RENAL IMPAIRMENT

The kidney is an important organ in regulating body fluids, electrolyte balance, removal of metabolic waste, and drug excretion from the body. Impairment or degeneration of kidney function affects the pharmacokinetics of drugs. Some of the more common causes of kidney failure include disease, injury, and drug intoxication. lists some of the conditions that may lead to chronic or acute renal failure. Acute diseases or trauma to the kidney can cause *uremia,* in which glomerular filtration is impaired or reduced, leading to accumulation of excessive fluid and blood nitrogenous products in the body. Uremia generally reduces glomerular filtration and/or active secretion, which leads to a decrease in renal drug excretion resulting in a longer elimination half-life of the administered drug.

Table 21.1 Common Causes of Kidney Failure

Pyelonephritis	Inflammation and deterioration of the pyelonephrons due to infection, antigens, or other idiopathic causes.
Hypertension	Chronic overloading of the kidney with fluid and electrolytes may lead to kidney insufficiency.
Diabetes mellitus	The disturbance of sugar metabolism and acid-base balance may lead to or predispose a patient to degenerative renal disease.
Nephrotoxic drugs/metals	Certain drugs taken chronically may cause irreversible kidney damage—eg, the aminoglycosides, phenacetin, and heavy metals, such as mercury and lead.
Hypovolemia	Any condition that causes a reduction in renal blood flow will eventually lead to renal ischemia and damage.
Neophroallergens	Certain compounds may produce an immune type of sensitivity reaction with nephritic syndrome—eg, quartan malaria nephrotoxic serum.

In addition to changing renal elimination directly, uremia can affect drug pharmacokinetics in unexpected ways. For example, declining renal function leads to disturbances in electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug. Pharmacokinetic processes such as drug distribution (including both the volume of distribution and protein binding) and elimination (including both biotransformation and renal excretion) may also be altered by renal impairment. Both therapeutic and toxic responses may be altered as a result of changes in drug sensitivity at the receptor site. Overall, uremic patients have special dosing considerations to account for such pharmacokinetic and pharmacodynamic alterations.

PHARMACOKINETIC CONSIDERATIONS

Uremic patients may exhibit pharmacokinetic changes in bioavailability, volume of distribution, and clearance. The oral bioavailability of a drug in severe uremia may be decreased as a result of disease-related changes in gastrointestinal motility and pH caused by nausea, vomiting, and diarrhea. Mesenteric blood flow may also be altered. However, the oral bioavailability of a drug such as propranolol (which has a high first-pass effect) may be increased in patients with renal impairment as a result of the decrease in first-pass hepatic metabolism ().

The apparent volume of distribution depends largely on drug protein binding in plasma or tissues and total body water. Renal impairment may alter the distribution of the drug as a result of changes in fluid balance, drug protein binding, or other factors that may cause changes in the apparent volume of distribution (see). The plasma protein binding of weak acidic drugs in uremic patients is decreased, whereas the protein binding of weak basic drugs is less affected. The decrease in drug protein binding results in a larger fraction of free drug and an increase in the volume of distribution. However, the net elimination half-life is generally increased as a result of the dominant effect of reduced glomerular filtration. Protein binding of the drug may be further compromised due to the accumulation of metabolites of the drug and accumulation of various biochemical metabolites, such as free fatty acids and urea, which may compete for the protein-binding sites for the active drug.

Total body clearance of drugs in uremic patients is also reduced by either a decrease in the glomerular filtration rate and possibly active tubular secretion or reduced hepatic clearance resulting from a decrease in intrinsic hepatic clearance.

In clinical practice, estimation of the appropriate drug dosage regimen in patients with impaired renal function is based on an estimate of the remaining renal function of the patient and a prediction of the total body clearance. A complete pharmacokinetic analysis of the drug in the uremic patient is not possible. Moreover, the patient's uremic condition may not be stable and may be changing too rapidly for pharmacokinetic analysis. Each of the approaches for the calculation of a dosage regimen have certain assumptions and limitations that must be carefully assessed by the clinician before any approach is taken. Dosing guidelines for individual drugs in patients with renal impairment may be found in various reference books, such as the *Physicians' Desk Reference,* and in the medical literature (, ;).

GENERAL APPROACHES FOR DOSE ADJUSTMENT IN RENAL DISEASE

Several approaches are available for estimating the appropriate dosage regimen for a patient with renal impairment. Each of these approaches has similar assumptions, as listed in . Most of these methods assume that the required therapeutic plasma drug concentration in uremic patients is similar to that required in patients with normal renal function. Uremic patients are maintained on the same C^{∞}_{av} after multiple oral doses or multiple IV bolus injections. For IV infusions, the same C_{SS} is maintained. (C_{SS} is the same as C^{∞}_{av} after the plasma drug concentration reaches steady state.)

Table 21.2 Common Assumptions in Dosing Renal-Impaired Patients

Asumption	Comment
Creatinine clearance accurately measures the degree of renal impairment	Creatinine clearance estimates may be biased. Renal impairment should also be verified by physical diagnosis and other clinical tests.
Drug follows dose-independent pharmacokinetics	Pharmacokinetics should not be dose-dependent (nonlinear).
Nonrenal drug elimination remains constant	Renal disease may also affect the liver and cause a change in nonrenal drug elimination (drug metabolism).
Drug absorption remains constant	Unchanged drug absorption from gastrointestinal tract.
Drug clearance, Cl_u, declines linearly with creatinine clearance, Cl_{Cr}	Normal drug clearance may include active secretion and passive filtration and may not decline linearly.
Unaltered drug protein binding	Drug protein binding may be altered due to accumulation of urea, nitrogenous wastes, and drug metabolites.
Target drug concentration remains constant	Changes in electrolyte composition such as potassium may affect sensitivity to the effect of digoxin. Accumulation of active metabolities may cause more intense pharmacodynamic response compared to parent drug alone.

The design of dosage regimens for uremic patients is based on the pharmacokinetic changes that have occurred as a result of the uremic condition. Generally, drugs in patients with uremia or kidney impairment have prolonged elimination half-lives and a change in the apparent volume of distribution. In less severe uremic conditions there may be neither edema nor a significant change in the apparent volume of distribution. Consequently, the methods for dose adjustment in uremic patients are based on an accurate estimation of the drug clearance in these patients.

Several specific clinical approaches for the calculation of drug clearance based on monitoring kidney function are presented later in this chapter. Two general pharmacokinetic approaches for dose adjustment include methods based on drug clearance and methods based on the elimination half-life.

Dose Adjustment Based on Drug Clearance

Methods based on drug clearance try to maintain the desired C^{∞}_{av} after multiple oral doses or multiple IV bolus injections as total body clearance, Cl_T, changes. The calculation for C^{∞}_{av} is

$$C_{av}^{\infty} = \frac{FD_0}{Cl_T \tau} \qquad (21.1)$$

For patients with a uremic condition or renal impairment, total body clearance of the uremic patient will change to a new value, Cl^u_T. Therefore, to maintain the same desired C^{∞}_{av}, the dose must be changed to a uremic dose, D^u_0 or the dosage interval must be changed to τ^u, as shown in the following equation:

$$C_{av}^{\infty} = \underbrace{\frac{D_0^N}{Cl_T^N \tau^N}}_{\text{(normal)}} = \underbrace{\frac{D_0^u}{Cl_T^u \tau^u}}_{\text{(uremic)}} \qquad (21.2)$$

where the superscripts N and u represent normal and uremic conditions, respectively.

Rearranging Equation 21.2 and solving for D^u_0.

$$D_0^u = \frac{D_0^N Cl_T^u \tau^u}{Cl_T^N \tau^N} \qquad (21.3)$$

If the dosage interval τ is kept constant, then the uremic dose D^u_0 is equal to a fraction (Cl^u_T/Cl^N_T) of the normal dose, as shown in the equation

$$D_0^u = \frac{D_0^N Cl_T^u}{Cl_T^N} \qquad (21.4)$$

For IV infusions the same desired C_{SS} is maintained both for patients with normal renal function and for patients with renal impairment. Therefore, the rate of infusion, R, must be changed to a new value, R^u, for the uremic patient, as described by the equation

$$C_{SS} = \frac{R}{Cl_T^N} = \frac{R^u}{Cl_T^u} \qquad (21.5)$$

(normal) (uremic)

Dose Adjustment Based on Changes in the Elimination Rate Constant

The overall elimination rate constant for many drugs is reduced in the uremic patient. A dosage regimen may be designed for the uremic patient either by reducing the normal dose of the drug and keeping the frequency of dosing (dosage interval) constant, or by decreasing the frequency of dosing (prolonging the dosage interval) and keeping the dose constant. Doses of drugs with a narrow therapeutic range should be reduced—particularly if the drug has accumulated in the patient prior to deterioration of kidney function.

The usual approach to estimating a multiple-dosage regimen in the normal patient is to maintain a desired C^{∞}_{av}, as shown in Equation 21.1. Assuming the V_D is the same in both normal and uremic patients and τ is constant, then the uremic dose D^u_0 is a fraction (k^u/k^N) of the normal dose:

$$D_0^u = \frac{D_0^N k^u}{k^N} \qquad (21.6)$$

When the elimination rate constant for a drug in the uremic patient cannot be determined directly, indirect methods are available to calculate the predicted elimination rate constant based on the renal function of the patient. The assumptions on which these dosage regimens are calculated include the following.

1. The renal elimination rate constant (k_R) decreases proportionately as renal function decreases. (Note that k_R is the same as k_e as used in previous chapters.)
2. The nonrenal routes of elimination (primarily, the rate constant for metabolism) remain unchanged.
3. Changes in the renal clearance of the drug are reflected by changes in the creatinine clearance.

The overall elimination rate constant is the sum total of all the routes of elimination in the body, including the renal rate and the nonrenal rate constants:

$$k^u = k_{nr} + k_R^u \qquad (21.7)$$

where k_{nr} is the nonrenal elimination rate constant and k_R is the renal excretion rate constant.

Renal clearance is the product of the apparent volume of distribution and the rate constant for renal excretion:

$$Cl_R^u = k_R^u V_D^u \qquad (21.8)$$

Rearrangement of Equation 21.8 gives

$$k_R^u = Cl_R^u \frac{1}{V_D^u} \qquad (21.9)$$

Assuming that the apparent volume of distribution and nonrenal routes of elimination do not change in uremia, then $k^u_{nr} = k^N_{nr}$ and $V^u_D = V^N_D$.

Substitution of Equation 21.9 into Equation 21.7 gives

$$k^u = k_{nr} + \frac{1}{V_D} Cl_R^u \qquad (21.10)$$

From Equation 21.10, a change in the renal clearance, Cl^u_R, due to renal impairment will be reflected in a change in the overall elimination rate constant k_u. Because changes in the renal drug clearance cannot be assessed directly in the uremic patient, Cl^u_R is usually related to a measurement of kidney function by the glomerular filtration rate (GFR), which in turn is estimated by changes in the patient's creatinine clearance.

MEASUREMENT OF GLOMERULAR FILTRATION RATE

Several drugs and endogenous substances have been used as markers to measure GFR. These markers are carried to the kidney by the blood via the renal artery and are filtered at the glomerulus. Several criteria are necessary to use a drug to measure GFR:

1. The drug must be freely filtered at the glomerulus.
2. The drug must not be reabsorbed nor actively secreted by the renal tubules.
3. The drug should not be metabolized.

4. The drug should not bind significantly to plasma proteins.

5. The drug should not have an effect on the filtration rate nor alter renal function.

6. The drug should be nontoxic.

7. The drug may be infused in a sufficient dose to permit simple and accurate quantitation in plasma and in urine.

Therefore, the rate at which these drug markers are filtered from the blood into the urine per unit of time reflects the glomerular filtration rate of the kidney. Changes in GFR reflect changes in kidney function that may be diminished in uremic conditions.

Inulin, a fructose polysaccharide, fulfills most of the criteria listed above and is therefore used as a standard reference for the measurement of GFR. In practice, however, the use of inulin involves a time-consuming procedure in which inulin is given by intravenous infusion until a constant steady-state plasma level is obtained. Clearance of inulin may then be measured by the rate of infusion divided by the steady-state plasma inulin concentration. Although this procedure gives an accurate value for GFR, inulin clearance is not used frequently in clinical practice.

The clearance of creatinine is used most extensively as a measurement of GFR. *Creatinine* is an endogenous substance formed from creatine phosphate during muscle metabolism. Creatinine production varies with the age, weight, and gender of the individual. In humans, creatinine is filtered mainly at the glomerulus, with no tubular reabsorption. However, a small amount of creatinine may be actively secreted by the renal tubules, and the values of GFR obtained by the creatinine clearance tend to be higher than GFR measured by inulin clearance. Creatinine clearance tends to decrease in the elderly patient. As mentioned in , the physiologic changes due to aging may necessitate special considerations in administering drugs in the elderly.

