# 3

# DRUG DOSING IN SPECIAL POPULATIONS: RENAL AND HEPATIC DISEASE, DIALYSIS, HEART FAILURE, OBESITY, AND DRUG INTERACTIONS

## INTRODUCTION

All medications have specific disease states and conditions that change the pharmacokinetics of the drug and warrant dosage modification. However, the dosing of most drugs will be altered by one or more of the important factors discussed in this chapter. Renal or hepatic disease will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent. Dialysis procedures, conducted using artificial kidneys in patients with renal failure, removes some medications from the body while the pharmacokinetics of other drugs are not changed. Heart failure results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ blood flow. Obesity adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication. Finally, drug interactions can inhibit or induce drug metabolism, alter drug protein binding, or change blood flow to organs that eliminate or metabolize the drug.

## RENAL DISEASE

Most water-soluble drugs are eliminated unchanged to some extent by the kidney. In addition to this, drug metabolites that were made more water soluble via oxidation or conjugation are typically removed by renal elimination. The nephron is the functional unit of the

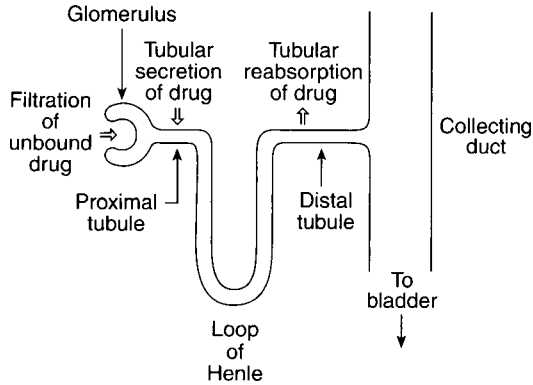


**FIGURE 3-1** The nephron is the functional unit of the kidney responsible for drug elimination. Unbound drug is filtered freely at the glomerulus *(shown by arrow).* Active tubular secretion of drug *(denoted by arrow into nephron)* usually occurs in the proximal tubule of the nephron. Passive tubular reabsorption *(denoted by arrow out of nephron)* usually occurs in the distal tubule of the nephron. Tubular reabsorption requires un-ionized drug molecules so that the molecules can pass through the lipid membranes of the nephron and surrounding capillaries.

kidney that is responsible for waste product removal from the body and also eliminates drug molecules (Figure 3-1). Unbound drug molecules that are relatively small are filtered at the glomerulus. Glomerular filtration is the primary elimination route for many medications. Drugs can be actively secreted into the urine, and this process usually takes place in the proximal tubules. Tubular secretion is an active process conducted by relatively specific carriers or pumps that move the drug from blood vessels in close proximity to the nephron into the proximal tubule. Additionally, some medications may be reabsorbed from the urine back into the blood by the kidney. Reabsorption is usually a passive process and requires a degree of lipid solubility for the drug molecule. Thus, tubular reabsorption is influenced by the pH of the urine, the pKa of the drug molecule, and the resulting extent of molecular ionization. Compounds that are not ionized in the urine are more lipid soluble, better able to pass through lipid membranes, and more prone to renal tubular reabsorption. The equation that describes these various routes of renal elimination is:

$$Cl_R = \left[ (f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

where $f_B$ is the free fraction of drug in the blood, GFR is glomerular filtration rate, RBF is renal blood flow, $Cl'_{sec}$ is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed.[1]

When infants are born, renal function is not yet completely developed in full-term neonates (~40 weeks gestational age). Kidney development is complete and renal function stabilizes 3–6 months after birth. In premature infants (<35 weeks), kidney development may take even longer during the postpartum period. Kidney function, as measured by glomerular filtration rate, typically averages ~120–140 mL/min in young, healthy adults between the ages of 18–22 years. As humans age, there is a gradual decline in glomerular function so that by 65 years of age, the average glomerular filtration rate

is ~50–60 mL/min. The expected glomerular filtration rate for otherwise healthy, normal 80-year-old adults is ~30–40 mL/min. A glomerular filtration rate of 80–120 mL/min is usually considered the normal range by most clinical laboratories.

In patients with renal disease, there is a functional loss of nephrons. Depending on the etiology of the renal disease, patients with acute kidney failure may recoup their baseline renal function after a period of supportive care and dialysis long enough for their kidneys to recover. Patients with acute renal failure due to a sudden decrease in renal blood flow, such as that seen during hypotension, shock, or hypovolemia, or due to nephrotoxic drug therapy such as aminoglycoside antibiotics or vancomycin, often have their kidney function return to its preinsult level if they survive the underlying causes of their renal dysfunction. Patients with chronic renal failure sustain permanent loss of functional nephrons due to irreversible damage and do not recover lost kidney function.

## Measurement and Estimation of Creatinine Clearance

Glomerular filtration rate can be determined by administration of special test compounds such as inulin or $^{125}$I-iothalamate; this is sometimes done for patients by nephrologists when precise determination of renal function is needed. Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation: GFR (in mL/min / 1.73 $m^2$) = $186 \cdot S_{Cr}^{-1.154} \cdot Age^{-0.203} \cdot$ (0.742, if female) · (1.21, if African-American).[2,3] For example, the estimated GFR for a 53-year-old African-American male with a $S_{Cr}$ = 2.7 mg/dL would be computed as follows: GFR = $186 \cdot (2.7 \text{ mg/dL})^{-1.154} \cdot (53 \text{ y})^{-0.203} \cdot 1.21 = 32$ mL/min / 1.73 $m^2$.

However, the method recommended by the Food and Drug Administration (FDA) and others to estimate renal function for the purposes of drug dosing is to measure or estimate creatinine clearance (CrCl).[4–9] Creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration. Because of this property, it is used as a surrogate measurement of glomerular filtration rate. Since creatinine is also eliminated by other routes, CrCl does not equal GFR, so the two parameters are not interchangeable.[3,5]

Creatinine clearance rates can be measured by collecting urine for a specified period and collecting a blood sample for determination of serum creatinine at the midpoint of the concurrent urine collection time: CrCl (in mL/min) = $(U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T)$, where $U_{Cr}$ is the urine creatinine concentration in mg/dL, $V_{urine}$ is the volume of urine collected in mL, $S_{Cr}$ is the serum creatinine collected at the midpoint of the urine collection in mg/dL, and T is the time in minutes of the urine collection. Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24-hour urine collection period for the determination of creatinine clearance. For example, a 24-hour urine was collected for a patient with the following results: $U_{Cr}$ = 55 mg/dL, $V_{urine}$ = 1000 mL, $S_{Cr}$ = 1.0 mg/dL, T = 24 h × 60 min/h = 1440 min, and CrCl (in mL/min) = $(U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T) = (55 \text{ mg/dL} \cdot 1000 \text{ mL}) / (1.0 \text{ mg/dL} \cdot 1440 \text{ min}) = 38$ mL/min. However, for the purpose of drug dosing, collection periods of 8–12 hours have been sufficient and provide a quicker turnaround time in emergent situations. Also, if renal function is stable, the blood sample for determination of serum creatinine may not need to be collected at the precise midpoint of the urine collection.

Routine measurement of creatinine clearances in patients has been fraught with problems. Incomplete urine collections, serum creatinine concentrations obtained at incorrect times, and collection time errors can produce erroneous measured creatinine clearance values. This realization has prompted investigators to derive methods which estimate

creatinine clearance from serum creatinine values and other patient characteristics in various populations. The most widely used of these formulas for adults aged 18 years and older is the method suggested by Cockcroft and Gault:[10] for males, $CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr})$; for females, $CrCl_{est} = [0.85(140 - age)BW]/(72 \cdot S_{Cr})$; where $CrCl_{est}$ is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and $S_{Cr}$ is serum creatinine in mg/dL. The Cockcroft-Gault method should only be used in patients ≥18 years old, actual weight within 30% of their ideal body weight [$IBW_{males}$ (in kg) = 50 + 2.3(Ht − 60) or $IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60), where Ht is height in inches], and stable serum creatinine concentrations. The 0.85 correction factor for females is present because women have smaller muscle mass than men and, therefore, produce less creatinine per day. For example, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be: $IBW_{males} = 50 + 2.3\ (Ht - 60) = 50 + 2.3(71 - 60) = 75$ kg, so the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used; $CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 55\ y)80\ kg]/(72 \cdot 1.9\ mg/dL) = 50$ mL/min.

Some patients have decreased muscle mass due to disease states and conditions that effect muscle or prevent exercise. Patients with spinal cord injury, cancer patients with muscle wasting, HIV-infected patients, cachectic patients, and patients with poor nutrition are examples of situations where muscle mass may be very small resulting in low creatinine production. In these cases, serum creatinine concentrations are low because of the low creatinine production rate and not due to high renal clearance of creatinine. In these cases, investigators have suggested that if serum creatinine values are <1.0 mg/dL for a patient an arbitrary value of 1 mg/dL be used in the Cockcroft-Gault formula to estimate creatinine clearance.[11–13] While it appears that the resulting estimate of creatinine clearance is closer to the actual creatinine clearance in these patients, it can still result in misestimates. It may be necessary to measure creatinine clearance in these types of patients if an accurate reflection of glomerular filtration rate is needed.

If serum creatinine values are not stable, but increasing or decreasing in a patient, the Cockcroft-Gault equation cannot be used to estimate creatinine clearance. In this case, an alternate method must be used which was suggested by Jelliffe and Jelliffe.[14] The first step in this method is to estimate creatinine production. The formula for this is different for males and females due to gender-dependent differences in muscle mass: $Ess_{male} = IBW[29.3 - (0.203 \cdot age)]$; $Ess_{female} = IBW[25.1 - (0.175 \cdot age)]$, where Ess is the excretion of creatinine, IBW is ideal body weight in kilograms, and age is in years. The remainder of the equations correct creatinine production for renal function, and adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse:

$$Ess_{corrected} = Ess[1.035 - (0.0337 \cdot Scr_{ave})]$$

$$E = Ess_{corrected} - \frac{[4IBW(Scr_2 - Scr_1)]}{\Delta t}$$

$$CrCl\ (in\ mL/min/1.73m^2) = E/(14.4 \cdot Scr_{ave})$$

where $Scr_{ave}$ is the average of the two serum creatinine determinations in mg/dL, $Scr_1$ is the first serum creatinine and $Scr_2$ is the second serum creatinine both in mg/dL, and $\Delta t$ is the time that expired between the measurement of $Scr_1$ and $Scr_2$ in minutes.

If patients are not within 30% of their ideal body weight, other methods to estimate creatinine clearance should be used.[15,16] It has been suggested that use of ideal body weight or adjusted body weight (ideal body weight plus 40% of obese weight) instead of actual body weight in the Cockcroft-Gault equation gives an adequate estimate of creatinine clearance for obese individuals. However, a specific method suggested by Salazar and Corcoran[17] for estimating creatinine clearance for obese patients has been shown to be generally superior:

$$\mathrm{CrCl}_{\mathrm{est(males)}} = \frac{(137 - \mathrm{age})[(0.285 \cdot \mathrm{Wt}) + (12.1 \cdot \mathrm{Ht}^2)]}{(51 \cdot \mathrm{S_{Cr}})}$$

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - \mathrm{age})[(0.287 \cdot \mathrm{Wt}) + (9.74 \cdot \mathrm{Ht}^2)]}{(60 \cdot \mathrm{S_{Cr}})}$$

where age is in years, Wt is weight in kg, Ht is height in m, and $S_{Cr}$ is serum creatinine in mg/dL.

Methods to estimate creatinine clearance for children and young adults are also available according to their age:[18] age 0–1 year, $\mathrm{CrCl_{est}}$ (in mL/min / 1.73 $\mathrm{m^2}$) = (0.45 · Ht) / $S_{Cr}$; age 1–20 years, $\mathrm{CrCl_{est}}$ (in mL/min / 1.73 $\mathrm{m^2}$) = (0.55 · Ht)/$S_{Cr}$, where Ht is in cm and $S_{Cr}$ is in mg/dL. Note that for these formulas, estimated creatinine clearance is normalized to 1.73 $\mathrm{m^2}$ which is the body surface area of an adult male with a height and weight of approximately 5 ft 10 in and 70 kg, respectively.

## Estimation of Drug Dosing and Pharmacokinetic Parameters Using Creatinine Clearance

It is common to base initial doses of drugs that are renally eliminated on creatinine clearance. The basis for this is that renal clearance of the drug is smaller in patients with a reduced glomerular filtration rate, and measured or estimated creatinine clearance is a surrogate marker for glomerular filtration rate. An implicit assumption made in this approach is that all drug excreting processes of the kidney, including tubular section and reabsorption, decline in parallel with glomerular filtration. The basis of this assumption is the intact nephron theory. While tubular secretion and reabsorption may not always decline in proportion to glomerular filtration, this approach approximates the decline in tubular function and is a useful approach to initial drug dosing in patients with renal dysfunction. However, clinicians should bear in mind that the suggested doses for patients with renal impairment is an initial guideline only, and doses may need to be increased in patients that exhibit suboptimal drug response and decreased in patients with adverse effects.

