

## VANCOMYCIN

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Vancomycin is an antibiotic with a gram-positive spectrum of activity that is effective in the treatment of nafcillin- or methicillin-resistant *Staphylococcus aureus* (NRSA or MRSA). It is also an alternative to penicillin in patients who have a history of serious penicillin allergy.<sup>1-6</sup> Vancomycin is bactericidal for most gram-positive organisms, except against enterococci, and it is synergistic with gentamicin against most strains of *S. aureus* and enterococci.<sup>5,7</sup> It is not an effective agent for gram-negative bacteria. There has been a resurgence in the use of vancomycin because of the increased prevalence of MRSA.

Vancomycin is poorly absorbed orally and has been used to treat gastrointestinal overgrowths of gram-positive bacteria. When used to treat systemic infections, vancomycin must be given by the intravenous route or intraperitoneally for those patients receiving continuous ambulatory peritoneal dialysis (CAPD). The usual adult dose, in patients with normal renal function, is 1 g (10 to 15 mg/kg) administered intravenously over 60 minutes every 8 to 12 hours.<sup>4-6</sup> Although 2 g/day (20 to 30 mg/kg/day) of vancomycin had been recommended in the past, this dose can be excessive, particularly in the elderly and in patients with diminished renal function. Generally in these individuals, doses should be adjusted. Vancomycin is not administered intramuscularly because it is painful and causes local irritation and a histamine reaction.

### THERAPEUTIC AND TOXIC PLASMA CONCENTRATIONS

The ideal vancomycin dosing regimen is one that results in peak vancomycin plasma concentrations that are less than 40 to 50 mg/L and trough concentrations that are in the range of 5 to 20 mg/L.<sup>1,2,5,6,8-15</sup> Peak concentrations greater than 50 mg/L have been associated with ototoxicity; however, vancomycin-induced ototoxicity has been primarily reported in patients with vancomycin concentrations > 80 mg/L.<sup>1,3,16</sup>

Although the above concentrations are widely accepted, there is some debate about their validity and the necessity for routinely monitoring plasma vancomycin concentrations.<sup>17,18</sup> Vancomycin exhibits

**KEY PARAMETERS: Vancomycin**

Therapeutic Plasma Concentration <sup>a</sup>	< 40–50 mg/L
Peak	5–15 mg/L
Trough <sup>b</sup>	
F (oral)	< 5%
V <sup>c,d</sup>	$V(L) = 0.17 \text{ (Age in years)} + 0.22 \text{ (TBW in kg)} + 15$
Cl <sup>d</sup>	Equal to Cl <sub>Cr</sub>
t <sub>1/2</sub>	6–7 hr
f <sub>u</sub> <sup>e</sup> (fraction unbound in plasma)	0.45–0.7

<sup>a</sup>A peak concentration of approximately 30 mg/L is a reasonable target; however, to ensure efficacy, trough concentrations should be maintained at or above 5 mg/L.

<sup>b</sup>Trough concentrations as high as 15 to 20 mg/L have been suggested for patients with nosocomial infections or with systemic *S. aureus* infections with MICs  $\geq 2.0 \text{ mg/L}$ .

<sup>c</sup>The average volume of distribution for vancomycin is approximately 0.7 L/kg, and TBW represents total body weight including any excess adipose and/or third space fluid weight.

<sup>d</sup>For adult patients (older than 18 years of age).

<sup>e</sup>The fraction unbound in plasma may be as high as 0.8 to 0.9 in patients with end-stage renal disease.

concentration-independent killing, and specific peak plasma concentrations have not been correlated with efficacy. Another confounding issue is the fact that peak concentrations are often obtained at different times relative to the end of the infusion. Furthermore, the minimum inhibitory concentration (MIC) for sensitive bacteria is  $< 5 \text{ mg/L}$  and there is a limited postantibiotic effect of 0.5 to 3 hours,<sup>5,19</sup> making it difficult to establish exactly when and how long over the dosing interval plasma concentrations should exceed 5 mg/L. In 2006, the Clinical Laboratory Standards Institute reduced the vancomycin susceptibility break point from 4 to 2 mcg/mL for *S. aureus*.<sup>20</sup>

Certainly, the patients most likely to require vancomycin plasma concentration monitoring are those at highest risk for therapeutic failure or potential drug toxicity. These include pediatric patients because they have high clearances and short half-lives; consequently, their trough concentrations are frequently well below 5 mg/L. It also seems prudent to monitor plasma vancomycin concentrations in patients with poor renal function who are receiving empiric dosages because they are at greater risk of toxicity from vancomycin concentrations that significantly exceed those required for efficacy.

The MIC for most strains is therefore, trough concentrations above 15 mg/L. Some clinicians recommend concentrations above 10 mg/L for patients with endocarditis. At these concentrations, those with pneumonia and an MIC  $\geq 2.0 \text{ mg/L}$ , in some cases, it has been suggested to achieve trough concentrations  $\geq 400$ , where AUC<sub>24</sub> is  $\geq 1000 \text{ mg} \cdot \text{hr}/\text{L}$ .<sup>14,15,22,23</sup>

A relatively high incidence of adverse effects is associated with vancomycin. However, these reactions were due to impurities. Impurities are more pure.<sup>1</sup> Other adverse effects associated with vancomycin should be considered. During infusion, some patients develop an allergic reaction to single agent, vancomycin, which is dose-related. However, when administered in combination with other antibiotics, the incidence may be as high as 20% (vs 10% for vancomycin alone).<sup>24</sup> Patients with serum concentrations of 15 to 20 mg/L are targets for therapy.

With respect to pharmacokinetic parameters, methods have been developed to estimate plasma vancomycin concentrations. The kinetic parameters used are those that best describe the pharmacokinetics such that they are indicated.

**BIOAVAILABILITY**

Vancomycin is poorly absorbed ( $< 5\%$ ); as a result, pharmacokinetic parameters necessary for the treatment of *C. difficile*-produced diarrhea are not available. Oral vancomycin and *C. difficile*-produced diarrhea can be precipitated by oral metronidazole. However, metronidazole is expensive for a course of therapy.

The MIC for most strains of staphylococcus is less than 5 mg/L; therefore, trough concentrations should be maintained in the range of 5 to 15 mg/L. Some clinicians recommend maintaining plasma trough concentrations above 10 mg/L because there is evidence of increased efficacy in patients with endocarditis and there is no known increased risk of toxicity at these concentrations.<sup>8,10,11,21</sup> Patients with nosocomial infections, and those with pneumonia and other systemic infections with MRSA having an MIC  $\geq$  2.0 mg/L, are at greater risk of therapeutic failure. In these cases, it has been suggested that doses of vancomycin be tailored to achieve trough concentrations of 15 to 20 mg/L or an AUC<sub>24</sub>/MIC ratio of  $\geq$  400, where AUC<sub>24</sub> is expressed as mg  $\times$  hr/L and MIC is expressed as mg/L.<sup>14,15,22,23</sup>

A relatively high incidence of adverse effects was initially associated with vancomycin. However, it is believed that some of these adverse reactions were due to impurities in the original products; the current formulations are more pure.<sup>1</sup> Other major side effects associated with vancomycin therapy include phlebitis and a histamine reaction that presents as flushing, tachycardia, and hypotension. To minimize the histamine response, vancomycin should be infused slowly over 60 minutes. Even at this rate of infusion, some patients will experience flushing and tachycardia.<sup>24,25</sup> As a single agent, vancomycin is associated with a low incidence of nephrotoxicity; however, when it is combined with aminoglycoside antibiotics, the incidence may be as high as 30%.<sup>16</sup> Higher rates of nephrotoxicity (11% to 20%) have been observed when trough vancomycin concentrations of 15 to 20 mg/L are targeted, and more so (30% to 45%) when high-dose therapy is maintained for 2 weeks or longer.<sup>15,26,27</sup>

With respect to determining patient-specific dosages, a variety of methods have been developed and proposed to estimate the pharmacokinetic parameters.<sup>28–30</sup> While most of the methods yield reasonable estimates of plasma vancomycin concentrations from a given dosage, the parameters used are based on population averages with sufficient variability such that therapeutic drug monitoring is still necessary when indicated.

## BIOAVAILABILITY (F)

Vancomycin is poorly absorbed following oral administration (i.e., < 5%); as a result, parenteral or intraperitoneal administration is necessary for the treatment of systemic infections. Vancomycin's limited oral bioavailability has been used advantageously to treat enterocolitis.<sup>1,4–6</sup> Oral vancomycin and metronidazole are commonly used to treat *Clostridium difficile*-produced pseudomembranous colitis, a clinical condition that can be precipitated by the use of broad-spectrum antibiotics. However, metronidazole is usually recommended as the drug of choice in the treatment of *C. difficile* as it appears to be as effective and is much less expensive for a course of treatment.

