

AMINOGLYCOSIDE ANTIBIOTICS

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The aminoglycosides are bactericidal antibiotics used in the treatment of serious gram-negative infections. Because absorption from the gastrointestinal tract is poor, the aminoglycosides must be administered parenterally to achieve therapeutic concentrations in the systemic circulation. In most instances, aminoglycosides are administered by intermittent intravenous (IV) infusions. The choice of an aminoglycoside dose is influenced by the specific agent (e.g., gentamicin vs. amikacin), infection (e.g., site and organism), renal function, and weight or body composition of the patient. The three most commonly monitored aminoglycoside antibiotics are gentamicin, tobramycin, and amikacin. The usual dose for gentamicin and tobramycin is 5 to 7 mg/kg/day, administered over 30 to 60 minutes as a single daily dose or in divided doses every 8 to 12 hours; the dose of amikacin is 15 to 20 mg/kg/day, administered over 30 to 60 minutes as a single daily dose or in divided doses every 8 to 12 hours. The clearance, volume of distribution, and half-life of all aminoglycosides are similar.¹ Therefore, the same pharmacokinetic model can be used for all the aminoglycosides, and the principles, which are described in this chapter for any given aminoglycoside generally, apply to the others as well. The aminoglycosides have different ranges of "therapeutic" serum concentrations and have different propensities for interaction with penicillin compounds.

PHARMACODYNAMICS OF AMINOGLYCOSIDES

Traditionally, aminoglycosides have been dosed multiple times a day. Over the past decade, investigations into the pharmacodynamic properties of aminoglycosides have yielded data that favor extended interval administration. Bactericidal activity of the aminoglycosides has been demonstrated to be concentration dependent [i.e., plasma concentrations that exceed 10 times the minimum inhibitory concentration (MIC) for a given bacteria are more effective than concentrations just above the MIC].²⁻⁵ In addition to the concentration-dependent killing, there is also a post-antibiotic effect that results in depressed bacterial growth after plasma concentrations have fallen below the MIC.^{2,6,7} Taken together, the pharmacodynamic properties

of aminoglycosides suggest that one can maximize bactericidal activity by dosing at intervals that allow concentrations within the renal cortex to exceed the MIC. Extended interval dosing may also minimize the risk of ototoxicity.⁸⁻¹⁰ Experience favors once-daily administration of aminoglycosides, perhaps a decreased risk of nephrotoxicity compared with traditional dosing.^{11,12}

THERAPEUTIC AND TOXICITY

Peak plasma concentrations following extended interval dosing (i.e., every 24 hours) are in the range of 20 to 30 mg/L. These concentrations are well above the pharmacodynamic goal of about 10 times the MIC, and the breakpoint for susceptibility to the aminoglycosides are below the limit of detection (i.e., < 2 mg/L).¹³ These concentrations, which reduce the risk for ototoxicity, are associated with trough concentrations following treatment in the range of 5 to 8 mg/L.¹⁴⁻¹⁶ Trough concentrations in this range are likely to be ineffective,¹⁵ and concentrations below the limit of detection are usually < 10 mg/L.¹

Most available data concern the risk of aminoglycoside ototoxicity and nephrotoxicity. Although some data suggest a dose-related increase in both toxicities,^{17,18} although some data suggest a dose-related increase in both toxicities,^{17,18} other data indicate that the risk of ototoxicity and nephrotoxicity may be the result of elevated trough concentrations.¹⁹ This association has been suggested by some studies in which patients who develop renal dysfunction during aminoglycoside therapy regain normal renal function when the drug is discontinued.¹⁷⁻¹⁹

Ototoxicity has been associated with concentrations of gentamicin exceeding 4 mg/L.²⁰ The risk of ototoxicity increases as the concentration is multiplied by the number of days of therapy. Nephrotoxicity is increased when the drug is administered in high doses.²¹ Aminoglycoside ototoxicity also seems to be more common in patients with existing impaired renal function, particularly during the course of their treatment.¹⁷⁻¹⁹

Although it is the standard practice to use trough concentrations as predictors of toxicity, it is not clear whether this is valid.²⁴ Trough concentrations are often measured at many institutions, and they are not always measured at the same time. The nomogram

of aminoglycosides suggest that less frequent administration of larger doses can maximize bactericidal activity. In addition, saturable uptake mechanisms within the renal cortex and inner ear indicate that extended interval dosing may also minimize the likelihood of developing nephrotoxicity and ototoxicity.^{8–10} Experience from randomized controlled trials suggests that once-daily administration of aminoglycosides results in similar efficacy and perhaps a decreased risk of developing toxicities when compared with traditional dosing.^{11,12}

THERAPEUTIC AND TOXIC PLASMA CONCENTRATIONS

Peak plasma concentrations for gentamicin and tobramycin using extended interval dosing (i.e., 5 to 7 mg/kg every 24 hours) are in the range of 20 to 30 mg/L. This peak concentration target is based on the pharmacodynamic goal of achieving a peak to MIC ratio of greater than 10 and the breakpoint for susceptibility of 2 mg/L.¹³ Trough concentrations are below the limit of detection by design to provide a drug-free interval, which reduces the risk for development of nephrotoxicity. Peak plasma concentrations following traditional multiple daily dosing regimens are in the range of 5 to 8 mg/L.^{14–16} Peak plasma concentrations < 2 to 4 mg/L are likely to be ineffective,¹⁵ and successful treatment of pneumonia may require peak concentrations of 8 mg/L or more.¹⁴ Desirable peak concentrations for amikacin are usually 20 to 30 mg/L; trough concentrations are usually < 10 mg/L.¹

Most available data correlating aminoglycoside concentrations with ototoxicity and nephrotoxicity refer to trough plasma concentrations, although some data suggest a correlation between peak concentrations and toxicity.^{17,18} Although gentamicin trough concentrations of > 2 mg/L have been associated with renal toxicity, the high trough concentrations may be the result, and not the cause, of renal dysfunction. In fact, the use of elevated trough concentrations as an indication of early renal damage has been suggested by some investigators.^{19,20} Fortunately, most patients who develop renal dysfunction during aminoglycoside therapy appear to regain normal renal function after the drug has been discontinued.²¹

Ototoxicity has been associated with trough plasma concentrations of gentamicin exceeding 4 mg/L for more than 10 days. When the trough concentration is multiplied by the number of days of therapy, the risk of ototoxicity is increased when the product exceeds 40 mg/day/L. Aminoglycoside ototoxicity also seems to be most prevalent in patients who have existing impaired renal function or have received large doses during the course of their treatment.^{17–19,22,23}

Although it is the standard practice to use aminoglycoside plasma concentrations as predictors for both efficacy and toxicity, it is controversial whether this is valid.²⁴ The adoption of once-daily aminoglycoside dosing at many institutions has led to less intensive monitoring of serum concentrations. The nomogram developed by Nicolau et al. recommends

KEY PARAMETERS: Aminoglycoside Antibiotics

Therapeutic Serum Concentrations

Gentamicin, tobramycin	Conventional dosing Peak 5–8 mg/L Trough < 2 mg/L	“Once-daily” dosing 20 mg/L Undetectable
Amikacin	Peak 20–30 mg/L Trough < 10 mg/L	60 mg/L Undetectable
V ^a	0.25 L/kg	
Cl		
Normal renal function	Equal to Cl _{Cr}	
Functionally anephric patients ^b	0.0043 L/kg/hr	
Surgically anephric patients ^b	0.0021 L/kg/hr	
Hemodialysis ^b	1.8 L/hr	
AUC ₂₄	70–100 mg × hr/L	Gentamicin and tobramycin (amikacin) approximately threefold higher
t _½		
Normal renal function	2–3 hr	
Functionally anephric patients	30–60 hr	
fu (fraction unbound in plasma)	> 0.95	

^aVolume of distribution should be adjusted for obesity and/or alterations in extracellular fluid status.

^bA functionally anephric patient is a dialysis patient with kidneys intact. A surgically anephric patient is a dialysis patient with kidneys removed. Hemodialysis clearance of 1.8 L/hr refers to low-flux hemodialysis, not high-flux or peritoneal dialysis.

that a single level be drawn 6 to 14 hours after the dose.¹³ The nomogram then defines in graphical form whether the dosing interval is appropriate or needs to be extended. This type of approach is much more simplified than the traditional method of determining the individualized pharmacokinetic parameters based on measured peak and trough concentrations; however, it may not provide the same precise control of drug exposure [i.e., peak, area under the curve (AUC)] in patients who exhibit altered pharmacokinetics (i.e., third space fluid, burns, cystic fibrosis, spinal cord injury). Alternatively, Barclay et al. have defined a method of dosage individualization of extended interval aminoglycoside dosing based on a measured peak concentration and an estimation of the AUC.²⁵ This dosing method is based on the assumption that the goal is to provide a similar

degree of drug exposure as traditionally used to minimize the risk of toxicity but provide maximal bactericidal activity. The dose of gentamicin and tobramycin is 70 to 100 mg × hr/L.

BIOAVAILABILITY (F)

The aminoglycoside antibiotics are lipid soluble compounds. As a result, they must be administered orally and must be administered parenterally for systemic infections.

VOLUME OF DISTRIBUTION (V)

The volume of distribution is relatively wide, although a relatively wide range of values has been reported. Since aminoglycosides distribute very well, the volume of distribution is often greater than total body weight (TBW) shown in the following nomogram of V in obese patients.³³ The volume of distribution in obese subjects also could be estimated by multiplying total body weight (IBW) plus 10% of his/her excess weight by 0.7. Measurements in the estimation of amino-glycoside volumes in obese patients seem reasonable because aminoglycosides appear to distribute into extracellular fluid spaces. The volume of adipose tissue is approximately 25% which is an average for all the obese patients. This would be used to approximate the volume of distribution.

$$\text{Aminoglycoside } V = (0.25 \times \text{IBW}) + 0.7 \times (\text{Excess Weight} \times 0.7)$$

The non-obese or IBW can be calculated by the following formula: IBW = 50 + (height – 154) × 0.423 and 1.3 [see Part I: Creatinine Clearance].

$$\text{Ideal Body Weight for Males in kg} = 50 + (42.9 \times \text{height in inches} - 50.3)$$

$$\text{Ideal Body Weight for Females in kg} = 45 + (42.9 \times \text{height in inches} - 50.3)$$

The volume of distribution of aminoglycosides in patients with ascites, edema, or other enlarged extracellular fluid spaces is increased. An approach to approximating the increased volume of distribution in patients with ascites or edema is to increase the dose.

degree of drug exposure as traditional daily dosing methods (i.e., AUC) to minimize the risk of toxicity but provide a higher peak concentration to maximize the bactericidal activity. The target AUC₂₄ range for gentamicin and tobramycin is 70 to 100 mg × hr/L.

BIOAVAILABILITY (F)

The aminoglycoside antibiotics are highly water soluble and poorly lipid soluble compounds. As a result, they are poorly absorbed when administered orally and must be administered parenterally for the treatment of systemic infections.

VOLUME OF DISTRIBUTION (V)

The volume of distribution of aminoglycosides is \approx 0.25 L/kg, although a relatively wide range of 0.1 to 0.5 L/kg has been reported.^{26–32} Since aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight (TBW) should result in a more accurate approximation of V in obese patients.³³ The aminoglycoside volume of distribution in obese subjects also could be adjusted based on the patient's ideal body weight (IBW) plus 10% of his or her excess weight.^{34,35} These adjustments in the estimation of aminoglycoside volumes of distribution in obese patients seem reasonable because aminoglycoside antibiotics appear to distribute into extracellular space, and the extracellular fluid volume of adipose tissue is approximately 10% of adipose weight versus 25% which is an average for all the other tissues. Equation 1.1 can be used to approximate the volume of distribution (V) in obese patients:

$$\text{Aminoglycoside V}_{(\text{Obese Patients})} = (0.25 \text{ L/kg})(\text{IBW}) + 0.1(\text{TBW} - \text{IBW}) \quad [\text{Eq. 1.1}]$$

The non-obese or IBW can be approximated using Equations 1.2 and 1.3 [see Part I: Creatinine Clearance (Cl_{Cr})].

$$\text{Ideal Body Weight}_{\text{for Males in kg}} = 50 + (2.3)(\text{Height in Inches} > 60) \quad [\text{Eq. 1.2}]$$

$$\text{Ideal Body Weight}_{\text{for Females in kg}} = 45 + (2.3)(\text{Height in Inches} > 60) \quad [\text{Eq. 1.3}]$$

The volume of distribution of aminoglycosides is increased in patients with ascites, edema, or other enlarged “third space” volume.^{36,37} One approach to approximating the increased volume of distribution for patients with ascites or edema is to increase the V by 1 L for each kg of weight gain.

This approach is based on the assumption that the volume of distribution of aminoglycoside antibiotics is approximately equal to the extracellular fluid volume. This is consistent with the low plasma protein binding¹ and the fact that aminoglycosides cross membranes very poorly.

Aminoglycoside V (L) =

$$\left(\begin{array}{l} 0.25 \text{ L/kg} \times \text{Non-Obese,} \\ \text{Non-Excess Fluid Weight (kg)} \end{array} \right) + 0.1 \left(\begin{array}{l} \text{Excess} \\ \text{Adipose} \\ \text{Weight (kg)} \end{array} \right) + \left(\begin{array}{l} \text{Excess Third} \\ \text{Space Fluid} \\ \text{Weight (kg)} \end{array} \right) \quad [\text{Eq. 1.4}]$$

The volume of distribution of aminoglycosides can be estimated using Equation 1.4, in which the non-obese, non-excess fluid weight can usually be estimated as the IBW, and the excess adipose weight as the difference between the non-obese weight and the patient's total weight without excess third space fluid. The excess third space fluid weight is estimated clinically. In cases in which a rapid increase in weight has occurred over several days, this weight gain is likely to represent fluid in a third space; it is therefore easily estimated by taking a difference between the initial and current weights. Some patients may exhibit significant third spacing of fluids (apparent as either edema or ascites) on initial evaluation. It is most difficult to estimate an aminoglycoside V in the obese patient with significant third spacing of fluid. As Equation 1.4 illustrates, assigning excess third space fluid to adipose weight could result in a significant underestimation of the volume of distribution. For this reason, it should be recognized that Equation 1.4 only approximates the V, and plasma concentration measurements are needed to make patient-specific adjustments.

Pediatric patients younger than 5 years of age tend to have a larger volume of distribution. Between birth and 5 years of age, the volume of distribution probably continues to decline from an initial value of 0.5 L/kg to the adult value of 0.25 L/kg.³⁸

$$\text{Aminoglycoside V(L) in Children} = \left[0.5 \text{ L/kg} - \left(\frac{\text{Age in Years}}{5} \times 0.25 \right) \right] \left(\frac{\text{Weight in kg}}{1 \text{ to } 5 \text{ Years}} \right) \quad [\text{Eq. 1.5}]$$

Because the change in volume of distribution is gradual, some clinicians have chosen to use the above algorithm to estimate the volume of distribution for patients between 1 and 5 years of age. After 5 years of age, a V of 0.25 L/kg is generally used. Note that in Equation 1.5, it is assumed that the child's weight in kg represents a weight that is not obese and does not contain significant excess third space fluid. Although there are no data on the subject, obese children should have a smaller-than-average volume

of distribution for their age and spacing of fluid should have a large

The pharmacokinetics of the described by a two- or three-compartment model has been cilitate aminoglycoside pharmacokinetic calculations.⁴⁰⁻⁴² For this reason, the distribution phase following a gentamicin injection may be dose dependent. In addition, there is some evidence that the distribution phase may be dose dependent, however, they are important in terms of measured serum concentrations. The third compartment phase, for gentamicin has also been described. The distribution phase for gentamicin is large and is decreased when plasma concentrations associated with this third compartment are large final volume of distribution and significant when evaluating a patient's response.

Despite the existence of the aminoglycosides, pharmacokinetic compartment model that utilizes the errors encountered when using aminoglycosides can be minimized if plasma times that avoid the first and third distribution times that therapy has been initiated.⁴⁵ Aminoglycosides should be evaluated cautiously because the compartment will become greater at

CLEARANCE (CI)

The aminoglycoside antibiotics are given by the renal route.^{1,31} Since the aminoglycosides are excreted by the kidney over a wide range of renal function, it is important to take into account the patient's renal function when calculating the dose (see Chapters 1 and 17) when concentrations are within the therapeutic range.

$\text{Cl}_{\text{Cr}} \text{ for Males (mL/min)} = \frac{(140 - \text{Age})}{2}$

Cl_{Cr} for Females (mL/min) = (

of distribution for their age and size, and children with significant third spacing of fluid should have a larger-than-average V.