Breakpoints to consider altering drug doses are useful for clinicians to keep in mind. Generally, one should consider a possible, modest decrease in drug doses when creatinine clearance is <50–60 mL/min, a moderate decrease in drug doses when creatinine clearance is <25–30 mL/min, and a substantial decrease in drug doses when creatinine clearance is ≤15 mL/min. In order to modify doses for patients with renal impairment, it is possible to decrease the drug dose and retain the usual dosage interval, retain the usual dose and increase the dosage interval, or simultaneously decrease the dosage and prolong the dosage interval. The approach used depends on the route of administration, the dosage forms available, and the pharmacodynamic response to the drug. For example, if the drug is prescribed orally and only a limited number of solid dosage forms are available, one

will usually administer the usual dose and increase the dosage interval. If the drug is given parenterally, a smaller dose can be administered, and it is more likely that the usual dosage interval will be retained. Finally, for drugs with narrow therapeutic ranges like aminoglycoside antibiotics and vancomycin where target serum concentrations for maximum and minimum steady-state concentrations are established, both the dose and dosage interval can be manipulated to achieve the targeted drug levels. If the drug dose is reduced and the dosage interval remains unaltered in patients with decreased renal function, maximum drug concentrations are usually lower and minimum drug concentrations higher than that encountered in patients with normal renal function receiving the typical drug dose (Figure 3-2). If the dosage interval is prolonged and the drug dosage remains the same, maximum and minimum drug concentrations are usually about the same as in patients with good renal function receiving the usual drug dose.

Since the mid-1980s, the FDA has required pharmacokinetic studies to be done for agents that are renally eliminated in patients with decreased creatinine clearance rates before receiving agency approval.[8] In these cases, the package insert for the drug probably contains reasonable initial dosage guidelines. For example, the manufacturer's suggested guidelines for the dosing of gabapentin in patients with renal dysfunction are listed in Table 3-1. Guidelines to change drug doses for patients with decreased renal function are available for older drugs as well as updated guidelines for newer drugs that may not be included in the package insert.[4,6,7,19–21] Also, the primary literature should be consulted to ensure that the newest guidelines are used for all drugs. If no specific information is available for a medication, it is possible to calculate modified initial drug doses using the method described by Dettli.[22]

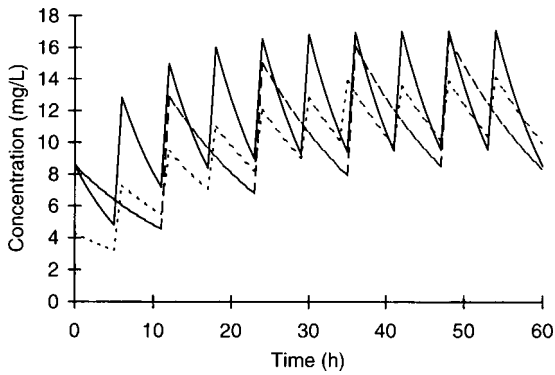


**FIGURE 3-2** Serum concentration versus time profile for a patient with normal kidney function receiving a renally eliminated drug at the dose of 300 mg every 6 hours *(solid line).* In a patient with renal dysfunction, it is possible to give the same dose and prolong the dosage interval (300 mg every 12 hours, *dashed line),* or a reduced dose at the same dosage interval (150 mg every 6 hours, *dotted line).* Giving the same dose at a longer dosage interval in the patient with renal disease usually results in a concentration/time profile similar to that seen in a normal patient receiving the normal dose. However, giving a smaller dose and keeping the dosage interval the same usually produces a concentration/time profile with a lower peak steady-state concentration and a higher trough steady-state concentration. Note that since the total daily dose is the same for both renal disease dosage regimens (600 mg/d), the average steady-state concentration is identical for both dosage schemes. The same dosage options are available for liver-metabolized drugs for patients with hepatic dysfunction.

**TABLE 3-1 Manufacturer's Recommended Dosing Schedule for Renal Dysfunction and Hemodialysis Patients Receiving Gabapentin[23]**

| CRCL (mL/min) | DAILY DOSE (mg/d) | DOSAGE (mg) | | | | |
|---|---|---|---|---|---|---|
| ≥60 | 900–3600 | 300 TID | 400 TID | 600 TID | 800 TID | 1200 TID |
| 30–59 | 400–1400 | 200 BID | 300 BID | 400 BID | 500 BID | 700 BID |
| 15–29 | 200–700 | 200 QD | 300 QD | 400 QD | 500 QD | 700 QD |
| 15* | 100–300 | 100 QD | 125 QD | 150 QD | 200 QD | 300 QD |
| ***Supplemental post-hemodialysis dose (mg)*** | | | | | | |
| Hemodialysis | | 125** | 150** | 200** | 250** | 350** |

Symbol key: TID is three times daily, BID is twice daily, QD is once daily
*For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).
**Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

For drugs with narrow therapeutic indexes, measured or estimated creatinine clearance may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction. Estimated pharmacokinetic parameters are then used in pharmacokinetic dosing equations to compute initial doses for patients. Clearance is the best pharmacokinetic parameter to estimate using creatinine clearance because it is an independent parameter that deals solely with drug elimination. The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the nonrenal clearance of the drug (Figure 3-3). For digoxin, an equation that describes the relationship between digoxin clearance (Cl) and creatinine

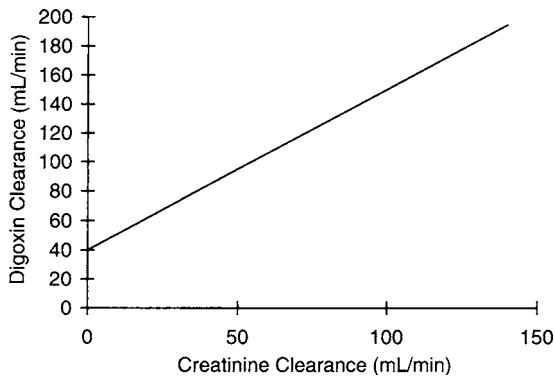


**FIGURE 3-3** Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The y-axis intercept (40 mL/min) is nonrenal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, nonrenal clearance is set to a value of 20 mL/min.

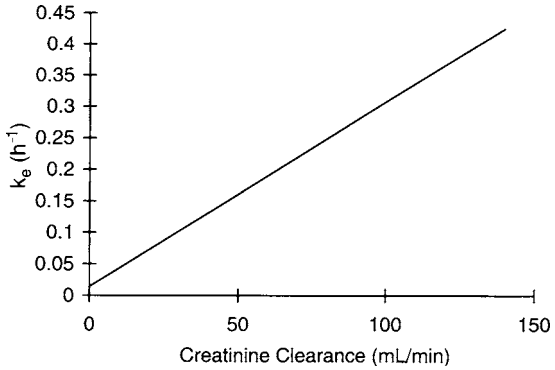


**FIGURE 3-4** Relationship between creatinine clearance and aminoglycoside elimination rate constant *($k_e$)* used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept (0.014 $h^{-1}$) is nonrenal elimination for aminoglycosides.

clearance (CrCl in mL/min) is: Cl (in mL/min) = 1.303 · CrCl + $Cl_{NR}$, where $Cl_{NR}$ is nonrenal clearance and equals 20 mL/min in patients with moderate-severe heart failure and 40 mL/min in patients with no or mild heart failure.[24]

Elimination rate constant ($k_e$) can also be estimated using creatinine clearance, but it is a dependent pharmacokinetic parameter whose result is reliant on the relative values of clearance and volume of distribution ($k_e$ = Cl/V). Because of this, changes in elimination rate constant may not always be due to changes in the renal elimination of the drug. The relationship between elimination rate constant and creatinine clearance is usually approximated by a straight line with a slope that is a function of renal elimination for the agent and an intercept that is related to the elimination of drug in functionally anephric patients (glomerular filtration rate ≈ 0; Figure 3-4). For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant ($k_e$) and creatinine clearance (CrCl in mL/min) is: $k_e$ (in $h^{-1}$) = 0.00293 · CrCl + 0.014.[25]

Volume of distribution can also change in patients with decreased renal function. Plasma protein binding displacement of drug by endogenous or exogenous substances that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function can increase the volume of distribution of drugs. Conversely, the volume of distribution of a drug can decrease if compounds normally excreted by the kidney accumulate to the extent that displacement of drug from tissue binding sites occurs. Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:[26] V (in L) = 226 + [(298 · CrCl)/(29.1 + CrCl)] where CrCl is in mL/min. The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

## HEPATIC DISEASE

Most lipid-soluble drugs are metabolized to some degree by the liver. Phase I type reactions, such as oxidation, hydrolysis, and reduction, are often mediated by the cytochrome P-450 enzyme system (CYP) which is bound to the membrane of the endoplasmic

reticulum inside hepatocytes. Phase II type reactions, including conjugation to form glucuronides, acetates, or sulfates, may also be mediated in the liver by cytosolic enzymes contained in hepatocytes. Phase I and phase II drug metabolism generally results in metabolites that are more water soluble and prone to elimination by the kidney. Transport proteins, such as P-glycoprotein, actively secrete drug molecules into the bile.

The liver receives its blood supply via the hepatic artery, which contains oxygenated blood from the aorta via the superior mesenteric artery, and the portal vein, which drains the gastrointestinal tract (Figure 3-5). Liver blood flow averages 1–1.5 L/min in adults with about one-third coming from the hepatic artery and about two-thirds coming from the portal vein. Orally administered medications must pass through the liver before entering the systemic circulation, so if the drug is metabolized by the liver, a portion of the dose may be inactivated by the hepatic first-pass effect before having a chance to exert a pharmacologic effect. In addition to hepatic metabolism, drugs can be eliminated unchanged by liver in the bile. The equation that describes hepatic drug metabolism is[27]:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, $f_B$ is the fraction of unbound drug in the blood, and $Cl'_{int}$ is intrinsic clearance.

Hepatic metabolism of drugs is not completely developed in neonates (~40-weeks gestational age), and continues to increase so that by age 3–6 months it is stable. In premature infants (<35 weeks), hepatic metabolism may take even longer to develop in the postpartum period. On a per kilogram basis, drug metabolism is more rapid in children until puberty. At that point, metabolic rate gradually decreases to adult values. The effect of advanced age on hepatic drug metabolism is quite variable. Patients over the age of 65 years may have decreased hepatic clearance of some drugs, but oftentimes concurrent disease states and conditions that effect drug pharmacokinetics obscure the influence of age in these older individuals. Elderly individuals have decreased liver mass, and it appears that hepatocytes which are still present have decreased ability to metabolize drugs.

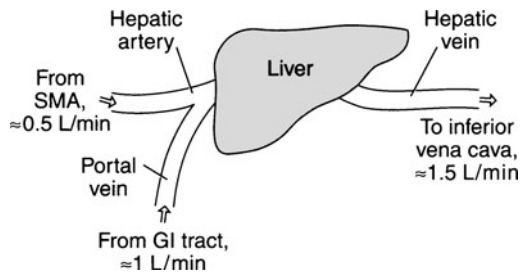


**FIGURE 3-5** Schematic representation of the liver. Liver blood flow to the organ is supplied by the hepatic artery and the portal vein. The hepatic artery branches off of the superior mesenteric artery and provides oxygenated blood to the liver at the rate of ~0.5 L/min. The portal vein drains blood from the gastrointestinal tract at the rate of ~1 L/min and passes its contents to the liver. Any chemicals, including orally administered drugs, must pass through the liver before it enters the systemic circulation. The hepatic vein drains the liver of blood and empties into the inferior vena cava.

There are two major types of liver disease: hepatitis and cirrhosis. Patients with hepatitis experience an inflammation of the liver, and as a result, hepatocytes may experience decreased ability to function or die. Patients with acute hepatitis usually experience mild, transient decreases in drug metabolism that require no or minor changes in drug dosing. If the patient develops chronic hepatitis, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes will be required at some point. In patients with hepatic cirrhosis, there is a permanent loss of functional hepatocytes. Drug dosage schedules usually need to be modified in patients with severe cirrhosis. With sufficient long-term hepatocyte damage, patients with chronic hepatitis can progress to hepatic cirrhosis.

When hepatocytes are damaged they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduces the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase. A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely large increases in steady-state concentrations for orally administered drugs. Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by nonfunctional connective tissue which increases intraorgan pressure causing portal vein hypertension and shunting of blood flow around the liver. The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further. The liver produces albumin and, probably, $\alpha_1$-acid glycoprotein, the two major proteins that bind acidic and basic drugs, respectively, in the blood. In patients with cirrhosis, the production of these proteins decline. When this is the case, the free fraction of drugs in the blood increases because of a lack of binding proteins. Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites. The increased free fraction in the blood will alter hepatic and renal drug clearance as well as the volume of distribution for drugs that are highly protein bound ($V = V_B + (f_B/f_T)V_T$, where V is the volume of distribution, $V_B$ and $V_T$ are the physiologic volume of blood and tissues, respectively, and $f_B$ and $f_T$ are the free fraction of drug in the blood and tissues, respectively). Since clearance typically decreases and volume of distribution usually increases or does not appreciably change for a drug in patients with liver disease, the elimination rate constant ($k_e$) almost always increases in patients with decreased liver function ($k_e = Cl/V$, where Cl is clearance and V is volume of distribution).

## Determination of Child-Pugh Scores

Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that measured or estimated creatinine clearance is used to measure renal function. The most common way to estimate the ability of the liver to metabolize drug is to determine the Child-Pugh score for a patient.[28] The Child-Pugh score consists of five laboratory tests or clinical symptoms. The five areas are serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal)–3 (severely abnormal; Table 3-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15.

**TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]**

| TEST/SYMPTOM | SCORE 1 POINT | SCORE 2 POINTS | SCORE 3 POINTS |
|---|---|---|---|
| Total bilirubin (mg/dL) | <2.0 | 2.0–3.0 | >3.0 |
| Serum albumin (g/dL) | >3.5 | 2.8–3.5 | <2.8 |
| Prothrombin time (seconds prolonged over control) | <4 | 4–6 | >6 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Moderate | Severe |

A Child-Pugh score equal to 8–9 is grounds for a moderate decrease (~25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized, and a score of 10 or greater indicates that a significant decrease in initial daily dose (~50%) is required for drugs that are mostly liver metabolized. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects.

For example, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d. For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours. The patient would be closely monitored for pharmacologic and toxic effects due to the medication, and the dose would be modified as needed.

## Estimation of Drug Dosing and Pharmacokinetic Parameters for Liver Metabolized Drugs

For drugs that are primarily liver metabolized, pharmacokinetic parameters are assigned to patients with liver disease by assessing values previously measured in patients with the same type of liver disease (e.g., hepatitis or cirrhosis) and a similar degree of liver dysfunction. Table 3-3 gives values for theophylline clearance in a variety of patients, including patients with cirrhosis.[29] The dose and dosing interval needed to achieve steady-state concentrations in the lower end of the therapeutic range using pharmacokinetic parameters measured in patients with liver disease are computed using pharmacokinetic equations. For example, the theophylline dosage rates listed in Table 3-3 are designed to produce steady-state theophylline concentrations between 8 and 12 mg/L. They were computed by multiplying theophylline clearance and the desired steady-state concentration ($MD = Css \cdot Cl$, where MD is the maintenance dose, Css is the steady-state concentration, and Cl is drug clearance). Average theophylline clearance is about 50% less in adults with liver cirrhosis compared to adults with normal hepatic function. Because of this, initial theophylline doses for patients with hepatic cirrhosis are one-half the usual dose for adult patients with normal liver function.

When prescribing medications that are principally eliminated by the liver in patients with liver dysfunction, it is possible to decrease the dose while retaining the normal

**TABLE 3-3 Theophylline Clearance and Dosage Rates for Patients with Various Disease States and Conditions[28]**

| DISEASE STATE/CONDITION | MEAN CLEARANCE (mL/min/kg) | MEAN DOSE (mg/kg/h) |
|---|---|---|
| Children 1–9 years | 1.4 | 0.8 |
| Children 9–12 years or adult smokers | 1.25 | 0.7 |
| Adolescents 12–16 years or elderly smokers (>65 years) | 0.9 | 0.5 |
| Adult nonsmokers | 0.7 | 0.4 |
| Elderly nonsmokers (>65 years) | 0.5 | 0.3 |
| Decompensated CHF, cor pulmonale, cirrhosis | 0.35 | 0.2 |

Mean volume of distribution = 0.5 L/kg.

dosage interval, retain the normal dose and prolong the dosage interval, or modify both the dose and dosage interval. Compared to individuals with normal liver function receiving a drug at the usual dose and dosage interval, patients with hepatic disease that receive a normal dose but a prolonged dosage interval will have similar maximum and minimum steady-state serum concentrations (Figure 3-2). However, if the dose is decreased but the dosage interval kept at the usual frequency, maximum steady-state concentrations will be lower and minimum steady-state concentrations will be higher for patients with liver disease than for patients with normal hepatic function. The actual method used to reduce the dose for patients with liver dysfunction will depend on the route of administration and the available dosage forms. For example, if the medication is only available as an oral capsule, it is likely that the usual dose will be given to a patient with liver disease but the dosage interval will be prolonged. However, if the drug is given parenterally, it may be possible to simultaneously modify the dose and dosage interval to attain the same maximum and minimum steady-state concentrations in patients with hepatic dysfunction as those encountered in patients with normal liver function.

## Implications of Hepatic Disease on Serum Drug Concentration Monitoring and Drug Effects

The pharmacokinetic alterations that occur with hepatic disease result in complex changes for total and unbound steady-state concentrations and drug response. The changes that occur depend on whether the drug has a low or high hepatic extraction ratio. As previously discussed, hepatic drug metabolism is described by the following equation:[25]

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, $f_B$ is the fraction of unbound drug in the blood, and $Cl'_{int}$ is intrinsic clearance. For drugs with a low hepatic extraction ratio (≤30%), the numeric

value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound ($LBF >> f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [$LBF \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

Similarly, for drugs with a high hepatic extraction ratio (≥70%), the numeric value of liver blood flow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent ($LBF << f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to the product of free fraction of drug in the blood and intrinsic clearance [$f_B \cdot Cl'_{int} \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to liver blood flow for a drug with a high hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{f_B \cdot Cl'_{int}} = LBF$$

For drugs with intermediate hepatic extraction ratios, the entire liver clearance equation must be used and all three factors, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account. An extremely important point for clinicians to understand is that the factors which are important determinants of hepatic clearance are different depending on the liver extraction ratio for the drug.

In order to illustrate the differences that may occur in steady-state drug concentrations and pharmacologic effects for patients with liver disease, a graphical technique will be used (Figure 3-6). The example assumes that a low hepatic extraction ratio drug (100% liver metabolized) is being given to a patient as a continuous intravenous infusion, and that all physiologic, pharmacokinetic, and drug effect parameters (shown on the y-axis) are initially stable. On the x-axis, an arrow indicates that intrinsic clearance decreases due to the development of hepatic cirrhosis in the patient; an assumption made for this illustration is that any changes in the parameters are instantaneous. An increase in the parameter is denoted as an uptick in the line while a decrease in the parameter is shown as a downtick in the line. The first three parameters are physiologic values (LBF, $f_B$, and $Cl'_{int}$) that will change in response to the development of hepatic dysfunction. In this case, only intrinsic clearance decreased due to the destruction of hepatocytes, and liver blood flow and free fraction of drug in the blood was not altered (Figure 3-6). This change will decrease the hepatic clearance of the drug, volume of distribution will not be modified because blood and tissue volume or plasma protein and tissue binding did not change, and half-life will increase because of the decrease in clearance [$t_{1/2} = (0.693 \cdot V)/Cl$, where $t_{1/2}$ is half-life, Cl is clearance, and V is volume of distribution]. Total and unbound steady-state drug concentrations will increase in tandem, and the pharmacologic response will increase because of the increase in unbound serum concentration.

Using the same baseline conditions as in the previous example, it is possible to examine what would happen if the major change in a similar patient receiving the same drug

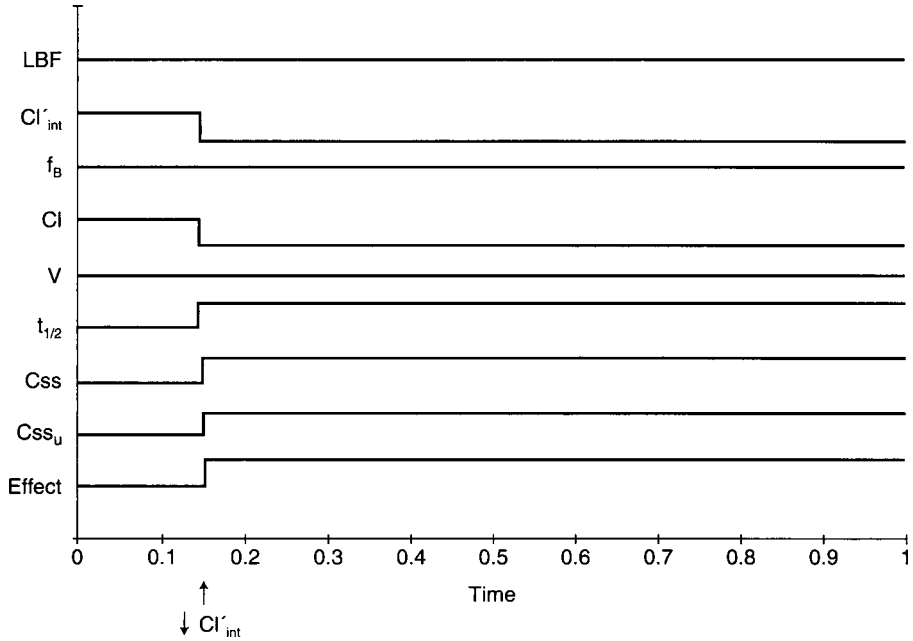


**FIGURE 3-6** Changes in physiologic parameters *(LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

decreased plasma protein binding due to hypoalbuminemia and hyperbilirubinemia (Figure 3-7). Under these circumstances, liver blood flow and intrinsic clearance would not change, but free fraction of drug in the blood would increase. Because of the increased free fraction of drug in the blood, both clearance and volume of distribution would simultaneously increase. Clearance increases for a low hepatic extraction ratio drug because more is free to leave the bloodstream and enter hepatocytes where it can be metabolized. Volume of distribution increases because more drug is free to leave the vascular system and enter various tissues. Depending on the relative changes in clearance and volume of distribution, half-life could increase, decrease, or not change; for the purpose of this example the assumption is made that alterations in these independent parameters are similar so half-life does not change. The total steady-state concentration would decrease because total clearance increased, but the unbound steady-state concentration would remain unchanged because the decrease in total concentration is offset by the increase in free fraction of unbound drug. Finally, the pharmacologic effect of the drug is the same because free steady-state concentrations of the drug did not change. This can be an unexpected outcome for the decrease in protein binding, especially because the total

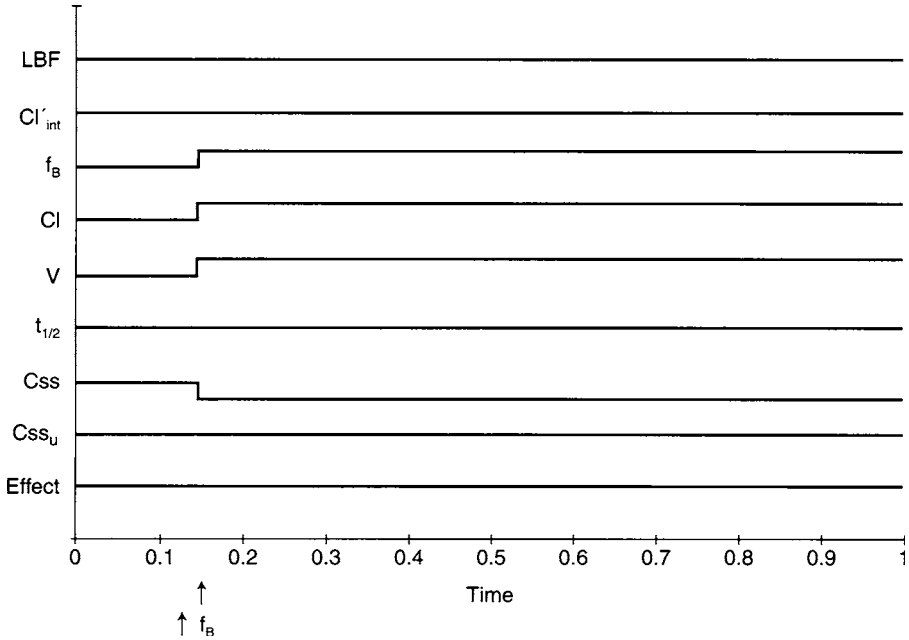


**FIGURE 3-7** Changes in physiologic parameters *(LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if decreased protein binding occurred ($\uparrow f_B$, indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Increased free fraction of drug in the blood secondary to decreased plasma protein binding could happen during liver dysfunction because of hypoalbuminemia or hyperbilirubinemia. Increased free fraction of drug can occur in patients with normal liver function secondary to a plasma protein binding displacement drug interaction.

steady-state concentration of the drug decreased. Clinicians need to be on the outlook for situations like this because the total drug concentration (bound + unbound) can be misleading and cause an unwarranted increase in drug dosage. Unbound drug concentrations are available for several agents that are highly plasma protein bound, such as phenytoin, valproic acid, and carbamazepine, and are valuable tools to guide drug dosage in liver disease patients.

Finally, decreases in liver blood flow need to be considered for drugs with low hepatic extraction ratios. A decrease in liver blood flow will not change intrinsic clearance, plasma protein binding, clearance or volume of distribution under usual circumstances, and, thus, will not change total steady-state concentrations, unbound steady-state concentrations, or the pharmacologic effects of the drug. However, a drastic decrease in liver blood flow can effectively stop delivery of drug to the liver and change liver clearance even for compounds with a low hepatic extraction ratios.

For drugs with high hepatic extraction ratios, the pattern of changes using the above model is entirely different. If intrinsic clearance changes due to hepatocyte destruction for

a high hepatic extraction ratio drug, liver blood flow and unbound fraction of drug in the blood remain unaltered (Figure 3-8). Pharmacokinetic constants also do not change, because none are influenced by intrinsic clearance. Because of this, unbound and total steady-state drug concentrations and pharmacologic effect are unchanged. If the drug were administered orally, the hepatic first-pass effect would be decreased which would increase the bioavailability of the drug. Since this is effectively an increase in drug dosage, average total and unbound drug concentrations and pharmacologic effect would increase for this route of administration ($Css = [F(D/\tau)/Cl]$, where F is the bioavailability fraction, Css is the total steady-state drug concentration, D is dose, $\tau$ is the dosage interval, and Cl is clearance).

