PHA 5127 HOMEWORK-2 DUE: 09/13/2013

Please do not forget the units of the results. 0.1 points will be deducted each time an answer is provided without the appropriate unit.

1) A patient was given drug A by i.v. bolus at a dose of 1000mg, and blood samples were taken at 1h and 4h following the first injection to monitor the drug levels in blood (See table below for the information). Assume first order elimination for this drug. (**6 points**)

Dose (mg)	Cp at 1h (mg/L)	Cp at 4h (mg/L)	Cp at 8h (mg/L)	Plasma protein binding %
1000	5.706	3.227	1.509	95

a) Please estimate the initial free plasma concentration and tissue binding (Vp=3L, VT= 38L)

$$ke = \frac{ln3.227 - ln1.509}{8-4} = \frac{0.76}{4} = 0.19\ hr^{-1}$$ (**0.5 point**)

$$C_0 = 3.227 * \exp(0.19 * 4) = 6.9\ mg/L$$

$$free\ C_0 = 6.9 * 0.05 = 0.345 \frac{mg}{L}$$ (**0.5 point**)

$$V_d = \frac{Dose}{Co} = \frac{1000}{6.9} = 144.92\ L$$

$$V_d = V_p + V_T * \frac{f_u}{f_{u,T}} = 3 + 38 * \frac{0.05}{f_{u,T}} = 144.92$$ (**0.5 point**)

$$f_{u,T} = 0.013 \sim Tissue\ Binding = 98.7\%$$ (**0.5 point**)

b) Please calculate AUC∞ (**2 points**)

$$Clearance = ke * Vd$$

$$Cl = 0.19 * 144.92 = 27.53\ L/hr$$

$$AUC = \frac{Dose}{Clearance} = \frac{1000}{27.53} = 36.32 \frac{mg}{L} * hr$$

Please award full points if the trapezoidal rule has been used and the value of AUC is close to that calculated above.

c) If the plasma protein binding of this drug decreases by 20%, predict the dose that should be administered to reach the same initial concentration.

$$New\ protein\ binding = 0.95 - (0.95 * 0.2) = 0.76 = 76\%$$

$f_{u,new} = 1 - 0.76 = 0.24$ (**0.5 point**)

$V_{d,new} = 3 + 38 * \frac{0.24}{0.013} = 704.54\ L$ (**0.5 point**)

$Dose_{new} = V_{d,new} * C_0 = 704.54 * 6.9 = 4861.3\ mg$ (**1 point**)

2. True or False (**4 points**)

1. Free plasma levels of drugs with high plasma protein binding (99%) are more prone to be affected by changes in plasma protein binding than drugs with low plasma protein binding (10%). (Assume that $f_{u,\ tissue}$ = 0.1 and consider only effects of protein binding on Vd). (**TRUE**)

2. Increase in plasma protein binding will increase the volume of distribution of a lipophilic drug. (**FALSE**)

3. The volume of distribution (Vd) of a given drug relates the dose with the free plasma concentration at time. (**FALSE**)

4. If a drug is unable to cross membranes, the volume of distribution cannot be larger than the extracellular space. (**TRUE**)