Name: Key

UFID:

PHA 5127

Third Exam

Fall 2013

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

Name

Question/Points

Set I 25

Set II 25

Set III 25

Set IV 20

Set V 20

Set VI 15

Set VII 10

Total 140

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Question Set I (25 points)

1. Please select the CORRECT answer(s) for a multiple dose, short-term intravenous infusion scenario from the choices given below. **(5 points)**

   $t_{1/2}\downarrow \; K_e\uparrow$

   1) The shorter a drug's half-life, the larger the fluctuation ✓
   2) The faster a drug is cleared, the smaller the fluctuation ✗ $K_e\uparrow$
   3) For a given dosing interval (tau), the slower the drug dose is infused, the lower the peak plasma concentration ✓
   4) The larger the dose for a defined dosing interval, the higher the peak concentrations will be ✓
   5) For a given dose, the longer the dosing interval, the smaller the fluctuation. ✗ $\tau\uparrow$

   A. 1, 3, 4
   B. 1, 2, 3, 4
   C. 2, 3, 4, 5
   D. All of the above
   E. None of the above

   A

2. A 500mg dose of drug Z is given every 12 hours as an intravenous bolus injection until steady-state levels are reached. At steady-state, the AUC for one dosing interval is 36 mg/L*h. What is the average concentration for that dosing interval? **(5 points)**

   A. 2.1ug/mL
   B. 3ug/mL
   C. 3.5ug/mL
   D. 4.1ug/mL
   E. None of the above

   $C_{ss\,avg} = \frac{AUC}{\tau} = \frac{36}{12} = 3\ mg/L$

   $= 3\ \mu g/mL$

   B

3. A patient was given 100mg of gentamicin via a constant rate infusion over 1 hour every 8 hours. His peak plasma concentration at steady-state was determined to be 9mg/L. What will his plasma concentration be 4 hours after the start of the last infusion given the drug's half-life of 5 hours? **(5 points)**

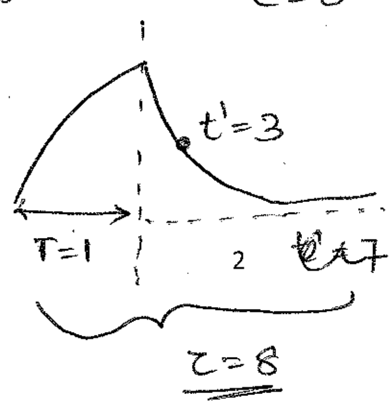
   A. 3.93mg/L
   B. 4.32mg/L
   C. 5.93mg/L
   D. 6.72mg/L
   E. 7.41mg/L

   $C_{max\,ss} = 9 mg/L$

   $\tau = 8$

   $C = 9 \times e^{-(0.1386 \times 3)} = 5.93$

   (4 hrs after start of last infusion)

   C

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4. A 30-year-old male (71kg) is admitted to the hospital for a colectomy. He develops a post-operative wound infection and is put on vancomycin. Please assume for your calculations that vancomycin is solely eliminated via the kidneys (filtration only) and that the volume of distribution is 0.8L/kg. Further assume that vancomycin is 35% plasma protein bound and that the patient's glomerular filtration rate is 119mL/min.

   Please compute an appropriate dosing interval to achieve steady-state peak and trough concentrations of 25mg/L and 10mg/L, respectively, following a 1-hour infusion. **(10 points)**

$V_d = 56.8\,L \qquad f_u = 0.65$

A. Every 4 hours
B. Every 6 hours
C. Every 8 hours
D. Every 12 hours
E. Every 24 hours

$CL = 119\,\frac{ml}{min} \times 0.65 = 77.35\,ml/min = 4.644\,l/hr$

$K_e = \frac{CL}{V_d} = \frac{4.64}{56.8} = 0.082\,hr^{-1}$

D

$F = \frac{25}{10} = 2.5$

$F = e^{K_e(\tau - T)}$

$$\boxed{\frac{\ln F}{K_e} + T = \tau}$$

$$\frac{\ln 2.5}{0.082} + 1 = \tau$$

$\tau = 12.17\,hr$

$\tau \approx 12\,hr$

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Question Set II (25 points)