A decrease in plasma protein binding due to lack of binding protein or displacement from binding sites causes severe problems for high hepatic extraction ratio drugs (Figure 3-9). Decreased plasma protein binding results in an increased free fraction of drug in the blood, but no change in liver blood flow or intrinsic clearance. Since clearance is a function of liver blood flow, it does not change. However, a higher free fraction of drug in the blood increases the volume of distribution and this change causes a longer half-life for

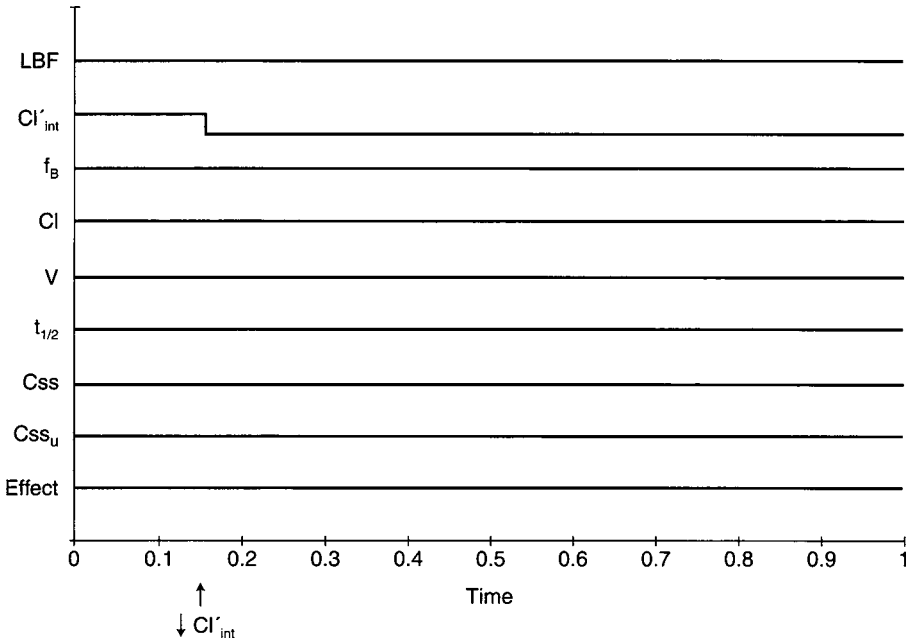


**FIGURE 3-8** Changes in physiologic parameters *(LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

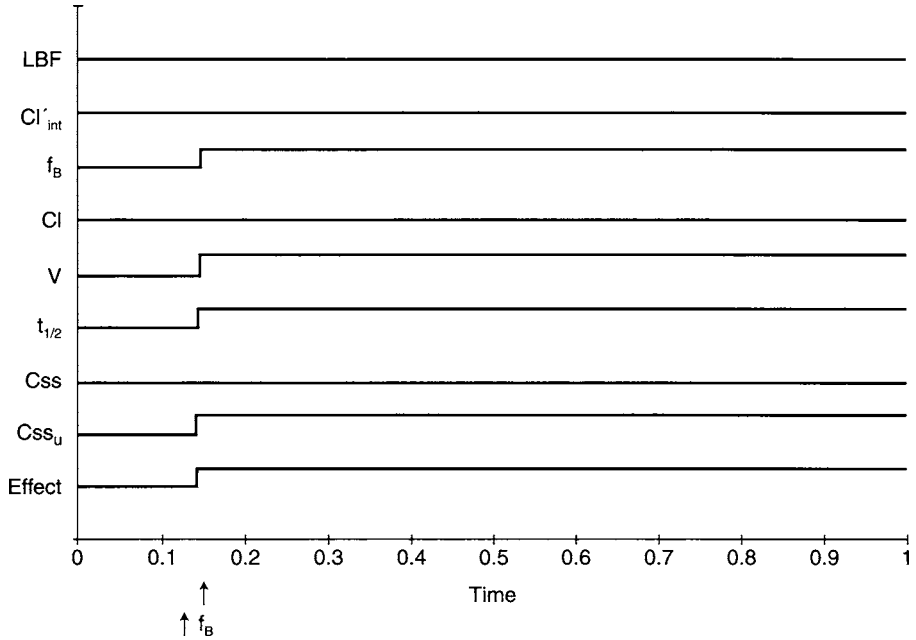


**FIGURE 3-9** Changes in physiologic parameters *(LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if decreased protein binding occurred ($\uparrow f_B$, indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Increased free fraction of drug in the blood secondary to decreased plasma protein binding could happen during liver dysfunction because of hypoalbuminemia or hyperbilirubinemia. Increased free fraction of drug can occur in patients with normal liver function secondary to a plasma protein binding displacement drug interaction.

the drug. Total steady-state concentration does not change because clearance did not change. But, unbound steady-state concentration increases because of the increased free fraction of drug in the blood. Pharmacologic effect increases due to the increased unbound steady-state concentration. This is a very subtle change in drug metabolism, because total steady-state concentrations do not change, but the pharmacologic effect is augmented. Clinicians need to keep this possible change in mind and order unbound drug concentrations, if available, when they suspect that this phenomenon may be taking place. If unbound drug concentrations (or no drug concentrations) are available, a trial decrease in dose may be warranted. Orally administered drug would result in a similar pattern of change, but the increased free fraction of drug in the blood would result in a larger hepatic first-pass effect and an effective reduction in dose which would partially offset the increase in unbound steady-state concentration.

If liver blood flow decreases, the pharmacokinetic and pharmacologic changes are more straightforward for medications with large hepatic extraction ratios (Figure 3-10). Decreased liver blood flow does not change intrinsic clearance or the unbound fraction of

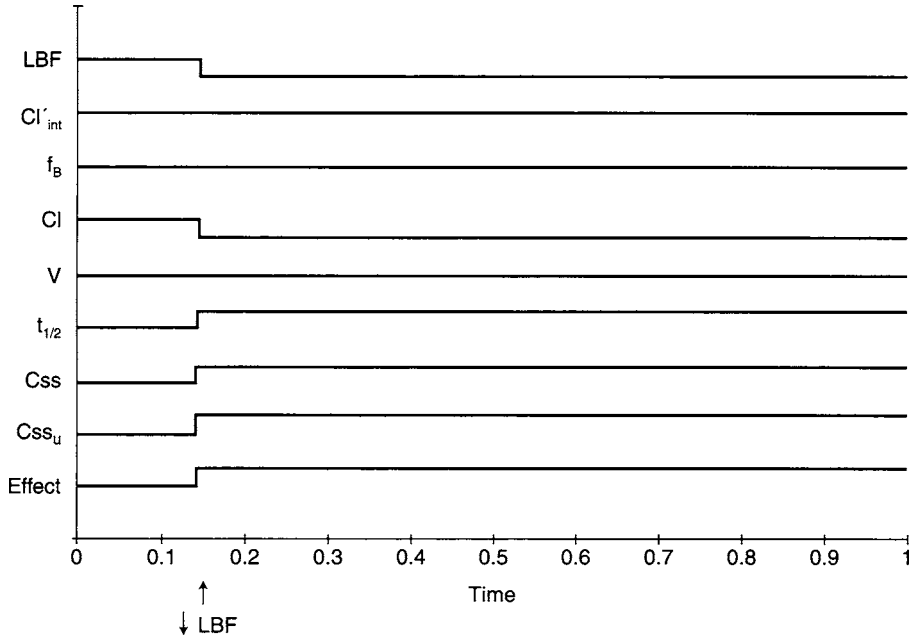


**FIGURE 3-10** Changes in physiologic parameters *(LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if liver blood flow decreases (↓LBF, indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Decreased liver blood flow could happen because of portal hypertension secondary to hepatic cirrhosis. Decreased liver blood flow can occur in patients with normal liver function secondary to a drug interaction with an agent that decreases cardiac output such as β-blockers.

drug in the blood. Clearance decreases because it is dependent on liver blood flow for drugs with a high hepatic extraction ratio. Volume of distribution remains constant, but half-life increases because of the decrease in clearance. Total steady-state concentration increases because of the decrease in clearance, free steady-state concentration rises due to the increase in total steady-state concentration, and the increase in pharmacologic effect tracks the change in free concentration. If the drug is given orally, the first-pass effect would increase, and bioavailability would decrease, partially offsetting the increase in total and unbound steady-state concentrations.

## HEART FAILURE

Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow. Changes in drug pharmacokinetics due to decreased renal blood flow are not widely reported. However, declines in hepatic clearance, especially for

compounds with moderate-to-high hepatic extraction ratios, are reported for many drugs. Additionally, decreased drug bioavailability has been reported in patients with heart failure. The proposed mechanisms for decreased bioavailability are collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract. The volume of distribution for some drugs decreases in patients with heart failure. Because clearance and volume of distribution may or may not simultaneously change, the alteration in half-life, if any, is difficult to predict in patients with heart failure.

## DIALYSIS

Dialysis is a process whereby substances move via a concentration gradient across a semipermeable membrane (Figure 3-11). Artificial kidneys (also known as dialysis coils or filters) are available for use in hemodialysis that use a synthetic semipermeable membrane to remove waste products from the blood. Also, physiologic membranes, such as those present in the peritoneal cavity in the lower abdomen, can be used with peritoneal dialysis as an endogenous semipermeable membrane. Substances that are small enough to pass through the pores in the semipermeable membrane will pass out of the blood into the dialysis fluid. Once in the dialysis fluid, waste products and other compounds can be removed from the body. In some cases, dialysis is used to remove drugs from the bodies of patients that have taken drug overdoses or are experiencing severe adverse effects from the drug. However, in most cases drug molecules are removed from the blood coincidental to the removal of toxic waste products that would usually be eliminated by the kidney.

Because drugs can be removed by dialysis, it is important to understand when drug dosing needs to be modified in renal failure patients undergoing the procedure. Often,

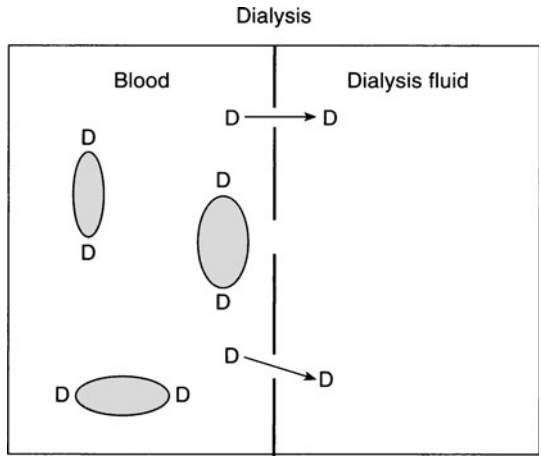


**FIGURE 3-11** Dialysis removal of drug can occur when a patient's blood comes in contact with a semipermeable membrane that has drug-free dialysis fluid on the other side. In this schematic, the semipermeable membrane has pores in it large enough for unbound drug to pass through (represented by *D*), but not for protein-bound drug to pass through (denoted by *Ds attached to ovals* representing plasma proteins).

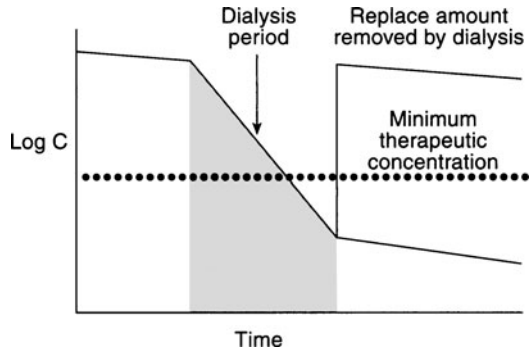


**FIGURE 3-12** Concentration-time graph for a drug removed by dialysis. The *shaded area* indicates the time period that a dialysis procedure was conducted. Because extra drug was removed from the blood during dialysis, concentrations dropped much faster during that period. After dialysis is finished, the concentrations again drop at the predialysis rate. If drug concentrations drop below the minimum therapeutic concentration (shown by the *dark, dotted horizontal line)*, it may be necessary to give a supplemental dose to retain the pharmacologic effect of the drug (indicated by increase in drug concentration after dialysis).

dialysis removes enough drug from a patient's body that supplemental doses need to be given after dialysis has been completed (Figure 3-12). In a renal failure patient, the only clearance mechanism available to remove drugs from the body are nonrenal ($Cl = Cl_{NR}$, where Cl is total clearance and $Cl_{NR}$ is nonrenal clearance). When the patient is receiving dialysis, clearance from both nonrenal routes and dialysis are present which will accelerate drug removal from the body during the dialysis procedure if the compound is significantly removed by dialysis ($Cl = Cl_{NR} + Cl_D$, where $Cl_D$ is dialysis clearance). In order to determine if dialysis clearance is significant, one should consider the absolute value of dialysis clearance and the relative contribution of dialysis clearance to total clearance. Additionally, if dialysis clearance is ≥30% of total clearance or if the total amount of drug removed by the dialysis procedure is enough to warrant a postdialysis replacement dose, dialysis clearance is considered to be significant.

## Drug Characteristics that Effect Dialysis Removal

*MOLECULAR SIZE*

Molecular size relative to pore size in the semipermeable membrane is a factor that influences dialysis clearance of a compound. Most hemodialysis procedures are conducted using "low-flux" artificial kidneys which have relatively small pores in the semipermeable membranes. However, "high-flux" filters are now available and widely used in some patients. The semipermeable membranes of these artificial kidneys have much larger pore sizes and larger surface areas so large drug molecules, such as vancomycin, that were previously considered unable to be removed by hemodialysis can be cleared by high-flux filters. It is important that clinicians know which type of artificial kidney is used for a patient before assessing its potential to remove drug molecules.

