PHA 5127

Third Exam

Fall 2013

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

______________________________
Name

Question/Points

Set I   25
Set II  25
Set III 25
Set IV  20
Set V   20
Set VI  15
Set VII 10
Total  140
Question Set I (25 points)

1. Please select the CORRECT answer(s) for a multiple dose, short-term intravenous infusion scenario from the choices given below. (5 points)

1) The shorter a drug’s half-life, the larger the fluctuation \( t_{1/2} \uparrow k_e \uparrow \)
2) The faster a drug is cleared, the smaller the fluctuation \( \times k_e \uparrow \)
3) For a given dosing interval (tau), the slower the drug dose is infused, the lower the peak plasma concentration \( \checkmark \)
4) The larger the dose for a defined dosing interval, the higher the peak concentrations \( \checkmark \)
5) For a given dose, the longer the dosing interval, the smaller the fluctuation. \( \checkmark \)

A. 1, 3, 4
B. 1, 2, 3, 4
C. 2, 3, 4, 5
D. All of the above
E. None of the above

2. A 500mg dose of drug Z is given every 12 hours as an intravenous bolus injection until steady-state levels are reached. At steady-state, the AUC for one dosing interval is 36 mg/L*h. What is the average concentration for that dosing interval? (5 points)

\[
C_{ss\,avg} = \frac{AUC}{\tau} = \frac{36}{12} = 3 \text{ mg/L}
\]

A. 2.1ug/mL
B. 3ug/mL
C. 3.5ug/mL
D. 4.1ug/mL
E. None of the above

3. A patient was given 100mg of gentamicin via a constant rate infusion over 1 hour every 8 hours. His peak plasma concentration at steady-state was determined to be 9mg/L. What will his plasma concentration be 4 hours after the start of the last infusion given the drug’s half-life of 5 hours? (5 points)

\[
C_{max\,ss} = 9\text{mg/L} \\
C = 9 \times e^{-(0.1386 \times 3)}
\]

A. 3.93mg/L
B. 4.32mg/L
C. 5.93mg/L
D. 6.72mg/L
E. 7.41mg/L

\[
C = 9 \times e^{-(0.1386 \times 3)} = 5.93
\]
4. A 30-year-old male (71kg) is admitted to the hospital for a colectomy. He develops a post-operative wound infection and is put on vancomycin. Please assume for your calculations that vancomycin is solely eliminated via the kidneys (filtration only) and that the volume of distribution is 0.8L/kg. Further assume that vancomycin is 35% plasma protein bound and that the patient’s glomerular filtration rate is 119mL/min.

Please compute an appropriate dosing interval to achieve steady-state peak and trough concentrations of 25mg/L and 10mg/L, respectively, following a 1-hour infusion. (10 points)

\[ V_d = 56.8 \text{L} \quad f_o = 0.65 \]

\[ CL = \frac{119 \text{mL/min}}{56.8} \times 0.65 = 77.35 \text{mL/min} = 4.64 \text{L/hr} \]

\[ k_e = \frac{CL}{V_d} = \frac{4.64}{56.8} = 0.082 \text{hr}^{-1} \]

\[ F = e^{k_e(T-T)} \]

\[ \frac{\ln F}{k_e} + T = T \]

\[ \frac{\ln 2.5}{0.082} + 1 = 2 \]

\[ T = 12.17 \text{hr} \]

\[ T \approx 12 \text{hr} \]
Question Set II (25 points)

Consider the following equation:

\[
C_{p, min, ss} = \frac{Dose}{k_e \cdot V_d} \cdot \frac{1 - e^{-k_eT}}{1 - e^{-k_e\tau}} \cdot e^{-k_e\tau'}
\]

You join a new company and your supervisor tells you to work on a new drug about which you know only the following information: it is given as a short-term infusion (1 hour) every 8 hours and its half-life is 7 hours. On the bubble sheet mark A for true or B for false.

