

Name: _____

SS # (optional): _____

PHA 5127

**Final Exam KEY
Fall 2002**

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

Name

Question/Points

1. _____ /12 pts
2. _____ /8 pts
3. _____ /12 pts
4. _____ /27 pts
5. _____ /20 pts
6. _____ /15 pts
7. _____ /20 pts
8. _____ /25 pts
9. _____ /15 pts
10. _____ /6 pts
11. ___ 5 ___ /5 Bonus pts

TOTAL _____ /160 (out 165 possible)

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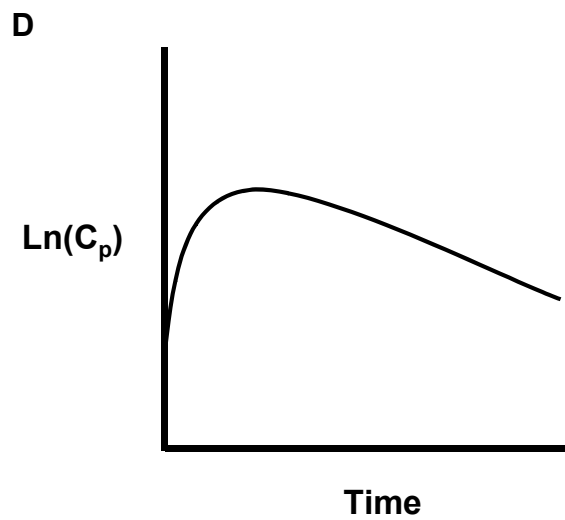
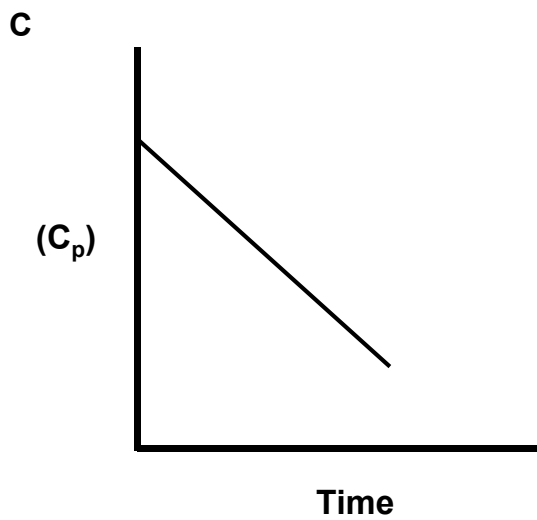
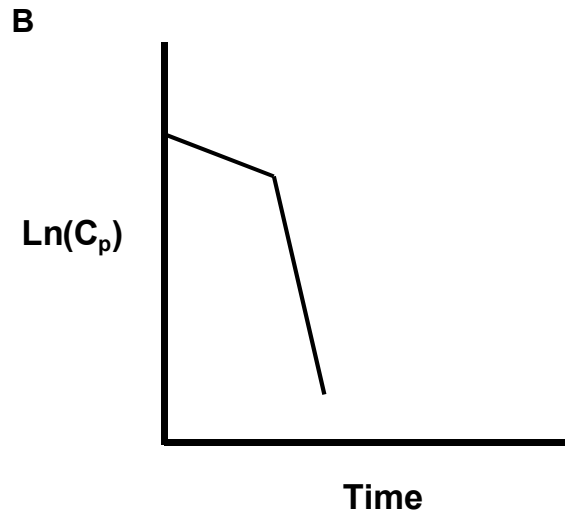
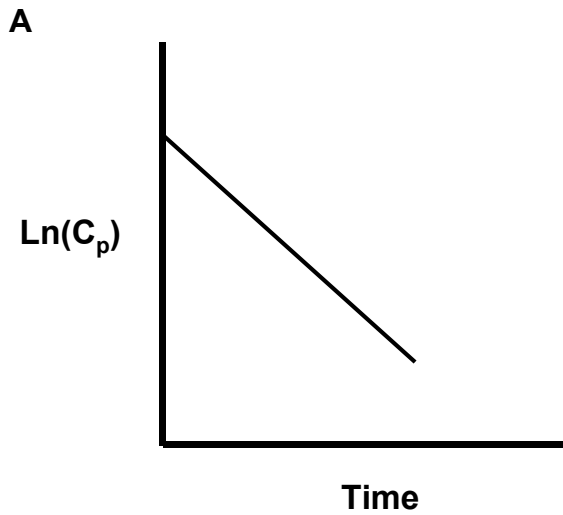
1.) Mark the following statements as True or False (12 points)