The pharmacokinetics of the aminoglycoside antibiotics has been described by a two- or three-compartment model.^{39,40} However, a one-compartment model has been used widely in the clinical setting to facilitate aminoglycoside pharmacokinetic calculations. The initial distribution phase following a gentamicin IV infusion is not considered when the one-compartment model is utilized for gentamicin pharmacokinetic calculations.⁴⁰⁻⁴² For this reason, reported values for plasma samples obtained near the conclusion of an IV infusion may be higher than expected. In addition, there is some evidence that the length of the distribution phase may be dose dependent.⁴³ These reported values probably have no correlation with the therapeutic or toxic effects of the drug; however, they are important in terms of the optimal timing and interpretation of measured serum concentrations. A third distribution phase, or gamma phase, for gentamicin has also been identified.³⁹ This final volume of distribution phase for gentamicin is large, and because gentamicin clearance is decreased when plasma concentrations are low, the average half-life associated with this third compartment is in excess of 100 hours.^{39,40} This large final volume of distribution and long terminal half-life may be significant when evaluating a patient's potential for aminoglycoside toxicity.⁴⁴

Despite the existence of the three-compartment model for the aminoglycosides, pharmacokinetic calculations can be based on a one-compartment model that utilizes the second volume of distribution. The errors encountered when using a single-compartment model for aminoglycosides can be minimized if plasma drug concentrations are obtained at times that avoid the first and third distribution phases and at 24 hours after therapy has been initiated.⁴⁵ Aminoglycoside concentrations < 1 mg/L should be evaluated cautiously because the influence of the large third compartment will become greater at these low concentrations.⁴⁰

CLEARANCE (Cl)

The aminoglycoside antibiotics are eliminated almost entirely by the renal route.^{1,31} Since the aminoglycoside and creatinine clearances are similar over a wide range of renal function, aminoglycoside clearance can be estimated from the formulas used to estimate creatinine clearance (Equations 1.6 and 1.7) when concentrations are within the therapeutic range.^{1,26,31,40}

$$\text{Cl}_{\text{Cr}} \text{ for Males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{Scr}_{\text{ss}})} \quad [\text{Eq. 1.6}]$$

$$\text{Cl}_{\text{Cr}} \text{ for Females (mL/min)} = (0.85) \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{Scr}_{\text{ss}})} \quad [\text{Eq. 1.7}]$$

As presented in Part I, the age is in years, weight is in kg, and serum creatinine is in mg/dL. Correct estimates of creatinine clearance can only be obtained if the patient's weight represents a normal ratio of muscle mass to TBW and the serum creatinine is at steady state. For this reason, pharmacokinetic calculations for obese patients and patients who have significant third spacing of fluid should take into consideration adjustments for obesity and third spacing. Generally, the IBW for obese subjects calculated from Equations 1.2 and 1.3 can be used; adjustments for IBW in patients who are < 20% overweight are probably unnecessary.

In patients who are morbidly obese (i.e., actual body weight approximately double their IBW), creatinine and aminoglycoside clearances are best estimated by using a weight that falls between the IBW and TBW.^{46,47} For this reason, some clinicians prefer to estimate the non-obese weight by using the following equation:

Non-Obese Weight \approx IBW + 0.4 (TBW - IBW)

where IBW is the ideal body weight as estimated by Equations 1.2 and 1.3, and TBW represents the patient's total body weight without the presence of excess third space fluid.

Predicted creatinine clearance is the most commonly employed method of estimating aminoglycoside clearance; however, this formula is known to be inaccurate at low creatinine concentrations. The Modification of Diet in Renal Disease (MDRD) equation was recently developed to provide a more accurate estimate of glomerular filtrations rate. Data correlating estimated glomerular filtration rates using the MDRD equation and measured aminoglycoside clearance are currently limited.^{47a} More recently, the use of cystatin c concentrations have been utilized to estimate glomerular filtration. Cystatin c is an endogenous protein that is constitutively expressed from all nucleated cells and is eliminated by glomerular filtration. One advantage of cystatin c is that it is unaffected by changes in muscle mass. Several studies have demonstrated improved sensitivity in identifying early renal disease. A recent study demonstrated an improved ability to predict amikacin clearance with cystatin c clearance compared with creatinine clearance.^{47b} Until more definitive data are available, use of predicted creatinine clearance as a marker of aminoglycoside clearance is still recommended.

Non-Renal Clearance

Another factor that should be considered when estimating the clearance of aminoglycosides is the non-renal clearance, which is ≈ 0.0021 L/kg/hr (or ≈ 2.5 mL/min/70 kg). The non-renal clearance of aminoglycosides is generally ignored in most patients, but it is significant in patients whose renal function is significantly diminished. In patients who are functionally anephric and receiving intermittent hemodialysis, a clearance value of ≈ 0.0043 L/kg/hr (5 mL/min/70 kg) represents the residual renal

clearance and the non-renal clearance approximations; serum concentrations monitored in patients with poor renal

Penicillin Interaction

Carbenicillin, ticarcillin, and related compounds chemically inactivate gentamicin and this interaction can become clinically significant. Although this interaction is usually not a major side clearance, it does act as a mechanism for the interaction is a function of the species, compound, the concentration of the drug, and temperature. In general, tobramycin and amikacin react in a similar manner; amikacin is more reactive than the penicillins.⁴⁸⁻⁵³ The newer semisynthetic penicillins may be less reactive than carbenicillin, and ampicillin is relatively non-reactive.⁵⁴⁻⁵⁶ For patients who are receiving carbenicillin or ticarcillin, the clearance can be approximated by multiplying the volume of distribution for the aminoglycoside by the

Tobramycin, Gentamicin
Clearance by Carbenicillin = (0.017 h⁻¹)
or Ticarcillin (L/hr)

The elimination rate constant (K_e) estimate in vitro elimination rate for amikacin concentrations of 250 to 500 mg/L attained by carbenicillin is only an approximation because the interaction between amikacin and carbenicillin is relatively minor. The additional clearance of amikacin by carbenicillin or other penicillins is minimal in patients with reasonably normal renal function. Elimination of amikacin by this interaction is small and usually negligible in anephric patients (0.3 L/hr or 5 mL/min). Cephalosporin antibiotics have, to a lesser extent than carbenicillin derivatives, the interaction between amikacin and penicillin derivatives is encountered in patients with

ELIMINATION HALF-LIFE

The elimination half-life of amine is a function of the volume of distribution varies considerably among individuals.

clearance and the non-renal clearance. These values, however, are only approximations; serum concentrations of aminoglycosides should be monitored in patients with poor renal function.

Penicillin Interaction

Carbenicillin, ticarcillin, and related extended-spectrum penicillins chemically inactivate gentamicin and tobramycin *in vitro*. This inactivation can become clinically significant *in vivo* in patients with renal failure. Although this interaction is usually not considered a route of aminoglycoside clearance, it does act as a mechanism for drug “elimination.” This interaction is a function of the specific aminoglycoside, the penicillin compound, the concentration of the penicillin compound, and the temperature. In general, tobramycin and gentamicin interact with penicillins in a similar manner; amikacin is much less likely to interact with these penicillins.^{48–53} The newer semisynthetic acylureido penicillins appear to be less reactive than carbenicillin, and the cephalosporins appear to be relatively non-reactive.^{54–56} For patients with very poor renal function who are receiving carbenicillin or ticarcillin, the additional gentamicin clearance can be approximated by multiplying the patient’s apparent volume of distribution for the aminoglycoside by 0.017 hr⁻¹.

Tobramycin, Gentamicin

$$\text{Clearance by Carbenicillin} = (0.017 \text{ hr}^{-1}) \left(\frac{\text{Volume of Distribution}}{\text{for Aminoglycosides}} \right) \quad [\text{Eq. 1.8}]$$

or Ticarcillin (L/hr)

The elimination rate constant (K) of 0.017 hr⁻¹ represents the approximate *in vitro* elimination rate for aminoglycosides exposed to carbenicillin concentrations of 250 to 500 mg/L at a temperature of 37°C. This clearance by carbenicillin is only an approximation and should not be used for amikacin because the interaction between amikacin and carbenicillin is relatively minor. The additional clearance secondary to inactivation by carbenicillin or other penicillins is not clinically relevant in patients with reasonably normal renal function. Enhancement of gentamicin clearance by this interaction is small and usually of consequence only in functionally anephric patients (0.3 L/hr or 5 mL/min). Because the third-generation cephalosporin antibiotics have, to a large degree, replaced the use of penicillin derivatives, the interaction between aminoglycoside antibiotics and penicillin derivatives is encountered infrequently in most clinical practices.

ELIMINATION HALF-LIFE

The elimination half-life of aminoglycoside antibiotics from the body is a function of the volume of distribution and clearance. Since renal function varies considerably among individuals, the half-life is also variable.

For example, a 70-kg, 25-year-old man with a serum creatinine of 0.8 mg/dL might have an aminoglycoside clearance of 100 mL/min or more. If his volume of distribution is 0.25 L/kg, the corresponding elimination half-life will be approximately 2 hours. In contrast, a 75-year-old man with a similar V and a serum creatinine of 1.4 mg/dL might have an aminoglycoside clearance of \approx 35 mL/min and a half-life of \approx 6 hours. For this reason, the initial aminoglycoside dose and dosing interval should be selected with care. Although initial estimates of the patient's aminoglycoside pharmacokinetic parameters may be highly variable, it is hoped that pharmacokinetic adjustments will optimize the achievement of therapeutic, yet nontoxic, concentrations of aminoglycoside antibiotics.

NOMOGRAMS AND COMPUTERS

The wide availability of nomograms to dose aminoglycosides may lead one to question the necessity for pharmacokinetic calculations.¹⁰ One nomogram which is utilized at a number of centers is the Hartford high-dose extended interval dosing nomogram.¹³ The dose in this nomogram is 7 mg/kg which targets a peak concentration of 20 to 30 mg/L which is 10 times the breakpoint for susceptibility for gentamicin and tobramycin (i.e., 2 mcg/mL). The dosing interval is adjusted based on the degree of renal function in order to maintain the target peak concentration and also achieve a drug-free interval of \approx 6 hours to reduce accumulation within the renal cortex and inner ear.

Creatine Clearance	Initial Dose and Interval
> 60 mL/min	7 mg/kg every 24 hr
40–60 mL/min	7 mg/kg every 36 hr
20–40 mL/min	7 mg/kg every 48 hr
< 20 mL/min	7 mg/kg, then follow levels to determine time of next dose (level < 1 mcg/mL)

The nomogram also provides the ability to adjust the dosing interval based on a measured serum concentration obtained 6 to 14 hours after a dose. Three regions are defined in the nomogram corresponding to the appropriate dosing interval that should be chosen based on the single measured concentration. For example, if a patient was initiated on a dose of 7 mg/kg every 24 hours and had a measured concentration of 8.2 mg/L \approx 9 hours after the dose, the nomogram indicates that the dosing interval should be extended to every 36 hours (see Figure 1.1).

The limitation of these types of nomograms is that they are usually designed to achieve fixed peak and trough serum concentrations, and they do not allow the clinician to individualize the dosing regimens to account

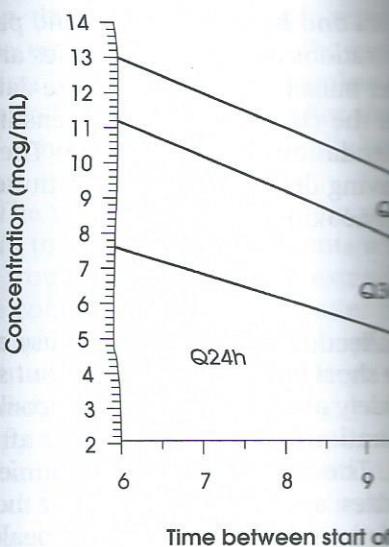


FIGURE 1.1 Gentamicin or tobramycin concentrations after a 7 mg/kg dose are plotted on the nomogram according to the measured time after the dose. Concentrations that fall within the Q24h range indicate that the dosing interval should be extended. (Data from Nicolau D, et al. Experience with a once-daily regimen of gentamicin in 2,184 adult patients. *Antimicrob Agents Chemother*. 1999;43:2132–2136. Copyright © 1999, American Society for Microbiology.)

for the type of infection treated or the patient. Furthermore, nomograms are based on average pharmacokinetic parameters and do not provide a means to individualize therapy for specific patients (e.g., obese individuals or those with significant edema or ascites or fluid). Patient-specific adjustments to the dosing regimen and dosing intervals also cannot be extrapolated from the nomogram. A better understanding of the basic pharmacokinetic principles of aminoglycoside doses, coupled with a good knowledge of pharmacokinetics, allows the clinician to provide optimal therapy.

A number of computer programs are available to calculate aminoglycosides and other therapeutic agents. These programs are more flexible than nomograms in that they can calculate the pharmacokinetic parameters and peak or trough concentrations for a given dose and administration route. They enable dosage determinations based on multiple sets of measurements (e.g., trough and peak concentrations) obtained over time. Bayesian analysis has been incorporated into some pharmacokinetic programs and has been proved useful in determining the pharmacokinetic parameters. However, the user must be familiar with the analysis and interpretation of the results.

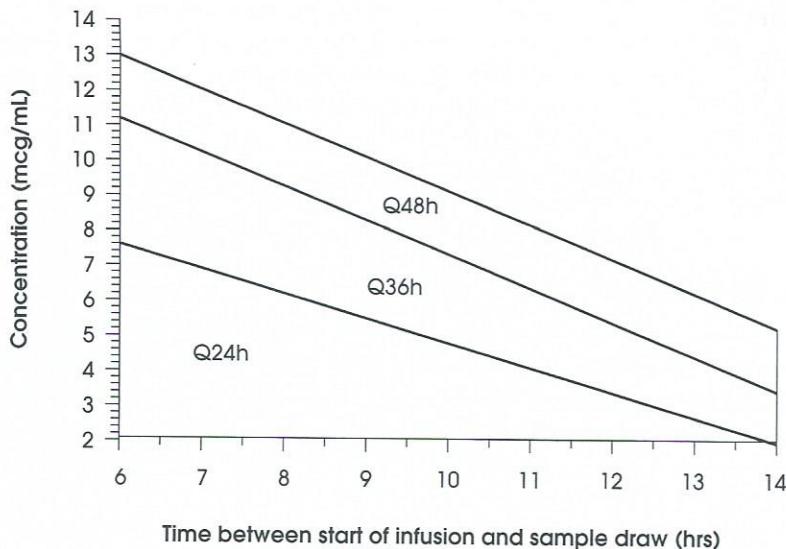


FIGURE 1.1 Gentamicin or tobramycin concentrations obtained 6 to 14 hours following a 7 mg/kg dose are plotted on the nomogram relative to the time of sampling following the dose. Concentrations that fall within the Q24h quadrant indicate that the dosing interval of 24 hours should be maintained. Concentrations that fall in the Q36h or Q48h quadrant indicate that the dosing interval should be extended to 36 or 48 hours. (Adapted from Nicolau D, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650–655, with permission from the American Society for Microbiology.)

for the type of infection treated or the benefit-to-risk ratio for the individual patient. Furthermore, nomograms are based on average pharmacokinetic parameters and do not provide a method for dose adjustment for unique patients (e.g., obese individuals or those who have significant third spacing of fluid). Patient-specific adjustments based on measured plasma concentrations also cannot be extrapolated from these nomograms. An understanding of the basic pharmacokinetic principles used to individualize aminoglycoside doses, coupled with a rational clinical approach, will enable the clinician to provide optimal therapy for the patient.

A number of computer programs are available to help clinicians dose aminoglycosides and other therapeutic agents. Computers tend to be more flexible than nomograms in that the user often can select dosing intervals and peak or trough concentrations based on clinical judgment. In addition, they enable dosage determination based on data (including multiple sets of measurements) obtained under non-steady-state conditions, which is particularly important in patients with changing renal function. Bayesian analysis has been incorporated into most computerized pharmacokinetic programs and has been proven to provide very precise estimates of the pharmacokinetic parameters. One potential pitfall, however, is that the user must be familiar with the algorithms initially used to define the

expected pharmacokinetic parameters and how patient-specific parameters are revised when plasma concentrations and dosing histories are supplied. In the revision process, the user must be able to recognize data that are obviously wrong and to interpret the computer output to ensure that the parameters and dosing recommendations are reasonable. The computer should be viewed as a labor-saving device, not as a substitute for a thorough understanding of the pharmacokinetic process.

TIME TO SAMPLE

Correct timing of the sample collection is important because aminoglycoside antibiotics have a relatively short half-life and a small but significant distribution phase. The most widely accepted guidelines recommend that samples for peak serum concentrations be obtained 1 hour after the maintenance dose has been initiated. This recommendation assumes that the drug is infused over about 30 minutes; an acceptable range for the infusion period is 20 to 40 minutes. If it is longer than 40 minutes, peak concentrations should be obtained \approx 30 minutes after the end of the infusion to ensure that distribution is complete. Others have suggested that peak measurements should be obtained later in the dosing interval to avoid the distribution phase, particularly with extended interval dosing due to the potential dose-dependent distribution phase.⁴⁵ Trough concentrations generally should be obtained within the half-hour before the administration of the next maintenance dose. In cases in which the trough concentrations are expected to be lower than the assay sensitivity (particularly with extended interval dosing), an earlier sampling time may be appropriate so that measurable trough concentrations can be obtained and patient-specific pharmacokinetic parameters derived. Ideally, the interval between the two concentration measurements should be two to four half-lives to provide more precise estimates of the half-life and reduce the potential for the later concentration to fall below the level of assay sensitivity. In all cases, the exact time of sampling and dose administration should be recorded.

When aminoglycoside plasma concentrations are sampled at a time that extends beyond the expected peak, it is possible to calculate the plasma concentration at the earlier time by simply rearranging

$$C = C^0 e^{-kt} \quad [\text{Eq. 1.9}]$$

where C^0 is the initial plasma concentration, C a concentration at some time t later, to

$$C^0 = \frac{C}{e^{-kt}} \quad [\text{Eq. 1.10}]$$

In the above equation, t is the time from the time of administration of the drug to the plasma concentration (C) to the time of sampling. The equation is used to back-extrapolate the "peak," which is 1 hour after the "trough." The "trough" concentration has generally been considered to have the lowest efficacy.

The optimal time to sample aminoglycoside concentrations is difficult to determine. For patients receiving a single daily dose, the trough (or midpoint for extended interval dosing) concentration obtained after the first dose provides the most rapid evaluation of patient response and allows for early dose adjustment, if necessary. In a large study of aminoglycoside therapy, sampling may not be necessary, as the trough concentration is relatively short (i.e., 30–60 minutes). In many institutions, the goal of therapy has been to obtain three or four doses of aminoglycosides before the trough concentration of patients will be approaching the therapeutic range. With the wide availability of computerized dosing programs, it is not absolutely necessary to measure trough concentrations. With extended interval dosing, the trough concentration may be approached with multiple dosing; therefore, the trough concentration may be measured at any dose.