## VOLUME OF DISTRIBUTION (V)

The volume of distribution for vancomycin ranges between 0.5 and 1 L/kg.<sup>28,31,32</sup> In clinical practice, an average value of 0.7 L/kg is often used; however, age and gender may also influence the distribution of vancomycin.<sup>28,32</sup> The following method of estimating V for vancomycin in adults (i.e., those older than 18 years of age) incorporates both total body weight (TBW) and patient age:<sup>28</sup>

$$V(L) = 0.17(\text{age in years}) + 0.22(\text{TBW in kg}) + 15 \quad [\text{Eq. 13.1}]$$

A two- or three-compartment model best describes the distribution of vancomycin. The complexity of this model can be problematic when peak plasma samples are obtained during the distribution phase. In clinical practice, a one-compartment model is frequently used.<sup>13,28,33</sup>

Vancomycin has moderate plasma protein binding. The percentage unbound in plasma is approximately 60%, with a reported range of 45% to 70%.<sup>31,34–36</sup> Data in patients with end-stage renal disease suggest that the fraction unbound (fu) in plasma may be as high as 0.8 to 0.9.<sup>37,38</sup>

## CLEARANCE (Cl)

Vancomycin is eliminated primarily by the renal route; approximately 5% of the dose is metabolized.<sup>31,39</sup> The clearance of vancomycin approximates that of creatinine clearance:<sup>28,32,33</sup>

$$Cl_{Cr} \text{ for males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(SCr_{ss})} \quad [\text{Eq. 13.2}]$$

$$Cl_{Cr} \text{ for females (mL/min)} = (0.85) \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(SCr_{ss})} \quad [\text{Eq. 13.3}]$$

$$\text{Vancomycin Cl} \approx Cl_{Cr} \quad [\text{Eq. 13.4}]$$

For issues that should be considered when estimating creatinine clearance (e.g., whether SCr should be normalized to 1.0 mg/dL), see Part I: Creatinine Clearance.

Very little vancomycin is cleared by standard hemodialysis or peritoneal dialysis.<sup>10,40,41</sup> In patients undergoing CAPD, the small but continuous drug loss due to peritoneal dialysis exchanges is significant. The usual approach is to replace vancomycin with intermittent intravenous injections on a somewhat more frequent basis than is usually done for patients with end-stage renal disease (in some cases as often as every 3 to 5 days), or to instill vancomycin directly into the peritoneal space to treat

peritonitis and achieve systemic concentrations. Caution should be used in evaluating vancomycin removal with end-stage renal disease. Some immunoassays overestimate actual vancomycin removal because of cross-react with the assay.<sup>44,45</sup> In peritoneal dialysis, a significant amount of vancomycin is removed during the dialysis process, but not recognize that a redistribution of vancomycin occurs during dialysis.<sup>46,47</sup> Due to wide interindividual differences in plasma vancomycin concentrations, individualized dosing requirements are often required.

## HALF-LIFE (t½)

The usual serum half-life of vancomycin is 1.5 to 2 hours. Patients with end-stage renal disease have a longer half-life (2 to 4 hours). This wide range in the serum half-life is likely related to the dose and dosing intervals used. Vancomycin clearance with end-stage renal disease may be reduced to 10% to 20% of normal.

## NOMOGRAMS

Dosing nomograms for vancomycin provide a quick and easy understanding of the desired therapeutic doses and dosing intervals which are based on pharmacokinetic parameters of vancomycin. For example, using pharmacokinetic nomograms, vancomycin concentrations above the minimum inhibitory concentration are advantageous when treating infections caused by sensitive bacteria.

## TIME TO SAMPLE

Wide fluctuations in vancomycin concentrations during a normal dosing interval suggest that the drug levels should be monitored. In general, trough concentrations appear to be adequate in most patients. Vancomycin is dosed with an interval of approximately 12 hours. The average volume of distribution, peak concentration, and reasonable accuracy based on the time to sample are especially true in patients with end-stage renal disease.

peritonitis and achieve systemic concentrations of vancomycin.<sup>42,43</sup> Some caution should be used in evaluating plasma concentrations in patients with end-stage renal disease. Some immunoassays that use polyclonal antibodies overestimate actual vancomycin concentrations due to an accumulation of pseudometabolites (crystalline degradation products) that cross-react with the assay.<sup>44,45</sup> In patients undergoing high-flux or high-efficiency hemodialysis, a significant amount of vancomycin can be removed. Early studies estimated that as much as 30% of vancomycin was removed during high-flux hemodialysis; recent reports indicate only 17% of vancomycin is removed during these procedures. Early investigators did not recognize that a redistribution of vancomycin occurs after the completion of dialysis.<sup>46,47</sup> Due to wide interpatient variability, monitoring plasma vancomycin concentrations to determine individual dosing requirements is often required.

### HALF-LIFE ( $t_{1/2}$ )

The usual serum half-life of vancomycin is 5 to 10 hours; in patients with end-stage renal disease the half-life may approach 7 days.<sup>10,28,31,38</sup> This wide range in the serum half-life partially explains the variability in the dose and dosing intervals used for vancomycin. Patients with normal renal function may receive the drug every 8 to 12 hours, whereas those with end-stage renal disease may receive a dose once a week.<sup>10,40</sup>

### NOMOGRAMS

Dosing nomograms for vancomycin are available.<sup>10,48</sup> However, an understanding of the desired therapeutic range and the pharmacokinetic parameters of vancomycin provides the clinician more flexibility to tailor doses and dosing intervals which meet the specific needs of the patient. For example, using pharmacokinetic parameters allows targeting plasma vancomycin concentrations above a specific MIC, which is particularly advantageous when treating infections with vancomycin-intermediate-sensitive bacteria.

### TIME TO SAMPLE

Wide fluctuations in vancomycin plasma concentrations within a normal dosing interval suggest that both peak and trough concentrations should be monitored. In general, however, steady-state trough concentrations appear to be adequate in most cases. As a general rule, vancomycin is dosed with an interval of approximately one half-life. Assuming an average volume of distribution, peak concentrations can be estimated with reasonable accuracy based on the dose administered, an estimate of the volume of distribution, and a measured trough concentration. This is especially true in patients with diminished renal function and a long

vancomycin half-life. Although the bulk of the literature suggests that both peak and trough concentrations are appropriate, the concept of using only trough concentrations is supported by both the pharmacokinetic and clinical characteristics of the drug.<sup>18,49,50</sup> However, for patients in whom the pharmacokinetic parameters may be difficult to estimate with confidence (e.g., very overweight or underweight patients), monitoring both peak and trough concentrations is advisable, particularly for seriously ill patients.

If the highest expected peak concentration is below 40 to 50 mg/L for a dose that produces a trough concentration of 5 to 20 mg/L, the dose is acceptable. If the trough concentration is known, the peak concentration ( $C_{ss\ max}$ ) can be approximated using Equation 13.5.

$$C_{ss\ max} = [C_{ss\ min}] + \left[ \frac{(S)(F)(Dose)}{V} \right] \quad [\text{Eq. 13.5}]$$

The  $\frac{(S)(F)(Dose)}{V}$  represents the change in concentration ( $\Delta C$ ) following a dose.

As described in Part I, the use of the above equation requires that several conditions be met. They are as follows:

1. Steady state has been achieved.
2. The measured plasma concentration is a trough concentration.
3. The bolus dose is an acceptable model.

In the clinical setting, trough concentrations are often obtained slightly before the true trough. Because vancomycin has a relatively long half-life, most plasma concentrations obtained within 1 hour of the true trough can be assumed to have met condition 2 above.

Since vancomycin follows a multicompartmental model, it is difficult to avoid the distribution phase when obtaining peak plasma concentrations.<sup>51</sup> If peak levels are to be measured, samples should be obtained at least 1 or possibly 2 hours after the end of the infusion period. It is difficult to evaluate the appropriateness of a dosing regimen that is based on plasma samples obtained before steady state. Additional plasma concentrations are required to more accurately estimate a patient's apparent clearance and half-life, and to ensure that any dosing adjustments based on a non-steady-state trough concentration actually achieve the targeted steady-state concentrations.

**QUESTION #1.** B.C., a 65-year-old, 45-kg man with a serum creatinine concentration of 2.2 mg/dL, is being treated for a presumed hospital-acquired, MRSA infection. Design a dosing regimen that will produce peak concentrations less than 40 to 50 mg/L and trough concentrations of 5 to 15 mg/L.

The first step in calculating an to estimate his pharmacokinetic p clearance, elimination rate constant

The volume of distribution fo tion 13.1 (see Key Parameters, this shown below, B.C.'s expected volu

$$V(L) = 0.17(65 \text{ yrs}) +$$

Using Equations 13.2 and 13 comycin clearance are estimated shown:

$$Cl_{cr} \text{ for males (mL/min)}$$

Using Equation 13.4, the com B.C. is 1.28 L/hr.

$$\text{Vancomycin } Cl \approx Cl_{cr}$$

$$= 21$$

$$= 21$$

$$= 1.2$$

The calculated vancomycin cl distribution of 36.0 L then can be constant of  $0.036 \text{ hr}^{-1}$ .

