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PHARMACY 324 PHARMACOKINETICS

Term #1 EXAM December 15th, 2005

Examination time is 3 hours

[This examination contains 14 pages (not including equations and extra graph paper)]

BUDGET YOUR TIME! WATCH THE VALUE OF THE QUESTIONS!
PLEASE PLACE YOUR NAME ON EACH PAGE

Please read the ensuing examination questions and data provided carefully before attempting any calculations. **Show all your calculations**. **Use the back of the exam pages if necessary**. All mathematical calculations should be written and organized in a logical, neat order. Double-check all your answers where possible. Please express your final answers to **three significant figures unless specified otherwise**. If necessary, graph paper can be found at the back of this examination.

NOTE: 1. This exam is worth **35% of the final overall grade** in PHM 324. Please note however that the value of all questions total **100** marks.

2. The allotment of marks for each question is indicated beside each question.

3. Potential equations needed to answer the questions are found in the equation booklet.

4. Graph paper is found in the body of the exam. If you require more, you must ask for it.

5. This exam is designed to test your knowledge of pharmacokinetics and possibly even teach you about its use in problem situations. Some issues may be presented which were not specifically dealt with in lectures, but the context of the question should make their meaning clear.

WHERE IT APPEARS NECESSARY,
STATE YOUR ASSUMPTIONS WHEN ANSWERING A QUESTION.
IF SUCH ASSUMPTIONS ARE VALID THEY WILL BE CONSIDERED IN THE GRADING.

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QUESTION 1: (35 marks)

In each of the following questions some information is given. Answer each question based on the DATA provided.

[1] **(i)** **DATA** At 2.5 hours after an IV bolus dose of 2000 mg of ceftriaxone the concentration is 10 mg/L. The concentration 3 half-lives later is

__1.25 ± 0.00___ mg/L. (2 decimal places)

[1] **(ii)** **DATA**

V = 100 L
Dose = 300 mg
K = 0.01 hr^{-1}

The $AUC_{0-\infty}$ is __300.00 ± 0.00__ mg*hr/L (2 decimal places)

$[]_0$ = dose/V = 300 mg/100L = 3 mg/L
$AUC_{0-\infty}$ = $[\ ]_0$ / K = 3 mg/L / 0.01 hr-1 = 300.00 mg*hr/L

[1] **(iii)** **DATA**

Following an oral dose of 100 mg the following concentrations were observed:

$C_{0.5}$ = 2.5 mg/L at time 0.5 hr
$C_{1.0}$ = 6.1 mg/L at time 1.0 hr

The $AUC_{0.5-1.0}$ is ____2.15 ± 0.00__ mg*hr/L (2 decimal places)

$AUC_{0.5-1.0}$ = (C1+C2)/2))(t2-t1) = ((2.5 + 6.1)/2)(1.0-0.5) = (4.3)(0.5) = 2.15

(iv) **DATA**

Following an IV bolus dose the following information is known:

Dose (IV) = 200 mg
K = 0.1155 hr-1
Volume = 60 L
Dosing Interval = 8 hr

[1] The concentration at 0.5 hours is ___3.15 ± 0.02___ mg/L (2 decimal places).
Ct = (dose/V) e(-kt) = 200 mg/60L)e(-0.1155* 0.5) = 3.146 mg/L

[1] The amount remaining in the body at 8 hours is 79.39 ± 0.02_ mg (2 decimal places).
C_{amt} = (dose) e(-kt) = (200 mg)e(-0.1155* 8) = 79.385 mg

[2] 3 hours after the 3rd IV bolus dose, the concentration is ____3.66 ± 0.02_ mg/L.
Ct = (dose/V) [((1-e(-nKJ)/(1-e(-KJ))]e(-kt) = 3.664 mg/L
Ct@ 3 hrs = 2.3572 Ct @ 11 hrs = 0.9356 Ct@ 19 hrs = 0.3714
Ct@ 3 hrs after 3rd dose = 2.3572 + 0.9356 + 0.3714 = 3.664 mg/L

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[1] (v) DATA ke = 0.06 hr^{-1}
kme = 1.5 hr^{-1}
K = 0.08 hr^{-1}
km = 0.01 hr^{-1}

The metabolite will have a terminal phase half-life of; 8.66 ± 0.01 hr.(2 decimal places).
Elimination will be rate limited by K. T½ = 0.693/0.08 = 8.6625 hr.

