

Case Study 4
PHA 5127
Aminoglycosides
Answers provided by
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Background

Gentamicin is used to treat a wide variety of infections. However, due to its toxicity, its use must be restricted to the therapy of life-threatening infections and those for which a less toxic antimicrobial agent is ineffective. Gentamicin follows a one-compartment body model with first-order elimination. Protein binding is low for gentamicin (depending on the test performed, binding is reported to be 0-30%). The volume of distribution is in the range of 10-40L and the half-life is around 2 hours (although there may be considerable variation in this parameter). Dosage is normally 1.0 mg/kg every 8 hours for 7-10 days. The therapeutic range is 1-6 mg/L. Gentamicin is commonly administered via short-term infusions. However, for this case study, assume that the infusions are sufficiently short as to allow IV bolus equations to be used for any necessary calculations. (Don't worry, we'll see all of the infusion expressions soon enough. Perhaps too soon for many of you, especially the algebraically and exponentially challenged).

Patient information

Mr. I.P. Little (the names have been changed to protect the innocent) is a 69 year old black male with a history of diabetes and hypertension. He is being treated with gentamicin for an infection in his lower leg. The infection was the result of a puncture wound which progressed due to poor circulation and immune response. Additional patient information is given below.

height 5'9''
weight 170 lb
SCr 1.3 mg/100mL

Note: Serum creatinine may also be expressed as 1.3 mg/dL

While the patient is most likely on other medications as well, assume no drug-drug interactions when addressing the following questions.

Questions

- (1) Predict the creatinine clearance of this patient. Is this in the “normal” range? If not, explain and propose a plausible reason for any deviation from the normal value. Of what importance is Cl_{creat} in this case study? Why is the ideal body weight (IBW) used in the calculation rather than the actual weight?

Calculate Cl_{creat} for this patient.

This may be done with the equation,

$$Cl_{creat} (male) = \frac{(140 - age) \cdot IBW}{72 \cdot Cp_{creat}}$$

Note: this is an empirically derived equation. Age is in years, IBW is in kg, and Cp_{creat} is in mg/100ml. This results in Cl_{creat} in mL/min. First, we must find IBW:

$$\begin{aligned} IBW (male) &= 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 ft.} \\ &= 50 \text{ kg} + (2.3\text{kg})(9) \quad \text{Since patient is 5'9"} \\ &= 70.7 \text{ kg} \end{aligned}$$

Returning to the Cl_{creat} calculation.

$$Cl_{creat} (male) = \frac{(140 - 69)(70.7)}{(72)(1.3)} = 53.6 \text{ ml / min}$$

Normal GFR = 125 ml/min. since Cl_{creat} reflects GFR, we know that there is some renal dysfunction in this patient. This GFR is well below half the normal value and could be due to some undisclosed disease state or simply the age of the patient.

Cl_{creat} is an important consideration in this case study because aminoglycosides are eliminated via glomerular filtration. Any change in GFR will affect the clearance of gentamicin. We must use IBW in the calculation of Cl_{creat} since creatinine is produced by muscle metabolism and not fat. Special equations are employed when the patient is obese (the adjusted body weight).

- (2) Predict the k_e and $t_{1/2}$ of gentamicin starting with the equation which relates k_e to creatinine clearance. Then, calculate these parameters based on the expression $Cl = k_e \cdot V_d$ assuming a V_d of, say, 15L (which falls within the normal range). Discuss any difference between the two values.

The equation relating k_e to Cl_{creat} is

$$k_e = (0.00293) \cdot Cl_{creat} + 0.014$$

Again, this is an empirically derived equation. Cl_{creat} is in ml/min and k_e is in hr^{-1} . For this patient,

$$k_e = (0.00293)(53.6) + 0.014 = 0.171hr^{-1}$$

This k_e would give a gentamicin half-life of

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.171hr^{-1}} = 4.1hr$$

Of course, we may calculate k_e if Cl and V_d are known (since these two independent parameters dictate the elimination rate);

$$Cl = k_e \cdot V_d$$

may be rearranged to give

$$k_e = \frac{Cl}{V_d}$$

Using the creatinine clearance calculated in question (1) and assuming $V_d = 15L$, we find

$$k_e = \frac{53.6ml/min}{15L} \cdot \frac{1L}{1000ml} \cdot \frac{60min}{1hr} = .214hr^{-1}$$

