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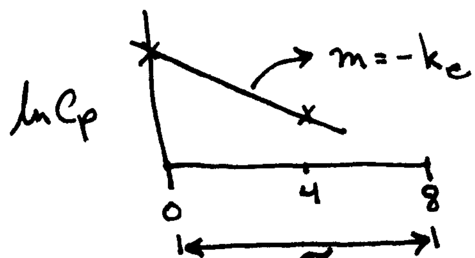
PHA 5127 Fall 1999

Case Study 5 - Solutions

Given information
- 300 mg IV every 8 hrs
- Cp_{ss} (peak) = 30 μg/ml
- Cp = 9 μg/ml 4 hrs after peak

1) Estimate k_e.

Although not stated in the information provided, we assume this antimicrobial drug follows a one-compartmental model with first order elimination.



Since the dose is administered by an IV bolus injection and two concentrations are given, k_e may be found quite easily.

$$k_e = -m$$

$$= -\frac{\ln Cp_1 - \ln Cp_2}{t_1 - t_2} = -\frac{\ln(Cp_1/Cp_2)}{t_1 - t_2}$$

$$= -\frac{\ln(30/9)}{0-4} = \underline{0.30\,hr^{-1}}$$

2) Calculate Vd.

Since we are given the peak concentration at steady state, we may calculate Vd using the expression for C_{pss} (peak).

$$C_{pss}(\text{peak}) = \frac{C_{p0}}{(1-e^{-k_e\tau})} \quad ; \quad C_{p0} = D/V_d$$

$$= \frac{D}{V_d \cdot (1-e^{-k_e\tau})}$$

Solving this equation for Vd gives

$$V_d = \frac{D}{C_{pss}(\text{peak}) \cdot (1-e^{-k_e\tau})}$$

$$= \frac{300\text{ mg}}{(30\,\mu g/ml) \cdot (1-e^{-(0.30\,hr^{-1})(8\,hr)})} \cdot \frac{1000\,\mu g}{1\,mg} \cdot \frac{1L}{1000\,ml}$$

$$= \underline{11\text{ L}}$$

3) Average concentration @ steady state

$$\bar{C}_{pss} = \frac{D}{Cl \cdot \tau}$$

$$= \frac{D}{k_e \cdot V_d \cdot \tau}$$

$$\bar{C}_{pss} = \frac{300\,mg}{(0.30\,hr^{-1})(11\,L)(8\,hr)} \cdot \frac{1000\,\mu g}{1\,mg} \cdot \frac{1\,L}{1000\,ml}$$

$$= \underline{11.4\ \mu g/ml}$$

4) Trough concentration.
The trough concentration is found 8 hrs (τ, the dosing interval) after the peak. Thus,

$$C_{pss}\,(trough) = C_{pss}\,(peak) \cdot e^{-k_e \tau}$$

$$= (30\ \mu g/ml) \cdot e^{-(0.30\,hr^{-1})(8\,hr)}$$

$$= \underline{2.7\ \mu g/ml}$$

5) Steady state concentrations may be modulated by changing either the dose (D) or the dosing interval (τ). In order to increase $\bar{C}_{pss}$ without changing the dose, the drug must be administered more frequently, i.e. decrease τ.
Both C_{pss} (peak) and C_{pss} (trough) will increase due to greater accumulation of drug in the body. (With a shorter dosing interval, there is less time for ~~each~~ drug elimination before subsequent doses).

6) What dose is required to attain a peak level of 40 μg/ml at steady state?

$$C_{pss}(\text{peak}) = \frac{D}{V_d \cdot (1 - e^{-k_e \tau})}$$

Solving this expression for dose gives

$$D = C_{pss}(\text{peak}) \cdot V_d \cdot (1 - e^{-k_e \tau})$$

$$= (40\ \mu g/ml)(11\ L)(1 - e^{-(0.30 hr^{-1})(8 hr)}) \cdot \frac{1\ mg}{1000\ \mu g} \cdot \frac{1000\ ml}{1\ L}$$

$$= \underline{400\ mg}$$

7) If giving 500 mg every 8 hr

$$C_{pss}(\text{peak}) = \frac{D}{V_d \cdot (1 - e^{-k_e \tau})}$$

$$= \frac{500\ mg}{(11\ L)(1 - e^{-(0.3 hr^{-1})(8 hr)})}$$

$$= \underline{50\ mg/L} \text{ (or } \mu g/ml)$$

$$C_{pss}(\text{trough}) = C_{pss}(\text{peak}) \cdot e^{-k_e \tau}$$

$$= (50\ \mu g/ml) \cdot e^{-(0.3 hr^{-1})(8 hr)}$$

$$= \underline{4.5\ \mu g/ml}$$