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## **PHA 5127**

### **Final Exam**

### **Fall 2007**

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

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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.**

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**Question 1:** Select the **correct** statement(s) concerning a two-compartment body model. (5pts)

1. For a two-compartment-body model drug, the rate constant describing the elimination of the drug from the central compartment ( $K_{10}$ , quantifying urinary and/or metabolic elimination) is larger number than beta,
2. The bi-exponential concentration time-profile, is due to the fact that  $K_{10}$  changes over time.
3.  $V_{d_{ss}}$  is smaller than  $V_{D_c}$
4. Let us assume that the toxicity of aminoglycosides is related to the drug-concentration in a deep peripheral compartment into which the drug enters and leaves very slowly. Drug toxicity will be observed immediately after an iv bolus of this aminoglycoside.

The **correct** statement(s) is (are):

- A:**        **1**
- B:**        2 and 3
- C:**        1 and 4
- D:**        1 and 3
- E:**        1, 2 and 3

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**Question 2:**

Select from the following statements the **correct** statement(s) (5pts)

1. For a sustained release formulation (drug shows flip-flop kinetics), the time to reach steady state depends on the rate of release.
2. The time to reach steady state is determined by the half-life of the drug.
3. The time to reach steady state is affected by clearance and volume of distribution.
4. Time to reach steady state depends on the dosing interval.

A: (1, 2, 3, 4)

B: (1, 2, 4)

C: (1, 3)

**D: (1, 2, 3)**

E: (2, 3)

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**Question 3-7:** The following applies to questions 3-7:

A 60-kg patient is to be started on a **continuous intravenous infusion**. To achieve an immediate effect, a loading dose is administered over 30 min. **(given as short term infusion over 30 min)**. The continuous infusion is started immediately after the loading dose. From a previous regimen of the same drug, the patient's  $k_e$  is  $0.07 \text{ h}^{-1}$  and the  $V_d$  is 40 L. Assume that none of this drug has been administered beforehand.

**Question 3:** In order to achieve a  $C_{p_{ss}}$  of 7.5 mg/L, what would be the loading dose (mg) given over 30 min? (5pts)

- A 300 mg
- B 305 mg**
- C 600 mg
- D 610 mg
- E none of the above

In this question we want our concentration at the end of a 30 min infusion to be 7.5 mg/L. It is stated that this is the first dose so we can use the  $C_{max}$  equation for a single dose. The purpose of a loading dose is to reach the desired concentration quickly.

$$Cl = k_e * V_d = 0.07 \text{ hr}^{-1} * 40 \text{ L} = 2.8 \text{ L/hr}$$

$$C_{max} = \text{Dose} / Cl * T * (1 - e^{-k_e * T}) \text{ where}$$

T = infusion time

$$\text{Dose} = C_{max} * Cl * T / (1 - e^{-k_e * T})$$

$$\text{Dose} = 7.5 \text{ mg/L} * 2.8 \text{ L/hr} * 0.5 \text{ hr} / (1 - e^{-0.07 * 0.5}) = 305.23 \text{ mg} \sim 305 \text{ mg}$$

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A 60-kg patient is to be started on a **continuous intravenous infusion**. To achieve an immediate effect, a loading dose is administered over 30 min. **(given as short term infusion over 30 min)**. The continuous infusion is started immediately after the loading dose. From a previous regimen of the same drug, the patient's  $k_e$  is  $0.07 \text{ h}^{-1}$  and the  $V_d$  is 40 L. Assume that none of this drug has been administered beforehand.

**Question 4:** In order to achieve a  $C_{p_{ss}}$  of 7.5 mg/L, what will be the rate of the continuous infusion? ( **$k_0$  for the following constant rate infusion**)  
(5pts)

- A:  $2.1 \text{ hr}^{-1}$
- B: 21 mg/ 0.5 hours
- C: 21 mg/hr**
- D: 21 mg
- E: none of the above

The key to this question is to watch your units. From the equation sheet

$C_{p_{ss}} = k_0 / Cl$        $k_0 = C_{p_{ss}} * Cl = 7.5 \text{ mg/L} * 2.8 \text{ L/hr} = 21 \text{ mg/hr}$  You can see that the L cancels out.