[1] (vi) DATA
Following an oral dose, the parent compound is metabolized and excreted into the urine and the following information is known:

ke = 0.07 hr^{-1}
kme = 1.5 hr^{-1}
ka = 0.08 hr^{-1}
km = 0.05 hr^{-1}

The parent compound will have a terminal phase half-life of:8.66 ± 0.01 hr. (2 decimal places).
Assume all individual rate constants are shown. K = ke+km = 0.05 + 0.07 = 0.12 hr-1
Therefore, the slowest exponential for parent compound is ka. T½ = 0.693/0.08 = 8.6625hr.

[2] (vii) DATA Dose = 200 mg
Cmax = 8.58 mg/L
Tmax = 3.8 hr
AUC = 93.154 mg*hr/L
F = 0.8
K = 0.1155 hr-1

The volume of distribution for the parent compound is: 14.87 ± 0.02 L. (2 decimal places).
Clearance = F*Dose/AUC and KV. Therefore, V = F*Dose/K*AUC
V = F*Dose/K*AUC = 0.8 * 200 / 0.1155 * 93.154 = 14.8708 L

[1] (viii) DATA

Dose (IV - bolus)	= 200 mg
Volume	= 50 L
Half-life	= 5 hr
Dosing Interval	= 8 hr

The Maximum Accumulation Factor is __1.492 ± 0.008 . (3 decimal places).
K = 0.693/5 = 0.1386 hr-1
Equation: MAF = (1/1-e(-KJ)) = (1/(1-e-(0.1386*8)) = 1.4924

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[2] **(ix)** **DATA** Dose (IV - bolus) = 200 mg
Volume = 50 L
Half-life = 5 hr
Dosing Interval = 8 hr

The end of interval (trough) concentration at Steady State is: 1.97 ± 0.01 mg/L. (2 decimal places).
K = 0.693/5 = 0.1386 hr-1
Equation: Ct = (dose/V) [((1-e(-nKJ)/(1-e(-KJ))]e(-kt) = 1.970 mg/L
By Summation: Ct@ 8 hrs = 1.3198 Ct@ 16 hrs = 0.4355
Ct@ 24 hrs = 0.1437 Ct@ 32 hrs = 0.0474
Ct@ 40 hrs = 0.0156 Ct@ 48 hrs = 0.0052
Ct@ 8 hrs after SS dose = 1.3198+0.4355+0.1437+0.0474+0.0156+0.0052 = 1.9672 mg/L

[1] **(x)** **DATA** Dose = 200 mg
Volume = 50 L
Half-life = 2 hr
Ka = 0.2 hr-1
Dosing Interval = 8 hr

Following multiple 200 mg oral doses given every 8 hours, 90% of the eventual steady state concentrations is achieved within __11.43 to 11.51_ hours.
K = 0.693/2 = 0.3465 hr-1 and ka = 0.2 hr-1. Therefore, this profile is rate limited by ka and time to SS will be determined by ka. 90% of eventual steady state occurs after 3.322 T½.
T½ = 0.693/0.2 = 3.465 hr. 90% of SS after 3.322 half-lives = 3.322x3.465 = 11.51 hr.
or 90% of SS after 3.3 half-lives = 3.3x3.465 = 11.43 hr.

[1] **(xi)** **DATA** Dose, oral = 200 mg
F (fraction abs.) = 0.9
Volume = 50 L
Half-life = 7 hr
Ka = 1.0 hr-1
Dosing Interval = 8 hr

True or False. Following multiple 200 mg oral doses given every 8 hours, the eventual steady state trough concentrations ($Cmin_{SS}$) can be determined accurately* by MAF.

T or F *circle* * accurately means within 10%.

MAF works well for iv bolus dosing and immediate release (rapidly absorbed) products. The K value is 0.099 hr-1, which indicated a ka/K ratio of 10, also an indicator that MAF will work. Furthermore, there is less error with Cmin than Cmax. Therefore, **True** is the correct answer.
It is not intended that the student complete the calculation, but actual comparison of estimated MAF and observed from multiple dosing equation indicates that the error is ~0.03%.