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

$$= 1.2$$

$$= 1.2$$

The first step in calculating an appropriate dosing regimen for B.C. is to estimate his pharmacokinetic parameters (i.e., volume of distribution, clearance, elimination rate constant, and half-life).

The volume of distribution for B.C. can be calculated by using Equation 13.1 (see Key Parameters, this chapter). According to the calculations shown below, B.C.'s expected volume of distribution would be 36.0 L.

$$V(L) = 0.17(65 \text{ yrs}) + 0.22(45 \text{ kg}) + 15 = 36.0 \text{ L}$$

Using Equations 13.2 and 13.4, B.C.'s creatinine clearance and vancomycin clearance are estimated to be approximately 21.3 mL/min, as shown:

$$\begin{aligned} Cl_{Cr} \text{ for males (mL/min)} &= \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(Scr_{ss})} \\ &= \frac{(140 - 65 \text{ yrs})(45 \text{ kg})}{(72)(2.2 \text{ mg/dL})} \\ &= 21.3 \text{ mL/min} \end{aligned}$$

Using Equation 13.4, the corresponding vancomycin clearance for B.C. is 1.28 L/hr.

$$\begin{aligned} \text{Vancomycin Cl} &\approx Cl_{Cr} \\ &= 21.3 \text{ mL/min} \end{aligned}$$

or

$$\begin{aligned} &= 21.3 \text{ mL/min} \times \frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \\ &= 1.28 \text{ L/hr} \end{aligned}$$

The calculated vancomycin clearance of 1.28 L/hr and the volume of distribution of 36.0 L then can be used to estimate the elimination rate constant of  $0.036 \text{ hr}^{-1}$ .

$$\begin{aligned} K &= \frac{Cl}{V} && [\text{Eq. 13.6}] \\ &= \frac{1.28 \text{ L/hr}}{36 \text{ L}} \\ &= 0.036 \text{ hr}^{-1} \end{aligned}$$

and the corresponding vancomycin half-life can be calculated using Equation 13.7.

$$\begin{aligned} t_{1/2} &= \frac{(0.693)(V)}{Cl} & [\text{Eq. 13.7}] \\ &= \frac{(0.693)(36.0 \text{ L})}{1.28 \text{ L/hr}} \\ &= 19.5 \text{ hr} \end{aligned}$$

In clinical practice, loading doses of vancomycin are seldom administered. This is probably because most clinicians prescribe about 15 mg/kg as their maintenance dose. Using Equation 13.8, our patient's weight, and the volume of distribution of 36 L that we calculated above, and substituting the usual maintenance dose as mg/kg for the dose, it can be seen that the initial plasma concentration should be approximately 20 mg/L.

$$\begin{aligned} C^0 &= \frac{(S)(F)(\text{Loading Dose})}{V} & [\text{Eq. 13.8}] \\ C^0 &= \frac{(1)(1)(15 \text{ mg/kg} \times 45 \text{ kg})}{36 \text{ L}} \\ &= 18.8 \text{ mg/L} \approx 20 \text{ mg/L} \end{aligned}$$

Although this value is below the usual targeted peak concentration of about 30 mg/L, it is well above that needed for efficacy (5 to 15 mg/L). If one wanted to calculate an initial dose, Equation 13.9 and the assumed volume of distribution of 36.0 L could be used. The salt form and bioavailability are assumed to be 1.0 when vancomycin is administered intravenously. Using an initial target of 30 mg/L, the loading dose would be approximately 1,000 mg.

$$\begin{aligned} \text{Loading Dose} &= \frac{(V)(C)}{(S)(F)} & [\text{Eq. 13.9}] \\ &= \frac{(36.0 \text{ L})(30 \text{ mg/L})}{(1)(1)} \\ &= 1080 \text{ mg or } \approx 1000 \text{ mg} \end{aligned}$$

There are no known renal or ototoxicities associated with elevated vancomycin levels that occur during the distribution phase. However, to

minimize the cardiovascular effects of the drug, it is recommended that the initial and subsequent doses be given over a period of at least 60 minutes. In addition, if peak concentrations are to be avoided, samples should be drawn at least 1 to 2 half-lives after the end of the infusion period to avoid the distribution phase.

The maintenance dose can be calculated using Equation 13.10. One approach might be to first determine the desired average infusion rate required to maintain the desired average concentration. This can be done by dividing the desired average concentration by the half-life. The infusion rate can then be multiplied by an adjustment factor to account for the time between the desired peak concentration and the actual peak concentration. For example, if the desired average concentration is 20 mg/L and the half-life is 19.5 hours, the infusion rate would be approximately 1.05 mg/kg/min. This can then be multiplied by the patient's weight to get the maintenance dose.

Maintenance Dose =

Although a number of dosing intervals have been proposed, the most reasonable because it is a convenient and safe approach. A half-life of 19.5 hours is considered to be reasonable for vancomycin. A half-life of 19.5 hours should result in a peak concentration of approximately 30 mg/L and a trough concentration of approximately 15 mg/L. The range of concentrations is approximately 15 to 30 mg/L. If an interval of 24 hours is used, the dose would be approximately 600 mg.

Maintenance Dose =

This method assumes that the drug's half-life is constant between the peak and trough concentrations. As long as the dosing interval is less than twice the drug's half-life, the dose will be correct as long as the dosing interval is less than twice the drug's half-life. When dosing intervals are greater than twice the drug's half-life, the dose will be incorrect. The true average concentration is much lower than the peak and trough levels.

A second approach that can be used to calculate the maintenance dose is to select a desired peak concentration and a desired trough concentration. The dose can then be calculated using the following equation:

minimize the cardiovascular effects associated with rapid administration, the initial and subsequent doses should be administered over approximately 60 minutes. In addition, if peak concentrations are measured, samples should be drawn at least 1 to 2 hours after completion of the infusion period to avoid the distribution phase.

The maintenance dose can be calculated by a number of methods. One approach might be to first approximate the hourly infusion rate required to maintain the desired average concentration. Then, the hourly infusion rate can be multiplied by an appropriate dosing interval to calculate a reasonable dose to be given on an intermittent basis. For example, if an average concentration of 20 mg/L is selected (approximately halfway between the desired peak concentration of  $\approx$  30 mg/L and trough concentration of  $\approx$  10 mg/L), the hourly administration rate would be 25.6 mg/hr (Equation 13.10).

$$\text{Maintenance Dose} = \frac{(Cl)(C_{ss\ ave})(\tau)}{(S)(F)} \quad [\text{Eq. 13.10}]$$

$$= \frac{(1.28 \text{ L/hr})(20 \text{ mg/L})(1 \text{ hr})}{(1)(1)}$$

$$= 25.6 \text{ mg/hr}$$

Although a number of dosing intervals could be selected, 24 hours is reasonable because it is a convenient interval and approximates B.C.'s half-life for vancomycin of 19.5 hours. A dosing interval of approximately 1 half-life should result in peak concentrations that are below 40 to 50 mg/L and trough concentrations that are within the 5 to 15 mg/L range, in this case. If an interval of 24 hours is selected, the dose would be approximately 600 mg.

$$\text{Maintenance Dose} = \frac{(1.28 \text{ L/hr})(20 \text{ mg/L})(24 \text{ hr})}{(1)(1)}$$

$$= 614 \text{ or } \approx 600 \text{ mg}$$

This method assumes that the average concentration is halfway between the peak and trough. As mentioned in Part I, this is approximately correct as long as the dosing interval is less than or approximately equal to the drug's half-life. When dosing intervals greatly exceed the half-life, the true average concentration is much lower than halfway between the peak and trough levels.

A second approach that can be used to calculate the maintenance dose is to select a desired peak and trough concentration that is

consistent with the therapeutic range and B.C.'s vancomycin half-life. For example, if steady-state peak concentrations of 30 mg/L are desired, it would take approximately two half-lives for that peak level to fall to 7.5 mg/L (a level of 30 mg/L declines to 15 mg/L in one half-life and to 7.5 mg/L in the second half-life). Since the vancomycin half-life in B.C. is approximately 1 day, the dosing interval would be 48 hours. The dose to be administered every 48 hours can be calculated using Equation 13.11.

$$\text{Dose} = \frac{(V)(\text{Css max} - \text{Css min})}{(S)(F)} \quad [\text{Eq. 13.11}]$$

$$= \frac{(36.0 \text{ L})(30 \text{ mg/L} - 7.5 \text{ mg/L})}{(1)(1)}$$

$$= 810 \text{ mg or } \approx 800 \text{ mg}$$

The peak and trough concentrations that are expected using this dosing regimen can be calculated by using Equations 13.12 and 13.14, respectively.

$$\text{Css max} = \frac{(S)(F)(\text{Dose})}{V} \quad [\text{Eq. 13.12}]$$

$$= \frac{1}{1 - e^{-KT}}$$

$$= \frac{(1)(1)(800 \text{ mg})}{36.0 \text{ L}}$$

$$= \frac{1}{1 - e^{-(0.036 \text{ hr}^{-1})(48 \text{ hr})}}$$

$$= 27.0 \text{ mg/L}$$

Note that although 27 mg/L is an acceptable peak, the actual clinical peak would normally be obtained approximately 1 hour after the end of a 1-hour infusion, or 2 hours after this calculated peak concentration, and would be about 25 mg/L, as calculated by Equation 13.13.

