PHA 5127

First Exam
Fall 2012

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. 20 pts
IV 15 pts
V. 25 pts
VI. 20 pts
VII. 15 pts
VIII. 20 pts
IX. 35 pts

TOTAL: 200 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 Assume a drug that is eliminated through metabolism. The drug’s plasma concentration decreases by 4 ng/ml every 2 hours. It is likely that the enzymes involved in the metabolism are saturated.

2:  T (F) Assume a drug eliminated through enzymatic metabolism. The drug’s plasma concentration decreases by 4 ng/ml every 2 hours. The elimination rate constant describing this metabolism will have the unit: 1/hr

3:  (T) F The rate at which a lipophilic drug, of low molecular weight that is not an acid nor a base, is taken up by tissues will significantly be related to the blood flow through those tissues.

4:  T (F) The rate at which a lipophilic drug that is not an acid nor a base is taken up by fat tissue is likely to be faster than the rate at which it is taken up by the kidney.

5:  (T) F The same dose of a drug is given either as a solution or in form of a slow dissolving crystal suspension. The solution will have to be given more often during the day.

6:  T (F) Plasma can be prepared by letting the collected patient’s blood clot. The resulting supernatant is called plasma.
Question Set II (20 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false. Consider the lipophilic drug A and a drug B which is even more lipophilic. Both do not show any affinity to transporters (Ficks law applies), show the same tissue and plasma protein binding.

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

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

9:  T  F  Both drugs will have the same volume of distribution.

10: T  F  Drug B is more likely to show permeability limited tissue uptake.
Question Set III
(20 points)

11: Listed in the Table are two properties of acidic drug molecules:
   • the fraction unionized 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>

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.
Assume the same dose of penicillin G is given to patients as iv bolus injection (as solution in saline), intramuscular (i.m.) oily injection or orally.

12: \( \bigcirc \) F Giving the drug orally will result in a much smaller AUC than after i.m. and iv injection.

13: T \( \bigcirc \) Penicillin G is stable in the gastro-intestinal tract.

14: T \( \bigcirc \) iv injections allow a less frequent dosing.
Question Set V (True or False)

(25 points)

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

15: [T] F Drug A's rate of elimination is affected by the amount of drug in the body.

16: [T] F Drug B's elimination rate constant has the unit "ng/ml".

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

18: [T] F Drug B's concentration-time profile might be explained by saturated metabolic enzymes.

19: [T] F The half-life of Drug B depends on the concentration that should be cut into half.
Question Set VI

(20 points)

20: 200 mg of Drug A was administered to a patient through iv bolus injection. A plasma drug concentration of 0.78 mg/L was measured after 2 hours. A plasma drug concentration of 0.16 mg/L was measured after 8 hours. The drug’s distribution is instantaneous.

Assuming a first order process, calculate the elimination rate constant

A: 0.16 h⁻¹
B: 0.16 mg/ (L*h)
C: 0.264 mg/ (L*h)
D: 0.264 h⁻¹
E: None of the above

21: 200 mg of Drug A was administered to a patient through i.v bolus injection. A plasma drug concentration of 0.78 mg/L was measured after 2 hours. A plasma drug concentration of 0.16 mg/L was measured after 4 hours. The drug’s distribution is instantaneous.

Assuming a zero order process, calculate the initial drug concentration

A: 1.32 mg/L
B: 1.32 L
C: 1.4 mg/L
D: None of the above
Question Set VII
(15 points)

A drug (lipophilic, unionized, low molecular weight) is showing in average a pronounced binding to plasma proteins of 99%. Between-subject variability of protein binding is pronounced. 1000mg of the drug is given as IV bolus injection to two patients. **Patient 1 has a much stronger plasma protein binding** for the drug (99.995%) than the second patient (99.99%). The tissue binding is the same in both patients and is equal to 90%

Based on the given information please indicate whether **patient 1** will have a larger (↑), smaller (↓) identical (↔) value than patient 2 for:

- total initial total plasma drug concentration (\(C_0\)),
- free initial total plasma drug concentration (**free** \(C_0\)),
- \(f_u\)
- \(V_d\)

