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

Name

Put all answers on the bubble sheet

TOTAL ______/160 pts
Question Set I (True or False)
(25 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false

Mark whether the following statements as true or false for drug A, which is cleared only by hepatic metabolism and has a CL\text{tot} of 80 L/h

1: T  F  This drug is a low extraction drug

2: T  F  The clearance of another drug eliminated only by the kidney (only filtered not re-absorbed) will be smaller than that of Drug A

3: T  F  The oral bioavailability of this drug will be significantly smaller than 80%

4: T  F  The oral bioavailability will depend on liver blood flow

5: T  F  Drug C, known to induce enzymes also responsible for metabolism of Drug A will significantly affect the clearance of Drug A
Imagine a high extraction drug that is only eliminated via hepatic metabolism. Two patients have been injected with the same dose of this drug. They show the following pharmacokinetic properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ [µg/ml]</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>$K_e$ [1/h]</td>
<td>0.55</td>
<td>0.73</td>
</tr>
<tr>
<td>$V_d$ [L]</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>$C_L$ [L/h]</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>$F$ (%)</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

6: A list of physiological parameter is shown below. Identify the one physiological parameter that would explain all differences in above pharmacokinetic parameters.

- A. GFR
- B. $f_u$
- C. $f_{ut}$
- D. $Q_{\text{hep}}$
- E. $C_{\text{int}}$
Question Set III (Matching)  
(20 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a lipophilic, unionizable (no acid or basic group in the molecule), protein bound drug that is eliminated only through the kidneys (some answers may be used more than once).

Select the effect on kinetics  
(A) $CL_{REN}$ ↑  
(B) $CL_{HEP}$ ↓  
(C) $V_D$ ↑  
(D) oral bioavailability $F$ ↑  
(E) factor not listed in A-D

Physiological change
7: Decrease in plasma protein binding____

8: Increase in tissue binding ____

9: Decrease in liver blood flow____

10: Increase in urine flow_____
Question Set IV (Matching)  
(20 points)

(Assume GFR is 130 mL min$^{-1}$, urine flow is 1.5 ml min$^{-1}$) For the following situations, indicate whether the drug is:

Select from the following choices:  
(A) filtered  
(B) reabsorbed  
(C) actively secreted  
(D) reabsorbed through transporters

11: A drug with $f_u = 0.02$ and a $\text{Cl}_{\text{REN}} = 20$ mL min$^{-1}$ is ___ 
12: A drug with $f_u = 0.40$ and a $\text{Cl}_{\text{REN}} = 52$ mL min$^{-1}$ is ___  
13: A drug with $f_u = 0.60$ and a $\text{Cl}_{\text{REN}} = 0.9$ mL min$^{-1}$ is ___  
14: A drug with $f_u = 1.0$ and a $\text{Cl}_{\text{REN}} = 0.3$ mL min$^{-1}$ is ___
A hydrophilic drug (predominantly ionized at pH=7.4) is eliminated only by the kidney. **Plasma protein binding is 90%**. Glomerular filtration rate is normal (130 ml/min). Urine flow is 2ml/min. No **active** renal secretion or **active** reabsorption after renal filtration is observed. The volume of distribution is 40 L.

15: What is the clearance? (10 points)

A. 0.15 mL/min  
B. 13 mL/min  
C. 1 mL/min  
D. 130 mL/min

16: Assume a one compartment body model? What is the renal clearance of a typical aminoglycoside in a patient showing a creatinine clearance of 65 ml/min(10 points). The plasma protein binding for this aminoglycoside is 55 %.

A. 58.5 ml/min  
B. 130 ml/min  
C. 65 ml/min  
D. 29.3 ml/min  
E. 35.8 ml/min
Robert is very sick and needs treatment with an aminoglycoside. In order to start him on the aminoglycoside an iv bolus loading dose shall be given. Your responsibility is to give him the first dose. In order to do so, you have to estimate Robert’s creatinine clearance. Robert is 5 ft 10 inches tall, 34 years old, male, and weights 280 pounds. His serum creatinine is 1.5 mg/dl. What creatinine clearance do you come up with?