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A 60-kg patient is to be started on a **continuous intravenous infusion**. To achieve an immediate effect, a loading dose is administered over 30 min. **(given as short term infusion over 30 min)**. The continuous infusion is started immediately after the loading dose. From a previous regimen of the same drug, the patient's  $k_e$  is  $0.07 \text{ h}^{-1}$  and the  $V_d$  is 40 L. Assume that none of this drug has been administered beforehand.

**Question 5:** What will be the plasma concentration 12 hours after the continuous infusion was started? *[Remember a loading dose infusion was given, see question 3]* (5pts)

- A: 4.5 mg/L
- B: 6.5 mg/L
- C: 7.5 mg/L**
- D: 15 mg/L
- E: None of the above.

Due to the fact a loading dose was administered and we calculated the loading dose and infusion rate to remain at 7.5 mg/L in this patient, this will be the concentration until the infusion is stopped despite how long the constant infusion continues.

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**Question 6:** If the continuous infusion is stopped after 3 days, what will be the plasma concentration 12 hours after the stop of the infusion? Please perform calculations, we will check. (5 points)

- A 0.6 mg/L
- B: 3.25 mg/L
- C: 3.75 mg/L
- D: 6.0 mg/L
- E: None of the above

**Answer: B**

**At steady-state,  $C_{pss} = 7.5 \text{ mg/L}$ . After stop of the infusion: drug follows one-compartmental model with first-order elimination:**

$$C_{p(t')} = C_{pss} * e^{(-k_e * t')} \rightarrow C_{p(12hr)} = 7.5 \text{ mg/L} * e^{(-0.07 \text{ hr}^{-1} * 12 \text{ hr})} = 3.24 \text{ (mg/L)}$$

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A 60-kg patient is to be started on a **continuous intravenous infusion**. To achieve an immediate effect, a loading dose is administered over 30 min. **(given as short term infusion over 30 min)**. The continuous infusion is started immediately after the loading dose. From a previous regimen of the same drug, the patient's  $k_e$  is  $0.07 \text{ h}^{-1}$  and the  $V_d$  is 40 L. Assume that none of this drug has been administered beforehand.

**Question 7:** The infusion is continued for 3 days and the steady state concentration has been maintained at 7.5 mg/L. This infusion is stopped because the physician wants to increase the steady state concentration to 15 mg/L. What will be the new infusion rate? Please perform calculations, we might check. (5 points)

- A: 21 mg/L
- B: 42 mg/0.5 h
- C: 21 mg/0.5 h
- D: 21 mg/h
- E: None of the above.

**Answer: C**

$$C_{pss} = K_0 / CL \rightarrow K_0 = C_{pss} * CL \rightarrow K_0 = 15 \text{ mg/L} * 0.07 \text{ h}^{-1} * 40 \text{ L}$$
$$\rightarrow = 42 \text{ mg/hr} = 21 \text{ mg/0.5hr}$$

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**The following pertains to Questions 8-9**

A 60 kg patient is started on 80 mg of Drug A, every 6 hr given as a one-hour infusion.