Blood urea nitrogen (BUN) is a commonly used clinical diagnostic laboratory test for renal disease. Urea is the end product of protein catabolism and is excreted through the kidney. Normal BUN levels range from 10 to 20 mg/dL. Higher BUN levels generally indicate the presence of renal disease. However, other factors, such as excessive protein intake, reduced renal blood flow, hemorrhagic shock, or gastric bleeding, may affect increased BUN levels. The renal clearance of urea is by glomerular filtration and partial reabsorption in the renal tubules. Therefore, the renal clearance of urea is less than creatinine or inulin clearance and does not give a quantitative measure of kidney function.

SERUM CREATININE CONCENTRATION AND CREATININE CLEARANCE

Under normal circumstances, creatinine production is roughly equal to creatinine excretion, so the serum creatinine level remains constant. In a patient with reduced glomerular filtration, serum creatinine will accumulate in accordance with the degree of loss of glomerular filtration in the kidney. The serum creatinine concentration alone is frequently used to determine creatinine clearance, Cl_{Cr}. Creatinine clearance from the serum creatinine concentration is a rapid and convenient way to monitor kidney function.

Creatinine clearance may be defined as the rate of urinary excretion of creatinine/serum creatinine. Creatinine clearance can be calculated directly by determining the patient's serum creatinine concentration and the rate of urinary excretion of creatinine. The approach is similar to that used in the determination of drug clearance. In practice, the serum creatinine concentration is determined at the midpoint of the urinary collection period and the rate of urinary excretion of creatinine is measured for the entire day (24 hr) to obtain a reliable excretion rate. Creatinine clearance is expressed in mL/min and serum creatinine concentration in mg/dL or mg%. Other Cl_{Cr} methods based solely on serum creatinine are generally compared to the creatinine clearance obtained from the 24-hour urinary creatinine excretion.

The following equation is used to calculate creatinine clearance in mL/min when the serum creatinine concentration is known:

$$Cl_{Cr} = \frac{\text{rate of urinary excretion of creatinine}}{\text{serum concentration of creatinine}}$$

$$Cl_{Cr} = \frac{C_u V \times 100}{C_{Cr} \times 1440} \qquad (21.11)$$

where C_{Cr} = creatinine concentration (mg/dL) of the serum taken at the 12th hour or at the midpoint of the urine-collection period, V = volume of urine excreted (mL) in 24 hours, C_u = concentration of creatinine in urine (mg/mL), and Cl_{Cr} = creatinine clearance in mL/min.

Creatinine is eliminated primarily by glomerular filtration. A small fraction of creatinine also is eliminated by active secretion and some nonrenal elimination. Therefore, Cl_{Cr} values obtained from creatinine measurements overestimate the actual glomerular filtration rate.

Creatinine clearance has been normalized both to body surface area, using 1.73 m^2 as the average, and to body weight for a 70-kg adult male. Creatinine distributes into total body water, and when clearance is normalized to a standard V_D, similar drug half-lives in adults and children correspond to identical clearances.

Creatinine clearance values must be considered carefully in special populations such as the elderly, obese, and emaciated patients. In elderly and emaciated patients, muscle mass may have declined, thus lowering the production of creatinine. However, serum creatinine concentration values may appear to be in the normal range, because of lower renal creatinine excretion. Thus, the calculation of creatinine clearance from serum creatinine may give an inaccurate estimation of the renal function. For obese patient, generally defined as patients more than 20% over *ideal body weight*, IBW, creatinine clearance should be based on ideal body weight. Estimation of creatinine clearance based on *total body weight,* TBW, would exaggerate the Cl_{Cr} values in the obese patient. Women with normal kidney function have smaller creatinine clearance values than men,

approximately 80–85% of that in men with normal kidney function.

Several empirical equations have been used to estimate lean body weight, LBW, based on the patient's height and actual (total) body weight (see). The following equations have been used to estimate LBW in renally impaired patients:

$$\text{LBW (males)} = 50\ \text{kg} + 2.3\ \text{kg for each inch over 5 ft}$$
$$\text{LBW (females)} = 45.5\ \text{kg} + 2.3\ \text{kg for each inch over 5 ft}$$

For the purpose of dose adjustment in renal patients, normal creatinine clearance is generally assumed to be between 100 and 125 mL/min per 1.73 m^2 for a subject of ideal body weight: for a female adult, Cl_{Cr} = 108.8 ± 13.5 mL/1.73 m^2, and for an average adult male, Cl_{Cr} = 124.5 ± 9.7 mL/1.73 m^2 (*Scientific Table*, 1973). Creatinine clearance is affected by diet and salt intake. As a convenient approximation, the normal clearance has often been assumed by many clinicians to be approximately 100 mL/min.

Calculation of Creatinine Clearance from Serum Creatinine Concentration

The problems of obtaining a complete 24-hour urine collection from a patient, the time necessary for urine collection, and the analysis time preclude a direct estimation of creatinine clearance. *Serum creatinine concentration,*C_{Cr}, is related to creatinine clearance and is measured routinely in the clinical laboratory. Therefore, creatinine clearance, Cl_{Cr}, is most often estimated from the patient's C_{Cr}. Several methods are available for the calculation of creatinine clearance from the serum creatinine concentration. The more accurate methods are based on the patient's age, height, weight, and gender. These methods should be used only for patients with intact liver function and no abnormal muscle disease, such as hypertrophy or dystrophy. Moreover, most of the methods assume a stable creatinine clearance. The units for Cl_{Cr} are mL/min.

ADULTS

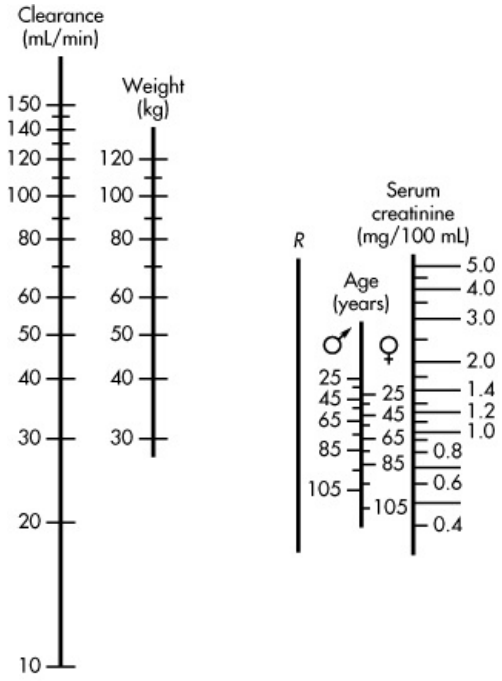
The method of shown in Equation 21.12 is used to estimate creatinine clearance from serum creatinine concentration. This method considers both the age and the weight of the patient. For males,

$$Cl_{Cr} = \frac{[140 - \text{age (yr)}] \times \text{body weight (kg)}}{72\ (C_{Cr})} \qquad (21.12)$$

For females, use 90% of the Cl_{Cr} value obtained in males.

The nomogram method of *Siersback-Nielsen* et al (1971) estimates creatinine clearance on the basis of age, weight, and serum creatinine concentration, as shown in . compared their method with the nomogram method in adult males of various ages. Creatinine clearance estimated by both methods were comparable. Both methods also demonstrated an age-related linear decline in creatinine excretion (), which may be due to the decrease in muscle mass with age.

Figure 21-1.



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

Nomogram for evaluation of endogenous creatinine clearance. To use the nomogram, connect the patient's weight on the second line from

the left with the patient's age on the fourth line with a ruler. Note the point of intersection on *R* and keep the ruler there. Turn the right part of the ruler to the appropriate serum creatinine value and the left side will indicate the clearance in mL/min.

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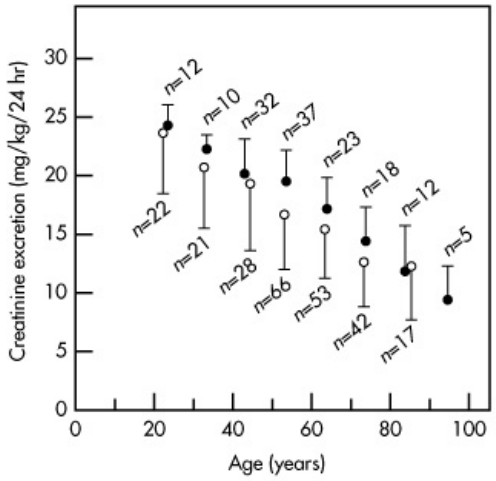
Figure 21-2.



Creatinine excretion estimated by two different methods. ● = , 149 males aged 20–99 years; O = , 249 males aged 18–92 years.

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CHILDREN

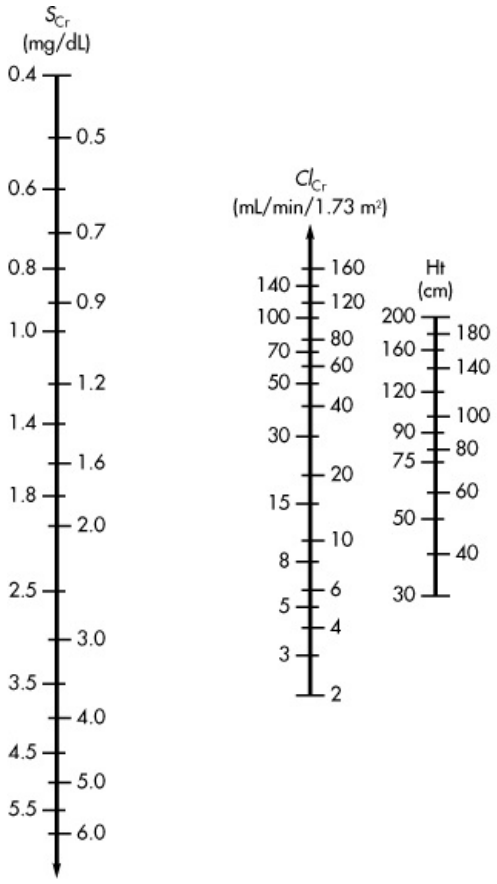
There are a number of methods for calculation of creatinine clearance in children, based on body length and serum creatinine concentration. Equation 21.13 is a method developed by :

$$Cl_{Cr} = \frac{0.55 \text{ body length (cm)}}{C_{Cr}} \qquad (21.13)$$

where Cl_{Cr} is given in mL/min/1.73 m^2.

Another method of calculating creatinine clearance in children uses the nomogram of , shown in . This nomogram is based on observations of 81 children aged 6 to 12 years and requires the patient's height and serum creatinine concentration.

Figure 21-3.



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

Nomogram for rapid evaluation of endogenous creatinine clearance (Cl_{Cr}) in pediatric patients (aged 6–12 yr). To predict Cl_{Cr}, connect the child's S_{Cr} (serum creatinine) and Ht (height) with a ruler and read the Cl_{Cr} where the ruler intersects the center line.

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Practice Problems

1. What is the creatinine clearance for a 25-year-old male patient with C_{Cr} of 1 mg/dL and a body weight of 80 kg?

Solution

Using the nomogram (), join the points at 25 years (male) and 80 kg with a ruler—let the line intersect line *R*. Connect the intersection point at line *R* with the creatinine concentration point of 1 mg/dL, and extend the line to intersect the "clearance line." The extended line will intersect the clearance line at 110 mL/min, giving the creatinine clearance for the patient.

2. What is the creatinine clearance for a 25-year-old male patient with a C_{Cr} of 1 mg/dL? The patient is 5 ft, 4 inches in height and weighs 103 kg.

Solution

The patient is obese and the Cl_{Cr} calculation should be based on ideal body weight.

$$\text{LBW (males)} = \frac{50\text{ kg} + [2.3 \times 4]}{\text{kg} = 59.2\text{ kg}}$$

Using the Cockcroft and Gault method (Eq. 21.12), the Cl_{Cr} can be calculated.

$$Cl_{Cr} = \frac{(140 - 25) \times (59.2\text{ kg})}{72(1)} = 94.6\text{ mL/min}$$

The serum creatinine methods for the estimation of the creatinine clearance assume stabilized kidney function and a steady-state serum creatinine concentration. In acute renal failure and in other situations in which kidney function is changing, the serum creatinine may not represent steady-state conditions. If C_{Cr} is measured daily and the C_{Cr} value is constant, then the serum creatinine concentration is probably at steady state. If the C_{Cr} values are changing daily, then kidney function is changing.

Although the Cockcroft and Gault method for estimating Cl_{Cr} has some biases, this method has gained general acceptance for

the determination of renal impairment (; ;). A suggested representation of patients with various degrees of renal impairment based on creatinine clearance is shown in .

Table 21.3 Renal Impairment Based on Creatinine Clearance

Group	Description	Estimated Creatinine Clearance (mL/min)
1	Normal renal function	>80 mL/min
2	Mild renal impairment	50–80 mL/min
3	Moderate renal impairment	30–50 mL/min
4	Severe renal impairment	<30 mL/min
5	ESRD[a]	Requires dialysis

[a]ESRD = end-stage renal disease.