With this k_e , we would expect the gentamicin half-life to be

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.214hr^{-1}} = 3.2hr$$

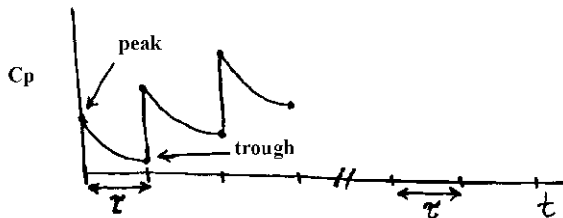
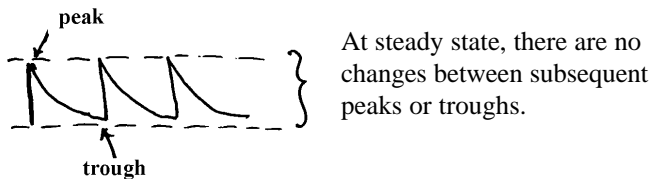
The values calculated from the two methods are rather close. A half-life of 3.7 hr is not that different from one of 3.2 hr. since the first method is a rough estimate of k_e and we guessed at the V_d in the second method, we really cannot comment as to which is closest to the actual k_e . We need actual data points (gentamicin concentration at different time points) in order to calculate the pertinent pharmacokinetic parameters for this patient.

- (3) Using the kinetic parameters found in the part of question (2), calculate the peak and trough levels for gentamicin expected from a dose of 70mg every 8 hours. Do this for the first dose and for the steady-state conditions.

Dosing regimen: 70 mg gentamicin every 8 hrs.

In this question, we are asked to calculate peak and trough levels for gentamicin following the dosing regimen above. Although short-term infusions are used, we will assume the infusions are short enough as to allow the IV bolus equations to be substituted for the more complex infusion equations. This may not always be possible. However since you must first learn to walk before you begin to run, we will make things a bit easier.

Start with a simple sketch



Calculating the peak and trough levels after the first dose is easy. The peak is simply the initial concentration following an IV bolus dose of 70 mg:

$$Cp_0 = \frac{D}{V_d}$$

To use this equation, we need the value of V_d . Using the Cl and k_e values based on serum creatine levels calculated in question (2), we find

$$Cl = k_e \cdot V_d$$

Solving for V_d to give

$$V_d = \frac{Cl}{k_e} = \frac{53.6 \text{ ml/min}}{0.171 \text{ hr}^{-1}} \cdot \frac{60 \text{ min}}{1 \text{ hr}} \cdot \frac{1 \text{ L}}{1000 \text{ ml}} = 18.8 \text{ L}$$

Note: If this is correct, we underestimated the V_d used in the previous question.

The Cp_0 is thus,

$$Cp_0 = Cp(peak)_1 = \frac{70mg}{18.8L} = 3.7mg / L$$

The trough occurs 8 hours later (just prior to the 2nd dose)

$$Cp(trough)_1 = Cp(peak)_1 \cdot e^{-k_e t}$$

This is the exact equation we used previously,

$$Cp(t) = \frac{D}{V_d} \cdot e^{-k_e t} = Cp_0 \cdot e^{-k_e t}$$

Since we want the Cp at the end of the dosing interval, we set $t = 8 \text{ hours} = \tau$.

So,

$$Cp(trough)_1 = (3.7mg / L) \cdot e^{-(0.171hr^{-1})(8hr)} = 0.94mg / L$$

The equations for calculating concentrations at steady-state are easy to identify. They always include the accumulation factor $(1 - e^{-k_e t})$ in the denominator.

The peak at SS is

$$\begin{aligned} Cp(peak)_{ss} &= \frac{Cp_0}{(1 - e^{-k_e t})} = \frac{D}{V_d \cdot (1 - e^{-k_e t})} \\ &= \frac{3.7mg / L}{[1 - e^{-(0.171hr^{-1})(8hr)}]} = 4.96 \sim 5.0mg / L \end{aligned}$$

Just as with the trough after the 1st dose, the trough after a dose at steady-state is found by multiplying the peak value by a factor to account for elimination during the dosing interval (here we have 8 hours for elimination).

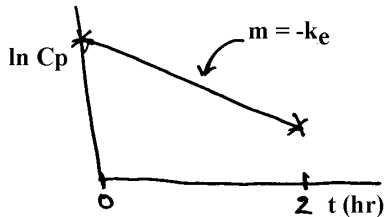
$$\begin{aligned} Cp(trough)_{ss} &= Cp(peak)_{ss} \cdot e^{-k_e t} \\ &= (5.0mg / L) \cdot e^{-(0.171hr^{-1})(8hr)} = 1.3mg / L \end{aligned}$$

- (4) Plasma levels were drawn and gentamicin levels determined after the first dose (70mg every 8 hours). The concentrations were 5.8 mg/L and 3.8 mg/L at 0 and 2 hours post infusion, respectively. Using this data, recalculate the k_e , $t_{1/2}$, V_d , and Cl for this patient.

