduce the patient’s digoxin maintenance dose by 50% if our goal was to maintain the same steady-state digoxin concentration after the initiation of amiodarone. Although the change in digoxin occurs slowly, most clinicians reduce the digoxin maintenance dose at the time of starting amiodarone to ensure that the change in the digoxin regimen is not forgotten. If the digoxin steady-state concentration was very low at the time of initiating amiodarone, no change in digoxin may be necessary if the goal was to approximately double the digoxin concentration.

Although not related to the question at hand, many if not most patients with atrial fibrillation are receiving warfarin. Amiodarone also reduces the clearance of warfarin and as a result the INR (International Normalized Ratio) increases. If the patient’s INRs are not closely monitored and the warfarin doses adjusted, the patient’s INR will almost certainly increase significantly. It would not be good pharmaceutical care to prevent a digitalis intoxication only to have the patient develop a major bleeding episode.

**Question #15.** What if patient C.B. above was to be given quinidine? Are the considerations the same as for amiodarone?

Although quinidine is no longer one of the more common antiarrhythmic agents, it is still used on occasion. Understanding how quinidine alters the disposition of digoxin helps to explain the differences in how the interaction is managed. Patients receiving digoxin have a rapid and sustained rise in the serum digoxin concentration following the addition of quinidine \(^{69-71}\) (see Fig. 3.3, line B). This rapid rise in digoxin within the first 24 hours apparently results from the displacement of digoxin by quinidine from tissue sites. The increased digoxin concentration reflects a decrease in digoxin’s volume of distribution to 70% of the original value. The initial rise in digoxin concentrations to approximately 1.5 times the original concentration is followed by a relatively slow accumulation over the next week to a steady-state digoxin concentration that is approximately double the original value.\(^{69,72}\) Many patients develop signs of digitalis toxicity (primarily gastrointestinal in nature), which subside when the dose and plasma concentrations of digoxin are adjusted.\(^{69}\) However, it should be recognized that while gastrointestinal side effects are the most common for digitalis, side effects do not occur in a progressive order from least to most toxic or dangerous. The first sign of digoxin toxicity could be a life-threatening cardiac arrhythmia.

The rapid and sustained changes in digoxin concentrations (see Fig. 3.3) suggest that the initial change in digoxin concentration is due to a decline in the volume of distribution, which is slightly smaller than the decline in the clearance. This is illustrated by the initial rapid increase in
serum digoxin concentration followed by a gradual increase in the serum concentration to the final steady-state value.

Given the initial rapid rise in digoxin concentration (decrease in V) and the eventual doubling of the steady-state concentration (decrease in Cl), the usual approach is to hold one daily dose of digoxin in an attempt to blunt the initial rapid rise in digoxin, and then reinitiate the digoxin maintenance dose at half the previous rate.\(^{73-77}\) Again, this approach assumes that the goal is to maintain the same digoxin concentration following the initiation of quinidine therapy.\(^{78-80}\)

The patient’s digoxin concentration at the time of adding quinidine should be considered carefully. For example, adding quinidine to a patient with a digoxin level of 0.5 mcg/L may require no digoxin dose adjustment. A patient with a level of \(\approx 1\) mcg/L may have one dose withheld and the maintenance dose halved. In a patient with a digoxin concentration of 2 mcg/L or higher, it may not be appropriate to add quinidine, given the expected increase in digoxin concentrations and the potential risk of toxicity.

In addition, digoxin concentrations also may vary within a quinidine dosing interval because of varying degrees of tissue displacement. This has been demonstrated at relatively low quinidine concentrations and should be considered when obtaining digoxin plasma levels. For this reason, it is generally advisable to obtain plasma digoxin concentrations just before a quinidine dose so that the digoxin plasma levels will be reasonably reproducible. Any change in digoxin concentration sampled in this way should represent actual changes in digoxin disposition rather than transient changes within a quinidine dosing interval\(^{74}\) (Fig. 3.4). Recent literature