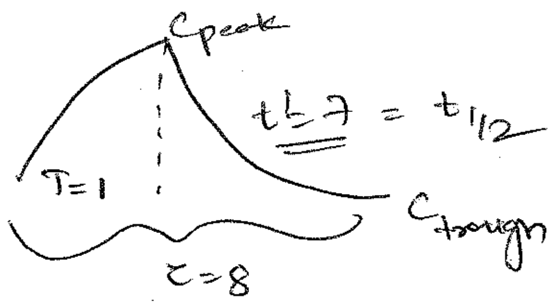
Consider the following equation:

$$Cp_{min,ss} = \frac{\frac{Dose}{T}}{k_e \cdot V_d} \cdot \frac{1 - e^{-k_e \cdot T}}{1 - e^{-k_e \cdot \tau}} \cdot e^{-k_e \cdot t'}$$

You join a new company and your supervisor tells you to work on a new drug about which you know only the following information: it is given as a short-term infusion (1 hour) every 8 hours and its half-life is 7 hours. On the bubble sheet mark A for true or B for false.

$$F = e^{+k_e(\tau - T)} = e^{0.099 \times 7} = 2$$

5.	T	F	Fluctuation will be 2
6.	T	F	There is insufficient information to compute the volume of distribution
7.	T	F	Drug input into the systemic circulation is in this case characterized by a first order process
8.	T	F	Half of the administered dose is eliminated during each dosing interval at steady-state
9.	T	F	If t′ equals T minus T, the trough concentration will be half of the the peak concentration



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Question Set III (25 points)

10. Please select the correct answer regarding a two-compartment body model from the choices given below. **(10 points)**

✓ 1) Macro constants can be used to characterize the concentration-time profile T

T ✓ 2) The concentration-time profile of a two-compartment model is represented by a biexponential curve

F ✗ 3) Beta is the terminal elimination half-life

T ✓ 4) The method of residuals (feathering) can be used to compute the rate constant of drug distribution into peripheral tissues

F 5) Xp typically represents the amount of drug in the central compartment following parenteral drug administration

A. 2, 4
B. 1, 2, 4
C. 2, 3, 4, 5
D. 1, 2, 3, 4
E. None of the above

B

11. A 65-kg patient is started on a continuous intravenous constant rate infusion of theophylline at 40mg/h. His respective steady-state concentrations are determined to be 10mg/L. If you assume the theophylline distribution volume to be 40L, what would be the patient's plasma concentrations 10 hours after the continuous infusion is stopped (please assume that steady-state had been reached previously for your computations)? **(10 points)**

$C_{ss} = \frac{k_0}{k_e \cdot V_d}$ $V_d = 40\ L$

A. 2.5mg/L
B. 2.9mg/L
C. 3.7mg/L
D. 4.8mg/L
E. None of the above

C

~~10 mg/L = 40 mg/hr~~

$10 = \frac{40\ mg/h}{k_e \cdot 40\ L}$

$K_e = 0.1\ hr^{-1}$

10 hrs after infusion is stopped

$C_{10} = 10\ \frac{mg}{L} \times e^{-0.1 \times 10}$

$= 3.67$

$\sim 3.7\ mg/L$

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12. What impact will a decrease in plasma protein binding have for a high-extraction drug that is solely cleared via Phase I and II enzymes in the liver following intravenous administration? Please select the correct answer. **(5 points)**

    A. An increase in hepatic clearance ✗
    B. An increase in glomerular filtration rate ✗
    C. An increase in free average steady-state concentrations ✓
    D. An increase in total steady-state concentrations ✗
    E. None of the above

$f_u \uparrow$

$$C_{ss_{avg}} = \frac{D}{CL \cdot \tau}$$

$$C_{ss_{avg,\,free}} = \frac{f_u \cdot D}{CL \cdot \tau}$$

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Question Set IV (20 points)

Please indicate whether the following statements for an oral dosing regimen are **True (A)** or **False (B)**.

