FALL 2013 PHA 5127 – Case Study 3

First Order and Zero Order Processes

1. Given below are the plasma concentration time profiles of Drugs A and B after a 600ng I.V. bolus dose in tables A and B correspondingly. Both drugs follow a one compartment body model with respect to distribution (Instantaneous distribution). The elimination however of one drug is a zero order process while that of the other is a first order process. Please answer the following questions:

Table A	
Time(hr)	Conc (ng/ml)
0	6.00
1	4.72
2	3.71
3	2.92
4	2.30
5	1.81
6	1.42
7	1.12

Table B	
Time(hr)	Conc (ng/ml)
0	16
1	14
2	12
3	10
4	8
5	6
6	4
7	2

a) Identify the drug that follows first order elimination process?

Drug A follows first order elimination process.

b) Calculate the elimination rate constant (**ke**) for drug A and drug B. Clearly state the units in each case.

ke for drug A = 0.24 hr^{-1}

Ke for drug B = 2 ng/ml/hr

c) Calculate the area under the curve from time 0 to infinity (**$AUC_{0\text{-}inf}$**) for both drugs A and B.

AUC for drug A = 25.1ng/ml*hr

AUC for drug B = 64 ng/ml*hr

Protein Binding

1) Lipophilic and unionized drug Phenytoin has a volume of distribution of 100L. Valproic acid displaces phenytoin from albumin binding sites (plasma) making a two-fold change in the fraction unbound in plasma. Predict the change in volume of distribution of phenytoin when co-administered with valproic acid.

$$VD = Vp + VT * fu/fuT$$

The above equation can be approximated to

$$VD = VT * fu/fuT$$

Hence the volume of distribution of phenytoin increases by a factor of 2 when co-administered with valproic acid.

2) Drug A and drug B are both lipophilic drugs. The plasma protein binding for drug A is 95% and for drug B is 5%, both drug A and drug B have tissue binding 75%. The same doses (200mg) of the two drugs are given to a healthy volunteer through I.V bolus at two different times (2 weeks of wash out period in between), assume Vp =3L, VT =38L for both drugs.
   a) Calculate the volume of distribution and initial free drug concentration of drug A and drug B.

      Since both drug A and B are lipophilic drugs, Vp = 3L, V_T = 38L

$$f_u(A) = 0.05\ ;\ f_u(B) = 0.95$$

$$f_{u,T}(A) = \ f_{u,T}(B) = 0.25$$

$$V_d(A) = 10.6L$$

$$V_d(B) = 147.4\ L$$

$$freeC_0(A) = \frac{0.94mg}{L}$$

$$freeC_0(B) = 1.29mg/L$$

b) Suppose the healthy volunteer got liver disease which results in a twofold decrease in plasma protein binding (halved) for both drug A and drug B (assume tissue binding remains the same), recalculate the volume of distribution and initial free drug concentration of drug A and drug B. What conclusions could you make?

$$f'_u(A) = 1 - \frac{0.95}{2} = 0.525\ ;\ f'_u(B) = 1 - \frac{0.05}{2} = 0.975$$

$$f_{u,T}(A) = f_{u,T}(B) = 0.25$$

$$V'_d(A) = 82.8L$$

$$V'_d(B) = 151.2\ L$$

$$freeC'_0(A) = \frac{1.27mg}{L}$$

$$freeC'_0(B) = 1.29mg/L$$

By looking at the initial free drug concentrations before and after disease, we could see that for drugs with high plasma protein binding (drug A), the initial free drug concentration changed a lot (approximately 35%), but for drug with low plasma protein binding (drug B), the initial free drug concentration remains the same (1.29 mg/L), therefore we conclude that the free drug levels of drugs with high plasma protein binding are more prone to be affected by changes in plasma protein binding.

True or False

Since $CL = ke * Vd$, a change in clearance will result in a change in volume of distribution. **(FALSE)**