Aminoglycoside Pharmacokinetics

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First Dose Kinetics

- A 38 year old male with burns over 85% of total body surface area is admitted to the hospital. He weighs 75 kg and is 5’11” tall. He is empirically started on cefotaxime 1gm IV q8h and gentamicin 100 mg IV q8h. Tmax=101.1°F, S.cr=0.9, WBC=10,000. The following PK study is performed after the first gentamicin dose:

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2100-2200</td>
<td>100 mg gentamicin infused</td>
</tr>
<tr>
<td>2230</td>
<td>4.5 mg/L</td>
</tr>
<tr>
<td>0224</td>
<td>1.2 mg/L</td>
</tr>
<tr>
<td>0430</td>
<td>0.4 mg/L</td>
</tr>
</tbody>
</table>

Graph the data...

What is the trough?

- The trough is zero because this is the first dose.
- Important point to remember in understanding and calculating Vd.
- An estimation of Vd is dose/Δconcentration.
  - Do NOT apply this on the test: the equation for Vd with aminoglycosides is more complex to account for drug elimination during administration.
  - When calculating the Vd after an initial dose, where no AG has previously been given, you are actually subtracting zero from the Cmax.
  - When calculating the Vd for aminoglycosides after a first dose, don’t put anything in the denominator that would indicate there is drug on board when the first dose was given.

At 2 hours post dose, concentration appears to be 2.5 mg/L.
At time 5 hours post dose, concentration appears to be 0.8 mg/L. Change in y over change in x is \( \frac{\ln 2.5 - \ln 0.8}{5-2} \), which is 0.3798.

What is the half-life?
- Change in y over change in x reveals an elimination rate constant of 0.3798 hr\(^{-1}\) (half life = 1.83 hours)
- Remember to use natural logs when calculating change in y – semi log paper only shows the relationship (and gives you the Cmax) but does not actually transform the data
- Dettli value \( k = 0.293 \) h\(^{-1}\), AHHH!!!

What is the extrapolated peak?
- By reading graph, appears to be about 6 mg/L
- Can pick a point on the best fit line & extrapolate to peak
  - We’ll pick 2.5 mg/L at 2 hours post dose again
  - Use the equation \( C_2 = C_1 e^{\pm kt} \) to move forward or back on the line
    - \( e^{+t} \) moves forward in time ("down" the line)
    - \( e^{-t} \) moves back in time ("up" the line)
  - \( 2.5 e^{0.3798*2} = 5.34 \) mg/L

What is the volume of distribution?
- \([100 (1-e^{-0.3798*1})]/[0.3798 (5.34 -0)] = 15.6 \) L or 0.21 L/kg

\[
C_2 = C_1 e^{(\pm k \Delta t)}
\]
What dose and interval will provide peak serum concentrations of 8 mg/L and troughs of ≤ 1 mg/L?

- Interval
  - \([(-1/0.3798)*\ln(1/8)] +1 = 6.5\) hours
  - Round to 8 hours
- Infusion rate
  - \([0.3798*15.6*8*(1-e^{-0.3798*8})]/[1-e^{-0.3798*1}] = 142.8\) mg/hr
  - Round to 140 mg
- 140 mg q8h

What will the \(C_{\text{max}}\) and \(C_{\text{min}}\) be on the regimen you have determined?

- \(C_{\text{max}}\)
  - \([140 (1-e^{-0.3798*1})]/[0.3798*15.6*(1-e^{-0.3798*8})] = 7.84\) mg/L
- \(C_{\text{min}}\)
  - \(7.84e^{-0.3798*7} = 0.55\) mg/L

Steady State Pharmacokinetics

- MH is a 20 year old woman with an intra-abdominal infection who has been receiving ampicillin/sulbactam (Unasyn) 3 g IV q6h and gentamicin 120 mg IV q6h for the past two days
  - \(S_c = 1.0\) mg/dL
  - WBC = 13,000
  - Temp = 100°F
  - Wt = 52 kg
  - Ht = 5’3”

Pharmacokinetic study, 3rd Day of therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0845</td>
<td>1.6 mg/L</td>
</tr>
<tr>
<td>0900-1000</td>
<td>gentamicin 120 mg</td>
</tr>
<tr>
<td>1015</td>
<td>9.23 mg/L</td>
</tr>
</tbody>
</table>

Graph the data...
At steady state, $C_{\text{max}}$ and $C_{\text{min}}$ remain the same, and given a time post dose, the concentration at that time remains the same. Here, the concentration is 1.6 mg/L at 0845 (0.25 hrs pre dose or 5.75 hours post previous dose). So, the concentration will be 1.6 mg/L at 1445 (0.25 hrs pre next dose or 5.75 hours post dose).

To arrive at the elimination rate constant, calculate $\Delta y$ over $\Delta x$, or $(\ln 9.23 - \ln 1.6)/(5.75-1.25)$, or 0.3894 hr$^{-1}$. This is the same as plugging the values into the formula $C_2 = C_1 e^{-kt}$ where $C_1$ is 9.23 mg/L, $C_2$ is 1.6 mg/L, and $t$ is the difference in time between the 2 points, or 4.5 hours.

Remember, you can always calculate an elimination rate constant, given only two post-infusion data points. If you have three points, you should graph and pick two points on the line to calculate the slope ($k_d$). In clinical practice, you will rarely have three data points.

