PHA 5127 Homework 5 solution

1. The elimination half-life of drug X is 1.386 hours with an apparent volume of distribution of 10 L. The usual therapeutic range for this drug is between 10 and 20 mg/L. Calculate a dosing regimen (multiple IV bolus doses) that will just maintain the serum drug concentrations between 10 and 20 mg/L. (C_{max} cannot exceed 20mg/L.)
    a. Calculate ke and CL.
    b. Calculate fluctuation factor.
    c. Calculate the dosing interval (τ).
    d. Calculate the dose during each interval.**Answers:**

a. $ke=0.693/t_{1/2}=0.693/1.386=0.5$ hr-1 $\quad$ $CL=V_d*ke=10*0.5=5$ L/hr

b. $F=C_{pssmax}/C_{pssmin}=20/10=2$

c. $\tau=\ln F/ke=\ln 2/0.5=1.386$ hr

d. $D=C_{max}*V_d*(1-e^{-ke\tau})=20*10*(1-e^{-0.5*1.386})=100$ mg

2. 200mg of drug Y is given orally to a 75kg male patient. Two tablets (A and B) are available. Ka is 0.5 hr^{-1} for A and 0.25 hr^{-1} for B. All the other pharmacokinetic parameters are the same (Circle the right choice).
    a. T_{max} for A is (longer, equal, shorter) than/to T_{max} for B
    b. C_{max} for A is (higher, equal, lower) than/to C_{max} for B
    c. AUC_∞ for A is (larger, equal, smaller) than/to AUC_∞ for B

Answers:

a. shorter
b. higher
c. equal

3. A patient (75 kg) is to be given drug Z intravenously. It is known that the desired steady-state plasma concentrations are 30mg/L for the peak (drawn 2 hr after the end of a 1 hr infusion. Do not get confused, draw a scheme for the dosing, remember the discussion about calculated and measured peak, see equation sheet) and about 10 mg/L for the trough. The population average pharmacokinetic parameters are: $t_{1/2}$=5 hr and V_d=1 L/kg. The patient has NORMAL elimination of this drug.
    a. Calculate an intravenous loading dose to achieve a plasma concentration of 30 mg/L 2 hr after the end of a 1 hr infusion.
    b. Suppose a loading dose of 3200 mg is given over 1 hr infusion. Two hours after the end of this loading dose, the plasma concentration was 45 mg/L. Another plasma concentration was measured at 11 hours after the end of this infusion and it was 15 mg/L. Calculate the elimination rate constant, half-life and volume distribution in this specific patient.
    c. With the individual pharmacokinetic parameters just determined, calculate when the next dose should be given and what it should be. Remember the plasma concentration should be 10 mg/L before another dose is given and the plasma concentration 2 hr after the end of the infusion should be 30mg/L.

Answers:

a. $K_e=0.693/t_{1/2}=0.693/5=0.14\ h^{-1}$ $\quad$ $V_d=1*75=75$ L

$$C_{\text{peak(steady state)}} = \frac{X_0/t}{V_d K_e}(1-e^{-K_e t})e^{-K_e t'}$$

$$X_0 = \frac{C_{\text{peak(steady state)}} V_d K_e t}{(1-e^{-K_e t})e^{-K_e t'}} = \frac{30\times 75\times 0.14\times 1}{(1-e^{-0.14\times 1})e^{-0.14\times 2}} = 3190mg$$

b. Ke=-ln(C_2/C_1)/(t_2-t_1)=-ln(45/15)/9=0.122 h^{-1}

$t_{1/2}$=0.693/Ke=0.693/0.122=5.68 h

$$C_{\text{peak(steady state)}} = \frac{X_0/t}{V_d K_e}(1-e^{-K_e t})e^{-K_e t'}$$

$$V_d = \frac{X_0/t}{C_{\text{peak(steady state)}} K_e}(1-e^{-K_e t})e^{-K_e t'} = \frac{3200/1}{45\times 0.122}(1-e^{-0.122\times 1})e^{-0.122\times 2} = 52L$$

$$C_{\text{trough}} = C_{\text{peak(steady state)}} e^{-K_e t} \qquad t = -\ln(C_{\text{trough}}/C_{\text{peak(steady state)}})/K_e = 12.3h$$

the first infusion.

Next we determine dosing interval and maintenance dose as follows:

$$\tau_{\text{desired}} = \frac{-1}{K_e}(\ln C_{\text{trough(desired)}} - \ln C_{\text{peak(desired)}}) + t + t' = 12\text{h}$$

The maintenance dose can then be calculated as follows:

$$C_{\text{peak(steady state)}} = \frac{X_0/t}{V_d K_e}\frac{(1-e^{-K_e t})}{(1-e^{-K_e \tau})}e^{-K_e t'}$$

$$X_0 = \frac{C_{\text{peak(steady state)}} V_d K_e t(1-e^{-K_e \tau})}{(1-e^{-K_e t})e^{-K_e t'}} = \frac{30\times 52\times 0.122\times 1\times(1-e^{-0.122\times 12})}{(1-e^{-0.122\times 1})e^{-0.122\times 2}} = 1626mg$$ rounde

d down to 1600mg.