Although one can estimate pharmacokinetic parameters more accurately with three or four plasma concentrations (particularly using a computer program), pharmacokinetic parameters can be estimated with a two-point model and two plasma samples in a single dosing interval.

When aminoglycoside antibiotics are administered by injection (IM), the time for absorption or distribution is uncertain. In most patients, plasma concentrations are low immediately after injection.⁵⁷ For this reason, a peak concentration is often not attained 1 hour after the IM dose is administered. As a result, the absorption or distribution is uncertain, it is difficult to estimate trough concentrations following IM administration, and unusual pharmacokinetic parameters may be derived.

QUESTION #1. R.W. is a 30-year-old man with a creatinine clearance of 50 mL/min and a serum creatinine of 0.9 mg/dL. He was admitted to the hospital with a diagnosis of pneumonia and was infused intravenously over 30 minutes with a total dose of gentamicin 1 hour after admission. A trough concentration of gentamicin 1 hour after admission was 1.5 mg/L. What was the peak concentration? (i.e., one-half hour after the infusion)

A rough estimate of the peak concentration can be calculated using Equation 1.11 by treating the patient as having a creatinine clearance of 50 mL/min.

In the above equation, t represents the time from the measured plasma concentration (C) to the earlier plasma concentration (C^0). This equation is used to back-extrapolate a plasma concentration to the “clinical peak,” which is 1 hour after the start of the infusion. The “clinical peak” concentration has generally been used as a guide to aminoglycoside efficacy.

The optimal time to sample within the first 24 hours of therapy is difficult to determine. For patients who are critically ill, a peak and subsequent trough (or midpoint for extended interval dosing) serum aminoglycoside concentration obtained after the initial loading dose allows for the most rapid evaluation of patient-specific parameters and subsequent dose adjustment, if necessary. In a large number of cases, however, this early sampling may not be necessary, particularly if the expected duration of therapy is relatively short (i.e., 3 to 5 days). The standard of practice in many institutions has been to obtain the first aminoglycoside samples after three or four doses of aminoglycoside have been administered. The majority of patients will be approaching steady state by this time; however, with the wide availability of computers and pharmacokinetic software programs, it is not absolutely necessary to wait until steady state is achieved. With extended interval dosing, there should be no significant accumulation with multiple dosing; therefore, measurements can be obtained after any dose.

Although one can estimate patient-specific pharmacokinetic parameters more accurately with three or four aminoglycoside plasma concentrations (particularly using a multi-compartment model), reasonable pharmacokinetic parameters can be estimated using a one-compartment model and two plasma samples in most cases.

When aminoglycoside antibiotics are administered intramuscularly (IM), the time for absorption or drug input is less predictable; however, in most patients, plasma concentrations peak about 1 hour after the IM injection.⁵⁷ For this reason, a peak plasma concentration should be obtained 1 hour after the IM dose is administered. Because the rate of absorption is uncertain, it is difficult to know whether unusual plasma concentrations following IM administration represent delayed absorption or unusual pharmacokinetic parameters (e.g., a large volume of distribution).

QUESTION #1. R.W. is a 30-year-old, 70-kg, non-obese woman with a serum creatinine of 0.9 mg/dL. An initial gentamicin dose of 140 mg was infused intravenously over 30 minutes. Calculate the plasma concentration of gentamicin 1 hour after the infusion was started (i.e., one-half hour after the infusion was completed).

A rough estimate of the peak gentamicin concentration can be calculated using Equation 1.11 by treating the 60-minute infusion as a bolus

dose. The 140-mg dose would be divided by the literature value for the volume of distribution ($\approx 0.25 \text{ L/kg}$ or 17.5 L) in this 70-kg woman.

$$C_1 = \frac{(S)(F)(\text{Loading Dose})}{V} \quad [\text{Eq. 1.11}]$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg})}{17.5} \\ &= 8.0 \text{ mg/L} \end{aligned}$$

The salt form (S) and bioavailability (F) were both assumed to be 1.0, and the plasma concentration of 8.0 mg/L is an approximation that assumes absorption was very rapid and that no significant drug elimination took place during the time of administration. In addition, it is assumed that the drug is distributed into a single compartment. Even though there is clearly a distribution phase associated with the IV injection of aminoglycosides, the initially high drug concentration can be ignored as long as plasma sampling is avoided during this distribution phase.^{30,31,41}

A more precise calculation of the plasma concentration 1 hour after the half-hour infusion has been initiated would take into account the decay of gentamicin levels from the peak concentration as calculated by Equation 1.9. In Equation 1.12 for C_1 below, t_1 is the time elapsed from the beginning of the IV infusion to the time of sampling at 1 hour, and the elimination rate constant (K) represents the clearance of gentamicin divided by its volume of distribution (V) (Equation 1.13).

$$C_1 = \frac{(S)(F)(\text{Loading Dose})}{V} (e^{-Kt_1}) \quad [\text{Eq. 1.12}]$$

$$K = \frac{Cl}{V} \quad [\text{Eq. 1.13}]$$

A creatinine clearance (and therefore gentamicin clearance) of $\approx 101 \text{ mL/min}$ or 6.06 L/hr can be calculated for R.W., using Equation 1.7:

$$Cl_{cr} \text{ for Females (mL/min)} = (0.85) \frac{(140 - \text{Age})(\text{Weight})}{(72)(Scr_{ss})}$$

$$= (0.85) \left(\frac{(140 - 30)(70)}{(72)(0.9)} \right)$$

$$= 101 \text{ mL/min}$$

$$Cl_{cr}(\text{L/hr}) = (101 \text{ mL/min}) \left(\frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \right)$$

$$= 6.06 \text{ L/hr}$$

Using this clearance of $\approx 6.06 \text{ L/hr}$, the volume of distribution of 17.5 L , an elimination rate constant of 0.346 hr^{-1} , and the loading dose, results in a predicted concentration of 8.0 mg/L .

$$\begin{aligned} K &= \frac{Cl}{V} \\ &= \frac{6.06}{17.5} \\ &= 0.346 \text{ hr}^{-1} \\ C_1 &= \frac{(S)(F)(\text{Loading Dose})}{V} \\ &= (8.0)(1)(140) \\ &= (8.0)(140) \\ &= 5.60 \text{ mg/L} \end{aligned}$$

To evaluate whether the IV infusion duration of one-half hour is greater than one-sixth of the drug half-life. When the duration of infusion is less than one-sixth of the half-life, then the equation for calculating the AUC_{0-t} is Equation 1.12. Selecting the Appropriate Equation 1.12 is appropriate if the infusion duration is greater than one-sixth of the half-life. Using Equation 1.12, the drug's half-life is calculated as follows:

$$\begin{aligned} t_{1/2} &= \frac{0.693}{K} \\ &= \frac{0.693}{0.346} \\ &= 2.0 \text{ hours} \end{aligned}$$

Since the duration of infusion was approximately one-fourth of the drug's half-life, the infusion duration was greater than one-sixth of the half-life, so the infusion model (see Part I) is appropriate.

QUESTION #2. Using the clearance of 101 mL/min , the elimination rate constant of 0.346 hr^{-1} , and the loading dose of 140 mg , calculate the expected plasma concentration of gentamicin in R.W. 1 hour after initiating the infusion.

Equation 1.15 represents the equation used to calculate the plasma concentration of gentamicin at time t after initiating the infusion.

Using this clearance of ≈ 6 L/hr and the apparent volume of distribution of 17.5 L, an elimination rate constant of 0.346 hr^{-1} can be calculated using Equation 1.13. This elimination rate constant, when used in Equation 1.12 to calculate the gentamicin concentration 1.0 hour after the dose, results in a predicted concentration of 5.7 mg/L.

$$\begin{aligned} K &= \frac{Cl}{V} \\ &= \frac{6.06 \text{ L/hr}}{17.5 \text{ L}} \\ &= 0.346 \text{ hr}^{-1} \\ C_1 &= \frac{(S)(F)(\text{Loading Dose})}{V} (e^{-Kt_1}) \\ &= (8 \text{ mg/L})(e^{-(0.346 \text{ hr}^{-1})(1 \text{ hr})}) \\ &= (8 \text{ mg/L})(0.71) \\ &= 5.7 \text{ mg/L} \end{aligned}$$

To evaluate whether the IV bolus dose model is appropriate, the duration of infusion (one-half hour) should be compared to the apparent drug half-life. When the duration of infusion or absorption is less than one-sixth of the half-life, then the bolus dose model can be used (see Part I: Selecting the Appropriate Equation). If, however, the duration of drug input is greater than one-sixth of the half-life, then an infusion model should be used. Using Equation 1.14 and the elimination rate constant of 0.346 hr^{-1} , R.W.'s half-life is calculated to be ≈ 2 hours as follows:

$$\begin{aligned} t_{1/2} &= \frac{0.693}{K} && [\text{Eq. 1.14}] \\ &= \frac{0.693}{0.346 \text{ hr}^{-1}} \\ &= 2.0 \text{ hr} \end{aligned}$$

Since the duration of infusion was one-half hour, the absorption time was approximately one-fourth of the half-life. In practice, an infusion time of greater than one-sixth of the half-life is often used as the criterion for requiring the infusion model (see Part I: Selecting the Appropriate Equation).

QUESTION #2. *Using the clearance of 6.06 L/hr, the volume of distribution of 17.5 L, the elimination rate constant of 0.346 hr^{-1} , and the short infusion model, calculate the expected gentamicin concentration for R.W. 1 hour after initiating the one-half hour infusion of a 140-mg dose.*

Equation 1.15 represents the short infusion model and can be used to calculate the plasma concentration 1 hour after starting the half-hour

infusion. The duration of infusion or t_{in} would be 0.5 hours, and t_2 , or the time of decay from the end of the infusion, would be 0.5 hours. Using these values, the plasma concentration 1 hour after initiation of the half-hour infusion would be 6.2 mg/L.

$$C_2 = \frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}})(e^{-Kt_2}) \quad [\text{Eq. 1.15}]$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} (1 - e^{-(0.346 \text{ hr}^{-1})(0.5 \text{ hr})})(e^{-(0.346 \text{ hr}^{-1})(0.5 \text{ hr})}) \\ &= (46.2 \text{ mg/L})(0.16)(0.84) \\ &= (7.4 \text{ mg/L})(0.84) \\ &= 6.2 \text{ mg/L} \end{aligned}$$

Note that the plasma concentration of 7.4 mg/L at the end of the half-hour infusion is lower than the calculated peak concentration of 8 mg/L following a bolus dose (see Question 1). This lower concentration at the end of the infusion reflects the clearance of drug during the infusion process. Also note that the plasma concentration of 6.2 mg/L at 1 hour calculated by the infusion model is greater than the comparable plasma concentration (5.7 mg/L) calculated by the bolus dose model in Question 1. Less drug remains in the body at this time when the bolus dose model is used because this model assumes that the entire dose entered the body at the beginning of the infusion. The total dose, therefore, has been exposed to the body's clearing mechanisms for a longer time.

QUESTION #3. In what types of patients is it more appropriate to use the infusion equation for the prediction of aminoglycoside concentrations? When can the bolus dose model be used satisfactorily?

Since the difference between the results obtained from these two approaches is primarily related to the amount of drug cleared from the body during the infusion period, it is reasonable to assume that in patients with decreased renal function and longer aminoglycoside half-lives, the bolus dose model could be used satisfactorily. In patients with good renal function (e.g., young adults and children), use of the infusion model is more appropriate because these patients often have very short aminoglycoside half-lives.

QUESTION #4. R.W., the 70-kg woman described in Question 1, was given 140 mg of gentamicin over one-half hour every 8 hours. Predict her peak and trough plasma concentrations at steady state.

Again, one could treat this problem as if R.W. were receiving intermittent IV boluses or as if she were receiving one-half-hour infusions

every 8 hours. If the bolus dose model is used to predict the peak levels, when the bolus dose is given, the "peak" is sampled (1 hour), and the trough level is sampled 8 hours later. Using the volume of distribution of 17.5 L and the elimination rate constant of 0.346 hr⁻¹, the calculated peak and trough concentrations would be 8.5 mg/L and 6.1 mg/L.

$$CSS_1 = \frac{(S)(F)(Dose)}{V} (1 - e^{-Kt_1})$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg})}{17.5 \text{ L}} (1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})}) \\ &= \left(\frac{8 \text{ mg/L}}{1 - 0.06} \right) \\ &= \left(\frac{8 \text{ mg/L}}{0.937} \right) \\ &= (8.5 \text{ mg/L}) \\ &= 6.1 \text{ mg/L} \end{aligned}$$

The trough concentration can also be calculated using the infusion equation. At steady state, the trough level is sampled just before the start of the next infusion. The trough concentration would be 0.54 mg/L.

$$CSS_{\text{min}} = \frac{(S)(F)(Dose)}{V} (1 - e^{-Kt_1})$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg})}{17.5 \text{ L}} (1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})}) \\ &= \left(\frac{8 \text{ mg/L}}{0.937} \right) \\ &= 0.54 \text{ mg/L} \end{aligned}$$

every 8 hours. If the bolus dose model is applied, Equation 1.16 can be used to predict the peak levels, where t_1 represents the time interval between the start of the infusion and the time at which the “peak concentration” is sampled (1 hour), and τ is the interval between the doses (8 hours). Using the volume of distribution of 17.5 L and the elimination rate constant of 0.346 hr^{-1} , the calculated peak concentration would be 6.1 mg/L.

$$\text{Css}_1 = \frac{(S)(F)(\text{Dose})}{V} e^{-kt_1} \quad [\text{Eq. 1.16}]$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg})}{17.5 \text{ L}} (e^{-(0.346 \text{ hr}^{-1})(1 \text{ hr})}) \\ &= \frac{(1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})})}{(1 - e^{-(0.346 \text{ hr}^{-1})(1 \text{ hr})})} \\ &= \left(\frac{8 \text{ mg/L}}{1 - 0.063} \right) (0.71) \\ &= \left(\frac{8 \text{ mg/L}}{0.937} \right) (0.71) \\ &= (8.5 \text{ mg/L})(0.71) \\ &= 6.1 \text{ mg/L} \end{aligned}$$

The trough concentration can also be calculated using Equation 1.16, where t_1 is the time interval between the start of the infusion and the time at which trough level is sampled (8 hours). If the trough sample is obtained just before the start of the next infusion, then Equation 1.17 for Css_{\min} also can be used. Using the appropriate values for volume of distribution, elimination rate constant, and dosing interval, the calculated trough concentration would be 0.54 mg/L.

$$\text{Css min} = \frac{(S)(F)(\text{Dose})}{V} e^{-kt_1} \quad [\text{Eq. 1.17}]$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg})}{17.5 \text{ L}} (e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})}) \\ &= \frac{(1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})})}{(1 - e^{-(0.346 \text{ hr}^{-1})(1 \text{ hr})})} \\ &= \frac{8 \text{ mg/L}}{0.937} (0.063) \\ &= 0.54 \text{ mg/L} \end{aligned}$$

If the infusion input model,

$$C_{t_{in}} = \frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}}) \quad [\text{Eq. 1.18}]$$

where t_{in} is the duration of the infusion, and is used to replace the bolus dose model

$$\frac{(S)(F)(Dose)}{V} \quad [\text{Eq. 1.19}]$$

in Equations 1.16 and 1.17, the resultant substitution results in an equation describing the intermittent infusion steady-state model (also see Part I: Selecting the Appropriate Equation).

$$Css_2 = \frac{\frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2}) \quad [\text{Eq. 1.20}]$$

where τ is the dosing interval and t_2 the time interval between the end of the infusion and the time at which the concentration is measured. That is, when peak concentrations are measured 1 hour after the initiation of a half-hour infusion, t_2 is 0.5 hours. For trough concentrations that are sampled just before the start of a subsequent infusion (i.e., administered on an 8-hour schedule), t_2 is 7.5 hours.

Again, assuming S and F to be 1.0, the infusion time to be 0.5 hours, the dosing interval (τ) to be 8 hours, the clearance (Cl) and the elimination rate constant (K) to be 6.06 L/hr and 0.346 hr⁻¹, respectively, the “peak” concentration 1 hour after starting the half-hour infusion would be calculated using Equation 1.20 as follows:

$$\begin{aligned} Css_2 &= \frac{\frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2}) \\ &= \frac{\frac{(1)(1)(140 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} (1 - e^{-(0.346 \text{ hr}^{-1})(0.5 \text{ hr})})}{(1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})})} (e^{-(0.346 \text{ hr}^{-1})(0.5 \text{ hr})}) \\ &= \frac{(46.2 \text{ mg/L})(0.16)}{0.937} (0.84) \\ &= (7.9 \text{ mg/L})(0.84) \\ &= 6.6 \text{ mg/L} \end{aligned}$$

Note that this steady-state “peak concentration” is not the true peak value which would occur at the end of the infusion, but a concentration

that is obtained 1 hour after start that is traditionally used to make side efficacy. Concentrations measured due to the two-compartment model of the aminoglycosides.