(xii) **DATA** Following a 500 mg IV bolus dose, samples are drawn and the blood concentration determined. Analysis reveals that the concentration can be described by the following equation:

$$C_t = 16.04\ e^{-5.0(t)} + 3.96\ e^{-0.2(t)}$$

[1] What is the initial concentration, immediately following the bolus dose 20.00 ± 0.00 mg/L
[1] What is the initial distribution space (V1) = 25.00 ± 0.00 L 500 mg / 20 mg/L
[1] What is the Area Under the Curve (0-∞) ($AUC_{0-\infty}$) = 23.01 ± 0.01 mg*hr/L ($A/\alpha + B/\beta$)

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(xiii) DATA Following a 500 mg IV bolus dose, samples are drawn and the blood concentration determined in 4 different patients. Analysis reveals that the concentrations in each patient can be described by one of the following equations, which match 1 of the 4 graphs. Match the equations & graphs.

Concentrations are shown as open diamonds and residuals are shown as open squares

This problem can be solved by visual inspection of the profiles and the values A, B, α and β. It is most easily completed by an evaluation of B.

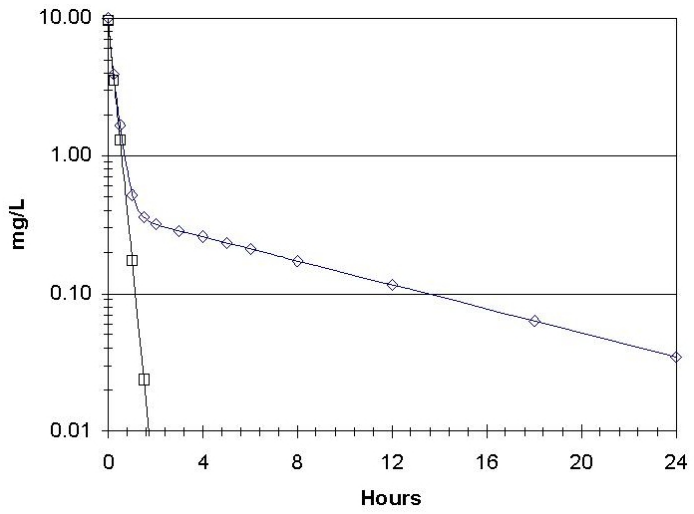
[1] Patient A $C_t = 7.9\ e^{-1.0(t)} + 2.1\ e^{-0.05(t)}$ which corresponds to graph 1, 2, **3**, or 4

[1] Patient B $C_t = 5.6\ e^{-0.5.0(t)} + 4.5\ e^{-0.05(t)}$ which corresponds to graph 1, 2, 3, or **4**

[1] Patient C $C_t = 9.6\ e^{-4.0(t)} + 0.39\ e^{-0.1(t)}$ which corresponds to graph **1,** 2, 3, or 4

[1] Patient D $C_t = 9.2\ e^{-2.0(t)} + 0.79\ e^{-0.1(t)}$ which corresponds to graph 1, **2**, 3, or 4

1



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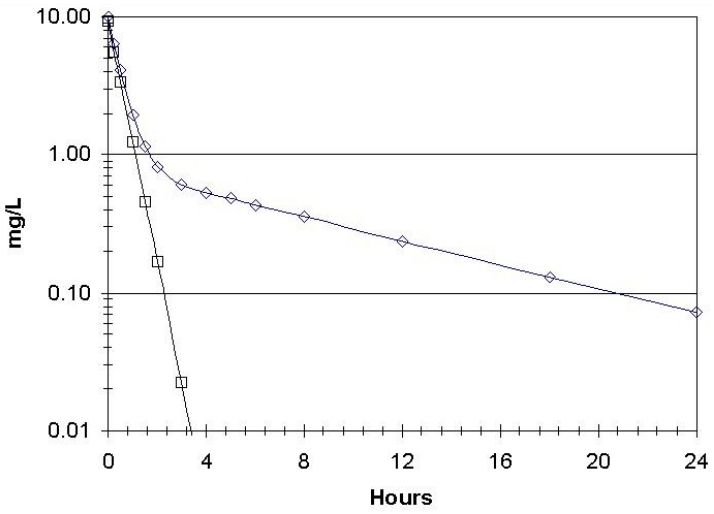

