HW # 2 Solution
PHA 5128
Spring 2009 10 pts

1a. What are the two pharmacokinetic parameters that are evaluated in a bioequivalance study whose log-transformed ratios (test:reference) must pass the two one-sided test about the 90% confidence intervals? **1 pt**

AUC and Cmax

1b. What is the lower and upper value of this interval?

80- 125 % or 0.80 – 1.25

2. An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.40 L/min in subjects with an average liver blood flow of 1.50 L/min. Is it possible to calculate the drugs approximate clearance in a congestive heart failure patient with a liver blood flow of 1.0 L/min but no change in hepatic extraction ratio? If yes, whats the clearance, if no, explain why ? **2 pts**

Yes it is possible.
We know that
$E = CLi*fu / (Q_H + CLi*fu)$
$CL = Q_H * E = Q_H * CLi*fu / (Q_H + CLi*fu)$
$1.4 = 1.5 * CLi*fu / (1.5 + CLi*fu)$
Solving this we get
$CLi*fu = 21$ L/min

Now with new liver blood flow of 1 L/min …… $Q_{H\,(new)} = 1$ L/min
$E_{(new)} = CLi*fu / (Q_{H\,(new)} + CLi*fu)$
$E_{(new)} = 21/(1 + 21) = 21/22 = 0.954$
$Cl_{hep} = 1 * 0.954 = 0.954$ L/min

However with such a high extraction ratio, one could assume negligible change in its value with the decreased liver blood flow and assume it to remain same and may use the following method:

$Cl_{hep} = Q_H * E$
$E = Cl_{hep} / Q_H = 1.4 / 1.5 = 0.933$

For CHF patient: $Q_H = 1.1$ L/min
$Cl_{hep} = Q_H * E = 1.0$ L/min $* 0.933 = 0.933$ L/min

Note that the change in E is practically negligible. So you could use the same E. But if you wanted to calculate the exact amounts one could calculate the change in E with change in liver blood flow. Either of the answers will be accepted.

3. Define the pharmacokinetic parameters Vd_{ss} and Vd_{area} and explain, why Vd_{ss} is always smaller than Vd_{area}. **3 pts**

Vd_{ss} Volume of distribution at steady state
Central and peripheral compartment are in equilibrium (equal unbound concentrations)
Vd_{area} Volume of distribution during the elimination phase. There is a concentration gradient from the peripheral to the central compartment. (unbound concentration is higher in the peripheral compartment, lower in the central compartment)
Lower concentration in central compartment
→ larger Vd

Hence → $Vd_{ss} < Vd_{area}$

4. A drug showed increase in tissue binding due a clinical condition. The pharmacist is of the opinion that the drug clearance remains the same but some other parameter changes. Is the pharmacist correct? Explain why ? **2 pts**

Yes, the pharmacist is right

$Vd = V_B + (fu / fu_T)* V_T$

With increase in tissue binding, fu_T decreases and Vd increases

- Clearance and bioavailability are not changed
- Half-life is increased due to increase in Vd (decrease in Ke)

5. In general, what are the reasons an oral dosage form will have <100% bioavailability (List 3 reasons)? 1 pt

- Solubility/dissolution rate
- Degradation
- P-glycoprotein
- Incomplete active transport
- First-pass effect
- Poor permeability

6. Chronic liver disease causes a 50% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold in chronic liver disease. Clearly the volume of distribution has changed due to the chronic liver disease. What is the volume of distribution of verapamil in a patient with chronic liver disease? (Healthy population values: CL= 50L/h; VD= 300 L) 1 pt

Healthy CL = ke · Vd
50 = ke · 300 L
ke = 0.167 L/h
t1/2 = 4.15 h (or 4 hrs)
Hepatic CL 50% = 25 L/h
If t1/2 = 16.6 (or 16 -17 hrs)

Vd= CL/ke = 25 /(0.693/16.6) = 599 L (613 L)