Name: _____

UFID: _____

PHA 5127

Final Exam

Fall 2011

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.

Question/ ---Points

TOTAL _____134_/pts

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Question set I (10 pts)**:** A drug has been formulated as a capsule with true zero order release kinetics. The drug content per capsule is 100 mg. The release rate is 20 mg/hr. Release of the drug from the capsule is the rate limiting step for absorption. Oral bioavailability is 100%. The half-life of the drug is 1 hours. The patient receives one capsule every 8 hours. The fluctuation for this drug should be less than 3. Select whether the following statements are True (A) or False (B).

1: T F By looking just at the plasma concentration time profiles, one can not make the decision whether the drug was given orally with above formulation or as iv. Injection.

2: T F By looking just at the plasma concentration time profiles, one can not make the decision whether the drug was given orally with above formulation or as i.v. Infusion.

3: T F Assuming that the half-life of the drug is 1 hours, drug concentrations after 4 and 5 hours will be very similar.

4: T F If given every 8 hours, steady state will be observed already for the second dose.

5: T F The fluctuation for this drug should be smaller than 3. Dosing every 8 hours will be okay.

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Question set II (6 pts)**:** Select from the following statements whether the statements are True (A) or False (B). Assume Drug A is fully converted into its Metabolite B. Both are full agonists and show the same receptor affinity. V_d and tissue and plasma protein binding are identical. However, Metabolite B has a total clearance 10 times larger than that of Drug A. Assume drug A is given as an iv bolus injection.

6: T F Metabolite B's terminal slope will be steeper when plotted on semi-log paper than that of the parent, drug A.

7: T F Metabolite B and parent drug A will be equally contributing to the pharmacological effect.

8: T F k_e of the parent drug will be identical to the rate constant with which Metabolite B will be formed.

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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 that is cleared through metabolism (**low extraction drug**) and for which $\mathbf{f_u=f_{uT}}$ (even if f_u changes) one can state: The stronger the tissue and plasma protein binding the more pronounced the degree of accumulation.

10: T F For a lipophilic drug that is cleared through metabolism (**low extraction drug**) and for which $\mathbf{f_u=f_{uT}}$ (even if f_u changes) one can state: The stronger the tissue and plasma protein binding the smaller the fluctuation between peak and trough concentration.

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Question set IV (20 pts)**:**

The following applies to questions 11-14: A 60-kg patient is to be started on a **continuous intravenous infusion (the pump will continuously work, not multiple short term infusions)**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Drug from a previous dose is remaining in the body of the patient. This drug concentration is 10 mg/L directly before the start of the constant rate infusion.

Question 11: What rate of infusion **(k_0 for the following constant rate infusion**) should result in a steady state drug concentration of Cp_{ss} of 20 mg/L. **Round appropriately**. (5 pts)

A: 56 mg/ 0.5 hours

B: 56 mg/ 1 hours

C: 28 mg/hr

D: 28 mg

E: none of the above

Name: _____

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The following applies to questions 11-14: A 60-kg patient is to be started on a **continuous intravenous infusion (the pump will continuously work, NOT multiple short term infusions)**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Drug from a previous dose is remaining in the body of the patient. This drug concentration is 10 mg/L directly before the start of the constant rate infusion.

Question 12: If the Cp_{ss} is to be 20 mg/L, what should be the loading dose (mg) given as intravenous bolus injection. Remember the drug concentration before the start of the infusion was 10 mg/L. **Round appropriately**. (5 pts)

A: 400 mg

B: 800 mg

C: 1200 mg

D: 1220 mg

E: none of the above

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The following applies to questions 11-14: A 60-kg patient is to be started on a **continuous intravenous infusion (the pump will continuously work, NOT multiple short term infusions)**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Drug from a previous dose is remaining in the body of the patient. This drug concentration is 10 mg/L directly before the start of the constant rate infusion.

Question 13: What will be the plasma concentration 1 hour after start of the continuous infusion (**remember a loading dose was given**). **Round appropriately**. (5 pts)

A: 3.9 mg/L

B: 4.0 mg/L

C: 30 mg/L

D: 20 mg/L

E: None of the above.

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The following applies to questions 11-14: A 60-kg patient is to be started on a **continuous intravenous infusion (the pump will continuously work, NOT multiple short term infusions)**. From a previous regimen of the same drug, you estimate the patient's k_e is 0.07 h^{-1} and the V_d is 40 L. Drug from a previous dose is remaining in the body of the patient. This drug concentration is 10 mg/L directly before the start of the constant rate infusion.