A. 72 ml/min  
B. 84 ml/min  
C. 93 ml/min  
D. 103 ml/min  
E. none of the above
Question Set VII

The same dose of Alprazolam was given either alone or with ketoconazole. Explain what is going on by selecting the correct answer from the following list. (5 points)

1: The clearance of alprazalam is increased in the presence of Ketoconazole.
2: Alprazalam is likely to be a low extraction drug.
3: Ketoconazole decreases the volume of distribution of Alprazolam, thereby increasing the half-life of the drug
4: Ketoconazole is likely to increase liver blood flow.

18. The correct answer is: __________

A. 1 
B. 2 
C. 3, 4
D. 2, 3 
E. 1, 2, 3, 4
Question Set VIII (True or False)
(30 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false

Mark whether the following statements are true (A) or False (B)

19: T  F The renal clearance of a drug depends the tissue binding of the drug.

20: T  F The half-life of a drug increases with increasing tissue binding.

21: T  F To determine the clearance of a drug, one needs to know whether the drug is a one or two compartment drug.

22: T  F Drinking a lot of water (urine flow is doubled) will increase the renal clearance of aminoglycosides.

23: T  F For an acidic drug with a pka of 2.0, adjustment of the urine pH within physiological ranges will significantly change the renal clearance.

24: T  F For a drug with linear pharmacokinetics, hepatic clearance depends on the drug plasma concentration, as the rate of metabolism increases with increasing drug concentrations in the blood.
Question Set IX (True or False)
(15 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false

Mark whether the following statements are true (A) or false (B). Assume linear pharmacokinetics for all questions.

25: T  F The larger the volume of distribution, the smaller the AUC of a given drug.

26: T  F Doubling the dose will double the AUC of a drug

27: T  F An increase in fu will decrease AUC of a high-extraction drug given orally.
Useful Pharmacokinetic Equations

Symbols

D = dose  
τ = 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

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

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)

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

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)

\[ C_{\text{ss}} = \frac{D}{CL \cdot \tau} \]

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)

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

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

\[ C_{\text{ss}} = \frac{F \cdot D}{CL \cdot \tau} \]

Clearance

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

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

**Plasma concentration (during infusion)**

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

**Plasma concentration (steady state)**

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

**Calculated clearance (Chiou equation)**

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

**Short-term infusion**

**Peak (single dose)**

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

**Trough (single dose)**

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

**Peak (multiple dose)**

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

**Trough (multiple dose)**

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

**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**

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

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

**Calculated trough**

\[ C_{\text{min}} = C_{\text{min}}^* \cdot e^{-k_e \cdot \tau^*} \]

with \( C_{\text{min}}^* \) = measured trough, measured at time \( \tau^* \) 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**

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

**Calculated recommended dose**

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

**Two-Compartment-Body Model**

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

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

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

**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 CL\(_{\text{creat}}\) in ml/min
**Ke for aminoglycosides**

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

**Metabolic and Renal Clearance**

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

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

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

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

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

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

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

**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**

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

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

**Clearance**

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

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Equation</th>
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<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For a single I.V. bolus administration:</strong></td>
<td>$C_0 = \frac{D}{V}$</td>
<td><strong>For multiple I.V. bolus administration:</strong></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>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>at trough: $t = \tau$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max ss}} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e \tau})}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{min ss}} = C_{\text{max ss}} \cdot e^{-k_e \tau}$</td>
<td></td>
</tr>
<tr>
<td><strong>If the dosing involves the use of I.V. bolus administration:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>For a single short-term I.V. infusion:</strong></td>
<td>$C_{\text{max}} = \frac{D}{Vk_e T} \cdot \left(1 - e^{-k_e T}\right)$</td>
<td><strong>For multiple short-term I.V. infusion at steady state:</strong></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></td>
<td>$C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau - T)}$</td>
</tr>
</tbody>
</table>

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

\[
C_t = \frac{D}{Vk_e T} \cdot (e^{k_e T} - 1) \cdot e^{-k_e t} \quad (\text{most general eq.})
\]

during infusion \( t = T \) so,

\[
C_t = \frac{D}{Vk_e T} \cdot \left(1 - e^{-k_e t}\right) \quad (\text{during infusion})
\]

at steady state \( t \to \infty, e^{-k_e t}, t \to 0 \) so,

\[
C_{pss} = \frac{D}{Vk_e T} = \frac{k_0}{Vk_e} = \frac{k_0}{CL} \quad (\text{steady state})
\]

remembering \( k_0 = \frac{D}{T} \) and \( CL = V \cdot k_e \)

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:

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

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