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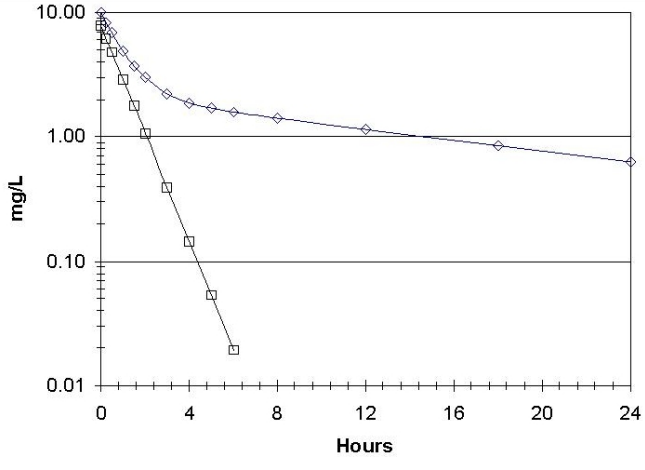

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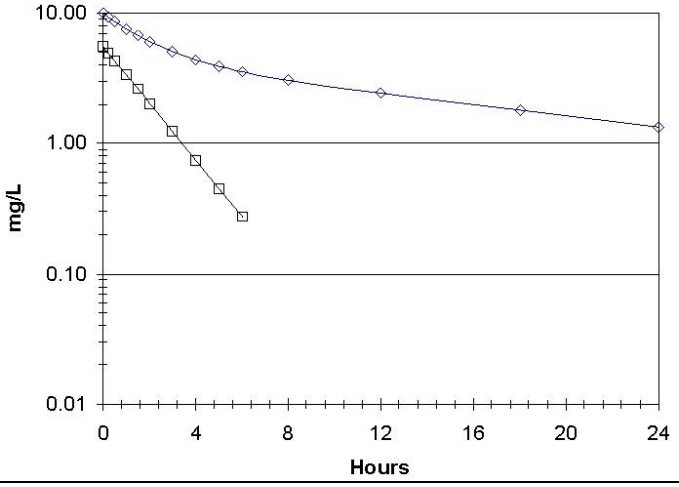

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(xiv) DATA Following a 500 mg oral dose, samples are drawn and the blood concentration determined in 4 different patients. Analysis reveals that the concentrations in each patient can be described by one of the following equations, which match 1 of the 4 graphs. Match the equations & graphs.

Concentrations are shown as closed diamonds and residuals are shown as open squares

This problem can be solved by visual inspection of the profiles and the values α (residual slope) and β (terminal phase slope). The half-life is reported to 2 hours, (K = 0.3465 hr-1) but graph 2 has a slower terminal phase because ka rate limits this profile (only ka small than 0.3465 is for patient D. Assign other by evaluation of α.

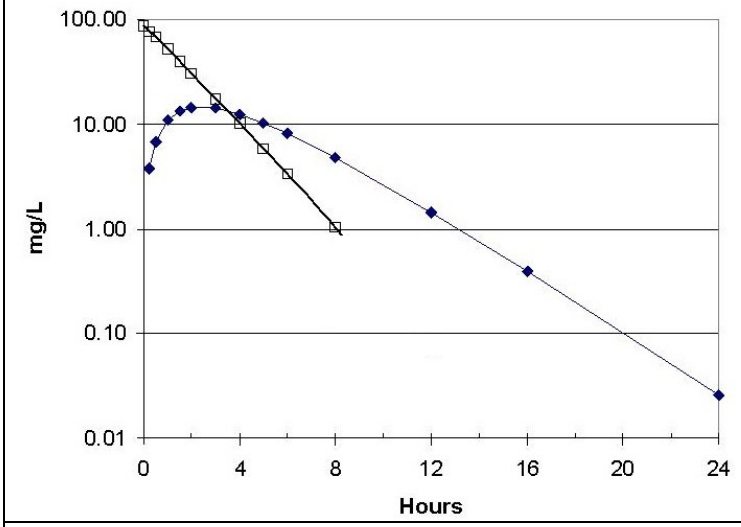
[1] Patient A ka = 2 hr^{-1} and Half-Life = 2 hrs, corresponds to graph 1, 2, **3**, or 4

