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=101.1ºF, S_{cr}=0.9, WBC=10,000. The following PK study is performed after the first gentamicin dose:
PK study

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration</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>
What is the trough?

- As this is a first dose--the trough is zero
- 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 \((\ln 2.5 - \ln 0.8)/(5-2)\), 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
- By regression, elimination rate constant is 0.3953 hr\(^{-1}\)
What is the extrapolated peak

- By reading graph, appears to be about 6
- 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 $C_2 = C_1 e^{-kt}$ to move forward or back on the line
    - $e^{-kt}$ moves forward in time
    - $e^{kt}$ moves back in time
  - $2.5 e^{(0.3798 \times 2)} = 5.34$ mg/L
- By regression, is 5.8 mg/L
\( C_2 = C_1 e^{-k \Delta t} \)
What is the volume of distribution

\[ \frac{100 \ (1-e^{-0.3798 \times 1})}{0.3798 \ (5.34 - 0)} = 15.6 \text{ L} \]
What dose and interval will provide peak serum concentrations of 8 mg/L and troughs of 1 mg/L

- Interval
  - $\left[\frac{-1}{0.3798}\right] \times (\ln(1/8)) + 1 = 6.5$
    - Round to 8 hours

- Infusion rate
  - $\left[0.3798 \times 15.6 \times 8 \times (1 - e^{-0.3798 \times 8})\right] / \left[\left(1 - e^{-0.3798 \times 1}\right)\right] = 142.8$ mg/hr
    - Round to 140 mg
What will the $C_{p_{\text{max}}}$ and $C_{p_{\text{min}}}$ be on the regimen you have determined?

- **Cmax**
  - $\frac{[140 \times (1-e^{-0.3798\times1})]}{[0.3798\times15.6\times(1-e^{-0.3798\times8})]} = 7.84$ mg/L

- **Cmin**
  - $7.84e^{-0.3798\times7} = 0.55$ 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

- \( S_{cr} = 1.0 \text{ mg/dL} \)
- WBC = 13,000
- Temp = 100\(^\circ\)F
- Wt = 52 kg
- Ht = 5’3’’
Pharmacokinetic study--around 0900 Dose, 3\textsuperscript{rd} Day of therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0845</td>
<td>1.6 mg/L</td>
</tr>
<tr>
<td>0900-1000</td>
<td>gentamicin 120 mg infused</td>
</tr>
<tr>
<td>1015</td>
<td>9.23 mg/L</td>
</tr>
</tbody>
</table>
At steady state, $C_{p_{\text{max}}}$ and $C_{p_{\text{min}}}$ 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.
Here, there are only two data points. As two points define a straight line, there is no reason to pick any other points on the line you draw. That would only introduce error. Here, there is no real point in graphing the data as long as you understand what is going on.
Remember, you can always calculate an elimination rate constant, given only two post-infusion data points. If you have three points, you should graph or use regression. In clinical practice, you will likely only very rarely have three data points.
A vertical line has been drawn in to represent the end of the infusion, and thus the intersection between the line describing the elimination and this vertical line is the Cmax. The Cmax appears to be slightly above 10 mg/L.
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 Vd, be sure to plug in the correct values for Cmax and Cmin (must be those immediately before and after the infusion that produced your two post-infusion levels)
What is the half-life

- Half life = \ln (2)/elimination rate constant
  - \ln (2)/0.3894\text{hr}^{-1} = 1.78 \text{ 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
  - \( C_{\text{max}} = 9.23 \ e^{(0.3894 \times 0.25)} = 10.2 \ \text{mg/L} \)
Determine the extrapolated trough

- 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)
  - $1.6 \times e^{-0.3894 \times 0.25} = 1.45 \text{ mg/L}$
Determine the volume of distribution

\[
\frac{120 \times (1 - e^{-0.3894 \times 1})}{0.3894 \times (10.2 - (1.45 \times e^{-0.3894 \times 1}))} = 10.8 \text{ L}
\]
Recommend an appropriate gentamicin dose and interval that would result in peaks of 6-7 and trough<1.

- **Interval**
  
  $$\left[\frac{-1}{0.3894}\ln \left(\frac{1}{7}\right)\right] + 1 = 6 \text{ hours}$$

- **Dose**
  
  $$\frac{0.3894 \times 10.8 \times 7 \times (1-e^{-0.3894 \times 6})}{(1-e^{-0.3894 \times 1})} = 82 \text{ mg, round to 80}$$
Calculate the peak and trough you expect on the new regimen

- $C_{p_{\text{max}}}$
  - $[80 * (1 - e^{-0.3894 \times 1})] / [0.3894 \times 10.8 \times (1 - e^{-0.3894 \times 6})] = 6.8$

- $C_{p_{\text{min}}}$
  - $6.8e^{-0.3894 \times 5} = 0.97 \text{ mg/L}$
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 $S_{Cr}=1.2$ 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**
  - $45.5 + (2.3)(7) = 61.1$ kg

- **CrCl**
  - $[((140-45)*(61.1))/((72)*(1.2))]*0.85 = 57.1$ ml/min
Using the Dettli equation, calculate an estimated half-life for aminoglycosides in this patient

- $0.0024 \times (57.1) + 0.01 = 0.147 \text{ hr}^{-1}$
- Half life
  - $\ln(2)/0.148 = 4.71 \text{ hours}$
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
  - 
    \[
    \frac{80}{61.1} - 1 \times 100 = 31, \text{ patient is } 31\% \text{ above LBW, should use DBW to get an initial dose.}
    \]
  - 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
    - \[
    1.5 \times 4.71 = 7 - 8 \text{ hours}
    \]