PHA 5127

First Exam
Fall 2010

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

Name

Question Set/Points

I. 30 pts
II. 20 pts
III. 15 pts
IV. 15 pts
V. 25 pts
VI. 10 pts
VII. 10 pts
VIII. 10 pts
IX. 35 pts

TOTAL: 170 pts
Question Set I (True or False)  
(30 points)

**True (A) or False (B). On the bubble sheet mark A for true or B for false. Assume passive diffusion as the driving force for distribution.**

1: T F  If the elimination of a drug is described by a first order process, it will be described by a one compartment model of drug distribution.

2: T F  A lipophilic drug can not have a volume of distribution that is smaller than $V_T$.

3: T F  The pka of an acidic drug that shows perfusion limited distribution into tissues is likely to be small.

4: T F  Two drugs that have similar elimination half-lives will have similar clearance estimates.

5: T F  The same dose of a drug is given orally either as a solution or in form of a slow dissolving crystal suspension. The solution will show higher maximum concentrations in plasma.

6: T F  Serum can be prepared by adding heparin to blood.
Question Set II (20 points) True (A) or False (B). On the bubble sheet mark A for true or B for false.

Consider a lipophilic acidic drug (pKa=14, logP=5) and a lipophilic neutral drug B (logP=5). Both do not show any affinity to transporters and show similar tissue and plasma protein binding.

7:  T  F  Drug B will enter the brain faster.

8:  T  F  Drug A will be unable to enter the interstitial fluid.

9:  T  F  Drug B be is likely to have a larger volume of distribution.

10: T  F  When the same dose of Drug A and B is given as an iv bolus injection, Drug A’s C₀ will be higher than Drug’s B C₀.
Question Set III

(15 points)

Listed in the Table are two properties of acidic drug molecules:

- the fraction ionized at pH=7.4 and
- the partition coefficient of the unionized form.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Fraction Unionized at pH=7.4</th>
<th>Partition Coefficient of Unionized form</th>
<th>Molecular Weight (Dalton)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>2.1</td>
<td>240</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>0.07</td>
<td>290</td>
</tr>
<tr>
<td>3</td>
<td>0.074</td>
<td>10</td>
<td>320</td>
</tr>
<tr>
<td>4</td>
<td>0.72</td>
<td>0.005</td>
<td>456</td>
</tr>
</tbody>
</table>

11: Select the correct rank order with which drugs 1-4 will enter brain tissue. Assume that the drugs are not subject to transporters at the blood-brain barrier.

A: 1 slower than 2 slower than 3 slower than 4
B: 1 slower than 3 slower than 2 slower than 4
C: 4 slower than 2 slower than 3 slower than 1
D: 4 slower than 2 slower than 1 slower than 3
E: 3 slower than 1 slower than 4 slower than 2
Question Set IV (True or False)
(15 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false. Assume no active transport.

12:  
T F  Compared to fat, the liver is likely to have a higher rate of uptake for small lipophilic drugs due to its higher blood flow rate.

13:  
T F  The rate with which hydrophilic compounds will move across well-built membranes will depend on the concentration gradient between total drug in plasma and total drug in tissue.

14:  
T F  Permeability limited distribution is generally seen for small, lipophilic drugs
True (A) or False (B). On the bubble sheet mark A for true or B for false

15: T F Drug B’s rate of elimination is affected by the amount of drug in the body.

16: T F Drug A’s elimination rate constant has the unit “ng/ml”.

17: T F For Drug B, the fraction of drug eliminated per hour is constant.

18: T F Drug A’s concentration-time profile might be explained by saturated metabolic enzymes.

19: T F The half-life of drug B is 5 hours.
**Question Set VI**

(10 points)

20: An investigational new drug is eliminated entirely by hepatic metabolism, with a clearance of 1.40 L/min in subjects with an average liver blood flow of 1.50 L/min. What would be the expected clearance in a congestive heart failure patient with a liver blood flow of 1.10 L/min but no change in hepatic extraction ratio?

A) 1.10 L/min  
B) 1.40 L/min  
C) 1.18 L/min  
D) 1.03 L/min  
E) None of the above

21: The lipophilic drug A has a volume of distribution of 100 L. In the presence of drug B, drug A is displaced from plasma albumin sites binding sites only (1.5-fold change in fraction unbound in plasma). Predict the change in volume of distribution for drug A. Assume negligible change in tissue binding

A) 115 L  
B) 150 L  
C) 200 L  
D) 300 L  
E) None of the above
Question Set VII

(10 points)

22: How will the increase in both tissue binding and liver blood flow affect the initial concentration (C₀), clearance (CL), bioavailability (F) for tablet, AUC, and half-life (t₁/₂) of a low-extraction drug? (Please note that ↔ means no change)