[1] Patient B ka = 1 hr^{-1} and Half-Life = 2 hrs, corresponds to graph 1, 2, 3, or **4**

[1] Patient C ka = 0.5 hr^{-1} and Half-Life = 2 hrs, corresponds to graph **1,** 2, 3, or 4

[1] Patient D ka = 0.1 hr^{-1} and Half-Life = 2 hrs, corresponds to graph 1, **2**, 3, or 4

1



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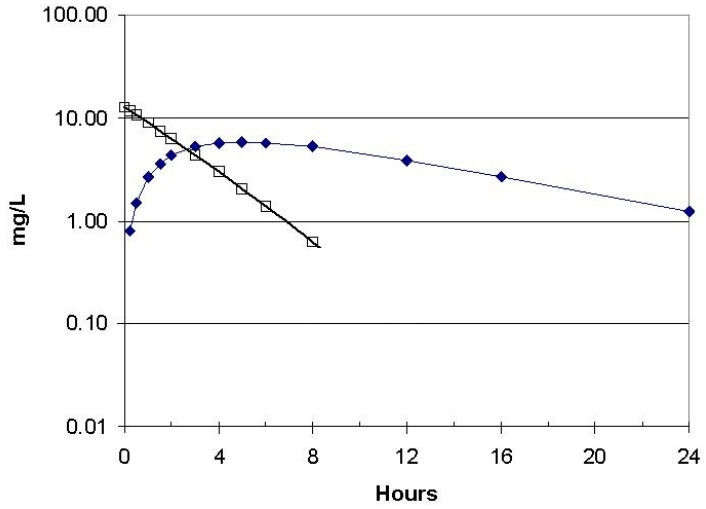

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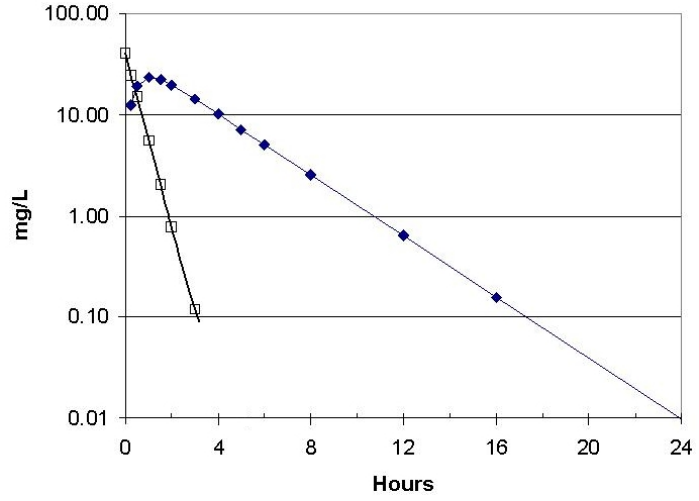

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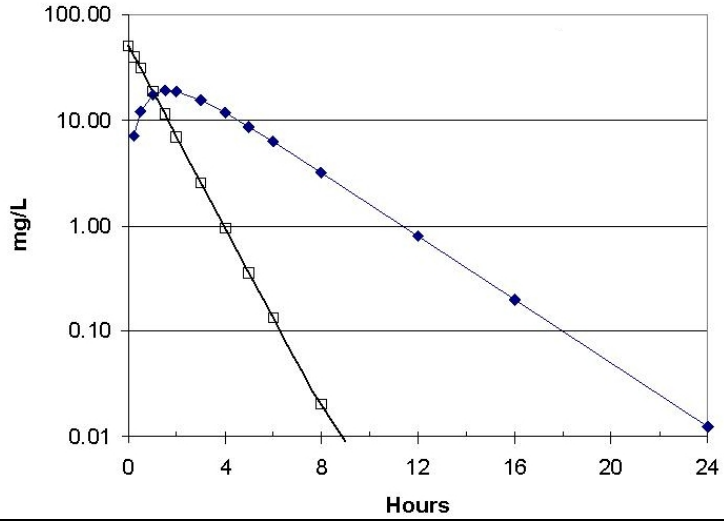