If the trough concentration is fusion, a modification of Equation 1.18 is presented by $(\tau - t_{in})$. A trough concentration is making the appropriate substitution (Fig. 1.2).

$$\begin{aligned} Css_{\min} &= \frac{\frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-K(\tau - t_{in})})}{(1 - e^{-K\tau})} \\ &= \frac{\frac{(1)(1)(140 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} (1 - e^{-(0.346 \text{ hr}^{-1})(7.5 \text{ hr})})}{(1 - e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr})})} \\ &= (7.9 \text{ mg/L})(e^{-(0.346 \text{ hr}^{-1})(7.5 \text{ hr})}) \\ &= (7.9 \text{ mg/L})(0.075) \\ &= 0.59 \text{ mg/L} \end{aligned}$$

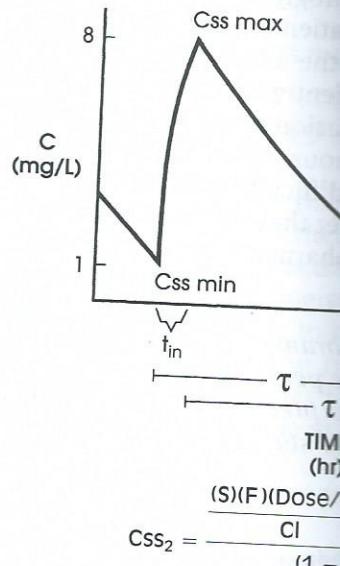


FIGURE 1.2 Intermittent intravenous infusion over t_{in} hours, and τ is the dosing interval; t_2 is the time of sampling.

that is obtained 1 hour after starting the infusion. It is this 1-hour value that is traditionally used to make the clinical correlation with aminoglycoside efficacy. Concentrations measured earlier may be considerably higher due to the two-compartment modeling associated with the IV administration of the aminoglycosides.

If the trough concentration is sampled just before the start of an infusion, a modification of Equation 1.20 can be used, where t_2 is represented by $(\tau - t_{in})$. A trough concentration of 0.59 mg/L is calculated, making the appropriate substitution of 8 hours for τ and 0.5 hours for t_{in} (Fig. 1.2).

$$Css_{min} = \frac{\frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-K(\tau - t_{in})}) \quad [Eq. 1.21]$$

$$\begin{aligned} &= \frac{(1)(1)(140 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} (1 - e^{-(0.346 \text{ hr}^{-1})(0.5 \text{ hr})}) \\ &\quad - (e^{-(0.346 \text{ hr}^{-1})(8 \text{ hr} - 0.5 \text{ hr})}) \\ &= (7.9 \text{ mg/L})(e^{-(0.346 \text{ hr}^{-1})(7.5 \text{ hr})}) \\ &= (7.9 \text{ mg/L})(0.075) \\ &= 0.59 \text{ mg/L} \end{aligned}$$

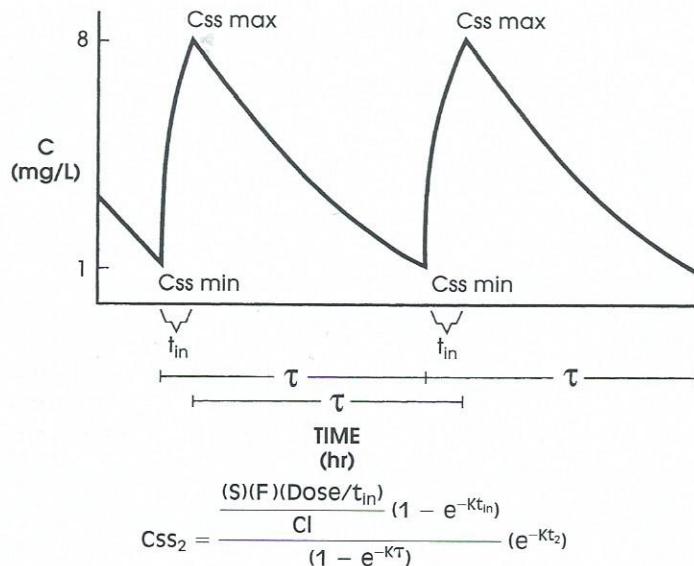


FIGURE 1.2 Intermittent intravenous infusion at steady state. The infusion is administered over t_{in} hours, and τ is the dosing interval; t_2 represents the time from the end of the infusion to the time of sampling.

Note that if the trough concentration is obtained at a time earlier than just before the next dose, Equation 1.21 should not be used. Instead, Equation 1.20 should be used where t_2 represents the time interval from the end of the infusion to the time of sampling. For example, if the trough concentration were obtained one-half hour before the next dose, then t_2 in Equation 1.20 would be 7 hours rather than 7.5 hours in Equation 1.21.

Trough concentrations can also be calculated by multiplying the peak concentration 1 hour after the dose by the fraction of drug remaining at the time the trough level is sampled (Equation 1.9):

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

where C^0 represents the peak concentration 1 hour after the dose, and t is the time from the peak concentration to the time of the trough sampling (7 hours if trough samples are obtained just before a dose, and 6.5 hours if trough samples are obtained one-half hour before a dose administered at a dosing interval of 8 hours).

QUESTION #5. When aminoglycosides are administered intramuscularly, how should the steady-state peak and trough plasma concentrations be calculated?

Although the time required to achieve peak plasma concentrations following IM injection varies, aminoglycoside concentrations peak after approximately 1 hour in most patients.^{15,31,40} Since it is difficult to estimate the rate of absorption from the site of injection, IM injections can be approached as though the patient were given an IV infusion over 1 hour. Therefore, the intermittent infusion model (Equation 1.20) can be used, with a t_{in} of 1 hour and t_2 of 0 hour. As noted earlier, unusual measured plasma concentrations will be difficult to evaluate in this situation because one cannot determine whether they represent unusual aminoglycoside absorption characteristics or pharmacokinetic parameters.

QUESTION #6. If R.W. was given tobramycin 7 mg/kg QD, what would be the calculated steady-state peak concentration 1 hour after starting the half-hour infusion? Also predict subsequent steady-state plasma concentrations 12 hours after starting the infusion and at the trough.

Using the previously calculated gentamicin pharmacokinetic parameters of 6.06 L/hr for clearance, 17.5 L for volume, and 0.346 hr^{-1} for K ,

the expected steady-state peak concentration for a 7 mg/kg per hour infusion would be a $\approx 21 \text{ mg/L}$.

$$\begin{aligned} \text{CSS}_2 &= \frac{(S)(F)(\text{Dose}/t_{in})}{\text{Cl}} \\ &= \frac{(1)(1)(480 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} \\ &= \frac{161.7 \text{ mg/L}(1 - e^{-0.346 \times 7})}{(1 - 0.0002)} \\ &= 21.6 \text{ mg/L} \end{aligned}$$

The plasma concentrations would be 11 hours for the mid-concentration.

$$\begin{aligned} C &= C^0 e^{-kt} \\ &= (21 \text{ mg/L}) e^{-0.346 \times 11} \\ &= (21 \text{ mg/L}) e^{-3.806} \\ &= 0.47 \text{ mg/L} \end{aligned}$$

12 hours after starting the infusion:

$$\begin{aligned} C &= (21 \text{ mg/L}) e^{-0.346 \times 12} \\ &= (21 \text{ mg/L}) e^{-4.152} \\ &= 0.007 \text{ mg/L} \end{aligned}$$

These calculations show that a trough concentration of $\approx 0.47 \text{ mg/L}$ is well above the usual accepted therapeutic range of 0.5 mg/L . The mid-interval and trough concentrations are similar. The trough concentration is slightly higher than the mid-interval concentration. This is because the administration of aminoglycosides over a period of 12 hours appears in most cases to be equivalent to a continuous infusion of the divided dose and may reduce the risk of nephrotoxicity. Most institutions have guidelines for the use of aminoglycoside therapy. This type of regimen is appropriate for patients who have reasonable renal function (e.g., normal glomerular filtration rate), normal body composition (e.g., no third space fluid).

One common question is whether trough concentrations should be monitored in patients receiving aminoglycosides.

the expected steady-state peak concentration one-half hour after the half-hour infusion would be a ≈ 21 mg/L as calculated from Equation 1.20.

$$\begin{aligned} \text{CSS}_2 &= \frac{(S)(F)(\text{Dose}/t_{in})}{\text{Cl}} \frac{(1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2}) \\ &= \frac{(1)(1)(480 \text{ mg}/0.5 \text{ hr})}{6.06 \text{ L/hr}} \frac{(1 - e^{-0.346(0.5)})}{(1 - e^{-0.346(24)})} (e^{-0.346(0.5)}) \\ &= \frac{161.7 \text{ mg/L}(1 - 0.84)}{(1 - 0.0002)} (0.84) \\ &= 21.6 \text{ mg/L} \end{aligned}$$

The plasma concentrations at 12 and 24 hours can be estimated using Equation 1.9, where C^0 would be approximately 21 mg/L, and t would be 11 hours for the mid-concentration and 23 hours for the trough concentration.

$$\begin{aligned} C &= C^0 e^{-Kt} \\ &= (21 \text{ mg/L})(e^{-(0.346)(11 \text{ hr})}) \\ &= (21 \text{ mg/L})(0.022) \\ &= 0.47 \text{ mg/L} \end{aligned}$$

12 hours after starting the infusion and

$$\begin{aligned} C &= (21 \text{ mg/L})(e^{-(0.346)(23 \text{ hr})}) \\ &= (21 \text{ mg/L})(0.00035) \\ &= 0.007 \text{ mg/L at the trough} \end{aligned}$$

These calculations show that the initial plasma concentrations are well above the usual accepted therapeutic range for tobramycin, and the mid-interval and trough concentrations are very low. As previously discussed, administration of aminoglycosides as a total daily dose once every 24 hours appears in most cases to be as efficacious as the usual 8-hour divided dose and may reduce the risk of development of nephrotoxicity. Most institutions have guidelines for use of high-dose, once-daily aminoglycoside therapy. This type of regimen is usually restricted to patients who have reasonable renal function (e.g., $\text{Cl}_{\text{Cr}} > 60 \text{ mL/min}$) and reasonably normal body composition (e.g., not excessively obese or having excessive third space fluid).

One common question is whether aminoglycoside plasma concentrations should be monitored in patients receiving the drug once daily. In

most cases, peak concentrations will have little meaning because they are likely to be well above the usual therapeutic range: ≈ 20 to 30 mg/L for gentamicin and tobramycin and about three times that value for amikacin. Trough plasma concentrations do not appear to be useful in that they are likely to be well below the usual detectable range and may be misinterpreted due to the tissue redistribution (gamma phase). In patients with diminished renal function, plasma level monitoring may be warranted to guard against excessive drug accumulation. One method that has been described is the peak AUC method of dosing. With this method, serum concentrations are obtained at a peak and approximately two to four half-lives later. The two levels are then used to calculate the 24-hour AUC and the extrapolated peak concentration at 1 hour into the dosing interval. The assumption with this method is that the level of drug exposure with extended interval dosing should be the same as conventional multiple daily dosing regimens (i.e., AUC_{24} 70 to 100 mg \times hr/L).²⁵

QUESTION #7. Y.B., a 70-kg, 38-year-old patient with a serum creatinine of 1.8 mg/dL, has been receiving IV tobramycin, 100 mg over one-half hour every 8 hours, for several days. A peak plasma concentration obtained 1 hour after the start of an infusion was 8 mg/L, and a trough concentration obtained just before the initiation of a dose was 3 mg/L. Estimate the apparent elimination rate constant (K), clearance (Cl), and volume of distribution (V) for tobramycin in Y.B.

The two reported plasma concentrations were measured from samples obtained during the elimination phase of the plasma concentration-versus-time curve. Since the 7-hour time interval between samples exceeds the half-life of tobramycin in Y.B. (i.e., the trough concentration is less than one-half the measured peak concentration), the two concentrations can be used to estimate the elimination rate constant [see Part I: Elimination Rate Constant (K) and Half-Life ($t^{1/2}$) and Equation 1.22].

$$K = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t} \quad [\text{Eq. 1.22}]$$

$$\begin{aligned} &= \ln \frac{\left(\frac{8.0}{3.0}\right)}{7 \text{ hr}} \\ &= \frac{0.98}{7 \text{ hr}} \\ &= 0.14 \text{ hr}^{-1} \end{aligned}$$

Using the elimination rate constant of 0.14 hr^{-1} , the observed peak concentration of 8 mg/L, and the dosing regimen of 100 mg administered

over one-half hour every 8 hours, calculated by rearranging Equation 1.22, sample is obtained 0.5 hours after t₁ 1 hour

$$Cs_{0.5} = \frac{V}{(1 - e^{-Kt})}$$

$$V = \frac{(Cs_{0.5})(1 - e^{-Kt})}{e^{-Kt}}$$

$$\begin{aligned} V &= \frac{12.5 \text{ L} \cdot (1 - e^{-0.14 \text{ hr}^{-1} \cdot 0.5 \text{ hr}})}{e^{-0.14 \text{ hr}^{-1} \cdot 0.5 \text{ hr}}} \\ &= 12.5 \text{ L} \cdot 0.57 \\ &= 16.2 \text{ L} \end{aligned}$$

and the clearance can be calculated

to solve for Cl .

$$\begin{aligned} Cl &= (K \cdot V) \\ &= (0.14 \text{ hr}^{-1} \cdot 16.2 \text{ L}) \\ &= 2.3 \text{ L/hr} \end{aligned}$$

This volume of distribution of tobramycin is unusual. The value of calculating tobramycin's volume of distribution specific for Y.B. is that they may now administer any dose that will produce any desired peak concentration.

QUESTION #8. The microbiology laboratory has isolated *Escherichia coli* with an MIC of 1 mcg/mL. Calculate the dose required to achieve a peak concentration of 8 mg/L and a AUC_{24} in the range of 70 to 100 mg \times hr/L.

As before, the dose required to achieve a peak concentration of 8 mg/L can be calculated from Equation 1.22. However, since the dosing interval is 8 hours, one should

over one-half hour every 8 hours, Y.B.'s volume of distribution can be calculated by rearranging Equation 1.16 for C_{ss_1} where τ is 8 hours and the sample is obtained 0.5 hours after the end of the 0.5-hour infusion making t_1 1 hour

$$C_{ss_1} = \frac{(S)(F)(Dose)}{V} \frac{e^{-Kt_1}}{(1 - e^{-KT})}$$

$$V = \frac{(S)(F)(Dose)}{C_{ss_1}} \frac{e^{-KT}}{(1 - e^{-KT})} \quad [\text{Eq. 1.23}]$$

$$\begin{aligned} V &= \frac{(1)(1)(100 \text{ mg})}{8 \text{ mg/L}} \frac{e^{-(0.14 \text{ hr}^{-1})(1 \text{ hr})}}{(1 - e^{-(0.14 \text{ hr}^{-1})(8 \text{ hr})})} \\ &= \frac{12.5 \text{ L}}{0.67} (0.87) \\ &= 16.2 \text{ L} \end{aligned}$$

and the clearance can be calculated using a rearrangement of Equation 1.13

$$K = \frac{Cl}{V}$$

to solve for Cl.

$$\begin{aligned} Cl &= (K)(V) \quad [\text{Eq. 1.24}] \\ &= (0.14 \text{ hr}^{-1})(16.2 \text{ L}) \\ &= 2.3 \text{ L/hr} \end{aligned}$$

This volume of distribution of 16.2 L corresponds to about 0.23 L/kg. The value of calculating tobramycin pharmacokinetic parameters that are specific for Y.B. is that they may now be used to calculate a dosing regimen that will produce any desired peak and trough concentrations.

QUESTION #8. *The microbiology report reveals *Pseudomonas aeruginosa* with an MIC of 1 mcg/mL. Calculate a dosing regimen for Y.B. that will achieve a peak concentration of > 10 mg/L (peak:MIC > 10:1) and a AUC_{24} in the range of 70 to 100 mg × hr/L.*

As before, the dose required to achieve a specific peak concentration can be calculated from Equation 1.16. To select an appropriate dosing interval, however, one should first consider Y.B.'s apparent half-life,

which can be calculated using Equation 1.14 and the elimination rate constant of 0.14 hr^{-1} .

$$\begin{aligned} t_{1/2} &= \frac{0.693}{K} \\ &= \frac{0.693}{0.14 \text{ hr}^{-1}} \\ &= 4.9 \text{ hr} \end{aligned}$$

As presented earlier, a dosing interval of approximately four to five half-lives is desirable to maximize the peak concentration and bactericidal activity while minimizing drug accumulation and potential nephrotoxicity and ototoxicity. Because Y.B.'s tobramycin half-life is ≈ 5 hours, the most convenient dosing interval is 24 hours. Using this dosing interval and the appropriate volume of distribution and elimination rate constant, Equation 1.25 (a rearrangement of Equation 1.16 to solve for dose) indicates that a dose of 200 mg administered every 24 hours should result in a peak concentration of $\approx 10 \text{ mg/L}$ 1 hour after the start of a half-hour infusion.

$$\text{Dose} = \frac{(C_{ss1})(V)(1 - e^{-KT})}{(S)(F)(e^{-Kt_1})} \quad [\text{Eq. 1.25}]$$

$$\begin{aligned} \text{Dose} &= \frac{(10 \text{ mg/L})(17.5 \text{ L})(1 - e^{-(0.14 \text{ hr}^{-1})(24 \text{ hr})})}{(1)(1)(e^{-(0.14 \text{ hr}^{-1})(1 \text{ hr})})} \\ &= \frac{(10 \text{ mg/L})(17.5 \text{ L})(0.97)}{(1)(1)(0.87)} \\ &= 195.1 \text{ mg or } \approx 200 \text{ mg} \end{aligned}$$

Equation 1.9 can be used to determine the trough concentration. A "t" of 23 hours and a C^0 of 10 mg/L should be used.

$$\begin{aligned} C &= C^0 e^{-Kt} \\ &= (10 \text{ mg/L})(e^{-(0.14 \text{ hr}^{-1})(23 \text{ hr})}) \\ &= (10 \text{ mg/L})(0.04) \\ &= 0.4 \text{ mg/L} \end{aligned}$$

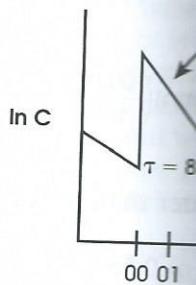
To confirm whether the level of drug exposure is in the desirable range, Equation 1.26 can be used to calculate the AUC_{24} .

$$AUC_{24} = \frac{(\text{Dose in mg})(24 \text{ hr})/\tau \text{ in hr}}{Cl \text{ in L/hr}} \quad [\text{Eq. 1.26}]$$

$$\begin{aligned} &= \frac{(200 \text{ mg})(24 \text{ hr})/24 \text{ hr}}{2.3 \text{ L/hr}} \\ &= 87 \text{ mg} \cdot \text{hr/L} \end{aligned}$$

QUESTION #9. C.I. is a 50-year-old man of 1.5 mg/dL, who is receiving 300 mg every 8 hours at midnight. The trough concentration of 6 mg/L and a peak concentration of 15 mg/L. Calculate C.I.'s elimination rate constant and distribution. Evaluate whether the dose should be used to adjust C.I.'s dose.