For low-flux filters, small drug molecules (molecular weight <500 Da, such as theophylline, lidocaine, procainamide) relative to the pore size of the semipermeable membrane

tend to be readily eliminated by dialysis and have high extraction ratios for the artificial kidney. In this case, dialyzability of the drug is influenced by blood flow to the artificial kidney, dialysis fluid flow rate to the artificial kidney, and the surface area of the semipermeable membrane inside the artificial kidney. Increased blood flow delivers more drug to the dialysis coil, increased dialysis fluid flow rate removes drug that entered the dialysis fluid more quickly from the artificial kidney and increases the concentration gradient across the semipermeable membrane, and increased semipermeable membrane surface area increases the number of pores that a drug molecule will encounter, making it easier for drug molecules to pass from the blood into the dialysis fluid.

Drug molecules with moderate molecular weights (molecular weight 500–1000 Da, such as aminoglycoside antibiotics [~400–500 Da] and digoxin) have a decreased ability to pass through the semipermeable membrane contained in low-flux filters. However, many drugs that fall in this intermediate category have sufficient dialysis clearances to require postdialysis replacement doses. Large drug molecules (molecular weight >1000 Da, such as vancomycin) are not removed to a significant extent when low-flux filters are used for dialysis because pore sizes in these artificial kidneys are too small for the molecules to fit through. However, many large molecular weight drugs can be removed by dialysis when high-flux filters are used, and, in some of these cases, supplemental postdialysis drug doses will be needed to maintain therapeutic amounts of drug in the body.

*WATER/LIPID SOLUBILITY*

Drugs that have a high degree of water solubility will tend to partition into the water-based dialysis fluid, while lipid-soluble drugs tend to remain in the blood.

*PLASMA PROTEIN BINDING*

Only unbound drug molecules are able to pass through the pores in the semipermeable membrane; drug–plasma protein complexes are too large to pass through the pores and gain access to the dialysis fluid side of the semipermeable membrane. Drugs that are not highly plasma protein bound have high free fractions of drug in the blood and are prone to better dialysis clearance. Drugs that are highly bound to plasma proteins have low free fractions of drug in the blood and poor dialysis clearance rates.

*VOLUME OF DISTRIBUTION*

The volume of distribution for a drug is a function of blood volume ($V_B$), organ size ($V_T$), drug plasma protein binding ($f_B$, free fraction of drug in the blood), and drug tissue binding [$f_T$, free fraction of drug in the tissues; $V = V_B + (f_B/f_T)V_T$]. Medications with large volumes of distribution are principally located at tissue binding sites and not in the blood where dialysis can remove the drug. Because of this, agents with large volumes of distribution are not easily removed from the body. In fact, some compounds such as digoxin, have good hemodialysis clearance rates, and drug contained in the bloodstream is very effectively eliminated. However, in this case the majority of the drug is present in the tissues and only a small amount of the total drug present in the body is removed. If serum concentrations of these types of drugs are followed closely during hemodialysis, the concentrations decrease by a substantial amount. But, when dialysis is completed, the blood and tissues have a chance to reequilibrate and serum concentrations increase, sometimes to their predialysis concentration. This “rebound” in serum concentration has been reported for several drugs.

Compounds with small volumes of distribution (<1 L/kg, such as the aminoglycoside antibiotics and theophylline) usually demonstrate high dialysis clearance rates. Drugs with moderate volumes of distribution (1–2 L/kg) have intermediate dialysis clearance values, while agents with large volumes of distribution (>2 L/kg, such as digoxin and tricyclic antidepressants) have poor dialysis characteristics.

## HEMODIALYSIS

Hemodialysis is a very efficient procedure to remove toxic waste from the blood of renal failure patients (Figure 3-13). Blood is pumped out of the patient at the rate of 300–400 mL/min and through one side of the semipermeable membrane of the artificial kidney by the hemodialysis machine. Cleansed blood is then pumped back into the vascular system of the patient. In acute situations, vascular access can be obtained through centrally placed catheters. For patients with chronic renal failure, vascular shunts made of synthetic materials will be surgically placed between a high blood flow artery and vein in the arm or other site for the purpose of conducting hemodialysis. Dialysis fluid is pumped through the artificial kidney at a rate of 400–600 mL/min on the other side of the semipermeable membrane, in the opposite direction of blood flow. This "countercurrent" flow is more efficient in removing waste products than running the blood and dialysis fluid in parallel to each other. Dialysis fluid is electrolyte and osmotically balanced for the individual patient. It is possible to increase or decrease serum electrolytes by increasing or decreasing the concentration of the ion in the dialysis fluid compared to the concurrent serum value. Also, by adding solutes in order to increase the osmolality of the dialysis fluid relative to the blood, it is possible to remove fluid from the patient's body by osmotic pressure across the semipermeable membrane of the artificial kidney. This process is known as ultrafiltration. Using low-flux filters, hemodialysis is usually performed for 3–4 hours three times weekly.

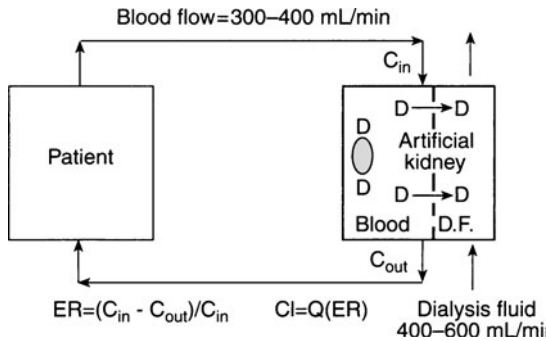


**FIGURE 3-13** Hemodialysis removes blood from the patient's body (indicated by *arrows from patient to artificial kidney)* and passes it through an artificial kidney that contains a semipermeable membrane. Inside the artificial kidney, waste products pass into the dialysis fluid and are eliminated from the body. If drug molecules can pass through the pores in the semipermeable membrane, they will also be eliminated from the body. The extraction ratio of the artificial kidney can be computed using the concentration into ($C_{in}$) and out of ($C_{out}$) the device. Dialysis clearance can be calculated by taking the product of the dialysis extraction ratio and blood flow to the dialysis machine (Q). D = drug; D.F. = dialysis fluid.

The Food and Drug Administration has required pharmacokinetic studies to be done for renally eliminated drugs in patients receiving chronic hemodialysis since the mid-1980s. Because of this, the package insert for the drug may include manufacturer recommended doses to be administered to patients in the posthemodialysis period (Table 3-1). Guidelines for the administration of post-hemodialysis replacement doses are available for older drugs as well as updated guidelines for newer drugs that may not be included in the package insert.[4,6,7] Also, the primary literature should be consulted to ensure that the newest guidelines are used for all drugs. When assessing the hemodialysis removal characteristics of a drug and the need for postdialysis replacement doses, it should be recognized that the majority of information available is for low-flux artificial kidneys. If a high-flux dialysis coil is used, the primary literature is probably the best source of information, but in many cases studies have not been conducted using this technology.

## Computation of Initial Doses and Modification of Doses Using Drug Serum Concentrations

Initial drug doses of patients with renal failure undergoing hemodialysis can be based on expected pharmacokinetic parameters for this population when published information for a drug is inadequate or the agent has a very narrow therapeutic index. For example, an initial dosage regimen for tobramycin needs to be computed for a patient to achieve peak concentrations of 6–7 mg/L and postdialysis concentrations 1–2 mg/L. The patient is a 62-year-old, 5-ft 8-in male who weighs 65 kg, has chronic renal failure, and receives hemodialysis three times weekly with a low-flux dialysis filter. Patients with renal failure are prone to having poor fluid balance because their kidneys are not able to provide this important function. Because of this, the patient should be assessed for overhydration (due to renal failure) or underhydration (due to renal failure and increased loss due to fever). Weight is a good indication of fluid status, and this patient's weight is less than his ideal weight [$IBW_{male}$ = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(68 in − 60) = 68 kg]. Other indications of state of hydration (skin turgor, etc.) indicate that the patient has normal fluid balance at this time. Because of this, the average volume of distribution for aminoglycoside antibiotics equal to 0.26 L/kg can be used.

A loading dose of tobramycin would be appropriate for this patient because the expected half-life is long (~50 hours); administration of maintenance doses only might not result in therapeutic maximum concentrations for a considerable time period while drug accumulation is occurring. The loading dose is to be given after hemodialysis ends at 1300 H on Monday (hemodialysis conducted on Monday, Wednesday, and Friday from 0900–1300 H). Because the patient is expected to have a long half-life compared to the infusion time of the drug ($^1/_2$–1 hour), little drug will be eliminated during the infusion period, and IV bolus one-compartment model equations can be used. The loading dose for this patient would be based on the expected volume of distribution: V = 0.26 L/kg · 65 kg = 16.9 L; LD = $C_{max}$ · V = 6 mg/L · 16.9 L = 101 mg, rounded to 100 mg (LD is loading dose, $C_{max}$ is the maximum concentration after drug administration). This loading dose was given at 1400 H (Figure 3-14). Until the next dialysis period at 0900 H on Wednesday, tobramycin is cleared only by the patient's own body mechanisms. The expected elimination rate constant ($k_e$) for a patient with a creatinine clearance of approximately zero is: $k_e$ (in $h^{-1}$) = 0.00293 · CrCl + 0.014 = 0.00293 (0 mL/min) + 0.014 = 0.014 $h^{-1}$. The expected concentration at 0900 H on Wednesday is: $C = C_0e^{-k_et}$,

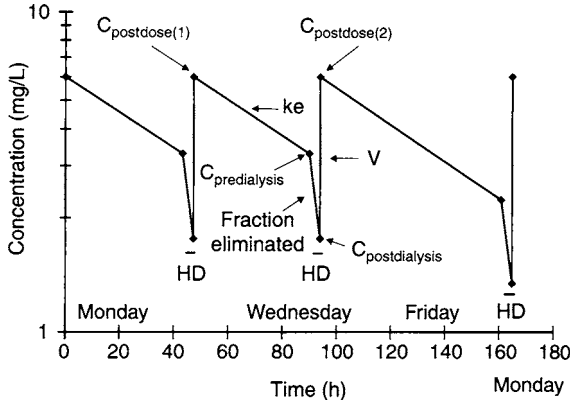


**FIGURE 3-14** Concentration/time graph for tobramycin in a hemodialysis patient using estimated, population pharmacokinetic parameters. The initial dose was given postdialysis at 1400 H on Monday (time = 0 hour). Hemodialysis periods are shown by small horizontal bars labeled with HD, and days are indicated on the time line. In order to compute patient-specific pharmacokinetic parameters, four serum concentrations are measured. The elimination rate constant ($k_e$) is computed using two concentrations after dosage administration ($C_{postdose(1)}$ and $C_{predialysis}$), the fraction eliminated by dialysis by two concentrations ($C_{predialysis}$ and $C_{postdialysis}$) before and after dialysis, and the volume of distribution using two concentrations ($C_{postdialysis}$ and $C_{postdose(2)}$) after another dosage administration.

where C is the concentration at t hours after the initial concentration of $C_0$; $C = (6\ mg/L)e^{-(0.014\ h^{-1})(43\ h)} = 3.3\ mg/L$.

While the patient is receiving hemodialysis, tobramycin is eliminated by the patient's own mechanisms plus dialysis clearance. During hemodialysis with a low-flux filter, the average half-life for aminoglycosides is 4 hours. Because the patient is dialyzed for 4 hours, the tobramycin serum concentration should decrease by $^1/_2$ to a value of 1.7 mg/L, or using formal computations: $k_e = 0.693/(t_{1/2}) = 0.693/4\ h = 0.173\ h^{-1}$; $C = C_0e^{-k_et} = (3.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.7\ mg/L$. At this time, a postdialysis replacement dose could be given to increase the maximum concentration to its original value of 6 mg/L: Replacement dose = $(C_{max} - C_{baseline})V = (6\ mg/L - 1.7\ mg/L)16.9\ L = 73\ mg$, round to 75 mg (where $C_{max}$ is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The postdialysis replacement dose of 75 mg was administered at 1400 H on Wednesday. Because all time frames and pharmacokinetic parameters are the same for Monday–Wednesday and Wednesday–Friday, the postdialysis replacement dose on Friday at 1400 H would also be 75 mg. However, more time elapses from Friday after drug administration to Monday before dialysis (67 hours), the next day for hemodialysis to be conducted in the patient, and this needs to be accounted for: $C = C_0e^{-k_et} = (6\ mg/L)e^{-(0.014\ h^{-1})(67\ h)} = 2.3\ mg/L$. Again, a 4-hour hemodialysis period would decrease serum concentrations by $^1/_2$ to a value of 1.2 mg/L: $C = C_0e^{-k_et} = (2.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.2\ mg/L$. At this time, a postdialysis replacement dose could be given to increase the maximum concentration to the original value of 6 mg/L: Replacement dose = $(C_{max} - C_{baseline})V = (6\ mg/L - 1.2\ mg/L)16.9\ L = 81\ mg$, round to 80 mg (where $C_{max}$ is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The postdialysis replacement dose of 80 mg was administered at 1400 H on Monday. Because all time frames and

pharmacokinetic parameters subsequent weeks, the following postdialysis replacement doses would be prescribed postdialysis at 1400 H: Wednesday and Friday 75 mg, Monday 80 mg. In this particular example, recommended doses are within 5 mg of each other, and if the clinician wished, the same postdialysis dose could be given on each day. However, this will not be true in every case.