(Adapted from *FDA Guidance for Industry* (1988).

The practice problems show that, depending on the formula used, the calculated Cl_{Cr} can vary considerably. Consequently, unless a significant change in the creatinine clearance occurs, use of these methods will result in a rather large margin of error. According to , dose adjustment of many antibiotic drugs is necessary only when the glomerular filtration rate as measured by Cl_{Cr} is less than 50 mL/min. For the aminoglycoside antibiotics and vancomycin, dose adjustment is individualized according to the wide range of Cl_{Cr}. Therefore, dose adjustment for all drugs on the basis of these Cl_{Cr} methods alone is not justified.

DOSE ADJUSTMENT FOR UREMIC PATIENTS

Dose adjustment for drugs in uremic or renally impaired patients should be made in accordance with changes in pharmacodynamics and pharmacokinetics of the drug in the individual patient. Active metabolites of the drug may also be formed and must be considered for additional pharmacologic effects when adjusting dose. The following methods may be used to estimate an initial and maintenance dose regimen. After initiating the dosage, the clinician should continue to monitor the pharmacodynamics and pharmacokinetics of the drug. He or she should also evaluate the patient's renal function, which may be changing.

Basis for Dose Adjustment in Uremia

The loading drug dose is based on the apparent volume of distribution of the patient. It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore that the loading dose of the drug is the same in uremic patients as in subjects with normal renal function.

The maintenance dose is based on clearance of the drug in the patient. In the uremic patient, the rate of renal drug excretion has decreased, leading to a decrease in total body clearance. Most methods for dose adjustment assume nonrenal drug clearance to be unchanged. The fraction of normal renal function remaining in the uremic patient is estimated from creatinine clearance.

After the remaining total body clearance in the uremic patient is estimated, a dosage regimen may be developed by (1) decreasing the maintenance dose, (2) increasing the dosage interval, or (3) changing both maintenance dose and dosage interval.

Although total body clearance is a more accurate index of drug dosing, the elimination half-life of the drug is more commonly used for dose adjustment because of its convenience. Clearance allows for the prediction of steady-state drug concentrations, while elimination half-life yields information on the time it takes to reach steady-state concentration.

Nomograms

Nomograms are charts available for use in estimating dosage regimens in uremic patients (; ;). The nomograms may be based on serum creatinine concentrations, patient data (height, weight, age, gender), and the pharmacokinetics of the drug. As discussed by , each nomogram has errors in its assumptions and drug database.

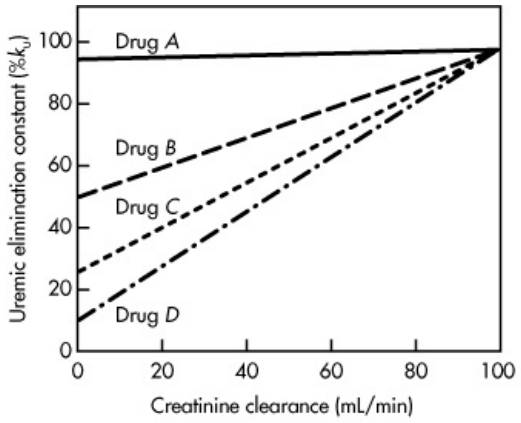
Most methods for dose adjustment in renal disease assume that nonrenal elimination of the drug is not affected by renal impairment and that the remaining renal excretion rate constant in the uremic patient is proportional to the product of a constant and the creatinine clearance, Cl_{Cr}:

$$k_u = k_{nr} + \alpha Cl_{Cr} \qquad (21.14)$$

where k_{nr} is the nonrenal elimination rate constant and α is a constant. Equation 21.14 is similar to Equation 21.10, where $\alpha = 1/V_D$, and can be used for the construction of a nomogram. shows a graphical representation of Equation 21.14 for four different drugs, each with a different renal excretion rate constant. The fractions of drug excreted in the urine unchanged, *fe*, for drugs A, B, C, and D are 5%, 50%, 75%, and 90%, respectively. A creatinine clearance of ≥80 mL/min is considered an adequate glomerular filtration rate in subjects with normal renal function. The uremic elimination rate constant (k_u) is the sum of the nonrenal elimination rate constant and the renal elimination rate constant, which is decreased due to renal impairment. If the patient has complete renal shutdown (ie, creatinine clearance = 0 mL/min), then the intercept on the *y* axis represents the percent of drug elimination due to nonrenal drug elimination routes. Drug D, which is excreted 90% unchanged in the urine, has

the steepest slope (equivalent to α in Eq. 21.14) and is most affected by small changes in creatinine clearance; whereas drug A, which is excreted only 5% unchanged in the urine (ie, 95% eliminated by nonrenal routes), is least affected by a decrease in creatinine clearance.

Figure 21-4.

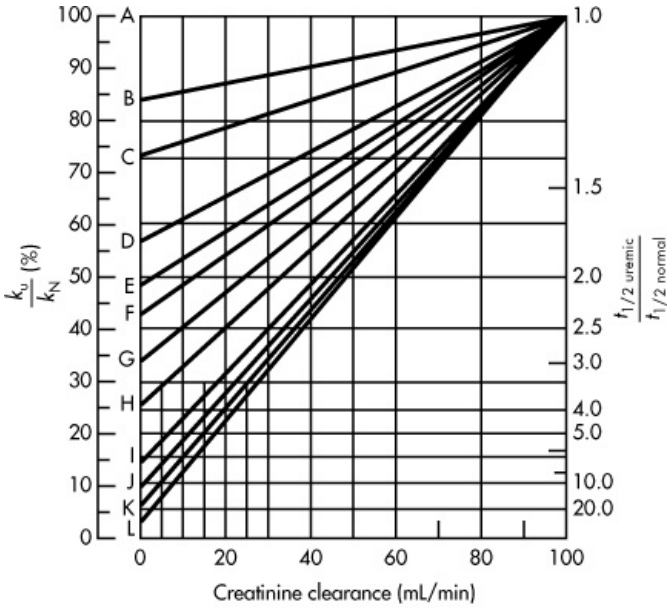


Relationship between creatinine clearance and the drug elimination rate constant.

The nomogram method of provides an estimate of the ratio of the uremic elimination rate constant (k_u) to the normal elimination rate constant (k_N) on the basis of creatinine clearance (). For this method, provided a list of drugs grouped according to the amount of drug excreted unchanged in the urine (). From the k_u/k_N ratio, the uremic dose can be estimated according to Equation 21.15:

$$\text{Uremic dose} = \frac{k_u}{k_N} \times \text{normal dose} \qquad (21.15)$$

Figure 21-5.



This nomograph describes the changes in the percentage of normal elimination rate constant (left ordinate) and the consequent geometric increase in elimination half-life (right ordinate) as a function of creatinine clearance. The drugs associated with the individual slopes are given in .

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Table 21.4 Elimination Rate Constants for Various Drugs[a]

Group	Drug	k_N (hr^{-1})	k_{nr} (hr^{-1})	k_{nr}/k_N%
A	Minocycline	0.04	0.04	100.0
	Rifampicin	0.25	0.25	100.0
	Lidocaine	0.39	0.36	92.3
	Digitoxin	0.114	0.10	87.7
B	Doxycycline	0.037	0.031	83.8
	Chlortetracycline	0.12	0.095	79.2
C	Clindamycin	0.16	0.12	75.0
	Chloramphenicol	0.26	0.19	73.1
	Propranolol	0.22	0.16	72.8
	Erythromycin	0.39	0.28	71.8
D	Trimethoprim	0.054	0.031	57.4
	Isoniazid (fast)	0.53	0.30	56.6
	Isoniazid (slow)	0.23	0.13	56.5
E	Dicloxacillin	1.20	0.60	50.0
	Sulfadiazine	0.069	0.032	46.4
	Sulfamethoxazole	0.084	0.037	44.0
F	Nafcillin	1.26	0.54	42.8
	Chlorpropamide	0.020	0.008	40.0
	Lincomycin	0.15	0.06	40.0
G	Colistimethate	0.154	0.054	35.1
	Oxacillin	1.73	0.58	33.6
	Digoxin	0.021	0.007	33.3
H	Tetracycline	0.120	0.033	27.5
	Cloxacillin	1.21	0.31	25.6
	Oxytetracycline	0.075	0.014	18.7
I	Amoxicillin	0.70	0.10	14.3
	Methicillin	1.40	0.19	13.6
J	Ticarcillin	0.58	0.066	11.4
	Penicillin G	1.24	0.13	10.5
	Ampicillin	0.53	0.05	9.4
	Carbenicillin	0.55	0.05	9.1
K	Cefazolin	0.32	0.02	6.2
	Cephaloridine	0.51	0.03	5.9
	Cephalothin	1.20	0.06	5.0
	Gentamicin	0.30	0.015	5.0
L	Flucytosine	0.18	0.007	3.9
	Kanamycin	0.28	0.01	3.6
	Vancomycin	0.12	0.004	3.3
	Tobramycin	0.32	0.010	3.1
	Cephalexin	1.54	0.032	2.1

[a] k_N is for patients with normal renal function, k_{nr} is for patients with severe renal impairment, and k_{nr}/k_N% = percent of normal elimination in severe renal impairment.

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When the dosage interval τ is kept constant, the uremic dose is always a smaller fraction of the normal dose. Instead of reducing the dose for a uremic patient, the usual dose is kept constant and the dosage interval τ is prolonged according to the following equation:

$$\text{Dosage interval in uremia, } \tau_u = \frac{k_N}{k_u} \times \tau_N \qquad (21.16)$$

where τ is the dosage interval for the dose in uremic patients and τ_N is the dosage interval for the dose in patients with normal renal function.

PRACTICE PROBLEM

Lincomycin is given at 500 mg every 6 hours to a 75-kg normal patient. What doses would be used **(a)** in complete renal shutdown ($Cl_{Cr} = 0$) and **(b)** when $Cl_{Cr} = 10$ mL/min?

Solution

To use the nomogram method, follow the steps below:

1. Locate the group to which the drug belongs in .

2. Find k_u/k_N at the point corresponding to the Cl_{Cr} of the patient ().

3. Determine k_u for the patient.

4. Make the dose adjustment in accordance with pharmacokinetic principles.

a. When $Cl_{Cr} = 0$,

$$k_u = k_{nr} + k_R$$

In complete renal shutdown ($k_R = 0$),

$$k_u = k_{nr} = 0.06\ \text{hr}^{-1}$$ (, group F)

or find k_u/k_N in , group F, at $Cl_{Cr} = 0$ mL/min:

$$\frac{k_u}{k_N} = 0.425$$

$$k_u = 0.425\ (0.15) = 0.0638\ \text{hr}^{-1}$$

$$\text{Uremic dose} = 500\ \text{mg} \times \frac{0.0638}{0.15} = 212\ \text{mg every 6 hr}$$

b. At $Cl_{Cr} = 10$ mL/min,

$$\frac{k_u}{k_N} = 0.48$$

$$k_N = 0.15\ \text{hr}^{-1}$$

$$k_u = (0.48)\,(0.15) = 0.072\ \text{hr}^{-1}$$

$$\text{Dose} = 500\ \text{mg} \times \frac{0.072}{0.15} = 240\ \text{mg}$$

Alternatively,

$$\text{Dose} = (0.48)\,(500) = 240\ \text{mg}$$

Fraction of Drug Excreted Unchanged (*fe*) Methods

For many drugs, the fraction of drug excreted unchanged (*fe*) is available in the literature. lists various drugs with their *fe* value and elimination half-life. The *fe* method for estimating a dosage regimen in the uremic patient is a general method that may be applied to any drug whose *fe* is known.

