

**Case Study**  
**Vancomycin**  
**Answers Provided by**  
**Jeffrey Stark, Graduate Student**

The antibiotic Vancomycin is eliminated almost entirely by glomerular filtration. For a patient with normal renal function, the half-life is about 6 hours. The volume of distribution is 0.9 L/kg. For systemic infections, vancomycin is given intravenously and shows a pronounced distribution phase (with a duration of up to one hour) after administration. Vancomycin is usually given via short term infusions (1 hr) with a dosing interval of either 6 or 12 hours. Although, like many other antibiotics, vancomycin has a wide therapeutic margin, the desired steady-state concentrations are 20 mg/L (1 hr post-infusion) and 5-10 mg/L at the end of the dosing interval.

A 43 year old patient (70 kg) develops a wound infection (found to be *Staphylococcus aureus*). Since this bacteria is resistant to penicillins, the patient is begun on vancomycin. Answer the following questions concerning dosage regimens for this patient.

Questions

- 1) If vancomycin is given as an i.v. bolus, which equation will best describe the concentration-time profile? Do we have sufficient information (given above) to apply equations of this form?
- 2) Calculate an appropriate loading dose for this patient using both the i.v. bolus and short-term infusion equations. Compare the results. Are they significantly different? Explain.
- 3) Using a dosing interval of 12 hrs, determine a dosing regimen for this patient. How many doses are required to reach steady-state levels? What are the peak (clearly indicate what "peak" refers to) and trough values at steady-state?

4) Consider the fact that this patient's creatinine clearance is only 30 ml/min and the dosing regimen is 500 mg every 12 hrs. What are the peak and trough values at steady-state? The elimination rate constant may be calculated using the empirically derived equation:

$$k = (0.00083 \text{ hr}^{-1}) \times (\text{Creatinine Cl}) + 0.0044,$$

which has units of  $\text{hr}^{-1}$ .

5) If the actual peak and trough values are 23 mg/L and 14 mg/L (giving 500 mg every 12 hrs), what are  $k$  and  $V_d$  for this patient? Suggest a new dosing regimen (dose and dosing interval) to provide peak and trough values of 25 mg/L and 7 mg/L respectively.

These questions are based on those found in Case Studies 9-12 in the white book.

1) Since vancomycin shows a pronounced distribution phase, a multicompartment model is needed. The general i.v. bolus equation for a two-compartment is:

$$C_p(t) = ae^{-\alpha t} + be^{-\beta t}$$

We are not given the hybrid constants  $\alpha$  &  $\beta$ ; rather we are given a single overall elimination rate constant  $k_e$  (actually  $t_{1/2}$ ). Therefore, we cannot use the two compartment model equation for the following calculations. We must "skip over" the distribution ( $\alpha$ ) phase and discuss only plasma levels one or two hours after administration of the drug.

2) For a single i.v. bolus dose, the concentration is given by

$$C_{p_0} = \frac{Dose}{V_d}$$

Since we want to obtain steady-state levels with one loading dose (LD),

$$C_{p_{ss}} = \frac{LD}{V_d}$$

which rearranges to give

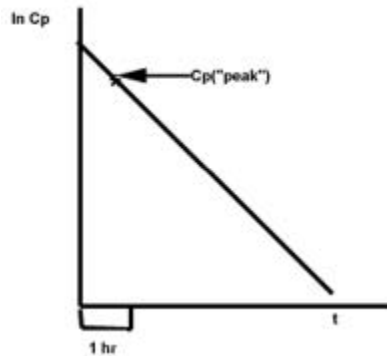
$$LD = C_{p_{ss}} \cdot V_d$$

Here, we can use 20 mg/L as the  $C_{p_{ss}}$  value, since we want to achieve the peak level (steady-state) with a single dose.

