

Name: KEY

UFID#: XXXX-XXXX

PHA 5127

Final Exam

Fall 2010

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

~~Name _____~~

Please transfer the answers onto the bubble sheet. The question number refers to the number on the bubble sheet. Please fill in all the information necessary to identify yourself.

The proctors will also collect your exams.

Good LUCK.

No of Questions – 36

Question Sets – XII

No of pages - 23

TOTAL _____ 110 /pts

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Question set I (10 pts): Select whether the following statements are True (A) or False (B) concerning an orally administered drug that is absorbed by a **zero order** process and eliminated by a first order process

- 1: T F Such a dosage form can be used for slow release formulations.
- 2: T F The unit for the absorption rate will be [1/h].
- 3: T F The absorption rate constant can be calculated as dose (D) and time necessary to absorb the dose (T) with absorption rate being T/D.
- 4: T F Absorption rate and absorption rate constant are identical.
- 5: T F The oral bioavailability of a drug that is absorbed through a zero order process is likely to show the same or lower oral bioavailability than when the same dose of the same drug is absorbed through a first order process (assume transporters are not involved).

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Question set II (6 pts): Select from the following statements whether the statements are True (A) or False (B).

- 6: T F // Assume steady state has been reached after having started a constant rate infusion. At steady state, the steady state concentration will depend on the volume of distribution of the drug.
- 7: T F // The time to reach steady state after an constant rate infusion is affected by the clearance and volume of distribution of the drug.
- 8: T F // The fluctuation (difference between peak and trough concentration is affected by the clearance and volume of distribution of the drug.

Question set III (4 pts):

Select from the following statements whether the statements are True (A) or False (B).

Assume a multiple dosing situation.

- 9: T F // For a lipophilic drug whose clearance is constant under the given conditions, the following statement can be made: The stronger the plasma protein binding the more pronounced the degree of accumulation.
- 10: T F // For a lipophilic drug whose clearance is constant under the given conditions and given as multiple iv injections, the following statement can be made: The stronger the plasma protein binding, the more pronounced the fluctuation between peak and trough concentration.

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Question set IV (25 pts):

A 30 year old male (63 kg) is admitted to the hospital for a right colectomy because of colon cancer. He develops a post-operative wound infection which is found to be resistant to penicillins. The patient has a creatinine clearance of 134 ml/min. You are responsible to determine an appropriate dosing regimen for vancomycin (to achieve the desired *steady state plasma concentration* of 20 mg/L for the peak, drawn two hours after the end of a 1 hour infusion) and about 7 mg/L for the trough. Assume that vancomycin is eliminated through the kidneys only (only filtered and not reabsorbed). The volume of distribution is 0.9 L/kg. Assume f_u of vancomycin being 1. (Use $k_e = CL/V_d$ and TBW to calculate V_d)

Question 11:

Calculate the projected dosing interval. (5 pts) $CL = 134 \text{ mL/min} = 8.04 \text{ L/h}$

$$V_D = 56.7 \text{ L}$$

$$k_e = \frac{CL}{V_D} = \frac{8.04 \text{ L/h}}{56.7 \text{ L}} = 0.142 \text{ 1/h}$$

A: 8 h

B: 12 h

C: 24 h

D: 36 h

E: none of the above

$$C_{max, SS} = \frac{20 \text{ mg/L}}{e^{-0.142 \text{ 1/h} \cdot 2 \text{ h}}} = 26.57 \text{ mg/L}$$

$$\tau = \ln\left(\frac{26.57 \text{ mg/L}}{7 \text{ mg/L}}\right) \cdot \frac{1}{0.142 \text{ 1/h}} + 1 \text{ h}$$

