PHA 5127

Homework #2

Question #1.

A 24 years old, 60kg, female patient was admitted into Shands hospital because of drug intoxication. The clinicians decided to give her drug A through I.V bolus at a dose of 10mg/kg to control the symptoms. The table below listed her plasma drug concentrations at 5 different time points. Suppose the drug follows a one compartment body model, with first-order elimination.

Time(hr)	Cp(mg/L)
1	4.02
2	2.70
4	1.21
6	0.54
8	0.25

1.1. Use trapezoidal rule to calculate $AUC_{0\to\infty}$. (3pt)

$$k_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} = -\frac{\ln 2.70 - \ln 4.02}{2-1} = 0.40\ h^{-1} \quad (.5\text{pt})$$

$$Conc = C_0 \cdot e^{-k_e t} \Rightarrow C_0 = \frac{Conc}{e^{-k_e t}} = \frac{4.02}{e^{-0.40\bullet 1}} = 6.0\ \text{mg/L} \quad (.5\text{pt})$$

$$AUC_{0\to\infty} = AUC_{0\to last} + AUC_{last\to\infty}$$

$$AUC_{0\to last} = \frac{(6.0+4.02)\times(1-0)}{2} + \frac{(2.70+4.02)\times(2-1)}{2} + \frac{(2.70+1.21)\times(4-2)}{2}$$

$$+\frac{(1.21+0.54)\times(6-4)}{2} + \frac{(0.54+0.25)\times(8-6)}{2} = 14.82\ \text{mg}\cdot\text{h/L} \quad (1\text{pt})$$

$$AUC_{last\to\infty} = \frac{C_{last}}{k_e} = \frac{0.25}{0.40} = 0.625\ \text{mg}\cdot\text{h/L}$$

$$AUC_{0\to\infty} = 14.82 + 0.625 = 15.445\ \text{mg}\cdot\text{h/L} \quad (1\text{pt})$$

1.2. If the plasma protein binding of drug A in the patient is 60%, calculate the initial free plasma drug concentration and tissue binding. (V_p=3L, V_T=38L) (2pt)

$$f_u(A) = 1 - 0.60 = 0.40$$

$$C_0(free) = f_u(A) \cdot C_0 = 0.40 \cdot 6.0 = 2.4 \text{ mg/L} \quad (1\text{pt})$$

$$V_d(A) = V_p(A) + V_T(A) \cdot \frac{f_u(A)}{f_{u,T}(A)} = 3 + 38 \cdot \frac{0.40}{f_{u,T}(A)} = 100 \text{ L}$$

$$\Rightarrow f_{u,T}(A) = 0.1567$$

$\Rightarrow$ The tissue binding is 84.33% (1pt)

Question #2

4OH-GTS21 is an active compound for Alzheimer's disease which has very high water solubility. To achieve fast and effective response, even after i.v. administration we have to deliver its lipophilic pro-drug GTS21 to patients. Explain the reason of doing this. (2pt)

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.

Question #3

3.1. **T** F Lipophilic unionized drugs are likely to enter tissues relatively fast. (.5pt)

3.2. T **F** When the drug has no difficulty to cross the membrane, the concentration gradient is an important factor in determine the rate of drug uptake into tissues. (.5pt)

3.3. **T** F If drug is unable to cross membrane, V_d cannot be larger than the extracellular space. (.5pt)

3.4. **T** F If the volume of distribution of drug B in a patient is 150L, then the tissue binding has to be stronger than plasma protein binding. (.5pt)

3.5. **T** F A lipophilic drug of volume of distribution of 15L indicates that the drug's plasma protein binding is more pronounced than tissue binding. (.5pt)

3.6. **T** F For a drug that binds to high affinity-low capacity binding protein in plasma, the f_u and V_d might depend on the dose of the drug. (.5pt)