22:

A: \(C_0 \uparrow, \text{free } C_0 \uparrow, f_u \downarrow, V_d \downarrow\)
B: \(C_0 \downarrow, \text{free } C_0 \leftrightarrow, f_u \downarrow, V_d \uparrow\)
C: \(C_0 \uparrow, \text{free } C_0 \downarrow, f_u \downarrow, V_d \downarrow\)
D: \(C_0 \uparrow, \text{free } C_0 \uparrow, f_u \uparrow, V_d \leftrightarrow\)
E: none of above combinations.
Question Set VIII

(20 points)

Assume a drug is substrate of a specific transport protein. What of the following statements are True (A) or False (B). On the bubble sheet mark A for true or B for false

23: T [ ] F [ ] Transporters do not use energy.
24: T [ ] F [ ] Transporters only eliminate drugs from the body.
25: T [ ] F [ ] Transporters are only present in liver and kidney.
26: T [ ] F [ ] Transporters are saturable.
27: T [ ] F [ ] Transporters work often in conjunction with enzymes.
Question Set IX

(35 points)

28: T F Free drug concentrations are assumed to be the same in plasma and tissues, when the distribution is assumed to be instantaneous.

29: 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.

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

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

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

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

34: 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

\[ D = \text{dose} \]
\[ \tau = \text{dosing interval} \]
\[ V_d = \text{volume of distribution} \]
\[ k_e = \text{elimination rate constant} \]
\[ k_s = \text{absorption rate constant} \]
\[ F = \text{fraction absorbed (bioavailability)} \]
\[ K_i = \text{infusion rate} \]
\[ T = \text{duration of infusion} \]
\[ C = \text{plasma concentration} \]

General

Elimination rate constant

\[ k_e = \frac{C_L}{V_d} = \frac{\ln \left( \frac{C_1}{C_2} \right)}{(t_2 - t_1)} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)} \]

Half-life

\[ t_{1/2} = \frac{0.693 \cdot V_d}{C_L} = \frac{\ln(2)}{k_e} \]

\[ t_{1/2} = \frac{0.693}{k_e} \]

Intravenous bolus

Initial concentration

\[ C_0 = \frac{D}{V_d} \]

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)

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

Trough (multiple dose)

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

Average concentration (steady state)

\[ C_{\text{ave}} = \frac{D}{V_d \cdot \tau} \]

Oral administration

Plasma concentration (single dose)

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

Time of maximum concentration (single dose)

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

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

\[ C_{\text{ave}} = \frac{F \cdot D}{C_L \cdot \tau} \]

Clearance

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

\[ C_L = k_e \cdot V_d \]
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)
\[ CL = \frac{2 \cdot k_{0} + 2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (C_1 + C_1) \cdot (t_2 - t_1)} \]

Short-term infusion

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

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

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

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

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
\[ C_{\text{max}} = \frac{C_{\text{max}}}{e^{-k_e \cdot t'}} \]
with \( C_{\text{max}} \) = measured peak, measured at time \( t' \) after the end of the infusion

Calculated trough
\[ C_{\text{min}} = C_{\text{min}} \cdot e^{-k_e \cdot t'} \]
with \( C_{\text{min}} \) = measured trough, measured at time \( t' \) before the start of the next infusion

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

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

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

Two-Compartment-Body Model
\[ C = a \cdot e^{-\alpha t} + b \cdot e^{-\beta t} \]

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

\[ Vd_{\text{sys}} > Vd_{\text{ss}} > Vc \]

Creatinine Clearance
\[ CL_{\text{crea}} = \frac{\text{weight}}{72 \cdot C_{\text{crea}}} \]
\[ CL_{\text{crea}} = \frac{\text{weight}}{85 \cdot C_{\text{crea}}} \]

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{crea} in ml/min
**K_e for aminoglycosides**

\[ K_e = 0.00293(\text{CrCL}) + 0.014 \]