$$C_2 = C_1(e^{-Kt}) \quad [\text{Eq. 13.13}]$$

$$= 27.0 \text{ mg/L } (e^{-(0.036 \text{ hr}^{-1})(2 \text{ hr})})$$

$$= 27.0 \text{ mg/L } (0.93)$$

$$= 25.1 \text{ mg/L}$$

The calculated trough concentrations are 13.14 and 13.15.

$$\text{Css min} = \frac{(S)(F)(\text{Dose})}{V}$$

$$= (27 \text{ mg})$$

$$= (27 \text{ mg})$$

$$= 4.8 \text{ mg}$$

This process of checking the calculations is most appropriate when the value has been changed from a calculated value (e.g., 8, 12, 18, 24, 36, or 48 hours) to a different value (e.g., 12, 18, 24, 36, or 48 hours) when the next dose is to be given due to errors. If different plasma vancomycin concentrations 13.12 and 13.14 can be used to calculate trough concentrations by adjusting the dose and/or dosage regimen of 1,000 mg every 36 hours, peak and trough concentrations of 30.6 mg/L and a trough concentration of 30.6 mg/L and a trough state.

A third alternative is to rearrange

$$\text{Css min} = \frac{(S)(F)(\text{Dose})}{V}$$

such that the dose can be calculated

$$\text{Dose} = \frac{(\text{Css min})(V)}{(S)(F)}$$

Note that it is the Css min or Css max that is used to solve for dose. This is because it is the

The calculated trough concentration would be about 5 mg/L (Equations 13.14 and 13.15).

$$C_{ss\ min} = \frac{(S)(F)(Dose)}{V} \frac{1}{1 - e^{-kT}} [Eq. 13.14]$$

$$C_{ss\ min} = (C_{ss\ max})(e^{-kT}) [Eq. 13.15]$$

$$\begin{aligned} &= (27 \text{ mg/L})(e^{(-0.036 \text{ hr}^{-1})(48 \text{ hr})}) \\ &= (27 \text{ mg/L})(0.178) \\ &= 4.8 \text{ mg/L} \end{aligned}$$

This process of checking the expected peak and trough concentrations is most appropriate when the dose or the dosing interval has been changed from a calculated value (e.g., twice the half-life) to a practical value (e.g., 8, 12, 18, 24, 36, or 48 hours). Many institutions generally prefer not to use dosing intervals of 18 or 36 hours because the time of day when the next dose is to be given changes, potentially resulting in dosing errors. If different plasma vancomycin concentrations are desired, Equations 13.12 and 13.14 can be used to target specific vancomycin concentrations by adjusting the dose and/or the dosing interval. For example, a dosage regimen of 1,000 mg every 48 hours would result in calculated peak and trough concentrations of 33.8 and 6.0 mg/L, respectively. Alternatively, 800 mg every 36 hours would result in an expected peak concentration of 30.6 mg/L and a trough concentration of 8.4 mg/L, at steady state.

A third alternative is to rearrange Equation 13.14:

$$C_{ss\ min} = \frac{(S)(F)(Dose)}{V} \frac{1}{1 - e^{-kT}} [Eq. 13.14]$$

such that the dose can be calculated.

$$Dose = \frac{(C_{ss\ min})(V)(1 - e^{-kT})}{(S)(F)(e^{-kT})} [Eq. 13.16]$$

Note that it is the  $C_{ss\ min}$  or trough concentration that is used to solve for dose. This is because it is the trough concentration that has been

associated with efficacy and therefore is the primary target for dosing. Making the appropriate substitutions for the parameters indicated in Equation 13.16 and choosing a target trough concentration of 10 mg/L and a dosing interval of 24 hours, a dose of approximately 500 mg is calculated.

$$\text{Dose} = \frac{(10 \text{ mg/L})(36.0 \text{ L})(1 - e^{-(0.036 \text{ hr}^{-1})(24 \text{ hr})})}{(1)(1)(e^{-(0.036 \text{ hr}^{-1})(24 \text{ hr})})}$$

$$= \frac{(10 \text{ mg/L})(36.0 \text{ L})(1 - 0.42)}{(1)(1)(0.42)}$$

$$= 497 \text{ mg} \approx 500 \text{ mg}$$

Alternatively, doses could have been calculated for dosing intervals of 36 or 48 hours if those intervals were deemed to be appropriate.

**QUESTION #2.** E.K., a 60-year-old, 50-kg woman with a serum creatinine of 1.0 mg/dL, has been empirically started on 500 mg of vancomycin every 8 hours for treatment of a hospital-acquired staphylococcal infection. What are the expected peak and trough vancomycin concentrations for E.K.?

To calculate the peak and trough concentrations, E.K.'s volume of distribution, clearance, and elimination rate constant (or half-life) need to be estimated. Using Equation 13.1, the expected volume of distribution for E.K. is 36.2 L.

$$V(L) = 0.17(60 \text{ yrs}) + 0.22(50 \text{ kg}) + 15 = 36.2 \text{ L}$$

E.K.'s creatinine clearance can be calculated using Equation 13.3, and Equation 13.4 can be used to calculate her vancomycin clearance of 2.83 L/hr, as shown below.

$$\text{Cl}_{\text{Cr}} \text{ for females (mL/min)} = (0.85) \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCr}_{\text{ss}})}$$

$$= (0.85) \frac{(140 - 60 \text{ yrs})(50 \text{ kg})}{(72)(1.0 \text{ mg/dL})}$$

$$= 47.2 \text{ mL/min}$$

Using Equation 13.4 to calculate

$$\text{Vancomycin Cl} \approx \text{Cl}_{\text{Cr}}$$

$$\text{Vancomycin Cl} = 47.2$$

$$= 47.2$$

$$= 2.83$$

Equation 13.6 can now be used with the clearance constant and Equation 13.7 to calculate

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

$$= \frac{2.83}{36.2}$$

$$= 0.0779$$

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

$$= \frac{0.693}{0.0779}$$

$$= 8.9 \text{ h}$$

Equations 13.12 and 13.15 can now be used to calculate the peak and trough concentrations for E.K.

$$\text{Css max} =$$

$$= 11$$

$$= 29.8$$

Using Equation 13.4 to calculate vancomycin clearance:

$$\text{Vancomycin Cl} \approx \text{Cl}_{\text{Cr}}$$

$$\text{Vancomycin Cl} = 47.2 \text{ mL/min}$$

or

$$= (47.2 \text{ mL/min}) \left( \frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \right)$$

$$= 2.83 \text{ L/hr}$$

Equation 13.6 can now be used to calculate E.K.'s elimination rate constant and Equation 13.7 to calculate the corresponding half-life.

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

$$= \frac{2.83 \text{ L/hr}}{36.2 \text{ L}}$$

$$= 0.078 \text{ hr}^{-1}$$

$$t_{1/2} = \frac{(0.693)(V)}{\text{Cl}}$$

$$= \frac{(0.693)(36.2 \text{ L})}{2.83 \text{ L/hr}}$$

$$= 8.9 \text{ hr}$$

Equations 13.12 and 13.15 can be used to calculate the expected peak and trough concentrations for E.K.

$$C_{\text{ss max}} = \frac{(S)(F)(\text{Dose})}{V} \cdot \frac{1}{1 - e^{-KT}}$$

$$= \frac{(1)(1)(500 \text{ mg})}{36.2 \text{ L}} \cdot \frac{1}{1 - e^{-(0.078 \text{ hr}^{-1})(8 \text{ hr})}}$$

$$= 29.8 \text{ mg/L}$$

To calculate the clinical peak concentration, which is usually sampled 2 hours after the start of a vancomycin infusion (1 hour after the end of a 1-hour infusion), the  $C_{ss\ max}$  could be decayed for 2 hours using Equation 13.13.

$$\begin{aligned} C_2 &= C_1(e^{-kt}) \\ &= 29.8 \text{ mg/L } (e^{-(0.078 \text{ hr}^{-1})(2 \text{ hr})}) \\ &= 29.8 \text{ mg/L } (0.86) \\ &= 25.6 \text{ mg/L } (2 \text{ hours after starting infusion}) \end{aligned}$$

$C_{ss\ min}$  can be calculated using Equation 13.15 and the dosing interval of 8 hours.

$$\begin{aligned} C_{ss\ min} &= (C_{ss\ max})(e^{-kT}) \\ &= (29.8 \text{ mg/L})(e^{(-0.078 \text{ hr}^{-1})(8 \text{ hr})}) \\ &= (29.8 \text{ mg/L})(0.536) \\ &= 16.0 \text{ mg/L} \end{aligned}$$

Although the expected peak concentration of  $\approx 30 \text{ mg/L}$  is not above the usually accepted range for peak concentrations, the trough concentration of  $16 \text{ mg/L}$  is slightly above the usual targeted range of  $5$  to  $15 \text{ mg/L}$ , which is required for efficacy. This suggests that decreasing the dose and/or increasing the dosing interval, as well as monitoring plasma concentrations of vancomycin, would be appropriate.