**Question 8:** If this patient is assumed to have an “average” volume of distribution (value of the population mean) of 0.25 L/kg and a normal half-life of 3 hr. What will be the  $C_{\max}$  at steady state? Please provide calculations. (5 points)

- A: 6.3 mg/L
- B: 8.9 mg/L
- C: 12.2 mg/L
- D: 4.8 mg/L
- E: None of the above

**Answer: A**

$$V_d = 0.25 \text{ L/kg} \cdot 60 \text{ kg} = 15 \text{ L}$$

$$k_e = \ln 2 / t_{1/2} = 0.693 / 3 \text{ hr} = 0.231 \text{ (hr}^{-1}\text{)}$$

$$CL = V_d \cdot k_e = 15 \text{ L} \cdot 0.231 \text{ hr}^{-1} = 3.465 \text{ (L/hr)}$$

**Peak (multiple dose)**

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

$$C_{\max} = 80 \text{ mg} / 3.465 \text{ L/hr} / 1 \text{ hr} \cdot (1 - e^{(-0.231 \text{ hr}^{-1} \cdot 1 \text{ hr})}) / (1 - e^{(-0.231 \text{ hr}^{-1} \cdot 6 \text{ hr})})$$

$$\rightarrow = 6.35 \text{ mg/L}$$

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**The following pertains to Questions 8-9**

A 60 kg patient is started on 80 mg of gentamycin, every 6 hr given as a one-hour infusion.

**Question 9:** Based on the above volume of distribution and  $t_{1/2}$  estimates, is the 6 hr dosing interval sufficient to achieve a fluctuation of at least 6? Please provide calculations. (5 points)

- A:       yes
- B:       no
- C:       Don't have enough information to make this conclusion.

**Answer: B**

**Peak (multiple dose)**

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

**Trough (multiple dose)**

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

$$k_e = \ln 2 / t_{1/2} = 0.693 / 3 \text{ hr} = 0.231 \text{ (hr}^{-1}\text{)}$$

$$\text{Fluctuation} = C_{\max} / C_{\min} = 1 / e^{(-k_e \cdot (\tau - T))} = 1 / e^{(-0.231 \cdot (6 - 1))} = 3.17 \ll 6$$

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### Questions 10 -13

The following questions 10-13 are related to the equation shown below. Explain the meaning of the blocked parts of the equation in the following questions 10-13.

$$C_{p \min} = \frac{k_0}{CL} \cdot \frac{1 - e^{-k_e \cdot T}}{1 - e^{-k_e \cdot \tau}} \cdot e^{-k_e \cdot (\tau - T)}$$

**Question 10:** What information does  $k_0/CL$  provide (5 points)

$$\frac{k_0}{CL}$$

- A:  $C_{\max}$  after the first dose when given as iv infusion over the infusion time T.
- B: Trough concentration at steady state when given as infusion.
- C:  $C_{\max}$  after the first dose when given as iv bolus injection.
- D: Degree of accumulation.
- E: Concentration observed at steady state when first infusion would never stop.

**Answer: E**

	<b>Peak (single dose)</b>	<b>Trough (multiple dose)</b>
<b>A:</b>	$C_{\max(1)} = \frac{D}{CL \cdot T} \cdot (1 - e^{-k_e \cdot T})$	<b>B:</b> $C_{\min} = C_{\max} \cdot e^{-k_e \cdot (\tau - T)}$

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**Question 11:** What does this part of the equation tells us (5 points)

$$\frac{1}{1 - e^{-k_e \cdot \tau}}$$

- A: Quantifies to what degree steady state has been achieved for the first constant rate infusion with T being the infusion time of a short term infusion.
- B: Degree of accumulation observed at steady state when the drug is given as short term infusion with an infusion time T and a dosing interval tau.
- C:  $C_{\max}$  after the first dose when given as short-term infusion.
- D: Allows the calculation of the trough concentration, without this part of the equation, one would obtain the true  $C_{\max}$ .
- E: None of the above.

