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:

\[ VD = Vp + VT \times fu/fuT \]

\[ 100 = 3 + 38 \times fu/fuT \]

Therefore,

\[ 2.55 = fu/fuT \] (1)

When administered with valproic acid

\[ VD = 3 + 38 \times 2 \times fu/fuT \] (1.5)

Therefore,

\[ 100 = 3 + 38 \times 2 \times 2.55 \] (1.5)

\[ VD = 196.8 \text{ L} \] (1)

2nd solution:

\[ VD = Vp + VT \times fu/fuT \]

The above equation can be approximated to

\[ VD = VT \times fu/fuT \]

When administered with valproic acid

\[ VD = VT \times 2 \times fu/fuT \] (2.5)
Therefore, \( VD = 100 \times 2 = 200 \text{L} \) \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.

![Plasma concentration time profiles](image)

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

a) Clearance \( (CL > CL) \) \hspace{1cm} (1)

b) Volume of Distribution \( (VD = VD) \) \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 \( (C_0 = C_0; fu = fu) \) \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)*