The approach to calculating K for C.I. is essentially the same. First, the elimination rate constant is calculated using Equation 1.22 and the 7-hour time concentrations (Fig. 1.3):



Next, the volume of distribution is calculated using Equation 1.23. A dose of 350 mg and a time of 8 hours represents the time from the beginning of the "trough" sampling time ($t_1 = 1 \text{ hr}$).

FIGURE 1.3 Calculating K by transposing the equation for AUC_{24} . Note that steady state must have been achieved (at least 5 t_{1/2}s). Also, the $C_{ss \max}$ is moved to the start of the next bolus dose (i.e., from 09:00 in one interval to 09:00 in the next). The intermittent bolus dose model has been used for these concentrations so that the decay phase is a straight line.

QUESTION #9. C.I. is a 50-year-old, 60-kg man with a serum creatinine of 1.5 mg/dL, who is receiving 350 mg of amikacin IV over one-half hour every 8 hours at midnight, 8:00 a.m., and 4:00 p.m. He had a trough concentration of 6 mg/L obtained just before the 8:00 a.m. dose, and a peak concentration of 15 mg/L obtained at 9:00 a.m. Assuming these peak and trough concentrations represent steady-state levels, calculate C.I.'s elimination rate constant, clearance, and volume of distribution. Evaluate whether these parameters seem reasonable and should be used to adjust C.I.'s amikacin maintenance dose.

The approach to calculating the revised pharmacokinetic parameters for C.I. is essentially the same as that used in the previous questions. First, the elimination rate constant of 0.13 hr^{-1} can be calculated using Equation 1.22 and the 7-hour time interval between the peak and trough concentrations (Fig. 1.3):

$$\begin{aligned} K &= \frac{\ln\left(\frac{C_1}{C_2}\right)}{t} \\ &= \frac{\ln\left(\frac{15}{6}\right)}{7 \text{ hr}} \\ &= 0.13 \text{ hr}^{-1} \end{aligned}$$

Next, the volume of distribution can be calculated by using Equation 1.23. A dose of 350 mg and a “ τ ” of 8 hours can be used. The latter t_1 represents the time from the beginning of the infusion to the “peak concentration” sampling time ($t_1 = 1 \text{ hr}$).

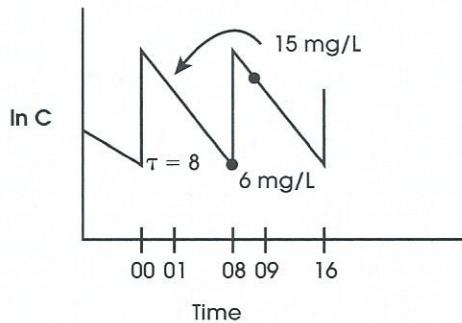


FIGURE 1.3 Calculating K by transposing $C_{ss \max}$ into the same interval as $C_{ss \min}$. Note that steady state must have been achieved (same dose, same interval for greater than 3 to 5 $t\frac{1}{2}$ s). Also, the $C_{ss \max}$ is moved to the same time within the interval relative to the preceding dose (i.e., from 09:00 in one interval to 01:00 in the preceding interval). The intermittent bolus dose model has been used for the input model and the concentrations are \ln concentrations so that the decay phase is a straight line.

$$\begin{aligned}
 V &= \frac{(S)(F)(Dose)}{\frac{C_{SS_1}}{(1 - e^{-KT})} e^{-Kt_1}} \\
 &= \frac{(1)(1)(350 \text{ mg})}{\frac{15 \text{ mg/L}}{(1 - e^{-(0.13 \text{ hr}^{-1})(8 \text{ hr})})} (e^{-(0.13 \text{ hr}^{-1})(1 \text{ hr})})} \\
 &= \frac{(23.3 \text{ L})(0.88)}{(0.65)} \\
 &= 31.5 \text{ L}
 \end{aligned}$$

Using the calculated volume of distribution of 31.5 L and the elimination rate constant of 0.13 hr^{-1} , a clearance value of 4.1 L/hr can be calculated using Equation 1.24.

$$\begin{aligned}
 Cl &= (K)(V) \\
 Cl &= (0.13 \text{ hr}^{-1})(31.5 \text{ L}) \\
 &= 4.1 \text{ L/hr}
 \end{aligned}$$

Before these parameters are used to calculate an adjusted amikacin dosing regimen that will bring C.I.'s peak concentration into the range of 20 to 30 mg/L and the trough concentration below 10 mg/L, care should be taken to evaluate whether these parameters appear reasonable. The calculated clearance of 4.1 L/hr is slightly greater than the expected clearance of 3 L/hr, which would be calculated using Equation 1.6 and C.I.'s age, weight, and serum creatinine.

$$\begin{aligned}
 Cl_{Cr} \text{ for Males (mL/min)} &= \frac{(140 - \text{Age})(\text{Weight})}{(72)(SCr_{SS})} \\
 &= \frac{(140 - 50)(60 \text{ kg})}{(72)(1.5 \text{ mg/dL})} \\
 &= 50 \text{ mL/min}
 \end{aligned}$$

or

$$\begin{aligned}
 Cl_{Cr}(\text{L/hr}) &= (50 \text{ mL/min}) \left(\frac{60 \text{ min/hr}}{100 \text{ mL/L}} \right) \\
 &= 3 \text{ L/hr}
 \end{aligned}$$

While this clearance value is greater than expected, it is not so unusual as to be considered unrealistic.

The volume of distribution value of 0.53 L/kg (31.5 L/60 kg), however, is unusually large. In general, volumes of distribution $> 0.35 \text{ L/kg}$ are only observed in patients who have significant third spacing of fluid (e.g., ascites or edema). If there is no evidence of any third spacing in C.I., then the volume of distribution would be unrealistically large. Therefore, the dosing history or the measured plasma concentrations are probably in error. If C.I. had received tobramycin or gentamicin, the possibility of a penicillin interaction resulting in spuriously low plasma concentrations

would have to be considered; however, penicillins to a significant extent, for the unusually large volume of distribution.

In any case, when pharmacokinetic parameters that are very different from those expected based on sampling, assay results, or dosing regimens, it is prudent to use the expected rather than calculated pharmacokinetic parameters. When this is suspected, it is important to reassess the patient and another set of plasma drug concentrations, and special attention to precise sampling times.

QUESTION #10. D.H., a 40-year-old male, was admitted to the hospital following an automobile accident. He was admitted to the hospital weighing 85 kg. He was found to be hypotensive and tachycardic. He required multiple doses of epinephrine to maintain his blood pressure. Current laboratory values include a serum creatinine of 2 mg/dL. D.H. has a history of hypertension and diabetes mellitus. He underwent abdominal surgery after his abdominal surgery. Estimate the dose to achieve peak gentamicin concentration and an AUC₂₄ between 70 and 100 mg·hr/L.

To calculate D.H.'s pharmacokinetic parameters, it is necessary to identify his non-obese, excess weight. Using Equation 1.2, D.H.'s ideal body weight is:

Ideal body weight for males in kg = $50 + (2.3 \times (\text{Actual weight} - \text{IBW}))$

Assuming D.H. did not have any significant third spacing of fluid, his excess adipose weight is $85 \text{ kg} - 61.5 \text{ kg} = 23.5 \text{ kg}$. The difference between the IBW of 61.5 kg from his admission and the calculated ideal body weight of 61.5 kg from his current weight is 0 kg. The estimated ideal body weight for D.H. is 61.5 kg. The estimated total body water space fluid weight of 20 kg can be subtracted from the total body weight of 85 kg from his current weight to estimate the total body water space fluid weight of 65 kg. The estimated total body water space fluid weight of 65 kg can be used to estimate the aminoglycoside volume of distribution.

$$\text{Aminoglycoside } V(\text{L}) = \left(\frac{0.25 \text{ L}}{\text{Non-obese, excess weight}} \right) \times \text{Total body weight}$$

$$\begin{aligned}
 &= (0.25 \text{ L}) \times 85 \text{ kg} \\
 &= 37.7 \text{ L}
 \end{aligned}$$

would have to be considered; however, amikacin does not interact with penicillins to a significant extent. Therefore, this is an unlikely explanation for the unusually large volume of distribution.

In any case, when pharmacokinetic calculations lead to parameters that are very different from those expected, there may be an error in the time of sampling, assay results, or dosing history. In such cases, it may be more prudent to use the expected rather than the calculated parameters to adjust doses. In some cases, however, the patient may actually have unusual parameters. When this is suspected, the dosing history should be reevaluated and another set of plasma drug concentrations should be obtained, with special attention to precise sampling times and the dosing history.

QUESTION #10. *D.H., a 40-year-old man, was admitted to the hospital following an automobile accident. He is 5 feet 5 inches tall and on admission weighed 85 kg. He was taken for abdominal surgery and post-operatively became hypotensive and required large volumes of fluid to maintain his blood pressure. Currently, he weighs 105 kg and has a serum creatinine of 2 mg/dL. D.H. is to receive gentamicin empirically after his abdominal surgery. Estimate his pharmacokinetic parameters and dose to achieve peak gentamicin concentrations > 10 mg/L and an AUC₂₄ between 70 and 100 mg × hr/L.*

To calculate D.H.'s pharmacokinetic parameters, it is first necessary to identify his non-obese, excess adipose, and excess third space fluid weight. Using Equation 1.2, D.H.'s IBW is calculated to be ≈ 61.5 kg.

$$\begin{aligned}\text{Ideal body weight for males in kg} &= 50 + (2.3)(\text{Height in Inches} > 60) \\ &= 50 + 2.3(5 \text{ Inches}) \\ &= 61.5 \text{ kg}\end{aligned}$$

Assuming D.H. did not have any excess third space fluid on admission, his excess adipose weight is ≈ 23.5 kg (estimated by subtracting his IBW of 61.5 kg from his admission weight of 85 kg). D.H.'s excess third space fluid weight of 20 kg can be estimated by subtracting his initial weight of 85 kg from his current weight of 105 kg. Using these weight estimates for his body composition, Equation 1.4 can be used to estimate an aminoglycoside volume of distribution of ≈ 38 L:

$$\begin{aligned}\text{Aminoglycoside V(L)} &= \left(0.25 \text{ L/kg} \times \text{Non-Obese, Non-Excess Fluid Weight (kg)} \right) + \\ &\quad 0.1 \left(\begin{array}{c} \text{Excess} \\ \text{Adipose} \\ \text{Weight (kg)} \end{array} \right) + \left(\begin{array}{c} \text{Excess Third-} \\ \text{Space Fluid} \\ \text{Weight (kg)} \end{array} \right) \\ &= (0.25 \text{ L/kg} \times 61.5 \text{ kg}) + 0.1(23.5 \text{ kg}) + (20 \text{ kg}) \\ &= 37.7 \text{ L or } 38 \text{ L}\end{aligned}$$

To estimate D.H.'s gentamicin clearance, one would use Equation 1.6, his IBW of 61.5 kg, and his current serum creatinine of 2 mg/dL.

$$\begin{aligned} \text{Cl}_{\text{Cr}} \text{ for males (mL/min)} &= \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCr}_{\text{ss}})} \\ &= \frac{(140 - 40 \text{ yr})(61.5 \text{ kg})}{(72)(2 \text{ mg/dL})} \\ &= 42.7 \text{ mL/min} \\ &= 42.7 \text{ mL/min} \times \frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \\ &= 2.56 \text{ L/hr} \end{aligned}$$

Using the estimated creatinine clearance of 2.56 L/hr as the gentamicin clearance and the volume of distribution of 38 L, the elimination rate constant (Equation 1.13) and half-life (Equation 1.14) are calculated to be 0.067 hr^{-1} and 10.34 hr, respectively:

$$\begin{aligned} K &= \frac{\text{Cl}}{V} \\ &= \frac{2.56 \text{ L/hr}}{38 \text{ L}} \\ &= 0.067 \text{ hr}^{-1} \\ t_{1/2} &= \frac{0.693}{K} \\ &= \frac{0.693}{0.067 \text{ hr}^{-1}} \\ &= 10.34 \text{ hr} \end{aligned}$$

Given D.H.'s half-life of approximately 10 hours and an infusion time of one-half hour, Equation 1.25, the steady-state bolus dose model, can be used to calculate his regimen.

$$\text{Dose} = \frac{(\text{Css}_1)(V)(1 - e^{-KT})}{(S)(F)(e^{-Kt_1})}$$

Because aminoglycoside dosing intervals are now typically greater than four to five half-lives, a dosing interval of 48 hours is reasonable given D.H.'s half-life of approximately 10 hours. Making the appropriate substitution in the rearranged equation where Css_1 is assumed to be 10 mg/L, t_1 is 1 hour (indicating that the peak concentration is to be obtained 1 hour after the start of the infusion), a dose of ≈ 400 mg is calculated.

$$\begin{aligned} \text{Dose} &= \frac{(10 \text{ mg/L})(38 \text{ L})(1 - e^{-(0.067 \text{ hr}^{-1})(48 \text{ hr})})}{(1)(1)(e^{-(0.067 \text{ hr}^{-1})(1 \text{ hr})})} \\ &= \frac{(10 \text{ mg/L})(38 \text{ L})(1 - 0.04)}{(1)(1)(0.94)} \\ &= 388 \text{ mg or } \approx 400 \text{ mg} \end{aligned}$$

Although a dose of 400 mg is extensive third spacing fluid and a somewhat lower dose might be a proportionately less seems large, D.H. is receiving this non-obese or IBW of 61.5 kg, below the lower end of the usual tant to ensure that AUC_{24} is in the

$$\text{AUC}_{24} = \frac{(\text{Dose})}{\text{Cl}_{\text{Cr}}}$$

$$\text{AUC}_{24} = \frac{(400 \text{ mg})}{2.56 \text{ L/hr}}$$

$$= 78 \text{ mg} \cdot \text{hr/L}$$

The AUC_{24} value of 78 mg · hr/L is in the normal range (70 to 100 mg · hr/L), indicating that a dose increase is necessary depending on the severity of infection. If the infusion remains 48 hours, an increase in dose will result in a further increase in AUC_{24} and peak concentrations. For example, a 30% increase in dose would result in a dose of 520 mg · hr/L and a peak concentration of 100 mg/L.

QUESTION #11. D.L., a 38-year-old man, is receiving gentamicin and ticarcillin combination therapy for a known origin. How might the combination influence the pharmacokinetics of the two antibiotics that may influence each other?

The beta-lactam ring of the penicillins and in vitro with one of the penicillins, such as carbenicillin or ticarcillin, to form an inactive metabolite. The mechanism of inactivation by penicillins is not fully understood, but it probably is significant only for the beta-lactamase function.^{49–51} In these patients, the use of carbenicillin or ticarcillin can decrease the half-life of gentamicin from approximately 46 to 22 hours. It has been shown that the beta-lactam compounds and aminoglycosides interact with each other. In the case of carbenicillin, the dose of gentamicin must be reduced in patients with poor renal function, which this interaction affects gentamicin. A dose reduction is used to calculate an apparent half-life of 22 hours.

Although a dose of 400 mg appears to be large, this is due in part to the extensive third spacing fluid and large volume of distribution. In many cases, a somewhat lower dose might be employed; however, the peak concentration would be proportionately decreased. Also, although the dose of 400 mg seems large, D.H. is receiving this dose only every other day and based on his non-obese or IBW of 61.5 kg, this equates to $\approx 3.0 \text{ mg/kg/day}$, which is below the lower end of the usual range (5 to 7 mg/kg/day). It is also important to ensure that AUC_{24} is in the desired range (70 to 100 mg \times hr/L).

$$AUC_{24} = \frac{(Dose \text{ in mg})(24 \text{ hr})/\tau \text{ in hr}}{Cl \text{ in L/hr}}$$

$$AUC_{24} = \frac{(400 \text{ mg})(24 \text{ hr})/48 \text{ hr}}{2.56 \text{ L/hr}}$$

$$= 78 \text{ mg} \cdot \text{hr/L}$$

The AUC_{24} value of 78 mg \times hr/L is in the lower end of the desired range (70 to 100 mg \times hr/L), indicating that the dose could be increased if necessary depending on the severity of the infection. If the dosing interval remains 48 hours, an increase in dose will result in a proportional increase in AUC_{24} and peak concentration (see Equations 1.16 and 1.26). For example, a 30% increase in dose would result in an AUC_{24} of approximately 100 mg \times hr/L and a peak concentration of 13 mg/L.