$$= 10.39 \text{ h}$$

round to 12 h

Note: Points were awarded

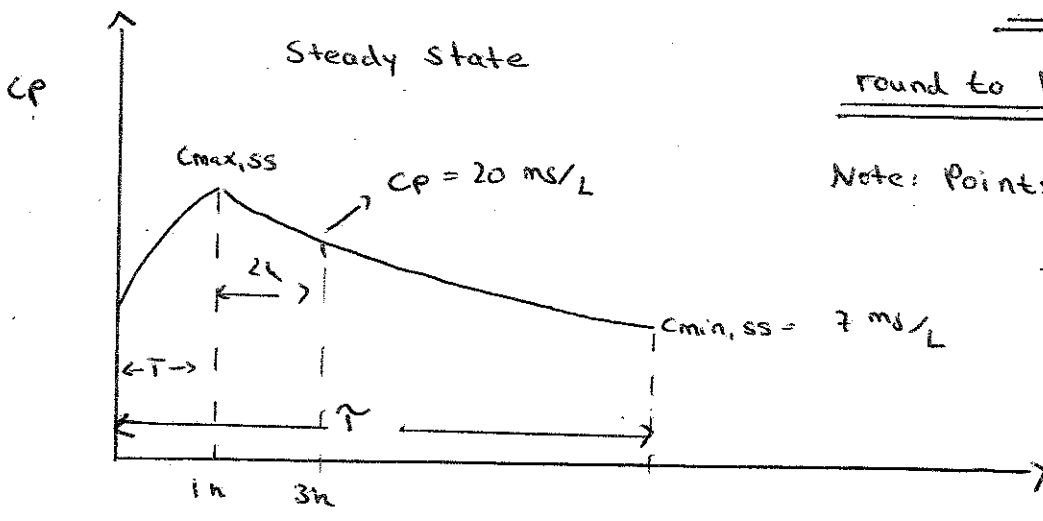
if 10.39 h was

calculated but

rounded down to 8

or "none of the

above" was chosen



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A 30 year old male (63 kg) is admitted to the hospital for a right colectomy because of colon cancer. He develops a post-operative wound infection which is found to be resistant to penicillins. The patient has a creatinine clearance of 134 ml/min. You are responsible to determine an appropriate dosing regimen for vancomycin (to achieve the desired *steady state plasma concentration* of 20 mg/L for the peak, drawn two hours after the end of a 1 hour infusion) and about 7 mg/L for the trough. Assume that vancomycin is eliminated through the kidneys only (only filtered and not reabsorbed). The volume of distribution is 0.9 L/kg. Assume fu of vancomycin being 1. (Use $k_e = CL/V_d$ and TBW to calculate Vd)

Question 12: Calculate a suitable maintenance dose, given as short term infusion over one 1 hour? Round appropriately. (5 pts)

- A: 700 mg
- B: 900 mg
- C: 1100 mg
- D: 1300 mg
- E: none of the above

$$C_{max,ss} = \frac{\text{Dose}}{T \cdot CL} \cdot \frac{1 - e^{-k_e \cdot T}}{1 - e^{-k_e \cdot \tau}}$$

$$C_{max,ss} = 26.56 \text{ mg/L} \quad T = 1 \text{ h} \quad CL = 8.04 \text{ L/h}$$
$$\tau = 12 \text{ h} \quad k_e = 0.142 \text{ 1/h}$$

⇒ Maintenance Dose =

$$\frac{26.56 \frac{\text{mg}}{\text{L}} \cdot 1 \text{ h} \cdot 8.04 \frac{\text{L}}{\text{h}} \cdot \left(1 - e^{-0.142 \frac{1}{\text{h}} \cdot 12 \text{ h}}\right)}{\left(1 - e^{-0.142 \frac{1}{\text{h}} \cdot 1 \text{ h}}\right)}$$

$$= \underline{\underline{1313.04 \text{ mg}}} \quad \underline{\underline{\text{round to } 1300 \text{ mg}}}$$

Note that: C = 1100 mg and E = "none of the above" ~~was~~ were awarded points because C ^{or} E would be the answer if $\tau = 8 \text{ hr}$ or $\tau = 24$ or 36 hr was chosen in Q11, respectively.