---

**FIGURE 3.3 Digoxin.** This figure represents the anticipated changes in digoxin concentration following the initiation of an interacting agent (†). The solid line A represents the effect of a drug that changes the volume of distribution in proportion to the decrease in the digoxin clearance. Broken line B represents the effect of a drug that produces a decrease in volume of distribution that is less than proportional to the decrease in digoxin clearance (e.g., quinidine). Line C represents the effect of a drug that decreases the digoxin clearance to approximately the same extent as quinidine, but produces no apparent change in the volume of distribution (e.g., amiodarone). Line D represents the effect of a drug that decreases digoxin clearance to a lesser extent than that observed with quinidine (e.g., verapamil). Line E represents a drug that decreases bioavailability or increases clearance or both and hence the decline in digoxin concentrations (e.g., St. John’s wort).
has also cited that amiodarone like quinidine may cause variations of digoxin concentrations during the dosing interval.\(^{42}\) This report would suggest that amiodarone may in fact change the volume of distribution as a rise and fall of the digoxin concentration during the interval not associated with the administration of the digoxin dose must be due to transient changes in plasma and tissue concentrations and hence altered volume. This is a single report and until more data are available to confirm and quantify this observation, the authors will continue to assume that amiodarone does not affect digoxin volume to a significant degree.

In the case of both amiodarone\(^{67}\) and verapamil, if a reduction in digoxin dose is contemplated, it is not necessary to skip a daily dose. Instead, the maintenance regimen should be reduced by the appropriate amount at about the time the amiodarone or verapamil therapy is instituted.

**QUESTION #16. What other drugs commonly used in patients receiving digoxin are likely to cause a significant change in its disposition?**

Amiodarone is probably the most significant and common drug that interacts with digoxin. However, other compounds, such as propafenone and verapamil, also reduce digoxin clearance.\(^{77,81-84}\) The decrease in digoxin clearance with the addition of propafenone ranges from less than 25% to more than 50%. Most of the change appears to be associated with the metabolic route of digoxin elimination. In addition, the decrease in metabolism appears to increase as the concentration of propafenone increases. Monitoring digoxin plasma levels may be helpful in evaluating the
extent of the propafenone–digoxin interaction. Careful consideration should be given to those patients with renal dysfunction or who are to be given large doses of propafenone.

Although the change in clearance for verapamil is not remarkable, approximately a 25% reduction, there may be individual patients in whom a modest reduction in the digoxin maintenance dose is warranted. Broken line D in Figure 3.3 depicts the anticipated rise in digoxin concentration following the institution of verapamil therapy. Note that the slow rise in digoxin concentration suggests that the volume of distribution for digoxin is not altered. The clearance, while reduced, is not reduced to the same extent as that associated with concomitant amiodarone or quinidine therapy; this is consistent with the smaller increase in steady-state digoxin concentrations associated with verapamil. Nifedipine and diltiazem appear to have relatively little influence on digoxin disposition; verapamil has modest effects.

St. John’s wort can reduce digoxin concentrations by approximately 25%. The most common explanation is a reduced bioavailability, but hepatic enzyme induction and an increase in clearance have also been proposed as a possible mechanism. Note in Figure 3.3, Line E, that the digoxin concentration decreases with the addition of an agent that either reduces bioavailability or increases clearance.

Macrolide antibiotics (e.g., clarithromycin, erythromycin) and ritonavir have been reported to increase digoxin serum levels. In addition, depending on the assay procedure, other drugs, including herbal and non-traditional agents may result in assay interference with digoxin, resulting in either false elevation or decrease in the reported digoxin concentration.

QUESTION #17. A.P., a 75-year-old, 60-kg man, was admitted with complaints of increased shortness of breath (SOB) and yellow sputum production. He has a medical history of chronic obstructive pulmonary disease (COPD) and CHF. During his hospital stay, he developed atrial fibrillation and was given digoxin to slow his ventricular rate. He received 250 mcg IV every 3 hours × 3 doses (starting at 9:00 p.m., day 1) and was given a maintenance dose of 250-mcg tablets each morning (starting at 9:00 a.m., day 2). His serum creatinine is stable at 1.5 mg/dL. A digoxin level obtained at 9:00 a.m. on the morning of day 4 (2.5 days after the loading dose) was reported to be 1.5 mcg/L. A.P. had, therefore, received his initial IV loading dose and two oral maintenance doses when a plasma sample was drawn on the morning of day 4. What would you expect his digoxin concentration to be?