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[1] (xv) DATA Infusion Rate = 50 mg/hr
Volume = 72.15 L
Clearance = 10 L/hr

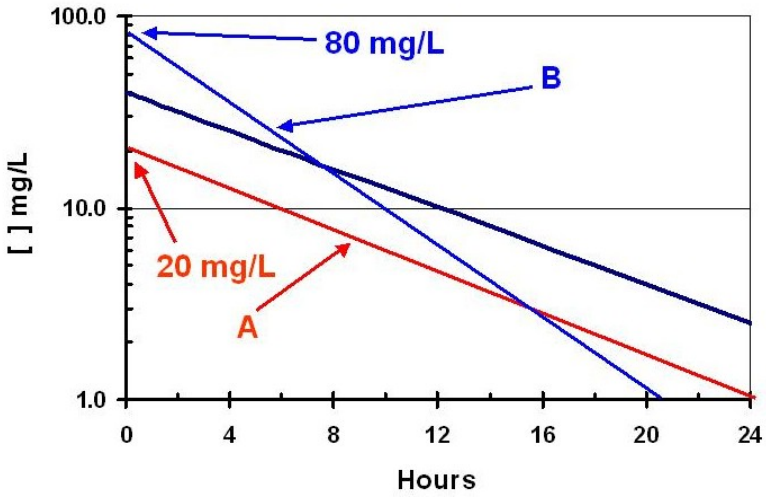
At Steady State (t > 72 hr) the concentration will be 5.00 ± 0.05 mg/L (2 decimal places)
By Equation: Ct = (K0/(KV))*(1-e-Kt) where t is infusion duration.
If we use 72 hrs as t, then Ct = 4.9998 mg/L. If we assume t is large, then the (e-Kt) approaches zero and (1-e-Kt) approaches 1. This will yield a concentration of 5.0 mg/L

[1] (xvi) DATA Dose = 200 mg
Infusion duration = 4 hr
Clearance = 10 L/hr
Half-life = 5 hours

Two hours ***after the end*** of a 4-hour infusion the concentration is 1.61 ± 0.05 mg/L (2 decimal places).
By Equation: Ct = (K0/(KV))*(1-e-Kt)*(e-Kt')
where t is infusion duration and t' is the post infusion time
Ct = 1.613 mg/L

(xvii) DATA Following a 400 mg IV dose of moxifloxacin to Mr. BB, the following serum concentrations are observed. The graph below plots these concentrations.

[1] (a) What is the Volume of Distribution (L)?
Initial Conc = 40 mg/L
Volume = Dose/ Conc
= 400 mg / 40 mg/L
= 10 L ± 1.0



[1] (b) What is K (hr-1)?
By inspection initial concentration is 40 mg/L and it declines to 10 mg/L after 12 hours (2 half-lives) or a half-life of 6 hours. ± 0.5 hr. The corresponding K value is 0.1155 hr^{-1} (range 0.1066 – 0.1260 hr^{-1})

[1] (c) What is the total clearance of ciprofloxacin in Mr. BB.(L/hr)?
Clearance = KV
= 0.1155 x 10 = 1.155 L/hr ± 0.5

On the graph above, draw 2 more lines clearly identified as line **A** and **B**.

[2] (d) **Draw Line A** which will represent a moxifloxacin profile where the distribution space is twice that observed in Mr. BB but the half-life is identical to that observed in Mr. BB.
Line A must have an intercept of 20 mg/L and a slope parallel to the original line

[2] (e) **Draw Line B** which will represent a moxifloxacin profile where the distribution space is half that observed in Mr. BB but the clearance is identical to that observed in Mr. BB.
Line B must have an intercept of 80 mg/L and a greater slope than the original line (intersection of the x-axis *close* to coordinates of 1 mg/L & ~ 20 hrs is acceptable.

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QUESTION 2. (20 Marks)

A patient is given an IV bolus dose of 400-mg of ketorolac. One blood sample is drawn and the plasma concentration determined as is the concentration for 2 urine collections. The observed data is shown in the table below.

Time (hr)	Plasma Concentration (mg/L)	Urine Collection Period (Start – Stop in hrs)	Excretion Rate (mg/hr)
1	4.45		
2		0 – 2 hours	33.0
4			
6		2 - 6 hours	23.5
8			

[2] (i) Calculate the elimination rate constant (K) _0.113 ± 0.002___ hr-1.