Table 21.5 Fraction of Drug Excreted Unchanged (*fe*) and Elimination Half-Life Values

Drug	*fe*	$t_{1/2\ \text{normal}}$ (hr)[a]
Acebutolol	0.44 ± 0.11	2.7 ± 0.4
Acetaminophen	0.03 ± 0.01	2.0 ± 0.4
Acetohexamide	0.4	1.3
Allopurinol	0.1	2–8
Active metabolite		16–30
Alprenolol	0.005	3.1 ± 1.2
Amantadine	0.85	10
Amikacin	0.98	2.3 ± 0.4
Amiloride	0.5	8 ± 2

Amoxicillin	0.52 ± 0.15	1.0 ± 0.1
Amphetamine	0.4–0.45	12
Amphotericin B	0.03	360
Ampicillin	0.90 ± 0.08	1.3 ± 0.2
Atenolol	0.85	6.3 ± 1.8
Azlocillin	0.6	1.0
Bacampicillin	0.88	0.9
Baclofen	0.75	3–4
Bleomycin	0.55	1.5–8.9
Bretylium	0.8 ± 0.1	4–17
Bumetanide	0.33	3.5
Carbenicillin	0.82 ± 0.09	1.1 ± 0.2
Cefalothin	0.52	0.6 ± 0.3
Cefamandole	0.96 ± 0.03	0.77
Cefazolin	0.80 ± 0.13	1.8 ± 0.4
Cefoperazone	0.2–0.3	2.0
Cefotaxime	0.5–0.6	1–1.5
Cefoxitin	0.88 ± 0.08	0.7 ± 0.13
Cefuroxime	0.92	1.1
Cephalexin	0.96	0.9 ± 0.18
Chloramphenicol	0.05	2.7 ± 0.8
Chlorphentermine	0.2	120
Chlorpropamide	0.2	36
Chlorthalidone	0.65 ± 0.09	44 ± 10
Cimetidine	0.77 ± 0.06	2.1 ± 1.1
Clindamycin	0.09–-0.14	2.7 ± 0.4
Clofibrate	0.11–0.32	13 ± 3
Clonidine	0.62 ± 0.11	8.5 ± 2.0
Colistin	0.9	3
Cytarabine	0.1	2
Cyclophosphamide	0.3	5
Dapsone	0.1	20
Dicloxacillin	0.60 ± 0.07	0.7 ± 0.07
Digitoxin	0.33 ± 0.15	166 ± 65
Digoxin	0.72 ± 0.09	42 ± 19
Disopyramide	0.55 ± 0.06	7.8 ± 1.6
Doxycycline	0.40 ± 0.04	20 ± 4
Erythromycin	0.15	1.1–3.5
Ethambutol	0.79 ± 0.03	3.1 ± 0.4
Ethosuximide	0.19	33 ± 6
Flucytosine	0.63–0.84	5.3 ± 0.7
Flunitrazepam	0.01	15 ± 5
Furosemide	0.74 ± 0.07	0.85 ± 0.17
Gentamicin	0.98	2–3
Griseofulvin	0	15
Hydralazine	0.12–0.14	2.2–2.6
Hydrochlorothiazide	0.95	2.5 ± 0.2
Indomethacin	0.15 ± 0.08	2.6–11.2
Isoniazid		
Rapid acetylators	0.07 ± 0.02	1.1 ± 0.2
Slow acetylators	0.29 ± 0.05	3.0 ± 0.8
Isosorbide dinitrate	0.05	0.5
Kanamycin	0.9	2.1 ± 0.2

Lidocaine	0.02 ± 0.01	1.8 ± 0.4
Lincomycin	0.6	5
Lithium	0.95 ± 0.15	22 ± 8
Lorazepam	0.01	14 ± 5
Meperidine	0.04–0.22	3.2 ± 0.8
Methadone	0.2	22
Methicillin	0.88 ± 0.17	0.85 ± 0.23
Methotrexate	0.94	8.4
Methyldopa	0.63 ± 0.10	1.8 ± 0.2
Metronidazole	0.25	8.2
Mexiletine	0.1	12
Mezlocillin	0.75	0.8
Minocycline	0.1 ± 0.02	18 ± 4
Minoxidil	0.1	4
Moxalactam	0.82–0.96	2.5–3.0
Nadolol	0.73 ± 0.04	16 ± 2
Nafcillin	0.27 ± 0.05	0.9–1.0
Nalidixic acid	0.2	1.0
Netilmicin	0.98	2.2
Neostigmine	0.67	1.3 ± 0.8
Nitrazepam	0.01	29 ± 7
Nitrofuraniton	0.5	0.3
Nomifensine	0.15–0.22	3.0 ± 1.0
Oxacillin	0.75	0.5
Oxprenolol	0.05	1.5
Pancuronium	0.5	3.0
Pentazocine	0.2	2.5
Phenobarbital	0.2 ± 0.05	86 ± 7
Pindolol	0.41	3.4 ± 0.2
Pivampicillin	0.9	0.9
Polymyxin B	0.88	4.5
Prazosin	0.01	2.9 ± 0.8
Primidone	0.42 ± 0.15	8.0 ± 4.8
Procainamide	0.67 ± 0.08	2.9 ± 0.6
Propranolol	0.005	3.9 ± 0.4
Quinidine	0.18 ± 0.05	6.2 ± 1.8
Rifampin	0.16 ± 0.04	2.1 ± 0.3
Salicylic acid	0.2	3
Sisomicin	0.98	2.8
Sotalol	0.6	6.5–13
Streptomycin	0.96	2.8
Sulfisoxazole	0.53 ± 0.09	5.9 ± 0.9
Sulfinpyrazone	0.45	2.3
Tetracycline	0.48	9.9 ± 1.5
Thiamphenicol	0.9	3
Thiazinamium	0.41	
Theophylline	0.08	9 ± 2.1
Ticarcillin	0.86	1.2
Timolol	0.2	3–5
Tobramycin	0.98	2.2 ± 0.1
Tocainide	0.20-0.70 (0.40 mean)	1.6–3
Tolbutamide	0	5.9 ± 1.4

Triamterene	0.04 ± 0.01	2.8 ± 0.9
Trimethoprim	0.53 ± 0.02	11 ± 1.4
Tubocurarine	0.43 ± 0.08	2 ± 1.1
Valproic acid	0.02 ± 0.02	16 ± 3
Vancomycin	0.97	5–6
Warfarin	0	37 ± 15

[a]Half-life is a derived parameter that changes as a function of both clearance and volume of distribution. It is independent of body size, because it is a function of these two parameters (*Cl*, V_D), each of which is proportional to body size. It is important to consider that half-life is the time to eliminate 50% of the "drug" from the body (plasma), not the time in which 50% of the effect is lost.

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The *Giusti–Hayton* (1973) method assumes that the effect of reduced kidney function on the renal portion of the elimination constant can be estimated from the ratio of the uremic creatinine clearance, Cl^{u}_{Cr}, to the normal creatinine clearance, Cl^{N}_{Cr}:

$$\frac{k_r^u}{k^N} = \frac{Cl_{Cr}^u}{Cl_{Cr}^N} \qquad (21.17)$$

where k^{u}_{r} is the uremic renal excretion rate constant and k^{N}_{r} is the normal renal excretion rate constant.

$$k_r^u = k_r^N \frac{Cl_{Cr}^u}{Cl_{Cr}^N} \qquad (21.18)$$

Because the overall uremic elimination rate constant, k_u, is the sum of renal and nonrenal elimination,

$$k_u = k_{nr}^u + k_r^u \qquad (21.19)$$

$$k_u = k_{nr}^u + k_r^N \left(\frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right)$$

Dividing Equation 21.19 by k_N on both sides yields

$$\frac{k_u}{k_N} = \frac{k_{nr}^u}{k_N} + \frac{k_r^N}{k_N}\left(\frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right) \qquad (21.20)$$

Let $fe = k^{N}_{r}/k_N$ = fraction of drug excreted unchanged in the urine and $1 - fe = k^{u}_{nr}/k_N$ = fraction of drug excreted by nonrenal routes. Substitution into Equation 21.20 yields the Giusti–Hayton equation, where *G* is the Giusti–Hayton factor, which can be calculated from the *fe* and the ratio of uremic to normal clearance:

$$\frac{k_u}{k_N} = (1 - fe) + fe\left(\frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right)$$

or

$$\frac{k_u}{k_N} = 1 - fe\left(1 - \frac{Cl_{Cr}^u}{Cl_{Cr}^N}\right) = G \qquad (21.21)$$

The Giusti–Hayton equation is useful for most drugs for which the fraction of drug excreted by renal routes has been reported in the literature. The ratio k^{u}_{nr}/k_N can be calculated from the fraction of drug excreted by the kidney, normal creatinine clearance, and the creatinine clearance in the uremic patient.

PRACTICE PROBLEM

The maintenance dose of gentamicin is 80 mg every 6 hours for a patient with normal renal function. Calculate the maintenance dose for a uremic patient with creatinine clearance of 20 mL/min. Assume a normal creatinine clearance of 100 mL/min.

Solution

From the literature, gentamicin is reported to be 100% excreted by the kidney (ie, *fe* = 1). Using Equation 21.21,

$$\frac{k_u}{k_N} = 1 - 1\left(1 - \frac{20}{100}\right) = 0.2$$

Because

$$\frac{D_u}{D_N} = \frac{k_u}{k_N} \quad \text{or} \quad D_u = D_N \times \frac{k_u}{k_N}$$

where D_u = uremic dose and D_N = normal dose,

$$D_u = 80\ \text{mg} \times 0.2 = 16\ \text{mg}$$

The maintenance dose is 16 mg every 6 hours. Alternatively, the dosing interval can be adjusted without changing the dose:

$$\frac{\tau_u}{\tau_N} = \frac{k_N}{k_u} \qquad \text{or} \qquad \tau_u = \tau_N \times \frac{k_N}{k_u}$$

$$\tau_u = 6\ \text{hr} \times \frac{1}{0.2} = 30\ \text{hr}$$

where t_u and t_N are dosing intervals for uremic and normal patients, respectively. The patient may be given 80 mg every 30 hours.

Other approaches for using fraction of drug excreted unchanged have been developed by and . These methods use *fe* for dosing regimen design and the following equation:

$$Q = 1 - fe\,(1 - k_f) \qquad (21.22)$$

where Q is the dosage adjustment factor, $k_f = Cl^u_{Cr}/Cl^N_{Cr}$, and *fe* is the fraction of unchanged drug excreted renally. Actually Q is exactly the same as G in Eq. 21.21, the Giusti-Hayton approach developed in 1973.

The value of Q in Equation 21.22 is multipled by the normal dose, D_N, to give the uremic dose, D_u:

$$D_u = Q \times D_N \qquad (21.23)$$

All the methods discussed so far assume that nonrenal elimination, k_{nr}, is unchanged, thereby ignoring potential side effects resulting from an increase in the half-life of metabolism of the parent drug and/or an accumulation of active metabolites of the drug.

have shown that although lorazepam pharmacokinetics were not significantly altered in patients with chronic renal failure, the clearance of lorazepam glucuronide, a major metabolite, was reduced significantly. Therefore, there are potential sedative side effects in the renally impaired patient as a result of the longer metabolite half-life. also cited literature references to potentiation of sedative and analgesic drug effects in renal, liver, and other multisystem disease states.

In addition to pharmacokinetic changes, possible changes in pharmacodynamic effects in patients with renal and other diseases must be considered. Neuromuscular-blocking drugs may be potentiated or antagonized by changes in potassium, phosphate, and hydrogen ion concentration brought about by uremic states. Morphine potentiation has been reported in hypocalcemic states. In many patients, plasma creatinine concentration may not rise for some time, until creatinine clearance has fallen significantly, thereby adding to the uncertainty of any method that depends on plasma C_{Cr} for dose adjustment.

Comparison of the Various Methods for Dose Adjustment in Uremic Patients

All of the methods mentioned previously have similar limitations (see). For example, the drug must follow dose-independent kinetics and the volume of distribution of the drug must remain relatively constant in the uremic patient. As mentioned, it is usually assumed that the nonrenal routes of elimination, such as hepatic clearance, do not change. Because no correction for metabolites is made, any drug having an active pharmacologic metabolite must be additionally modified. Another assumption in the use of these methods is that pharmacologic response is unchanged in the uremic patient. This assumption may be unrealistic for drugs that act differently in the disease state. For example, the pharmacologic response with digoxin is dependent on the potassium level in the body, and the potassium level in the uremic patient may be rather different from that of the normal individual. In a patient undergoing dialysis, loss of potassium may increase the potential of toxic effect of the drug digoxin. For many drugs, studies have shown that the incidence of adverse effects is increased in uremic patients. It is often impossible to distinguish whether the increase in adverse effect is due to a pharmacokinetic change or to a pharmacodynamic change in the receptor sensitivity to the drug. In any event, these observations point out the fact that dose adjustment must be regarded as a preliminary estimation to be followed with further adjustments in accordance with the observed clinical response.

PRACTICE PROBLEMS

1. An adult male patient (52 years old, 75 kg) whose serum creatinine is 2.4 mg/dL is to be given gentamicin sulfate for a confirmed Gram-negative infection. The usual dose of gentamicin in adult patients with normal renal function is 1 mg/kg every 8 hours by multiple IV bolus injections. Gentamicin sulfate (Garamycin) is available in 2-mL vials containing 40 mg of gentamicin sulfate per milliliter. Calculate **(a)** the creatinine clearance in this patient by the Cockcroft and Gault method and **(b)** the appropriate dosage regimen of gentamicin sulfate for this patient in mg and mL.

