PHA 5127
Key to Homework #2
Fall, 2003.

Question 1:

An 80-year-old, male patient was admitted to hospital with gram-negative pneumonia infection, and was given an iv bolus of drug X. (200 mg). The drug concentration of X was reported as following. Assuming the drug follows one compartment body model with first-order elimination, please answer the questions.

T (hr.)	Conc.(mg/L)	
0	10.0000	ND
1	8.4093	9.2046
2	7.0716	7.7404
4	5.0007	12.072
6	3.5363	8.5370
8	2.5007	6.0370
12	1.2506	7.5025
AUC0-12		51.0941
AUC0-infinity		58.3126

1.) Please calculate the total Cl, AUC $_{0\text{-}\infty}$, Vd, t $_{1/2}$ for drug X.

Recall case study#1:

Firstly, we need to calculate Ke:

Please pick up two time points: t $_1$ = 1 hr, C $_1$ = 8.4093 (mg/L)

t $_2$ = 12hr, C $_2$ = 1.2506 (mg/L)

Then $\boldsymbol{Ke} = \dfrac{\boldsymbol{ln(C_2 / C_1)}}{\boldsymbol{(t_1 - t_2)}} = \dfrac{\boldsymbol{ln(}1.2506/8.4093\boldsymbol{)}}{\boldsymbol{(}1-12\boldsymbol{)}} = 0.1733\boldsymbol{(hr^{-1})}$

Once we know Ke, then we can find out t ½ by using,

$$t_{1/2} = \frac{0.693}{0.1733} = 4(hr.)$$

Secondly, we can calculate C_0:

$$C_t = C_0 \cdot e^{-Ke \cdot t}$$

Then, $C_0 = C_t \cdot e^{Ke \cdot t} = 1.2506 \cdot e^{0.1733 \cdot 12} = 10(mg/l)$

Once we find out C_0, it is easy to calculate Vd:

$$Vd = \frac{Dose}{C_0} = \frac{200}{10} = 20(l)$$

Thirdly, we can get $AUC_{0\text{-}\infty}$.

You can use the way we mentioned in case study #1 by employing trapezoidal rule.

Recall: $AUC_{1\text{-}2} = 0.5*(C_1+C_2)*(t_2-t_1)$

Results were shown on the table.

Note: $$AUC_{t-\infty} = \frac{C_t}{K_e} = \frac{1.2506}{0.1733} = 7.2182(mg \cdot hr / L)$$

Then, $AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty} = 58.3123(mg \cdot hr / L)$

Fourthly,
we can calculate total Cl:

$Cl = Ke \cdot V_d = 0.1733 \cdot 20 = 3.465(l / hr)$

OR.

$$Cl = \frac{Dose}{AUC_{0-\infty}} = \frac{200}{58.3123} = 3.42(l / hr.)$$

2.) Suppose the 80-year-old patient was suffering from hepatic disease, his total clearance of drug X was only half of that of a normal patient. Please calculate the half-life of drug X in normal patient. (Assume there is no change on Vd in the 80-year-old patient.).

Firstly, $Cl_{normal} = 2 \cdot Cl = 2 \cdot 3.42 = 6.93(l / hr)$

$$Ke = \frac{C\ln ormal}{V_d} = \frac{6.93}{20} = 0.3465(1 / hr)$$

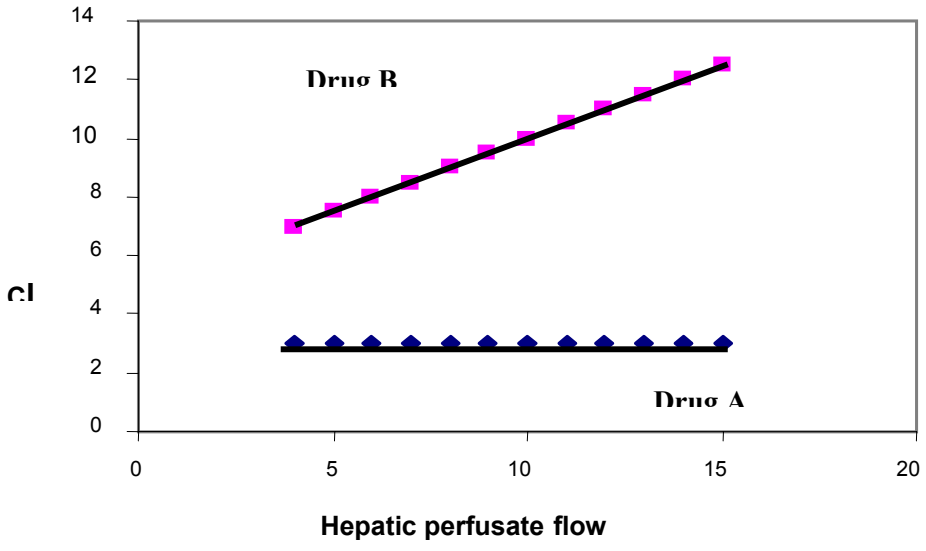
Then:

$$t_{1/2} = \frac{0.693}{Ke} = \frac{0.693}{0.3465} = 2(hr.)$$

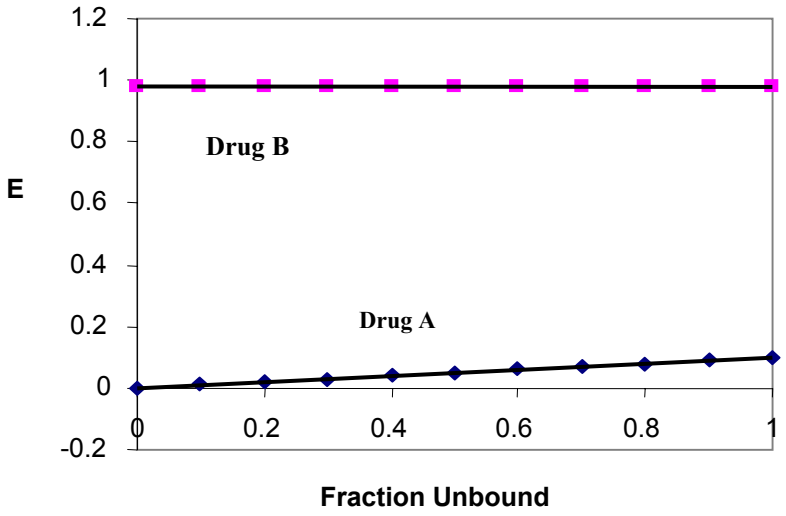
So in normal patient, the half-life is about 2 hours.

Question 2:

Drug A and B are mainly metaolized in liver. Dr. Hochhaus did a research project to understand 1.) the relationship between clearance of the two drugs and hepatic blood flow, and 2.) the extraction ratios of two drugs versus fraction unbound in rats. Results were plotted as following. 1.) Please explain the results based on what you learned in the class. 2.) Also please help Dr. Hochhaus to predict what will be the relationship between F (bioavailability), and hepatic blood flow for drug A and B.(Please plot your prediction).



(Fig 1)



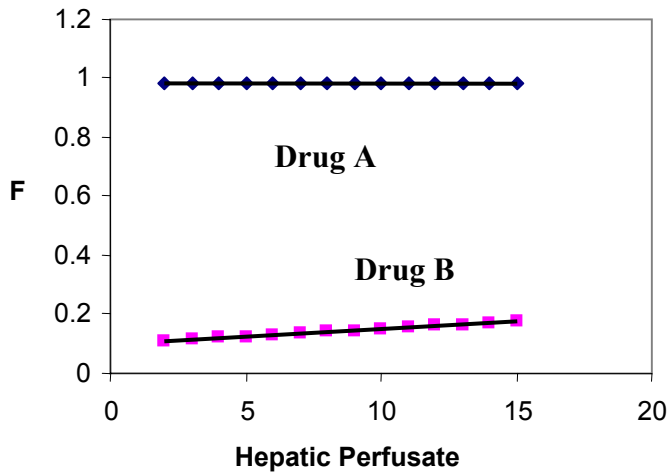
(Fig2)

Cl: means **clearance**. **E:** means **extraction ratio**.

Since both drug A and B are mainly metabolized in liver, the total body clearance of A and B should be determined by the hepatic clearance of drug A and B. From the plotted curve in Fig 1, we notice that drug A and B behavior differently when hepatic blood flow changes. There was almost no change in the clearance of drug A when blood flow changes whereas a significant change in clearance was observed from drug B. Recall in class, we discussed that, for low extraction drug, $CL_H = f_u * CL_{int}$. Hepatic blood flow does not change the hepatic clearance. Therefore, drug A probably belongs to low extraction drug. For high extaction drug, $CL_H = Q_H$, hepatic blood flow changes the hepatic clearance greatly. Then, drug B belongs to high extraction drug.

The results from extraction ratio versus fraction unbound further approved what we saw on Fig1. Drug B has high extraction ratio, which is close to 1, and it does not change as fraction unbound changes, since for high extraction drug, $E = f_u * CL_{int} / f_u * CL_{int} = 1$. Drug A's extraction ratio values are low, and it increases when fraction unbound increases, since for low extraction drug, $E = f_u * CL_{int} / Q_H$.

Prediction Plotting: In high extraction drug, $F = (Q_H / f_u * CL_{int})$. Increasing in hepatic blood flow results a higher bioavailability. Low extraction drug, on the other hand, has almost constant bioavailability when hepatic blood flow changes. F is almost 1.



(Fig 3.)

Question 3:

Researchers recently found out that grape fruit juice is CYP3A4 inhibitor. When taking together with grape fruit juice, the intrinsic hepatic clearance (CL int) of drug B is decreased by 30%. Main pharmacokinetic parameters of drug B were listed as following: Hepatic clearance (WITHOUT taking grape fruit juice), CL hep = 9 L / hr. Fraction unbound: fu = 0.3. Please calculate what is the new hepatic clearance, when drug B is taking together with grape fruit juice.
Assume the hepatic blood flow is 90 L / hr.

Firstly, calculate the original CL int.

$$CL_{hep} = \frac{Q \cdot f_u \cdot CL_{\text{int}}}{Q + f_u \cdot CL_{\text{int}}} = \frac{90 \cdot 0.3 \cdot CL_{\text{int}}}{90 + 0.3 \cdot CL_{\text{int}}} = 9$$

CL int = 33.3 L / hr.

Secondly, calculate the new CL hep.

$$CL_{hep} = \frac{90 \cdot 0.3 \cdot 33.3 \cdot 0.7}{90 + 0.3 \cdot 33.3 \cdot 0.7} = 6.49(L/hr.)$$