If we ignore any short-lived peaks ( $\alpha$ -phase) and consider vancomycin has a wide therapeutic window, we choose the "peak" level for 1 hr post-infusion. The  $V_d$  (given as a per-kilogram value) can be found using the patient's weight,

$$V_d = \frac{0.9L}{kg} \cdot 70kg = 63L$$

The loading dose is then:



$$Cp(\text{"peak"}) = 20 \text{ mg/L} = Cp(0) \cdot e^{-k_e t'} = \frac{D}{V_d} \cdot e^{-k_e t'}$$

In the equation above,  $t'$  is the 1 hr allowed for distribution. This equation must be solved for  $D$  which will be the loading dose:

$$\begin{aligned} LD &= \frac{(20 \text{ mg/L}) \cdot V_d}{e^{-k_e t'}} \\ &= \frac{(20 \text{ mg/L})(63 \text{ L})}{e^{-(0.1155 \text{ hr}^{-1})(1 \text{ hr})}} = 1414 \text{ mg} \end{aligned}$$

For a single short term infusion, the peak level is given by

$$Cp(\text{peak}) = \frac{\text{Dose}}{k_e \cdot V_d \cdot T} (1 - e^{-k_e T})$$

where  $T$  is the infusion time. recall that we should define "peak" levels as those that occur one or two hours after the infusion is stopped. Thus, we need to multiply the above equation by  $e^{-k_e t'}$ , where  $t'$  is the post-infusion time (1hr).  $Cp(\text{peak})$  is 20 mg/L (the desired steady-state level) and  $V_d$  is 63L as just determined.  $k_e$  may be found from the half-life ( $t_{1/2} = 6 \text{ hrs}$ );

$$k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{6 \text{ hrs}} = 0.1155 \text{ hrs}^{-1}$$

After the above equation is multiplied by  $e^{-k_e t'}$ , it may be solved for dose (or loading dose) to give

$$LD = \frac{Cp(\text{peak}) \cdot k_e \cdot V_d \cdot T}{(1 - e^{-k_e T}) \cdot e^{-k_e t'}}$$

$$= \frac{(20\text{mg} / \text{L})(0.1155\text{hr})(63\text{L})(1\text{hr})}{[1 - e^{-(0.1155\text{hr}^{-1})(1\text{hr})}] \cdot e^{-(0.1155\text{hr}^{-1})(1\text{hr})}}$$

$$= 1498 \text{ mg}$$

This value calculated with the infusion equation is somewhat larger than that calculated using the i.v. bolus equation. For a patient with normal renal function, a significant amount may be eliminated during the infusion and also in the 1 hr post-infusion time (distribution phase). In these calculations, the infusion dose is roughly 6% greater than the i.v. bolus.

3) Since  $\tau$  is given as 12 hours, we need only to determine the maintenance dose. This is easily done by solving the  $C_{p_{ss}}(\text{max})$  short term infusion equation for D,

$$C_{p_{ss}}(\text{peak}) = \frac{D}{k_e \cdot V_d \cdot T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e t'})} \cdot e^{-k_e t'}$$

Again, we define the "peak" level to be that at 1 hour post-infusion and have multiplied the multiple dose peak equation by  $e^{-k_e t'}$  (where  $t' = 1 \text{ hr}$ ) to account for this. Solving this equation for D gives,

$$D = \frac{C_{p_{ss}}(\text{peak}) \cdot k_e \cdot V_d \cdot T \cdot (1 - e^{-k_e t'})}{(1 - e^{-k_e T}) \cdot e^{-k_e t'}}$$

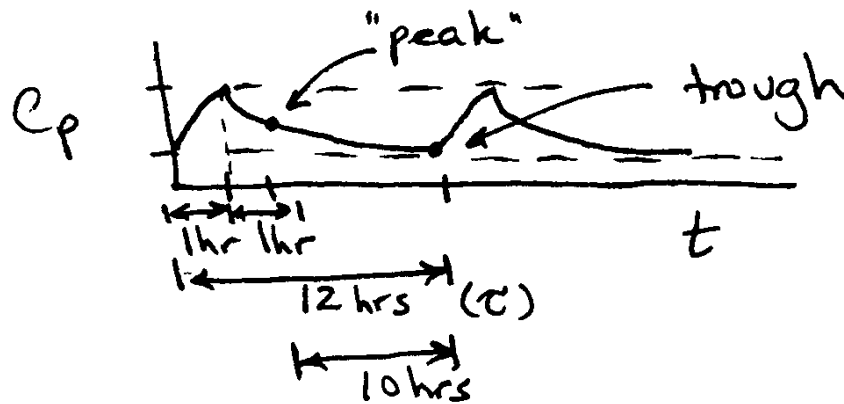
$$D = \frac{(20\text{mg} / \text{L})(0.1155\text{hr}^{-1})(63\text{L})(1\text{hr})[1 - e^{-(0.1155\text{hr}^{-1})(12\text{hr})}]}{[1 - e^{-(0.1155\text{hr}^{-1})(1\text{hr})}] \cdot e^{-(0.1155\text{hr}^{-1})(1\text{hr})}}$$