To calculate the expected concentration, just before the third maintenance dose, one would first need to calculate A.P.’s expected digoxin
pharmacokinetic parameters. Using Equation 3.5 for Cl_{Cr}, an estimate of 36.1 mL/min is calculated.

\[
Cl_{Cr \text{ for males}} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(SCr_{ss})} = \frac{(140 - 75 \text{ yrs})(60 \text{ kg})}{(72)(1.5 \text{ mg/dL})} = 36.1 \text{ mL/min}
\]

Then using Equation 3.1 for digoxin V and Equation 3.4 for the digoxin clearance in patients with CHF, the corresponding values can be obtained.

\[
V_{\text{Digoxin}} (\text{L}) = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(Cl_{Cr} \text{ in mL/min}) = (3.8 \text{ L/kg})(60 \text{ kg}) + (3.1)(36.1 \text{ mL/min}) = 228 \text{ L} + 112 \text{ L} = 340 \text{ L}
\]

\[
\text{Total Cl}_{\text{Digoxin}} \text{ (mL/min) (Patients with CHF)} = (0.33 \text{ mL/kg/min})(\text{Weight in kg}) + (0.9)(Cl_{Cr} \text{ in mL/min}) = (0.33 \text{ mL/kg/min})(60 \text{ kg}) + (0.9)(36.1 \text{ mL/min}) = 19.8 \text{ mL/min} + 32.5 \text{ mL/min} = 52.3 \text{ mL/min}
\]

The Cl_{Digoxin} in mL/min can be converted to the more convenient units of L/day using Equation 3.11.

\[
Cl \text{ (L/day)} = (Cl \text{ as mL/min}) \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right) = (52.3 \text{ mL/min}) \left( \frac{1440 \text{ min/day}}{1000 \text{ mL/L}} \right) = 75.3 \text{ L/day}
\]

Using the calculated volume of distribution of 340 L and clearance of 75.3 L/day, Equation 3.16 estimates an elimination rate constant of 0.22 day^{-1}.

\[
K = \frac{Cl}{V} = \frac{75.3 \text{ L/day}}{340 \text{ L}} = 0.22 \text{ day}^{-1}
\]
Equation 3.17 estimates a half-life of approximately 3 days.

\[
t\frac{1}{2} = \frac{(0.693)(V)}{Cl} = \frac{(0.693)(340 \text{ L})}{75.3 \text{ L/day}} = 3.1 \text{ days}
\]

To calculate A.P.’s digoxin plasma concentration, one needs to consider the loading dose plus the two maintenance doses. To model this series of doses, refer to Part I: Selecting the Appropriate Equation: Series of Individual Doses, Fig. 27, in which the loading dose plus the two maintenance doses are depicted as \(D_1\), \(D_2\), and \(D_3\). Because his loading dose of 750 mcg (250 mcg \(\times\) 3 doses) was given over a total of 6 hours and A.P.’s expected digoxin half-life is 3.1 days, one can group the entire loading dose together as though it were administered as a single dose, all administered when the first 250 mcg dose was given (i.e., time from start to end of loading \(t_{in}\) is \(\leq 1/6 t\frac{1}{2}\)).

\[
C_{(\text{sum})} = \frac{(S)(F)(D_1)}{V}(e^{-kt_1}) + \frac{(S)(F)(D_2)}{V}(e^{-kt_2}) + \frac{(S)(F)(D_3)}{V}(e^{-kt_3}) \ldots \text{[Eq. 3.22]}
\]

\[
= \frac{(1)(1)(750 \text{ mcg})}{340 \text{ L}}(e^{-0.22 \text{ L/day}^{-1})(2.5 \text{ days})}) + \frac{(1)(0.7)(250 \text{ mcg})}{340 \text{ L}}(e^{-0.22 \text{ L/day}^{-1})(2 \text{ days})})
\]

\[
= \frac{(1)(0.7)(250 \text{ mcg})}{340 \text{ L}}(e^{-0.22 \text{ L/day}^{-1})(1 \text{ day})})
\]

\[
= (2.2 \text{ mcg/L})(0.58) + (0.51 \text{ mcg/L})(0.64) + (0.51 \text{ mcg/L})(0.8)
\]

\[
= 1.3 \text{ mcg/L} + 0.33 \text{ mcg/L} + 0.41 \text{ mcg/L}
\]

\[
= 2 \text{ mcg/L}
\]

