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

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Name

Question Set/Points

I. 15 pts
II. 10 pts
III. 10 pts
IV. 6 pts
V. 15 pts
VI. 15 pts
VII. 10 pts
VIII. 4 pts
IX. 5 pts

TOTAL: 90 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**

1: T  F  A water-soluble drug will pass across muscle membranes faster than across brain membranes (assume permeability-rate limitations).

2: T  F  A neutral, lipophilic drug is likely to be absorbed faster in the intestines than in the stomach. Remember that stomach and intestine differ in their properties.

3: T  F  Lipophilic drugs are generally taken up fast by highly perfused organs.

4: T  F  Ionized and lipophilic drugs are most likely to cross most membrane barriers.

5: T  F  Drugs with a high tissue binding always have a large volume of distribution.
Question Set II

(10 points)

6: J. Mary was admitted into hospital due to drug intoxication. Her body weight is 60kg.
Drug U5127 was used to control the symptoms. U5127 is administered via IV bolus at a
dose of 0.25 mg/kg. After drug exposure, they found that U5127 concentration-time
profile can be best described by one-compartmental linear model with the equation,
\[ C = 0.33 \cdot e^{-0.116t} \text{ (Unit: mg/L)} \], where \( C \) represents U5127 concentration at time \( t \) (hr).
Calculate U5127 volume of distribution.

A: 45 L  
B: 0.76 L  
C: 38 L  
D: 18 L  
E: none of the above
Question Set III
(10 points)

7: Quinidine is bound to both of plasma albumin and alpha-1-acid glycoprotein. In patients with chronic liver disease, plasma protein binding is decreased by 20%. How will the volume of distribution change in patients? (Assume the fraction unbound in tissue is 70% in both patients and normal subjects, and the fraction bound in plasma is 80% in normal subjects.)

A: Increase to 37.74 L
B: Increase to 22.54 L
C: Stay the same as 13.86 L
D: Stay the same as 46.43 L
E: Decrease to 11.69 L
Question Set IV  (True or False)
(6 points)
True (A) or False (B). On the bubble sheet mark A for true or B for false

8: T  F  Compared to skin, liver would have a higher rate of uptake of perfusion-limited lipophilic drugs due to its higher blood flow rate.

9: T  F  Distribution to a specific tissue for permeability-limited hydrophilic drugs depends on how much and how quickly the blood gets to the specific tissue.

10: T  F  Perfusion limited distribution is a type of drug distribution into tissue that occurs when the drug is able to cross membranes easily.
Question Set V (True or False)

(15 points)

11: T  F  Figure A shows a first order elimination process, and ke has a unit of hr$^{-1}$.

12: T  F  Figure B shows a zero order elimination process, and ke has a unit of hr$^{-1}$.

13: T  F  In Figure B, the fraction of drug eliminated per hour is constant.

14: T  F  In Figure A, the eliminated drug amount per hour is changing.

15: T  F  In Figure A, the rate of elimination is dependent of amount of drug in body.
Question Set VI

(15 points)

16: A 25 yr old, 70 kg male patient with gram-negative pneumonia, was being treated with gentamicin. Gentamicin had been given as an iv bolus (2 mg/kg). Two samples were taken after dose, and data is shown as following:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Calculate the AUC\(_{0-\infty}\). (Assume first-order elimination for gentamicin, and please use trapezoidal rule to calculate.)

A: 30.5 mg/L*hr
B: 34.1 mg/L*hr
C: 19.6 mg/L*hr
D: 9.0 mg/L*hr
E: none of the above
Question Set VII

(10 points)

17: A 100 mg dose of a drug was administered to two patients by IV bolus injection. For patients A and B, the initial concentrations ($C_0$) were 1.25mg/L and 2.5mg/L, respectively. This drug follows a one-compartment body model, crosses membranes easily, distributes well into all tissues, and is around 50% bound to plasma proteins. Why is the initial plasma concentration different for these two patients? Select the correct answer from below.

A: Patient B has more fat tissue than Patient A.
B: Plasma unbound fraction in Patient B is higher than that in Patient A.
C: Tissue unbound fraction in Patient B is higher than that in Patient A.
D: Patient B has larger volume of distribution than Patient A.
E: None of Above
Question Set VIII

(4 points)

18: Given a lipophilic drug that can enter all tissues easily, state how the volume of distribution will change under the following condition. If not mentioned, other parameters are assumed to be fixed.

- Both $f_u$ and $f_{u,T}$ double

A: Increase;
B: Decrease
C: No change
D: Not enough information given to answer question
Question Set IX

(5 points)

19: Drug A follows a perfusion-limited distribution. Drug concentration-time profiles from several tissues (A, B, and C) were plotted as below. Which of following answer is correct?