- T F Increasing the dosing interval (τ) of an oral dosing regimen will cause the fluctuation to increase.
- T F If a patient's plasma protein binding is decreasing for a certain drug so will its volume of distribution (Assume no other changes).
- T F The absorption rate constant (k_a) is always larger than the elimination rate constant (k_e).
- T F For a drug which behaves like a two compartment body model drug, $V_{d_{ss}}$ is larger than $V_{d_{area}}$ (also called $V_{d\beta}$)
- T F The maximum value of renal clearance is that of the glomerular filtration rate.
- T F Loading doses are more relevant for drugs with long half-lives.

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- 2.) Which graph(s) best depicts a one-compartment body model drug after iv. administration? (8 points)



Answer(s): A _____

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- 3.) The male patient Whoami is not feeling well. His doctor wants him to take 200 mg of the Drug Yaningho given orally as a tablet. There are two different formulations of the tablet available which differ in the rate with which the tablets disintegrate. Pharmacokinetic studies have shown that the corresponding k_a of tablet A is 3.0 h^{-1} while that of tablet B is 0.01 h^{-1} . Both tablets contain the same amount of Yaningho. Yaningho shows a k_e value of 0.3 h^{-1} after iv bolus administration of the drug. Mark whether the following statements are true or false (12 points)

- T F T_{\max} after administration of tablet A will be shorter (smaller) than t_{\max} observed after administration of tablet B
- T F C_{\max} after administration of tablet A will be somewhat lower than C_{\max} observed after iv bolus administration of the same dose
- T F C_{\max} after administration of tablet B will be lower than C_{\max} observed after iv bolus administration of the same dose
- T F The AUC observed after administration of tablet B will be smaller than that observed after administration of tablet A (assume that drug from both tablets is fully absorbed)
- T F The correct k_e value of Yaningho can be obtained from the terminal phase of the concentration time profile observed after tablet A was administered.
- T F The correct k_e value of Yaningho can be obtained from the terminal phase of the concentration time profile observed after tablet B was administered.

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- 4.) A 14 year old male with history of asthma, patient BG (52 kg) was presented to the hospital in status asthmaticus. On admission the patient's theophylline levels were not detectable (0 mg/L). The expected therapeutic range is 5-15 mg/L and the desired peak plasma concentration is 12 mg/L. He is given aminophylline as a 400 mg intravenous loading dose over 30 minutes followed by 200 mg intravenous over 30 minutes every 6 hours as maintenance dose (Remember aminophylline is a salt of theophylline and contains 80% theophylline equivalent).

The expected pharmacokinetic parameters are a volume of distribution of 26 L and a half-life of 4.5 hours. This information was obtained from published literature for patients similar to BG. (27 points)

- A. What concentration of theophylline do you expect 4 hours after the stop of the loading dose infusion?

$$Vd = 26L$$

$$t_{1/2} = 4.5h \quad k_e = \frac{0.693}{t_{1/2}} = \frac{0.693}{4.5h} = 0.154h^{-1}$$

$$CL = k_e \cdot Vd = 0.154h^{-1} \cdot 26L = 4L/h$$

$$\begin{aligned} C(4h) &= \frac{Dose}{CL \cdot T} \cdot (1 - e^{-k_e \cdot T}) \cdot e^{-k_e \cdot t} = \frac{400mg \cdot 0.8}{4L/h \cdot 0.5h} \cdot (1 - e^{-0.154 \cdot 0.5}) \cdot e^{-0.154 \cdot 4} \\ &= 160mg/L \cdot 0.074 \cdot 0.54 = 6.4mg/L \end{aligned}$$