QUESTION #11. *D.L., a 38-year-old, 70-kg patient with renal failure, is receiving gentamicin and ticarcillin for treatment of a fever of unknown origin. How might the concurrent administration of ticarcillin influence the pharmacokinetics of gentamicin? Are there other antibiotic combinations that may influence gentamicin dosing?*

The beta-lactam ring of the penicillin compounds interacts in vivo and in vitro with one of the primary amines on both gentamicin and tobramycin to form an inactive amide.^{48–50} The rate of gentamicin and tobramycin inactivation by penicillins is slow, however, and this interaction probably is significant only in patients with severely impaired renal function.^{49–51} In these patients, the concurrent administration of carbenicillin or ticarcillin can decrease the half-life of gentamicin from approximately 46 to 22 hours. It has been recommended that the penicillin compounds and aminoglycosides be administered separately, and that in the case of carbenicillin, the dose be decreased to avoid excessive accumulation in patients with poor renal function. To estimate the degree to which this interaction affects gentamicin clearance, Equation 1.8 can be used to calculate an apparent ticarcillin-related clearance value for D.H.

Using a standard volume of distribution of 0.25 L/kg for this 70-kg patient and the apparent rate constant for the in vitro interaction between ticarcillin and gentamicin of 0.017 hr^{-1} , a clearance value of 0.3 L/hr can be calculated:

Tobramycin, Gentamicin

Clearance by Carbenicillin = $(0.017 \text{ hr}^{-1}) \left(\frac{\text{Volume of Distribution}}{\text{for Aminoglycosides}} \right)$
or Ticarcillin (L/hr)

$$= (0.017 \text{ hr}^{-1})(0.25 \text{ L/kg})(70 \text{ kg}) = 0.3 \text{ L/hr}$$

This clearance value of 0.3 L/hr would be added to the estimated gentamicin clearance associated with D.H.'s residual renal function and non-renal clearance (0.0043 L/kg/hr). This is only an estimate, however, and plasma levels must be monitored to make patient-specific adjustments.

Plasma samples for patients receiving aminoglycosides and penicillins concurrently must be obtained at a time when the in vitro interaction is minimal. Plasma samples for assay of aminoglycoside concentrations should be obtained when the penicillin is at its lowest concentration and assayed as soon as possible. If storage is required, samples should be frozen to minimize the continual in vitro effect of this interaction. Amikacin appears to be more resistant to degradation by penicillins.⁴⁸ Some of the more recent penicillin compounds (e.g., azlocillin, mezlocillin) appear to interact with gentamicin and tobramycin similarly but to a lesser extent than carbenicillin and ticarcillin.⁵⁴ Furthermore, the in vitro interaction between the cephalosporins (e.g., cefazolin, cefamandole) and the aminoglycoside antibiotics appears to be minimal.^{54,56}

Although somewhat debatable, the combined use of cephalosporins and aminoglycosides may place patients at a greater risk for nephrotoxicity.^{58,59}

QUESTION #12. What is the significance of a changing serum creatinine in a patient receiving gentamicin?

A rising serum creatinine in a patient always raises the question of gentamicin-induced nephrotoxicity. In this event, the drug may be discontinued, the plasma concentration reevaluated, and/or the dose adjusted, since gentamicin may accumulate substantially when renal function is impaired. Dose modification should be based on plasma gentamicin levels rather than serum creatinine levels because serum creatinine concentrations that are not at steady state can be misleading [see Part I: Creatinine Clearance (Cl_{Cr})]. The reason for this is that despite the similarity between gentamicin and creatinine clearances,^{31,40} their volumes of distribution differ. Gentamicin's V of 0.25 L/kg is smaller than that of creatinine, which is 0.5 L/kg.^{26,27,32,60} Since the half-life is determined by the clearance and volume of distribution (see Equation 1.27 below), the half-life for creatinine is approximately twice as long as that

of gentamicin and the other aminoglycosides. Thus, it may take longer for creatinine to reach steady state and to change in renal function.

$t_{1/2} =$

When the serum creatinine is elevated, the patient's renal function is worse than that would be expected for a normal individual. Thus, any gentamicin dose calculated on the basis of the patient's serum creatinine will be overestimated. Conversely, when the patient's renal function may be better than that of a normal individual, the doses calculated on the basis of the patient's serum creatinine will be underestimated.

QUESTION #13. D.W., a 20-year-old man, has been receiving 1 g of tobramycin infused IV over a 30-min period every 8 h. His baseline serum creatinine has increased from 0.8 mg/dL to 1.2 mg/dL in 24 hours. Because his renal function is impaired, his plasma samples were obtained to calculate the elimination rate constants as follows: just before a dose, 4 h after a dose, and 8 h after that dose (two trough concentrations). The measured gentamicin concentrations at these times were 1.2, 0.8, and 0.6 mg/dL, respectively. Calculate the volume of distribution and clearance of tobramycin for D.W.

Since the second trough concentration is less than the first, it is apparent that the drug is not at steady state. Therefore, the equations used to calculate the elimination rate constant and volume of distribution should not be used. The first step that should be taken is to calculate the elimination rate constant for the two concentrations that were obtained during the first 8-h period. Equation 1.22 can be used to estimate the elimination rate constant. However, this K should only be used as an estimate if the two concentrations were obtained less than 8 h apart.

$\ln \frac{C_1}{C_2} = -Kt$

$\ln \frac{1.2}{0.8} = -K(4)$

$= 0.0833 = K$

This elimination rate constant can be used to calculate the volume of distribution that the peak concentration of tobramycin is approximately twice as long as that of gentamicin and the other aminoglycosides. Thus, it may take longer for creatinine to reach steady state and to change in renal function.

of gentamicin and the other aminoglycosides. It will, therefore, take creatinine a longer time to arrive at a new steady-state concentration after a change in renal function.

$$t_{1/2} = \frac{(0.693)(V)}{Cl} \quad [\text{Eq. 1.27}]$$

When the serum creatinine is rising (i.e., not at steady state), the renal function is worse than that would be predicted by use of the serum creatinine, and any gentamicin dose calculated using the serum creatinine would be overestimated. Conversely, when the serum creatinine is falling, renal function may be better than that reflected by the serum creatinine, and the doses calculated on the basis of these levels would be underestimated.

QUESTION #13. *D.W., a 20-year-old, 60-kg man, is receiving 80 mg of tobramycin infused IV over a 30-minute period every 8 hours. His serum creatinine has increased from 1 to 2 mg/dL over the past 24 hours. Because his renal function appears to be decreasing, three plasma samples were obtained to monitor serum gentamicin concentrations as follows: just before a dose, 1 hour after that same dose, and 8 hours after that dose (two troughs and one peak level). The serum gentamicin concentrations at these times were 4, 8, and 5 mg/L, respectively. Calculate the volume of distribution, elimination rate constant, and clearance of tobramycin for D.W.*

Since the second trough concentration of tobramycin is higher than the first, it is apparent that the drug is accumulating. Therefore, steady-state equations should not be used to calculate D.W.'s pharmacokinetic parameters. The first step that should be taken to resolve this dilemma is to calculate the elimination rate constant from the two plasma concentrations that were obtained during the elimination phase (8 and 5 mg/L). Equation 1.22 can be used to estimate the elimination rate constant; however, this K should only be used as an estimate since the two plasma concentrations were obtained less than one half-life apart.

$$\begin{aligned} K &= \frac{\ln\left(\frac{C_1}{C_2}\right)}{t} \\ &= \frac{\ln\left(\frac{8 \text{ mg/L}}{5 \text{ mg/L}}\right)}{7 \text{ hr}} \\ &= 0.067 \text{ hr}^{-1} \end{aligned}$$

This elimination rate constant of 0.067 hr^{-1} was calculated by assuming that the peak concentration of 8 mg/L was obtained 1 hour after the

start of the tobramycin infusion and that the trough concentration was obtained just before the next dose, resulting in a time interval of 7 hours. The elimination rate constant of 0.067 hr^{-1} corresponds to a half-life of 10.3 hours (Equation 1.14):

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

$$= \frac{0.693}{0.067 \text{ hr}^{-1}}$$

$$= 10.3 \text{ hr}$$

This half-life of 10.3 hours suggests that relatively little drug is lost during the infusion period; therefore, a bolus model is most appropriately used in this situation. The volume of distribution can be estimated by assuming that the bolus dose is administered instantaneously and calculating the theoretical peak concentration using Equation 1.10. C is the measured concentration of 8 mg/L, t is the 1-hour interval between the start of the infusion and the time of sampling, and C^0 is the theoretical peak concentration for an IV bolus.

$$\begin{aligned}
 C^0 &= \frac{C}{e^{-Kt}} \\
 &= \frac{8 \text{ mg/L}}{e^{-(0.067 \text{ hr}^{-1})(1 \text{ hr})}} \\
 &= \frac{8 \text{ mg/L}}{0.94} \\
 &= 8.5 \text{ mg/L}
 \end{aligned}$$

Since the change in concentration (peak minus trough) is the result of the dose administered and the volume of distribution, the V can be calculated using Equation 1.28 below.

$$V = \frac{\text{Dose}}{(C_{\text{peak}} - C_{\text{min}})} \quad [\text{Eq. 1.28}]$$

$$V = \frac{80 \text{ mg}}{(8.5 \text{ mg/L} - 4 \text{ mg/L})}$$

$$= 17.8 \text{ L}$$

This volume of distribution of 17.8 L can then be used with the elimination rate constant of 0.067 hr^{-1} in Equation 1.24 to calculate D.W.'s clearance of 1.2 L/hr or 20 mL/min :

$$\begin{aligned} \text{Cl} &= (K)(V) \\ &= (0.067 \text{ hr}^{-1})(17.8 \text{ L}) \\ &= 1.2 \text{ L/hr or } 20 \text{ mL/min} \end{aligned}$$

QUESTION #14. Using the plan for D.W. in Question 13, develop reasonable peak and trough com-

Because D.W.'s tobramycin necessary to reduce his maintenance dose and maintain the dose and the dosing interval AUC_{24} will be approximately respectively.

Reduce the Dose and Maximize the Dosing Interval

method is not acceptable for DDT (≈ 10 hours). If a dose that achieves a therapeutic level is used and the dosing interval is increased, the time to achieve a therapeutic level will be ≈ 4.7 mg/L.

Css min =

Css min =

This level may place D.W. at
Adjust Both the Dose and I
Peak Concentration and AUC₂₄
this approach is that most clinic during which the gentamicin co pathogen because of the possibility ence with dosing intervals in exc some animal data suggest that d trough concentrations are less li same dose administered as a cont age levels).⁶¹ A first estimate of th ining D.W.'s tobramycin half-life o half-lives is chosen, a dosing inter half-life of tobramycin is long re hour, the bolus dose model can b 1.26 can be used to calculate a dos Using Equation 1.26 with the prev eters and a dosing interval of 48 h A peak concentration that occurs at is also assumed (i.e., $t_1 = 1$ ho

$$AUC_{24} = \frac{\text{(Dose)}}{}$$

QUESTION #14. Using the pharmacokinetic parameters calculated for D.W. in Question 13, develop a dosing regimen that will produce reasonable peak and trough concentrations of tobramycin.

Because D.W.'s tobramycin clearance is low (1.2 L/hr), it will be necessary to reduce his maintenance dose. There are two alternatives: (1) reduce the dose and maintain the same dosing interval, or (2) adjust both the dose and the dosing interval such that the peak concentration and AUC_{24} will be approximately 10 mg/L and 70 to 100 mg \times hr/L, respectively.

Reduce the Dose and Maintain the Same Dosing Interval. This method is not acceptable for D.W. because he has such a long half-life (\approx 10 hours). If a dose that achieves a maximum concentration of 8 mg/L is used and the dosing interval of 8 hours is maintained, the trough level will be \approx 4.7 mg/L.

$$C_{ss\ min} = (C_{ss\ max})(e^{-k\tau}) \quad [\text{Eq. 1.29}]$$

$$\begin{aligned} C_{ss\ min} &= (8 \text{ mg/L})(e^{-(0.067 \text{ hr}^{-1})(8 \text{ hr})}) \\ &= 4.68 \text{ mg/L} \end{aligned}$$

This level may place D.W. at risk for tobramycin toxicity.

Adjust Both the Dose and Dosing Interval to Achieve Reasonable Peak Concentration and AUC_{24} values. The only potential limitation to this approach is that most clinicians prefer to avoid prolonged periods during which the gentamicin concentration is below the MIC of the pathogen because of the possibility of organism regrowth. Clinical experience with dosing intervals in excess of 48 hours is limited. Nevertheless, some animal data suggest that doses which result in high peak and low trough concentrations are less likely to produce renal toxicity than the same dose administered as a continuous IV infusion (i.e., the same average levels).⁶¹ A first estimate of the dosing interval can be made by examining D.W.'s tobramycin half-life of 10 hours. If an interval of four to five half-lives is chosen, a dosing interval of 48 hours can be used. Since the half-life of tobramycin is long relative to the infusion time of one-half hour, the bolus dose model can be used. As previously stated, Equation 1.26 can be used to calculate a dose required to achieve a specific AUC_{24} . Using Equation 1.26 with the previously derived pharmacokinetic parameters and a dosing interval of 48 hours, a dose of \approx 240 mg is calculated. A peak concentration that occurs 1 hour after the infusion has been initiated is also assumed (i.e., $t_1 = 1$ hour).

$$AUC_{24} = \frac{(Dose \text{ in mg})(24 \text{ hr})/\tau \text{ in hr}}{Cl \text{ in L/hr}}$$

or

$$\begin{aligned}\text{Dose in mg} &= \frac{(AUC_{24})(Cl \text{ in L/hr})(\tau \text{ in hr})}{24 \text{ hr}} \\ &= \frac{(100 \text{ mg} \cdot \text{hr/L})(1.2 \text{ L/hr})(48 \text{ hr})}{24 \text{ hr}} \\ &= 240 \text{ mg given every 48 hr}\end{aligned}$$

The peak concentration can be calculated using the bolus dose model (Equation 1.16).

$$\begin{aligned}Css_1 &= \frac{(S)(F)(\text{Dose})}{V} e^{-Kt_1} \\ &= \frac{V}{(1 - e^{-Kt})} e^{-Kt_1} \\ &= \frac{(1)(1)(240 \text{ mg})}{(1 - e^{-(0.067 \text{ hr}^{-1})(48 \text{ hr})})} (e^{-(0.067 \text{ hr}^{-1})(1 \text{ hr})}) \\ &= \frac{17.8 \text{ L}}{(1 - e^{-(0.067 \text{ hr}^{-1})(48 \text{ hr})})} (0.94) \\ &= 13.4 \text{ mg/L} (0.94) \\ &= 13.96 \text{ mg/L} (0.94) \\ &= 13.1 \text{ mg/L}\end{aligned}$$

The trough concentration, 47 hours later, calculated using Equation 1.29, would be 0.6 mg/L.

$$\begin{aligned}Css_{\min} &= (Css_{\max})(e^{-K\tau}) \\ Css_{\min} &= (13.96 \text{ mg/L})(e^{-(0.067 \text{ hr}^{-1})(47 \text{ hr})}) \\ &= 0.6 \text{ mg/L}\end{aligned}$$

QUESTION #15. M.S., a 70-kg non-obese female, undergoes 4 hours of hemodialysis every 48 hours. She is functionally (not surgically) anephric, and gentamicin is to be started. Calculate a dosing regimen that achieves a peak concentration of 6 mg/L and then maintains average levels of 3.5 mg/L.

Because the gentamicin half-life for a patient who is functionally anephric is probably in excess of 30 hours, very little drug will be eliminated from the body over the 1-hour period following initiation of the infusion. Therefore, the loading dose may be calculated as though it were a bolus (Equation 1.30). Assuming S and F to be 1 and the volume of distribution to be 17.5 L (0.25 L/kg), a loading dose of ≈ 100 mg would be calculated as follows:

$$\begin{aligned}\text{Loading Dose} &= \frac{(V)(C)}{(S)(F)} \quad [\text{Eq. 1.30}] \\ &= \frac{(17.5 \text{ L})(6 \text{ mg/L})}{(1)(1)} \\ &= 105 \text{ mg}\end{aligned}$$

Since gentamicin eliminates at higher rates during the dialysis, it should not be used. As presented in Table 1.1, two approaches to the resolution of this problem are to administer a daily dose such that the drug is removed and then to calculate a replacement dose. One approach is to administer the drug after dialysis, so that the drug lost during the interdialysis period is replaced by the use of the patient's clearance rate. The volume of distribution will be reduced, so the glycosides in functionally anephric patients have an aminoglycoside clearance by low dialysis, with an average value of ≈ 30 mL/min.

If the approach of giving a bolus dose is chosen, the maintenance dose on non-dialysis days (Equation 1.31, with a patient clearance rate of ≈ 13 mL/min) and a dosing interval of 24 hours will result in a trough concentration between 3 and 4 mg/L. Therefore, a dose of ≈ 25 mg would be required.

$$\begin{aligned}\text{Dose} &= \frac{(Css_{\max})(V)}{Kt} \\ \text{Dose} &= \frac{(3.5 \text{ mg/L})(17.5 \text{ L})}{(0.067 \text{ hr}^{-1})(24 \text{ hr})} \\ &= 25.2 \text{ mg}\end{aligned}$$

If the patient had been surgically anephric, the clearance would be approximately halved, and the trough concentrations would also have been one-half or ≈ 13 mg/L. To calculate the postdialysis replacement dose, assuming a dialysis time (T_d) of 4 hours, the replacement dose would be:

$$\begin{aligned}\text{Post dialysis Replacement Dose} &= (V)(Cs_{\max}) \\ &= [17.5 \text{ L}](6 \text{ mg/L}) \\ &= (17.5 \text{ L})(3.5 \text{ mg/L}) \\ &= 23.3 \text{ mg}\end{aligned}$$

Note that the dialysis clearance is ≈ 30 mL/min and that this is the same as the patient's clearance rate.

