PHA 5128
Case Study #2 – Answers

1. The volume of distribution of diazepam in a group of normal subjects (59 kg, ideal body weight) was found to be 91 L. In another group of patients (105 kg), the volume of distribution was found to be 229 L. Derive an equation that allows estimation of the volume of distribution based on ideal and actual body weight.

   Normal: IBW (59kg) $\rightarrow$ 91L $\rightarrow$ 1.5 L/kg

   Excess: EBW(105-59 = 46kg) $\rightarrow$ 229-91 = 138 L $\rightarrow$ 3L/kg (twofold of normal)

   $V_d = 1.5 \cdot (IBW + 2 \cdot EBW) = 1.5 \cdot IBW + 3 \cdot EBW$

2. Based on the Cockcroft-Gault-Equation, calculate the amount of creatinine that is produced every hour from muscle in a normal 25 year old and 70 year old male subject (body weight 70 kg) with a serum creatinine of 1 mg/dl.

   - The Cockroft-Gault equation allows us to predict the creatinine clearance (and therefore renal function/GFR) for patients differing in age and weight. For male patients,

$$Cl_{creat}(male) = \frac{(140 - age) \cdot weight}{72 \cdot Cp_{creat}}$$

   where age is in years, weight is in kg, and Cp_{creat} is in mg/dL. The Cl_{creat} is then in ml/min. This is an empirical equation which works only if the age, weight, and Cp_{creat} (or Scr) are entered in the units specified.

   - <u>For the 25 y.o.</u>

$$Cl_{creat} = \frac{(140 - 25)(70)}{(72)(1)} = 111.81 \text{ml/min}$$

   Although clearance is expressed in volume-per-time, the amount of creatinine eliminated-per-time may be found using the creatinine concentration given:

   Creatinine cleared per hour =

$$(111.81\text{ml/min})(1\text{mg/dL}) \cdot \frac{60\text{min}}{1\text{hr}} \cdot \frac{10\text{dL}}{1\text{L}} \cdot \frac{1\text{L}}{1000\text{ml}}$$

   = 67.1 <u>mg/hr</u>

(so in 1 day, about 1.6 g of creatinine is lost which is balanced by eating and producing 1.6 g of creatine per day))

- <u>For the 70 y.o.</u>

$$Cl_{creat} = \frac{(140-70)(70)}{(72)(1)} = 68.1\text{ml/min}$$

Creatinine cleared per hour =

$$(68.1\text{ml/min})(1\text{mg/dL}) \cdot \frac{60\text{min}}{1\text{hr}} \cdot \frac{10\text{dL}}{1\text{L}} \cdot \frac{1\text{L}}{1000\text{ml}}$$

= <u>40.9 mg/hr</u>

(Remember, elderly have less muscle mass which means less creatinine production)

3. Compare the pharmacokinetic properties of amoxicillin and cloxacillin:

	amoxicillin	cloxacillin
CL [L/h]	18	15
Vd [L]	14	7
F_{oral}	0.93	0.43
f_b	0.18	0.95
F_{ren}	0.86	0.75

Calculate and compare for both drugs the total daily oral dose necessary to maintain an average unbound concentration of 20 mg/L in plasma and urine. Assume a urine flow of 1 ml/min.

<u>Plasma</u>

$$C = \frac{F \cdot D}{CL \cdot 24} = \frac{Cu}{fu}$$

$$D = \frac{Cu \cdot CL \cdot 24}{F \cdot fu} = \frac{20 \cdot 18 \cdot 24}{0.93 \cdot 0.82} = 11.3g \quad \text{(amoxicillin)}$$

$$\frac{20 \cdot 15 \cdot 24}{0.43 \cdot 0.05} = 335g \quad \text{(cloxacillin) (!)}$$

<u>Urine</u> $\rightarrow$ to obtain 20 mg/L or 20 μg/mL $\rightarrow \frac{dE}{dt} = 20\mu g/\min = 1.2mg/h$

(Excretion Rate)

(Flow 1 mL/min)

Cl_{ren} = 15.5 L/h (amoxicillin)
= 11.3 L/h (cloxacillin)

$$CL_{ren} = \frac{\frac{dE}{dt}}{C} \rightarrow C = \frac{1.2}{15.5} = 0.077mg/L \quad \text{(amoxicillin)}$$

$$\frac{1.2}{11.3} = 0.106mg/L \quad \text{(cloxacillin)}$$

$$D = \frac{C \cdot CL \cdot 24}{F} = \frac{0.077 \cdot 18 \cdot 24}{0.93} = 35.8mg \quad \text{(amoxicillin)}$$

$$\frac{0.106 \cdot 15.24}{0.43} = 88.7mg \quad \text{(cloxacillin)}$$

4. Given the data below for two prednisolone tablet formulations, are these products bioequivalent? What pharmacokinetic criteria did you use to draw this conclusion?

	Product A	**Product B**	**Ratio (%) A/B**	**90% Confidence Limits**
$AUC_{0\text{-}15\ h}$ (μg min/mL)	204.5	216	94.7	98.1-100.1
$AUC_{0\text{-}\infty}$ (μg min/mL)	212	222	95.5	98.1-100.4
C_{MAX} (ng/mL)	1020	1053	96.9	97.8-101.3
T_{MAX} (min)	39.6	52.8	75.0	
$T_{1/2}$ (min)	186.2	170.4	109.3	

Bioequivalence is determined by the $AUC_{0\text{-}15\ h}$ $AUC_{0\text{-}\infty}$ and C_{MAX} (and in some cases T_{MAX}). The 90% confidence limits of the RATIO of product A/Product B must fall within 80-125% (see figure below). From this data, you would conclude that these two tablets are bioequivalent.

5 Look up in the Orange Book how many AB-rated oral cyclosporine products are available right now. The brand name product is Neoral. Look up the prices for 90 capsules (100 mg) for both brand name and generic.

Two (Abbott and Eon)

Prices (Drugstore.com):

Brand name	$478.18
Generic	$383.99