Pre steady state kinetics

- In some of the problems, you are given two post infusion levels, and one pre-infusion level, and the patient is not yet at steady state.
- Here, calculate the elimination rate constant from the two post infusion levels and use that to get the trough by extrapolating forward from the pre-infusion level.
- Again, when calculating $V_d$, be sure to plug in the correct values for $C_{\text{max}}$ and $C_{\text{min}}$ (must be those immediately before and after the infusion that produced your two post-infusion levels).
What is the half-life?
- Kd = 0.3894 hr⁻¹
- Thus, t₁/₂ = 0.693/0.3894 hr⁻¹ = 1.8 hours

What is the extrapolated peak concentration?
- Recall from the graph, the peak appeared to be about 10 mg/L
- Can calculate a more exact peak
  - Concentration 15 minutes post infusion end was 9.23 mg/L
  - Elimination rate constant is 0.3894 hr⁻¹
  - Cmax = 9.23 e^(0.3894*1/4) = 10.2 mg/L

What is the extrapolated trough concentration?
- Again, move “down” the line to get the trough
  - Can apply 10.2 mg/L (time to trough would be 5 hours), 9.23 mg/L (time to trough would be 4.75 hours) or 1.6 mg/L (time to trough of 0.25 hours)
  - 1.6 e^(-0.3894*0.25) = 1.45 mg/L

What is the volume of distribution?
- \[ \frac{[120(1-e^{-0.3894})] [0.3894 (10.2 - 1.45e^{-0.3894})]}{0.3894 (10.2 - 1.45e^{-0.3894})} = 10.8 \text{ L or } 0.21 \text{ L/kg} \]

Recommend an appropriate gentamicin dose and interval that would result in peaks of 6-7 and troughs <1.
- Interval
  - \[ [(-1/0.3894) \ln (1/7)] + 1 = 6 \text{ hours} \]
- Dose
  - \[ 0.3894 \times 10.8 \times 7(1-e^{-0.3894})/([1-e^{-0.3894}]^2) = 82 \text{ mg, round to } 80 \text{ mg} \]
  - 80 mg q6h
Calculate the peak and trough you expect on the new regimen

- \( C_{\text{max}} \)
  \[ 80 \times (1-e^{-0.3894 \times 1}) /[0.3894 \times 10.8 \times (1-e^{-0.3894 \times 6})] = 6.8 \text{ mg/L} \]
- \( C_{\text{min}} \)
  \[ 6.8e^{-0.3894 \times 5} = 0.97 \text{ mg/L} \]

Initial Dose

- A 45 year old diabetic woman with signs and symptoms of pyelonephritis (fever, nausea, vomiting, flank pain, dysuria) is admitted to your hospital. Urinalysis was significant for 23 RBC/hpf, 35 WBC, and many bacteria. Gram stain of the urine revealed Gram negative bacilli; culture and sensitivities are pending. The physician wants to cover Gram negative rods, including *Pseudomonas* sp., until culture results are available. The physician has ordered ceftazidime, 1g IV q12hr, and tobramycin, 80 mg IV q8hr.
- Wt=80 kg Ht=5’7”  \( S_{\text{Cr}}=1.2 \text{ mg/dl} \)  BUN=38 mg/dl

You receive the consult before the first dose has been given. What is this patient’s estimated creatinine clearance (using the method of Cockroft and Gault)?

- LBW
  \[ 45.5 + (2.3)(7) = 61.1 \text{ kg} \]
- CrCl
  \[ (((140-45)(61.1))/(72)(1.2)) \times 0.85 = 57.1 \text{ ml/min} \]

Using the Dettli equation, calculate an estimated half-life for aminoglycosides in this patient

- 0.0024 (57.1) +0.01 = 0.147 hr\(^{-1} \)
- Half life
  \[ \text{Ln} (2)/0.148 = 4.71 \text{ hours} \]

What is an appropriate first dose of tobramycin; and over what period of time should you collect levels for a first dose pharmacokinetic study?

- Dose
  \* Pt wt is 80 kg, LBW is 61.1 kg
  \* \[ ([80/61.1]-1) \times 100=31, \text{ patient is 31% above LBW, should use DBW to get an initial dose.} \]
  \* DBW = 61.1 + (0.4*(80-61.1)) = 70 kg
  \* Dose = 2 mg/kg * 70 kg, 140 mg
  \* Levels should be over at least 1.5x anticipated half-life
    \* 1.5 x 4.71 = 7-8 hours

Summary

- Empiric Dosing
  \* No patient-specific data
  \* Use population estimate equations/values (Cockroft-Gault, Dettli, typical dosing ranges, etc.)
- 1\(^{st}\) Dose Kinetics
  \* 3 post-dose levels \( \Rightarrow \) need to graph
    \* Pick two random points on the best-fit line to calculate kd
  \* Trough is zero
- 2\(^{nd}\) Dose Kinetics (Pre-Steady State)
  \* 1 pre-dose and 2 post-dose levels \( \Rightarrow \) don’t need to graph
    \* Use the 2 post-dose levels for the kd
  \* Use the pre-dose level to extrapolate the trough
- Steady State Kinetics
  \* Peak and trough around the dose \( \Rightarrow \) don’t need to graph
    \* At steady state, the Cmax and Cmin remain the same