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 t_{1/2} of a drug eliminated through a zero order process is a drug specific constant.

2: T    F  A lipophilic drug of low molecular weight, cannot have a volume of distribution that is smaller than V_T.

3: T    F  The fraction of the drug being eliminated per hour is increasing in a first order process.

4: T    F  Two drugs that have similar elimination half-lives will have similar volumes of distributions.

5: T    F  The same dose of a drug is given orally either as a solution or in form of a slow dissolving crystal suspension. The solution will show higher maximum concentrations in plasma.

6: T    F  When heparin is added to blood and the blood is centrifuged, the resulting supernatant is called serum.
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 A (pka=14, logP=5, If you have difficulties with pKa values: The pKa of HCl is close to zero) 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 The Ke of both drugs will only differ, if CL differs.
Question Set III
(15 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.

<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>0.6</td>
<td>3.1</td>
<td>240</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>0.1</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>

11: 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) 4 slower than 2 slower than 3 slower than 1
C) 4 slower than 2 slower than 1 slower than 3
D) 3 slower than 1 slower than 4 slower than 2
E) 1 slower than 3 slower than 2 slower than 4
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.

12:  T  F  Assume a drug is substrate of a specific transport protein. Transporters only eliminate drugs from the body.

13:  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.

14:  T  F  Assuming that a protein drug does not bind to plasma and tissue component, the volume of distribution is likely to be 41 liters.
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 B’s rate of elimination is affected by the amount of drug in the body.

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

17: T  F  For drug B, the fraction of drug eliminated per hour is constant.

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

19: T  F  For drug A, the elimination rate constant does not depend on the amount of drug in the body.
20: An investigational new drug is eliminated entirely by hepatic metabolism, with a clearance of 1 L/h in healthy subjects. Assume an average liver blood flow of 80 L/h in these healthy subjects. What would be the expected clearance in a congestive heart failure patient with a liver blood flow of 66 L/h? Use the most appropriate relationships

A) 0.83 L/h  
B) 1.0 L/h  
C) 0.66 L/h  
D) 66 L/h  
E) None of the above
Question Set VI

21: A drug has an intrinsic clearance of 40,000 L/min. The plasma protein binding and liver blood flow are 60% and 80 L/h, respectively.

Calculate the hepatic clearance.

A) 80 L/h  
B) 35 L/h  
C) 48 L/h  
D) 320 L/h  
E) None of the above
Question Set VII

(10 points)

22: Assume drug A is predominantly cleared through hepatic metabolism. Drug A has an intrinsic clearance of 40,000 L/min. The plasma protein binding and liver blood flow are 60% and 80 L/h, respectively.

How will the increase in both tissue binding and liver blood flow affect the initial concentration ($C_0$ when given as i.v. bolus), hepatic clearance (CL), bioavailability (F) for tablet, AUC, and half-life ($t_{1/2}$)? (Please note that ↔ means: about the same)

A) $\downarrow C_0$, $\uparrow$ CL, $\downarrow$ F, $\downarrow$ AUC, $\downarrow$ $t_{1/2}$
B) $\leftrightarrow C_0$, $\leftrightarrow$ CL, $\uparrow$ F, $\uparrow$ AUC, $\leftrightarrow t_{1/2}$
C) $\downarrow C_0$, $\leftrightarrow$ CL, $\leftrightarrow$ F, $\leftrightarrow$ AUC, $\uparrow$ $t_{1/2}$
D) $\uparrow C_0$, $\downarrow$ CL, $\leftrightarrow$ F, $\uparrow$ AUC, $\uparrow$ $t_{1/2}$
E) $\downarrow C_0$, $\uparrow$ CL, $\uparrow$ F, $\downarrow$ AUC, $\leftrightarrow t_{1/2}$
23. A new analysis technique has enabled you to measure the drug concentration before and after the blood passes the liver. The plasma concentrations before and after the liver was passed were 6.5 and 2.4 mg/mL, respectively.