**QUESTION #3.** A culture obtained demonstrated that the infection is from MRSA with an MIC of  $1.0 \text{ mg/L}$ . A steady-state trough concentration of  $35 \text{ mg/L}$  was obtained for E.K. Design a dosing regimen that will produce lower therapeutic vancomycin concentrations and an  $AUC_{24}/MIC \geq 400$  for E.K.

To design such a regimen, E.K.'s pharmacokinetic parameters should first be revised so that they are consistent with the observed trough concentration of  $35 \text{ mg/L}$ . Some assumptions will have to be made. Because the measured trough concentration is much higher than predicted, her half-life is much longer than the estimate of 8.9 hours. For E.K., the percentage fluctuation between peak and trough concentrations should be relatively small at steady state because her dosing interval of 8 hours is much shorter than her apparent half-life. Therefore, the best approach is to use the literature estimate for volume of distribution and then

calculate the corresponding elimination values.

If E.K.'s volume of distribution above using Equation 13.1) and  $35 \text{ mg/L}$  is used, a peak concentration calculated by using Equation 13.5, is

$$C_{ss\ max} = [C_{ss\ min}] e^{kt}$$

$$C_{ss\ max} = [35 \text{ mg/L}] e^{(0.078 \text{ hr}^{-1})(8 \text{ hr})}$$

$$\approx 49 \text{ mg/L}$$

Using the observed trough concentration of  $35 \text{ mg/L}$  and the predicted peak concentration of  $49 \text{ mg/L}$ , the apparent elimination rate constant  $k$  can be calculated using Equation 13.1. If the target trough concentration of  $49 \text{ mg/L}$ ,  $C_2$  is the trough concentration between those two concentrations, and  $T$  is the dosing interval of 8 hours.

This apparent elimination rate constant is approximately  $0.078 \text{ hr}^{-1}$ , or a half-life of approximately 8.9 hours, which is much longer than the target value below.

calculate the corresponding elimination rate constant and clearance values.

If E.K.'s volume of distribution is assumed to be 36.2 L (see calculation above using Equation 13.1) and the observed trough concentration of 35 mg/L is used, a peak concentration of approximately 49 mg/L can be calculated by using Equation 13.5, as follows:

$$C_{ss\ max} = [C_{ss\ min}] + \left[ \frac{(S)(F)(Dose)}{V} \right]$$

$$C_{ss\ max} = [35\ mg/L] + \left[ \frac{(1)(1)(500\ mg)}{36.2\ L} \right]$$

$$\approx 49\ mg/L$$

Using the observed trough concentration of 35 mg/L and the predicted peak concentration of 49 mg/L, an elimination rate constant ( $K$ ) can be calculated using Equation 13.17, where  $C_1$  is the peak concentration of 49 mg/L,  $C_2$  is the trough concentration of 35 mg/L, and the interval between those two concentrations,  $t$ , is the dosing interval of 8 hours.

$$K = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t} \quad [\text{Eq. 13.17}]$$

$$= \frac{\ln\left(\frac{49\ mg/L}{35\ mg/L}\right)}{8\ hr}$$

$$= 0.042\ hr^{-1}$$

This apparent elimination rate constant of  $0.042\ hr^{-1}$  corresponds to a half-life of approximately 16.5 hours (Equation 13.18) as shown below.

$$t_{1/2} = \frac{0.693}{K} \quad [\text{Eq. 13.18}]$$

$$= \frac{0.693}{0.042\ hr^{-1}}$$

$$= 16.5\ hr$$

The apparent elimination rate constant of  $0.042 \text{ hr}^{-1}$  and the assumed volume of distribution of 36.2 L can be used in Equation 13.19 to calculate E.K.'s vancomycin clearance.

$$Cl = (K)(V) \quad [\text{Eq. 13.19}]$$

$$\begin{aligned} &= (0.042 \text{ hr}^{-1})(36.2 \text{ L}) \\ &= 1.52 \text{ L/hr} \end{aligned}$$

Because the revised  $t_{1/2}$  is  $\geq \tau$ , we expect  $C_{ss \text{ ave}}$  to be halfway between  $C_{ss \text{ max}}$  and  $C_{ss \text{ min}}$ . Therefore, clearance could have been approximated by assuming  $C_{ss \text{ ave}}$  is approximately equal to:

$$C_{ss \text{ ave}} = C_{ss \text{ min}} + \left( \frac{1}{2} \right) \frac{(S)(F)(\text{Dose})}{V} \quad [\text{Eq. 13.20}]$$

and then calculating clearance by using Equation 13.21:

$$Cl = \frac{(S)(F)(\text{Dose}/\tau)}{C_{ss \text{ ave}}} \quad [\text{Eq. 13.21}]$$

(See Part I: Interpretation of Plasma Drug Concentrations: Choosing a Model to Revise or Estimate a Patient's Clearance at Steady State.)

The maintenance dose can then be calculated by using Equation 13.16. Because the apparent half-life is approximately 16 hours, the most logical dosing interval and  $C_{ss \text{ min}}$  would be 24 hours and 10 to 15 mg/L, respectively.

$$\begin{aligned} \text{Dose} &= \frac{(C_{ss \text{ min}})(V)(1 - e^{-KT})}{(S)(F)(e^{-KT})} \\ \text{Dose} &= \frac{(10 \text{ mg/L})(36.2 \text{ L})(1 - e^{-(0.042 \text{ hr}^{-1})(24 \text{ hr})})}{(1)(1)(e^{-(0.042 \text{ hr}^{-1})(24 \text{ hr})})} \\ &= 630 \text{ mg} \end{aligned}$$

We can round the dose to 750 mg every 24 hours, which should result in a steady-state peak concentration of approximately 33 mg/L by

using Equation 13.12.

$$C_{ss \text{ max}} = \underline{\hspace{1cm}}$$

$$= \underline{\hspace{1cm}}$$

$$= 32.6$$

A trough concentration of  $C_{ss \text{ min}}$  can be calculated by using Equation 13.15.

$$\begin{aligned} C_{ss \text{ min}} &= (C_{ss \text{ max}}) e^{-KT} \\ &= (32.6 \text{ mg/L}) e^{-(0.042 \text{ hr}^{-1})(24 \text{ hr})} \\ &= (32.6 \text{ mg/L}) e^{-0.9768} \\ &= 11.9 \approx 12 \text{ mg/L} \end{aligned}$$

The target trough concentration is 12 mg/L, which is within the usual therapeutic range (5 to 15 mg/L).

The  $AUC_{24}/MIC$  for this case is approximately 4.5, which is within the target range of 3 to 5.

$$AUC_{24}/MIC = \underline{\hspace{1cm}}$$

$$= \underline{\hspace{1cm}}$$

Hence, the dose of 750 mg every 24 hours will result in vancomycin concentrations within the therapeutic range. This dose yields a desirable  $AUC_{24}/MIC > 4$ .

**QUESTION #4.** A.C., a 50-year-old man with chronic kidney disease and a serum creatinine of 2.5 mg/dL, is on intermittent hemodialysis treatment. He has an apparent shunt infection and requires vancomycin. Calculate an appropriate dose.

using Equation 13.12.

$$\text{Css max} = \frac{(S)(F)(\text{Dose})}{V} \cdot \frac{1}{1 - e^{-kT}}$$

$$= \frac{(1)(1)(750 \text{ mg})}{36.2 \text{ L}} \cdot \frac{1}{1 - e^{-(0.042 \text{ hr}^{-1})(24 \text{ hr})}}$$

$$= 32.6 \approx 33 \text{ mg/L}$$

A trough concentration of approximately 12 mg/L can be calculated by using Equation 13.15.

$$\text{Css min} = (\text{Css max})(e^{-kT})$$

$$= (32.6 \text{ mg/L})(e^{(-0.042 \text{ hr}^{-1})(24 \text{ hr})})$$

$$= (32.6 \text{ mg/L})(0.365)$$

$$= 11.9 \approx 12 \text{ mg/L}$$

The target trough concentration of approximately 12 mg/L is within the usual therapeutic range (5 to 15 mg/L).

The AUC<sub>24</sub>/MIC for this case can be determined by employing Equation 13.22:

$$\text{AUC}_{24}/\text{MIC} = \frac{\text{Dose}_{24}(\text{mg})}{\text{Cl(L/hr)} \times \text{MIC(mg/L)}} \quad [\text{Eq. 13.22}]$$

$$= \frac{750 \text{ mg}}{(1.52 \text{ L/hr})(1 \text{ mg/L})}$$

$$= 493$$

Hence, the dose of 750 mg every 24 hours produces peak and trough vancomycin concentrations within the usual therapeutic range, and also yields a desirable AUC<sub>24</sub>/MIC > 400.