$$= \frac{109.1368}{0.09718} \text{ mg} = 1123 \text{ mg}$$

For 1123 mg every 12 hours, the "peak" and trough values are:

$$C_{p_{ss}}(\text{peak}) = 20 \text{ mg/L}$$

It is unnecessary to calculate this value; this value and the "peak" equation were used to determine the dose.

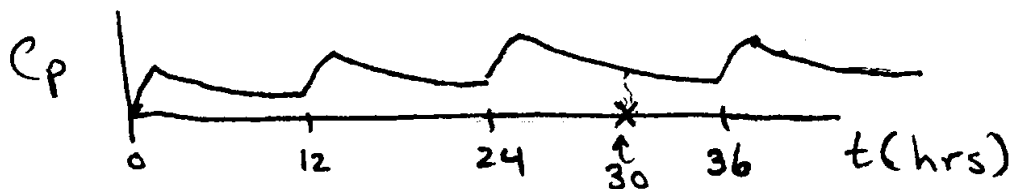


Since the dosing interval is 12 hours and 2 hours passed before our "peak" level (one hour for infusion and one hour for distribution), the trough occurs 10 hrs after the peak.

$$\begin{aligned}
 C_{p_{ss}} (\text{trough}) &= C_{p_{ss}} (\text{peak}) \cdot e^{-k_e t} \quad (t=10 \text{ hrs}) \\
 &= (20 \text{ mg/L}) e^{-(0.1155 \text{ hr}^{-1})(10 \text{ hr})} \\
 &= 6.3 \text{ mg/L}
 \end{aligned}$$

Recall that 5 half-lives are needed to reach steady-state levels. Since  $t_{1/2} = 6$  hours,

$(5) \cdot (6 \text{ hrs}) = 30$  hours are required to reach the steady-state. With a dosing interval of 12 hours, 3 doses will have been administered,



4) Since glomerular filtration is the main elimination pathway for vancomycin, renal function is an important factor in determining an optimal dosing regimen. Recall that creatinine clearance reflects GFR (normally 125 ml/min). Lower creatinine clearance means that GFR is lower than normal. In this situation, the amount of dose should be lowered since it is not being eliminated as rapidly. To calculate expected peak and trough levels for the new dosing regimen (500 mg every 12 hours), we will need the actual  $k_e$ . Using the formula given (Case Study 11)

$$\begin{aligned}
 k_e &= (0.00083 \text{ hr}^{-1}) \cdot Cl_{\text{creat}} + 0.0044 \\
 &= (0.00083 \text{ hr}^{-1})(30 \text{ ml/min}) + 0.0044
 \end{aligned}$$

$$= 0.0293 \text{ hr}^{-1}$$

We can now apply the peak and trough expressions used in the previous question.

$$Cp_{ss}(\text{peak}) = \frac{D}{V_d \cdot k_e \cdot T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e t})} \cdot e^{-k_e t}$$

$$= \frac{(500\text{mg})[1 - e^{-(0.0293\text{hr}^{-1})(1\text{hr})}]}{(63\text{L})(0.0293\text{hr}^{-1})(1\text{hr})[1 - e^{-(0.0293\text{hr}^{-1})(12\text{hr})}]} \cdot e^{-(0.0293)(1)}$$