Since gentamicin elimination in M.S. will be irregular, occurring at higher rates during the dialysis, the usual maintenance dose equation cannot be used. As presented in Part I: Dialysis of Drugs, there are two possible approaches to the resolution of this problem. One approach is to administer a daily dose such that average concentrations are maintained and then to calculate a replacement dose postdialysis. A second approach is to administer the drug after dialysis only. The dose used is the amount of drug lost during the interdialysis and intradialysis period. In both cases, the use of the patient's clearance (Cl_{pat}), dialysis clearance (C_{dial}), and the volume of distribution will be required. The reported clearance for aminoglycosides in functionally anephric patients is $\approx 0.0043 \text{ L/kg/hr}$,^{27,62} and aminoglycoside clearance by low-flux hemodialysis is 20 to 40 mL/min, with an average value of $\approx 30 \text{ mL/min}$.^{27,62-64}

If the approach of giving daily and postdialysis doses is taken, then the maintenance dose on non-dialysis days can be calculated using Equation 1.31, with a patient clearance of 0.3 L/hr ($0.0043 \text{ L/hr/kg} \times 70 \text{ kg}$) and a dosing interval of 24 hours. In most dialysis patients, a gentamicin concentration between 3 and 4 mg/L (average: 3.5 mg/L) is set as a goal. Therefore, a dose of ≈ 25 mg would be appropriate:

$$\text{Dose} = \frac{(\text{Css ave})(\text{Cl}_{\text{pat}})(\tau)}{(S)(F)} \quad [\text{Eq. 1.31}]$$

$$\begin{aligned} \text{Dose} &= \frac{(3.5 \text{ mg/L})(0.3 \text{ L/hr})(24 \text{ hr})}{(1)(1)} \\ &= 25.2 \text{ mg or } \approx 25 \text{ mg} \end{aligned}$$

If the patient had been surgically anephric, the Cl_{pat} would have been approximately halved, and the corresponding maintenance dose would also have been one-half or ≈ 13 mg/day. Equation 1.32 can be used to calculate the postdialysis replacement dose. Using the average C_{dial} and a dialysis time (T_d) of 4 hours, the replacement dose is calculated to be ≈ 25 mg.

$$\begin{aligned} \text{Post dialysis} \\ \text{Replacement} &= (V)(\text{Css ave}) \left(1 - e^{-\left(\frac{(\text{Cl}_{\text{pat}} + \text{Cl}_{\text{dial}})}{V} \right)(T_d)} \right) \quad [\text{Eq. 1.32}] \\ \text{Dose} \\ &= [17.5 \text{ L}][3.5 \text{ mg/L}] \left[1 - e^{-\left(\frac{0.3 \text{ L/hr} + 1.8 \text{ L/hr}}{17.5 \text{ L}} \right)(4 \text{ hr})} \right] \\ &= (17.5 \text{ L})(3.5 \text{ mg/L})[1 - 0.62] \\ &= 23.3 \text{ mg or } \approx 25 \text{ mg} \end{aligned}$$

Note that the dialysis clearance of 1.8 L/hr represents a clearance of ≈ 30 mL/min and that this is the primary route of elimination during the

introdialysis period. Also, the postdialysis dose of 25 mg can be added to the maintenance dose of \approx 25 mg, resulting in a gentamicin dose on dialysis days of 50 mg.

If it is decided to administer the aminoglycoside only after dialysis, Equation 1.33 can be used to calculate the postdialysis replacement dose. In this situation, a steady-state peak concentration of \approx 4 to 5 mg/L is set as a goal (peak concentrations of 6 to 8 mg/L would expose M.S. to continuously elevated concentrations of gentamicin).

Using Equation 1.33, a C_{ss} peak of 5.0 mg/L, a patient clearance of 0.3 L/hr, and a t_1 of 44 hours [derived from a 48-hour interval between the dialyses and a dialysis time (T_d) of 4 hours], the postdialysis replacement dose is 62 mg.

Post dialysis

$$\text{Replacement} = (V)(\text{Css peak}) \left(1 - \left[\left(e^{-\left(\frac{Cl_{pat}}{V}\right)(t_1)} \right) \left(e^{-\left(\frac{Cl_{pat} + Cl_{dial}}{V}\right)(T_d)} \right) \right] \right)$$

Dose

[Eq. 1.33]

$$\begin{aligned} &= (17.5 \text{ L})(5 \text{ mg/L}) \left(1 - \left[\left(e^{-\left(\frac{0.3 \text{ L/hr}}{17.5 \text{ L}}\right)(44 \text{ hr})} \right) \left(e^{-\left(\frac{0.3 \text{ L/hr} + 1.8 \text{ L/hr}}{17.5 \text{ L}}\right)(4 \text{ hr})} \right) \right] \right) \\ &= (17.5 \text{ L})(5 \text{ mg/L})(1 - [(0.47)(0.62)]) \\ &= (17.5 \text{ L})(5 \text{ mg/L})(1 - 0.29) \\ &= 62 \text{ mg} \end{aligned}$$

To ensure that trough concentrations just before dialysis are not excessively low, the predialysis drug concentration should be calculated using Equation 1.34

$$\begin{aligned} \text{Predialysis Drug Concentration} &= [\text{Css peak}] \left[e^{-\left(\frac{Cl_{pat}}{V}\right)(t_1)} \right] \quad \text{[Eq. 1.34]} \\ &= (5 \text{ mg/L}) \left[e^{-\left(\frac{0.3 \text{ L/hr}}{17.5 \text{ L}}\right)(44 \text{ hr})} \right] \\ &= (5 \text{ mg/L})(0.47) \\ &= 2.35 \text{ mg/L} \end{aligned}$$

This predialysis concentration of \approx 2.4 mg/L is higher than usually desired; however, because the gentamicin half-life is unusually long, it will be difficult to maintain peak levels in the range of 5 mg/L and predialysis trough concentrations of $<$ 2 mg/L. Unfortunately, the persistence of relatively high concentrations between dialysis periods will place M.S. at

greater risk for ototoxicity.⁶⁵ In addition, postdialysis concentrations can be calculated, these probably do not correlate well with patients. If postdialysis concentrations have been allowed for equilibration between concentrations have been lowered in the tracellular fluid compartment.⁶⁶

QUESTION #16. How would the postdialysis dose be calculated if peritoneal dialysis rather than hemodialysis were used?

Peritoneal dialysis is much less effective than hemodialysis. The usual clearance value is \approx 4 mL/min, or \approx 10% of the total body volume removed during dialysis may be removed. Intermittent peritoneal dialysis is used to remove waste products.

Aminoglycosides can be administered intraperitoneally to achieve systemic plasma concentrations. After a single intraperitoneal injection, an initial loading dose of \approx 3 mg/kg is given. The first peritoneal dialysis exchange removes \approx 40% of the drug. Subsequent exchanges daily (usually the night-time) remove \approx 10% of the drug until a dialysate concentration of \approx 6 to 8 mg/L is reached. Both of these regimens result in a steady-state plasma concentration of \approx 3 mg/L with relatively little fluctuation. Antibiotics are placed in each peritoneal dialysis bag to maintain the steady-state plasma concentration. As an example, a patient with a peritoneal dialysis volume of 8 mg/L and a dialysate concentration of 8 mg/L would be 3.2 mg/L, or 40% of the drug removed by dialysis exchanges.^{69,70}

QUESTION #17. A patient with meningitis is being treated with intramuscular (IM) or intrathecal (IT) or intraventricular (IV) routes. Which of these routes is preferred and why? What are the expected side effects?

Gentamicin does not cross the blood-brain barrier. Therefore, CSF and cerebrospinal fluid (CSF) levels are not affected by IM or IV injections. Intrathecal or intraventricular injections are given directly into the CSF. These routes are preferred to ensure adequate ventricular concentrations throughout the subarachnoid space. The bioavailability of aminoglycosides is approximately 60% to 70%. The recommended dose of aminoglycosides is 5 to 10 mg/kg.

greater risk for ototoxicity.⁶⁵ In addition, although postdialysis concentrations can be calculated, these lower concentrations are transient and probably do not correlate well with the incidence of ototoxicity in dialysis patients. If postdialysis concentrations are to be measured, time should be allowed for equilibration between the plasma compartment (in which concentrations have been lowered during the dialysis period) and the extracellular fluid compartment.⁶⁶

QUESTION #16. *How would the above situation have differed if peritoneal dialysis rather than hemodialysis had been used?*

Peritoneal dialysis is much less effective in removing gentamicin; the usual clearance value is \approx 4 mL/min/m², with an average value of 5 to 10 mL/min for the 70-kg patient. Nonetheless, the total amount of drug removed during dialysis may be as much as 30% or more because acute intermittent peritoneal dialysis is usually continued for \approx 36 hours.^{62,67}

Aminoglycosides can be administered either parenterally or intraperitoneally to achieve systemic plasma concentrations. When administered intraperitoneally, an initial loading dose of 2 to 3 mg/kg is added to the first peritoneal dialysis exchange. Then, 1.2 mg/kg/day is added to one exchange daily (usually the night-time exchange), or a dose that produces a dialysate concentration of \approx 6 to 10 mg/L is added to each dialysate exchange. Both of these regimens result in steady-state plasma concentrations of \approx 3 mg/L with relatively little fluctuation.⁶⁸ When aminoglycoside antibiotics are placed in each peritoneal exchange, many clinicians estimate the steady-state plasma concentration to be \approx 40% of the peritoneal dialysate concentration. As an example, if 16 mg were added to each 2 L peritoneal exchange volume (8 mg/L), the steady-state plasma concentration would be 3.2 mg/L, or 40% of the 8 mg/L concentration in the dialysate exchanges.^{69,70}

QUESTION #17. *A patient with meningitis is being considered for treatment with intrathecal (IT) or intraventricular gentamicin. Which of these routes is preferred and what pharmacokinetic parameters are expected?*

Gentamicin does not cross the blood-brain barrier very effectively, and cerebrospinal fluid (CSF) levels are usually subtherapeutic unless IT or intraventricular injections are given.⁷¹⁻⁷³ The intraventricular route is preferred to ensure adequate ventricular levels and uniform concentration throughout the subarachnoid space.^{71,73} The apparent CSF half-life of aminoglycosides is approximately 6 hours.^{71,72} The usual intraventricular dose of aminoglycosides is 5 to 10 mg and is usually repeated on a daily

basis. This dosing regimen is similar for gentamicin, tobramycin, and amikacin, even though doses administered systemically vary considerably. If the intraventricular route is to be used, neurosurgery will be required to insert a special access shunt that allows daily administration. CSF peak concentrations measured soon after intraventricular injection approach 100 mg/L or higher; trough concentrations 24 hours later are usually 5 to 15 mg/L.⁷³

QUESTION #18. T.C. is receiving tobramycin 360 mg IV over one-half hour every 24 hours at 9:00 a.m. Levels drawn at 11:00 a.m. and 9:00 p.m. were 15.0 mg/L and 0.9 mg/L, respectively. Calculate the peak concentration expected at 10:00 a.m., or 1 hour after starting the 9:00 a.m. tobramycin infusion, and the AUC₂₄ to determine the appropriateness of the current dosing regimen.

The time interval between 11:00 a.m. and 9:00 p.m. is 10 hours, and Equation 1.22 can be used to determine the elimination rate constant for T.C.

$$\begin{aligned} K &= \frac{\ln\left(\frac{C_1}{C_2}\right)}{t} \\ &= \frac{\ln\left(\frac{15 \text{ mg/L}}{0.9 \text{ mg/L}}\right)}{10 \text{ hr}} \\ &= \frac{2.8}{10 \text{ hr}} \\ &= 0.28 \text{ hr}^{-1} \end{aligned}$$

This patient-specific elimination rate constant of 0.28 hr⁻¹ can be used in Equation 1.10 to calculate the expected plasma concentration at 10:00 a.m. (1 hour after the start of the infusion) or 1.0 hour before the observed peak of 15 mg/L.

$$\begin{aligned} C^0 &= \frac{C}{e^{-kt}} \\ &= \frac{15 \text{ mg/L}}{e^{-(0.28 \text{ hr}^{-1})(1 \text{ hr})}} \\ &= \frac{15 \text{ mg/L}}{0.76} \\ &= 19.8 \text{ mg/L} \end{aligned}$$

The steady-state infusion must

(S)(F)(Dose)

Css₂ =

can be rearranged to solve for clear-

$$Cl = \frac{(S)(F)(Dose)}{Css_2}$$

$$\begin{aligned} Cl &= \frac{(1)(1)(360 \text{ mg}/0.5 \text{ hr})}{0.9 \text{ mg/L}} \\ &= \frac{(800 \text{ L/hr})(0.13)}{(0.99)}(0.04) \\ &= 4.2 \text{ L/hr} \end{aligned}$$

The AUC₂₄ can then be calculated:

$$\begin{aligned} AUC_{24} &= \frac{(Dose \times t)}{Cl} \\ &= \frac{(360 \text{ mg})}{4.2 \text{ L/hr}} \\ &= 86 \text{ mg} \cdot \text{hr} \end{aligned}$$

This peak concentration of 19.8 mg/L is within the target range (peak for susceptibility (2 mcg/mL). The AUC₂₄ of 86 mg · hr suggests that the dose of 360 mg every 8 hours is appropriate.

QUESTION #19. J.H. is a 25-year-old man with cystic fibrosis who is admitted to the hospital with a respiratory exacerbation. His serum creatinine level is 1.2 mg/dL. His renal function is normal. His serum creatinine clearance is 100 mg × hr/L and suggests that the dose of tobramycin should be adjusted.

The steady-state infusion model (Equation 1.20)

$$CSS_2 = \frac{\frac{(S)(F)(Dose/t_{in})}{Cl} (1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2})$$

can be rearranged to solve for clearance: ($t_{in} > \frac{1}{6}t_{1/2}$)

$$Cl = \frac{\frac{(S)(F)(Dose/t_{in})}{CSS_2} (1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2}) \quad [Eq. 1.35]$$

$$\begin{aligned} Cl &= \frac{\frac{(1)(1)(360 \text{ mg}/0.5 \text{ hr})}{0.9 \text{ mg/L}} (1 - e^{(0.28 \text{ hr}^{-1})(0.5 \text{ hr})})}{(1 - e^{-(0.28 \text{ hr}^{-1})(24 \text{ hr})})} (e^{-(0.28 \text{ hr}^{-1})(11.5 \text{ hr})}) \\ &= \frac{(800 \text{ L/hr})(0.13)}{(0.99)} (0.04) \\ &= 4.2 \text{ L/hr} \end{aligned}$$

The AUC_{24} can then be calculated using Equation 1.26.

$$\begin{aligned} AUC_{24} &= \frac{(Dose \text{ in mg})(24 \text{ hr})/\tau \text{ in hr}}{Cl \text{ in L/hr}} \\ &= \frac{(360 \text{ mg})(24 \text{ hr})/24 \text{ hr}}{4.2 \text{ L/hr}} \\ &= 86 \text{ mg} \cdot \text{hr/L} \end{aligned}$$

This peak concentration of 19.8 mg/L represents a concentration that is within the target range (peak:MIC > 10) based on the breakpoint for susceptibility (2 mcg/mL). The AUC_{24} is also in the target range (70 to 100 mg · hr/L) and suggests that T.C.'s tobramycin does not require dose adjustment.

QUESTION #19. J.H. is a 25-year-old man (height, 5'5"; weight, 55 kg) with cystic fibrosis who is admitted for treatment of an acute pulmonary exacerbation. His serum creatinine is 0.6 mg/dL. His treatment is initiated with tobramycin 180 mg infused over 30 minutes every 8 hours. Calculate the predicted steady-state peak and trough concentrations.

The pharmacokinetics of a number of compounds, including the aminoglycoside antibiotics, has been shown to be altered in patients with cystic fibrosis. In particular, the volume of distribution appears to be larger (0.3 to 0.35 L/kg) and the clearance is faster than age-matched control subjects.⁷⁴ One potential explanation for the apparent difference in pharmacokinetic parameters is due to altered body composition. Patients with cystic fibrosis often exhibit reduced adipose mass due to malnutrition secondary to pancreatic insufficiency. When the pharmacokinetic parameters are normalized by lean body mass, the parameters are not significantly different from that of age-matched controls.⁷⁴ J.H.'s V and Cl can be calculated using a V of 0.3 L/kg and Equation 1.6 to calculate creatinine clearance.

$$\begin{aligned} V &= (0.3 \text{ L/kg})(55 \text{ kg}) \\ &= 16.5 \text{ L} \\ \text{Cl}_{\text{Cr}} \text{ for Males (mL/min)} &= \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCr}_{\text{ss}})} \\ &= \frac{(140 - 25 \text{ yr})(55 \text{ kg})}{(72)(0.6 \text{ mg/dL})} \\ &= 146 \text{ mL/min} \\ &= 146 \text{ mL/min} \times \frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \\ &= 8.8 \text{ L/hr} \end{aligned}$$

Using the estimated creatinine clearance of 8.8 L/hr as the tobramycin clearance and the volume of distribution of 16.5 L, the elimination rate constant (Equation 1.13) and half-life (Equation 1.14) are calculated to be 0.53 hr⁻¹ and 1.3 hr, respectively:

$$\begin{aligned} K &= \frac{\text{Cl}}{V} \\ &= \frac{8.8 \text{ L/hr}}{16.5 \text{ L}} \\ &= 0.53 \text{ hr}^{-1} \\ t_{1/2} &= \frac{0.693}{K} \\ &= \frac{0.693}{0.53 \text{ hr}^{-1}} \\ &= 1.3 \text{ hr} \end{aligned}$$

The steady-state peak and using the short infusion model (1)

$$\begin{aligned} \text{Css}_2 &= \frac{(S)(F)(\text{Dose}/t_{in})}{\text{Cl}} (1 - e^{-Kt}) \\ &= \frac{(1)(1)(180 \text{ mg}/0.5 \text{ hr})}{8.8 \text{ L/hr}} (1 - e^{-0.53 \text{ hr}}) \\ &= \frac{(40.9 \text{ mg/L})(0.23)}{(0.99)} (0.7) \\ &= 7.3 \text{ mg/L} \end{aligned}$$

The trough concentration cission model as shown above, or by using Equation 1.9, where "t" is t

$$\begin{aligned} C &= C^0 e^{-Kt} \\ C &= (7.3 \text{ mg}) \\ &= (7.3 \text{ mg}) \\ &= 0.18 \text{ mg} \end{aligned}$$

Therefore, although the dose (10 mg/kg/day), the relatively low TBW results in predicted serum concentrations higher than the target concentrations in this patient. The relatively short elimination half-life of "once-daily" aminoglycoside regimens is associated with increased toxicity in populations. The results of a recent trial demonstrated once-daily amikacin to be equally effective, and reduced risk of nephrotoxicity in patients with cystic fibrosis when compared with "twice-daily" regimens.⁷⁵

QUESTION #20. O.L., a 52-year-old male with a history of cystic fibrosis and multiple organ failure, is receiving mechanical ventilation and hemodialysis. His current weight is 65 kg (up from 60 kg 2 days ago). His serum creatinine is 2.8 mg/dL. Pending cultures he is found to have a *Pseudomonas aeruginosa* infection. What would be a reasonable starting dose of tobramycin?