**QUESTION #4.** A.C., a 50-year-old, 60-kg woman with end-stage renal disease and a serum creatinine of 9 mg/dL, is undergoing standard intermittent hemodialysis treatments three times a week and currently has an apparent shunt infection which is to be treated with vancomycin. Calculate an appropriate dose for A.C.

Vancomycin is extensively cleared by the kidneys; consequently, patients with end-stage renal disease have prolonged half-lives that average 5 to 7 days. This extended half-life is consistent with a residual vancomycin clearance of 3 to 4 mL/70 kg/min (0.18 to 0.24 L/70 kg/hr) and an average volume of distribution. Depending on A.C.'s residual renal function, the half-life may be shorter or longer than this general range. Note that for dialysis patients, it is not appropriate to use their SCr to estimate creatinine clearance with Equation 13.2 or 13.3 because the SCr is not at steady state. The duration and frequency of A.C.'s hemodialysis is not a factor in vancomycin dosing because the amount of vancomycin cleared during standard hemodialysis is negligible.

The usual approach to the use of vancomycin in patients receiving intermittent hemodialysis is to administer 1 g every 5 days to 2 weeks. Using Equation 13.1 to estimate the volume of distribution:

$$V(L) = 0.17(50 \text{ yrs}) + 0.22(60 \text{ kg}) + 15 = 36.7 \text{ L}$$

Then one can see from Equation 13.8 that the first 1-g dose should result in an initial peak concentration of 27 mg/L.

$$C^0 = \frac{(S)(F)(\text{Loading Dose})}{V}$$

$$C^0 = \frac{(1)(1)(1000 \text{ mg})}{36.7 \text{ L}}$$

$$= 27.2 \text{ mg/L}$$

For a dose of 1 g administered weekly, steady-state peak and trough levels of approximately 44 and 17 mg/L, respectively, can be calculated using an average vancomycin clearance of 3.5 mL/min (0.21 L/hr), a volume of distribution of 36.7 L, and a corresponding elimination rate constant of  $0.00572 \text{ hr}^{-1}$  (Equations 13.12 and 13.15).

$$\text{Css max} = \frac{\frac{(S)(F)(\text{Dose})}{V}}{1 - e^{-kT}}$$

$$= \frac{\frac{(1)(1)(1000 \text{ mg})}{36.7 \text{ L}}}{(1 - e^{-(0.00572 \text{ hr}^{-1})(24 \text{ hr/day})(7 \text{ days})})}$$

$$= 44.1 \text{ mg/L} \approx 44 \text{ mg/L}$$

$$\text{Css min} = (\text{Css max})(e^{-kT})$$

$$= [44.1 \text{ mg/L}]e^{(-0.00572 \text{ hr}^{-1})(24 \text{ hr/day})(7 \text{ days})}$$

$$= (44.1 \text{ mg/L})(0.383)$$

$$= 16.9 \text{ mg/L} \approx 17 \text{ mg/L}$$

If the 1-g dose had been administered weekly, steady-state peak and trough vancomycin concentrations would be approximately 44 and 17 mg/L, respectively. However, if a dose of 500 mg was given weekly, steady-state peak and trough concentrations would be approximately 22 and 9 mg/L, respectively. The reason for this is that [(S)(F)(Dose/τ)] is administered as a loading dose, so the steady-state peak concentration is higher, but the average steady-state concentration is the same, as demonstrated by Equation 13.15 (Equation 13.15 is the equation for Plasma Drug Concentrations).

$$\text{Css ave} = \frac{\frac{(S)(F)(\text{Dose})}{V}}{1 - e^{-kT}}$$

$$= \frac{(1)(1)(1000 \text{ mg})}{(1 - e^{-(0.00572 \text{ hr}^{-1})(24 \text{ hr/day})(7 \text{ days})})}$$

$$= 14.2 \text{ mg/L}$$

$$= \frac{(1)(1)(500 \text{ mg})}{(1 - e^{-(0.00572 \text{ hr}^{-1})(24 \text{ hr/day})(7 \text{ days})})}$$

$$= 14.2 \text{ mg/L}$$

If an extended course of therapy is required, it is important to be able to obtain vancomycin plasma levels. If the patient's plasma levels are within an acceptable range, it might be appropriate to obtain an additional sample at the initiation of therapy. The purpose of this is to ensure that the clearance is not unusually large, which would result in levels below the desired therapeutic range.

If A.C. had been receiving hemodialysis, it is important to be aware that the vancomycin would be removed by the dialysis fluid. The usual approach is to administer a loading dose (approximately 1 to 2 g for A.C.) before the start of dialysis, which should result in approximately 50% of the total dose. This dose can be administered in one of two ways. It can be administered in single extracorporeal circulation, or it can be administered in a continuous manner during the dialysis session.

If the 1-g dose had been administered every 2 weeks, the expected peak and trough vancomycin concentrations would have been approximately 32 and 5 mg/L, respectively. However, because of the long half-life of vancomycin in renal failure (approximately 1 week) and a usual course of therapy of 2 weeks, steady state would not be achieved. Alternatively, if a dose of 500 mg was given weekly for a prolonged period, the expected steady-state peak and trough concentrations would have been approximately 22 and 9 mg/L, respectively. When the same average dosing rate  $[(S)(F)(Dose/\tau)]$  is administered as a smaller dose given more frequently, the steady-state peak concentration is lower, the steady-state trough concentration is higher, but the average steady-state concentration is the same, as demonstrated by Equation 13.23 (also see Part I: Interpretation of Plasma Drug Concentrations).

$$\text{Css ave} = \frac{(S)(F)(\text{Dose}/\tau)}{\text{Cl}} \quad [\text{Eq. 13.23}]$$

$$= \frac{(1)(1)(1000 \text{ mg})/(14 \text{ days})(24 \text{ hr/day})}{0.21 \text{ L/hr}}$$

$$= 14.2 \text{ mg/L}$$

vs.

$$= \frac{(1)(1)(500 \text{ mg})/(7 \text{ days})(24 \text{ hr/day})}{0.21 \text{ L/hr}}$$

$$= 14.2 \text{ mg/L}$$

If an extended course of therapy is anticipated, it is probably advisable to obtain vancomycin plasma levels to make certain that A.C.'s actual plasma levels are within an acceptable range. In seriously ill patients, it might be appropriate to obtain an initial vancomycin level 3 to 5 days after the initiation of therapy. The purpose is to ensure that the patient's actual clearance is not unusually large, resulting in vancomycin levels that are below the desired therapeutic range.

If A.C. had been receiving CAPD as her method of dialysis, it is probable that the vancomycin would be administered via her peritoneal dialysis fluid. The usual approach is to place 15 to 30 mg/kg of vancomycin (approximately 1 to 2 g for A.C.) into an initial dialysate exchange, which should result in approximately 50% of that dose being absorbed during the usual 4- to 6-hour dwell time. Her maintenance dose would then be administered in one of two ways. An additional 15 to 30 mg/kg dose could be administered in single exchanges every 3 to 5 days such that her

pre-dose trough vancomycin concentration would be maintained at  $\approx 10$  mg/L. A less common, alternative method for maintenance therapy is to place in each dialysis exchange enough vancomycin to achieve a dialysate concentration of 15 to 20 mg/L (30 to 40 mg in a 2 L exchange). This technique of placing vancomycin in each exchange results in an average steady-state plasma concentration approximately equal to the concentration of vancomycin in the dialysate fluid, after multiple exchanges (i.e., 15 to 20 mg/L).<sup>42,43</sup>

**QUESTION #5.** Suppose A.C. was given an initial 1-g dose and 3 days later, she underwent high-flux hemodialysis for 2 hours. Calculate a replacement dose after the dialysis session.

Although the amount of vancomycin removed by standard hemodialysis is negligible, high-flux hemodialysis has been reported to remove approximately 17% over 2 hours.<sup>47</sup> Assuming the initial plasma concentration is 27.2 mg/L and using the estimated  $K$  of  $0.00572 \text{ hr}^{-1}$ , as calculated above for A.C., the predialysis concentration can be determined by using Equation 13.13.

$$\begin{aligned} C_2 &= C_1(e^{-Kt}) \\ &= 27.2 \text{ mg/L } (e^{-(0.00572 \text{ hr}^{-1})(72 \text{ hr})}) \\ &= 27.2 \text{ mg/L } (0.66) \\ &= 18.0 \text{ mg/L } (\text{predialysis concentration}) \end{aligned}$$

If the plasma concentration declines by approximately 17% due to high-flux hemodialysis, then the postdialysis plasma concentration will be 83% of the predialysis concentration. This ignores any additional elimination from the intrinsic clearance during the 2-hour dialysis period, since it is negligible.

$$\begin{aligned} C_{\text{postdialysis}} &= 18.0 \text{ mg/L } (0.83) \\ &= 14.9 \text{ mg/L} \end{aligned}$$

If a replacement dose is desired at this point, the dose can be calculated by using Equation 13.24.

$$\text{Dose} = \frac{(V)(\Delta C)}{(S)(F)}$$

[Eq. 13.24]

$$\begin{aligned} &= \frac{(36.7 \text{ L})(27.2 \text{ mg/L} - 14.9 \text{ mg/L})}{(1)(1)} \\ &= 451 \text{ mg} \approx 450 \text{ mg} \end{aligned}$$

A similar approach can be used to determine the replacement dose. The actual drug loss will depend on the dialysis time, the dialysate flow rate, the ultrafiltration rate, and efficiency of the dialyzer.