Solution

a. The creatinine clearance is calculated by the Cockcroft and Gault method using Equation 21.13:

$$Cl_{Cr} = \frac{(140 - 52)\,(75)}{72\,(2.4)} = 38.19\ \text{mL/min}$$

b. The initial dose of gentamicin sulfate in this patient may be estimated using Equation 21.21. Normal creatinine clearance is assumed to equal 100 mL/min. The fraction of dose excreted unchanged in the urine, *fe* = 0.98 for gentamicin sulfate ().

$$\frac{k_u}{k_N} = Q = 1 - 0.98\left(1 - \frac{38.19}{100}\right) = 0.39$$

The usual dose of gentamicin sulfate = 1 mg/kg every 8 hours. Therefore, for a 75-kg adult, the usual dose is 75 mg every 8 hours. The uremic dose may be estimated by:

(1) Reducing the maintenance dose and keeping the dosing interval constant:

$$\text{Uremic dose} = \frac{k_u}{k_N} \times \text{normal dose}$$

$$\text{Uremic dose} = 0.39 \times 75 = 29.25 \text{ mg}$$

Give 29.25 mg (about 30 mg) every 8 hours. Because the concentration of gentamicin sulfate solution is 40 mg/mL, then 30 mg gentamicin sulfate is equivalent to 0.75 mL.

(2) Increasing the dosing interval and keeping the maintenance dose constant:

$$\text{Dosage interval in uremia, } \tau_u = \frac{k_N}{k_u} \times \tau_N$$

$$\tau_u = 2.564 \times 8 = 20.5 \text{ hr } (2.564 \text{ is the reciprocal of } 0.39)$$

Give 75 mg every 20.5 hours.

(3) Change both the maintenance dose and dosing interval. Using the dosing rate D_τ = 29.25 mg/8 hr = 3.66 mg/hr, a dose of 21.9 mg every 6 hours or 43.8 mg every 12 hours will produce the same average steady-state plasma drug concentration.

Although each estimated dosage regimen shown above produces the same average steady-state plasma drug concentration, the peak drug concentration, trough drug concentration, and duration of time in which the drug concentration will be above or below the minimum effective plasma drug concentration will be different. Choice of an appropriate dosage regimen requires consideration of these issues, the patient, and the safety and efficacy of the drug.

2. Calculate the dose adjustment needed for uremic patients with **(a)** 75% of normal kidney function (ie, Cl^u_{Cr}/Cl^N_{Cr} = 75%); **(b)** 50% of normal kidney function; and **(c)** 25% of normal kidney function. Make calculations for **(1)** a drug that is 50% excreted by the kidney, and **(2)** a drug that is 75% excreted by the kidney.

Solution

The values for percent of normal creatinine clearance in uremic patients with various renal functions are listed in . The percent of dose adjustment in a given uremic state is obtained using the procedure detailed below. The important facts to remember are **(1)** although the elimination rate constant is usually composed of two components, only the renal component is reduced in a uremic patient, and **(2)** the kidney function of the uremic patient may be expressed as a percent of uremic Cl^u_{Cr}/normal Cl^N_{Cr}. The reduction in the renal elimination rate constant can be estimated from the percent of kidney function remaining in the patient. The steps involved in making the calculations are as follows:

a. Determine *fe*, or the fraction of drug excreted by the kidney.

b. Determine k_f by dividing Cl^u_{Cr} of the uremic patient by Cl^N_{Cr}.

c. Calculate *Q* (Eq. 21.22).

d. Multiply *Q* by the normal dose to give the fraction of normal dose required for a uremic patient.

Table 21.6 Dosage Adjustment in Uremic Patients

	Percent of Normal Dose			
Fraction of Drug Excreted Unchanged (k_r/k_N) or *fe*	**50% Normal Cl_{Cr}**	**25% Normal Cl_{Cr}**	**10% Normal Cl_{Cr}**	**0% Normal Cl_{Cr}**
0.25	87	81	77	75
0.50	75	62	55	50
0.75	62	44	32	25
0.90	55	32	19	10

3. What is the dose for a drug that is 75% excreted unchanged through the kidney in a uremic patient with a creatinine clearance of 10 mL/min?

Solution

$$fe = 75\%$$

$$\text{Renal function of uremic patient} = \frac{10}{100} = 10\% \text{ normal}$$

$$\begin{aligned}\text{Percent of uremic patient's renal elimination constant} &= 75\% \times 10\% \\ &= 7.5\% \text{ normal}\end{aligned}$$

$$\begin{aligned}\text{Percent of uremic patient's overall elimination constant} &= 7.5\% + (100\% - 75\%) \\ &= 7.5\% + 25\% = 32.5\%\end{aligned}$$

Therefore, the uremic patient's dose should be 32.5% of that of normal patient. provides some calculated dose adjustments for drugs eliminated to various degrees by renal excretion in different stages of renal failure.

General Clearance Method

The general clearance method is based on the methods discussed above. This method is popular in clinical settings because of its simplicity. The method assumes that creatinine clearance, Cl_{Cr}, is a good indicator of renal function and that the renal clearance of a drug, Cl_R, is proportional to Cl_{Cr}. Therefore, renal drug clearance, Cl^u_R, in the uremic patient is

$$Cl^u_R = \frac{Cl^u_{Cr}}{Cl^N_{Cr}} \times Cl_R \qquad (21.24)$$

$$Cl_u = Cl_{nr} + Cl_R \frac{Cl^u_{Cr}}{Cl^N_{Cr}} \qquad (21.25)$$

where Cl_u is the total body clearance in the uremic patient.

If the ratio Cl^u_{Cr}/Cl^N_{Cr}, Cl_{nr}, and Cl_R are known, the total body clearance in the uremic patient may be estimated using Equation 21.25. Alternatively, if the normal total body clearance, *Cl*, and *fe* are known, Equation 21.26 may be obtained by substitution in Equation 21.25:

$$Cl_u = Cl(1 - fe) + fe\,Cl \frac{Cl^u_{Cr}}{Cl^N_{Cr}} \qquad (21.26)$$

Equation 21.26 calculates drug clearance in the uremic patient using the fraction of drug excreted unchanged (*fe*), total body clearance of the drug (*Cl*) in the normal subject, and the ratio of creatinine clearance of the uremic to that of the normal patient.

Dividing Equation 21.26 on both sides by *Cl* yields the ratio Cl_u/Cl, reflecting the fraction of the uremic/normal drug dose.

$$\frac{Cl_u}{Cl} = (1 - fe) + fe \frac{Cl^u_{Cr}}{Cl^N_{Cr}} \qquad (21.27)$$

PRACTICE PROBLEM

M.S., a 34-year-old, 110-lb female patient, is to be given tobramycin for sepsis. The usual dose of tobramycin is 150 mg twice a day by intravenous injection. The creatinine clearance in this patient has decreased to a stable level of 50 mL/min. Calculate the appropriate dose of tobramycin for this patient.

Solution

Obtain *fe* = 0.9 from the literature () and apply Equation 21.27:

$$\frac{Cl_u}{Cl} = (1 - fe) + fe \frac{Cl^u_{Cr}}{Cl^N_{Cr}}$$

$$\frac{Cl_u}{Cl} = 1 - 0.9 + 0.9\left(\frac{50}{100}\right) = 0.55$$

Therefore, the dose for the uremic patient = 150 mg x 0.55 = 82.5 mg (given twice a day).

The Wagner Method

The methods for renal dose adjustment discussed in the previous sections all assume that the volume of distribution and the fraction of drug excreted by nonrenal routes are unchanged. These assumptions are convenient and hold true for many drugs. However, in the absence of reliable information assuring the validity of these assumptions, the equations should be demonstrated as statistically reliable in practice. A statistical approach was used by , who established a linear relationship between creatinine concentration and the first-order elimination constant of the drug in patients. The Wagner method is described in greater detail in the previous edition.

This method takes advantage of the fact that the elimination constant for a patient can be obtained from the creatinine clearance, as follows:

$$k\% = a + bCl_{Cr} \qquad (21.28)$$

The values of *a* and *b* are determined statistically for each drug from pooled data on uremic patients. The method is simple to use and should provide accurate determination of elimination constants for patients when a good linear relationship exists between elimination constant and creatinine concentration. The theoretical derivation of this approach is as follows:

$k\%$ = total elimination rate constant
k_{nr} = nonrenal elimination rate constant (%)
k_R = renal excretion rate constant
Cl = Total body clearance of drug

$$R = \frac{Cl}{Cl_{Cr}} \qquad (21.29)$$

$$Cl = R\,Cl_{Cr}$$

$$k = k_{nr} + \frac{R}{V_D} Cl_{Cr}$$

$$100k = 100k_{nr} + \frac{100R}{V_D} Cl_{Cr}$$

$$k\% = a + b\,Cl_{Cr} \qquad (21.30)$$

Equation 21.30 can also be used with drugs that follow the two-compartment model. In such cases the terminal half-life is used and *b*, the terminal slope of elimination curve, is substituted for the elimination rate constant, *k*. Since the equation assumes a constant nonrenal elimination constant (k_{nr}) and volume of distribution, any change in these two parameters will result in an error in the estimated elimination constant.

EXTRACORPOREAL REMOVAL OF DRUGS

Patients with *end-stage renal disease* (ESRD) and patients who have become intoxicated with a drug as a result of a drug overdose require supportive treatment to remove the accumulated drug and its metabolites. Several methods are available for the extracorporeal removal of drugs, including hemoperfusion, hemofiltration, and dialysis. The objective of these methods is to rapidly remove the undesirable drugs and metabolites from the body without disturbing the fluid and electrolyte balance in the patient.

Patients with impaired renal function may be taking other medication concurrently. For these patients, dosage adjustment may be needed to replace drug loss during extracorporeal drug and metabolite removal.

Dialysis

Dialysis is an artificial process in which the accumulation of drugs or waste metabolites is removed by diffusion from the body into the dialysis fluid. Two common dialysis treatments are *peritoneal dialysis* and *hemodialysis*. Both processes work on the principle that as the uremic blood or fluid is equilibrated with the dialysis fluid across a dialysis membrane, waste metabolites from the patient's blood or fluid diffuse into the dialysis fluid and are removed. The dialysate contains water, dextrose, electrolytes (potassium, sodium, chloride, bicarbonate, acetate, calcium, etc), and other elements similar to normal body fluids without the toxins.

PERITONEAL DIALYSIS

Peritoneal dialysis uses the peritoneal membrane in the abdomen as the filter. The peritoneum consists of visceral and parietal components. The peritoneum membrane provides a large natural surface area for diffusion of approximately 1–2 m^2 in adults; the membrane is permeable to solutes of molecular weights ≤ 30,000 Da (). Total splanchnic flow is 1200 mL/min at rest, but only a small portion, approximately 70 mL/min, comes into contact with the peritoneum. Placement of a peritoneal catheter is surgically simpler than hemodialysis and does not require vascular surgery and heparinization. The dialysis fluid is pumped into the peritoneal cavity, where waste metabolites in the body fluid are discharged rapidly. The dialysate is drained and fresh dialysate is reinstilled and then drained periodically. Peritoneal dialysis is also more amenable to self-treatment. However, slower drug clearance rates are obtained with peritoneal dialysis compared to hemodialysis, and thus longer dialysis time is required.

Continuous ambulatory peritoneal dialysis (CAPD) is the most common form of peritoneal dialysis. Many diabetic patients become uremic as a result of lack of control of their diabetes. About 2 L of dialysis fluid is instilled into the peritoneal cavity of the patient through a surgically placed resident catheter. The objective is to remove accumulated urea and other metabolic waste in the body. The catheter is sealed and the patient is able to continue in an ambulatory mode. Every 4–6 hours, the fluid is emptied from the peritoneal cavity and replaced with fresh dialysis fluid. The technique uses about 2 L of dialysis fluid; it does not require a dialysis machine and can be performed at home.

HEMODIALYSIS

Hemodialysis uses a dialysis machine and filters blood through an artificial membrane. Hemodialysis requires access to the blood vessels to allow the blood to flow to the dialysis machine and back to the body. For temporary access, a shunt is created in the arm, with one tube inserted into an artery and another tube inserted in a vein. The tubes are joined above the skin. For permanent access to the blood vessels, an arteriovenous fistula or graft is created by a surgical procedure to allow access to the artery and vein. Patients who are on chronic hemodialysis treatment need to be aware of the need for infection control of the surgical site of the fistula. At the start of the hemodialysis procedure, an arterial needle allows the blood to flow to the dialysis machine, and blood is returned to the patient to the venous side. Heparin is used to prevent blood clotting during the dialysis period.

During hemodialysis, the blood flows through the dialysis machine, where the waste material is removed from the blood by diffusion through an artificial membrane before the blood is returned to the body. Hemodialysis is a much more effective method of drug removal and is preferred in situations when rapid removal of the drug from the body is important, as in overdose or poisoning. In practice, hemodialysis is most often used for patients with end-stage renal failure. Early dialysis is appropriate for patients with acute renal failure in whom resumption of renal function can be expected and in patients who are to be renally transplanted. Other patients may be placed on dialysis according to clinical judgment concerning the patient's quality of life and risk/benefit ratio ().

