

PHA 5127 – Fall 2006
Case study # 7
Answer sheet

#1: What do the following parts of the equation describe?

$$Cp_{\min} = \frac{k_o}{k_e \bullet V_d} \frac{(1 - e^{-k_e t})(1 - e^{-n \cdot k_e \tau})}{1 - e^{-k_e \tau}} e^{-k_e t'}$$

Answer:

a) $\frac{k_o}{k_e \bullet V_d}$ Plasma concentration if the infusion would never stop

b) $(1 - e^{-k_e t})$ Provides information on how far the first C_{\max} is away from steady-state level

c) $\frac{(1 - e^{-n \cdot k_e \tau})}{1 - e^{-k_e \tau}}$ Accumulation factor

d) $e^{-k_e t'}$ Elimination after the stop of infusion

#2: B.F. is given the infusion you recommended at 8:00 am. At 9:00 am a plasma sample is taken and yields a Cp^*_{\max} of 9.2 $\mu\text{g/ml}$. Another sample is taken one half hour before the next infusion to give a Cp^*_{\min} of 2.4 $\mu\text{g/ml}$. Calculate the actual k_e and V_d for B.F. and recommend a dosing change to give a true C_{\max} of 7.5 $\mu\text{g/m}$. What is the new true C_{\min} expected with this dosing change. Assume that tau is 8 hours, dose is 120 mg, and the infusion time is 0.5 hour.

First calculate the ke

$$k_e = \frac{\ln(9.2/2.4)}{(15:30 - 9:00)} = 1.34/6.5\text{hrs} = 0.21 \text{ h}^{-1}$$

Next in order to calculate the Vd you must calculate the true C_{max} and C_{min}

$$C_{\max} = 9.2/e^{-0.21*0.5} = 10.2 \mu\text{g/ml}$$

$$C_{\min} = 2.4 * e^{-0.21*0.5} = 2.1 \mu\text{g/ml}$$

Now you can calculate a Vd

$$V_d = \frac{120}{(0.21*0.5)} * \frac{(1 - e^{-0.21*0.5})}{(10.2 - 2.1e^{-0.21*0.5})} = 13.7\text{L}$$

Now you can calculate the new dose.

$$D = 7.5 * 0.21 * 13.7 * 0.5 * \frac{(1 - e^{-0.21*8})}{(1 - e^{-0.21*0.5})} = 88 \text{ mg} \sim 90\text{mg}$$

Now for your new C_{min}

$$C_{\min} = 7.5 * e^{-0.21*(8 - 0.5)} = 1.6 \mu\text{g/ml}$$

#3: Theophylline has a desired steady state concentration around 15 mg/L to achieve therapeutic effect, and the average half-life of theophylline is about 4 hr, and the apparent volume of distribution is about 25 L (assume one compartment and linear kinetics). If a patient receives an intravenous dose of theophylline 240 mg over 4 hours every 12 hr. Is it possible to get therapeutic effect based on current dose regimen? If yes, why can it be? If not, what kind of dose regimen will be proposed?

Answer:

$$T_{1/2} = 4 \text{ hr} \rightarrow k_e = 0.693/4 = 0.17 \text{ hr}^{-1}$$

$$V_d = 25 \text{ L}$$

$$\text{Tau} = 12\text{hr}$$

$$K_0 = 240\text{mg}/4\text{hr} = 60 \text{ mg/hr}$$

$$\text{Tau} = 12\text{hr}$$

Then:

$$C_{P_{\max}} = \frac{k_o}{k_e \cdot V_d} \frac{(1 - e^{-k_e t})}{(1 - e^{-k_e \tau})} = \frac{60\text{mg/hr} \cdot (1 - e^{-0.17 \cdot 4})}{0.17\text{hr}^{-1} \cdot 25\text{L} \cdot (1 - e^{-0.17 \cdot 12})} = 8\text{mg/L}$$