**QUESTION #6.** A.C. became hemodynamically unstable after her hemodialysis was discontinued and required continuous renal replacement therapy (CRRT) with a high-flux hemodialyzer. The CRRT had an ultrafiltration rate of 1 L/hr. How much vancomycin should be changed?

In this case, it would be advisable to continue the initial dose until the level declines to a pre-dialysis level (e.g., 5 to 15 mg/L). Using an  $f_u$  of 0.21 and  $K$  of  $0.00572 \text{ hr}^{-1}$ , we can calculate the time to CRRT as follows:

$$Cl_{\text{CRRT Maximum}} =$$

The total vancomycin clearance is the sum of the clearance due to CRRT and the estimated intrinsic clearance of  $0.21 \text{ L/hr}$ .

$$Cl = Cl_{\text{CRET}}$$

$$\begin{aligned} &= 0.6 \text{ L/hr} \\ &= 0.81 \text{ L/hr} \end{aligned}$$

Now that we have estimated the total vancomycin clearance, we can use Equation 13.6 to calculate the new dose. With a  $K$  of  $0.0221 \text{ hr}^{-1}$ , and Equation 13.7 to calculate the steady-state peak and trough concentrations, we can estimate the dose to be approximately 750 mg every 48 hours.

A similar approach can be used in a step-wise fashion to determine dosing needs on any particular day and dialysis schedule. The amount of actual drug loss will depend on the intrinsic Cl, V, time of decay (t), duration of hemodialysis, and efficiency of the dialysis treatment.

**QUESTION #6.** A.C. became hemodynamically unstable. Therefore, hemodialysis was discontinued and CRRT was initiated with an ultrafiltration rate of 1 L/hr. How should the vancomycin dosage be changed?

In this case, it would be advisable to monitor vancomycin concentrations until the level declines to a point where therapy can be reinstated (e.g., 5 to 15 mg/L). Using an fu of 0.6, we can estimate the clearance due to CRRT as follows:

$$Cl_{CRRT\ Maximum} = (fu)(CRRT\ Flow\ Rate) \quad [Eq. 13.25]$$

$$\begin{aligned} &= (0.6)(1\ L/hr) \\ &= 0.6\ L/hr \end{aligned}$$

The total vancomycin clearance would be the sum of the clearance due to CRRT and the estimated intrinsic clearance previously estimated as 0.21 L/hr.

$$Cl = Cl_{CRRT} + Cl_{pat} \quad [Eq. 13.26]$$

$$\begin{aligned} &= 0.6\ L/hr + 0.21\ L/hr \\ &= 0.81\ L/hr \end{aligned}$$

Now that we have estimated the Cl, using the previously estimated V, we can use Equation 13.6 to calculate the elimination rate constant as  $0.0221\ hr^{-1}$ , and Equation 13.7 to calculate the half-life of 31 hours. Based on this information, we can employ Equations 13.12 and 13.15 to estimate the steady-state peak and trough concentrations, respectively, for a dose of 750 mg every 48 hours.

$$\begin{aligned} Css\ max &= \frac{(S)(F)(Dose)}{V} \\ &\quad \frac{[(1)(1)(750\ mg)]}{1 - e^{-kT}} \\ &= \frac{36.7\ L}{(1 - e^{-(0.0221\ hr^{-1})(48\ hr)})} \\ &= 31.3\ mg/L \approx 31\ mg/L \end{aligned}$$

$$\begin{aligned}
 \text{Css min} &= (\text{Css max})(e^{-KT}) \\
 &= (31.3 \text{ mg/L})(e^{(-0.0221 \text{ hr}^{-1})(48 \text{ hr})}) \\
 &= (31.3 \text{ mg/L})(0.346) \\
 &= 10.8 \text{ mg/L} \approx 11 \text{ mg/L}
 \end{aligned}$$

**QUESTION #7.** K.G., a 50-year-old, 70-kg man with a serum creatinine of 1.2 mg/dL, is receiving vancomycin 1,000 mg IV every 12 hours at 10:00 a.m. and 10:00 p.m. for a methicillin-resistant *S. aureus* (MRSA) infection. A steady-state vancomycin level was drawn at 6:00 a.m. and was reported to be 18 mg/L. (Note: This level was drawn 8 hours after the start of the vancomycin infusion and is 4 hours before the trough.) Based on this information, estimate K.G.'s vancomycin Cl and K values and the true trough concentration.

Because this level was drawn 4 hours earlier, Equation 13.5 should not be used to estimate the peak concentration since Css min is not yet known.

$$\text{Css max} = [\text{Css min}] + \left[ \frac{(S)(F)(\text{Dose})}{V} \right]$$

Instead, an iterative search technique must be used to determine K.G.'s pharmacokinetic parameters. The usual technique is to use Equation 13.27 where  $t_1$  is 8 hours from the start of the infusion and to assume K.G. has an average volume of distribution of 38.9 L, using Equation 13.1.

$$\begin{aligned}
 V(L) &= 0.17(\text{age in years}) + 0.22(\text{TBW in kg}) + 15 \\
 &= (0.17)(50 \text{ yr}) + (0.22)(70 \text{ kg}) + 15 \\
 &= 38.9 \text{ L}
 \end{aligned}$$

Then, by trial and error, solve for the elimination rate constant (K) that predicts a plasma concentration equal to the observed value of 18 mg/L. For example, if a K of  $0.113 \text{ hr}^{-1}$  is inserted into the equation (the initial K is calculated from population V and Cl), a concentration of 14.0 mg/L is calculated. This value is lower than the observed concentration of 18 mg/L and therefore does not satisfy the equation. By trial and error, one can discover that an elimination rate constant of  $0.0935 \text{ hr}^{-1}$  calculates a concentration of approximately 18 mg/L.

$$\text{CSS}_1 = \frac{(S)(F)(\text{Dose})}{V} \frac{1}{1 - e^{-KT}} \quad [\text{Eq. 13.27}]$$

$$\begin{aligned}
 \text{CSS}_1 &= \frac{(1)(1)(1000 \text{ mg})}{38.9 \text{ L}} \frac{1}{1 - e^{-K(12 \text{ hr})}} \\
 &= \frac{25.7 \text{ mg/L}}{(1 - 0.26)} \\
 &= 14.0
 \end{aligned}$$

and so

$$\begin{aligned}
 \text{CSS}_1 &= \frac{(1)(1)(1000 \text{ mg})}{38.9 \text{ L}} \frac{1}{1 - e^{-(0.0935 \text{ hr}^{-1})(8 \text{ hr})}} \\
 &= \frac{25.7 \text{ mg/L}}{(1 - 0.326)} \\
 &= 18.0
 \end{aligned}$$

It can be reasonably assumed that the elimination rate constant of  $0.0935 \text{ hr}^{-1}$  is the value that best describes K.G. When this K is coupled with Equation 13.1, the calculated Cl and vancomycin clearance can be calculated.

$$\begin{aligned}
 t_{1/2} &= \frac{0.693}{K} \\
 &= \frac{0.693}{0.0935 \text{ hr}^{-1}} \\
 &= 7.4 \text{ hr} \\
 \text{Cl} &= (K \cdot V) \\
 &= (0.0935 \text{ hr}^{-1})(38.9 \text{ L}) \\
 &= 3.64 \text{ L/hr}
 \end{aligned}$$

Others may use the iterative method of trial and error for calculating the corresponding Cl and vancomycin clearance. However, the outcome is the same and matter of personal preference and experience.

$$\begin{aligned}
 \text{Css}_1 &= \frac{(1)(1)(1000 \text{ mg})}{38.9 \text{ L}} \left( e^{-K(8 \text{ hr})} \right) \\
 &= \frac{(1)(1)(1000 \text{ mg})}{1 - e^{-(0.113 \text{ hr}^{-1})(12 \text{ hr})}} \left( e^{-(0.113 \text{ hr}^{-1})(8 \text{ hr})} \right) \\
 &= \frac{25.7 \text{ mg/L}}{(1 - 0.26)} (0.405) \\
 &= 14.0
 \end{aligned}$$

*and subsequently*

$$\begin{aligned}
 \text{Css}_1 &= \frac{(1)(1)(1000 \text{ mg})}{38.9 \text{ L}} \left( e^{-(0.0935 \text{ hr}^{-1})(12 \text{ hr})} \right) \\
 &= \frac{25.7 \text{ mg/L}}{(1 - 0.326)} (0.473) \\
 &= 18.0
 \end{aligned}$$

It can be reasonably assumed, then, that this elimination rate constant of  $0.0935 \text{ hr}^{-1}$  is the value that would be most appropriate for K.G. When this K is coupled with Equations 13.18 and 13.19, a revised half-life and vancomycin clearance can be calculated for K.G.

$$\begin{aligned}
 t_{1/2} &= \frac{0.693}{K} \\
 &= \frac{0.693}{0.0935 \text{ hr}^{-1}} \\
 &= 7.4 \text{ hr} \\
 Cl &= (K)(V) \\
 &= (0.0935 \text{ hr}^{-1})(38.9 \text{ L}) \\
 &= 3.64 \text{ L/hr}
 \end{aligned}$$

Others may use the iterative method by adjusting the clearance value and calculating the corresponding K. This approach emphasizes that clearance is the independent pharmacokinetic parameter that is being revised. However, the outcome is the same using either technique and is a matter of personal preference and experience.