Dialysis may be required from once every 2 days to 3 times a week, with each treatment period lasting 2 to 4 hours. The time required for dialysis depends on the amount of residual renal function in the patient, any complicating illness (eg, diabetes mellitus), the size and weight of the patient, including muscle mass, and the efficiency of the dialysis process. Dosing of drugs in patients receiving hemodialysis is affected greatly by the frequency and type of dialysis machine used and by the physicochemical and pharmacokinetic properties of the drug. Factors that affect drug removal in hemodialysis are listed in . These factors are carefully considered before hemodialysis is used for drug removal.

Table 21.7 Factors Affecting Dialyzability of Drugs

Physicochemical and Pharmacokinetic Properties of the Drug	
Water solubility	Insoluble or fat-soluble drugs are not dialyzed—eg, glutethimide, which is very water insoluble.
Protein binding	Tightly bound drugs are not dialyzed because dialysis is a passive process of diffusion—eg, propranolol is 94% bound.
Molecular weight	Only molecules with molecular weights of less than 500 are easily dialyzed—eg, vancomycin is poorly dialyzed and has a molecular weight of 1800.
Drugs with large volumes of distribution	Drugs widely distributed are dialyzed more slowly because the rate-limiting factor is the volume of blood entering the machine—eg, for digoxin, V_D = 250–300 L. Drugs concentrated in the tissues are usually difficult to remove by dialysis.
Characteristics of the Dialysis Machine	
Blood flow rate	Higher blood flows give higher clearance rates.
Dialysate	Composition of the dialysate and flow rate.
Dialysis membrane	Permeability characteristics and surface area.
Transmembrane pressure	Ultrafiltration increases with increase in transmembrane pressure.
Duration and frequency of dialysis	

In hemodialysis, blood is pumped to the dialyzer by a roller pump at a rate of 300–450 mL/min. The drug and metabolites diffuse from the blood through the semipermeable membrane. In addition, hydrostatic pressure also forces the drug molecules into the dialysate by ultrafiltration. The composition of the dialysate is similar to plasma but may be altered according to the needs of the patient. Many dialysis machines use a hollow fiber or capillary dialyzer in which the semipermeable membrane is made into fine capillaries, of which thousands are packed into bundles with blood flowing through the capillaries and the dialysate is circulated outside the capillaries. The permeability characteristics of the membrane and the membrane surface area are determinants of drug diffusion and ultrafiltration.

The efficacy of hemodialysis membranes for the removal of vancomycin by hemodialysis has been reviewed by . Vancomycin is an antibiotic effective against most Gram-positive organisms such as *Staphylococcus aureus,* which may be responsible for vascular access infections in patients undergoing dialysis. In De Hart's study, vancomycin hemodialysis in patients was compared using a cuprophan membrane or a cellulose acetate and polyacrylonitrile membrane. The cellulose acetate and polyacrylonitrile membrane is considered a "high-flux" filter. Serum vancomycin concentrations decreased only 6.3% after dialysis when using the cuprophan membrane, whereas the serum drug concentration decreased 13.6–19.4% after dialysis with the cellulose acetate and polyacrylonitrile membrane.

In dialysis involving uremic patients receiving drugs for therapy, the rate at which a given drug is removed depends on the flow rate of blood to the dialysis machine and the performance of the dialysis machine. The term *dialysance* is used to describe the process of drug removal from the dialysis machine. Dialysance is a clearance term similar in meaning to renal clearance, and it describes the amount of blood completely cleared of drugs (in mL/min). Dialysance is defined by the equation

$$Cl_D = \frac{Q(C_a - C_v)}{C_a} \qquad (21.31)$$

where C_a = drug concentrations in arterial blood (blood entering kidney machine), C_v = drug concentration in venous blood (blood leaving kidney machine), Q = rate of blood flow to the kidney machine, and Cl_D = dialysance. Dialysance is sometimes referred to as *dialysis clearance*.

PRACTICE PROBLEM

Assume the flow rate of blood to the dialysis machine is 350 mL/min. By chemical analysis, the concentrations of drug entering and leaving the machine are 30 and 12 μg/mL, respectively. What is the dialysis clearance?

Solution

The rate of drug removal is equal to the volume of blood passed through the machine divided by the arterial difference in blood drug concentrations before and after dialysis. Thus,

$$\text{Rate of drug removal} = 350\ \text{mL/min} \times (30 - 12)\ \mu\text{g/mL} = 6300\ \mu\text{g/min}$$

Since clearance is equal to the rate of drug removal divided by the arterial concentration of drug,

$$Cl_D = \frac{6300\ \mu\text{g/min}}{30\ \mu\text{g/mL}} = 210\ \text{mL/min}$$

Alternatively, using Equation 21.31,

$$Cl_D = 350\ \text{mL/min} \times \frac{(30 - 12)}{30} = 210\ \text{mL/min}$$

These calculations show that the two terms are the same. In practice, dialysance has to be measured experimentally by determining C_a, C_v, and Q. In dosing of drugs for patients on dialysis, the average plasma drug concentration of a patient is given by

$$C_{av}^{\infty} = \frac{FD_0}{(Cl_T + Cl_D)\tau} \qquad (21.32)$$

where F represents fraction of dose absorbed, Cl_T is total body drug clearance of the patient, C^{∞}_{av} is average steady-state plasma drug concentration, and τ is the dosing interval.

In practice, if Cl_D is 30% or more of Cl_T, adjustment is usually made for the amount of drug lost in dialysis.

The elimination half-life, $t_{1/2}$, for the drug in the patient off dialysis is related to the remaining total body clearance Cl_T and the volume of distribution V_D, as shown below:

$$t_{1/2} = \frac{0.693\,V_D}{Cl_T} \qquad (21.33)$$

Drugs that are easily dialyzed will have a high dialysis clearance Cl_D, and the elimination half-life $t_{1/2}$ is shorter in a patient on dialysis.

$$t_{1/2} = \frac{0.693\,V_D}{Cl_T + Cl_D} \qquad (21.34)$$

$$k_{ON} = \frac{Cl_T + Cl_D}{V_D} \qquad (21.35)$$

where k_{ON} is the first-order elimination half-life of the drug in the patient on dialysis.

The *fraction of drug lost* due to elimination and dialysis may be estimated from Equation 21.36.

$$\text{Fraction of drug lost} = 1 - e^{-(Cl_T + Cl_D)\,t/V_D} \qquad (21.36)$$

Equation 21.36 is based on first-order drug elimination and the substitution of t hours for the dialysis period.

Several hypothetical examples illustrating the use of Equation 21.36 have been developed by . These are given in .

Table 21.8 Predicted Effects of Hemodialysis on Drug Half-Life and Removal in the Overdose Setting

Drug	V_D (L)	Cl (mL/min)	Cl_D (mL/min)	$t_{1/2\,off}$ (hr)	$t_{1/2\,on}$ (hr)	FL[a]
Digoxin [b]	560	150	20	43	38	0.07
Digoxin [c]	300	40	20	86	58	0.05
Ethchlorvynol	300	35	60	99	36	0.07
Phenobarbital	50	5	70	115	8	0.30
Phenytoin	100	5	10	231	77	0.04
Salicylic acid	40	20	100	23	4	0.51

[a]FL = fraction lost during a dialysis period of 4 hours.

[b]Parameters for a patient with normal renal function.

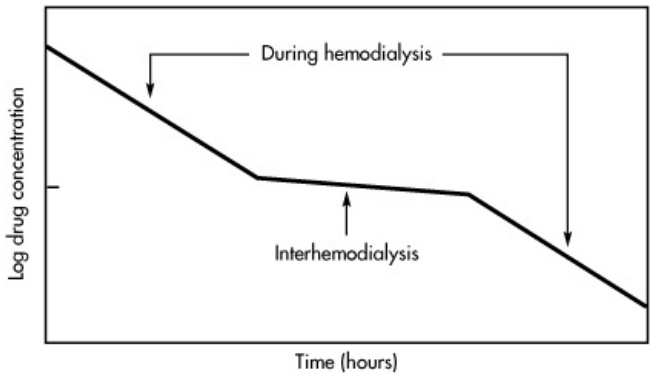
[c]Parameters for a patient with no renal function.

From , with permission.

Equation 21.36 shows that as V_D increases, the fraction of drug lost decreases. The fraction of drug lost during a 4-hour dialysis period for phenobarbital and salicylic acid was 0.30 and 0.50, respectively, whereas for digoxin and phenytoin, the fraction of drug lost was only 0.07 and 0.04, respectively. Both phenobarbital and salicylic acid are easily dialyzed because of their smaller volumes of distribution, small molecular weights, and aqueous solubility. In contrast, digoxin has a large volume of distribution and phenytoin is highly bound to plasma proteins, making these drugs difficult to dialyze. Thus, dialysis is not very useful for treating digoxin intoxication, but is useful for salicylate overdose.

An example of the effect of hemodialysis on drug elimination is shown in . During the interdialysis period, the patient's total body clearance is very low and the drug concentration declines slowly. In this example, the drug has an elimination $t_{1/2}$ of 48 hours during the interdialysis period. When the patient is placed on dialysis, the drug clearance (sum of the total body clearance and the dialysis clearance) removes the drug more rapidly.

Figure 21-6.



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

Effect of dialysis on drug elimination.

CLINICAL EXAMPLES

1. The aminoglycoside antibiotics, such as gentamicin and tobramycin, are eliminated primarily by the renal route. Dosing of these aminoglycosides is adjusted according to the residual renal function in the patient as estimated by creatinine clearance. During hemodialysis or peritoneal dialysis, the elimination half-lives for these antibiotics are significantly decreased, as shown in . After dialysis, the aminoglycoside concentrations are below the therapeutic range, and the patient needs to be given another dose of the aminoglycoside antibiotic. The data in also show that hemodialysis is more efficient in removing the aminoglycoside antibiotic, as shown by a smaller half-life during the dialysis period compared to peritoneal dialysis.

Table 21.9 Range of Aminoglycoside Half-Lives (Hours) during Dialysis[a]

Aminoglycoside	Interdialysis[b]	Hemodialysis	Peritoneal Dialysis
Kanamycin	40–96	5	12
Gentamicin	21–59	6–11	5–29
Tobramycin	27–70	3–10	10–37
Amikacin	28–87	4–7	18–29
Netlimicin	24–52	5	—

[a]Patient renal function creatinine clearance ≤5 mL/min.

[b]Interdialysis, period in between dialysis treatment.

From *Facts and Comparisons* (1992), with permission.

2. An adult male (73 years old, 65 kg) with diabetes mellitus is placed on hemodialysis. His residual creatinine clearance is <5 mL/min. The patient is given tobramycin, an aminoglycoside antibiotic, at a dose of 1 mg/kg by IV bolus injection. Tobramycin is 90% excreted unchanged in the urine, is less than 10% bound to plasma proteins, and has an elimination half-life of

approximately 2.2 hours in patients with normal renal function. In this patient, tobramycin has an elimination $t_{1/2}$ of 50 hours during the interdialysis period and an elimination $t_{1/2}$ of 8 hours during hemodialysis. The apparent volume of distribution for tobramycin is about 0.33 L/kg. For this patient, calculate **(a)** the initial plasma antibiotic concentration after the first dose of tobramycin; **(b)** the plasma drug concentration just before the start of hemodialysis (48 hours after the initial tobramycin dose); **(c)** the plasma drug concentration at the end of 4 hours of hemodialysis; **(d)** the amount of drug lost from the body after dialysis; and **(e)** the tobramycin dose (replenishment dose) needed to be given to the patient after hemodialysis.

Solution

a. Initial plasma antibiotic concentration after the first dose of tobramycin:

$$\text{Patient dose} = \frac{1\text{mg}}{\text{kg}} \times 65\ \text{kg} = 65\ \text{mg}$$

$$V_D = \frac{0.33\ \text{L}}{\text{kg}} \times 65\ \text{kg} = 21.45\ \text{L}$$

$$\text{Plasma drug concentration, } C_p^0 = \frac{D_0}{V_D} = \frac{65\ \text{mg}}{21.45\ \text{L}} = 3.03\ \text{mg/L}$$

b. Plasma drug concentration just before the start of hemodialysis (48 hours after the initial tobramycin dose): After 48 hours, the plasma drug concentration declines according to first-order kinetics:

$$C_p = 3.03e^{-(0.693/50)(48)} = 1.58\ \text{mg/L}$$

c. Plasma drug concentration at the end of a 4-hour hemodialysis:

$$C_p = 1.58e^{-(0.693/8)(4)} = 0.547\ \text{mg/L}$$

d. Amount of drug lost from the body after dialysis:

$$\text{Amt of drug lost after dialysis} =$$
$$\text{Amt of drug in the body before dialysis} - \text{Amt of drug in the body after dialysis} =$$
$$\frac{1.58\ \text{mg}}{\text{L}}(21.45\ \text{L}) - \frac{5.47\ \text{mg}}{\text{L}}(21.45\ \text{L}) = 22.16\ \text{mg}$$

e. Tobramycin dose (replenishment dose) needed to be given to the patient after hemodialysis: The recommended ranges of peak and trough concentrations of tobramycin () are 5 to 10 mg/L (peak) and 0.5 to <2 mg/L (trough). The usual replenishment dose of tobramycin after hemodialysis is 1 to 1.5 mg/kg.