A: ↓C₀, ↑CL, ↓F, AUC↓, ↓t₁/₂

B: ↔C₀, ↔CL, ↑F, AUC↑, ↔t₁/₂

C: ↓C₀, ↔CL, ↔F, AUC↔, ↑t₁/₂

D: ↑C₀, ↓CL, ↔F, AUC↑, ↑t₁/₂

E: none of above combinations.
Question Set VIII

(10 points)

23. Chronic liver disease causes a 20% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold. Clearly the volume of distribution has also 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= 60L/h; Vd= 300 L)

A.300L
B.1200L
C.960L
D.240L
E. None of above
Question Set IX
(35 points)

24: T  F  Free drug concentrations are always the same in plasma and tissues, when the distribution occurs instantaneously.

25: T  F  For a drug that shows permeability controlled uptake into all tissues, total drug concentrations are always higher in the plasma than in tissues.

26: T  F  When the Vd of a drug is 41L, we can conclude that the drug has no plasma protein binding or tissue binding.

27: T  F  A fast absorption might allow less frequent dosing.

28: T  F  A slower absorption might be advantageous for a drug with a narrow therapeutic window.

29: T  F  The Fick’s law is: \( \frac{dQ}{dt} = D \cdot K \cdot (C_{plasma} - C_{tissue})/h \). The k in the equation denotes the first order elimination rate constant.

30: T  F  Concentrations in plasma are of relevance for the drug therapy as they are generally identical to concentrations at the target site.
Useful Pharmacokinetic Equations

Symbols

\( D \) = dose  \\
\( \tau \) = dosing interval  \\
\( \text{CL} \) = clearance  \\
\( \text{Vd} \) = 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

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

Half-life

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

Intravenous bolus

Initial concentration

\[ C_0 = \frac{D}{\text{Vd}} \]

Plasma concentration (single dose)

\[ C = C_0 \cdot e^{-k_e \cdot \tau} \]

Plasma concentration (multiple dose)

\[ C = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{1 - e^{-k_e \cdot \tau}} \]

Peak (multiple dose)

\[ C_{\text{max}} = \frac{C_0}{1 - e^{-k_e \cdot \tau}} \]

Average concentration (steady state)

\[ \bar{C}_{\text{ss}} = \frac{D}{\text{CL} \cdot \tau} \]

Oral administration

Plasma concentration (single dose)

\[ C = \frac{F \cdot D}{\text{Vd}} \cdot \frac{k_a}{(k_a - k_e)} \cdot \left( e^{-k_a \cdot \tau} - e^{-k_e \cdot \tau} \right) \]

Time of maximum concentration (single dose)

\[
\ln \left( \frac{k_a}{k_e} \right) \\
t_{\text{max}} = \frac{\ln \left( \frac{k_a}{k_e} \right)}{(k_a - k_e)}
\]

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

\[ \bar{C} = \frac{F \cdot D}{\text{CL} \cdot \tau} \]

Clearance

\[ Cl = \frac{\text{Dose} \cdot F}{AUC} \]

\[ Cl = k_e \cdot \text{Vd} \]
**Constant rate infusion**

Plasma concentration (during infusion)
\[ C = \frac{k_0}{CL} \cdot (1 - e^{-k_e T}) \]

Plasma concentration (steady state)
\[ C = \frac{k_0}{CL} \]

Calculated clearance (Chiou equation)
\[ CL = \frac{2 \cdot k_0}{(C_1 + C_2)} + \frac{2 \cdot V_d \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)} \]

**Short-term infusion**

Peak (single dose)
\[ C_{\text{max}(1)} = \frac{D}{CL \cdot T (1 - e^{-k_e T})} \]

Trough (single dose)
\[ C_{\text{min}(1)} = C_{\text{max}(1)} \cdot e^{-k_e (T-T)} \]

Peak (multiple dose)
\[ C_{\text{max}} = \frac{D}{CL \cdot T} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e T})} \]

Trough (multiple dose)
\[ C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (T-T)} \]

Calculated elimination rate constant
\[ k_e = \frac{\ln\left(\frac{C_{\text{max}}}{C_{\text{min}}^*}\right)}{\Delta t} \]

with \( C_{\text{max}}^* \) = measured peak and \( C_{\text{min}}^* \) = measured trough, measured over the time interval \( \Delta t \)

**Calculated peak**
\[ C_{\text{max}} = \frac{C_{\text{max}}^*}{e^{-k_e T}} \]

with \( C_{\text{max}}^* \) = measured peak, measured at time \( T^* \) after the end of the infusion

**Calculated trough**
\[ C_{\text{min}} = C_{\text{min}}^* \cdot e^{-k_e T} \]

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

**Calculated volume of distribution**
\[ V_d = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e T}\right)}{[C_{\text{max}} - (C_{\text{min}} \cdot e^{-k_e T})]} \]