This must be determined from urine data, specifically the slope of the Ln (or L)og of the excretion rate plotted at the midpoint of the collection interval. (Ln(33)-Ln(23.5))/ (4-1) = 0.113169 hr-1. when using Log the slope must be multiplied by 2.303 to get the K value.

[2] (ii) Calculate the volume of distribution (L). 80.27 ± 0.50 L

with a K value of 0.113 hr-1, the initial concentration is estimated as 4.98 mg/L (range: 4.96 – 5.00 mg/L). Given a 400 mg bolus dose the volume is estimated as 80.27 L (range 80.00 –80.65 L)
2 marks for the correct answer. With the wrong answer, **1 mark** will be awarded if **both** equations are provided (half mark each): $C_0 = e^{(+Kt)}$ where t = 1 hr and Volume = Dose/C_0.

[2] (iii) What is the $AUC_{0-\infty}$ (mg*hr/L)? __44.03 ± 2.0__ mg*hr/L

Given the initial concentration of 4.98 mg/L (range: 4.96 – 5.00 mg/L) and a K value of 0.113 hr^{-1} (range (0.110 – 0.115 hr-1), the AUC is 44.033 mg*hr/L (range: 43.1 – 45.45 mg*hr/L)
2 marks for the correct answer. With the wrong answer, **0.5 marks** will be awarded if this equation is provided: $AUC_{0-\infty} = C_0/K$.

[2] (iv) Calculate Total Body Clearance (L/hr). 9.084 ± 0.500 L/hr

Clearance can be calculated by either K xV or Dose/AUC. The central answer based on possible estimates of both methods is 9.0840 L/hr (range: 8.800 – 9.2742 L/hr). **2 marks** for the correct answer. With the wrong answer, **0.5 marks** will be awarded if either one of these two equations is provided: $Cl_T = K \times V$ **or** Cl_T = Dose/AUC.

[2] (v) At 8 hour, how much drug (mg) remains in the body? _161.76 ± 5.00__ mg

with a K value of 0.113 hr-1, and a 400-mg dose given by IV bolus, the amount remaining at 8 hours is: Amount (t) = dose e-kt where t = 8 hours. The central answer based on possible estimates is 161.76 mg. (range: 159.408 – 165.913mg). **2 marks** for the correct answer. With the wrong answer, **0.5 marks** will be awarded if the equation is provided: $C_0 = e^{(-Kt)}$

[4] (vi) The renal clearance of ketorolac is _7.41 ± 0.20__ L/hr.

Renal clearance is calculated based on the slope of the line between urinary excretion rate and the mid-point plasma concentration. However, although there is only 1excretion rate (33.0 mg/hr) and mid point plasma concentration (4.45 mg/L), this can still be used to estimate renal clearance. This graph should go through an excretion rate of 0 with a plasma concentration of zero.
Therefore, Renal clearance = 33.0 / 4.45 = 7.416 L/hr

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It is also possible to estimate the concentration at 4 hours and with a range in potential K values, this will yield a range of renal clearance values from 7.317 to 7.595 L/hr.
4 marks for the correct answer. With the wrong answer, **1 mark** will be awarded if the proper procedure or equation is provided: Cl_R = Excretion Rate / Mid Point Concentration.

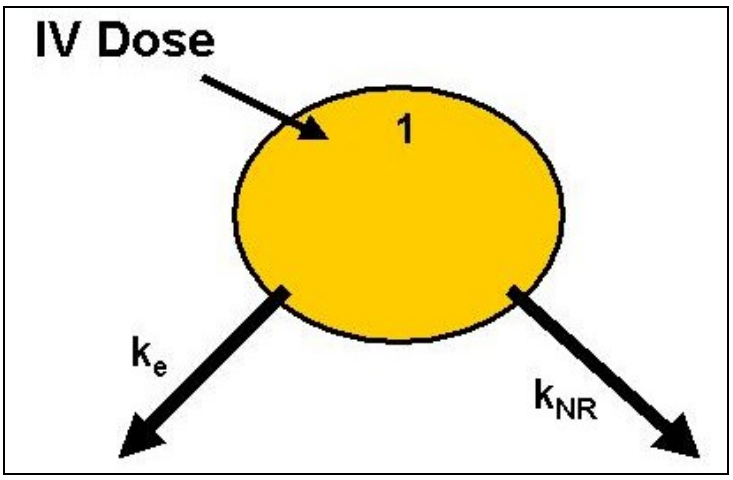
[2] **(vii)** The proportion of ketorolac excreted unchanged in the urine is 81.63 ± 5.0 %.
This can be calculated based on the ratio of clearances (renal : total body), the ratio of $Ae_{0-\infty}$ to Dose or the ratio of ke/K. However, we only have information to allow calculation of the ratio of clearances (renal: total body).

