PHA 5127 Homework 4 solution

1. Drug X follows a one-compartment model after an IV bolus administration. The half-life of drug X is 0.693 hour, the volume distribution is 150 L and f_u is 0.5. There are multiple routes for the elimination of drug X. We know that filtration is the only factor involved in renal elimination (no re-absorption or secretion). Assume GFR is 130mL/min.
    a. Calculate the elimination rate constant k_e
    b. Calculate the total clearance
    c. Calculate the renal clearance and the renal elimination rate constant k_{eren}
    d. Calculate the non-renal clearance
    e. Besides renal elimination, is it possible that hepatic elimination is the only other route of elimination? Why?

Answers:

a. $k_e=0.693/t_{1/2}=0.693/0.693=1\ hr^{-1}$

b. $CL_{tot}=k_e*V_d=1*150=150\ L$

c. $CL_{ren}=f_u*GFR=0.5*130=65\ mL/min=3.9\ L/hr$

$k_{eren}=CL_{ren}/V_d=3.9/150=0.026\ hr^{-1}$

d. $CL_{nonren}=CL_{tot}-CL_{ren}=150-3.9=146.1\ L/hr$

e. No, it is impossible because CL_{nonren}=146.1 L/hr, which is larger than 90 L/hr, the maximum hepatic clearance. There must be some other routes of elimination.

2. Drug Y follows a one-compartment model after an IV bolus administration. 66 mg is given to a 70kg male patient by IV bolus. The concentrations at 0.5 and 3 hours are 0.236 μg/mL and 0.042 μg/mL, respectively.
    a. Calculate the elimination rate constant k_e
    b. Calculate C_0
    c. Calculate V_d
    d. Calculate the total clearance
    e. Calculate $AUC_{0-\infty}$
    f. If the drug is given twice daily (8 a.m. and 8 p.m.)), the concentration at noon of day 30 is 0.021μg/mL. What will be the concentration right before the second dose of that day (8 p.m.)?

Answers:

a. $k_e=-(\ln C_2-\ln C_1)/(t_2-t_1)=-(\ln 0.042-\ln 0.236)/(3-0.5)=0.69\ hr^{-1}$

b. Since $C=C_0e^{-ket}$, $C_0=C/e^{-ket}=0.236/e^{-0.69*0.5}=0.33\ \mu g/mL=0.33 mg/L$

c. V_d=Dose/C_0=66/0.33=200 L

d. $CL_{tot}=k_e*V_d$=0.69*200=138 L

e. $AUC_{0-\infty}$=Dose/CL_{tot}=66/138=0.478 mg*h/L

f. $C_{8pm}=C_{noon}e^{-ket}=0.021*e^{-0.69*8}=8.4\times10^{-5}$mg/L

3. How will the following parameters change (increase ↑, decrease ↓, no change ↔) for a low extraction drug which also undergoes renal elimination if f_u change from 0.2 to 0.8?
    a. V_d ↑
    b. E_H (hepatic extraction ratio) ↑
    c. F (oral bioavailability) ↔
    d. CL_H (hepatic clearance) ↑
    e. CLren ↑
    f. CLtot ↑
    g. $AUC_{0-\infty}$ ↓