PHA 5127

First Exam

Fall 2006

On my honor, I have neither given nor received unauthorized aid in doing this assignment.

Name

Put all answers on the bubble sheet

TOTAL _____/125 pts

Question Set I (True or False)
(15 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

A drug that does not bind to plasma proteins and tissue components has a Vd of 41 L

1.) T ***F*** The drug is likely to be hydrophilic

2.) T ***F*** V_T is likely to be round 18 L

3.) T ***F*** The relatively small Vd of 41 L suggests that the hepatic clearance has to be pronounced.

4.) ***T*** F At equilibrium, the free drug concentrations in plasma and tissue will be identical.

5.) ***T*** ***F*** At equilibrium, the total blood concentrations in plasma and tissue will be identical.

Question Set II
(10 points)

Imagine a drug that is given as an intravenous bolus. The dose was 80 mg. The elimination follows first order principles. 2 hours after administration the drug a concentration C1 of 1.48 µg/ml is observed. Four hours after the administration the concentration C2 was 0.74 µg/ml

6.) What is the elimination rate constant of this drug? (10 points)

A) 0.346 h-1

B) 0.693 h

C) 0.693 h^{-1}

D) 0.346 µg/(ml*h)

E) 0.370 h^{-1}

7.) What will the concentration be 8 hours after injection? (10 points)

A) 0.370 µg/ml

B) 0.370 mg/ml

C) 0 µg/ml

D) 0.185 µg/ml

E) none of the above

Question Set II (continued)
Imagine a drug that is given as an intravenous bolus. The dose was 80 mg. The elimination follows first order principles. 2 hours after administration the drug a concentration C1 of 1.48 µg/ml is observed. Four hours after the administration the concentration C2 was 0.74 µg/ml

8.) What is the concentration best describing the concentration directly after injection of the drug. (10 points)

A) 2 µg/ml

B) 3 µg/ml

C) 4 µg/ml

D) 5 µg/ml

E) none of the above

9.) What is the half-life of this drug? (10 points)

A) 1.0 h

B) 1.3 h

C) 3.0 h

D) 4.0 h

E) none of the above

Question Set III

10.) A patient with renal dysfunction received a dose of vancomycin (first order elimination). Plasma concentrations were 22 and 15 mg/L at 24 and 48 hours after drug administration. Plot these two plasma concentrations on semilog paper and determine how many hours after drug administration the concentration would reach 10 mg/L (10 points)

A. 2 days
B. 3 days
C. 4 days
D. 5 days
E. None of the above

11.) Calculate the area under the concentration time profile observed in the last question during day 2. (11 points)

A. 220 mg*hours/Liters

B. 330 mg*hours/Liters

C. 440 mg*hours/Liters

D. 670 mg*hours/Liters

E. None of the above.

Question Set IV(points)

Mark the correct statements? (16 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

12.) T ***F*** The volume of distribution relates the amount of drug in the body to the amount of drug in the plasma

13.) ***T*** F The volume of distribution relates the amount of drug in the body to the concentration of drug in the plasma

14.) T ***F*** The volume of distribution relates the concentration of drug in the body to the concentration of drug in the plasma

15.) T ***F*** The larger the volume of distribution, the smaller the dose necessary to achieve a certain starting concentration.

Question Set V (Matching)
(16 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a lipophilic, acid (pka), protein bound drug

Select the effect on kinetics

A) $V_D \uparrow$
B) $V_D \downarrow$
C) decreased rate of uptake into liver tissue
D) increased rate of uptake into liver tissue
E) none of the above

Physiological change

16.) Decrease in pH of the blood ***A,D,E***

17.) Increase in tissue binding ***A***

18.) Decrease in liver blood flow ***C,E***

19.) Decreased blood flow through poorly perfused tissues (e.g. fat tissue) ***E***

Question Set VI (Select the most correct combination)

20.) What of the following drug properties is beneficial for efficient distribution into poorly perfused organs (8 points)

a) The neutral (uncharged) species of a weak acid that is highly lipophilic.
b) The drug is uncharged at all times and highly hydrophilic
c) A strong base whose uncharged form is lipophilic
d) An uncharged drug with a small octanol/water partition coefficient
e) An acid with a pk_a of 7.4 and a large partition coefficient.

