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

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).

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.

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 fu of vancomycin being 1. **(Use k_e= CL/Vd and TBW to calculate Vd)**

Question 11: Calculate the projected dosing interval. (5 pts)

A: 8 h

B: 12 h

C: 24 h

D: 36 h

E: none of the above

 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/Vd 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

Name: _____

UFID#: _____

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/Vd and TBW to calculate Vd)**

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

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 fu of vancomycin being 1. **(Use k_e= CL/Vd and TBW to calculate Vd)**

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

A: 900 mg

B: 1100 mg

C: 1300 mg

D: 1500 mg

E: none of the above

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 fu of vancomycin being 1. **(Use k_e= CL/Vd and TBW to calculate Vd)**

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 I 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

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.

Question set VII (10 pts)

Consider the following equation:

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

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_0/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

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.

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 (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
GFR	130	65
UF (Urine Flow)	1.5	3
f_u	1	0.5
f_{ut}	0.3	0.3
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

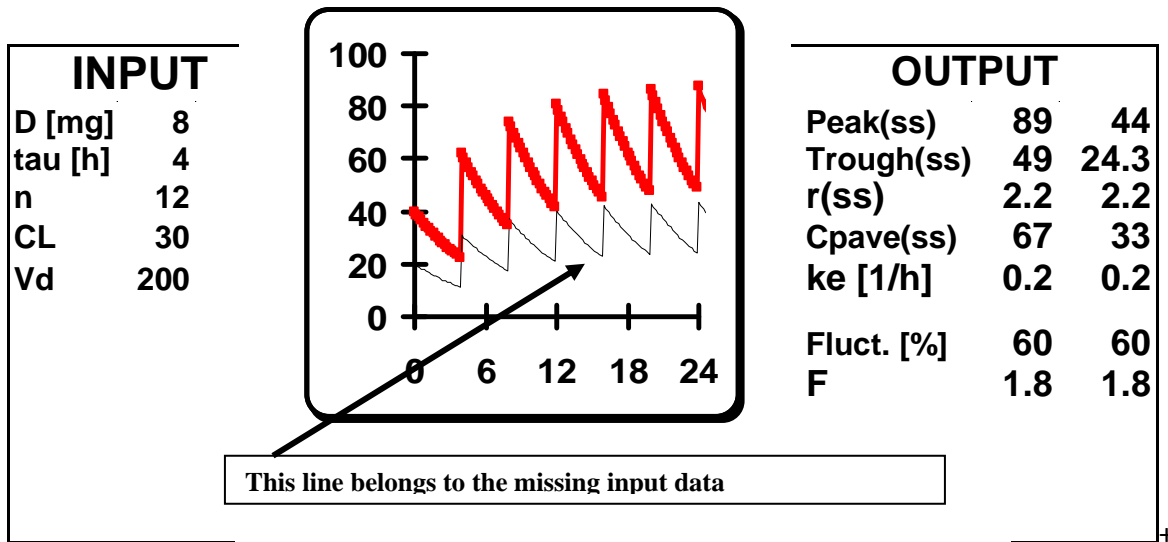| Question:		
26. (3 points)	Vd [L] of Patient 2	Larger (A), same (B), Smaller (C) than in Patient 1
27. (3 points)	CL [L/h] of Patient 2	Larger (A), same (B), Smaller (C) than in Patient 1
28. (3 points)	t1/2 [h] of Patient 2	Larger (A), same (B), Smaller (C) than in Patient 1
29. (3 points)	Peak [µg/ml] of Patient 2	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

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).

INPUT			OUTPUT		
D [mg]	8		Peak(ss)	89	44
tau [h]	4		Trough(ss)	49	24.3
n	12		r(ss)	2.2	2.2
CL	30		Cpave(ss)	67	33
Vd	200		ke [1/h]	0.2	0.2
			Fluct. [%]	60	60
			F	1.8	1.8

Plot axis: 100, 80, 60, 40, 20, 0 vs 0, 6, 12, 18, 24

This line belongs to the missing input data

Identify the one input parameter that differs (question 32)

A: Dose

B: Clearance

C: Volume of distribution

D: tau

E: none of the above

Question Set XI (10 pts)

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
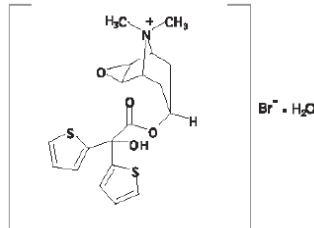
Tiotropium is not volatile and stable in plasma and other tissues. Thus, metabolism of tiotropium in the liver is negligible. No secretion through the bile is observed . Plasma protein binding is 70%. It has a low oral bioavailability (2-3%). The systemic availability after inhalation is 20%. Total clearance 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

