**Homework 2**
**PHA 5127 Fall 2007**
**(Total 10 Points)**

1. Mark whether the following statements are True or False (0.5 points each)

**T F** a. Apparent volume of distribution (Vd) will never excess the total body volume. (F)

**T F** b. At equilibrium, the free drug concentrations in plasma and tissue will be identical. (T)

**T F** c. Most drugs which are tightly bound to plasma protein tend to stay in the blood and thus have relatively low apparent volumes of distribution. (T)

**T F** d. Drugs that are extensively distributed into specific tissue regions, such as chloroquine into the liver, tend to have quite small values for the apparent volume of distribution. (F)

**T F** e. Disease state rarely affects the drug protein binding in the body. (F)

**T F** f. Since $CL = k_e \bullet Vd$ , so if the volume of distribution increases the clearance must increase. (F)

2. Two patients (A and B) were given 200mg IV bolus of the drug D. The $C_0$ for patient A was 2.5mg/L and for patient B was 1.5mg/L. Assume: the drug follows a one-compartment body model; the drug is 60% bound to plasma proteins; both patients have typical tissue volume of 38L and plasma volume of 3L.

Provide a quantitative explanation of why the two patients have different initial plasma concentrations (consider distribution and binding properties)? (3 points).

Given: IV Bolus, one-compartment model, permeable
D = 200 mg
$C_{0\_A}$=2.5mg/L $C_{0\_B}$=1.5mg/L
$f_u$ = 1 - 60% = 40% $V_p$=3L $V_T$=38L

Solution:

$$C_0 = \frac{D}{V_d} = \frac{D}{V_p + V_T \bullet \frac{f_u}{f_{u,T}}}$$

From given, we can see D, $V_p$,$V_T$, and $f_u$ are same for patient A and B. So the difference between $C_{0\_A}$ and $C_{0\_B}$ is caused by the different tissue binding (1- $f_{u,T}$) in these two patient.

$$C_{0\_A} = 2.5 = \frac{D}{V_{d\_A}} = \frac{D}{V_p + V_T \bullet \frac{f_u}{f_{u,T\_A}}} = \frac{200}{3 + 38 \times 40\% / f_{u,T\_A}}$$

$$\Rightarrow V_{d\_A} = 200 / 2.5 = 80L \qquad f_{u,T\_A} = \frac{38 \times 40\% \times 2.5}{200 - 7.5} = 19.7\%$$

$$C_{0\_B} = 1.5 = \frac{D}{V_{d\_B}} = \frac{D}{V_p + V_T \bullet \frac{f_u}{f_{u,T\_B}}} = \frac{200}{3 + 38 \times 40\% / f_{u,T\_B}}$$

$$\Rightarrow V_{d\_B} = 200 / 1.5 = 133L \qquad f_{u,T\_B} = \frac{38 \times 40\% \times 1.5}{200 - 4.5} = 11.7\%$$

From the class, you should understand what factors determine the rate of distribution and be able to tell the difference between perfusion and permeability limited distribution. Please apply your knowledge of distribution to the following situations:

3. It is well documented that physicochemical properties can be correlated to many ADME (Absorption, Distribution, Metabolism and Elimination) properties, particularly in terms of distribution rate in our case. Drug A has pKa of 7.4 and partition coefficient of unionized form of 0.21. Drug B has pKa of 11.3 and partition coefficient of unionized form of 0.005. Both Drug A and Drug B are weak acid drugs. Please use their physicochemical properties to predict their distribution rates in high perfused tissues, i.e. which one distributes faster and why (hint: since the partition coefficients of both drugs are small, you can assume the distribution is limited by the permeability) (2 points).

Solution:

In the permeability limited distribution, the drug uptake is determined by FICK'S law of diffusion (affected by surface area of membrane, membrane thickness, concentration gradient, partition coefficient, ionization). Therefore, the rate of distribution is highly correlated to the drug's effective partition coefficient at the blood pH (~pH 7.4). Drug A has pKa of 7.4. Therefore its "Fraction of Unionized" is about 0.5 at pH7.4. So its effective partition coefficient (≈Fraction Unionized * Partition Coefficient of Unionized) is ≈0.5*0.21≈0.1. Acid drug B has pKa of 11.3. Therefore its "Fraction of Unionized" is about 1 at pH7.4. So its effective partition coefficient is ≈1*0.005≈0.005. Hence, drug A will distribute much faster.

4. 4OH-GTS21 is a water soluble active compound for Alzheimer's disease. However, to achieve fast and effective response, we have to deliver its lipophilic pro-drug GTS21 to patients (usually orally). Explain the reason of doing this (2 points).

Solution: Since 4OH-GTS21 is a water-soluble compound, its distribution rate to its effect site, brain, is limited by the membrane permeability (Blood Brain Barrier, BBB). However the lipophilic pro-drug, GTS21, can pass the BBB easily and reach the effect site very fast since brain is a highly perfused organ. Then GTS21 will be transformed to the active 4OH-GTS21 in brain very fast to deliver a fast and effective response.