A) a, c, d

B) c, d, e

C) a,c,e

D) a, e

E) none of the above

Question Set VII (True or False)

(9 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

Mark whether the following statements are true (A) or false (B) for a drug that is distributed through permeability limited processes.

21.) ***T*** F Lipophilic unionized drugs are likely to enter tissues relatively fast.

22.) T ***F*** The uptake of a hydrophilic drug into tissue can be increased significantly by increasing the blood flow through the tissue

23.) ***T F*** Tissues with low blood flow should take up lipophilic unionized drugs the best.

Useful Pharmacokinetic Equations

Symbols

D = dose
τ = dosing interval
CL = clearance
Vd = volume of distribution
k_e = elimination rate constant
k_a = absorption rate constant
F = fraction absorbed (bioavailability)
K_0 = infusion rate
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

$$k_e = \frac{CL}{Vd} = \frac{\ln\left(\frac{C_1}{C_2}\right)}{(t_2 - t_1)} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)}$$

Half-life

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{\ln(2)}{k_e} = \frac{0.693}{k_e}$$

Intravenous bolus

Initial concentration

$$C_0 = \frac{D}{Vd}$$

Plasma concentration (single dose)

$$C = C_0 \cdot e^{-k_e \cdot t}$$

Plasma concentration (multiple dose)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Peak (multiple dose)

$$C_{max} = \frac{C_0}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Average concentration (steady state)

$$\overline{C}p_{ss} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(e^{-k_e \cdot t} - e^{-k_a \cdot t}\right)$$

Time of maximum concentration (single dose)

$$t_{max} = \frac{\ln\left(\frac{k_a}{k_e}\right)}{(k_a - k_e)}$$

Plasma concentration (multiple dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)} - \frac{e^{-k_a \cdot t}}{\left(1 - e^{-k_a \cdot \tau}\right)}\right)$$

Time of maximum concentration (multiple dose)

$$t_{max} = \frac{\ln\left(\frac{k_a \cdot \left(1 - e^{-k_e \cdot \tau}\right)}{k_e \cdot \left(1 - e^{-k_a \cdot \tau}\right)}\right)}{(k_a - k_e)}$$

Average concentration (steady state)

$$\overline{C} = \frac{F \cdot D}{CL \cdot \tau}$$

Clearance

$$Cl = \frac{Dose \cdot F}{AUC}$$

$$Cl = k_e \cdot V_d$$

Constant rate infusion

Plasma concentration (during infusion)

$$C = \frac{k_0}{CL} \cdot \left(1 - e^{-k_e \cdot t}\right)$$

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{\left(C_1 + C_2\right)} + \frac{2 \cdot Vd \cdot \left(C_1 - C_2\right)}{\left(C_1 + C_2\right) \cdot \left(t_2 - t_1\right)}$$

Short-term infusion

Peak (single dose)

$$C_{max(1)} = \frac{D}{CL \cdot T} \cdot \left(1 - e^{-k_e \cdot T}\right)$$

Trough (single dose)

$$C_{min(1)} = C_{max(1)} \cdot e^{-k_e \cdot (\tau - T)}$$

Peak (multiple dose)

$$C_{max} = \frac{D}{CL \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = C_{max} \cdot e^{-k_e \cdot (\tau - T)}$$

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C^*_{max}}{C^*_{min}}\right)}{\Delta t}$$

with C_{max}^* = measured peak and C_{min}^* = measured trough,
measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C^*_{max}}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C^*_{min} \cdot e^{-k_e \cdot t^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{C_{max} - C_{min} \cdot e^{-k_e \cdot T}}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{max(desired)}}{C_{min(desired)}}\right)}{k_e} + T$$