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

Question 34-36 (2 points) (Bonus Questions)

34   T   F   I think the case studies are a waste of time

35   T   F   I do not benefit from the home works.

36   T   F   I missed a textbook for this class.

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)

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

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

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

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

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

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

Equations/Useful_pharmacokinetic_equ_5127

2

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

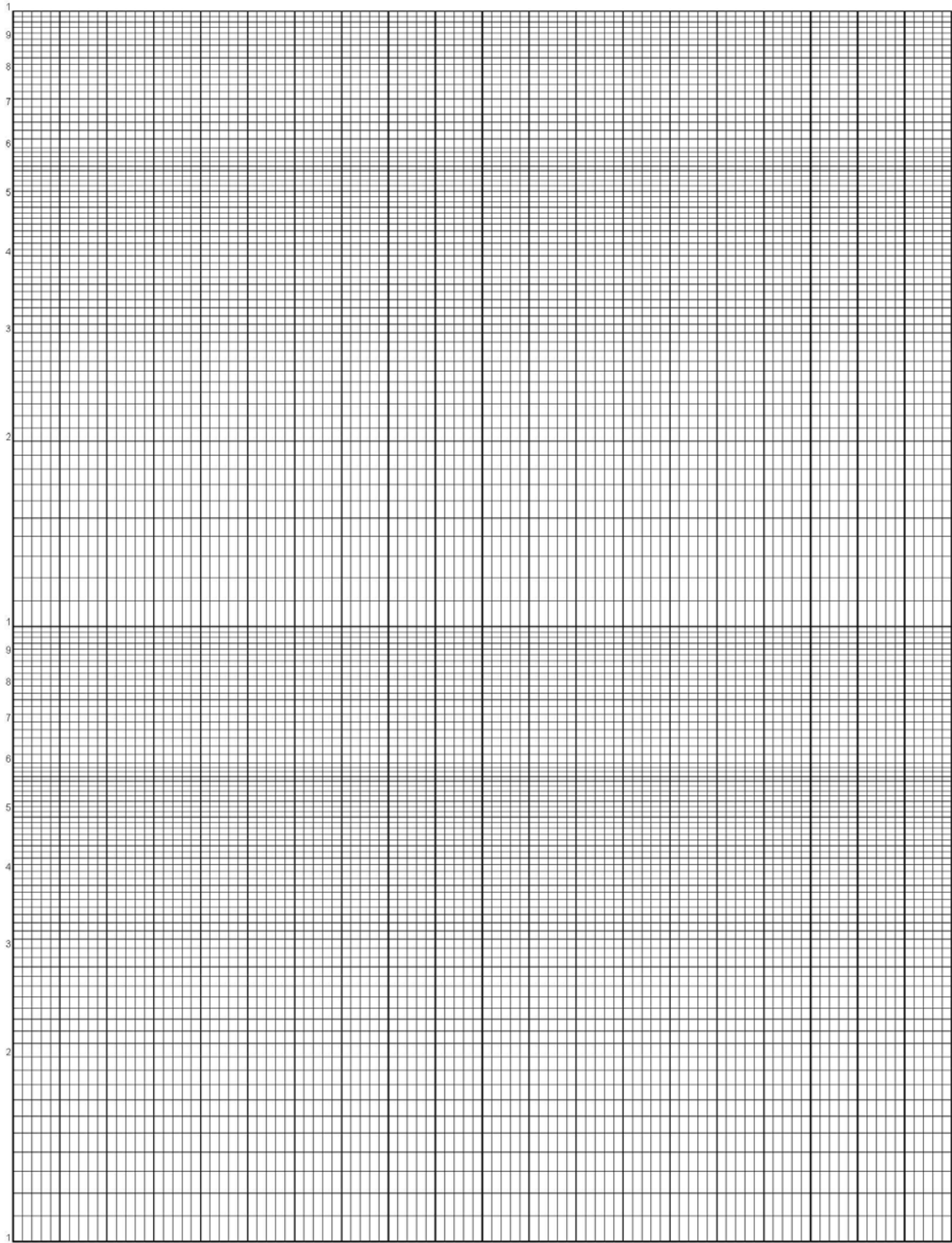|		
If the dosing involves the use of I.V. bolus administration:	**For a single I.V. bolus administration:** $$C_0 = \frac{D}{V}$$ $$C = C_0 \cdot e^{-k_e t}$$	**For multiple I.V. bolus administration:** $$Cn(t) = \frac{D}{V} \cdot \frac{\left(1 - e^{-n k_e \tau}\right)}{\left(1 - e^{-k_e \tau}\right)}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

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