Note that the predicted digoxin concentration of 2 mcg/L is greater than the observed value of 1.5 mcg/L. Unfortunately, revision of pharmacokinetic parameters at this point would be difficult. After only 2.5 days and with a half-life of 3 days, it is relatively easy to see that we have gone beyond one-third of the half-life since the loading dose was administered. Generally, to accurately estimate volume of distribution following a loading dose, we would want a plasma sample within one-third of a half-life. Furthermore, A.P.’s maintenance dose has not been administered longer than two half-lives, which limits our ability to extract information about clearance. The observed plasma concentration may reflect a larger-than-expected \(V\), a higher-than-expected \(Cl\), or some combination of both of these factors. To more accurately determine A.P.’s digoxin clearance, it will be necessary to wait several more days to obtain a plasma concentration...
that might reasonably be expected to yield information about clearance. Given his expected half-life of approximately 3 days and the probability that his half-life is less than expected, an additional 2 or 3 days would probably be sufficient to begin to obtain some additional information that will help to predict A.P.’s final steady-state concentration.

In the example above, the time intervals were based on the number of days. In the clinical setting, many times levels and doses are not administered in a way that days would be the most appropriate unit. Instead, hours may be more appropriate. If this is the case, it is important to have the units for clearance in L/hr and the units for elimination rate constant in hr\(^{-1}\) so that the units are consistent with the time in hours. The equations for calculating the concentrations would be the same and the end result would be the same, just the units would reflect hours and not days.

**QUESTION #18.** C.A. is a 60-year-old, 65-kg man with a serum creatinine of 1.3 mg/dL. He had been taking 0.25 mg of digoxin at 9:00 a.m. orally for his CHF. On the day of admission, a digoxin level of 0.8 mcg/L was measured just before his morning dose. His outpatient maintenance dose was continued. On the fifth day, just before his morning dose (four doses of digoxin having been administered each day at 9:00 a.m.), a second digoxin sample was obtained. Using the expected pharmacokinetic parameters, calculate C.A.’s digoxin concentration on the morning of the fifth day.

Again, to calculate the expected plasma concentration, one would first have to estimate C.A.’s creatinine clearance and then use the appropriate equations to calculate his volume of distribution, clearance, elimination rate constant, and half-life.

Using Equation 3.5, we calculate a creatinine clearance of 55.6 mL/min.

\[
Cl_{Cr} \text{ for males} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(SCr_{ss})}
\]

\[
= \frac{(140 - 60 \text{ yrs})(65 \text{ kg})}{(72)(1.3 \text{ mg/dL})}
\]

\[
= 55.6 \text{ mL/min}
\]

Then using Equation 3.1 for digoxin V, and Equation 3.4 for the digoxin clearance in patients with CHF, the corresponding values can be obtained.

\[
V_{\text{digoxin}} \text{ (L)} = (3.8 \text{ L/kg})(\text{Weight in kg}) + (3.1)(Cl_{Cr} \text{ in mL/min})
\]

\[
= (3.8 \text{ L/kg})(65 \text{ kg}) + (3.1)(55.6 \text{ mL/min})
\]

\[
= 247 \text{ L} + 172 \text{ L}
\]

\[
= 419 \text{ L}
\]
The ClDigoxin in mL/min can be converted to the units of L/day using Equation 3.11.

\[
\text{Cl (L/day)} = \left(\text{Cl as mL/min}\right) \left(\frac{1440 \text{ min/day}}{1000 \text{ mL/L}}\right)
\]

\[
= (71.5 \text{ mL/min}) \left(\frac{1440 \text{ min/day}}{1000 \text{ mL/L}}\right)
\]

\[
= 103 \text{ L/day}
\]

Using the calculated volume of distribution and clearance, Equation 3.16 estimates an elimination rate constant of 0.25 day\(^{-1}\).

\[
K = \frac{\text{Cl}}{V}
\]

\[
K = \frac{103 \text{ L/day}}{419 \text{ L}}
\]

\[
= 0.25 \text{ day}^{-1}
\]

Equation 3.17 estimates a half-life of approximately 3 days.

\[
\text{t}_{1/2} = \frac{(0.693)\text{Cl}}{V}
\]

\[
= \frac{(0.693)(419 \text{ L})}{103 \text{ L/day}}
\]

\[
= 2.8 \text{ days}
\]

To model the initial digoxin concentration decay and the four subsequent doses, several approaches could be used. One approach is to use Equation 3.23 to model the initial digoxin concentration and subsequent decay.

\[
C_{(\text{Sum})} = C_1(e^{-kt_1}) + \frac{(S)(F)(D_1)}{V}(e^{-kt_1}) + \frac{(S)(F)(D_2)}{V}(e^{-kt_2}) + \frac{(S)(F)(D_3)}{V}(e^{-kt_3}) \ldots
\]