Since the initial dosage scheme outlined for this patient used average, estimated pharmacokinetic parameters, it is likely that the patient has different pharmacokinetic characteristics. It is possible to measure the patient's own unique pharmacokinetic parameters using four serum concentrations (Figure 3-14). The intradialysis elimination rate constant can be determined by obtaining postdose ($C_{postdose(1)}$) and predialysis ($C_{predialysis}$) concentrations [$k_e = (C_{postdose(1)} - C_{predialysis})/\Delta t$, where $\Delta t$ is the time between the two concentrations], the fraction of drug eliminated by dialysis can be computed using predialysis and postdialysis ($C_{postdialysis}$) concentrations: Fraction eliminated = $[(C_{predialysis} - C_{postdialysis})/C_{predialysis}]$, and the volume of distribution can be calculated using postdialysis and postdose concentrations: $V = D/(C_{postdose(2)} - C_{postdialysis})$. Note that if the drug has a postdialysis "rebound" in drug concentrations, postdialysis serum samples should be obtained after blood and tissue have had the opportunity to reequilibrate. In the case of aminoglycosides, postdialysis samples should be collected no sooner than 3–4 hours after the end of dialysis. Once individualized pharmacokinetic parameters have been measured, they can be used in the same equations used to compute initial doses in the previous section in place of average population pharmacokinetic parameters, and used to calculate individualized doses for dialysis patients. It is also possible to use a mixture of measured and population-estimated pharmacokinetic parameters. For instance, a clinician may wish to measure the elimination rate constant or volume of distribution for a patient, but elect to use an average population estimate for fraction of drug removed by the artificial kidney.

### Methods to Measure Hemodialysis Clearance

If needed, hemodialysis clearance can be measured in patients. The extraction ratio method measures the extraction of drug across the artificial kidney by obtaining simultaneous blood samples on input ($C_{in}$) and output ($C_{out}$) side of the dialysis coil (Figure 3-13). The tubing carrying blood to and from the patient usually has injection ports that can be used as access points to get the necessary blood samples. The artificial kidney extraction ratio (ER) can be computed using serum concentrations measured from the blood samples: $ER = (C_{in} - C_{out})/C_{in}$. Blood flow from the hemodialysis machine (HDBF) is available as a continuous readout on the pump, and hemodialysis clearance ($Cl_{HD}$) can be computed by taking the product of the extraction ratio and blood flow parameters: $Cl_{HD} = HDBF \cdot ER$. The advantage to this technique is that it is methodologically simple. The disadvantage is if the dialysis extraction ratio is low, serum concentration differences between $C_{in}$ and $C_{out}$ will be small and difficult for the drug assay to determine.

Another method is to collect the waste dialysis fluid used during the dialysis procedure, and measure several serum drug concentrations during the same time interval (Figure 3-15). The amount of drug eliminated in the dialysis fluid ($A_{Dialysis}$) is determined by multiplying the volume of dialysis fluid ($V_{Dialysis}$), and the concentration of drug in the dialysis fluid ($C_{Dialysis}$): $A_{Dialysis} = V_{Dialysis} \cdot C_{Dialysis}$. Hemodialysis clearance ($Cl_{HD}$) is computed by dividing the amount of drug eliminated in the dialysis fluid by the area under the serum concentration/time curve during the dialysis period ($AUC_{Dialysis}$, calculated using the serum concentrations obtained during hemodialysis): $Cl_{HD} = A_{Dialysis}/AUC_{Dialysis}$. An

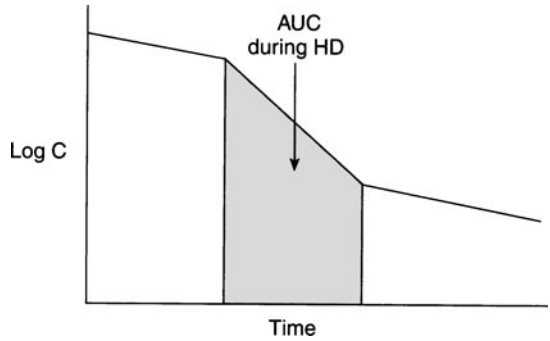


**FIGURE 3-15** One method to measure hemodialysis clearance is to take the quotient of the amount of drug eliminated by the dialysis procedure ($A_{Dialysis}$) and the area under the concentration/time curve *(AUC)* during the dialysis time period *(HD,* indicated by the *shaded area).*

advantage of this method is that it is determined using multiple serum concentrations and may be more accurate. Disadvantages include collection of a large volume of dialysis fluid (~120 L) and the large number of serum concentrations needed to determine $AUC_{Dialysis}$.

The final method is to collect all the waste dialysis fluid used during the dialysis period, and measure a single serum drug concentration at the midpoint of the procedure. Using this information, hemodialysis clearance ($Cl_{HD}$) can be computed using the following equation: $Cl_{HD} = (C_{Dialysis} \cdot V_{Dialysis}) / (C_{Serum} \cdot T_{Dialysis})$, where $C_{Dialysis}$ is the drug concentration in the dialysis fluid, $V_{Dialysis}$ is the volume of dialysis fluid, $C_{Serum}$ is the drug serum concentration, and $T_{Dialysis}$ is the duration of the hemodialysis procedure. An advantage of this technique is that it requires only one serum concentration. The chief disadvantage is that all dialysis fluid used during hemodialysis must be collected.

## HEMOFILTRATION

Hemofiltration comprises a family of techniques that have some similarities and some differences compared to hemodialysis.[30] The hemofilter used in hemofiltration is similar to the artificial kidney used in hemodialysis. The pore size in hemofilters is large, which allows drug molecules up to 20,000 Da to cross its semipermeable membrane.

Continuous arteriovenous hemofiltration (CAVH) and continuous venovenous hemofiltration (CVVH) use an extracorporeal circuit that runs from an artery to a vein or from a vein to a vein, respectively. These processes do not use a dialysis fluid, so plasma water that passes through the hemofilter is collected and discarded. Continuous arteriovenous hemodialysis with filtration (CAVHD) and continuous venovenous hemodialysis with filtration (CVVHD) is a hybrid of conventional hemodialysis and CAVH or CVVH, respectively. The hemofilter has hemodialysis fluid on the other side of the semipermeable membrane containing the patient's blood. For CVVH and CVVHD, a mechanical pump is used to propel blood through the hemofilter. For CAVH and CAVHD, the patient's own blood pressure usually provides the propulsion of blood through the hemofilter.

The sieving coefficient is the ratio of the drug concentration in the hemofiltrate to the drug concentration in the serum. Table 3-4 lists sieving coefficients for a variety of

**TABLE 3-4 Hemofiltration Sieving Coefficients for Selected Drugs[30,31]**

| DRUG | SIEVING COEFFICIENT |
|---|---|
| ***Antibiotics*** | |
| Amikacin | 0.95 |
| Amphotericin B | 0.35 |
| Amphotericin B (liposomal) | 0.10 |
| Ampicillin | 0.69 |
| Cefepime | 0.72 |
| Cefoperazone | 0.27 |
| Cefotaxime | 1.06 |
| Cefoxitin | 0.83 |
| Ceftazidime | 0.90 |
| Ceftriaxone | 0.20 |
| Cephapirin | 1.48 |
| Cilastatin | 0.75 |
| Ciprofloxacin | 0.58 |
| Clavulanic acid | 1.69 |
| Clindamycin | 0.49 |
| Doxycycline | 0.40 |
| Erythromycin | 0.37 |
| Fluconazole | 1.00 |
| Flucytosine | 0.80 |
| Ganciclovir | 0.84 |
| Gentamicin | 0.81 |
| Imipenem | 0.90 |
| Meropenem | 1.00 |
| Metronidazole | 0.84 |
| Mezlocillin | 0.71 |
| Nafcillin | 0.55 |
| Netilmicin | 0.93 |
| Oxacillin | 0.02 |
| Pefloxacin | 0.80 |
| Penicillin | 0.68 |
| Piperacillin | 0.82 |
| Streptomycin | 0.30 |
| Sulfamethoxazole | 0.30 |
| Teichoplanin | 0.05 |
| Ticarcillin | 0.83 |
| Tobramycin | 0.90 |
| Vancomycin | 0.80 |
| ***Other drugs*** | |
| Amrinone | 0.80 |
| Chlordiazepoxide | 0.05 |
| Cisplatin | 0.10 |
| Clofibrate | 0.06 |
| Cyclosporine | 0.58 |
| Diazepam | 0.02 |
| Digoxin | 0.70 |
| Digitoxin | 0.15 |
| Famotidine | 0.73 |
| Glyburide | 0.60 |
| Glutethimide | 0.02 |

(*Continued*)

**TABLE 3-4 (*Continued*)**

| DRUG | SIEVING COEFFICIENT |
|---|---|
| Lidocaine | 0.14 |
| Lithium | 0.90 |
| Metamizole | 0.40 |
| N-acetylprocainamide | 0.92 |
| Nizatidine | 0.59 |
| Nitrazepam | 0.08 |
| Nomifensin | 0.70 |
| Oxazepam | 0.10 |
| Phenobarbital | 0.80 |
| Phenytoin | 0.45 |
| Procainamide | 0.86 |
| Ranitidine | 0.78 |
| Tacrolimus | 0.26 |
| Theophylline | 0.80 |

drugs.[31,32] The ultrafiltration rate (UFR) is the filtration provided by the specific hemofiltration technique. Typical ranges for UFR are 10–16 mL/min for procedures that do not use extracorporeal blood pumps, and 20–30 mL/min for procedures that use extracorporeal blood pumps. When hemofiltration procedures that incorporate dialysis fluid are used, an additional 15–20 mL/min is added to these values.[31,32]

Several different methods of calculating additional doses during hemofiltration have been suggested:[31,32]

**1.** Based on the expected ultrafiltration rates noted above, hemofiltration is usually equivalent to a glomerular filtration rate (GFR) of 10–50 mL/min. In lieu of specific recommendations for a drug, clinicians can use this GFR rate with FDA or renal drug dosing guidelines to suggest an adjusted dose.[4,6,7]

**2.** A supplemental dose (SD) can be estimated using a measured or estimated steady-state drug concentration (Css), unbound fraction in the serum ($f_B$), ultrafiltration rate (UFR), and drug dosing interval ($\tau$): $SD = Css \cdot f_B \cdot UFR \cdot \tau$. Supplemental doses are given in addition to maintenance doses of the drug.

**3.** A booster dose (BD) can be computed using an actual measured concentration ($C_{actual}$), a desired concentration ($C_{desired}$), and an estimated or actual volume of distribution (V): $BD = (C_{desired} - C_{actual})V$. Booster doses are given in addition to maintenance doses of the drug.

## PERITONEAL DIALYSIS

Peritoneal dialysis involves the surgical insertion of a catheter in the lower abdomen into the peritoneal cavity (Figure 3-16). The peritoneal membrane covering the internal organs is highly vascularized, so when dialysis fluid (1–3 L) is introduced into the peritoneal cavity using the catheter, waste products move from the blood vessels of the peritoneal membrane (a semipermeable membrane) into the dialysis fluid along a concentration gradient. The dialysis fluid is periodically removed from the peritoneal cavity and discarded.

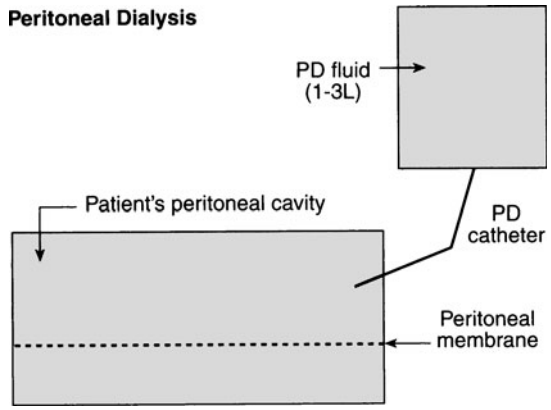


**FIGURE 3-16** Schematic of peritoneal dialysis procedure. A catheter (labeled *PD Catheter)* is surgically inserted into the patient's peritoneal cavity and used to introduce 1–3 L of dialysis fluid (labeled *PD Fluid).* The dialysis fluid comes into contact with capillaries in the peritoneal membrane where waste products and drugs pass from the blood into the fluid. After the dwell time has concluded, the dialysis fluid is removed from the peritoneal cavity via the catheter and discarded.

Outpatients undergoing chronic ambulatory peritoneal dialysis have dialysis fluid present in their peritoneal cavities all day or most hours of a day.

Compared to hemodialysis, peritoneal dialysis removes drug much less efficiently. So, it is less likely that replacement drug doses will need to be given during intermittent peritoneal dialysis, and that drug dosages will need to be increased while patients receive chronic peritoneal dialysis. For instance, in patients with end-stage renal disease, the half-life of aminoglycoside antibiotics is ~50 hours. During hemodialysis, the half-life reduces to ~4 hours, but, during peritoneal dialysis in patients without peritonitis, the half-life only decreases to ~36 hours. In patients receiving chronic peritoneal dialysis, dialysis removal of drug is simply another clearance mechanism taking place in the patient body, so the usual methods of measuring serum concentrations and dosage adjustment require little or no modification. For patients undergoing peritoneal dialysis, clinicians should consult the manufacturer's package insert for drugs recently marketed (mid-1980s or later), reviews listing the peritoneal dialysis removal of older drugs and updated information on newer agents,[4,6,7] and the primary literature for the newest guidelines for all compounds.

