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. 15 pts
VI. 25 pts
VII. 10 pts
VIII. 10 pts
IX. 10 pts

TOTAL: 150 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 form for distribution.

1: T  F  The value of $V_t$ is the same for all drugs (38 L)
2: T  F  The value of $V_p$ is the same for all drugs (3L)
3: T  F  For a drug that binds to a high affinity-low capacity binding protein in plasma, the $f_u$ and the volume of distribution might depend on the dose of the drug.
4: T  F  Assume two drugs (identical molecular weight, same dose given): one neutral drug (Drug A) and one acidic drug (pka=7.4, Drug B). Drug A and the unionized form of drug B have the same partition coefficient. The fraction unbound in plasma and tissue is 0.5 for both drugs. Drug B will enter tissues somewhat slower than drug A.
5: T  F  A weak acid, whose unionized form shows a high partition coefficient is likely to cross most membrane barriers.
6: T  F  A volume of distribution of 41 L for a lipophilic drug, suggest that the drug will not bind to tissue and plasma proteins.
Question Set II (20 points) True (A) or False (B). On the bubble sheet mark A for true or B for false.

What could be possible reasons for babies having often a smaller volume of distribution (expressed in L) for lipohilic drugs than adults. Assume for this question that plasma protein binding is the same in babies and adults. What statements might explain this finding?

7: T  F  The term $V_t$ is smaller in babies than in adult
8: T  F  The term $V_p$ is smaller in babies than in adult
9: T  F  Transporters pumping the drug into the tissues are more active in babies
10: T  F  Assuming that adults have more fat tissue, this fact could explain it.
Question Set III
(15 points)
Listed in the Table are two properties of acidic drug molecules:

- the fraction ionized and
- the partition coefficient of the unionized form.

<table>
<thead>
<tr>
<th>Fraction ionized at pH 7.4</th>
<th>Partition coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>0.5</td>
</tr>
<tr>
<td>Drug B</td>
<td>0.2</td>
</tr>
<tr>
<td>Drug C</td>
<td>1</td>
</tr>
<tr>
<td>Drug D</td>
<td>1</td>
</tr>
</tbody>
</table>

Select the drug(s) (A, B, C, or D) that fits best (selection of 1-4 drugs is possible)

11: Drug ……………... will cross well built membranes the fastest.
12: Drug ……. ……….will cross well built membranes the slowest
13: In areas of the body were membranes are extremely thin and larger aqueous pores exist, drug(s) …………………….. will be taken up with about the same rate.
Question Set V (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.

14:  T  F  Compared to skin, liver would have a higher rate of uptake for small lipophilic drugs due to its higher blood flow rate.

15:  T  F  The rate with which hydrophilic compounds will move across well-built membranes will depend on the plasma protein binding of this drug.

16:  T  F  Perfusion limited distribution is a type of drug distribution into tissue that occurs for drugs and tissues with high permeability.
Question Set VI (True or False)
(25 points)

17: T  F  Drug A’s rate of elimination depends on the amount of drug in the body

18: T  F  Drug B’s rate of elimination is constant

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

20: T  F  Drug B’s behavior might be explained with saturated metabolic enzymes.

21: T  F  For both drugs, the model assumes that drug distribution does not take any time.
Question Set VII
(10 points)

22: 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 dosing, 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>5.0</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Calculate the AUC\(_{0-\infty}\). (Assume first-order elimination for gentamicin)

A: 31 mg/L*hr
B: 61 mg/L*hr
C: 20 mg/L*hr
D: 9.0 mg/L*hr
E: none of the above

23: Calculate the half-life of this drug

A: 2.6 hr
B: 3.0 hr
C: 2.1 hr
D: 9.0 hr
E: none of the above
Question Set VIII
(5 points)
24: A 100 mg dose of a drug was administered to patient 1 by IV bolus injection. A 200 mg dose of the same drug was administered to patient 2 by IV bolus injection. For patients A and B, the initial concentrations 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?

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 IX

(10 points)

If we know that the plasma drug concentration just after a gentamycin dose was given is 12.8 mg/L and the half life is 3.46 hours, what is the concentration after 9 hours.

Assume that the result will be between 1.0 and 9.9 mg/L.

25: Mark A, B, C, or D, if the number before the decimal point is 1 (A), 2(B), 3(C), 4(D), 5(E). Leave blank if this is not the case

26: Mark A, B, C, or D, if the number before the decimal point is 6 (A), 7(B), 8(C), 9(D), Leave blank if this is not the case

27: Mark A, B, C, or D, if the number after the decimal point is 1 (A), 2(B), 3(C), 4(D), 5(E). Leave blank if this is not the case

28: Mark A, B, C, or D, if the number after the decimal point is 6 (A), 7(B), 8(C), 9(D), 0 (E) Leave blank if this is not the case
Useful Pharmacokinetic Equations

Symbols

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

General

Elimination rate constant

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

Half-life

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

Intravenous bolus

Initial concentration

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

Plasma concentration (single dose)

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

Plasma concentration (multiple dose)

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

Peak (multiple dose)

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

Trough (multiple dose)

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

Average concentration (steady state)

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

Oral administration

Plasma concentration (single dose)

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

Time of maximum concentration (single dose)

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

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

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

Clearance

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

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

**Plasma concentration (during infusion)**

\[ C = \frac{k_0}{CL} \cdot \left( 1 - e^{-k \cdot t} \right) \]

**Plasma concentration (steady state)**

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

**Calculated clearance (Chiou equation)**

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

**Short-term infusion**

**Peak (single dose)**

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

**Trough (single dose)**

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

**Peak (multiple dose)**

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

**Trough (multiple dose)**

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

**Calculated elimination rate constant**

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

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**

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

**Calculated recommended dosing interval**

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

**Calculated recommended dose**

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

**Two-Compartment-Body Model**

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

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

\[ V_{d_{\text{Vc}}} > V_{d_{\text{Vd}}} > V_c \]

**Creatinine Clearance**

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

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

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

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

**Metabolic and Renal Clearance**

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

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

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

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

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

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

**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**

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

\[
V = V_p + V_z \cdot \frac{fu}{fu_f}\]

**Clearance**

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

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

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

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

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

Short-term infusion

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

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

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

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

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
\[ C_{\text{max}} = C_{\text{min}} + \frac{C_{\text{max}}}{e^{-k_e \cdot T}} \]

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
\[ V_d = \frac{D}{k_e \cdot T} \cdot \left[1 - e^{-k_e \cdot T}\right] \]

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

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

Two-Compartment-Body Model

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

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

\[ V_{d_{\text{app}}} > V_d > V_c \]

Creatinine Clearance

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

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

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL in mL/min
Name: ___________________

UFID#: ___________________