If a replenishment dose of 65 mg (ie, 1 mg/kg) is given to the patient, then the estimated plasma drug concentration is estimated as

$$\text{Plasma drug conc. after 65 mg given by IV bolus injection after hemodialysis}$$
$$= \frac{65\ \text{mg}}{21.45\ \text{L}} + 0.547\ \text{mg/L} = 3.58\ \text{mg/L}$$

The patient is given 65 mg of tobramycin by IV bolus injection after completion of hemodialysis to produce a tobramycin plasma concentration of 3.58 mg/L.

Hemoperfusion

Hemoperfusion is the process of removing drug by passing the blood from the patient through an adsorbent material and back to the patient. Hemoperfusion is a useful procedure for rapid drug removal in accidental poisoning and drug overdosage. Because the drug molecules in the blood are in direct contact with the adsorbent material, any molecule that has great affinity for the adsorbent material will be removed. The two main adsorbents used in hemoperfusion include **(1)** activated charcoal, which adsorbs both polar and nonpolar drugs, and **(2)** Amberlite resins. Amberlite resins, such as Amberlite XAD-2 and Amberlite XAD-4, are available as insoluble polymeric beads, each bead containing an agglomerate of cross-linked polystyrene microspheres. The Amberlite resins have a greater affinity for nonpolar organic molecules than does activated charcoal. The important factors for drug removal by hemoperfusion include affinity of the drug for the adsorbent, surface area of the adsorbent, absorptive capacity of the adsorbent, rate of blood flow through the adsorbent, and the equilibration rate of the drug from the peripheral tissue into the blood.

Hemofiltration

An alternative to hemodialysis and hemoperfusion is hemofiltration. *Hemofiltration* is a process by which fluids, electrolytes, and small-molecular-weight substances are removed from the blood by means of low-pressure flow through hollow artificial fibers or flat-plate membranes (). Because fluid is also filtered out of the plasma during hemofiltration, replacement fluid is administered to the patient for volume replacement. Hemofiltration is a slow, continuous filtration process that removes nonprotein bound, small molecules (<10,000 Da) from the blood by convective mass transport. The clearance of the drug depends on the sieving coefficient and ultrafiltration rate. Hemofiltration provides a creatinine clearance of approximately 10 mL/min () and may have

limited use for drugs that are widely distributed in the body, such as aminoglycosides, cephalosporins, and acyclovir. A major problem with this method is the formation of blood clots within the hollow filter fibers.

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

Because of the initial loss of fluid that results during hemofiltration, intermittent hemofiltration results in concentration of red blood cells in the resulting reduced plasma volume. Therefore, viscous blood with a high hematocrit and high colloid oncotic pressure results at the distal end of the hemofilter. *Predilution* may be used to circumvent this problem, but this method is rarely used because of cost and inefficiency.

Continuous replacement therapy allows ongoing removal of fluid and toxins by relying on a patient's own blood pressure to pump blood through a filter. The continuous filtration is better tolerated by patients than intermittent therapy, provides optimal control of circulating volumes, and provides ongoing toxin removal. Because continuous replacement therapies are hemofiltration methods, replacement fluid must be administered to the patient to replace fluid lost to the hemofiltrate, though the volume of fluid removed can be easily controlled compared to intermittent hemofiltration. Heparin infusions are also provided for anticoagulation.

Continuous renal replacement therapy (CRRT) includes *continuous veno-venous hemofiltration* (CVVH) and *continuous arteriovenous hemofiltration* (CAVH). In CAVH, blood passes through a hemofilter that is placed between a cannulated femoral artery and vein. A dialysis filter may be added to CAVH to improve small-molecule clearance. Circulating dialysate on the outside of the filters allows more efficient toxin removal. However, this method is inefficient (10–15 mL filtered per minute) and complex, and is not widely used in comparison to CVVH.

CVVH provides a hemofilter that is placed between cannulated femoral, subclavian, or internal jugular veins. Rather than relying on arterial pressure to filter blood, a pump can be used to provide filtration rates greater than 100 mL/min. Like CAVH, a dialysis filter may be added to CVVH to improve clearance of small molecules.

As with other extracorporeal removal systems, hemofiltration methods can alter drug pharmacokinetics. A study by showed that acute renal failure patients on CVVH demonstrated a 50% decrease in clearance of levofloxacin. However, because of the high volume and moderate renal clearance of fluoroquinolones, levofloxacin did not require dosing adjustment.

DRUG REMOVAL DURING CONTINUOUS RENAL REPLACEMENT THERAPY

During CAVH, solutes are removed by convection, in which a *sieving coefficient, S*, reflects the solute removal ability during hemofiltration and is equal to the ratio of solute concentration in the ultrafiltrate to the solute concentration in the retentate. When $S = 1$, solute passes freely through the membrane, whereas when $S = 0$, the solute is retained in the plasma. S is constant and independent of blood flow; therefore,

$$Cl = S \times \text{rate}_{\text{uf}} \qquad (21.37)$$

where rate_{uf} if the ultrafiltration rate. The concentration of drug in the ultrafiltrate is also equal to the unbound drug concentration in the plasma, and so the amount of drug removed during CAVH is

$$\text{Amount removed} = C_{\text{p}} + \alpha \times \text{rate}_{\text{uf}} \qquad (21.38)$$

where α = the unbound fraction.

EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS

Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may also be excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug protein binding, and kidney function.

The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. In contrast, creatinine clearance has been used successfully to measure kidney function and renal clearance of drugs. Clinical laboratory tests measure only a limited number of liver functions. Some clinical laboratory tests, such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme tests that detect liver cell damage rather than liver function. Other laboratory tests, such as serum bilirubin, are used to measure biliary obstruction or interference with bile flow. Presently, no single test accurately assesses the total liver function. Usually, a series of clinical laboratory tests are used in clinical practice to detect the presence of liver disease, distinguish among different types of liver disorders, gauge the extent of known liver damage, and follow the response to treatment. A few tests have been used to relate the severity of hepatic impairment to predicted changes in the pharmacokinetic profile of the drug (*FDA Guidance for Industry*, 2003). Examples of these tests include the ability of the liver to eliminate marker drugs such as antipyrine, indocyanine green, monoethylglycine-xylidide, and galactose. Furthermore, endogenous substrates such as albumin or bilirubin, or a functional measure such as prothrombin time, have been used for the evaluation of liver impairment.

Dosage Considerations in Hepatic Disease

Several physiologic and pharmacokinetic factors are relevant in considering dosage of a drug in patients with hepatic disease (). Chronic disease or tissue injury may change the accessibility of some enzymes as a result of redirection or detour of hepatic blood circulation. Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that subsequently affect drug plasma protein binding and distribution (). As mentioned, most liver function tests indicate only that the liver has been damaged; they do not assess the function of the cytochrome P-450 enzymes or intrinsic clearance by the liver.

Table 21.10 Considerations in Dosing Patients with Hepatic Impairment	
Item	**Comments**
Nature and severity of liver disease	Not all liver diseases affect the pharmacokinetics of the drugs to the same extent
Drug elimination	Drugs eliminated by the liver >20% are less likely to be affected by liver disease. Drugs that are eliminated mainly via renal route will be least affected by liver disease
Route of drug administration	Oral drug bioavailability may be increased by liver disease due to decrease first-pass effects
Protein binding	Drug protein binding may be altered due to alteration in hepatic synthesis of albumin
Hepatic blood flow	Drugs with flow dependent hepatic clearance will be more affected by change in hepatic blood flow
Intrinsic clearance	Metabolism of drugs with high intrinsic clearance may be impaired
Biliary obstruction	Biliary excretion of some drugs and metabolites, particularly glucuronide metabolites, may be impaired
Pharmacodynamic changes	Tissue sensitivity to drug may be altered
Therapeutic range	Drugs with a wide therapeutic range will be less affected by moderate hepatic impairment

Because there is no readily available measure of hepatic function that can be applied to calculate appropriate doses, enzyme-dependent drugs are usually given to patients with hepatic failure in half-doses, or less. Response or plasma levels then must be monitored. Drugs with flow-dependent clearance are avoided if possible in patients with liver failure. When necessary, doses of these drugs may need to be reduced to as low as one-tenth of the conventional dose, for an orally administered agent. Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, efficacious treatment.

Fraction of Drug Metabolized

Drug elimination in the body may be divided into: **(1)** fraction of drug excretion unchanged, *fe*, and **(2)** fraction of drug metabolized. The latter is usually estimated from 1 – *fe*; alternatively, the fraction of drug metabolized may be estimated from the ratio of Cl_h/Cl, where Cl_h is hepatic clearance and Cl is total body clearance. Knowing the fraction of drug eliminated by the liver allows estimation of total body clearance when hepatic clearance is reduced. Drugs with low *fe* values (or, conversely, drugs with a higher fraction of metabolized drug) are more affected by a change in liver function due to hepatic disease.

$$Cl_h = Cl(1 - fe) \qquad (21.39)$$

Equation 21.39 assumes that all metabolism occurs in the liver, and all the unchanged drug is excreted in the urine. Assuming linear kinetics are applicable (after determining that there is no enzyme saturation), dosing adjustment may be based on residual hepatic function in patients with hepatic disease, as shown in the following example.

Practice Problem

The hepatic clearance of a drug in a patient is reduced by 50% due to chronic viral hepatitis. How is the total body clearance of the drug affected? What should be the new dose of the drug in the patient? Assume that renal drug clearance (*fe* = 0.4) and plasma drug protein binding are not altered.

Solution

$$RL = \text{residual liver function, estimated by } \frac{[Cl_h]_{hepatitis}}{[Cl_h]_{normal}}$$
$$[Cl_h]_{normal} = \text{hepatic clearance of drug in normal subject}$$
$$[Cl_h]_{hepatitis} = \text{hepatic clearance of drug in patient with hepatitis}$$
$$Cl_{normal} = \text{total clearance of drug in normal subject}$$
$$Cl_{hepatitis} = \text{total clearance of drug in patient with hepatitis}$$
$$fe = \text{fraction of drug excreted unchanged}$$
$$1 - fe = \text{fraction of drug metabolized}$$
$$[Cl_h]_{hepatitis} = RL\ [Cl_h]_{normal}$$

Substituting for $[Cl_h]_{normal}$ with $Cl_{normal}(1 - fe)$,

$$[Cl_h]_{hepatitis} = RL\, Cl_{normal}\,(1 - fe) \qquad (21.40)$$

Assuming no renal clearance deterioration due to hepatitis,

$$Cl_{hepatitis} = [Cl_h]_{hepatitis} + [Cl_R]_{normal} \qquad (21.41)$$

Substituting Equation 21.40 with Equation 21.41 in terms of total body clearance

$$Cl_{hepatitis} = RL\, Cl_{normal}(1 - fe) + Cl_{normal}\, fe \qquad (21.42)$$

$$Cl_{\text{hepatitis}} = Cl_{\text{normal}}[RL\ (1 - fe)\ + fe] \qquad (21.43)$$

$$\frac{D_{\text{hepatitis}}}{D_{\text{normal}}} = \frac{Cl_{\text{hepatitis}}}{Cl_{\text{normal}}} = \frac{RL\ (1 - fe)\ + fe}{1} \qquad (21.44)$$

where $D_{\text{hepatitis}}$ and D_{normal} are the doses in a hepatitis patient and in a normal liver function patient, respectively. Substituting in Equation 21.44 with RL = 0.5 and fe = 0.4,

$$\frac{D_{\text{hepatitis}}}{D_{\text{normal}}} = 0.5(1 - 0.4)\ + 0.4 = 0.3 + 0.4 = 0.7 \qquad (\text{or } 70\%)$$

The adjusted dose of the drug for the hepatic patient is 70% of that for the normal subject as a result of the 50% decrease in hepatic function in the above case (fe = 0.4).

An example of a correlation established between actual residual liver function (measured by marker) and hepatic clearance was reported for cefoperazone () and other drugs in patients with cirrhosis. The method should be applied only to drugs that have linear pharmacokinetics, low protein binding, or that are nonrestrictively bound.

Many variables can complicate dose correction when binding profoundly affects distribution, elimination, and penetration of the drug to the active site. For drugs with restrictive binding, the fraction of free drug must be used to correct the change in free drug concentration and the change in free drug clearance. In some cases, the increase in free drug is partly offset by a larger volume of distribution resulting from the decrease in protein binding. Since there are many variables that complicate dose correction for patients with hepatic disease, dose correction is limited to drugs whose hepatic metabolism is approximated by linear pharmacokinetics.

