PHA 5127 HW # 2 (Fall 2008) Answers

Q1. The usual plasma protein binding of drug A is 98% and the plasma protein binding of drug B is 10%. Comparing to their usual levels, what will happen with Vds and free drug levels if the protein bindings of both drugs decrease 50% in this patient (Assume same dose application, fuT=0.1, Vp= 3L, VT=38 L for both drugs, and no clearance are considered)? What can you conclude from your calculation? (4 points)

$$Vd = V_p + \frac{fu}{fu_T} V_T = 3 + \frac{fu}{0.1} \bullet 38$$

For drug A:

usual:

$$fu_{\_old} = 1 - 98\% = 0.02$$

$$Vd_{\_old} = V_p + \frac{fu_{\_old}}{fu_T} V_T = 3 + \frac{0.02}{0.1} \bullet 38 = 10.6L$$

after change:

$$fu_{\_new} = 1 - 0.5 \bullet 98\% = 0.51$$

$$Vd_{\_new} = V_p + \frac{fu_{\_new}}{fu_T} V_T = 3 + \frac{0.51}{0.1} \bullet 38 = 196.8L$$

$$\therefore \frac{Vd_{\_new}}{Vd_{\_old}} = \frac{196.8}{10.6} = 18.6$$ i.e. the Vd increased 17.6 fold

$$\frac{C_{f\_new}}{C_{f\_old}} = \frac{D/Vd_{\_new} \bullet fu_{\_new}}{D/Vd_{\_old} \bullet fu_{\_old}} = \frac{fu_{\_new} / fu_{\_old}}{Vd_{\_new}/Vd_{\_old}} = \frac{0.51/0.02}{18.6} = 1.37$$

i.e. the free drug concentration increased 37%

For drug B

usual:

$$fu_{\_old} = 1 - 10\% = 0.9$$

$$Vd_{\_old} = V_p + \frac{fu_{\_old}}{fu_T} V_T = 3 + \frac{0.9}{0.1} \bullet 38 = 345L$$

after change:

$$fu_{\_new} = 1 - 0.5 \bullet 10\% = 0.95$$

$$Vd_{\_new} = V_p + \frac{fu_{\_new}}{fu_T} V_T = 3 + \frac{0.95}{0.1} \bullet 38 = 364L$$

$$\therefore \frac{Vd_{\_new}}{Vd_{\_old}} = \frac{364}{345} = 1.055$$ i.e. the Vd increased 5.5%

$$\frac{C_{f\_new}}{C_{f\_old}} = \frac{D/Vd_{\_new} \bullet fu_{\_new}}{D/Vd_{\_old} \bullet fu_{\_old}} = \frac{fu_{\_new} / fu_{\_old}}{Vd_{\_new}/Vd_{\_old}} = \frac{0.95/0.9}{1.055} = 1$$

i.e. the free drug concentration almost had no change

Vd and free drug levels of drugs with high plasma protein binding (when compared to tissue binding) are more prone to be affected by changes in plasma protein binding

Say True or False (0.5 points each)

T **F** Drug A is lipophilic. The apparent volume of distribution of drug A cannot be greater than 38 L

T **F** Drug A is lipophilic and crosses membranes easily, while drug B is hydrophilic and crosses membranes poorly. At equilibrium, the free levels of drug B in tissue will always be higher than the free levels of drug B in plasma.

T **F** Drug A is lipophilic and crosses membranes easily, while drug B is hydrophilic and crosses membranes poorly. Drug A has lower clearance as compared to Drug B since there is very low amount of Drug A in plasma.

T **F** Drug A is lipophilic and crosses membranes easily, while drug B is hydrophilic and crosses membranes poorly. Drug A follows 2 compartment pharmacokinetics and hence has higher clearance as compared to Drug B

T **F** Of all the routes for a drug's clearance, only renal pathway determines the clearance for that drug.

T **F** The elimination half life of any drug depends on its clearance and the elimination rate constant.

Q3. Derive the half life equation for a first order elimination process (2pts)

$C(t) = C0 \exp(-ke^* t)$
$C(t1/2) = ½ * C0$
$½ C0 = C0 \exp(-ke^* t1/2)$
$½ = \exp(-ke^* t1/2)$
$\text{Ln } ½ = -ke^* t1/2$
$-0.693 = -ke^* t1/2$
$t1/2 = 0.693 / ke$

Q4. Match the following

a. Clearance	1. mg/hr
b. Half – life	2. mg*L/hr
c. AUC	3. hr
	4. mg*hr / L
	5. mg/ L
	6. L/ hr

Ans: A – 6
B – 3
C – 4