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4.) continued

B. Predict the **steady-state** peak concentration (1 hour after the stop of the infusion) for the maintenance regimen .

$$\begin{aligned} C_{\max,ss} &= \frac{Dose}{CL \cdot T} \cdot \frac{(1 - e^{-k_e \cdot T})}{(1 - e^{-k_e \cdot \tau})} \cdot e^{-k_e \cdot t} = \frac{200mg \cdot 0.8}{4L/h \cdot 0.5h} \cdot \frac{(1 - e^{-0.154 \cdot 0.5})}{(1 - e^{-0.154 \cdot 6})} \cdot e^{-0.154 \cdot 1} \\ &= 80mg/L \cdot \frac{0.074}{0.6} \cdot 0.857 = 8.5mg/L \end{aligned}$$

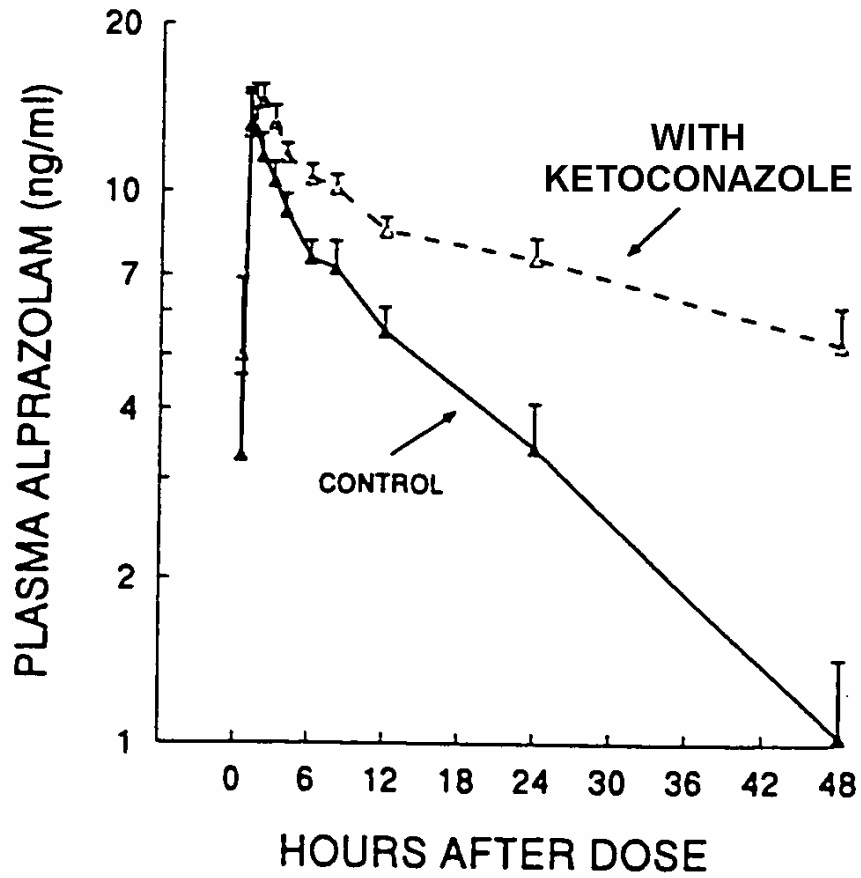
C. Predict the **steady-state** trough concentration (directly before the next infusion) for this regimen.

$$\begin{aligned} C_{\min,ss} &= C_{\max,ss} \cdot e^{-k_e \cdot (\tau - T)} \\ C_{\max,ss} &= \frac{Dose}{CL \cdot T} \cdot \frac{(1 - e^{-k_e \cdot T})}{(1 - e^{-k_e \cdot \tau})} = \frac{200mg \cdot 0.8}{4L/h \cdot 0.5h} \cdot \frac{(1 - e^{-0.154 \cdot 0.5})}{(1 - e^{-0.154 \cdot 6})} = 80mg/L \cdot \frac{0.074}{0.6} = 9.87mg/L \\ C_{\min} &= C_{\max} \cdot e^{-k_e \cdot (\tau - T)} = 9.87mg/L \cdot e^{-0.154 \cdot (6 - 0.5)} = 4.23mg/L \end{aligned}$$

