

**PHA 5128
Homework III
Spring 2005**

Question 1: (2 points)

A pharmaceutical company has developed a new aminoglycoside. The company got the following data from two patients from a small pilot study. Both patients have normal renal function ($CL_{Cr}=0.13$ L/min).

Patient I weighs 60 kg and Patient II weighs 90 kg. Both patients are 6' tall.

Answer:

In order to calculate the half-life we first have to find the elimination rate constant.

Since the clearance is given, the parameter that remains to be found is the Volume of Distribution for both patients. (Hint $CL=k_e \cdot V_d$)

The difference in weight of patient II is outside of ideal body weight $\pm 20\%$ so we use normal body weight. The weight of Patient II is within $\pm 20\%$ of IBW, so we use IBW. Using TBW or ABW is also considered as right answer.

$$\begin{aligned} \text{IBW} &= 50 + 2.3(\text{height in inches} > 60 \text{ in}) [\text{kg}] \\ &= 50 + 2.3 \cdot (12) \\ &= 77.6 \text{ kg} \end{aligned}$$

Calculation of the V_d :

$$\begin{aligned} V_d(60\text{kg}) &= 0.25 \text{ L/kg} \cdot 60\text{kg} = 15\text{L} \\ V_d(90\text{kg}) &= 0.25 \text{ L/kg} \cdot 90\text{kg} = 22.5\text{L} \end{aligned}$$

or for Patient II:

$$\begin{aligned} V_d &= 0.25[\text{IBW} + 0.4 \cdot (\text{TBW} - \text{IBW})] \\ &= 0.25[77.6 + 0.4(90 - 77.6)] \\ &= 20.6\text{L} \end{aligned}$$

$$k_e = 7.8 / 20.6 = 0.38 \text{ h}^{-1}$$

$$t_{1/2} = 1.8 \text{ h}$$

Calculation of the half-life:

k_e can be calculated using the relationship $CL=k_e \cdot V_d$

$$\begin{aligned} \text{Patient I: } k_e &= 0.13 \text{ L/min} / 15 \text{ L} = 0.0087 \text{ min}^{-1} \cdot 60 \text{ min} / 1\text{h} = 0.522 \text{ h}^{-1} \\ t_{1/2} &= \ln 2 / k_e = 0.693 / 0.522 \text{ h}^{-1} = 1.33 \text{ h} \end{aligned}$$

$$\begin{aligned} \text{Patient II: } k_e &= 0.13 \text{ L/min} / 22.5 \text{ L} = 0.0057 \text{ min}^{-1} \cdot 60 \text{ min} / 1\text{h} = 0.342 \text{ h}^{-1} \\ t_{1/2} &= \ln 2 / k_e = 0.693 / 0.342 \text{ h}^{-1} = 2.0 \text{ h} \end{aligned}$$

Question 2:(2 points)

Discuss, why the sampling time is important to monitor aminoglycoside administration.

Please include why it is important for the nurse to record the exact sampling time, and when peak and trough levels should be drawn.

Answer:

The sampling time is of great importance in aminoglycoside administration since aminoglycosides have a small but significant distribution phase. The most widely accepted method is to sample 1

hour after the maintenance dose has been initiated (for an 30 min infusion that would mean 30 min after the infusion is stopped). Trough concentrations are usually obtained in the half hour before the next maintenance dose. It is important to record the exact sampling time, so the clinical peak and trough (sampled 30 after ending the infusion and 30 min before the next maintenance dose) concentrations can be extrapolated to the true peak and trough concentrations.

Question 3:(2 points)

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.

Answer:

Aminoglycosides show concentration dependent killing and there is also a postantibiotic 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.

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 ototoxicity.

Question 4:

A 4 y.o. infant is administered to the Shands emergency room and is diagnosed with possible pneumonia. The infant weighs 13.5 kg and is 3.6 ft tall. He was started on a gentamicin therapy with 5mg q8h. On day three plasma samples were drawn for therapeutic drug monitoring.

The gentamicin dosing schedule is 8-16-24h.

The following plasma concentrations were obtained.

Gentamicin peak serum concentration drawn @ 9 am: 8 mg/L

Gentamicin trough serum concentration drawn @ 3:30 pm: 3mg/L

- a) Determine the estimated k_e and half life in this patient. (1point)

Answer:

$$k_e = \ln(\text{peak conc.} / \text{trough conc.}) / \tau = \ln(8\text{mg/L} / 3\text{mg/L}) / 6.5\text{h} = 0.151 \text{ h}^{-1}$$

$$t_{1/2} = \ln 2 / k_e = 0.693 / 0.151 \text{ h}^{-1} = 4.5\text{h}$$

- b) Calculate the patients Volume of Distribution. (1 point)

Answer:

$$V_d = (D/k_e * T) * ((1 - e^{-k_e * T}) / (C_{\text{max}} - C_{\text{min}} * e^{-k_e * T}))$$

$$C_{\text{max}} = C * \text{max} / e^{-k_e * T} = 8.6 \text{ mg/L}$$

$$C_{\text{min}} = C_{\text{min}} * e^{-k_e * T} = 2.78 \text{ mg/L}$$

$$V_d = (5 / 0.151 * 0.5) * ((1 - e^{-0.151 * 0.5}) / (8.6 - 2.78 * e^{-0.151 * 0.5}))$$

$$V_d = 0.793 \text{ L}$$

- c) Compare the measured peak and trough levels with the recommended therapeutic concentrations. (1 point)

Answer:

The measured peak concentration is located at the high end but still within the therapeutic range (5-8mg/L). The trough concentration however is higher than the recommended trough concentration (<2 mg/L). The dosing regimen should be adjusted.

- d) Calculate the dose and dosing regimen to achieve peak concentration of max. 5 mg/L and trough concentration of 1 mg/L. (1 point)

Answer:

$$\tau = \ln(5/1)/0.151 + 0.5 = 11.15 \approx 12\text{h}$$
$$D = 5 * 0.151 * 0.79 * 0.5 \left(\frac{1 - e^{-0.151 * 12}}{1 - e^{-0.151 * 5}} \right) = 3.43 \text{ mg q12h}$$