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  The larger the volume of distribution, the lower the plasma concentration.

2: T  F  The volume of distribution can not be larger than the actual volume of the patient taking the medicine.

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  A drug with a large volume of distribution is likely to have a narrow therapeutic window.

5: T  F  It is likely that drugs in liver disease patients might show a reduced volume of distribution.

6: T  F  A volume of distribution of 20 L for a lipophilic drug, suggest that the drug’s plasma protein binding is more pronounced than the tissue binding.
Question Set II (20 points) True (A) or False (B). On the bubble sheet mark A for true or B for false.

True (A) or False (B). On the bubble sheet mark A for true or B for false. Consider a lipophilic acidic drug (pKa=1, 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 and
- the partition coefficient of the unionized form.

<table>
<thead>
<tr>
<th></th>
<th>Fraction ionized at pH 7.4</th>
<th>Partition coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Drug B</td>
<td>0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Drug C</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Drug D</td>
<td>1</td>
<td>3</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, even drug……………………….. will be taken up at a relative good rate.
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.

14: 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.

15: 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.

16: 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

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

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

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

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

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

Drug A

Drug B
Question Set VI

(10 points)

Imagine a drug that is given as an intravenous bolus. The dose was 80 mg. The elimination follows first order principles. Three hours after administration the drug concentration C1 of 1.48 µg/ml is observed. Four hours after the administration the concentration C2 was 0.37 µg/ml.

22: What is the elimination rate constant of this drug?

A) 0.346 h⁻¹
B) 1.386 h
C) 1.386 h⁻¹
D) 0.555 µg/(ml*h)
E) 0.370 h⁻¹

23: What will the concentration be 4.5 hours after injection?

A) 0.185 µg/ml
B) 0.370 mg/ml
C) 0 µg/ml
D) 0.185 µg/ml
E) none of the above
Question Set VII

(10 points)

24: A 200 mg dose of a drug was administered to patient 1 and patient 2 by IV bolus injection. For patients 1 and 2, 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?

Select the INCORRECT ANSWER

A) Patient 1 has more fat tissue than Patient 2.
B) Fraction unbound in plasma in Patient 1 is higher than that in Patient 2.
C) Tissue unbound fraction in Patient 1 is higher than that in Patient 2.
D) Patient 1 has a smaller volume of distribution than Patient 1.
Question Set VIII

(10 points)

If we know that the plasma drug concentration 4 hours after a gentamycin dose was given is 4.2 mg/L and the half live is 3 hours, what was the concentration after 1 hour. 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.
**Question Set IX**

(35 points)

29: T  F  Free drug concentrations are always the same in plasma and tissues.

30: T  F  The slower the absorption from the muscle into the blood, the lower the maximum drug concentration observed in the plasma.

31: T  F  The slower the absorption of a drug from the muscle into the blood, the lower the plasma drug concentration at later time points.

32: T  F  A slow absorption might allow less frequent dosing.

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

34: T  F  Plasma is obtained from blood by letting it clot.

35: T  F  Concentrations in plasma are of relevance for the drug therapy as they are generally identical to concentrations at the target site.
Name: ____________________
UFID#: ___________________

Useful Pharmacokinetic Equations

Symbols

D = dose
τ = dosing interval
CL = clearance
Vd = volume of distribution
ka = elimination rate constant
ka = absorption rate constant
F = fraction absorbed (bioavailability)
K0 = infusion rate
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

\[ k_e = \frac{CL}{Vd} \left( \frac{ln(C_2)}{t_2-t_1} - \frac{ln(C_1)}{t_1-t_0} \right) \]

Half-life

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

Intravenous bolus

Initial concentration

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

Plasma concentration (single dose)

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

Plasma concentration (multiple dose)

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

Peak (multiple dose)

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

Trough (multiple dose)

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

Average concentration (steady state)

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

Oral administration

Plasma concentration (single dose)

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

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)

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

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)**

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

**Plasma concentration (steady state)**

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

**Calculated clearance (Chiou equation)**

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

**Short-term infusion**

**Peak (single dose)**

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

**Trough (single dose)**

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

**Peak (multiple dose)**

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

**Trough (multiple dose)**

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

**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**

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

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**

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

**Calculated recommended dosing interval**

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

**Calculated recommended dose**

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

**Two-Compartment-Body Model**

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

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

\[ Vd_{\alpha} > Vd_{\beta} > Vc \]

**Creatinine Clearance**

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

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

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

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

**Metabolic and Renal Clearance**

\[
E_{\text{H}} = \frac{C_{\text{int}} \cdot f_{u_b}}{Q_H + C_{\text{int}} \cdot f_{u_b}}
\]

\[
C_{\text{H}} = E_{\text{H}} \cdot Q_H = \frac{Q_H \cdot C_{\text{int}} \cdot f_{u_b}}{Q_H + C_{\text{int}} \cdot f_{u_b}}
\]

\[
F_{\text{H}} = \frac{Q_H}{Q_H + C_{\text{int}} \cdot f_{u_b}}
\]

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

\[
C_{\text{Ren}} = \frac{\text{rate of excretion}}{\text{plasma concentration}}
\]

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

\[
C_{\text{Ren}} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}
\]

**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**

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

\[ V = V_p + V_t \cdot \frac{f_{\text{u}}}{f_{\text{u}} - f_{\text{t}}} \]

**Clearance**

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

\[ Cl = k_e \cdot V_t \]
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)
\[ CL = \frac{2 \cdot k_u}{(C_1 + C_2) \cdot (C_1 + C_3) \cdot (t_2 - t_1)} + 2 \cdot V_d \cdot (C_1 - C_2) \]

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

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

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
\[ C_{\text{max}} = \frac{C_{\text{meas}}}{e^{-k_e \cdot t'}} \]

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

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

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

Two-Compartment-Body Model

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

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

\[ V_d_{a} > V_d_{b} > V_c \]

Creatinine Clearance

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

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

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL\text{crea} in ml/min