Drugs can also be added to peritoneal dialysis fluid. If the agent is absorbed from the dialysis fluid into the body, systemic effects due to the drug may occur. Epoetin and insulin have been administered in this fashion to patients receiving peritoneal dialysis. Because the development of peritonitis is a common problem in patients receiving peritoneal dialysis, antibiotics have been administered intraperitoneally for local treatment of the infection using dialysis fluid as the delivery vehicle.[33] In most cases, antibiotics are absorbed into the body when given this way, but therapeutic serum concentrations may not be achieved for all agents making systemically administered doses necessary. Clinicians should pay particular attention to whether studies measuring peritoneal dialysis removal or absorption of drugs were conducted in patients with peritonitis. Peritonitis involves inflammation of the peritoneal membrane and increases its permeability.

Increased permeability allows for greater flux of drug across the membrane which allows more drug removal during dialysis or more drug absorption if the drug is added to the peritoneal dialysis fluid.

### Methods to Measure Peritoneal Dialysis Clearance

If necessary, peritoneal dialysis clearance can be measured in patients. One method is to collect the waste dialysis fluid used during a peritoneal dialysis period, and measure several serum drug concentrations during the same time interval (Figure 3-15). The amount of drug eliminated in the dialysis fluid ($A_{Dialysis}$) is calculated by multiplying the volume of dialysis fluid ($V_{Dialysis}$), and the concentration of drug in the dialysis fluid ($C_{Dialysis}$): $A_{Dialysis} = V_{Dialysis} \cdot C_{Dialysis}$. Peritoneal clearance ($Cl_{PD}$) is computed by dividing the amount of drug eliminated in the dialysis fluid by the area under the serum concentration/time curve during the dialysis period ($AUC_{Dialysis}$, calculated using the serum concentrations obtained during peritoneal dialysis): $Cl_{PD} = A_{Dialysis} / AUC_{Dialysis}$. An advantage of this method is that the dialysate volume is relatively small. Disadvantages are the large number of serum concentrations needed to determine $AUC_{Dialysis}$, and if only a small amount of drug is removed via dialysis, the drug assay may not be sensitive enough to measure a small concentration.

Another method is to collect all the waste dialysis fluid used during a dialysis period, and measure a single serum drug concentration at the midpoint of the procedure. Using this information, peritoneal clearance ($Cl_{PD}$) can be computed using the following equation: $Cl_{PD} = (C_{Dialysis} \cdot V_{Dialysis}) / (C_{Serum} \cdot T_{Dialysis})$, where $C_{Dialysis}$ is the drug concentration in the dialysis fluid, $V_{Dialysis}$ is the volume of dialysis fluid, $C_{Serum}$ is the drug serum concentration, and $T_{Dialysis}$ is the duration that dialysis fluid remained in the peritoneal cavity. Advantages of this technique are that it requires only one serum concentration and the volume of dialysis fluid is relatively small. A disadvantage is if only a small amount of drug is removed via dialysis, the drug assay may not be sensitive enough to measure a low concentration.

## OBESITY

The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution. The general physiologic equation for volume of distribution can be broken down into separate parameters for individual tissue types:

$$V = V_B + \frac{f_B}{f_T} V_T = V_B + \frac{f_B}{f_{heart}} V_{heart} + \frac{f_B}{f_{muscle}} V_{muscle} + \frac{f_B}{f_{fat}} V_{fat} + \cdots + \frac{f_B}{f_n} V_n$$

Because of this, the sheer amount of adipose tissue will be a primary determinant of how much obesity will effect the volume of distribution of the drug. Also, the magnitude of effect that adipose tissue has on the volume of distribution for a drug is dependent on the binding of drug in the tissue itself. If the drug has a large affinity for adipose tissue and is highly bound there, the free fraction in adipose tissue will be small ($\downarrow f_{fat}$), and a large amount of drug will accumulate in that tissue. Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients. Examples of

lipophilic drugs with larger volume of distribution values in obese individuals are diazepam[34], carbamazepine[35], and trazodone[36]. However, hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients. The volumes of distribution for digoxin,[37] cimetidine,[38] and ranitidine[39] are similar in overweight- and normal-weight subjects.

Although the presence of excessive adipose tissue is the most obvious change that occurs in obese individuals, other physiologic changes are present. While adipose cells contain >90% fat, there are additional supportive tissues, extracellular fluid, and blood present in adipose tissue. Also, some lean tissues hypertrophy in obese individuals. The net result of these changes is that hydrophilic drugs with small volumes of distribution may experience distribution alterations in obese patients. For example, the aminoglycoside antibiotics are water-soluble molecules that have relatively small volumes of distribution similar to the value of extracellular fluid (V = 0.26 L/kg). Since the volume of distribution is so small (~18 L in a 70-kg person), the addition of just a few liters of extracellular fluid can alter the pharmacokinetics of these antibiotics. The additional extracellular fluid contained in excessive adipose tissue and other organs that hypertrophy in obese individuals causes larger volumes of distribution for the aminoglycoside antibiotics in overweight patients. Formulas that correct aminoglycoside volume of distribution for obese individuals are available.[40–43] However, if the volume of distribution for a hydrophilic drug is intermediate or large, the additional extracellular fluid contained in adipose tissue and other sources in obese individuals may not significantly alter the distribution of the agent. Examples of medications with larger and intermediate volumes of distribution are digoxin (V = 500 L) and vancomycin (V = 50 L); the addition of a few extra liters of extracellular fluid due to obesity will not substantially change the volume of distribution for these agents.[37,44]

Another change that is found in obese individuals is increased glomerular filtration rates. This alteration primarily affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent. Vancomycin,[44] the aminoglycosides,[40–42] and cimetidine[38] all have higher clearance rates in obese patients compared to normal weight individuals. Special methods are used to estimate creatinine clearance for obese patients, as previously noted in the Measurement and Estimation of Creatinine Clearance section of this chapter.[15–17]

Obesity has variable effects on the metabolism of drugs. For many agents, such as carbamazepine[35] and cyclosporine,[45] obesity does not significantly effect hepatic clearance. While for other drugs, obesity increases hepatic clearance, as with diazepam,[34] or decreases metabolic clearance, as with methylprednisolone.[46] Clinicians should be aware of this variability and dose hepatically metabolized drugs cautiously in obese individuals in the absence of specific recommendations.

Half-life changes vary according to the relative alterations in clearance (Cl) and volume of distribution (V): $t_{1/2} = (0.693 \cdot V)/Cl$, where $t_{1/2}$ is half-life. In the case of the aminoglycoside antibiotics, clearance and volume of distribution increases are about the same magnitude in obese patients, so half-life does not change.[40–42] If the volume of distribution increases with obesity, but clearance is unaffected, half-life can increase dramatically as with carbamazepine.[35] Finally, if clearance changes and volume of distribution remains constant, obesity may also cause a change in the half-life of a drug as is the case for methylprednisolone.[46]

## DRUG INTERACTIONS

Pharmacokinetic drug interactions occur between drugs when one agent changes the clearance or volume of distribution of another medication. There are several drug interaction mechanisms that result in altered drug clearance. A drug can inhibit or induce the enzymes responsible for the metabolism of other drugs. Enzyme inhibition decreases intrinsic clearance, and enzyme induction increases intrinsic clearance. If two drugs are eliminated by the same enzyme, they may compete for the metabolic pathway and decrease the clearance of one or both compounds. Two drugs eliminated by the same active renal tubular secretion mechanism can compete for the pathway and decrease the renal clearance of one or both agents. Another type of drug interaction displaces a drug from plasma protein binding sites because the two compounds share the same binding site, and the two compete for the same area on plasma proteins. By virtue of its pharmacologic effect, a drug may increase or decrease blood flow to an organ that eliminates or metabolizes another medication and thereby decrease the clearance of the medication.

Changes in plasma protein binding also cause alterations in volume of distribution. If two drugs share the same tissue binding sites, it is possible for tissue-binding displacement drug interactions to occur and change the volume of distribution for one of the medications. Half-life may change as a result of drug interactions, or, if clearance and volume of distribution alterations are about equal, half-life may remain constant even though a major drug interaction has occurred.

The same graphical scheme introduced in the hepatic disease section of this chapter can be used to understand the clinical impact of drug interactions (Figures 3-6–3-10). To use these charts it is necessary to know if the drug under discussion has a low extraction ratio or high extraction ratio. The hepatic clearance of drugs with low hepatic extraction ratios equals the product of free fraction in the blood and intrinsic clearance ($Cl_H = f_B Cl'_{int}$), while the hepatic clearance of drugs with high hepatic extraction ratios equals liver blood flow ($Cl_H = LBF$). Whether a drug has a high or low extraction ratio, the volume of distribution ($V = V_B + [f_B/f_T]V_T$) and half-life ($t_{1/2} = [0.693 \cdot V]/Cl$) relationships are the same. The unbound steady-state concentration of drug in the blood equals the product of the total steady-state concentration and the unbound fraction of drug in the blood: $Css_u = f_B Css$. The effect of the drug increases when the unbound steady-state concentration increases and decreases when $Css_u$ declines.

### Plasma Protein Binding Displacement Drug Interactions

For a drug with a low hepatic extraction ratio, plasma protein binding displacement drug interactions cause major pharmacokinetic alterations but are not clinically significant because the pharmacologic effect of the drug does not change (Figure 3-7). Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent, addition of a plasma protein binding displacing compound will increase clearance ($\uparrow Cl = \uparrow f_B Cl'_{int}$) and volume of distribution [$\uparrow V = V_B + (\uparrow f_B/f_T)V_T$]. Since half-life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change ($t_{1/2} = [0.693 \cdot \uparrow V]/\uparrow Cl$). However, it is possible that if either clearance or volume of distribution changes disproportionately, half-life will change. The total steady-state concentration will decline because of the increase in clearance ($\downarrow Css = k_0/\uparrow Cl$, where $k_0$ is the infusion

rate of drug). But, the unbound steady-state concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the drug interaction occurred ($Css_u = \uparrow f_B \downarrow Css$). The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged. An example of this drug interaction is the addition of diflunisal to patients stabilized on warfarin therapy.[47] Diflunisal displaces warfarin from plasma protein binding sites, but does not augment the anticoagulant effect of warfarin. If drug concentrations are available for the medication, it can be difficult to convince clinicians that a drug dosage increase is not needed even though total concentrations decline as a result of this interaction. When available, unbound drug concentrations can be used to document that no change in drug dosing is needed.

For drugs with high hepatic extraction ratios given intravenously, plasma protein binding displacement drug interactions cause both major pharmacokinetic and pharmacodynamic changes (Figure 3-9). Because the clearance of the drug is dependent solely on liver blood flow for an agent of this type, total clearance does not change. However, both volume of distribution [$\uparrow V = V_B + (\uparrow f_B/f_T)V_T$] and half-life [$\uparrow t_{1/2} = (0.693 \cdot \uparrow V)/Cl$] will increase because of plasma protein binding displacement of the drug. Since total clearance did not change, the total steady-state concentration remains unaltered. However, the free concentration ($\uparrow Css_u = \uparrow f_B Css$) and pharmacologic effect ($\uparrow effect \propto \uparrow Css_u$) of the drug will both increase. Currently, there are no clinically significant drug interactions of this type. But, clinicians should be on the outlook for this profile for highly protein-bound drugs with high hepatic extraction ratios given intravenously because the interaction is very subtle. Most noteworthy is the fact that although total concentrations remain unchanged, the pharmacologic effect of the drug is augmented. If available, unbound drug concentration could be used to document the drug interaction.

If a drug with a high hepatic extraction ratio is given orally, a plasma protein binding displacement drug interaction will cause a simultaneous increase in the unbound fraction of drug in the blood ($\uparrow f_B$) and the hepatic presystemic metabolism of the drug. Hepatic presystemic metabolism increases because the higher unbound fraction of drug in the blood allows more drug molecules to enter the liver where they are ultimately metabolized. The increase in hepatic presystemic metabolism leads to an increased first-pass effect and decreased drug bioavailability ($\downarrow F$). Total steady-state drug concentrations will be lower because of decreased drug bioavailability [$\downarrow Css = (\downarrow F[D/\tau])/Cl$]. However, the unbound steady-state drug concentration and pharmacologic effect remain unchanged due to this type of drug interaction because the increase in unbound fraction is offset by the decrease in the total steady-state concentration ($\sim Css_u = \uparrow f_B \downarrow Css$). Route of administration plays an important role in how important plasma protein binding displacement drug interactions are for agents with high hepatic extraction ratios.

