Case Study VI
Answers
Fall 2005

1. A 65-year-old, 75 kg, 5'8" tall male patient X with a serum creatinine of 1.3mg/dL, is about to receive drug X orally (assume: absorption is so fast that we can use IV bolus model). Design a dosing regimen (calculate dosing interval, dose, average concentration) that will produce a steady-state peak concentration of 15mg/L and a steady-state trough concentration of 9mg/L. How would you give the drug if only tablets of 200mg are available? Show all calculations. (Assume Vd=0.6L/kg, CL=CrCL)

First, let us calculate his IBW :

IBW = 50 + 8*2.3 = 68.4 kg

Then we can use this IBW to calculate his CL

CL=CrCL= (140-age)*IBW /(72*SeCr) = 75*68.4/ (72*1.3) = 5130/93.6=54.8ml/min=3288ml/hr=3.3L/hr

Then we can calculate his Vd by:

Vd=75*0.6L/kg=45L

So, the Ke = CL/Vd= 0.073/hr

$$\tau \text{ (dosing interval)} = \frac{ln\left(\frac{C\,max,desired}{C\,min,desired}\right)}{Ke} = \frac{ln\left(\frac{\mathbf{15}}{\mathbf{9}}\right)}{\mathbf{0.073}} = 6.9\text{hr} \approx 8\text{hr}$$

Dose=Cave*CL*τ=(15+9)/2*3.3*8=316.8mg ≈ 300mg

Therefore, 1.5 tablet every 8 hours.

2. Drug Y was given ORALLY to two patients, A and B, respectively. As reported from literature, drug X follows first order absorption and elimination. Please find out if the following statements are correct. (Assume the other pharmacokinetic parameters are the same)

1.) If the dose for patient A is 200 mg and the dose for patient B is 400 mg, then T max for A is larger than that for patient B.

False: Since Tmax is depend on Ka and Ke, however it has nothing to do with dose.

2.) Because patient A has chronic GI tract disease, Ka for patient A is 0.25 $hr.^{-1}$, whereas the Ka value for patient B is 0.5 $hr.^{-1}$, then the average steady state concentration for patient A is lower than that of patient B.

False: Since the average concentration at steady state for orally administration is independent of Ka. Recall the formula: *Cp=F*Dose/CL*τ* , there is no Ka in the equation.

3. A 60-kg patient is begun on a continuous intravenous infusion of theophylline at 40 mg/hr (based on theophylline, not aminophylline). Forty-eight hours after beginning of the infusion, the plasma concentration is 15 mg/L.

a. If we assume that this concentration is at steady state, what is the theophylline clearance.

Css=K0/CL

CL=K0/Css=40/15=2.7L/hr

b. If the volume of distribution is estimated to be 30 L, what is the half-life?
Ke=CL/Vd=2.7/30=0.09/hr
$T_{1/2}$=0.693/ke=0.693/0.09=7.7hr

c. What would the plasma concentration be 10 hr after beginning the infusion.
Cp=k0/CL*(1-exp(-Ke*t))=40/2.7*(1-exp(-0.09*10))=40/2.7*0.59=8.74mg/L

d. If the infusion is continued for 3 days and then discontinued, what would the plasma concentration be 12 hours after the stop of the infusion.
Cp=Css*exp(-Ke*t)=15*exp(-0.09*12)=5.1mg/L

4. A 58 kg patient is started on 80 mg of gentamycin and is given as 1-hr infusion every 6 hr. If this patient is assumed to have an "average" volume of distribution (value of the population mean) of 0.25 L/kg and a normal half –life of 3 hr, what would be the peak plasma concentration at steady state (the true C_{max} value)? Is the 6 hr dosing interval sufficient to achieve a fluctuation of not more than 6.

Vd= 0.25*58=14.5 L
Ke=0.693/3=0.231/hr
CL=Ke*Vd=3.35L/hr

Cmax = $\frac{Dose \times \left(1 - e^{-ke \times T}\right)}{CL \times T \times \left(1 - e^{-ke \times \tau}\right)} = \frac{80 \times \left(1 - e^{-0.231 \times 1}\right)}{3.35 \times 1 \times \left(1 - e^{-0.231 \times 6}\right)} = \frac{80 \times (1 - 0.79)}{3.35 \times 1 \times (1 - 0.25)} = \frac{16.8}{2.5125}$

≈6.7mg

F= $e^{ke \times \tau} = e^{0.231 \times 6}$ ≈4, therefore, 6 hr is enough to achieve a fluctuation of no more than 6.