$$Cp_{\min} = \frac{k_o}{k_e \cdot V_d} \frac{(1 - e^{-k_e t})}{(1 - e^{-k_e \tau})} \cdot e^{-k_e(\tau-t)} = \frac{60 \text{mg/hr} \cdot (1 - e^{-0.17 \cdot 4})}{0.17 \text{hr}^{-1} \cdot 25 \text{L} \cdot (1 - e^{-0.17 \cdot 12})} \cdot e^{-0.17 \cdot (12-4)} = 2.1 \text{mg/L}$$

$$Cp_{\text{ave}} = \frac{\text{DOSE}}{k_e \cdot V_d \cdot \tau} = \frac{240 \text{mg}}{0.17 \text{hr}^{-1} \cdot 25 \text{L} \cdot 12 \text{hr}} = 4.7 \text{mg/L}$$

Since both Cp_{\max} and Cp_{ave} are less than required therapeutic concentration (15 mg/L), a new dose regimen needs to be proposed. (As we can see from this example, infusion time does not affect average concentration at steady-state, but it does influence the other two concentrations and fluctuation.)

Once Cp_{ave} equals to 15 mg/L, therapeutic effect can be achieved.

$$Cp_{\text{ave}} = \frac{\text{DOSE}}{k_e \cdot V_d \cdot \tau} = 15 \text{mg/L}$$

$$\frac{\text{DOSE}}{0.17 \text{hr}^{-1} \cdot 25 \text{L} \cdot \tau} = 15 \text{mg/L}$$

$$\frac{\text{DOSE}}{\tau} = 63.75 \text{mg/hr}$$

We can either decrease τ or increase Dose to get Cp_{ave} to 15 mg/L.

Keep dose as 240 mg,

$$\frac{240 \text{mg}}{\tau} = 63.75 \text{mg/hr}$$

$\tau = 3.76$ hr, which is not feasible since the infusion time is 4 hr in this case, also, it is not convenient to patient to get infusion every 3.76 hr.

On the other hand, if we keep dosing interval as 12hr,

Dose level will increase to 765 mg.

$$\frac{\text{DOSE}}{12 \text{hr}} = 63.75 \text{mg/hr}$$

Other possible dose regimen can be proposed too based on this equation:

$$\frac{\text{DOSE}}{\tau} = 63.75 \text{mg/hr}$$

#4: A patient with pulmonary infection is going to begin multiple 30-minute intravenous infusion of gentamicin. The target clinical peak (1-hour after the infusion

start) and clinical trough (30-minute before the next infusion) at steady state are 10mg/L and 1mg/L respectively. If the patient is assumed to have first-order kinetics with K_e of 0.35 hr^{-1} :

a) How often should we give the drug to the patient (QD, BID, TID or QID)?

$$\tau = \frac{\ln\left(\frac{10}{1}\right)}{0.35} + 1 + 0.5 = 8.08 \text{ hr} \quad \therefore \text{we will use TID.}$$

b) If the patient has a V_d of 18 L, what is the daily dose we should give to this patient?

$$C_{\max_true} = C_{\max_clinical} \cdot e^{K_e \cdot \tau} = 10 \cdot e^{0.35 \cdot 0.5} = 11.9 \text{ mg/L}$$

$$C_{\max_true} = \frac{k_0}{K_e \cdot V_d} \cdot \frac{(1 - e^{-K_e \cdot T})}{(1 - e^{-K_e \cdot \tau})}$$

$$\Rightarrow k_0 = \frac{C_{\max_true} \cdot K_e \cdot V_d \cdot (1 - e^{-K_e \cdot \tau})}{(1 - e^{-K_e \cdot T})} = \frac{11.9 \cdot 0.35 \cdot 18 \cdot (1 - e^{-0.35 \cdot 8})}{(1 - e^{-0.35 \cdot 0.5})} \approx 440 \text{ mg/L}$$

$$\therefore \text{Dose}_{\text{-daily}} = k_0 \cdot T \cdot 24 / \tau = 440 \cdot 0.5 \cdot 3 = 660 \text{ mg}$$

c) How long will it take to reach steady state?

$$\sim 5 \text{ half-life} : 5 \cdot T_{1/2} = 5 \cdot \frac{\ln 2}{.35} \approx 10 \text{ hr}$$