PHA 5127 Homework – 3 (Due – Sep 21) **10 points**

Question 1 Drug-Drug Interaction

Lipophilic and unionized drug Phenytoin (Vp= 3L, VT = 38L) has a volume of distribution of 100L. Valproic acid displaces phenytoin from albumin binding sites (plasma) making a two-fold increase in the fraction unbound in plasma. Predict the change in volume of distribution of phenytoin when co-administered with valproic acid. **(5)**

There are 2 ways to solve this problem:

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

$$100 = 3 + 38 * fu/fuT$$

Therefore,

$$2.55 = fu/fuT \qquad (1)$$

When administered with valproic acid

$$VD = 3 + 38 * 2 * fu/fuT \qquad (1.5)$$

Therefore,

$$100 = 3 + 38 * 2 * 2.55 \qquad (1.5)$$

VD = 196.8 L (1)

2nd solution:

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

The above equation can be approximated to

$$VD = VT * fu/fuT$$

When administered with valproic acid

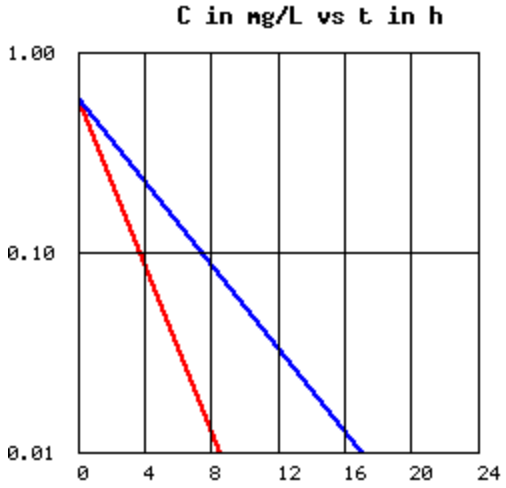
$$VD = VT * 2 * fu/fuT \qquad (2.5)$$

Therefore, VD = 100*2 = 200L (2.5)

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

Question 2 Drug-Drug Interactions (Enzyme Induction)

2 patients red and blue participated in a clinical study. Blue patient received 100mg IV bolus dose of Alprazolam, while the red patient received 100mg IV bolus Alprazolam+50mg IV bolus Carbamezapine. The plasma concentration time profiles of **Alprazolam** in red patient and the blue patient are shown in the figure below.



Please provide a qualitative comparison (greater than, lesser than or equal to) of parameters

a) Clearance (CL>CL) **(1)**
b) Volume of Distribution (VD=VD) **(1)**
c) Initial concentration (C_0) and free initial concentration (fu* C_0) in the red patient and the blue patient for Alprazolam (C_0 = C_0 ; fu = fu)**(1)**

True or False (2)

1) The maximum value hepatic clearance can approach is the liver blood flow. (T/F)
2) For drugs with a hepatic extraction ratio of 1, the hepatocyte does not represent a strong diffusion barrier? (T/F)