

Homework # 3 (Fall 2008) PHA 5127

Answers

Q1) Drug A is administered as a 125 mg IV bolus dose. 2 hours after administration the concentration in plasma is 2 mg/L and 10 hours after administration the concentration in plasma is 0.5 mg/L. This lipophilic drug is cleared by the liver and this patient has a liver blood flow of 80 L/hr. The tissue protein binding is 0.6. (total 6 points)

A. Calculate  $C_0$  (2 pts)

$$K_e = -\text{slope} \quad K_e = -(\ln 0.5 \text{ mg/L} - \ln 2 \text{ mg/L}) / (10 - 2) = .173 \text{ hr}^{-1}$$

$$C_0 = C_0 \cdot e^{(-K_e \cdot t)} \quad C_0 = C / e^{(-K_e \cdot t)} \quad C_0 = 2 \text{ mg/L} / (e^{-0.173 \text{ hr}^{-1} \cdot 2 \text{ hr}}) = 2.83 \text{ mg/L}$$

B. Calculate  $V_d$  (1 pts)

$$V_d = \text{Dose} / C_0 \quad V_d = 125 \text{ mg} / 2.83 \text{ mg/L} = 44.2 \text{ L}$$

C. Calculate  $f_u$  (1 pts)

$$V_d = V_p + V_t (f_u / f_{ut})$$

$$f_u = ((V_d - V_p) / V_t) * f_{ut}$$

$$f_u = ((44.2 \text{ L} - 3 \text{ L}) / 38 \text{ L}) * 0.4 = .43 \sim .4$$

D. Is this a high extraction drug or low extraction drug? (1 pt)

$$Cl = K_e * V_d \quad Cl = 0.173 \text{ hr}^{-1} * 44.2 \text{ L} = 7.65 \text{ L/hr}$$

If this drug were a high extraction drug, than the clearance would be close to liver blood flow, 80L/hr. However, it is much lower indicating that this drug is a low extraction drug.

E. If this drug were coadministered with Drug B, which is know to caused enzyme induction for the enzymes responsible for the metabolism of Drug A, would you expect to see a change in clearance? (1 pt)

Yes, this would change clearance. Since clearance of a low extraction drug is dependent on the fraction of free drug in plasma and the intrinsic clearance an enzyme induction would increase clearance.

Q2) How will the following parameters change for a drug that is a high extraction drug eliminated by hepatic clearance only if the free fraction in plasma is changed form 0.2 to 0.8. Indicate increase, decrease, or remain the same (half point each- total 2 points).

- A.  $V_d$  increase
- B.  $E_H$  remain the same
- C.  $Cl$  remain the same
- D.  $K_e$  decrease

Q3) Drug A has a hepatic clearance of 70 L/hr and a half life of 4 hrs. The plasma concentration immediately after an IV dose of 200mg of drug A was 0.289 mg/L. Which of the following statements is true and which is false ? (0.5 points each- total 2points)

- a. Drug A is cleared only by hepatic metabolism - False
- b. Drug A could be well distributed into tissues- True
- c. Drug A cannot have any plasma protein binding as it is distributed into tissues - False
- d. Drug A has AUC (0-inf) of approximately 2.87 mg\*hr/ L - False