**Calculated recommended dosing interval**
\[ \tau = \frac{\ln\left(\frac{C_{\text{max(desired)}}}{C_{\text{min(desired)}}}\right)}{k_e} + T \]

**Calculated recommended dose**
\[ D = C_{\text{max(desired)}} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e T}\right)}{\left(1 - e^{-k_e T}\right)} \]

**Two-Compartment-Body Model**

\[ C = a \cdot e^{-\alpha T} + b \cdot e^{-\beta T} \]

\[ \text{AUC}_{\infty} = a / \alpha + b / \beta \]

\[ V_{d_{\text{area}}} > V_{d_{ss}} > V_c \]

**Creatinine Clearance**
\[ CL_{\text{creat (male)}} = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot C_{\text{creat}}} \]

\[ CL_{\text{creat (female)}} = \frac{(140 - \text{age}) \cdot \text{weight}}{85 \cdot C_{\text{creat}}} \]

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL in ml/min
**Ke for aminoglycosides**

\[ Ke = 0.00293(CrCL) + 0.014 \]

**Metabolic and Renal Clearance**

\[
E_H = \frac{Cl_{int} \cdot fu_{b}}{Q_H + Cl_{int} \cdot fu_{b}}
\]

\[
Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_{b}}{Q_H + Cl_{int} \cdot fu_{b}}
\]

\[
F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_{b}}
\]

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

\[
Cl_{ren} = \text{rate of excretion} \div \text{plasma concentration}
\]

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

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

**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**

\[
Cl = \frac{Dose}{AUC}
\]

\[
Cl = k_e \cdot V_d
\]
**For One Compartment Body Model**

| If the dosing involves the use of I.V. bolus administration: | For a single I.V. bolus administration: |
| | For multiple I.V. bolus administration: |
| | $C_0 = \frac{D}{V}$ |
| | $C = C_0 \cdot e^{-k_e t}$ |
| | $Cn(t) = \frac{D}{V} \left( \frac{1-e^{-nk_e \tau}}{1-e^{-k_e \tau}} \right) \cdot e^{-k_e t}$ |
| | at peak: $t = 0$; at steady state $n \to \infty$ |
| | at trough: $t = \tau$ |
| | $C_{\text{max ss}} = \frac{D}{V} \cdot \frac{1}{(1-e^{-k_e \tau})}$ |
| | $C_{\text{min ss}} = C_{\text{max ss}} \cdot e^{-k_e \tau}$ |

| If the dosing involves the use of I.V. infusion: | For a single short-term I.V. infusion: |
| | For multiple short-term I.V. infusion at steady state: |
| Since $\tau = t$ for $C_{\text{max}}$ | $C_{\text{max}} = \frac{D}{Vk_e T} \cdot (1-e^{-k_e T})$ |
| | $C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau-T)}$ |
| | $C_{\text{max}} = \frac{D}{Vk_e T} \cdot \left( 1-e^{-k_e T} \right) / \left( 1-e^{-k_e \tau} \right)$ |
| | $C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau-T)}$ |
### If the dosing involves a I.V. infusion (more equations):

If the dosing involves a I.V. infusion (more equations):

If the dosing involves oral administration:

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_t = \frac{D}{V k_e T} \cdot \left( e^{k_e T} - 1 \right) \cdot e^{-k_e t}$</td>
<td>(most general eq.) during infusion $t = T$ so,</td>
</tr>
<tr>
<td>$C_t = \frac{D}{V k_e T} \cdot \left( 1 - e^{-k_e t} \right)$</td>
<td>(during infusion) at steady state $t \rightarrow \infty$, $e^{k_e t}$, $t \rightarrow 0$ so,</td>
</tr>
<tr>
<td>$C_{pss} = \frac{D}{V k_e T} = \frac{k_0}{V k_e} = \frac{k_0}{C_L}$</td>
<td>(steady state) remembering $k_0 = \frac{D}{T}$ and</td>
</tr>
<tr>
<td>$C_{pss} = \frac{D}{V k_e T} = \frac{k_0}{V k_e} = \frac{k_0}{C_L}$</td>
<td></td>
</tr>
<tr>
<td>$CL = V \cdot k_e$</td>
<td></td>
</tr>
</tbody>
</table>

### For a single oral dose:

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:

For multiple oral doses:

| $C = \frac{F \cdot D \cdot k_a}{V (k_a - k_e)} \cdot \left[ \frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}} \right]$ | |
| $t_{max} = \ln \left[ \frac{k_a \cdot (1 - e^{-k_e \tau})}{k_e \cdot (1 - e^{-k_a \tau})} \right] \cdot \frac{1}{(k_a - k_e)}$ | |

Last modified 2009
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