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

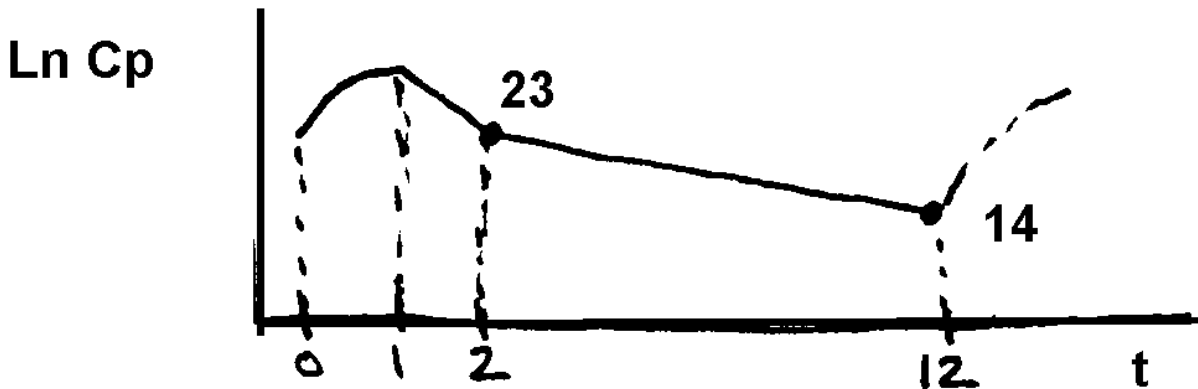
$$Cp_{ss}(\text{trough}) = Cp_{ss}(\text{peak}) \cdot e^{-k_e t} \quad \text{with } t = 10 \text{ hours}$$

$$= (25.6 \text{ mg/L}) \cdot e^{-(0.0293 \text{ hr}^{-1})(10\text{hr})}$$

$$= 19.1 \text{ mg/L}$$

Note how much higher the trough value is than was calculated previously when we assumed normal renal function.

5) With actual data points we can easily determine the  $k_e$  (by the slope) and  $V_d$  (by plugging the values into the  $Cp_{ss}(\text{peak})$  equation) for this patient.



$$k_e = -m = -\frac{(\ln 23 - \ln 14)}{(2 - 12)\text{hr}} = 0.0496 \text{ hr}^{-1}$$

$V_d$  may be found using the  $Cp_{ss}(\text{peak})$  equation,

$$Cp_{ss}(\text{peak}) = \frac{D}{k_e \cdot V_d \cdot T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e t})} \cdot e^{-k_e t'}$$

which may be rearranged to give

$$\begin{aligned} V_d &= \frac{D}{Cp_{ss}(\text{peak}) \cdot k_e \cdot T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e t})} \cdot e^{-k_e t'} \\ &= \frac{(500\text{mg}) \cdot [1 - e^{-(0.0496\text{hr}^{-1})(1\text{hr})}] \cdot e^{-(0.0496\text{hr}^{-1})(1\text{hr})}}{(23\text{mg/L})(0.0496\text{hr}^{-1})(1\text{hr}) \cdot [1 - e^{-(0.0496\text{hr}^{-1})(12\text{hr})}]} \\ &= 45.0 \text{ L} \end{aligned}$$

Determine a new dosing regimen to give peak and trough values of 25 mg/L and 7 mg/L. The first step is to determine the dosing interval. The expression for  $\tau$  uses the fluctuation factor,  $F = Cp_{ss}(\text{peak})/Cp_{ss}(\text{trough})$ .

$$F = \frac{25\text{mg/L}}{7\text{mg/L}} = 3.57$$

Now,

$$t = \frac{\ln F}{k_e} = \frac{\ln 3.57}{0.0496\text{hr}^{-1}} = 25.7\text{hr}$$

Actually for a short term infusion, we need to add in the infusion time  $T$  for determining  $\tau$ ,

$$t = \frac{\ln F}{k_e} = T = 26.7\text{hr}$$

Since administering medication every 26.7 hrs is impractical, we round the value to

$$\tau = 24\text{hr}$$

The new maintenance dose can be calculated using  $\tau$  and the  $Cp_{ss}$  (peak) expression solved for D,

$$\begin{aligned} D &= \frac{Cp_{ss}(\text{peak}) \cdot k_e \cdot V_d \cdot T \cdot (1 - e^{-k_e t})}{(1 - e^{-k_e T}) \cdot e^{-k_e t'}} \\ &= \frac{(25\text{mg} / \text{L})(0.0496\text{hr}^{-1})(45.0\text{L})(1\text{hr})[1 - e^{-(0.0496\text{hr}^{-1})(24\text{hr})}]}{[1 - e^{-(0.0496\text{hr}^{-1})(1\text{hr})}] \cdot e^{-(0.0496\text{hr}^{-1})(1\text{hr})}} \\ &= 843.3 \text{ mg} \end{aligned}$$

This may be rounded to  $D = 800 \text{ mg}$

Thus, the new dosing regimen is 800 mg every 24 hrs.