[Eq. 3.23]

In the above equation, the digoxin concentration of 0.8 would be \(C_1\), the first \(t_1\) the time from that concentration to the time of sampling.
(4 days), $D_1$ the initial dose of 250 mcg, and the second $t_1$ the time from that dose to the time of the sample (again 4 days). $D_2$ is the second dose, $t_2$ the second time interval (3 days), etc. The calculations would then be as follows:

\[
C_{(\text{sum})} = (0.8 \text{ mcg/L})(e^{-(0.25 \text{ day}^{-1})(4 \text{ days})}) + \frac{(1)(0.7)(250 \text{ mcg})}{419 \text{ L}}(e^{-(0.25 \text{ day}^{-1})(3 \text{ days})})
\]

\[
+ \frac{(1)(0.7)(250 \text{ mcg})}{419 \text{ L}}(e^{-(0.25 \text{ day}^{-1})(2 \text{ days})})
\]

\[
+ \frac{(1)(0.7)(250 \text{ mcg})}{419 \text{ L}}(e^{-(0.25 \text{ day}^{-1})(1 \text{ day})})
\]

Note that because $S$ and $F$ as well as each of the digoxin doses were the same, the above equation can be factored to the following:

\[
C_{(\text{sum})} = (0.8 \text{ mcg/L})(e^{-(0.25 \text{ day}^{-1})(4 \text{ days})})
\]

\[
+ \frac{(1)(0.7)(250 \text{ mcg})}{419 \text{ L}}[e^{-(0.25 \text{ day}^{-1})(4 \text{ days})} + e^{-(0.25 \text{ day}^{-1})(3 \text{ days})}]
\]

\[
+ \frac{(1)(0.7)(250 \text{ mcg})}{419 \text{ L}}[e^{-(0.25 \text{ day}^{-1})(2 \text{ days})} + e^{-(0.25 \text{ day}^{-1})(1 \text{ day})}]
\]

\[
C_{(\text{sum})} = (0.8 \text{ mcg/L})(0.37) + 0.42 \text{ mcg/L}[0.37 + (0.47) + (0.61) + (0.78)]
\]

\[
= 0.3 \text{ mcg/L} + 0.42 \text{ mcg/L} \times 2.23
\]

\[
= 0.3 \text{ mcg/L} + 0.94 \text{ mcg/L}
\]

\[
= 1.24 \text{ mcg/L}
\]

An alternative approach is to use a model that takes advantage of digoxin's long half-life relative to the dosing interval (see Part I: Selecting the Appropriate Equation, Fig. 25). In this model, one could choose to decay the initial digoxin plasma concentration and then add the four subsequent doses by treating them as a continuous infusion as depicted in Equation 3.24 below:

\[
C_t = (C_t)(e^{-\kappa t}) + \frac{(S)(F)(\text{Dose}/\tau)}{C_l}(1 - e^{-\kappa t}) \quad \text{[Eq. 3.24]}
\]

Note that, in the infusion part of the non-steady-state equation, $\text{Dose}/\tau$ is the rate of drug administration and $t_1$ is the duration of drug
administration. Therefore, Dose/τ × t₁ should equal the total amount of drug administered. In this case, there were four doses administered for 1000 mcg. Given that the rate of administration is 250 mcg/day, t₁ would be 4 days.

Using the appropriate doses, times, and pharmacokinetic parameters, a digoxin concentration of 1.37 mcg/L is calculated.

\[
C_t = (0.8 \text{ mcg/L})e^{-0.25 \text{ day}^{-1}(4 \text{ days})} + \frac{(1)(0.7)(250 \text{ mcg/day})}{103 \text{ L/day}}(1 - e^{-0.25 \text{ day}^{-1}(4 \text{ days})})
\]

\[= (0.8 \text{ mcg/L})(0.37) + (1.7 \text{ mcg/L})(1 - 0.37)
\]

\[= 0.3 \text{ mcg/L} + 1.07 \text{ mcg/L}
\]

\[= 1.37 \text{ mcg/L}
\]

The concentrations predicted by the first method (individual bolus doses) and the second method (digoxin given as an infusion) are similar, indicating that either method is a reasonable way to predict C.A.’s digoxin concentration on the morning of the fifth day. Also note that the predicted steady-state concentration produced by a maintenance dose of 0.25 mg/day (250 mcg/day) would be ≈ 1.7 mcg/L. See above part of Equation 3.24 that represents Css ave or Equation 3.20 below.