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- 5.) The same dose of Alprazolam was given either alone or with ketoconazole. Explain what is going on. (20 points)



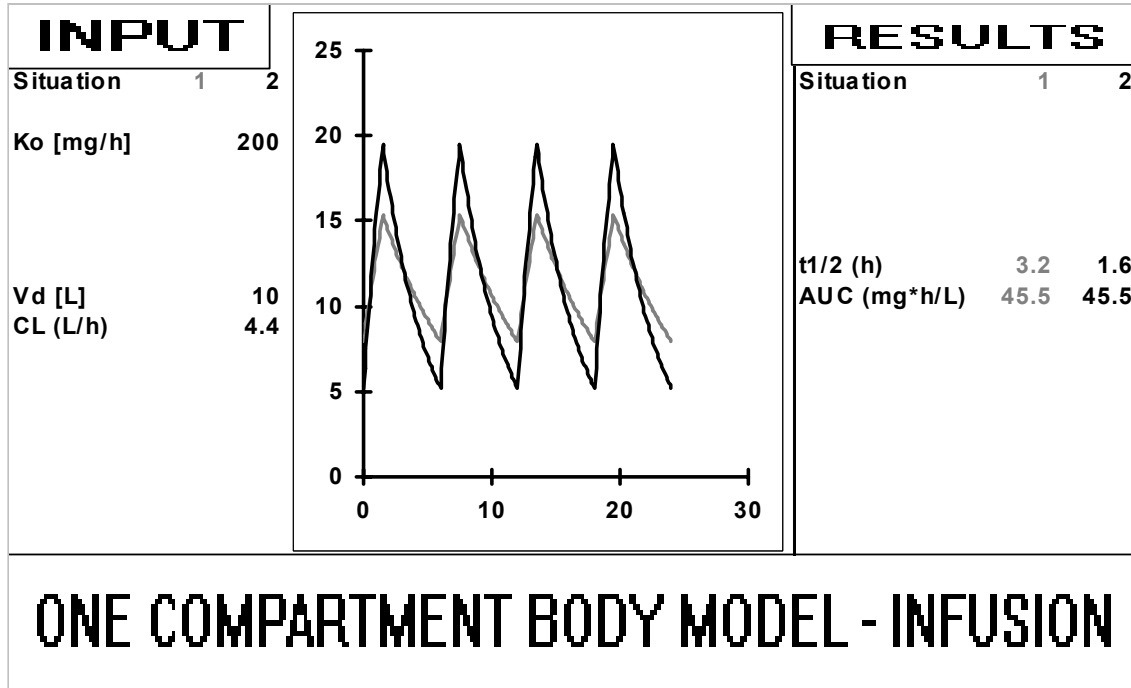
Greenblatt, 26 September 1998

ENZYME INHIBITION

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- 6.) The following concentration time profiles were observed after multiple short-term infusions over six hours at steady state of a drug. The two curves differ in one of the input parameters (k_o , CL , V_d). (AUC represents the AUC observed during one dosing interval) (15 points)



Identify the input parameter that differs.

$$k_e = \frac{0.693}{t_{1/2}} = \frac{0.693}{3.2h} = 0.217h^{-1}$$

$$V_d = \frac{CL}{k_e} = \frac{4.4L/h}{0.217h^{-1}} = 20.3L \quad \Rightarrow \quad V_d \text{ differs}$$

Explain your reasoning in one or two sentences.

