*Spring 2003*

**PHA 5128**

**Case Study II (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 (104 kg), the volume of distribution was found to be 292 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(104-59 = 45kg) $\rightarrow$ 292-91 = 201 L $\rightarrow$ 4.5 L/kg (threefold of normal)

   $V_d = 1.5 \cdot (IBW + 3 \cdot EBW) = 1.5 \cdot IBW + 4.5 \cdot EBW$

2. 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)

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

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

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

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

3. 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 $382.54

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. Is it possible for a generic product to be approved by the FDA without any testing in humans at all?

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BA and/or BE can be demonstrated using nonclinical studies. Generally, *in vivo* BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption.

Under certain circumstances, product quality BA and BE can be documented using *in vitro* approaches. For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) is appropriate based on the biopharmaceutics classification system. This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved NDAs and ANDAs.