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:

$$V_D = V_P + V_T \times \frac{f_u}{f_uT}$$

$$100 = 3 + 38 \times \frac{f_u}{f_uT}$$

Therefore,

$$2.55 = \frac{f_u}{f_uT}$$  \hspace{1cm} (1)

When administered with valproic acid

$$V_D = 3 + 38 \times 2 \times \frac{f_u}{f_uT}$$  \hspace{1cm} (1.5)

Therefore,

$$100 = 3 + 38 \times 2 \times 2.55$$  \hspace{1cm} (1.5)

$$V_D = 196.8 \text{ L}$$  \hspace{1cm} (1)

2\textsuperscript{nd} solution:

$$V_D = V_P + V_T \times \frac{f_u}{f_uT}$$

The above equation can be approximated to

$$V_D = V_T \times \frac{f_u}{f_uT}$$

When administered with valproic acid

$$V_D = V_T \times 2 \times \frac{f_u}{f_uT}$$  \hspace{1cm} (2.5)
Therefore, $VD = 100 \times 2 = 200L$ \hspace{1cm} (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 \hspace{1cm} (CL > CL) \hspace{1cm} (1)

b) Volume of Distribution \hspace{1cm} (VD = VD) \hspace{1cm} (1)

c) Initial concentration ($C_0$) and free initial concentration ($fu \times C_0$) in the red patient and the blue patient for Alprazolam \hspace{1cm} ($C_0 = C_0$; $fu = fu$)\hspace{1cm} (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)