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A 30 year old male (63 kg) is admitted to the hospital for a right colectomy because of colon cancer. He develops a post-operative wound infection which is found to be resistant to penicillins. The patient has a creatinine clearance of 134 ml/min. You are responsible to determine an appropriate dosing regimen for vancomycin (to achieve the desired *steady state plasma concentration* of 20 mg/L for the peak, drawn two hours after the end of a 1 hour infusion) and about 7 mg/L for the trough. Assume that vancomycin is eliminated through the kidneys only (only filtered and not reabsorbed). The volume of distribution is 0.9 L/kg. Assume f_u of vancomycin being 1. (Use $k_e = CL/V_d$ and TBW to calculate V_d)

Question 13: How long will it take to achieve steady state (assume relationship discussed for iv bolus injections). **Round appropriately.** (5 pts)

- A: 8 h
- B: 12 h
- C: 24 h
- D: 36 h
- E: none of the above

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A 30 year old male (63 kg) is admitted to the hospital for a right colectomy because of colon cancer. He develops a post-operative wound infection which is found to be resistant to penicillins. The creatinine clearance of the patient was determined by the lab to be 134 ml/min. You are responsible to determine an appropriate dosing regimen for vancomycin (to achieve the desired *steady state plasma concentration* of 20 mg/L for the peak, drawn two hours after the end of a 1 hour infusion) and about 7 mg/L for the trough. Assume that vancomycin is eliminated through the kidneys only (only filtered and not reabsorbed). The volume of distribution is 0.9 L/kg. Assume f_u of vancomycin being 1. (Use $k_e = CL/V_d$ and TBW to calculate V_d)

Question 14: Calculate a suitable loading dose, to be given as an iv short term infusion over one hour. Round appropriately. (5 points)

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

- A: 900 mg
- B: 1100 mg
- C: 1300 mg
- D: 1500 mg
- E: none of the above

$$C_{max,1} = 26.56 \text{ mg/L} \quad T = 1 \text{ h} \quad CL = 8.04 \text{ L/h}$$
$$k_e = 0.142 \text{ 1/h}$$

Loading Dose =

$$\frac{26.56 \frac{\text{mg}}{\text{L}} \cdot 1 \text{ h} \cdot 8.04 \text{ L/h}}{\left(1 - e^{-0.142 \text{ 1/h} \cdot 1 \text{ h}} \right)}$$
$$= \underline{\underline{1613.12 \text{ mg}}}$$

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Question set V (5 pts)

A 30 year old male (63 kg) is admitted to the hospital for a right colectomy because of colon cancer. He develops a post-operative wound infection which is found to be resistant to penicillins. The creatinine clearance of the patient was determined by the lab to be 134 ml/min. You are responsible to determine an appropriate dosing regimen for vancomycin (to achieve the desired *steady state plasma concentration* of 20 mg/L for the peak, drawn two hours after the end of a 1 hour infusion) and about 7 mg/L for the trough. Assume that vancomycin is eliminated through the kidneys only (only filtered and not reabsorbed). The volume of distribution is 0.9 L/kg. Assume f_u of vancomycin being 1. (Use $k_e = CL/V_d$ and TBW to calculate V_d)

Question 15:

The creatinine clearance of the patient was not determined correctly, as you just learned from the lab. It is actually 85 ml/min. You have 1 minute to adjust the dose, since the only nurse able to start the infusion is needed immediately in the ER. Can you give a safe dose adjustment without having to go through all your calculations that will at least provide a similar average steady state concentration for your selected dosing interval?

- A: 20% of previously selected
- B: 40% of previously selected
- C: 60% of previously selected
- D: 80% of previously selected
- E: None of the above

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Question set VI (5 points)

Question 16: A 60 kg patient is started on 80 mg of drug X, every 6 hr given as a one-hour infusion. The clearance of the drug is 80 ml/min. If the infusion is given the first time, how much lower is the first trough concentration when compared to the trough at steady state ($C_{min,ss}$).