13. T F There is only drug absorption until peak plasma concentrations are reached

14. T F The terminal slope of the concentration time profile is always reflective of the elimination rate constant ke

15. T F If two formulations of the same drug are tested and product A has a greater absorption rate than product B, product A will take a longer time to reach peak concentrations (Tmax)

16. T F The time it takes to reach peak plasma concentrations (Tmax) is independent of the dose and the oral bioavailability

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Question Set V (20 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.
- The ability to be actively pumped in (+++) or pumped out (---) **of the brain by extremely** active transporters. No activity to transporters (000)

DRUG	Fraction Unionized at pH=7.4	Partition Coefficient of Unionized form	Molecular Weight (Dalton)	Transporter activity	
1	0.72	0.005	456	+++	fastest 0.0036
2	0.72	0.005	456	---	slowest 0.0036
3	0.91	0.07	290	000	0.0637
4	0.074	10	320	000	0.74
5	0.72	0.005	456	000	0.0036

17. Select the correct rank order of uptake rate with which drugs 1-5 will **enter brain tissue.**

2 < 5 < 3 < 4 < 1

A. 1 slower than 2 slower than 3 slower than 4 slower than 5
B. 2 slower than 4 slower than 3 slower than 5 slower than 1
C. 1 slower than 4 slower than 3 slower than 5 slower than 2
D. 2 slower than 5 slower than 1 slower than 3 slower than 4
E. None of the above

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Question Set VI (~~15 points~~) 10 points

A drug (lipophilic, unionized, low molecular weight) is showing in average a pronounced binding to plasma proteins of 99%. Between-subject variability of protein binding is pronounced. It is given as i.v. bolus injection. Two patients receive this injection. **Patient 1 has a much stronger plasma protein binding** for the drug (99.995%) than the second patient (99.99%). **This is the only physiological difference between the two patients.**

18. Please indicate whether **patient 1** will have a larger (↑), smaller (↓) identical (↔) value than patient 2 for **(15 points)**:

$f_{u_1} = 0.00005$

$f_{u_2} = 0.0001$

- total initial total plasma drug concentration (C_o),
- f_u
- f_{uT}
- V_d

$f_u \downarrow$ $V_d \downarrow$ $C_0 \uparrow$ $f_{uT} \leftrightarrow$

A. $C_0 \uparrow$, $f_u \downarrow$ $f_{uT} \uparrow$, $V_d \downarrow$

B. $C_0 \downarrow$, $f_u \downarrow$ $f_{uT} \downarrow$, $V_d \uparrow$

C. $C_0 \uparrow$, $f_u \downarrow$ $f_{uT} \leftrightarrow$, $V_d \downarrow$

C

D. $C_0 \uparrow$, $f_u \uparrow$ $f_{uT} \uparrow$, $V_d \leftrightarrow$

E. None of above combinations.

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Question set VII (10 points)

A hydrophilic drug (not an acid, not a base) is cleared through renal and hepatic clearance (Cl_{ren}=32.5 ml/min; Cl_{tot}= 40.5 mL/min). Assume a GFR of 130 ml/min, Urine flow of 1.5 ml/min; liver blood flow of 80 L/h(1,333 ml/min).

hydrophilic drug

$Cl_{renal} = \cancel{\ldots}\, GFR \cdot fu$

$32.5 = \cancel{\ldots}\, 130 \times fu$

$fu = \frac{32.5}{130} = 0.25$

19. T F fu of this drug is 0.325

20. T F Cl_{int} is 1.9 L/h

$Cl_{hep} = 40.5 - 32.5$

$= 8\ ml/min$

$= 0.48\ L/hr$ = low extraction drug

$Cl_{hep} = Cl_{int} \times fu$

$0.48 = Cl_{int} \times 0.25$

$Cl_{int} = \frac{0.48}{0.25} = 1.92\ L/hr$

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

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

Half-life

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

Intravenous bolus

Initial concentration

$$C_0 = \frac{D}{Vd}$$

Plasma concentration (single dose)