In addition, Equation 13.13 can be used to calculate the expected trough concentration (12 hours after the dose was administered) by decaying the reported value at 8 hours for an additional 4 hours.

$$\begin{aligned} C_2 &= C_1(e^{-kT}) \\ &= 18 \text{ mg/L } (e^{-(0.0935 \text{ hr}^{-1})(4 \text{ hr})}) \\ &= 18 \text{ mg/L } (0.688) \\ &= 12.4 \text{ mg/L} \end{aligned}$$

This concentration is reasonable considering the usual target trough concentrations are 5 to 15 mg/L. If the estimated trough concentration was not acceptable, then the revised half-life and clearance coupled with the assumed volume of distribution for K.G. could be used to establish a new dosing regimen.

**QUESTION #8.** C.U. is a 40-year-old, 5-foot 7-inch, 105-kg man with a serum creatinine of 1.2 mg/dL. He has a penicillin allergy history and for that reason, vancomycin is being considered for empiric therapy. Should the dosing regimen of vancomycin be based on C.U.'s total or ideal body weight?

The volume of distribution of vancomycin is greater in obese subjects than in non-obese subjects. The apparent volume of distribution for vancomycin tends to correlate best with actual (total) body weight, although there is a fair degree of variability.<sup>9,28,32,52,53</sup> Whereas some investigators have reported higher vancomycin clearances in obese patients, others have observed that vancomycin clearance is still essentially equivalent to creatinine clearance.<sup>9,28,32,52,53</sup> Owing to the wide variability in the pharmacokinetic parameters, monitoring serum vancomycin concentrations in very obese patients is advisable.

The approach used here (Equations 13.2, 13.3, and 13.4) to estimate vancomycin clearance has been shown to correlate better with ideal rather than TBW in obese subjects.<sup>28</sup>

To calculate the expected pharmacokinetic parameters for C.U., first estimate ideal body weight and creatinine clearance using Equations 13.28 and 13.2, respectively.

$$\text{Ideal Body Weight for males in kg} = 50 + (2.3)(\text{Height in inches} - 60) \quad [\text{Eq. 13.28}]$$

$$\begin{aligned} &= 50 + (2.3)(7 \text{ inches}) \\ &= 66 \text{ kg} \end{aligned}$$

$$\begin{aligned} \text{Cl}_{\text{Cr}} \text{ for males (mL/min)} &= \frac{(140 - \text{age})}{(140 - \text{TBW})} \\ &= \frac{140 - 40}{140 - 105} \\ &= 76.4 \end{aligned}$$

Use Equation 13.4 to calculate

$$\text{Vancomycin Cl} \approx \text{Cl}_{\text{Cr}}$$

$$\text{Vancomycin Cl} = 76.4$$

Equation 13.1 can be used to calculate the volume of distribution of 44.9 L:

$$\begin{aligned} V(\text{L}) &= 0.17(\text{age in years}) + 0.032(\text{TBW in kg}) \\ &= 0.17(40 \text{ yrs}) + 0.032(105 \text{ kg}) \\ &= 44.9 \text{ L} \end{aligned}$$

and Equation 13.6 can be used with the calculated volume of distribution of 44.9 L to calculate the clearance of 0.102 hr<sup>-1</sup>.

Finally, using Equation 13.7, the half-life will be 6.8 hours.

$$\begin{aligned} t_{1/2} &= \frac{0.693}{\text{Cl}/V} \\ &= \frac{0.693}{0.102 \text{ hr}^{-1} / 44.9 \text{ L}} \\ &= 6.8 \text{ hours} \end{aligned}$$

$$\begin{aligned} \text{Cl}_{\text{Cr}} \text{ for males (mL/min)} &= \frac{(140 - \text{Age})(\text{Weight in kg})}{(72)(\text{SCr}_{\text{ss}})} \\ &= \frac{(140 - 40 \text{ yrs})(66 \text{ kg})}{(72)(1.2 \text{ mg/dL})} \\ &= 76.4 \text{ mL/min} \end{aligned}$$

Use Equation 13.4 to calculate vancomycin clearance:

$$\text{Vancomycin Cl} \approx \text{Cl}_{\text{Cr}}$$

$$\text{Vancomycin Cl} = 76.4 \text{ mL/min}$$

or

$$\begin{aligned} &= (76.4 \text{ mL/min}) \left( \frac{60 \text{ min/hr}}{1000 \text{ mL/L}} \right) \\ &= 4.58 \text{ L/hr} \end{aligned}$$

Equation 13.1 can be used to calculate C.U.'s volume of distribution of 44.9 L:

$$\begin{aligned} V(\text{L}) &= 0.17(\text{age in years}) + 0.22(\text{TBW in kg}) + 15 \\ &= 0.17(40 \text{ yrs}) + 0.22(105 \text{ kg}) + 15 \\ &= 44.9 \text{ L} \end{aligned}$$

and Equation 13.6 can be used with the clearance of 4.58 L/h and the volume of distribution of 44.9 L to calculate an elimination rate constant of  $0.102 \text{ hr}^{-1}$ .

$$\begin{aligned} K &= \frac{\text{Cl}}{V} \\ &= \frac{4.58 \text{ L/hr}}{44.9 \text{ L}} \\ &= 0.102 \text{ hr}^{-1} \end{aligned}$$

Finally, using Equation 13.7, the vancomycin  $t_{1/2}$  can be estimated to be 6.8 hours.

$$\begin{aligned} t_{1/2} &= \frac{(0.693)(V)}{\text{Cl}} \\ &= \frac{(0.693)(44.9 \text{ L})}{4.58 \text{ L/hr}} \\ &= 6.8 \text{ hr} \end{aligned}$$

Given the half-life and the desire to choose a dosing interval that is between one and two half-lives for vancomycin, a logical approach would be to use a convenient dosing interval of 12 hours, a trough concentration of 10 mg/L, and Equation 13.16 to solve for a dose.

$$\text{Dose} = \frac{(C_{ss\ min})(V)(1 - e^{-kT})}{(S)(F)(e^{-kT})}$$

$$\text{Dose} = \frac{(10 \text{ mg/L})(44.9 \text{ L})(1 - e^{-(0.102 \text{ hr}^{-1})(12 \text{ hr})})}{(1)(1)(e^{-(0.102 \text{ hr}^{-1})(12 \text{ hr})})}$$

$$= 1078 \text{ mg} \approx 1000 \text{ mg every 12 hours}$$

This dose would usually be rounded off to a reasonable amount, and 1,000 mg would probably be given every 12 hours. The steady-state peak and trough concentrations on this new dose could be confirmed by using Equations 13.12 and 13.15 and inserting the appropriate values.

$$C_{ss\ max} = \frac{(S)(F)(Dose)}{V}$$

$$= \frac{(1)(1)(1000 \text{ mg})}{44.9 \text{ L}}$$

$$= \frac{(1 - e^{-(0.102 \text{ hr}^{-1})(12 \text{ hr})})}{(1 - e^{-kT})}$$

$$= 31.5 \text{ mg/L}$$

$$C_{ss\ min} = (C_{ss\ max})(e^{-kT})$$

$$= (31.5 \text{ mg/L})(e^{-(0.102 \text{ hr}^{-1})(12 \text{ hr})})$$

$$= (31.5 \text{ mg/L})(0.294)$$

$$= 9.3 \text{ mg/L}$$

Alternatively, the expected trough concentration could have been calculated by simply using a ratio of the new dose to the current dose.

$$C_{ss\ New} = \frac{\text{New Dose}}{\text{Current Dose}} \times C_{ss\ Current} \quad [\text{Eq. 13.29}]$$

$$= \frac{1000 \text{ mg}}{1078 \text{ mg}} \times 10 \text{ mg/L}$$

$$= 0.928 \times 10 \text{ mg/L}$$

$$= 9.3 \text{ mg/L}$$

This technique of using a ratio of state concentration is appropriate of sampling has not changed for a cokinetics.

Note that any difference between the two methods is due to other assumptions.

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This technique of using a ratio of doses to calculate the new steady-state concentration is appropriate as long as the dosing interval and time of sampling has not changed for a drug that exhibits stable linear pharmacokinetics.

Note that any difference between the plasma concentrations calculated by the two methods is due to rounding-off errors and not to any other assumptions.

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