Question 14: The infusion is continued for 3 days and the steady state concentration has been maintained at 20 mg/L. The physician wants to change the drug delivery to multiple short term infusions with a C_{max} of 20 mg/L and a trough of 10mg/L. (Hint: The first short-term infusions should be administered when the remaining plasma concentration reaches 10 mg/L). How many hours after the continuous infusion has been stopped should the first short-term infusion be given. **Round appropriately**. (5 points)

A: 1 h

B: 2 h

C: 8 h

D: 10 h

E: None of the above.

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Question set V (10 points)

Question 15: A 59 year old white male, patient is hospitalized for GI surgery. Before surgery you are asked to start the patient on gentamycin (an aminoglycoside; Vd=0.25 L/kg). Additional patient data are

Height 5 ft, 1 in

Weight: 52 kg

Serum creatinine: 1.3 mg/dl

Vd=0.25 L/kg

Provide an appropriate gentamycin maintenance dosing regimen (tau and Dose/dosing interval), assuming an infusion time of 1 hour. Assume a desired C_{peak} of 6 mg/L and a trough of 1 mg/L. **Round appropriately**. (10 points)

You selected a **tau** of:

A: 6 hours

B: 12 hours

C: 13 hours

D: 23 hours

E: 24 hours

Question 16.

You selected a **Dose** of:

A: 50 mg per dosing interval

B: 60 mg per dosing interval

C: 70 mg per dosing interval

D: 80 mg per dosing interval

E: None of the above.

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Question set VI (5 points) continuation of question set V

Question 17: Calculate a loading dose (given as an 1 hour infusion) for the previous situation.

A: 40 mg

B: 60 mg

C: 70 mg

D: 80 mg

E: None of the above.

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Question set VII continuation of question set V and VI

(9 points)

Peak and trough concentrations were determined around the fourth dose. Use the tau you have calculated if necessary. At 7:55 am C_{trough} was taken to be 0.4 mg/L; 8-9 am infusion of the drug; 9 am C_{peak} was taken to be 4.6 mg/L. (9 points)

18: T F Trough samples are always taken before peak samples.

19: T F Trough samples were taken before peak samples as steady state was not yet reached.

20: T F To calculate k_e for the patient one has to divide ln (4.6/0.4) by the time that passed from 7:55 am to 9:00 am, namely 65 minutes (about 1 hr)

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Question set VIII (10 pts)

Consider the following equation:

$$Cp_{\max} = \frac{k_o}{k_e V_d} \bullet \frac{1 - e^{-k_e * T}}{1 - e^{-k_e \bullet \tau}} \bullet e^{-k_e \bullet t'}$$

Select the true statements concerning the following part of the equation: (**10 points)**

$$1 - e^{-k_e \bullet \tau}$$

21: T F This part provides information on how much the first C_{max} (after the first short term infusion) is away from the steady level of a continuous infusion using the same k_o.

22: T F This part allows the calculation of the trough concentration after the stop of the infusion, as it converts the peak levels into the trough value

23: T F This part makes sure that the calculated plasma concentrations will increase with increasing infusion time.

24: T F This expression will be a number between 0 and 1.

25: T F This part of the equation will be identical for a given drug independent on whether the drug is given as multiple bolus injection or multiple short time infusion as long as the dosing interval is the same for both forms of administration.

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Question set IX (8 pts)

Consider the following relationship.

$$tau = \frac{Vd * \ln F}{CL} + t$$

26: T F This equation can be used for multiple short term infusions if t is set to 0

27: T F $F = C_{peak}/C_{trough}$

28: T F This relationship can be used to calculate the dosing interval for multiple short-term infusions if one adds the infusion time to the above expression.

29: T F Let's assume t=0. Using this equation for the calculation of the dosing interval of oral dosage forms is safe, as the fluctuation will be less than assumed during these calculations.

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Question Set X (15 points)

Question 30-34: Two patients received a **drug, which is only cleared by the liver,** as an iv bolus injection. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma (fu), volume of plasma (Vp) 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**
CLint	**8000**	**16000**
fu	**1**	**0.5**
Vp [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:		
30. (3 points)	**Vd [L] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
31. (3 points)	**CL [L/h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
32. (3 points)	**t1/2 [h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
33. (3 points)	**Peak [μg/ml] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
34. (3 points)	**AUC [μg/ml*h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1