Calculated recommended dose

$$D = C_{max(desired)} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e \cdot \tau}\right)}{\left(1 - e^{-k_e \cdot T}\right)}$$

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_{\infty} = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

Creatinine Clearance

$$CL_{creat}(\text{male}) = \frac{(140 - \text{age}) \bullet \text{weight}}{72 \bullet Cp_{creat}}$$

$$CL_{creat}(\text{female}) = \frac{(140 - \text{age}) \bullet \text{weight}}{85 \bullet Cp_{creat}}$$

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

K_e for aminoglycosides

$K_e = 0.00293(CrCL) + 0.014$

Metabolic and Renal Clearance

$$E_H = \frac{Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_{ren} = RBF \cdot E = GFR \cdot \frac{C_{in} - C_{out}}{C_{in}}$$

$$Cl_{ren} = \frac{\text{rate of excretion}}{\text{plasma concentration}}$$

$$Cl_{ren} = fu \cdot GFR + \left[\frac{\text{Rate of secretion - Rate of reabsorption}}{\text{Plasma concentration}} \right]$$

$$Cl_{ren} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}$$

Ideal Body Weight

Male
IBW = 50 kg + 2.3 kg for each inch over 5ft in height

Female
IBW = 45.5 kg + 2.3 kg for each inch over 5ft in height

Obese
ABW = IBW + 0.4*(TBW-IBW)

Volume of Distribution

$$V = V_P + V_T \cdot K_P$$

$$V = V_P + V_T \cdot \frac{fu}{fu_T}$$

Clearance

$$Cl = \frac{Dose}{AUC}$$

$$Cl = k_e \cdot V_d$$

Name: _____

UFID #: _____

For One Compartment Body Model

If the dosing involves the use of I.V. bolus administration:	**For a single I.V. bolus administration:** $C_0 = \frac{D}{V}$ $C = C_0 \cdot e^{-k_e t}$	**For multiple I.V. bolus administration:** $Cn(t) = \frac{D}{V} \cdot \frac{\left(1 - e^{-nk_e\tau}\right)}{\left(1 - e^{-k_e\tau}\right)} \cdot e^{-k_e t}$ at peak: t = 0; at steady state n$\rightarrow\infty$ at trough: t = τ $C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e\tau})}$ $C_{\min ss} = C_{\max ss} \cdot e^{-k_e\tau}$
If the dosing involves the use of I.V. infusion:	**For a single short-term I.V. infusion:** Since τ = t for C_{max} $C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$	**For multiple short-term I.V. infusion at steady state:** $C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$
If the dosing involves a I.V. infusion (more equations):	$C_t = \frac{D}{Vk_eT} \cdot \left(e^{k_eT} - 1\right) \cdot e^{-k_e t}$ (most general eq.) $C_t = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_e t}\right)$ (during infusion) $Cpss = \frac{D}{Vk_eT} = \frac{k_0}{Vk_e} = \frac{k_0}{CL}$ (steady state)	during infusion t = T so, at steady state t $\rightarrow \infty$, $e^{-k_e t}$, t $\rightarrow$ 0 so, remembering $k_0 = \frac{D}{T}$ and $CL = V \cdot k_e$
If the dosing involves oral administration:	**For a single oral dose:** $C = \frac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left(e^{-k_e t} - e^{-k_a t}\right)$ $t_{\max} = \ln\left[\frac{k_a}{k_e}\right] \cdot \frac{1}{(k_a - k_e)}$	**For multiple oral doses:** $C = \frac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left[\frac{e^{-k_e t}}{\left(1 - e^{-k_e\tau}\right)} - \frac{e^{-k_a t}}{\left(1 - e^{-k_a\tau}\right)}\right]$ $t_{\max} = \ln\left[\frac{k_a \cdot \left(1 - e^{-k_e\tau}\right)}{k_e \cdot \left(1 - e^{-k_a\tau}\right)}\right] \cdot \frac{1}{(k_a - k_e)}$