PHA 5127

Case Study #2

Question #1

The table below listed some properties of five acidic drug molecules A, B, C, D, E, but some information is missing. Please complete the table by calculating the effective partition coefficient at pH=7.4 and give the rank order of the five drugs entering brain tissue.

Drug	Fraction ionized at pH=7.4	Partition coefficient of unionized form	Molecular weight (Dalton)	Effective Partition coefficient at pH=7.4	Rank order of entering brain tissue
A	0.49	3.5	360	*1.79*	*1*
B	0.083	0.2	280	*0.18*	*3*
C	0.921	1.0	475	*0.08*	*4*
D	0.27	0.004	328	*0.003*	*5*
E	0.16	0.38	490	*0.32*	*2*

Question #2

Drug A and drug B are both lipophilic drugs. The plasma protein binding for drug A is 95% and for drug B is 5%, both drug A and drug B have tissue binding 75%. The same doses (200mg) of the two drugs are given to a healthy volunteer through I.V bolus at two different times (2 weeks of wash out period in between), assume V_p=3L, V_T=38L for both drugs.

2.1. Calculate the volume of distribution and initial free drug concentration of drug A and drug B.

Since both drug A and drug B are lipophilic drugs, $V_p = 3L,\ V_T = 38L$

$f_u(A) = 1 - 0.95 = 0.05 \qquad f_{u,T}(A) = f_{u,T}(B) = 1 - 0.75 = 0.25$

$f_u(B) = 1 - 0.05 = 0.95$

$$V_d(A) = V_p(A) + V_T(A) \cdot \frac{f_u(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.05}{0.25} = 10.6 \text{ L}$$

$$C_0(A) = f_u(A) \cdot \frac{Dose}{V_d(A)} = 0.05 \cdot \frac{200}{10.6} = 0.94 \text{ mg/L}$$

$$V_d(B) = V_p(B) + V_T(B) \cdot \frac{f_u(B)}{f_{u,T}(B)} = 3 + 38 \cdot \frac{0.95}{0.25} = 147.4 \text{ L}$$

$$C_0(B) = f_u(B) \cdot \frac{Dose}{V_d(B)} = 0.95 \cdot \frac{200}{147.4} = 1.29 \text{ mg/L}$$

2.2. Suppose the healthy volunteer got liver disease, which results in a twofold decrease of plasma protein binding for both drug A and drug B (assume tissue binding remains the same), recalculate the volume of distribution and initial free drug concentration of drug A and drug B. What conclusions could you make?

$$f_u^{'}(A) = 1 - \frac{0.95}{2} = 0.525$$

$$f_u^{'}(B) = 1 - \frac{0.05}{2} = 0.975$$

$$f_{u,T}(A) = f_{u,T}(B) = 0.25$$

$$V_d^{'}(A) = V_p(A) + V_T(A) \cdot \frac{f_u^{'}(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.525}{0.25} = 82.8 \text{ L}$$

$$C_0^{'}(A) = f_u^{'}(A) \cdot \frac{Dose}{V_d^{'}(A)} = 0.525 \cdot \frac{200}{82.8} = 1.27 \text{ mg/L}$$

$$V_d^{'}(B) = V_p(B) + V_T(B) \cdot \frac{f_u^{'}(B)}{f_{u,T}(B)} = 3 + 38 \cdot \frac{0.975}{0.25} = 151.2 \text{ L}$$

$$C_0^{'}(B) = f_u^{'}(B) \cdot \frac{Dose}{V_d^{'}(B)} = 0.975 \cdot \frac{200}{151.2} = 1.29 \text{ mg/L}$$

By looking at the initial free drug concentration before and after disease, we could see that for drug with high plasma protein binding (drug A), the initial free drug concentration changed a lot (approximately 35%), but for drug with low plasma protein binding (drug B), the initial free drug concentration remains the same (1.29 mg/L), therefore we came to the conclusion that the free drug levels of drugs with high plasma protein binding are more prone to be affected by changes in plasma protein binding.

2.3. In the presence of drug C, drug A is displaced from plasma albumin binding sites, this leads to a 1.5-fold change in fraction unbound in plasma. Based on the information, calculate the volume of distribution of drug A in the healthy volunteer. (Ignore the change in tissue binding)

$$f_u^{''}(A) = 1.5 \cdot f_u(A) = 1.5 \cdot 0.05 = 0.075$$

$$V_d^{''}(A) = V_p + V_T \cdot \frac{f_u^{''}(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.075}{0.25} = 14.4 \text{ L}$$

Question #3

1. T **F** For both perfusion and permeability limited distributions, the faster the blood flow, the faster the drug uptakes into tissues.
2. T **F** According to Fick's Law, the diffusion rate of drug is proportional to the first order elimination rate constant K_e.
3. **T** F Protein binding is of significant importance if the drug shows a narrow therapeutic window.
4. T **F** Since $CL = k_e \cdot V_d$, change of volume of distribution will affect the drug clearance.