Drug monitoring allows us to customize a dosing regimen for a given patient. Here we are given two data points following the first dose. This will allow us to calculate the pharmacokinetic parameters for this patient and better predict plasma levels for repeated dosing.

The data points are.

Cp(mg/L)	t(hr)
5.8	0
3.8	2



From the data given, we can easily calculate k_e .

$$k_e = -m = \frac{-(\ln 5.8 - \ln 3.8)}{0 - 2} = 0.211 \text{ hr}^{-1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.211 \text{ hr}^{-1}} = 3.3 \text{ hr}$$

Since the first data point given is at time = 0 hr, we can find V_d with equal ease.

$$Cp_0 = \frac{D}{V_d}$$

Solving this for V_d gives

$$V_d = \frac{D}{Cp_0} = \frac{70 \text{ mg}}{5.8 \text{ mg/L}} = 12.1 \text{ L}$$

We may now calculate clearance:

$$Cl = k_e \cdot V_d = (0.211 \text{ hr}^{-1})(12.1 \text{ L}) = 2.55 \text{ L/hr}$$

- (5) Using the kinetic parameters found in question (4), calculate the steady-state gentamicin concentrations (peak and trough) expected for a dosing regimen of 70mg every 8 hours. Are these levels within the desired therapeutic range? If not, what changes in the dosing regimen would you recommend (keep the dosing interval at 8 hours)?

Determining peak and trough levels using the parameters just calculated for this patient. Although not required in this problem, peak and trough levels are shown below for the 1st dose as well as dosing at steady-state.

$$Cp(\text{peak})_1 = 5.8 \text{ mg/L} \quad (\text{one of the data points given})$$

$$\begin{aligned} Cp(\text{trough})_1 &= Cp(\text{peak})_1 \cdot e^{-k_e t} \\ &= (5.8 \text{ mg/L}) \cdot e^{-(0.211 \text{ hr}^{-1})(8 \text{ hr})} = 1.07 \sim 1.1 \text{ mg/L} \end{aligned}$$

At steady-state,

$$Cp_{ss}(\text{peak}) = \frac{Cp_0}{(1 - e^{-k_e t})} = \frac{5.8 \text{ mg/L}}{[1 - e^{-(0.211 \text{ hr}^{-1})(8 \text{ hr})}]} = 7.1 \text{ mg/L}$$

$$Cp_{ss}(\text{trough}) = Cp_{ss}(\text{peak}) \cdot e^{-k_e t} = (7.1 \text{ mg/L}) \cdot e^{-(0.211 \text{ hr}^{-1})(8 \text{ hr})} = 1.3 \text{ mg/L}$$

These are a little high. While the trough value is in the therapeutic range of 0-6 mg/L, the predicted peak of 7.1 mg/L may lead to toxic side effects. We might recommend decreasing the dose to give a steady-state peak of 6.0 mg/L (the upper limit of the therapeutic window). To calculate this dose, we must solve the appropriate equation for D.

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

which rearranged to yield

$$\begin{aligned} D &= Cp_{ss}(\text{peak}) \cdot V_d \cdot (1 - e^{-k_e t}) \\ &= (6.0 \text{ mg/L})(12.1 \text{ L}) \cdot [1 - e^{-(0.211 \text{ hr}^{-1})(8 \text{ hr})}] \\ &= 59.2 \text{ mg} \sim 60 \text{ mg} \end{aligned}$$

A dosing regimen of 60 mg every 8 hours would provide steady-state levels of

$$Cp_{ss}(peak) = \frac{D/V_d}{(1 - e^{-k_e t})} = \frac{(60mg/12.1L)}{[1 - e^{-(0.211hr^{-1})(8hr)}]} = 6.1mg/L$$

$$Cp_{ss}(trough) = Cp_{ss}(peak) \cdot e^{-k_e t} = (6.1mg/L) \cdot e^{-(0.211hr^{-1})(8hr)} = 1.1mg/L$$

This dosing regimen should be acceptable. Recall that we are using IV bolus equations even though the administration of the drug is actually via short-term infusions. These IV bolus equations will overestimate the Cp levels. The degree to which these equations overestimate the concentrations is dependent on the infusion rate and the rate of elimination.