PHA 5128

Homework III (Answers)

1. A 3 month old infant, born at full- term gestational age, is admitted to Shands Hospital for possible pneumonia. The infant weighs 3.5 kg. Ampicillin 175 mg iv q6h and Gentamicin 5 mg iv q8h (30 min infusion) is started. On day 3 of therapy, gentamicin serum concentrations are drawn as listed below:

Gentamicin dosing schedule 06-14-22 h.
Gentamicin peak serum conc. 6.6 μg/ml drawn at 0700 on 4/23.
Gentamicin trough serum conc. 1.1 μg/ml drawn at 1330 on 4/23.

a. Determine the estimated k_e and $t_{1/2}$ of gentamicin in this patient.

$$k = \frac{\ln \frac{6.6}{1.1}}{6.5} = 0.276h^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = 2.5h$$

b. Calculate the dose and dosage schedule necessary to achieve a peak serum gentamicin concentration of at least 10 μg/ml.

$$C_{\max} = \frac{6.6}{e^{-0.276 \cdot 0.5}} = 7.6 mg / mL$$

$$C_{\min} = 1.1 \cdot e^{-0.276 \cdot 0.5} = 0.96\ mg / mL$$

$$Vd = \frac{5}{0.276 \cdot 0.5} \cdot \frac{\left(1 - e^{-0.276 \cdot 0.5}\right)}{\left(7.6 - 0.96 \cdot e^{-0.276 \cdot 0.5}\right)} = 36.36 \cdot \frac{0.129}{6.76} = 0.69L$$

$$t = \frac{\ln\left(\frac{10}{1}\right)}{0.276} + 0.5 = 8.8h\ (8h)$$

$$D = 10 \cdot 0.276 \cdot 0.69 \cdot 0.5 \cdot \frac{\left(1 - e^{-0.276 \cdot 8}\right)}{\left(1 - e^{-0.276 \cdot 0.5}\right)} = 0.952 \cdot \frac{0.89}{0.129} = 6.6mg \Rightarrow 7mg\ q8h$$

2. How long after the end of an intravenous infusion do you draw a peak serum concentration of gentamicin? Discuss the reason for not drawing the peak concentration immediately following the end of the infusion.

Wait at least 30 minutes to allow for tissue distribution. You can sample at later points and correct by extrapolation.

By convention, the 30 min. sample after the end of the infusion represents the "clinical" peak.

3. A 40 year-old female patient (60 kg, SeCr 0.8 mg/dL) is treated with 100 mg gentamicin TID infused over 30 minutes.

a. Assuming normal pharmacokinetics (Vd = 0.25 L/kg, CL=CLcr), predict the measured peak concentration one hour after the infusion was started and the measured trough concentration one half-hour before the next infusion at steady state.

$$CL_{Cr} = \frac{(140-40)\cdot 60}{85\cdot 0.8} = 88.2 mL/\min = 5.3 L/h$$

$$k = \frac{CL}{V_d} = \frac{5.3}{15} = 0.35 h^{-1}$$

$$C_{\max} = \frac{100}{5.3\cdot 0.5}\cdot\frac{\left(1-e^{-0.35\cdot 0.5}\right)}{(1-e^{-0.35\cdot 8})} = 6.5 \mu g/mL$$

$$C_{\min} = 6.5\cdot e^{-0.35\cdot 7.5} = 0.47 \mu g/mL$$

$$C^*_{\max} = C_{\max}\cdot e^{-0.35\cdot 0.5} = 6.5\cdot e^{-0.35\cdot 0.5} = 5.5 \mu g/mL$$

$$C^*_{\min} = C_{\max}\cdot e^{-0.35\cdot 7} = 0.56 \mu g/mL$$

b. On the third day of treatment, the following measured peaks and troughs were obtained: 5.1 μg/ml and 1.3 μg/ml. Calculate the volume of distribution in this patient from these peak and trough concentrations.

$$k = \frac{\ln\frac{5.1}{1.3}}{6.5} = 0.21 h^{-1}$$

$$C_{\max} = \frac{5.1}{e^{-0.21\cdot 0.5}} = 5.7 \mu g/mL$$

$$C_{\min} = 1.3 \cdot e^{-0.21 \cdot 0.5} = 1.17\ mg / mL$$

$$V_d = \frac{100}{0.21 \cdot 0.5} \cdot \frac{(1 - e^{-0.21 \cdot 0.5})}{(5.7 - 1.17 \cdot e^{-0.21 \cdot 0.5})} = 952 \cdot \frac{0.1}{4.65} = 20.5L$$

c. Design a dosing regiment to produce a peak of 6 μg/mL and a trough of 1 μg/mL.