A: 30-40% of $C_{min,ss}$

B: 41-50% of $C_{min,ss}$

C: 61-75% of $C_{min,ss}$

D: None of the above

E: Don't have enough information to provide this information.

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Question set VII (10 pts)

Consider the following equation:

$$C_{p_{\min}} = \frac{k_o}{CL} \cdot \frac{1 - e^{-k_e * T}}{1 - e^{-k_e * \tau}} \cdot e^{-k_e * t'}$$

You join a new company and your supervisor tells you on the first day of work the following information: Our new drug has a half-life of 5 hours, it is given over two hours as a short term infusion with a dosing interval of 12 hours. This is all the information you were given. You needed to check whether former employees had provided the right information (10 points)

- 17: T F Fluctuation (Peak/Trough) will be 2.
- 18: T F Accumulation will be 2.5
- 19: T F If t' equals (tau minus T), Cp_{min} will be identical to the trough concentration.
- 20: T F k_o/CL gives the steady state concentration after one infusion if the pump does not stop.
- 21: T F Using above information on the dosing regimen, the above equation can be used to calculate the Vd

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Question set VIII (8 pts)

Consider the following relationship.

$$\tau = \frac{\ln F}{k_e}$$

- 22: T F F stands for fraction bound in plasma
- 23: T F This relationship indicates that the dosing interval depends only on half-life, but not clearance and volume of distribution.
- 24: T F This relationship will provide tau for multiple iv injections and short term infusion without any further adjustments.
- 25: T F When this equation is used for oral forms of administration, as we did for theophylline, a safety factor is build in, as tau is calculated for iv administration without considering the absorption process.

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Question Set IX (15 points)

Question 26-30: Two patients received a lipophilic unionized drug, which is only cleared by the kidney, as an iv bolus injection. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma (f_u), volume of plasma (V_p) and volume of the tissue water (VTW) in both patients are shown below. Assume that both patients show the same tissue protein binding.

TABLE 1: INPUT PARAMETERS

	Patient 1	Patient 2
D [mg]	40	40
GFR	130	65
UF (Urine Flow)	1.5	3
f_u	1	0.5
f_{ut}	0.3	0.3
V_p [L]	3	3
VTW [L]	38	38

Indicate which of the following parameters (questions 27- 31) in patient 2 will be clearly larger (A), be ABOUT the same (B), or will be clearly smaller (C) than those in Patient 1.

Table 2: OUTPUT PARAMETERS

Question:		
26. (3 points)	Vd [L] of Patient 2	C Larger (A), same (B), Smaller (C) than in Patient 1
27. (3 points)	CL [L/h] of Patient 2	B Larger (A), same (B), Smaller (C) than in Patient 1
28. (3 points)	t1/2 [h] of Patient 2	C Larger (A), same (B), Smaller (C) than in Patient 1
29. (3 points)	Peak [$\mu\text{g/ml}$] of Patient 2	A Larger (A), same (B), Smaller (C) than in Patient 1
30. (3 points)	F in Patient 2 when given as multiple short term infusions	Larger (A), same (B), Smaller (C) than in Patient 1

↓
A or B
↓ ↓
F = Fluctuation F = availability (systemic)