Active Drug and the Metabolite

For many drugs, both the drug and the metabolite contribute to the overall therapeutic response of the patient to the drug. The concentration of both the drug and the metabolite in the body should be known. When the pharmacokinetic parameters of the metabolite and the drug are similar, the overall activity of the drug can become more or less potent as a result of a change in liver function; that is, **(1)** when the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic-impaired patient because the parent drug concentration will be higher; **(2)** when the drug is less potent than the metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed.

Changes in pharmacologic activity due to hepatic disease () may be much more complex when both the pharmacokinetic parameters as well as the pharmacodynamics of the drug change as a result of the disease process. In such cases, the overall pharmacodynamic response may be greatly modified, making it necessary to monitor the response change with the aid of a pharmacodynamic model (see).

Table 21.11 Pugh's Modification of Child's Classification[a]

	1 Point	2 Points	3 Points
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1–2	2–3	>3
Albumin (gm/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec > control)	1–4	4–10	>10

[a]Total points: 5–6 = mild dysfunction; 7–9 = moderate dysfunction; >9 = severe dysfunction.

From .

Hepatic Blood Flow and Intrinsic Clearance

Blood flow changes can occur in patients with chronic liver disease (often due to viral hepatitis or chronic alcohol use). In some patients with severe liver cirrhosis, fibrosis of liver tissue may occur, resulting in intra- or extrahepatic shunt. Hepatic arterial-venous shunts may lead to reduced drug fraction of drug extracted (see) and an increase in the bioavailability of drug. In other patients, resistance to blood flow may be increased as a result of tissue damage and fibrosis, causing a reduction in intrisic hepatic clearance.

The following equation may be applied to estimate hepatic clearance of a drug after assessing changes in blood flow and intrinsic clearance (Cl_{int}):

$$Cl_{\text{h}} = \frac{QCl_{\text{int}}}{Q + Cl_{\text{int}}} \qquad (21.45)$$

Alternatively, when both Q and the extraction ratio, ER, are known in the patient, Cl may also be estimated:

$$Cl = Q\,(\text{ER}) \qquad (21.46)$$

Unlike changes in renal disease, in which serum creatinine concentration may be used to monitor changes in renal function such

as glomerular filtration (GFR), the above physiologic model equation may not be adequate to account for accurate prediction of changes in hepatic clearance. Calculations based on model equations must be corroborated by clinical assessment.

Pathophysiologic Assessment

In practice, patient information about changes in hepatic blood flow may not be available, because special electromagnetic () or ultrasound techniques are required to measure blood flow and are not routinely available. The clinician/pharmacist may have to make an empirical estimate of the blood flow change after examining the patient and reviewing the available liver function tests ().

Table 21.12 Severity Classification Schemes for Liver Disease

	Child–Turcotte Classification		
	Grade A	**Grade B**	**Grade C**
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (gm/dL)	>3.5	3.0–3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor

From .

While chronic hepatic disease is more likely to change the metabolism of a drug (), acute hepatitis due to hepatotoxin or viral inflammation is often associated with marginal or less severe changes in metabolic drug clearance (). The clinician may make an assessment based on acceptable risk criteria on a case-by-case basis. list useful endpoints for assessing the extent of hepatic dysfunction ().

In general, basic pharmacokinetics treats the body globally and more readily applies to dosing estimation. However, drug clearance based on individual eliminating organs is more informative and provides more insight into the pharmacokinetic changes in the disease process. A practical method for dosing hepatic-impaired patients is still in its early stages of development. While the hepatic blood flow model () is useful for predicting changes in hepatic clearance resulting from alterations in hepatic blood flow, Q_a, and Q_v, extrahepatic changes can also influence pharmacokinetics in hepatic-impaired patients. Global changes in distribution may occur outside the liver. Extrahepatic metabolism and other hemodynamic changes may also occur and can be accounted for more completely by monitoring total body clearance of the drug using basic pharmacokinetics. For example, lack of local change in hepatic drug clearance should not be prematurely interpreted as "no change" in overall drug clearance. Reduced albumin and α acid glycoprotein (AAG), for example, may change the volume of distribution of the drug and therefore alter total body clearance on a global basis.

Hormonal Influence

Hormones can also affect the rate of metabolism. In hyperthyroid patients, the rate of metabolism of many drugs is increased, as are, for example, the rates for theophylline, digoxin, and propranolol. In hypothyroid disease, the rate of metabolism of these drugs may be decreased (). In children with human growth hormone (HGH) deficiency, administration of HGH decreases the half-life of theophylline.

Table 21.13 Drugs with Significantly Decreased Metabolism in Chronic Liver Disease

Antipyrine	Caffeine
Cefoperazone	Chlordiazepoxide
Chloramphenicol	Diazepam
Erythromycin	Hexobarbital
Metronidazole	Lidocaine
Meperidine	Metoprolol
Pentazocine	Propranolol
Tocainide	Theophylline
Verapamil	Promazine

Sources: , , .

Example

After IV bolus administration of 1 g of cefoperazone to normal and chronic hepatitis patients, urinary excretion of cefoperazone was significantly increased in cirrhosis patients, from 23.95 ± 5.06% for normal patients to 51.09 ± 11.50% in cirrhosis patients (). Explain **(a)** why there is a change in the percent of unchanged cefoperazone excreted in the urine of patients with cirrhosis, and **(b)** suggest a quantitative test to monitor the hepatic elimination of cefoperazone. (*Hint:* consult .)

Liver Function Tests and Hepatic Metabolic Markers

Drug markers used to measure residual hepatic function may correlate well with hepatic clearance of one drug but correlate poorly with substrate metabolized by a different enzyme within the same cytochrome P-450 subfamily. Some useful marker compounds are listed below.

1.*Aminotransferase* (normal ALT, male, 10–55 U/L; female, 7–30 U/L; normal AST, male, 10–40, U/L; female, 9–25 U/L). Aminotransferases are enzymes found in many tissues that include serum glutamic oxaloacetic transaminase (AST, formerly SGOT) and alanine aminotransferase (ALT, formerly SGPT). ALT is liver-specific, but AST is found in liver and many other tissues, including cardiac and skeletal muscle. Leakage of aminotransferases into the plasma is used as an indicator of many types of hepatic disease and hepatitis. The AST/ALT ratio is used in differential diagnosis. In acute liver injury, AST/ALT is ≤ 1, whereas in alcoholic hepatitis the AST/ALT > 2.

2.*Alkaline phosphatase* (male, 45–115 U/L; female, 30–100 U/L). Like aminotransferase, alkaline phosphatase (AP) is normally present in many tissues, and is present on the canalicular domain of the hepatocyte plasma membrane. Plasma AP may be elevated in hepatic disease because of increased AP production and released into the serum. In cholestasis, or bile flow obstruction, AP release is facilitated by bile acid solubilization of the membranes. Marked AP elevations may indicate hepatic tumors or biliary obstruction in the liver, or disease in other tissues such as bone, placenta, or intestine.

3.*Bilirubin* (normal total = 0–1.0 mg/dL, direct = 0–0.4 mg/dL). Bilirubin consists of both a water-soluble, conjugated, "direct" fraction and a lipid-soluble, unconjugated, "indirect" fraction. The unconjugated form is bound to albumin and is therefore not filtered by the kidney. Since impaired biliary excretion results in increases in conjugated (filtered) bilirubin, hepatobiliary disease can result in increases in urinary bilirubin. Unconjugated hyperbilirubinemia results from either increased bilirubin production or defects in hepatic uptake or conjugation. Conjugated hyperbilirubinemia results from defects in hepatic excretion.

4. *Prothrombin time* (PT; normal, 11.2–13.2 sec). With the exception of Factor VIII, all coagulation factors are synthesized by the liver. Therefore, hepatic disease can alter coagulation. Decreases in PT (the rate of conversion of prothrombin to thrombin) therefore is suggestive of acute or chronic liver failure or biliary obstruction. Vitamin K is also important in coagulation, so vitamin K deficiency can also decrease PT.

Example

Paclitaxel, an anticancer agent for solid tumors and leukemia, has extensive tissue distribution, high plasma protein binding (approximately 90–95%), and variable systemic clearance. Average paclitaxel clearance ranges from 87 to 503 mL/min/m^2 (5.2 –30.2 L/h/m^2) with minimal renal excretion of parent drug, 10% (). Paclitaxel is extensively metabolized by the liver to three primary metabolites. Cytochrome P-450 enzymes of the CYP3A and CYP2C subfamilies appear to be involved in hepatic metabolism of paclitaxel. What are the precautions in administering paclitaxel to patients with liver disease?

Solution

Although paclitaxel has first-order pharmacokinetics at normal doses, its elimination may be saturable in some patients with genetically reduced intrinsic clearance due to CYP3A or CYP2C. The clinical importance of saturable elimination will be greatest when large dosages are infused over a shorter period of time. In these situations, achievable plasma concentrations are likely to cause saturation of binding. Thus, small changes in dosage or infusion duration may result in disproportionately large alterations in paclitaxel systemic exposure, potentially influencing patient response and toxicity.

FREQUENTLY ASKED QUESTIONS

1. What are the main factors that influence drug dosing in renal disease?

2. Name and contrast the two methods for adjusting drug dose in renal disease.

3. What are the pharmacokinetic considerations in designing a dosing regimen? Why is dosing once a day for aminoglycosides recommended by many clinicians?

4. Protein binding of drugs is often affected by renal and hepatic disease. How are those changes accounted for in dose adjustment?

5. Drug clearance is often decreased 20–50% in many patients with congestive heart failure (CHF). Explain how it may affect drug disposition.

LEARNING QUESTIONS

1. The normal dosing schedule for a patient on tetracycline is 250 mg PO (peroral) every 6 hours. Suggest a dosage regimen for this patient when laboratory analysis shows his renal function to have deteriorated from a Cl_{Cr} of 90 to 20 mL/min.

2. A patient receiving antibiotic treatment is on dialysis. The flow rate of serum into the kidney machine is 50 mL/min. Assays shows that the concentration of drug entering the machine is 5 µg/mL and the concentration of drug in the serum leaving the machine is 2.4 µg/mL. The drug clearance for this patient is 10 mL/min. To what extent should the dose be increased if the average concentration of the antibiotic is to be maintained?

3. Glomerular filtration rate may be measured by either insulin clearance or creat-inine clearance.

a. Why is creatinine or insulin clearance used to measure GFR?

b. Which clearance method, insulin or creatinine, gives a more accurate estimate of GFR? Why?

4. A uremic patient has a urine output of 1.8 L/24 hours and an average creatinine concentration of 2.2 mg/dL. What is the creatinine clearance? How would you adjust the dose of a drug normally given at 20 mg/kg every 6 hours in this patient (assume the urine creatinine concentration is 0.1 mg/mL and creatinine clearance is 100 mL/min)?

5. A patient on lincomycin at 600 mg every 12 hours intramuscular was found to have a creatinine clearance of 5 mL/min. Should

the dose be adjusted? If so, **(a)** adjust the dose by keeping the dosing interval constant; **(b)** adjust the dosing interval and give the same dose; and **(c)** adjust both dosing interval and dose. What are the significant differences in the adjustment methods?

6. Using the method of Cockcroft and Gault, calculate the creatinine clearance for a woman (38 years old, 62 kg) whose serum creatinine is 1.8 mg/dL.

7. Would you adjust the dose of cephamandole, an antibiotic which is 98% excreted unchanged in the urine, for the patient in Question 6? Why?

8. What assumptions are usually made when adjusting a dosage regimen according to the creatinine clearance in a patient with renal failure?

9. The usual dose of gentamicin in patients with normal renal function is 1.0 mg/kg every 8 hours by multiple IV bolus injections. Using the nomogram method (), what dose of gentamicin would you recommend for a 55-year-old male patient weighing 72 kg with a creatinine clearance of 20 mL/min?

10. A single intravenous bolus injection (1 g) of an antibiotic was given to a male anephric patient (age 68, 75 kg). During the next 48 hours, the elimination half-life of the antibiotic was 16 hours. The patient was then placed on hemodialysis for 8 hours and the elimination half-life was reduced to 4 hours.

a. How much drug was eliminated by the end of the dialysis period?

b. Assuming the apparent volume of distribution of this antibiotic is 0.5 L/kg, what was the plasma drug concentration just before and just after dialysis?

11. There are several pharmacokinetic methods for adjustment of a drug dosage regimen for patients with uremic disease based on the serum creatinine concentration in that patient. From your knowledge of clinical pharmacokinetics, discuss the following questions.

a. What is the basis of these methods for the calculation of drug dosage regimens in uremic patients?

b. What is the validity of the assumptions on which these calculations are made?

12. After assessment of the uremic condition of the patient, the drug dosage regimen may be adjusted by one of two methods: **(a)** by keeping the dose constant and prolonging the dosage interval, τ, or **(b)** by decreasing the dose and maintaining the dosage interval constant. Discuss the advantages and disadvantages of adjusting the dosage regimen using either method.

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