The steady-state peak and trough concentrations can be calculated using the short infusion model (Equation 1.20):

$$\text{Css}_2 = \frac{(S)(F)(\text{Dose}/t_{in})}{Cl} \frac{(1 - e^{-Kt_{in}})}{(1 - e^{-K\tau})} (e^{-Kt_2})$$

$$\text{Css}_2 = \frac{(1)(1)(180 \text{ mg}/0.5 \text{ hr})}{8.8 \text{ L/hr}} \frac{(1 - e^{-(0.53 \text{ hr}^{-1})(0.5 \text{ hr})})}{(1 - e^{-(0.53 \text{ hr}^{-1})(8 \text{ hr})})} (e^{-(0.53 \text{ hr}^{-1})(0.5 \text{ hr})})$$

$$= \frac{(40.9 \text{ mg/L})(0.23)}{(0.99)} (0.77)$$

$$= 7.3 \text{ mg/L}$$

The trough concentration could be calculated using the short infusion model as shown above, or by decaying down the peak concentration using Equation 1.9, where “t” is the time between the two drug levels.

$$C = C^0 e^{-Kt}$$

$$C = (7.3 \text{ mg/L}) (e^{-(0.53 \text{ hr}^{-1})(7 \text{ hr})})$$

$$= (7.3 \text{ mg/L})(0.024)$$

$$= 0.18 \text{ mg/L}$$

Therefore, although the dose of tobramycin appears quite high (10 mg/kg/day), the relatively rapid clearance (when expressed per TBW) results in predicted serum concentrations that are not different than the target concentrations in other patients. Because of the relatively short elimination half-life in these patients, the use of “once-daily” aminoglycoside regimens is not as widespread as in other patient populations. The results of a recent multicenter randomized controlled trial demonstrated once-daily aminoglycoside administration results in similar efficacy, and reduced risk of nephrotoxicity in children with cystic fibrosis when compared with traditional multiple daily dosing regimens.⁷⁵

QUESTION #20. O.L., a 52-year-old man in the critical care unit with multiple organ failure, is receiving CRRT with a total output of 2 L/hr (ultrafiltration and dialysis flow rate of 1 L/hr each). His current weight is 65 kg (up from 60 kg 2 days ago) and his serum creatinine is 2.8 mg/dL. Pending cultures he is to be started on tobramycin. What would be a reasonable starting dose for O.L.?

There are two approaches to dosing of aminoglycosides, traditional and high-dose extended interval dosing. With traditional dosing, tobramycin would be initiated at a dose of approximately 2 mg/kg targeting peak concentrations of 6 to 8 mg/L, and a dosing interval would be chosen in order to achieve trough concentrations of less than 2 mg/L and preferably less than 1 mg/L. With high-dose extended interval dosing, a dose of 5 to 7 mg/kg would be initiated targeting peak concentrations of 20 to 30 mg/L, and a dosing interval would be chosen to target an AUC_{24} of approximately 70 to 100 mg \times hr/L. In order to determine the tobramycin dosing regimen, we will have to estimate his residual renal function (Cl_{pat}), CRRT clearance (Cl_{CRRT}), and volume of distribution (V).

Because the patient has end-stage renal failure and is receiving CRRT, the Cockcroft and Gault equation is not a valid way to estimate renal function. Our best guess would be to use the average aminoglycoside clearance of 0.0043 L/hr/kg for functionally anephric patients. Excluding what appears to be 5 kg of excess third space weight, the weight of 60 kg would result in a Cl_{pat} of 0.258 L/hr ($0.0043 \text{ L/hr} \times 60 \text{ kg}$). Assuming that the aminoglycoside plasma binding is negligible, f_u would be approximately 1 and our maximum expected Cl_{CRRT} would be 2 L/hr.

$$\text{Cl}_{\text{CRRT}} \text{ Maximum} = (\text{fu})(\text{CRRT Flow Rate}) \quad [\text{Eq. 1.36}]$$

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

$$= 2 \text{ L/hr}$$

While the initial estimate of 2 L/hr is a reasonable first approach, the literature would suggest that the actual Cl_{CRRT} is approximately 0.8 of the CRRT flow rate.⁷⁶⁻⁷⁸ Using 0.8 as the fraction of the CRRT flow that is actually cleared, we would have a Cl_{CRRT} of 1.6 L/hr ($0.8 \times 2 \text{ L/hr}$). Now combining the Cl_{CRRT} and Cl_{pat} , we estimate a total Cl of 1.86 L/hr ($1.6 \text{ L/hr} + 0.258 \text{ L/hr} \approx 1.86 \text{ L/hr}$) while the patient is receiving CRRT.

The Volume of Distribution would be calculated using Equation 1.4 where 60 kg represents the “Non-Obese, non-Excess Fluid Weight,” 0 the “Excess Adipose Weight,” and 5 kg the “Excess Third Space Fluid Weight.”

Aminoglycoside V(L) =

$$\begin{aligned}
 & \left(0.25 \text{ L/kg} \times \text{Non-Obese, Non-Excess Fluid Weight (kg)} \right) + 0.1 \left(\begin{array}{l} \text{Excess} \\ \text{Adipose} \\ \text{Weight (kg)} \end{array} \right) + \left(\begin{array}{l} \text{Excess Third} \\ \text{Space Fluid} \\ \text{Weight (kg)} \end{array} \right) \\
 & = (0.25 \text{ L/kg} \times 60 \text{ kg}) + 0.1(0) + 1(5\text{kg}) \\
 & = 15 \text{ L} + 0 \text{ L} + 5 \text{ L} \\
 & = 20 \text{ L}
 \end{aligned}$$

Using Equations 1.13 and 1.14, calculate $T_{1/2}$ of hr.

ing that the usual dose is three to five half-lives (22.4 hr (3×7.45 hr)). At certain dosing intervals (e.g., a dosing interval of 24 hours), calculate the tobramycin dose to achieve our target peak concentration of 7 mg/L and 0.093 hr⁻¹, respectively. For τ = 1 hour, the above values indicate a dose of 137 mg.

$$\text{Dose} = \frac{(C_{ss1})(V)(1 - e^{-Ft})}{(S)(F)(e^{-kt})}$$

$$= \frac{(7 \text{ mg/L})(20 \text{ L})}{(1)(1)} = \frac{(140 \text{ mg})(1 - e^{-0.093 \text{ hr}^{-1} \times 1 \text{ hr}})}{(1)(1)(0.93)}$$

$$= 137 \text{ mg}$$

The calculated dose would be 140 mg given IV over 30 minutes even though our trough concentration is

where C^0 would be our steady-state
would be 23 hours. Note that because

Using Equations 1.13 and 1.14, we calculate a K value of hr^{-1} and a $t_{\frac{1}{2}}$ of hr.

$$\begin{aligned} K &= \frac{Cl}{V} \\ &= \frac{1.86 \text{ L/hr}}{20 \text{ L}} \\ &= 0.093 \text{ hr}^{-1} \\ t_{\frac{1}{2}} &= \frac{0.693}{K} \\ &= \frac{0.693}{0.093 \text{ hr}^{-1}} \\ &= 7.45 \text{ hr} \end{aligned}$$

Considering that the usual dosing interval for “traditional” aminoglycoside dosing is three to five half-lives, our dosing interval would be somewhere between 22.4 hr (3×7.45 hr) and 37.3 hr (5×7.45 hr). Given the desire to maintain dosing intervals that are easy to calculate and adhere to an initial dosing interval of 24 hours would seem most appropriate.

To calculate the tobramycin dose, we would use Equation 1.25 where C_{ss_1} would be our target peak concentration of 7 mg/L, V and K to be our estimates of 20 L and 0.093 hr^{-1} , respectively, and S and F would be 1. We would use 24 hours for τ and 1 hour for t_1 assuming we want our peak concentration of 7 mg/L, one hour after the start of the tobramycin infusion. Inserting the above values into Equation 1.25, we calculate a To-bramycin dose of 137 mg.

$$\begin{aligned} \text{Dose} &= \frac{(C_{ss_1})(V)(1 - e^{-KT})}{(S)(F)(e^{-Kt_1})} \\ &= \frac{(7 \text{ mg/L})(20 \text{ L})(1 - e^{-0.093 \text{ hr}^{-1} \times 24 \text{ hr}})}{(1)(1)(e^{-0.093 \text{ hr}^{-1} \times 1 \text{ hr}})} \\ &= \frac{(140 \text{ mg})(1 - 0.107)}{(1)(1)(0.911)} \\ &= 137 \text{ mg} \end{aligned}$$

The calculated dose would be rounded off to something like 135 or 140 mg given IV over 30 minutes every 24 hours. We would also want to calculate our trough concentration using Equation 1.9.

$$C = C^0 e^{-Kt}$$

where C^0 would be our steady-state peak concentration of 7 mg/L and t would be 23 hours. Note that because our steady-state peak concentration

of 7 mg/L is 1 hour after starting the infusion, the time remaining in the dosing interval to the trough is 23 and not the full dosing interval of 24 hours.

$$\begin{aligned} C &= C^0 e^{-kt} \\ &= 7 \text{ mg/L} \times e^{-0.093 \text{ hr}^{-1} \times 23 \text{ hr}} \\ &= 7 \text{ mg/L} \times 0.118 \\ &= 0.82 \text{ mg/L} \end{aligned}$$

Our calculated tobramycin regimen of approximately 140 mg IV every 24 hours is expected to result in a steady-state peak and trough concentration of approximately 7 and 0.8 mg/L, respectively.

With high-dose extended interval dosing, the dosing interval is approximately five half-lives in order to achieve a short drug-free interval which is thought to reduce accumulation within the renal cortex and inner ear. Therefore, the dosing interval should be every 48 hours ($5 \times 7.45 = 37.3$ hrs). Considering the *in vivo* post-antibiotic effect is reported to last up to 10 hours, this dosing interval would enable maximizing the peak concentration while reducing drug accumulation within the renal cortex and inner ear.

Once again we would calculate the tobramycin dose using Equation 1.25 where C_{ss1} would be our target peak concentration of 20 mg/L; V and K would be our estimates of 20 L and 0.093 hr⁻¹, respectively; and S and F would be 1. We would use 48 hours for τ and 1 hour for t_1 assuming we want our peak concentration of 20 mg/L, one hour after the start of the tobramycin infusion. Inserting the above values into Equation 1.25, we calculate a tobramycin dose of 434 mg which would be rounded off to a dose of 440 mg.

$$\begin{aligned} \text{Dose} &= \frac{(C_{ss1})(V)(1 - e^{-k\tau})}{(S)(F)(e^{-kt_1})} \\ &= \frac{(20 \text{ mg/L})(20 \text{ L})(1 - e^{-0.093(48 \text{ hr})})}{(1)(1)(e^{-0.093(1)})} \\ &= \frac{(400 \text{ mg})(1 - 0.0115)}{(1)(1)(0.911)} \\ &= 434 \text{ mg} \end{aligned}$$

We would also want to calculate the AUC_{24} to determine the risk for toxicity using Equation 1.26.

$$AUC_{24} = \frac{(\text{Dose in mg})(24 \text{ hr})/\tau \text{ in hr}}{\text{Cl in L/hr}}$$

Substituting K × V for clearance and 20 L for V:

$$\begin{aligned} &= \frac{(440 \text{ mg})(20 \text{ L})}{(0.093)(1.86 \text{ L/hr})} \\ &= \frac{220 \text{ mg}}{1.86 \text{ L/hr}} \\ &= 118 \text{ mg} \cdot \text{hr} \end{aligned}$$

This value of AUC_{24} exceeds our 100 mg · hr/L; therefore, the dose would be increased to 140 mg. Given the severity of O.L.'s infection, we may need to increase the dose to 85 to 100 mg · hr/L in order to maintain therapeutic levels. This can be determined by using a simple ratio of the new dose to the old dose to calculate a new dose.

$$\frac{AUC_{24} \text{ New}}{AUC_{24} \text{ Old}} = \frac{(\text{Dose New})}{(\text{Dose Old})}$$

$$\frac{85 \text{ mg} \cdot \text{hr/L}}{118 \text{ mg} \cdot \text{hr/L}} = \frac{(440 \text{ mg})}{(400 \text{ mg})}$$

or

$$\frac{100 \text{ mg} \cdot \text{hr/L}}{118 \text{ mg} \cdot \text{hr/L}} = \frac{(440 \text{ mg})}{(400 \text{ mg})}$$

The dose would be rounded off to 100 mg. Since the dose is significantly higher than the original dose, we should determine the new dose using Equation 1.16.

$$\begin{aligned} C_{ss1} &= \frac{(\text{S})(\text{F})(\text{Dose})}{V} \\ &= \frac{(1)(1)(320 \text{ mg})}{1 - e^{-0.093(48 \text{ hr})}} \\ &= \frac{16 \text{ mg/L}}{1 - 0.0115} \\ &= 14.7 \text{ mg/L} \end{aligned}$$

Similarly, the peak concentration at 48 hours can be calculated to be 17.5 mg/L.

Substituting $K \times V$ for clearance using the values of 0.093 hr^{-1} for K and 20 L for V :

$$\begin{aligned}&= \frac{(440 \text{ mg})(24 \text{ hr})/148 \text{ hr}}{(0.093 \text{ hr}^{-1})(20 \text{ L})} \\&= \frac{220 \text{ mg}}{1.86 \text{ L/hr}} \\&= 118 \text{ mg} \cdot \text{hr/L}\end{aligned}$$

This value of AUC_{24} exceeds our target range of approximately 70 to $100 \text{ mg} \times \text{hr/L}$; therefore, the dose would need to be reduced. Considering the severity of O.L.'s infection, we might consider targeting an AUC_{24} of 85 to $100 \text{ mg} \times \text{hr/L}$ in order to maximize the peak concentration. This can be determined by using a simple ratio of the AUCs multiplied by the old dose to calculate a new dose.

$$\frac{AUC_{24} \text{ New}}{AUC_{24} \text{ Old}} (\text{Dose Old}) = \text{New Dose} \quad [\text{Eq. 1.37}]$$

$$\frac{85 \text{ mg} \cdot \text{hr/L}}{118 \text{ mg} \cdot \text{hr/L}} (440 \text{ mg}) = 316 \text{ mg}$$

or

$$\frac{100 \text{ mg} \cdot \text{hr/L}}{118 \text{ mg} \cdot \text{hr/L}} (440 \text{ mg}) = 372 \text{ mg}$$

The dose would be rounded off to a dose of 320 mg or 380 mg every 48 hours. Since the dose is significantly different than the dose we calculated earlier, we should determine the estimated peak concentration with these new doses using Equation 1.16.

$$\begin{aligned}CSS_1 &= \frac{(S)(F)(\text{Dose})}{V} e^{-Kt_1} \\&= \frac{(1)(1)(320 \text{ mg})/20 \text{ L}}{1 - e^{-0.093(48 \text{ hr})}} e^{-0.093(1)} \\&= \frac{16 \text{ mg/L}}{1 - 0.0115} (0.91) \\&= 14.7 \text{ mg/L}\end{aligned}$$

Similarly, the peak concentration from a dose of 380 mg every 48 hours can be calculated to be 17.5 mg/L. Since the peak concentration

is directly proportional to the dose (as long as the interval is not changed), then we could also have estimated the peak concentrations based on a ratio of the dose and peak concentration already calculated. Therefore, a dose between 320 and 380 mg every 48 hours would provide a steady-state peak concentration of 14.7 to 17.5 mg/L and an AUC₂₄ of 85 to 100 mg × hr/L.

We would also want to confirm our estimates with measured concentration, usually obtained around the 3rd dose. Also as indicated in Part I: Dialysis of Drugs: Continuous Renal Replacement Therapy (CRRT), patients who are receiving CRRT are critically ill and the CRRT procedure is often interrupted or the CRRT flow rate changed depending on the condition of the patient. For that reason, the patient should be checked frequently (minimally each day) to ensure that CRRT is progressing as initially planned.

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