5. \( \text{T} \) \( \text{F} \) Fluctuation will be 2

6. \( \text{T} \) \( \text{F} \) There is insufficient information to compute the volume of distribution

7. \( \text{T} \) \( \text{F} \) Drug input into the systemic circulation is in this case characterized by a first order process

8. \( \text{T} \) \( \text{F} \) Half of the administered dose is eliminated during each dosing interval at steady-state

9. \( \text{T} \) \( \text{F} \) If \( t' \) equals \( T \) minus \( T \), the trough concentration will be half of the peak concentration

\[ F = e^{k_e(T-t)} = e^{0.099 \times 7} = 2 \]
Question Set III (25 points)

10. Please select the correct answer regarding a two-compartment body model from the choices given below. (10 points)

1) Macro constants can be used to characterize the concentration-time profile
2) The concentration-time profile of a two-compartment model is represented by a biexponential curve
3) Beta is the terminal elimination half-life
4) The method of residuals (feathering) can be used to compute the rate constant of drug distribution into peripheral tissues
5) $X_p$ typically represents the amount of drug in the central compartment following parenteral drug administration

A. 2, 4
B. 1, 2, 4
C. 2, 3, 4, 5
D. 1, 2, 3, 4
E. None of the above

11. A 65-kg patient is started on a continuous intravenous constant rate infusion of theophylline at 40mg/h. His respective steady-state concentrations are determined to be 10mg/L. If you assume the theophylline distribution volume to be 40L, what would be the patient’s plasma concentrations 10 hours after the continuous infusion is stopped (please assume that steady-state had been reached previously for your computations)? (10 points)

$$C_{ss} = \frac{K_e}{K_e \cdot V_d} = \frac{10\text{mg}}{40\text{L}}$$

10 hours after infusion is stopped

$$C_{10} = \frac{10\text{mg} \times e^{-0.1 \times 10}}{40\text{L}} = \frac{3.67\text{mg}}{40\text{L}} = 0.0917\text{mg/L}$$

$$K_e = \frac{40\text{mg/h}}{40\text{L}} = 1\text{hr}^{-1}$$
12. What impact will a decrease in plasma protein binding have for a high-extraction drug that is solely cleared via Phase I and II enzymes in the liver following intravenous administration? Please select the correct answer. (5 points)

A. An increase in hepatic clearance
B. An increase in glomerular filtration rate
C. An increase in free average steady-state concentrations
D. An increase in total steady-state concentrations
E. None of the above
Question Set IV (20 points)

Please indicate whether the following statements for an oral dosing regimen are True (A) or False (B).

13. T  F  There is only drug absorption until peak plasma concentrations are reached

14. T  F  The terminal slope of the concentration time profile is always reflective of the elimination rate constant ke

15. T  F  If two formulations of the same drug are tested and product A has a greater absorption rate than product B, product A will take a longer time to reach peak concentrations (Tmax)

16. T  F  The time it takes to reach peak plasma concentrations (Tmax) is independent of the dose and the oral bioavailability
Question Set V (20 points)

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.
- The ability to be actively pumped in (++) or pumped out (--) of the brain by extremely active transporters. No activity to transporters (000)

<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>
<th>Transporter activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.72</td>
<td>0.005</td>
<td>456</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>0.72</td>
<td>0.005</td>
<td>456</td>
<td>000</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>0.07</td>
<td>290</td>
<td>000</td>
</tr>
<tr>
<td>4</td>
<td>0.074</td>
<td>10</td>
<td>320</td>
<td>000</td>
</tr>
<tr>
<td>5</td>
<td>0.72</td>
<td>0.005</td>
<td>456</td>
<td>000</td>
</tr>
</tbody>
</table>

17. Select the correct rank order of uptake rate with which drugs 1-5 will enter brain tissue.

A. 1 slower than 2 slower than 3 slower than 4 slower than 5
B. 2 slower than 4 slower than 3 slower than 5 slower than 1
C. 1 slower than 4 slower than 3 slower than 5 slower than 2
D. 2 slower than 5 slower than 1 slower than 3 slower than 4
E. None of the above

2 < 5 < 3 < 4 < 1
Question Set VI (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. It is given as i.v. bolus injection. Two patients receive this injection. Patient 1 has a much stronger plasma protein binding for the drug (99.995%) than the second patient (99.99%). This is the only physiological difference between the two patients.

18. Please indicate whether patient 1 will have a larger (↑), smaller (↓) identical (↔) value than patient 2 for (15 points):

- total initial total plasma drug concentration (C₀),
- f₀
- fᵢᵣ
- Vᵰ

A. C₀ ↑, f₀ ↓ fᵢᵣ ↑, Vᵰ ↓
B. C₀ ↓, f₀ ↓ fᵢᵣ ↓, Vᵰ ↑
C. C₀ ↑, f₀ ↓ fᵢᵣ ↔, Vᵰ ↓
D. C₀ ↑, f₀ ↑ fᵢᵣ ↑, Vᵰ ↔
E. None of above combinations.

\[ f_{u₁} = 0.00005 \]
\[ f_{u₂} = 0.0001 \]
A hydrophilic drug (not an acid, not a base) is cleared through renal and hepatic clearance ($C_{\text{Hep}} = 32.5 \text{ ml/min}$; $C_{\text{Htot}} = 40.5 \text{ mL/min}$). Assume a GFR of 130 ml/min, Urine flow of 1.5 ml/min; liver blood flow of 80 L/h(1,333 ml/min).