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

Plasma concentration (multiple dose)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Peak (multiple dose)

$$C_{max} = \frac{C_0}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Average concentration (steady state)

$$\overline{Cp}_{ss} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

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

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)

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

Time of maximum concentration (multiple dose)

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

Average concentration (steady state)

$$\overline{C} = \frac{F \cdot D}{CL \cdot \tau}$$

Clearance

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

$$Cl = k_e \cdot V_d$$

Constant rate infusion

Plasma concentration (during infusion)

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

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{\left(C_1 + C_2\right)} + \frac{2 \cdot Vd \cdot \left(C_1 - C_2\right)}{\left(C_1 + C_2\right) \cdot \left(t_2 - t_1\right)}$$

Short-term infusion

Peak (single dose)

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

Trough (single dose)

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

Peak (multiple dose)

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

Trough (multiple dose)

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

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C^*_{max}}{C^*_{min}}\right)}{\Delta t}$$

with C_{max}^* = measured peak and C_{min}^* = measured trough,
measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C^*_{max}}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C^*_{min} \cdot e^{-k_e \cdot t^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

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

Calculated recommended dosing interval

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

Calculated recommended dose

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

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_\infty = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

Creatinine Clearance

$$CL_{creat}(\text{male}) = \frac{(140 - \text{age}) \bullet \text{weight}}{72 \bullet Cp_{creat}}$$

$$CL_{creat}(\text{female}) = \frac{(140 - \text{age}) \bullet \text{weight}}{85 \bullet Cp_{creat}}$$

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

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

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

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

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

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

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

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

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

If the dosing involves the use of I.V. bolus administration:	**For a single I.V. bolus administration:** $C_0 = \frac{D}{V}$ $C = C_0 \cdot e^{-k_e t}$	**For multiple I.V. bolus administration:** $Cn(t) = \frac{D}{V} \cdot \frac{\left(1 - e^{-nk_e\tau}\right)}{\left(1 - e^{-k_e\tau}\right)} \cdot e^{-k_e t}$ at peak: $t = 0$; at steady state $n \to \infty$ at trough: $t = \tau$ $C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e\tau})}$ $C_{\min ss} = C_{\max ss} \cdot e^{-k_e\tau}$
If the dosing involves the use of I.V. infusion:	**For a single short-term I.V. infusion:** Since $\tau = t$ for C_{max} $C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$	**For multiple short-term I.V. infusion at steady state:** $C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$ $C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$

If the dosing involves a I.V. infusion (more equations):	$C_t = \frac{D}{Vk_eT} \cdot \left(e^{k_eT} - 1\right) \cdot e^{-k_et}$ (most general eq.) during infusion t = T so, $C_t = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_et}\right)$ (during infusion) at steady state $t \to \infty$, e^{-k_et}, $t \to 0$ so, $Cpss = \frac{D}{Vk_eT} = \frac{k_0}{Vk_e} = \frac{k_0}{CL}$ (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:** $C = \frac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left(e^{-k_et} - e^{-k_at}\right)$ $t_{\max} = \ln\left[\frac{k_a}{k_e}\right] \cdot \frac{1}{(k_a - k_e)}$ **For multiple oral doses:** $C = \frac{F \cdot D \cdot k_a}{V(k_a - k_e)} \cdot \left[\frac{e^{-k_et}}{\left(1 - e^{-k_e\tau}\right)} - \frac{e^{-k_at}}{\left(1 - e^{-k_a\tau}\right)}\right]$ $t_{\max} = \ln\left[\frac{k_a \cdot \left(1 - e^{-k_e\tau}\right)}{k_e \cdot \left(1 - e^{-k_a\tau}\right)}\right] \cdot \frac{1}{(k_a - k_e)}$