### Inhibition Drug Interactions

Inhibition of hepatic drug metabolism is probably the most common drug interaction encountered in patients. For drugs with low hepatic extraction ratios, this type of drug interaction produces clinically significant changes in drug pharmacokinetics and effect (Figure 3-6). The addition of a hepatic enzyme inhibitor will decrease intrinsic clearance and total clearance for the drug ($\downarrow Cl = f_B \downarrow Cl'_{int}$). Since volume of distribution remains unaltered, the half-life of the drug will increase ($\uparrow t_{1/2} = [0.693 \cdot V]/\downarrow Cl$). As a result of the total clearance decrease, total steady-state drug concentrations will increase ($\uparrow Css = k_0/\downarrow Cl$). The rise in unbound steady-state drug concentration will mirror that seen with total drug

concentration, and the effect of the drug will increase in proportion to unbound concentration. An example of this drug interaction is the addition of ciprofloxacin to a patient stabilized on theophylline therapy.[48]

For drugs with high hepatic extraction ratios, this category of drug interaction produces variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inhibitor is added, the decrease in intrinsic clearance is usually not substantial enough to cause major pharmacokinetic and pharmacodynamic effects because clearance is a function of liver blood flow (Figure 3-8). However, if the drug is given orally and an enzyme inhibitor is added to therapy, presystemic metabolism of the medication may be greatly depressed, and the first-pass effect can decrease dramatically leading to improved drug bioavailability. This effective increase in administered oral dose will increase the total and unbound steady-state drug concentrations and lead to an increase in the pharmacologic effect of the drug.

## Induction Drug Interactions

Drugs with low hepatic extraction ratios exhibit clinically significant drug interactions that alter drug pharmacokinetics and pharmacologic response when hepatic enzyme inducers are coadministered (Figure 3-17). Enzyme inducers increase intrinsic clearance

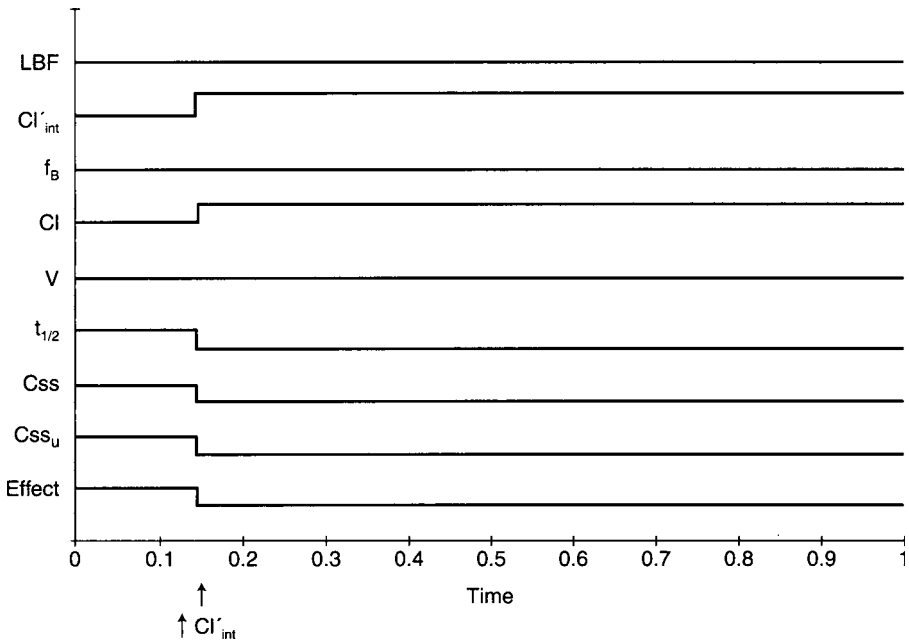


**FIGURE 3-17** Changes in physiologic parameters (*LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

of the drug and thereby increase the total clearance of the medication ($\uparrow Cl = f_B \uparrow Cl'_{int}$). The increase in total clearance will cause a shorter half-life since volume of distribution remains unchanged ($\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$). Increased total clearance will also cause decreased total steady-state concentration ($\downarrow Css = k_0 / \uparrow Cl$), unbound steady-state concentration ($\downarrow Css_u = f_B \downarrow Css$), and pharmacologic effect ($\downarrow effect \propto \downarrow Css_u$). Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of drug interaction with many other medications such as warfarin.[49]

For drugs with high hepatic extraction ratios, this type of drug interaction results in variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inducer is added, the increase in intrinsic clearance is usually not large enough to cause major pharmacokinetic and pharmacologic effect alterations because total clearance is a function of liver blood flow (Figure 3-18). However, if the drug is given orally and an enzyme inducer is added to the treatment regimen, presystemic metabolism of the medication may be increased, and the first-pass effect augmented leading to decreased drug bioavailability. This effective decrease in administered oral dose will decrease the total and unbound steady-state drug concentrations and lead to a decrease in the pharmacologic effect of the agent.

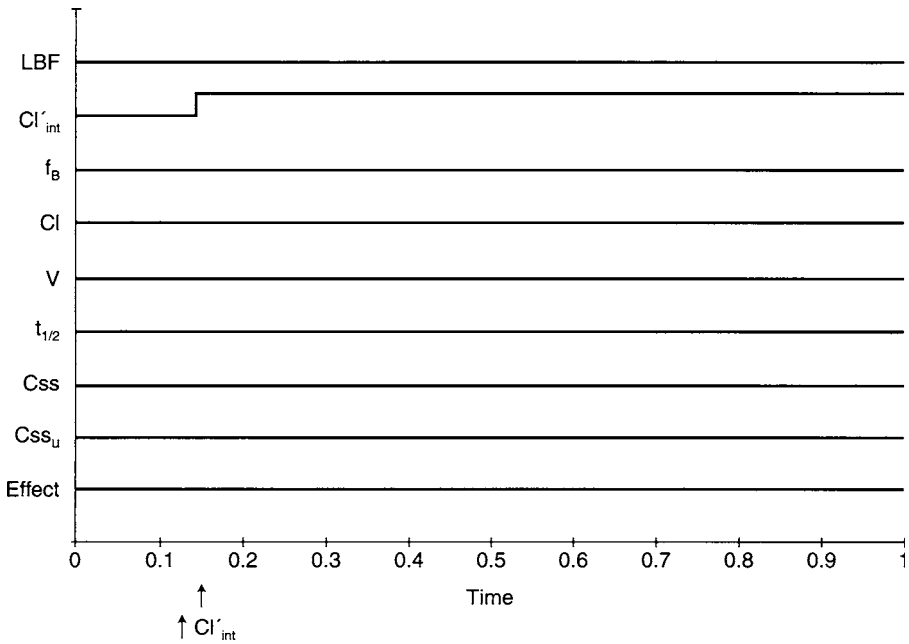


**FIGURE 3-18** Changes in physiologic parameters (*LBF* = liver blood flow, $Cl'_{int}$ = intrinsic clearance, $f_B$ = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; $Css_u$ = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

### Alteration in Organ Blood Flow

By virtue of the pharmacologic effect for a drug, it may be possible for an agent to change liver blood flow. For instance, β-blockers can decrease heart rate and cardiac output which decreases liver blood flow. Since liver blood flow is the predominate factor that determines clearance for high hepatic extraction ratio drugs, this type of interaction is only important for this category of medication. β-blockers decrease lidocaine clearance by decreasing liver blood flow.[50]

If a drug with a high hepatic extraction ratio is administered to a patient, and another agent that decreases liver blood flow is then added to the patient's therapy, total clearance will decrease (Figure 3-10). Since volume of distribution remains unaltered, the half-life of the drug will increase ($\uparrow t_{1/2} = [0.693 \cdot V] / \downarrow Cl$). As a result of the total clearance decrease, total steady-state drug concentrations will increase ($\uparrow Css = k_0 / \downarrow Cl$). The rise in unbound steady-state drug concentration will mirror that seen with total drug concentration, and the effect of the drug will increase in proportion to unbound concentration. If the coadministered drug increases liver blood flow, as can be the case with vasodilators like the calcium channel blockers,[51,52] all of the aforementioned changes will occur in the opposite direction ($\uparrow Cl = \uparrow LBF$; $\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$; $\downarrow Css = k_0 / \uparrow Cl$; $\downarrow Css_u = f_B \downarrow Css$), and the decline in unbound steady-state concentration will cause a decrease in pharmacologic effect of the drug.

## PROBLEMS

**1.** A creatinine clearance is measured in a 75-year-old Caucasian male patient with multiple myeloma to monitor changes in renal function. The serum creatinine, measured at the midpoint of the 24 hour urine collection, was 2.1 mg/dL. Urine creatinine concentration was 50 mg/dL, and urine volume was 1400 mL. (A). Calculate this patient's creatinine clearance. (B). Estimate the patient's glomerular filtration rate using the modified MDRD equation.

**2.** A 52-year-old, 65-kg, 5-ft 3-in tall female patient with a methicillin-resistant *Staphylococcus aureus* (MRSA) infection needs to have an initial vancomycin dose computed. In order to do this, an estimated creatinine clearance needs to be calculated. The patient has a serum creatinine value equal to 1.8 mg/dL. Calculate this patient's estimated creatinine clearance and estimated vancomycin clearance [assume vancomycin clearance is Cl (in mL/min/kg) = 0.695 (CrCl in mL/min/kg) + 0.05].

**3.** A 70-year-old, 80-kg, 5-ft 11-in tall male with a *Pseudomonas aeruginosa* infection needs to have an initial tobramycin dose computed. In order to do this, an estimated creatinine clearance must be calculated. The patient's current serum creatinine equals 2.5 mg/dL and is stable. Compute this patient's estimated creatinine clearance and estimated tobramycin elimination rate constant and half-life [assume tobramycin elimination rate constant is $k_e$ (in $h^{-1}$) = 0.00293 (CrCl in mL/min) + 0.014].

**4.** A 51-year-old, 54-kg, 5-ft 4-in female with worsening renal function needs to have her renal function assessed for drug dosage adjustment. Yesterday, at 0800 H, her serum creatinine was 1.3 mg/dL. Today at 0800 H, her serum creatinine was 2.1 mg/dL. Compute her estimated creatinine clearance.

5. A 66-year-old, 120-kg, 5-ft 2-in tall female has a serum creatinine equal to 3.1 mg/dL. Compute an estimated creatinine clearance for this patient.

6. A 59-year-old, 140-kg, 5-ft 8-in tall male with severe heart failure has a serum creatinine equal to 2.4 mg/dL. Compute an estimated creatinine clearance, digoxin clearance, and digoxin volume of distribution for this patient. Assume estimated digoxin clearance in severe heart failure: Cl (in mL/min) = 1.303 (CrCl in mL/min) + 20; estimated digoxin volume of distribution: V (in L) = 226 + [(298 · CrCl)/(29.1 + CrCl)].

7. A 62-year-old, 65-kg male with hepatic cirrhosis (total bilirubin = 2.6 mg/dL, serum albumin = 2.5 mg/dL, prothrombin time prolonged over normal by 8 seconds, slight amount of ascitic fluid, no hepatic encephalopathy) and severe chronic obstructive pulmonary disease needs to have an initial theophylline dose computed. The patient is not a tobacco smoker and does not have heart failure. Compute the patient's Child-Pugh score, estimated theophylline clearance, and theophylline dose to achieve a steady-state concentration equal to 10 mg/L.

8. A 32-year-old, 70-kg, 5-ft 8-in tall, female with chronic renal failure receiving hemodialysis developed atrial fibrillation. She is to receive a new antiarrhythmic, Defibfast, for the treatment of atrial fibrillation. In patients with chronic renal failure, the following average pharmacokinetic parameters were measured in six subjects: V = 0.5 L/kg, $t_{1/2}$ = 36 hours. When these subjects received hemodialysis, the hemodialysis extraction ratio was 33%. The patient just completed a hemodialysis run (Monday, 0800–1200 H). Compute a post-hemodialysis loading dose to achieve a peak concentration of 50 mg/L. The next dialysis period is Wednesday at the same time. Calculate a posthemodialysis dose that will raise the patient's concentration to 50 mg/L.

9. A 47-year-old, 75-kg, 5-ft 9-in tall, male hemodialysis patient with chronic renal failure has a serious gram-negative infection being treated with a new antibiotic, Bactocidal. The following concentrations were obtained: Monday, 1200 H (post-hemodialysis) = 15 mg/L, Monday, 1205 H (post-IV bolus 1000 mg dose) = 65 mg/L, Wednesday, 0800 H (pre-hemodialysis) = 32 mg/L, Wednesday, 1200 H (post-hemodialysis for 4 hours) = 8 mg/L. Compute volume of distribution, elimination rate constant, and half-life for the interdialysis period, and the hemodialysis extraction ratio. What post-hemodialysis dose on Wednesday would achieve a postdose concentration of 100 mg/L? What would be the pre- and posthemodialysis concentrations on Friday (hemodialysis from 0800–1200 H) if that dose was given?

10. A patient receiving hemodialysis has the following concentrations obtained during a hemodialysis run: concentration into artificial kidney = 75 mg/L, concentration leaving artificial kidney = 25 mg/L. Blood flow through the artificial kidney is 400 mL/min. Compute the hemodialysis extraction ratio and clearance.

11. A patient receiving peritoneal dialysis has the following drug concentrations obtained: concentration in the dialysis fluid = 35 mg/L, concentration in serum at midpoint of peritoneal dialysis = 50 mg/L. The volume of dialysis fluid is 2 L, and the dwell time in the peritoneal cavity is 6 hours. Compute peritoneal dialysis for the drug.

**12.** A patient is receiving phenytoin (a low hepatic extraction ratio drug) for the treatment of tonic-clonic seizures. Because of continued seizure activity, valproic acid is added to the patient's drug regimen. Valproic acid inhibits the clearance of phenytoin and displaces phenytoin from plasma protein binding sites. Assuming that these changes occur instantaneously with the institution of valproic acid therapy, diagram how the following parameters will change for phenytoin: liver blood flow, intrinsic clearance, free fraction of drug in the blood, clearance, volume of distribution, half-life, total steady-state concentration, unbound steady-state concentration, and drug effect.