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

Name

Put all answers on the bubble sheet

TOTAL _______/130 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

Mark whether the following statements as true (A) or false (B). Drug A is cleared only by hepatic metabolism and has an intrinsic clearance of 80,000 L/h

1:  T  F  The oral bioavailability of this drug will be larger than 80%.
2:  T  F  Plasma protein binding will affect the oral bioavailability of this drug.
3:  T  F  The hepatic clearance of this drug is 1333 L/min
4:  T  F  Plasma protein binding will affect the hepatic clearance of this drug.
5:  T  F  Drug B, known to induce enzymes also responsible for metabolism of Drug A, will significantly affect the clearance of Drug A if given together.
Question Set II
(18 points)

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

Imagine a lipophilic unionized drug A with a volume of distribution of 108 L. When given by an iv bolus injection, the peak concentration of 0.18 μg is observed (C₀). When given orally, the oral bioavailability is 99.9%. Plasma Protein Binding is 50% (fᵤ=0.5).

| Peak [μg/ml] | 0.18 |
|----------------|
| V [L] | 108 |
| F (%) | 99.9 |
| fᵤ | 0.5 |

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

6: T  F  The drug is highly metabolized in the liver.

7: T  F  Plasma protein binding will affect the oral bioavailability of this drug.

8: T  F  The hepatic clearance of this drug will be smaller than the Clₜₑₚ

9: T  F  Plasma protein binding will affect the hepatic clearance of this drug.

10: T  F  Drug B, known to induce enzymes also responsible for metabolism of Drug A will significantly affect the clearance of Drug A.

11: T  F  Drug B, known to induce enzymes that are also responsible for metabolism of Drug A is likely to decrease the clearance of A.
Question Set III (Matching)
(20 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for a hydrophilic strong acid, protein bound drug that is only eliminated through the kidneys (some answers may be used more than once).

Select the effect on kinetics
(A) Oral Bioavailability $F \downarrow$  (B) $Cl_{ren} \downarrow$  (C) $V_D \uparrow$  (D) oral bioavailability $F \uparrow$
(E) nothing happens or effect is not listed

Physiological change
12: Decrease in plasma protein binding____
13: Decrease in tissue binding ____
14: Decrease in GFR ____
15: Increase in urine flow____
A lipophilic acidic drug (pKₐ of 7) is eliminated only by the kidney. **Plasma protein binding is 90%**. Glomerular filtration rate is normal (130 ml/min). Urine flow is 2ml/min. Urine pH is similar to that of blood (about 7). The volume of distribution is 40L.

16: What value describes best the clearance? (10 points)

A: 0.15 mL/min  
B: 13 mL/min  
C: 130 mL/min  
D: 6.6 mL/min  
E: none of the above

17: 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 90%.

A: 58.5 ml/min  
B: 130 ml/min  
C: 65 ml/min  
D: 6.5 ml/min  
E: 35.8 ml/min
18: 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 weighs 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: 70 ml/min
D: 103 ml/min
E: none of the above
Question Set VI

(5 points)

19: The following patients differ in the

(A) dose received
(B) clearance
(C) volume of distribution

| Peak (mg/L) | 0.60 | 0.60 |
| Ke (1/h)    | 0.2  | 0.5  |
| t1/2 (h)    | 2.9  | 1.4  |
| AUC (mg/L*h)| 2.50 | 1.25 |
Question Set VII (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)

20: T   F  The renal clearance of a drug (as determined by filtration and reabsorption) always depends on the tissue binding of the drug.

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 significantly the renal clearance of aminoglycosides

23: T   F  For an acidic drug with a $pK_a$ of 1.0, adjustment of the urine pH within physiological ranges will significantly change the renal clearance.

24: T   F  Hepatic clearance depends on the drug plasma concentration, as the rate of metabolism increases with increasing drug concentrations in the blood.
Question Set VIII (True or False)

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) for a drug that is mainly eliminated through hepatic metabolism.

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

26:  T  F  Doubling the dose will generally double the AUC of a drug after iv bolus injection

27:  T  F  An increase in plasma protein binding will always result in a decrease of the drug’s hepatic clearance

28:  T  F  An increase in plasma protein binding will under no circumstances result in a decrease of the drug’s hepatic clearance
Question Set IX (5 points)

29. Which of the following statements are correct?

1) We can roughly assume that a change in clearance will result in a change in volume of distribution.

2) Drug A is 40% protein bound, drug B 98% protein bound. A two percent decrease in plasma protein binding will be most significant for drug A.

3) Genetic variability in metabolizing enzymes always alters hepatic clearance.

4) In general, we should always use IBW for drug recommendations for calculating creatinine clearance (CLcr)

A) 2, 3, 4
B) 1, 3 & 4
C) 2, 3
D) 3, 4
E) None of the above
Question Set X (10 points)

30. An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.35L/min in subjects with an average liver blood flow of 1.50L/min. What would be its expected clearance in a congestive heart failure patient with a liver blood flow of 1.10L/min but no change in hepatic extraction ratio?

A) 1.10L/min
B) 1.50L/min
C) 1.18L/min
D) 0.99L/min
E) Cannot be determined because the dose is not given.
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} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)}

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}_{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)} \cdot \left(\frac{e^{-k_e \cdot t} - e^{-k_a \cdot t}}{1 - e^{-k_e \cdot \tau}}\right)

Time of maximum concentration (single dose)

\ln\left(\frac{k_a}{k_e}\right)

\frac{t_{max}}{(k_a - k_e)}

Plasma concentration (multiple dose)

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

Time of maximum concentration (multiple dose)

\ln\left(\frac{k_a \cdot (1 - e^{-k_e \cdot \tau})}{k_e \cdot (1 - e^{-k_e \cdot \tau})}\right)

\frac{t_{max}}{(k_a - k_e)}

Average concentration (steady state)

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

Clearance

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

\text{Cl} = k_e \cdot V_d
Constant rate infusion

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

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

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

Short-term infusion

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

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

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

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

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

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

Two-Compartment-Body Model

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

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

\[ V_d_{area} > Vd_{ss} > Vc \]

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\text{creat} in ml/min

Equations/Useful_pharmacokinetic_equ_5127
**$K_e$ for aminoglycosides**

$K_e = 0.00293 \text{(CrCL)} + 0.014$

**Metabolic and Renal Clearance**

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

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

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

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

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

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

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

**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**

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

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

**Clearance**

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

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

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

<table>
<thead>
<tr>
<th></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>
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<td></td>
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<td>$C_{\text{min}} = C_{\text{max}} \cdot e^{-k_e (\tau - T)}$</td>
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<td>infusion:</td>
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| 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.)} \\
C_t = \frac{D}{V k_e T} \cdot \left( 1 - e^{-k_e t} \right) \quad \text{(during infusion)} \\
C_{pss} = \frac{D}{V k_e T} = \frac{k_0}{V k_e} = \frac{k_0}{CL} \quad \text{(steady state)} \\
\text{at steady state } t \to \infty, \ e^{-k_e t}, t \to 0 \text{ so,} \\
\text{remembering } k_0 = \frac{D}{T} \text{ and } CL = V \cdot k_e |
|---|---|
| If the dosing involves oral administration: | \[
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)} \\
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 (1 - e^{-k_e \tau})}{k_e \cdot (1 - e^{-k_a \tau})} \right] \cdot \frac{1}{(k_a - k_e)} |

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