\[
\text{Css ave} = \frac{(S)(F)(\text{Dose/τ})}{\text{Cl}}
\]

\[= \frac{(1)(0.7)(250 \text{ mcg/day})}{103 \text{ L/day}}
\]

\[= 1.7 \text{ mcg/L}
\]

**QUESTION #19.** C.A.’s digoxin level reported from the laboratory was 1.6 mcg/L. Since the observed digoxin concentration is greater than the predicted level (1.24 to 1.37 mcg/L), what would one expect C.A.’s digoxin clearance and subsequent steady-state digoxin concentration to be on his current regimen of 0.25 mg/day?

Either of the two approaches in the previous question can be used to resolve this problem. Clearance could be calculated by first assuming C.A.’s digoxin volume of distribution to be 419 L. Then, using a trial-and-error method or iterative search, one could substitute various clearance values and the corresponding elimination rate constant values until the
equation predicted the observed digoxin concentration of 1.6 mcg/L. Since this process could be laborious, an alternative approach is to use the mass balance technique and solve directly for C.A.’s clearance. See Part I: Interpretation of Plasma Drug Concentrations: Non-steady-state Revision of Clearance (Mass Balance). The expected steady-state digoxin concentration for C.A. could then be more easily calculated.

\[
\text{Eq. 3.25}
\]

\[
\text{In this equation, } t \text{ is the time interval between } C_1 \text{ and } C_2 \text{ and therefore is 4 days, since this is the interval between } C_1 \text{ (0.8 mcg/L) and } C_2 \text{ (1.6 mcg/L). } \text{C ave is calculated as the arithmetic mean of the two plasma concentrations.}
\]

\[
\text{Eq. 3.26}
\]

\[
\text{Substituting the appropriate values in Equation 3.25, a digoxin clearance of 76 L/day can be calculated.}
\]

\[
\text{Note that this calculated digoxin clearance and our assumed volume of distribution of 419 L is consistent with an expected half-life of approximately 3.8 days (Equation 3.17).}
\]
Evaluating the revised half-life is an important step in our assessment of the clearance prediction of 76 L/day. As mentioned in Part I, there are three key issues or rules to be considered when using the mass balance approach when solving for clearance, using non-steady-state data:

1. **t or time interval between C₁ and C₂** should be at least one half-life but not more than two half-lives. If t is very short, relative to the drug half-life, small differences in C₁ and C₂ can result in widely varying estimates of drug accumulation or drug loss. If t is much more than two half-lives, the second concentration would be approaching steady-state, and our C ave would be an underestimate of the average concentration within the time interval t. Hence, the rule that t should be at least one but not more than two half-lives.

2. The plasma concentration values should be reasonably close to one another; therefore, C₂/C₁ ≤ 2 if the concentration is increasing, and C₂/C₁ ≥ 0.5 if the concentration is decreasing. If there is a large difference between C₁ and C₂, it means that relatively little of the dose administered between C₁ and C₂ has been eliminated. In this situation, volume of distribution and the total dose administered are the critical factors, and the drug concentrations contain very little information about clearance. If the concentration has declined more than one t₁/₂, that is, C₂/C₁ < 0.5, there will be a significant curve in the decay line and the arithmetic mean of C₁ and C₂ [i.e., (C₁ + C₂)/2] will not be a good estimate of the average drug concentration over the time interval t. Ideally, C₁ and C₂ would be very close together and the net drug accumulation or loss would be approaching 0, suggesting near steady-state conditions and therefore ideal conditions for estimating clearance.

3. The rate of drug administration \[(S)(F)(Dose/τ)\] should be regular and result in a reasonably smooth progression from C₁ to C₂. If the doses are very irregular because either the interval is not consistent or the dose is changing, the accumulation pattern will not be a smooth transition from C₁ to C₂. Therefore, the C ave as calculated from the arithmetic mean of C₁ and C₂ [i.e., (C₁ + C₂)/2] will not accurately represent the true C ave between C₁ and C₂. Another potential problem with the mass balance approach is when the dosing interval is longer than the drug half-life. Under these conditions, there will be significant increases and decreases in the drug concentration within each dosing interval. The progression from C₁ to C₂ will not be smooth, and result in the arithmetic mean \[(C₁ + C₂)/2\] may be a poor estimate of the true average concentration.

