PHA 5127 – Case Study 3

First Order and Zero Order Processes

1. Given below are the plasma concentration time profiles of Drugs A and B after a 600ng I.V. bolus dose in tables A and B correspondingly. Both drugs follow a one compartment body model with respect to distribution (Instantaneous distribution). The elimination however of one drug is a zero order process while that of the other is a first order process. Please answer the following questions:

Table A	
Time(hr)	Conc (ng/ml)
0	6.00
1	4.72
2	3.71
3	2.92
4	2.30
5	1.81
6	1.42
7	1.12

Table B	
Time(hr)	Conc (ng/ml)
0	16
1	14
2	12
3	10
4	8
5	6
6	4
7	2

a) Identify the drug that follows first order elimination process?

Drug A follows first order elimination process.

b) Calculate the elimination rate constant (**ke**) for drug A and drug B. Clearly state the units in each case.

ke for drug A = 0.24 hr^{-1}

Ke for drug B = 2 ng/ml/hr

c) Calculate the area under the curve from time 0 to infinity (**$AUC_{0\text{-}inf}$**) for both drugs A and B.

AUC for drug A = 25.1ng/ml*hr

AUC for drug B = 64 ng/ml*hr

Protein Binding

Lipophilic and unionized drug Phenytoin has a volume of distribution of 100L. Valproic acid displaces phenytoin from albumin binding sites (plasma) making a two-fold change in the fraction unbound in plasma. Predict the change in volume of distribution of phenytoin when co-administered with valproic acid.

$$VD = Vp + VT * fu/fuT$$

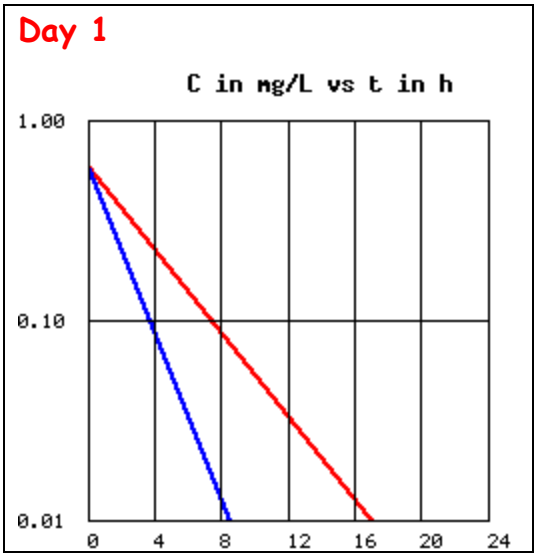
The above equation can be approximated to

$$VD = VT * fu/fuT$$

Hence the volume of distribution of phenytoin increases by a factor of 2 when co-administered with valproic acid.

Drug-Drug Interaction

2 patients red and blue participated in a clinical study. Blue patient received 100mg IV bolus dose of Alprazolam, while the red patient received 100mg IV bolus Alprazolam+50mg IV bolus Ketoconazole. The plasma concentration time profiles of **Alprazolam** in red patient and the blue patient are shown in the figure below.



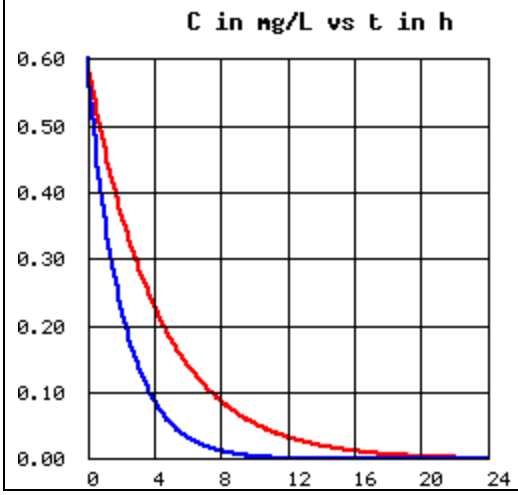
Please provide a qualitative comparison (greater than, lesser than or equal to) of parameters Clearance, Volume of Distribution, Initial concentration (C_0) and free initial concentration (fu* C_0) in the red patient and the blue patient for Alprazolam.

CL >CL; C0 = C0; VD = VD; free initial concentrations are the same (no change in protein binding). This is an example of enzyme inhibition.

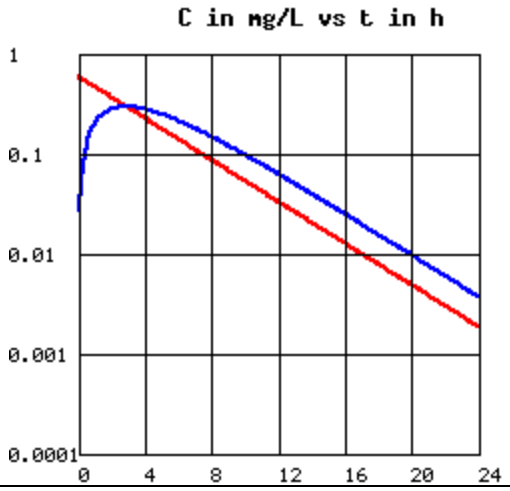
Parent Drug vs. Metabolite

Given below are the plasma concentration time profiles of a **Drug (red line)** and its **metabolite (blue line)** from 2 different scenarios. (Both scenarios correspond to the same drug and the same metabolite)

Scenario 1



Scenario 2



1) Write the route of administration of the metabolite in Scenarios 1 and 2?
   Scenario 1 – IV Bolus
   Scenario2 – Metabolite formed from the parent drug in the body.
2) Is the clearance of the metabolite lesser than the parent drug? Comment?
   No the clearance of the metabolite is larger than the parent drug as evidenced in scenario 1
3) Is the rate of elimination of the metabolite faster than that of the parent drug in scenario 2? Explain?

No the rate of elimination of the metabolite is same as that of the parent drug.