Question #1:
Explain why high peak concentrations of aminoglycosides do not lead to increased nephro- or ototoxicity, whereas high trough concentrations over a longer period of time show extended toxicity. (2pts)

Answer:
Aminoglycosides show concentration dependent killing and there is also a post-antibiotic effect that depresses bacterial growth after plasma concentrations have fallen below MIC. The pharmacodynamic properties suggest that less frequent administration of larger doses can maximize the bactericidal effect.

Nephro- or ototoxicity seems to be due to an active transporter into the inner ear where aminoglycosides exhibit their toxicity and due to the fact that aminoglycosides leave the inner ear only through passive diffusion. The active transport mechanism is saturable so that higher trough concentrations do not lead to increased nephro- or ototoxicity.

Question #2:
A patient was given 100 mg gentamicin over 30 minutes (i.v.) from 8:30 to 9:00 am. The following two serum levels were measured: 6μg/ml at 9:30 am and 2μg/ml at 4:00 pm. Calculate:

a. the elimination rate constant ke and half-life (1pt)

\[
k = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{\Delta t}
\]

\[
k = \frac{\ln \left( \frac{6}{2} \right)}{6.5} = 0.169 \, h^{-1}
\]

\[
t_{\frac{1}{2}} = \frac{0.693}{0.169} = 4.1 \, h
\]

b. the peak concentration at 9:00 am (0.5pt)
\[ C_{\text{max}} = \frac{C_{\text{max}}}{e^{-k \cdot t_{\text{max}}^*}} \]

\[ C_{\text{max}} = \frac{6}{e^{-0.169 \cdot 0.5}} = 6.53 \mu g / mL \]

c. the trough concentration at 4:30 pm (0.5pt)

\[ C_{\text{min}} = C_{\text{min}}^* \cdot e^{-k \cdot t_{\text{min}}^*} \]

\[ C_{\text{min}} = 2 \cdot e^{-0.169 \cdot 0.5} = 1.84 \mu g / mL \]

d. the volume of distribution (1pt)

\[ V_d = \frac{D}{k \cdot T} \cdot \frac{(1 - e^{-k \cdot T})}{\left( C_{\text{max}} - C_{\text{min}} \cdot e^{-k \cdot T} \right)} \]

\[ V_d = \frac{100}{0.169 \cdot 0.5} \cdot \frac{(1 - e^{-0.169 \cdot 0.5})}{(6.53 - 1.84 \cdot e^{-0.169 \cdot 0.5})} = 1183.43 \cdot \frac{0.081}{4.84} = 19.8 L \]

**Question #3:**

H.W., a 51-year-old, 5’8’’, 72 kg woman with a serum creatinine of 1.5mg/dL, has been started on 1.5g of vancomycin over one hour short-term infusion every 12h for the treatment MRSA skin infection.

a. Calculate the initial peak and trough vancomycin concentrations.

\((V_d = 0.17 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15)\) (2pts)

\[ V_d = 0.17 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 = 0.17 \cdot 51 + 0.22 \cdot 72 + 15 = 39.51 \text{ L} \]

\[ \text{IBW} = 45.5 + 2.3 \cdot (\text{height in inches} - 60) \text{ kg} = 45.5 + 2.3 \cdot 8 = 63.9 \text{ kg} \]

\[ 120\% \text{IBW} = 1.2 \cdot 63.9 = 76.68 \text{ kg} > \text{TBW} \]

Use TBW to calculate \( CL_{Cr} \)

\[ CL = CL_{Cr} \cdot \frac{(140 - \text{age}) \cdot \text{weight}}{85 \cdot C_{p_{\text{creat}}}} = \frac{(140 - 51) \cdot 72}{85 \cdot 1.5} = 50.26 \text{ mL/min} = 3.02 \text{ L/h} \]

\[ k_e = \frac{CL}{V_d} = \frac{3.02 \text{ L/h}}{39.51 \text{ L}} = 0.076 \text{ h}^{-1} \]
\[ C_{\text{peak}} = \frac{D}{CL \cdot T} \cdot (1 - e^{-keT}) = \frac{1500}{3.02 \cdot 1} \cdot (1 - e^{-0.076 \cdot 1}) = 36.3 \text{ mg/L} \]

\[ C_{\text{trough}} = C_{\text{peak}} \cdot e^{-ke \cdot (\tau - T)} = 36.3 \cdot e^{-0.076 \cdot 11} = 15.7 \text{ mg/L} \]

b. Predict the steady state peak and trough concentrations using the information from above and discuss the results. (2pts)

\[ C_{\text{peak\_ss}} = \frac{D \cdot (1 - e^{-ke\cdot T})}{CL \cdot T \cdot (1 - e^{-ke\cdot \tau})} = \frac{1500 \cdot (1 - e^{-0.076 \cdot 1})}{3.02 \cdot 1 \cdot (1 - e^{-0.076 \cdot 12})} = 60.8 \text{ mg/L} \]

\[ C_{\text{trough\_ss}} = C_{\text{peak\_ss}} \cdot e^{-ke \cdot (\tau - T)} = 60.8 \cdot e^{-0.076 \cdot 11} = 26.4 \text{ mg/L} \]

Vancomycin’s Therapeutic Range:

Peak: 25-40 mg/L (not routinely measured)

Trough: 5-15 mg/L (up to 20 mg/L for meningitis)

So the dose regimen needs to be adjusted. Decrease the dose and monitor the vancomycin plasma concentrations.

**Question #4:**

Which combination of the following pharmacokinetic changes best describes the elderly and neonates? (These groups share similar PK characteristics.) (1pt)

1. Low renal clearance
2. Longer half-lives
3. Low metabolic clearance
4. Decreased protein binding
5. Relatively less body water

A) 1 & 4

**B) 1, 2, 3 & 4**

C) 1, 3, 4 & 5

D) 1, 4, & 5

E) all of the above