Assuming we have met all the three rules described above and are using the revised clearance value and Equation 3.20, the expected
steady-state digoxin concentration of approximately 2.3 mcg/L can be calculated.

\[
\text{Css ave} = \frac{(S)(F)(\text{Dose}/\tau)}{\text{Cl}} = \frac{(1)(0.7)(250 \text{ mcg/day})}{76 \text{ L/day}} = 2.3 \text{ mcg/L}
\]

Because this value is above the upper limit of the usually accepted therapeutic range for heart failure, one would most likely choose to reduce the digoxin maintenance dose at this time. This is especially true given that most patients with CHF do well clinically with digoxin concentrations in the range of 0.5 to 0.9 mcg/L and evidence that digoxin has a potentially harmful effect if digoxin concentration is \(\geq 1.2 \text{ mcg/L} \). An alternative approach would be to obtain another digoxin sample after approximately one additional half-life (3 to 4 days) to determine if the digoxin concentration is accumulating as anticipated. In one half-life, the digoxin concentration should accumulate to a concentration of approximately 2 mcg/L, or half-way between the present concentration of 1.6 mcg/L and the expected steady-state value of 2.3 mcg/L. The time interval of one half-life was chosen for two reasons. First, a significant time interval is required, usually at least one half-life, to distinguish true drug accumulation from assay variability. Second, it is desirable to detect accumulation early enough to avoid unnecessary toxicity risks. In this case, the time interval chosen has placed C.A.’s digoxin concentration at the upper end of the therapeutic range. In discussing the second approach, it is important to recognize that the desire to obtain good pharmacokinetic data should not overshadow good clinical decision making. For this reason, most clinicians would probably follow the first approach and reduce C.A.’s digoxin dose at this time.

**QUESTION #20. When is Digibind indicated and how is the dose determined?**

Digibind is indicated for life-threatening digoxin intoxication, that is, severe ventricular arrhythmias or progressive bradyarrhythmias not responsive to treatment, or progressive elevation in serum potassium. Each vial of Digibind binds 0.5 mg or 500 mcg of digoxin. If the total amount of digoxin is known, Equation 3.27 can be used to calculate the dose of Digibind.

\[
\text{Digibind (No. of Vials)} = \frac{\text{mcg of Digoxin in Body}}{500} \quad \text{[Eq. 3.27]}
\]
If the total body stores is uncertain but a digoxin concentration is known, Equation 3.28 can be used to calculate the number of vials of Digibind that would be needed.

\[
\text{Digibind (No. of Vials)} = \left( \frac{C_{\text{Digoxin in mcg/L}} \times \text{Weight in kg}}{100} \right)
\]  

[Eq. 3.28]

Equation 3.28 assumes a digoxin volume of 5 L/kg. In obese patients, it is not clear what weight to use but the authors would recommend using the weight that best correlates with the digoxin volume of distribution, that is, IBW if obese. However, care should be taken not to “underdose” the patient. Also care should be taken in young healthy individuals as their digoxin volume of distribution may be larger than the assumed value of 5 L/kg in Equation 3.28. Lastly, when the calculated Digibind dose contains a fraction of a vial (e.g., 4.4 vials), most clinicians would round up to the next whole number of vials.

Another important issue is whether or not serum digoxin levels would be appropriate following the administration of Digibind. The answer depends on the assay being used.\textsuperscript{59,92} Digibind is a digoxin antibody fragment (Fab) that binds the plasma digoxin and thereby creating disequilibrium between the plasma and tissue concentrations. The tissue digoxin then re-equilibrates with the plasma and that re-equilibrated plasma digoxin is then bound to the Fab. This process continues until all or almost all of the digoxin is pulled from the tissue and bound in the plasma to the Fab. While the total plasma digoxin is very high, almost all is bound to the Fab and essentially “inactive.”

Some digoxin assays measure the unbound digoxin and some or all of the Fab-bound digoxin. These assays are of no clinical value following the administration of Digibind and can be clinically confusing as the reported digoxin concentration represents both the unbound “active” and the Fab-bound “inactive” digoxin. With this type of assay, depending on how much of the Fab-bound digoxin is being analyzed, it is possible for the digoxin concentration to increase following the administration of Digibind. Some digoxin assays measure only the unbound “active” digoxin concentration. These assays may be of some clinical value but in most cases the unbound digoxin concentration will be very low.

REFERENCES


