Key of Case Study 5
PHA 5127
Fall 2004

1. **A patient with pulmonary disease is receiving <u>IV bolus</u> injections of theophylline. The dose is 200 mg every 6 hr with satisfactory response. Recently, <u>steady state</u> theophylline plasma concentrations were determined to be 15 mg/L, 1 hour after the last dose administration and 8.2 mg/L 6 hr after the last dose administration (trough).**
   a. **Determine the elimination rate constant.**
      Ct1=Ct2*exp(-Ke*(t1-t2))
      8.2=15*exp(-Ke*(6-1)) Ke=Ln(8.2/15)/(-5)=0.12/hr
   b. **Volume of distribution.**
      At steady state,

$$Cpss(t) = \frac{Cp_0 \cdot e^{-k_e t}}{(1-e^{-k_e \tau})} = \frac{D \cdot e^{-k_e t}}{V_d \cdot (1-e^{-k_e \tau})}$$

where t is the time after last i.v. bolus injection. So, plug in the given plasma concentration one hour after administration.

$$V_d = \frac{D \cdot e^{-k_e t}}{Cp_{ss}(t) \cdot (1-e^{-k_e \tau})} = \frac{(200mg) \cdot e^{-(0.12hr^{-1}x1hr)}}{(15mg/L) \cdot [1-e^{-(0.12hr^{-1}x6hr)}]}$$

V_d = 23 L

   c. **Determine the clearance.**
      Cl=ke*Vd==(0.12hr^{-1})(23L) = 2.76 L/hr

   d **Estimate also the average steady state theophylline concentration (Cp_{ss}) with this regimen.**

$$\bar{C}pss = \frac{D}{Cl \cdot \tau} = \frac{200mg}{(0.12hr^{-1}x23L)\cdot(6hr)} = 12.07mg/L$$

2. **The population pharmacokinetics of a drug for a 70kg person are: V=260 liters, Cl=5L/hr. If a patient (69kg) take 40 mg of this drug daily after breakfast.**
    a. **The accumulation factor at steady state.**
    Ke= Cl/Vd=5/260= 0.019/hr
    Rss=1/(1-Exp(-ke*τ)=1/(1-Exp(-0.019*24))=2.73
    b. **How long it takes to achieve 50% of the steady state.**
    Need one half life to achieve 50% of the steady state.
    T1/2=0.693/0.019=36.5hr.
    c. **The maximum and minimum amount in the body at steady state.**
    Cmax=D/Vd*Rss=40/260*2.73=0.42mg/L
    Amax=Cmax*Vd=0.42*260=109.2mg
    Cmin=Cmax*exp(-Ke*24)=0.42*exp(-0.019*24)=0.27mg/L
    Amin=Cmin*Vd=0.27*260=70.2mg
3. **True and False**

1. **The smaller elimination constant, the bigger fluctuation.**
   Flase. F=Cmax/Cmin=exp(Ke*τ)
2. **The higher dose, the higher steady state average concentration.**
   True. Cave=Dose/Cl*τ
3. **The longer dosing interval, the longer to achieve steady state.**
   False. Time to achieve steady state is about 5 half-lives.
4. **The longer half life, the smaller degree of accumulation.**
   False. The longer half-life, smaller ke. Rss=1/(1-Exp(-ke*τ).
5. **The higher clearance, the smaller AUC during one dosing interval at steady state.**
   True. AUC=Dose/Cl. The AUC during one dosing interval at steady state. Is identical to AUCinf of the first dose.