If true peak and troughs are used

$$t = \frac{\ln \frac{6}{1}}{0.21} + 0.5 = 9.0h \rightarrow 8h$$

$$D = 6 \cdot 0.21 \cdot 20.5 \cdot 0.5 \cdot \frac{(1 - e^{-0.21 \cdot 8})}{(1 - e^{-0.21 \cdot 0.5})} = 12.9 \cdot \frac{0.814}{0.1} = 105mg$$

$\rightarrow$ 100 *mg* q8h

If measured peaks and troughs are used

$$C_{\max} = \frac{6}{e^{-0.21 \cdot 0.5}} = 6.7 g / mL$$

$$C_{\min} = 1 \cdot e^{-0.21 \cdot 0.05} = 0.9 g / mL$$

$$t = 10h \rightarrow 12h$$

$$D = 6.7 \cdot 0.21 \cdot 20.5 \cdot 0.5 \cdot \frac{\left(1 - e^{-0.21 \cdot 12}\right)}{\left(1 - e^{-0.21 \cdot 0.5}\right)} = 14.4 \cdot \frac{0.92}{0.1} = 132mg \rightarrow 130mg \text{ q12h}$$

4. Mr. B.G., a 23 year old, 58 kilogram patient with a gram-negative pneumonia, was being treated with gentamicin and ampicillin. Gentamicin had been given as an intravenous infusion (80 mg) over 30 minutes every 8 hours. Blood samples were obtained just before and 30 minutes after the end of the fourth infusion to prevent toxicity and to evaluate his therapy. The gentamicin concentrations reported were 0.4 and 4.9 milligrams/liter. The serum creatinine in the patient was 1.2 milligrams/deciliter.
   a. Compare the measured results with the population average.
   b. Make a dosing adjustment to achieve a peak concentration of 8 mg/L.
   c. Would this patient be a good candidate for once-a-day dosing? What daily dose would you recommend?

C_{peak}(t=+0.5h after stop of infusion)=4.9 mg/L

C_{trough}(t=7h after stop of infusion)=0.4 mg/L

Assume steady-state conditions.

For this patient:

$$k = \frac{\ln \frac{4.9}{0.4}}{7} = 0.358h^{-1}$$

$$t_{1/2} = 1.9h$$

$$V_d = \frac{80}{0.358 \cdot 0.5} \cdot \frac{(1 - e^{-0.358 \cdot 0.5})}{(5.9 - 0.4 \cdot e^{-0.358 \cdot 0.5})} = 447 \cdot \frac{0.163}{5.6} = 13L$$

Population:

$$V_D = 0.25*58 = 14.5 \text{ L}$$

$$\text{CL=CrCL=} \quad CL_{Cr} = \frac{(140 - 23) \cdot 58}{72 \cdot 1.2} = 78.5mL/\min = 4.71L/h$$

$$K = 4.71/14.5 = 0.325$$

$$T_{1/2} = 2.1$$

Patient half-life and population half-life are similar and you would expect peaks and troughs should be similiar.

Population C_{peak}=5.5 mg/L (C_{peak}*=4.7 mg/L) and C_{min}=0.40 mg/L (C_{min}*=0.47 mg/L)

b. Dosing adjustment

Using the same dosing interval (since trough values appear to be well below 1 mg/L):

Find a new V_D based on Cmax and Cmin= 13.0 L

$$D = 8 \cdot 0.358 \cdot 13 \cdot 0.5 \cdot \frac{(1 - e^{-0.358 \cdot 8})}{(1 - e^{-0.358 \cdot 0.5})} = 18.6 \cdot \frac{0.943}{0.16} = 110 mg$$

$\rightarrow$ 110 *mg* q8h

Patient half-life normal compared to population and could be a candidate for once-a-day dosing. Once a day dosing

7 mg/kg = (7)(58)=400 mg q24h