PHA 5127 Dose Optimization I

Case Study II

1. Two patients (A and B) were given a same drug through IV bolus, and this drug is 40% bound to plasma proteins in both two patients but has different tissue binding. There is 70% and 80% tissue binding in patient A and patient B, respectively. In order to reach same initial total plasma concentration of 2mg/L in both two patients, which doses should be given to them?

For patient A:

fu=1-40%=60%, fuT=1-70%=30%

Vd=Vp+ $\mathbf{V_T}$**(fu/fuT)=3L+38L*(60%/30%)=79L

Dose= C_0*Vd=2mg/L *79L=158mg

For patient B:

fu=1-40%=60%, fuT=1-80%=20%

Vd=Vp+ $\mathbf{V_T}$**(fu/fuT)=3L+38L*(60%/20%)=117L

Dose=C_0*Vd=2mg/L*117L=234mg

2. The plasma protein binding of drug A and drug B is 5% and 98% respectively. If the protein bindings of both drugs decreased 50% in one patient, what percentage of change will happen in Vd (volume of distributions) and initial free drug concentration? (Assume IV bolus application, fuT=0.1, V_p=3L, V_T=38L for both two drugs)?

For drug A:

f u,old=1-5%=95%, Vd,old=Vp+ $\mathbf{V_T}$**(fu,old/fuT)=3L+38L*(0.95/0.1)=364L

f u,new=1-5%*50%=97.5%, Vd,new=Vp+ $\mathbf{V_T}$**(fu,new/fuT)=3L+38L*(0.975/0.1)=373.5L

Vd,new/Vd,old=373.5L/364L=1.026. Hence, Vd for drug A increased by 2.6%

$$C_0,new/C_0,old = \frac{(Dose/Vd,new)*fu,new}{(Dose/vd,old)*fu,old} = \frac{Vd,old}{vd,new} \times \frac{fu,new}{fu,old}$$

=(364L/373.5L)*(0.975/0.95)≈100%, so the initial free concentration will not change.

For drug B:

f u,old=1-98%=2%, Vd,old=Vp+ $\mathbf{V_T}$**(**fu,old/fuT)=3L+38L*(0.02/0.1)=10.6L

f u,new=1-98%*50%=51%, Vd,new=Vp+ $\mathbf{V_T}$**(**fu,old/fuT)=3L+38L*(0.51/0.1)=196.8L

Vd,new/Vd,old=196.8/10.6=18.57, so Vd for drug A increased by 1756.6%

$$C0,new/C0,old = \frac{(Dose/Vd,new)*fu,new}{(Dose/vd,old)*fu,old} = \frac{Vd,old}{vd,new} \times \frac{fu,new}{fu,old}$$

=(10.6/196.8)*(0.51/0.02)≈1.37, so the initial free concentration will increase by 37%.

3. TRUE (T) or FALSE (F)

To determine the loading dose, volume of distribution is an important factor.

T **F**

Drug A has 3% protein binding and has a narrow therapeutic window. Small differences in protein binding are not so important since 97% drug is free and available for receptors.

T **F**

For a drug with high tissue binding, the volume of distribution will be always very high.

T **F**

Apparent volume of distribution (Vd) will never excess the total body volume.

T **F**

Lipophilic drugs are generally taken up fast by highly perfused organs

T **F**

The uptake of a hydrophilic drug into tissue can be increased significantly by increasing the blood flow through the tissue. (Assume permeability limited distribution)

T **F**