**Solution:** B

$$\frac{1}{1 - e^{-k_e \cdot \tau}} \text{ is accumulation factor}$$

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**Question 12:** What does this part of the equation allows us to calculate (5 points)

$$e^{-k_e \bullet (\tau - T)}$$

- A:  $C_{\max}$  after the first dose when given as an short-term iv infusion
- B: Allows calculation of Trough concentration at steady state from peak levels after multiple short-term infusions.
- C:  $C_{\max}$  observed some time after the stop of the infusion (the nurses  $C_{\max}$ , the one that will be send to the lab)
- D: Degree of accumulation
- E: None of the above

**Solution: B**

$t' = \tau - T$  is the time from peak to trough concentration

$$\therefore C_{trough} = C_{peak} e^{-k_e \bullet (\tau - T)}$$

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**Question 13:** For a lipophilic, protein bound, low extraction drug cleared by liver and kidney, select the **correct** answer(s) (5 points)

- 1: Increase in the liver blood flow will increase its clearance.
- 2: Liver enzyme inducers will increase its oral bioavailability
- 3: Increase in plasma protein binding will decrease its volume of distribution (assuming  $f_{uT}$  is the same)
- 4: Decrease in creatinine clearance will decrease its intrinsic clearance
- 5: Decrease in plasma protein binding will increase its oral bioavailability

Select the **correct** statement(s):

- A: 1, 2, 3, 4  
B: 1, 3  
C: 3  
D: 1, 2, 3, 5  
E: 3, 5

**Solution: C**

for low of extraction drug:

$$Cl = \frac{Q_H \cdot f_u \cdot Cl_{int}}{Q_H + f_u \cdot Cl_{int}} \approx f_u \cdot Cl_{int} \Rightarrow 1 \text{ is wrong}$$

$F \approx 1 \Rightarrow 2 \text{ and } 5 \text{ are wrong}$

$\therefore$  only C remained

also creatinine clearance will not affect hepatic intrinsic clearance

$\Rightarrow 4 \text{ is wrong}$

$$Vd = V_p + \frac{f_u}{f_{uT}} V_T = V_p + \frac{1}{f_{uT}} V_T - \frac{f_b}{f_{uT}} V_T \Rightarrow 3 \text{ is correct}$$

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**Question 14** (15 points)

A 50 year-old male is admitted to the hospital with a gram-negative abdominal infection. This patient is to be started on gentamicin given as a half-hour infusion. The patient weighs 72 kg and is 5'8". The serum creatinine for this patient is 1.1 mg/dL. The steady state peak concentration should be 10 mg/L with a trough of 1.5 mg/L. Design a dosing regimen based on population pharmacokinetics.

Clearance equals creatinine clearance

$V_d = 0.25 \text{ BW}$ . For  $V_d$  use ABW if the patient is obese. **Do not use the ke equation** for aminoglycosides.

- A. 120 mg TID
- B 180 mg QD
- C. 180 mg TID
- D. 130 mg BID
- E. none of the above

$$IBW = 50 + 2.3 \times 8 = 68.4 \text{ kg}$$

$$TBW = 72 \text{ kg} < 120\% IBW, \therefore \text{not obese}$$

$$Cl = CrCl = \frac{(140 - 50) \times 72}{72 \times 1.1} = 81.8 \text{ ml/min} = 4.9 \text{ L/h}$$

$$V_d = 0.25 \times 72 = 18 \text{ L}$$

$$K_e = Cl / V_d = 0.27 / \text{h}$$

$$\tau = \ln(10/1.5) / 0.27 = 7.04 \text{ hr} \approx 8 \text{ hr} \Rightarrow \text{TID}$$

$$D = C_{\max} \cdot Cl \cdot T \cdot \frac{(1 - e^{-k_e \cdot \tau})}{(1 - e^{-k_e \cdot T})} = 170 \text{ mg}$$