same AUC: $AUC = \frac{Dose}{CL} \Rightarrow$ same CL, same Dose

different $t_{1/2}$: $t_{1/2} = \frac{0.693}{k_e} \Rightarrow$ different k_e

different V_d : $V_d = \frac{CL}{k_e}$

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7.) Consider the following equation. (20 points)

$$C_p = \frac{\text{Dose}}{\text{Volume}} \cdot \frac{1}{(1 - e^{-k_e \cdot \tau})} \cdot e^{-k_e \cdot t}$$

a) What does this equation describe?

plasma concentration after multiple IV bolus injections

b) What do the blocked parts of the equation represent?

$$\frac{\text{Dose}}{\text{Volume}} = \text{initial concentration}$$

$$\frac{1}{(1 - e^{-k_e \cdot \tau})} = \text{accumulation}$$

$$e^{-k_e \cdot t} = \text{elimination}$$

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- 8.) Due to the stress of finals, the entire 2PD class comes down with the flu and students are admitted to Shands Hospital. All the students are to be given an antiviral therapy by IV infusion (**continuous constant** rate infusion, not multiple short term infusions). The average **population $t_{1/2}$ is 1 h**, the **average V_D is 80 L**, and the effective plasma concentration is 20 mg L^{-1} . (25points)

- A. Recommend an infusion rate in milligrams per hour to reach the steady state concentration of 15 mg L^{-1} .

$$t_{1/2} = 1h \quad k_e = \frac{0.693}{t_{1/2}} = \frac{0.693}{1} = 0.693h^{-1}$$

$$CL = k_e \cdot Vd = 0.693h^{-1} \cdot 80L = 55.4L/h$$

$$k_0 = C_{p,ss} \cdot CL = 15mg/L \cdot 55.4L/h = 831mg/h \approx 830mg/h$$

- B. How long will it take to approach this concentration? (no calculation expected)

steady-state is usually reached after about $5 t_{1/2}$

⇒ in this case it would be after around 5 h

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8 cont'd.) One student, J.R., does not seem to respond to therapy. Plasma protein binding for the drug is normally 20% ($f_u=0.8$) except in J.R. whose protein binding was 40% ($f_u = 0.6$). Tissue binding is similar to the rest of the class

C. (Circle best answer)

A possible reason why J.R. is not responding to therapy is:

- A. The drug is a high extraction drug and lowering f_u will increase clearance and plasma levels will become sub-therapeutic
- B. The drug is a low extraction drug and lowering f_u will increase clearance and plasma levels will become sub-therapeutic.
- C. The drug is a high extraction drug. Clearance will not change but there is less free-drug caused by increased protein binding and it is free-drug that is active.
- D. The drug is a high extraction drug. Clearance will be increased and the total and free drug levels will be decreased.

D. (Circle the best answer)

The volume of distribution in JR is LARGER THAN / SMALLER THAN / THE SAME AS the rest of the class.

E. (Circle the best answer)

To achieve the same **free** plasma steady-state concentrations, the daily dose in JR should be LARGER THAN / SMALLER THAN / THE SAME AS the rest of the class.

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9.) Fill in the blank with the most appropriate answer. (15 points)

- A. **Feathering** is the name of a pharmacokinetic technique used to calculate alpha and beta from concentration time profiles of two compartment body model drug.
- B. When the drug clearance decreases (and volume of distribution stays the same) steady state plasma concentrations will be **increased**.
- C. To increase the renal clearance of a drug with a carboxylic acid function, you would want to **increase** the pH of the urine.
- D. Drugs follow **zero**-order absorption when the amount of drug absorbed is constant over time.
- E. In pharmacokinetics, **intrinsic CL**, is a measure of the activity of hepatic enzymes.

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- 10.) What is the differential equation describing the change in drug concentration over time after an iv bolus injection for a one-compartment body model drug. (assume first order kinetics for elimination, linear pharmacokinetics). (6 points)

$$\frac{dC}{dt} = -k_e \cdot C$$

- 11) Today (Dec 18th) is an extremely important day because (5 Bonus points)
- A. It is when 2PD class has finals
 - B. It is a week after Frank Sinatra's birthday
 - C. Only 6 days till Christmas (or the third day of Hanukkah)
 - D. All the above
 - E. None of the above