Calculate the hepatic clearance (assume a liver blood flow of 1450 mL/min).

A) 15 L/h  
B) 35 L/h  
C) 55 L/h  
D) 75 L/h  
E) None of above
Question Set IX
(35 points)  Mark “A” for True or “B” for False

24:  T  F  Free drug concentrations are always the same in plasma and tissues, when the distribution occurs instantaneously.

25:  T  F  Enzyme induction affects the hepatic clearance of a low and high extraction drugs

26:  T  F  Enzyme induction affects the oral bioavailability of high extraction drugs

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

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

29:  T  F  The Fick’s law is: \( \frac{dQ}{dt} = D \times K \times (C_{\text{plasma}} - C_{\text{tissue}})/h \). The concentration terms (\( C_{\text{plasma}} \) and \( C_{\text{tissue}} \)) refer to total drug concentrations in either plasma or tissue.

30:  T  F  Concentrations in plasma are of relevance for drug therapy as they generally correlate well with concentrations observed at the effect (target) site.
Useful Pharmacokinetic Equations

Symbols

D = dose
\( \tau = \text{dosing interval} \)
CL = clearance
Vd = volume of distribution
\( k_e = \text{elimination rate constant} \)
\( k_a = \text{absorption rate constant} \)
F = fraction absorbed (bioavailability)
\( K_0 = \text{infusion rate} \)
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

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

Half-life

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

Intravenous bolus

Initial concentration

\[ C_0 = \frac{D}{\text{Vd}} \]

Plasma concentration (single dose)

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

Plasma concentration (multiple dose)

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

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)

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

Oral administration

Plasma concentration (single dose)

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

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)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

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

Clearance

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

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

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

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

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

**Short-term infusion**

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

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

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

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

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

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

**Calculated peak**
\[ C_{\text{max}} = \frac{C_{\text{max}}^*}{e^{-k_c \tau}} \]

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

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

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

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

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

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

**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**
\[ CL_{\text{creat}} \text{ (male)} = \frac{(140 - \text{age}) \cdot \text{weight}}{72 \cdot Cp_{\text{creat}}} \]
\[ CL_{\text{creat}} \text{ (female)} = \frac{(140 - \text{age}) \cdot \text{weight}}{85 \cdot Cp_{\text{creat}}} \]

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

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

**Metabolic and Renal Clearance**

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

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

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

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

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

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

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

**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*(TBW-IBW)

**Volume of Distribution**

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

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

**Clearance**

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

\[ Cl = k_e \cdot V_d \]
**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>$C_n(t) = \frac{D}{V} \cdot \left(1 - e^{-nk_e\tau} \right) \cdot e^{-k_e t}$</td>
</tr>
<tr>
<td></td>
<td>$C = C_0 \cdot e^{-k_e t}$</td>
<td>at peak: $t = 0$; at steady state $n \to \infty$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>at trough: $t = \tau$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max,ss}} = \frac{D}{V} \cdot \frac{1}{\left(1 - e^{-k_e \tau} \right)}$</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>$C_{\text{max}} = \frac{D}{Vk_e T} \cdot \left(1 - e^{-k_e T} \right)$</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):

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

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

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

\[
CL = V \cdot k_e
\]

<table>
<thead>
<tr>
<th>For a single oral dose:</th>
<th>For multiple oral doses:</th>
</tr>
</thead>
</table>
| \[
C = \frac{F \cdot D \cdot k_a}{V (k_a - k_e)} \cdot \left( e^{-k_e t} - e^{-k_a t} \right)
\] | \[
C = \frac{F \cdot D \cdot k_a}{V (k_a - k_e)} \cdot \left( e^{-k_e t} \right) \cdot \left( 1 - e^{-k_e \tau} \right) - \left( e^{-k_a t} \right) \cdot \left( 1 - e^{-k_a \tau} \right)
\] |

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

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

| If the dosing involves oral administration: |  |
|-------------------------------------------|  |