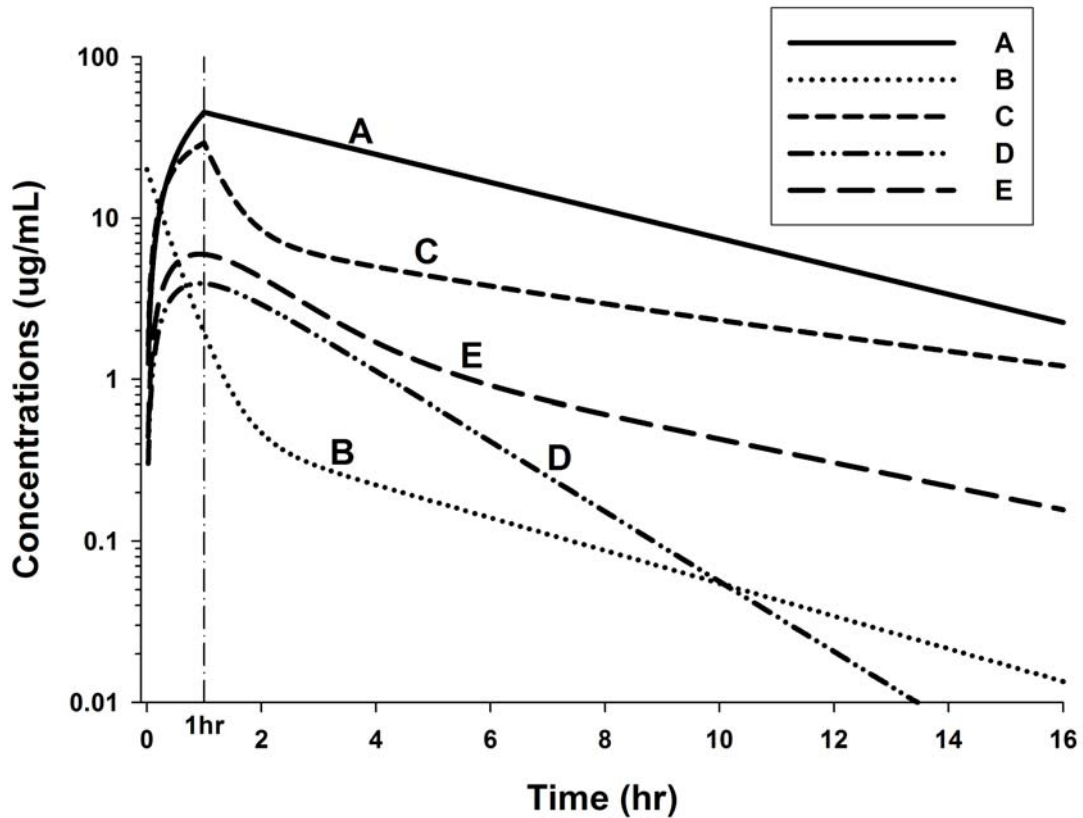
$\therefore$  C is correct (E is OK only if your calculation is right)

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**Question 15:** (5 points).

Drug-K follows a linear one-compartmental model. Which profile will represent Drug-K with 1-hr IV infusion in the following graph?



Select the correct graph.

- A.
- B.
- C.
- D.
- E.

**Solution: A**

$$1\text{-hr IV infusion} \Rightarrow C_{\text{peak}} = C_{1\text{h}}$$

linear one-compartmental model  $\Rightarrow$  a straight line after one hr in the semi-log plot

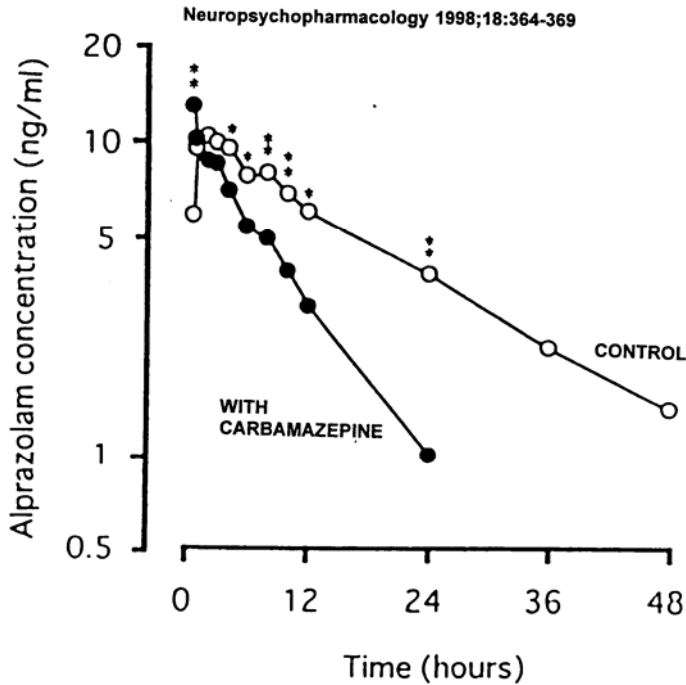
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**Question16:** (5 pts)