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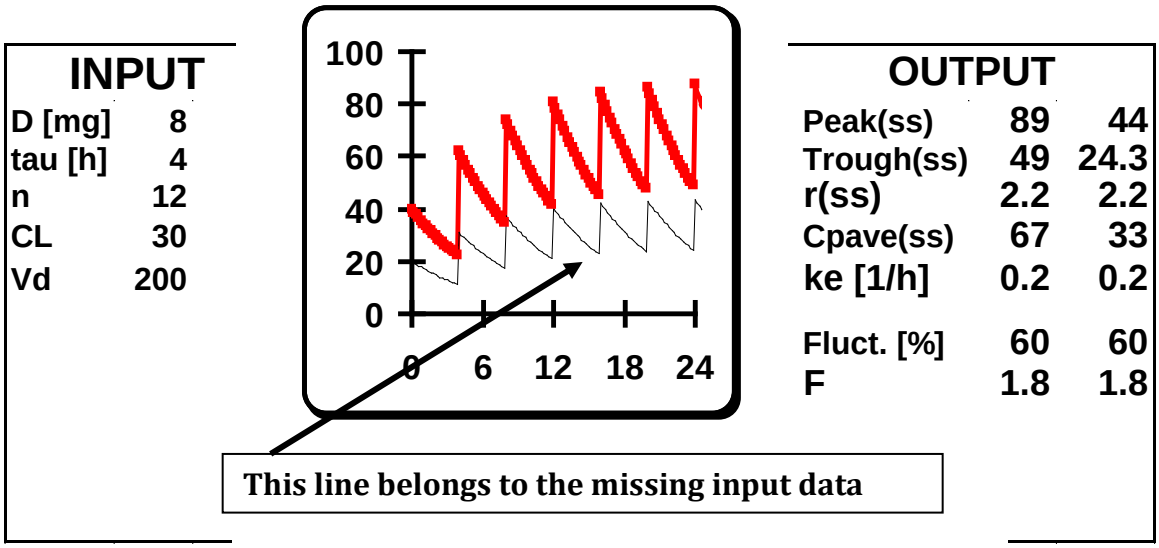
Question Set XI (6 points)

Question 35:

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

Name: _____

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Question Set XII (10 pts)

Question 36: Which of the following factors significantly **might** affect the renal clearance of methamphetamin:

1. plasma protein binding
2. Urine flow
3. Tissue protein binding
4. pH of urine
5. GFR

A: 1, 2, 4, 5

B: 1, 2, 4

C: 1, 5

D: 1, 3, 4, 5

E: all of the above combinations

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Question Set XIII (12 points)

Questions 37-40

Assume first-order processes. Mark whether the following statements are true (A) or false (B).

37: T F For a two compartment model drug, k10 is smaller than beta.

38: T F Assume that a drug is metabolized. The K_e^M of the metabolite is 20 h^{-1} while the k_e of the parent drug is 0.231 h^{-1}. If the plasma concentrations 10 hours after injection of the parent drug are 1 μg/ml for the parent drug and 0.5 μg/ml for the metabolite, the plasma concentrations 13 hours after injection of the parent drug must be 0.5 μg/ml for the parent drug and 0.25μg/ml for the metabolite. (Assume first-order kinetics for all elimination processes.)

39: T F For a two-compartment model drug, the volume of distribution just after administration of the drug is larger than that observed some time later.

40: T F Clearance and volume of distribution are always independent parameters.

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Question Set XIV

Questions 41-43 (9 points)

Select the most appropriate differential equation for the following situations. A given differential equation might have to be used more than once. Assume "**X"** is the amount of drug in the body (drug that has been absorbed and has not yet been eliminated) and "**A"** is the amount left at the absorption site.

A: $dx/dt = k_a - k_e$

B: $dx/dt = -k_a - k_e * X$

C: $dx/dt = -k_a * A + k_e * X$

D: $dx/dt = - k_e * X$

E: none of the above

41: A drug that is absorbed and eliminated through active transport. Both transporter systems are saturated (Select from A-E)

42: An immediate release tablet of a drug able to cross membranes easily and eliminated through renal filtration. (Select from A-E)

43: A high extraction drug given as an iv bolus injection showing linear pharmacokinetics (Select from A-E)

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)

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

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)

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

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)

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

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

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

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

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

<table>
<tr>
<td>If the dosing involves the use of I.V. bolus administration:</td>
<td>
For a single I.V. bolus administration:
$$C_0 = \frac{D}{V}$$
$$C = C_0 \cdot e^{-k_e t}$$
</td>
<td>
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$\rightarrow\infty$
at trough: t = τ
$$C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e\tau})}$$
$$C_{\min ss} = C_{\max ss} \cdot e^{-k_e\tau}$$
</td>
</tr>
<tr>
<td>If the dosing involves the use of I.V. infusion:</td>
<td>
For a single short-term I.V. infusion:
Since τ = t for C_{max}
$$C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
<td>
For multiple short-term I.V. infusion at steady state:
$$C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
</tr>
</table>

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:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left(e^{-k_et} - e^{-k_at}\right)$$

$$t_{\max} = \ln\left[\frac{k_a}{k_e}\right] \cdot \frac{1}{\left(k_a - k_e\right)}$$

For multiple oral doses:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left[\frac{e^{-k_et}}{\left(1 - e^{-k_e\tau}\right)} - \frac{e^{-k_at}}{\left(1 - e^{-k_}\right.}\right.$$

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