A: Tissue A: Brain; Tissue B: Skin; Tissue C: Liver
B: Tissue A: Skin; Tissue B: Kidneys; Tissue C: Fat
C: Tissue A: Lungs; Tissue B: Muscle; Tissue C: Fat
D: Tissue A: Kidneys; Tissue B: Fat; Tissue C: Liver
E: Tissue A: Skin; Tissue B: Muscle; Tissue C: Fat
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

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

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)

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

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)

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

Oral administration

Plasma concentration (single dose)

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

Time of maximum concentration (single dose)

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

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

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

Clearance

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

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

Plasma concentration (during infusion)

\[ C = \frac{k_0}{CL} \cdot (1 - e^{-k_{c} \cdot t}) \]

Plasma concentration (steady state)

\[ C = \frac{k_0}{CL} \]

Calculated clearance (Chiou equation)

\[ CL = \frac{2 \cdot k_0}{C_1 + C_2} \cdot (C_1 - C_2) \cdot (t_2 - t_1) \]

Short-term infusion

Peak (single dose)

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

Trough (single dose)

\[ C_{\text{min}(1)} = C_{\text{max}(1)} \cdot e^{-k_\text{e}(\tau - T)} \]

Peak (multiple dose)

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

Trough (multiple dose)

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

Calculated elimination rate constant

\[ k_\text{e} = \frac{\ln \left(\frac{C^*_{\text{max}}}{C^*_{\text{min}}}\right)}{\Delta t} \]

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

Calculated peak

\[ C_{\text{max}} = \frac{C^*_{\text{max}}}{e^{-k_\text{e} \cdot \tau}} \]

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

Calculated trough

\[ C_{\text{min}} = C^*_{\text{min}} \cdot e^{-k_\text{e} \cdot \tau} \]

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

Calculated volume of distribution

\[ V_d = \frac{D}{k_\text{e} \cdot T} \cdot \left(1 - e^{-k_\text{e} \cdot T}\right) \]

\[ \frac{C^*_{\text{max}}}{C^*_{\text{min}}} \]

Calculated recommended dosing interval

\[ \tau = \frac{\ln \left(\frac{C_{\text{max(desired)}}}{C_{\text{min(desired)}}}\right)}{k_\text{e}} + T \]

Calculated recommended dose

\[ D = C_{\text{max(desired)}} \cdot k_\text{e} \cdot V \cdot T \cdot \left(1 - e^{-k_\text{e} \cdot \tau}\right) \]

Two-Compartment-Body Model

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

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

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

Creatinine Clearance

\[ \text{CL}_{\text{creat (male)}} = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot \text{Cp}_{\text{creat}}} \]

\[ \text{CL}_{\text{creat (female)}} = \frac{(140 - \text{age}) \cdot \text{weight}}{85 \cdot \text{Cp}_{\text{creat}}} \]

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

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

**Metabolic and Renal Clearance**

\[
\begin{align*}
E_H &= \frac{\text{Cl}_{\text{int}} \cdot fu_b}{Q_H + \text{Cl}_{\text{int}} \cdot fu_b} \\
\text{Cl}_H &= E_H \cdot Q_H = \frac{Q_H \cdot \text{Cl}_{\text{int}} \cdot fu_b}{Q_H + \text{Cl}_{\text{int}} \cdot fu_b} \\
F_H &= \frac{Q_H}{Q_H + \text{Cl}_{\text{int}} \cdot fu_b} \\
\text{Cl}_{\text{ren}} &= \text{RBF} \cdot E = \text{GFR} \cdot \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{in}}} \\
\text{Cl}_{\text{ren}} &= \frac{\text{rate of excretion}}{\text{plasma concentration}} \\
\text{Cl}_{\text{ren}} &= fu \cdot GFR + \left[ \frac{\text{Rate of secretion} - \text{Rate of reabsorption}}{\text{Plasma concentration}} \right] \\
\text{Cl}_{\text{ren}} &= \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}
\end{align*}
\]

**Ideal Body Weight**

**Male**

\[ \text{IBW} = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5ft in height} \]

**Female**

\[ \text{IBW} = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5ft in height} \]

**Obese**

\[ \text{ABW} = \text{IBW} + 0.4 \ast (\text{TBW} - \text{IBW}) \]

**Volume of Distribution**

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

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

**Clearance**

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

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

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

<table>
<thead>
<tr>
<th>If the dosing involves the use of I.V. infusion:</th>
<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></td>
<td>$C_{\text{max}} = \frac{D}{Vk_e T} \cdot \left(1 - e^{-k_e T}\right)$</td>
<td>$C_{\text{max}} = \frac{D}{Vk_e T} \cdot \frac{1 - e^{-k_e T}}{1 - e^{-k_e \tau}}$</td>
</tr>
<tr>
<td></td>
<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>
If the dosing involves a I.V. infusion (more equations):

\[
C_t = \frac{D}{V k_e T} \cdot \left( e^{k_e T} - 1 \right) \cdot e^{-k_e t} \quad \text{(most general eq.)} \quad \text{during infusion } t = T \text{ so,}
\]

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

\[
C_{pss} = \frac{D}{V k_e T} = \frac{k_0}{V k_e} = \frac{k_0}{C_L} \quad \text{(steady state)} \quad \text{remembering } k_0 = \frac{D}{T} \quad \text{and} \quad C_L = V \cdot k_e
\]

If the dosing involves oral administration:

For a single oral dose:

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

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

For multiple oral doses:

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

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