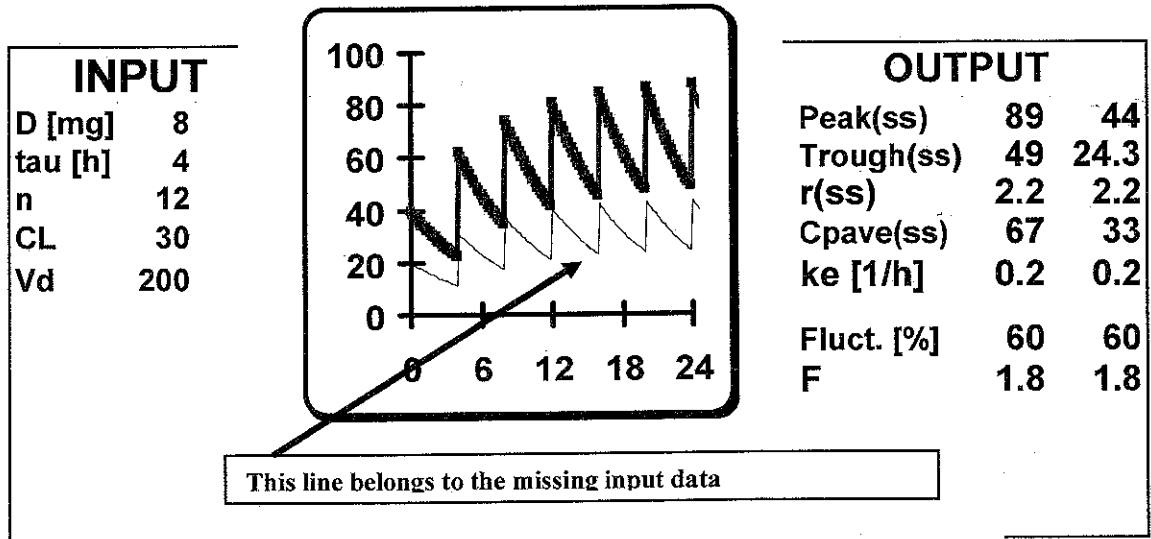
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Question Set X (5 points)

Question 31:

The following concentration time profiles were observed after multiple iv bolus injections of a drug. The two curves differ in one of the input parameters (Dose, tau, CL or Vd).



Identify the one input parameter that differs (question 32)

- A: Dose
- B: Clearance
- C: Volume of distribution
- D: tau
- E: none of the above

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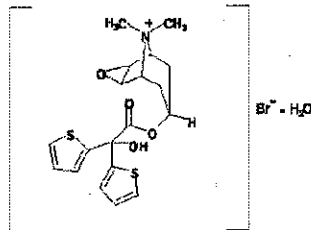
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Question Set XI (10 pts)

Question was considered as bonus question

=> Total points = 100

Question 32: Tiotropium is administered to the lung by means of dry powder inhalation to treat chronic obstructive pulmonary disease (COPD). The structural formula is



Tiotropium is not volatile and stable in plasma and other tissues. Thus, metabolism of tiotropium in the liver is negligible. No secretion through the bile is observed. Plasma protein binding is 70%. It has a low oral bioavailability (2-3%). The systemic availability after inhalation is 20%. Total clearance of tiotropium after i.v. administration in young healthy volunteers is 880 ml/min. Select the correct answers.

1. The information given suggests that the tiotropium clearance is likely to be associated with the age of the patient.
2. The low oral bioavailability is likely to be based on the insolubility of tiotropium.
3. The low oral bioavailability is likely to be due to the inability of the drug to cross membranes.
4. The clearance of the drug can be explained by the inability of the drug to cross membranes.
5. Tiotropium is able to cross membranes of the lung.

A: 1, 3

B: 2, 4, 5

C: 3, 5

D: 1, 3, 4, 5

E: none of the above combinations

The drug is listed as sparingly soluble in water. However, it may or may not affect oral bioavailability. Thus, 2 could be considered as TRUE or FALSE.

10 bonus points when D or E were chosen

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Question Set XII (12 points)

Questions 33

Assume a zero-order delivery of a drug into the blood stream for a defined time. Multiple doses are given with a specified dosing regimen. Select the correct answers.

- 1) The shorter the dosing interval, the smaller the fluctuation.
- 2) The smaller the clearance, the smaller the fluctuation
- 3) The smaller the volume of distribution, the smaller the fluctuation.
- 4) For a given dosing interval, the longer the infusion time the smaller the fluctuation.
- 5) Consider a defined dosing interval and dose. The smaller the clearance, the more pronounced the accumulation.
- 6) Consider a defined dosing interval. The larger the dose, the more pronounced the accumulation.

A) 1, 2, 4, 5, 6

B) 2, 4, 6

C) 3, 4, 5

D) 1, 2, 4, 5

E) None of the above