The same dose of Alprazolam was given either alone or with carbamazepine.

Explain what is going on by selecting the **correct** answer from the following list.



- 1: The clearance of alprazolam is increased in the presence of carbamazepine.
- 2: Alprazolam is likely to be a low extraction drug.
- 3: Carbamazepine is an enzyme inhibitor.
- 4: Carbamazepine decreases liver blood flow.

The **correct** answer(s) is(are):

A: 1

**B: 1, 2**

C: 3, 4

D: 2, 3

E: 1, 2, 4

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**Answer:**

- 1) The clearance of alprazolam is increased in the presence of carbamazepine.  
**True.** The alprazolam concentration decreases faster in the presence of carbamazepine → faster clearance
- 2) Alprazolam is likely to be a low extraction drug.  
**True.** The hepatic clearance of a low-extraction drug is dependent on the fraction unbound in plasma and intrinsic clearance. If an increase in the intrinsic clearance has a significant effect on the overall clearance, the drug is likely to be a low extraction drug.
- 3) Carbamazepine is an enzyme inhibitor.  
**False.** The alprazolam concentration decreases faster compared to the control → enzyme induction.
- 4) Carbamazepine decreases liver blood flow.  
**False.** There is no indication that it would do that.

**Questions 17- 21**

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

**Question 17 (5 points)**

T (A)      **F (B)**      Loading doses are mainly given for drugs with high  $k_e$  values

**Answer:**

In general, loading doses are given to achieve steady-state conditions right away. This becomes especially important for drugs with long half-lives (since it would take otherwise very long to reach steady-state) and consequently small  $k_e$  values.

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**Question 18 (5 points)**

**T (A)**    F (B)    A large volume of distribution during the elimination phase of a two-compartment body model might be due to the high metabolic clearance of this drug.

**Answer:**

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma concentration}}$$

The volume of distribution relates the amount of drug in the body to the respective plasma concentration. If a drug is cleared very fast from the central compartment, it might take some time for the drug to come out of the tissue. The actual amount of drug in the body is still high whereas the plasma concentration is low → high volume of distribution.

**Question 19 (5 points)**

T (A)    **F (B)**    “Linear pharmacokinetics” means that the plasma drug concentration versus time plots will result in a straight line.

**Answer:**

“Linear pharmacokinetics” is defined by a linear relationship between dose and AUC. Depending on the administration route, number of compartments and elimination kinetics, the concentration-time profile **can** show a linear relationship.

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**Question 20 (5 points)**

**T (A)**    F (B)    The dosing interval for multiple short term infusions is determined by the desired fluctuation, the half-life of the drug and the time over which the infusion is given.

**Answer:**

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

$\tau$  :    Dosing interval

T :    Infusion time

$$F = \frac{C_{\max(\text{SS})}}{C_{\min(\text{SS})}}$$

$$t_{1/2} = \frac{\ln 2}{k_e}$$

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**Question 21 (2 points) (Bonus Question)**

**I liked the new half-semester format.**

Please select the statement that best describes your opinion.

**All answers will be awarded 2 points.**

- A: I strongly agree
- B: I agree
- C: I don't care, either way is fine
- D: I disagree. I somewhat prefer the old format.
- E: I strongly disagree, I did not like it at all