**Metabolic and Renal Clearance**

\[
E_H = \frac{\text{Cl}_{\text{int}} \cdot f_{u_b}}{Q_{\text{in}} + \text{Cl}_{\text{int}} \cdot f_{u_b}}
\]

\[
\text{Cl}_{\text{H}} = E_H \cdot Q_{\text{H}} = \frac{Q_{\text{H}} \cdot \text{Cl}_{\text{int}} \cdot f_{u_b}}{Q_{\text{in}} + \text{Cl}_{\text{int}} \cdot f_{u_b}}
\]

\[
F_{\text{H}} = \frac{Q_{\text{H}}}{Q_{\text{in}} + \text{Cl}_{\text{int}} \cdot f_{u_b}}
\]

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

\[
\text{Cl}_{\text{ren}} = \frac{\text{rate of excretion}}{\text{plasma concentration}}
\]

\[
\text{Cl}_{\text{ren}} = f_{u} \cdot \text{GFR} + \left[ \frac{\text{Rate of secretion} - \text{Rate of reabsorption}}{\text{Plasma concentration}} \right]
\]

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

**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**

\[
V = V_p + V_f \cdot K_p
\]

\[
V = V_p + V_f \cdot \frac{f_{u}}{f_{u_p}}
\]

**Clearance**

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

\[
Cl = k_s \cdot V_f
\]
**Constant rate infusion**

**Plasma concentration (during infusion)**

\[ C = \frac{k_s}{CL} \left(1 - e^{-k_r t}\right) \]

**Plasma concentration (steady state)**

\[ C = \frac{k_s}{CL} \]

**Calculated clearance (Chiou equation)**

\[ CL = \frac{2 \cdot k_s}{(C_i + C_s)} + \frac{2 \cdot V_d \cdot (C_i - C_s)}{(C_i + C_s) \cdot (t_1 - t_)} \]

**Short-term infusion**

**Peak (single dose)**

\[ C_{\text{max}(t)} = \frac{D}{CL \cdot T} \left(1 - e^{-k_r t}\right) \]

**Trough (single dose)**

\[ C_{\text{min}(t)} = C_{\text{max}(t)} \cdot e^{-k_r (t-T)} \]

**Peak (multiple dose)**

\[ C_{\text{max}} = \frac{D}{CL \cdot T} \left(1 - e^{-k_r T}\right) \]

**Trough (multiple dose)**

\[ C_{\text{min}} = C_{\text{max}} \cdot e^{-k_r (t-T)} \]

**Calculated elimination rate constant**

\[ k_s = \frac{\ln \left(\frac{C_{\text{max}}}{C_{\text{min}}^*}\right)}{\Delta t} \]

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

**Calculated peak**

\[ C_{\text{max}} = \frac{C_{\text{min}}^*}{e^{-k_s^* \cdot t^*}} \]

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

**Calculated trough**

\[ C_{\text{min}}^* = C_{\text{min}}^* \cdot e^{-k_s^* \cdot t^*} \]

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

**Calculated volume of distribution**

\[ V_d = \frac{D \cdot \left(1 - e^{-k_s^* \cdot T}\right)}{k_s^* \cdot T} \left[\frac{C_{\text{max}}}{C_{\text{min}}^*} - \frac{C_{\text{min}}^* \cdot e^{-k_s^* \cdot T}}{C_{\text{min}}^*}ight] \]

**Calculated recommended dosing interval**

\[ \tau = -\frac{\ln \left(\frac{C_{\text{max(dosed)}}}{C_{\text{min(dosed)}}}\right)}{k_s} + T \]

**Calculated recommended dose**

\[ D = C_{\text{max(dosed)}} \cdot k_s \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_s^* \cdot T}\right)}{\left(1 - e^{-k_s^* \cdot T}\right)} \]

**Two-Compartment-Body Model**

\[ C = a \cdot e^{-\gamma \cdot \omega} + b \cdot e^{-\beta \cdot \omega} \]

\[ AUC_{\omega} = a / \alpha + b / \beta \]

\[ V_{d_{\omega}} > V_d_{\omega} > V_c \]

**Creatinine Clearance**

\[ CL_{\text{ur}} (\text{male}) = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot C_{P_{\text{crea}}}} \]

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

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