19. T F  fu of this drug is 0.325

20. T F  $C_{\text{Htot}}$ is 1.9 L/h

$$C_{\text{Hep}} = 40.5 - 32.5 = 8 \text{ ml/min}$$

$$= 0.48 \text{ L/hr} = \text{low extraction drug}$$

$$C_{\text{Hep}} = C_{\text{Htot}} \times fu$$

$$0.48 = C_{\text{Htot}} \times 0.25$$

$$C_{\text{Htot}} = \frac{0.48}{0.25} = 1.92 \text{ L/hr}$$
Useful Pharmacokinetic Equations

Symbols

\( D = \) dose
\( \tau = \) 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

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

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)

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

Peak (multiple dose)

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

Trough (multiple dose)

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

Average concentration (steady state)

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

Oral administration

Plasma concentration (single dose)

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

Time of maximum concentration (single dose)

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

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

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

Clearance

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

\[
 Cl = k_e \cdot V_d
\]
**Constant rate infusion**

Plasma concentration (during infusion)
\[
C = \frac{k_0}{CL} \left(1 - e^{-k_v \cdot t}\right)
\]

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

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

**Short-term infusion**

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

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

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

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

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

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

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

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

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

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

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

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

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

**Two-Compartment-Body Model**

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

\[
AUC_\infty = a / \alpha + b / \beta
\]

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

**Creatinine Clearance**

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

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

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

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

**Metabolic and Renal Clearance**

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

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

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

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

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

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

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

**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\(x\) (TBW - IBW)

**Volume of Distribution**

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

\[ V = V_p + V_T \cdot \frac{fu_T}{fu} \]

**Clearance**

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

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

<table>
<thead>
<tr>
<th>For a single I.V. bolus administration:</th>
<th>For multiple I.V. bolus administration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_0 = \frac{D}{V} )</td>
<td>( C_n(t) = \frac{D}{V} \left(1 - e^{-n k_e \tau}\right) \cdot e^{-k_e t} )</td>
</tr>
<tr>
<td>( C = C_0 \cdot e^{-k_e t} )</td>
<td>at peak: ( t = 0 ); at steady state ( n \to \infty )</td>
</tr>
<tr>
<td></td>
<td>at trough: ( t = \tau )</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max,ss}} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e \tau})} )</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{min,ss}} = C_{\text{max,ss}} \cdot e^{-k_e \tau} )</td>
</tr>
</tbody>
</table>

If the dosing involves the use of I.V. bolus administration:

<table>
<thead>
<tr>
<th>For a single short-term I.V. infusion:</th>
<th>For multiple short-term I.V. infusion at steady state:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since ( \tau = t ) for ( C_{\text{max}} )</td>
<td>( C_{\text{max}} = \frac{D}{V k_e T} \cdot \left(1 - e^{-k_e T}\right) )</td>
</tr>
<tr>
<td>( C_{\text{max}} = \frac{D}{V k_e T} \cdot \left(1 - e^{-k_e T}\right) )</td>
<td>( C_{\text{max}} = \frac{D}{V k_e T} \cdot \left(1 - e^{-k_e \tau}\right) )</td>
</tr>
<tr>
<td>( C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau - T)} )</td>
<td>( C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau - T)} )</td>
</tr>
</tbody>
</table>
\[ C_t = \frac{D}{Vk_e T} \left( e^{k_e T} - 1 \right) e^{-k_e t} \]  
\text{(most general eq.)} \quad \text{during infusion } t = T \text{ so,}

\[ C_t = \frac{D}{Vk_e T} \left( 1 - e^{-k_e t} \right) \]  
\text{(during infusion)} \quad \text{at steady state } t \to \infty, e^{k_e t}, t \to 0 \text{ so,}

\[ Cpss = \frac{D}{Vk_e} = \frac{k_0}{V} = \frac{k_0}{CL} \]  
\text{(steady state)} \quad \text{remembering } k_0 = \frac{D}{T} \text{ and}

\[ CL = V \cdot k_e \]

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

For a single oral dose:

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

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

For multiple oral doses:

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

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

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