Therefore, the proportion of ketorolac excreted unchanged in the urine is:
Proportion = 7.416/9.084 = 0.8163, with a potential range of 0.7889 to 0.8631.
And when expressed as a percent the central value is 81.63% with a range of 78.89 – 86.31%
2 marks for the correct answer. With the wrong answer, **0.5 marks** will be awarded if the proper procedure or equation is provided: Percent = 100 x Cl_R / Cl_T.

[4] **(viii)** Based on this information available in the Table on the previous page and that which you have determined through calculation, draw a model labeled with the rate constants (eg. ke, km or knr) ***and*** their values with units of hr^{-1}.

Based on a K value of 0.1132 hr-1 (range 0.1100 – 0.1150 hr-1),
the ke value is ~81% of this value: 0.0924hr-1 (range 0.0868 – 0.0993 hr-1)
And the knr value will be the difference between K and ke … therefore:

	Central answer	Lowest acceptable	Highest acceptable
K (hr-1)	**0.1132**	**0.1100**	**0.1150**
ke(hr-1)	**0.924**	**0.7889**	**0.0993**
By difference			
knr (hr-1)	**0.0208**	**0.0208**	**0.0157**



3 marks given for the labeled model, **1** for a single circle or square, **1** showing IV bolus or IV or IV dose input, **1** for two elimination pathways of ke and knr (half mark each) and **1** mark given for the calculation of knr and placing this value somewhere on the page.

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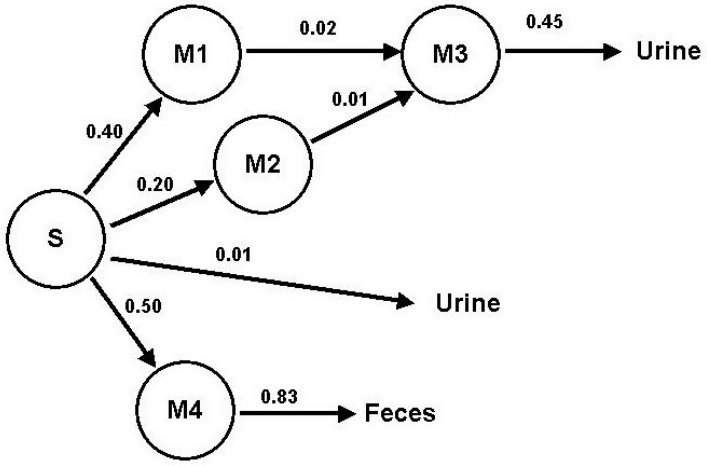
QUESTION 3 (16 Marks)

Selegiline (S) is excreted into the urine unchanged and is metabolized to 3 different metabolites (amphetamine, methamphetamine and N-desmethyl deprenyl) that appear in both urine and feces. After extensive research, the following metabolic scheme has been determined following a 10-millimole IV dose. The population average first order rate constants for each process are shown with units of hr-1.



[10] (i) Complete the table below based on this metabolic scheme.

Compound	Total Amount Excreted (millmole)	Excretion Location
S	0.01/ (0.40+020+0.01+0.50) = 0.01/1.11 =0.009 10 millimoles x 0.9% = **0.09 millimoles**	Urine
M1	Zero	Not Excreted
M2	Zero	Not Excreted
M3	0.04 + 0.20/ (0.40+020+0.01+0.50) = 0.60/1.11 =0.5405 10 millimoles x 0.5405 = **5.41 millimoles**	Urine
M4	0.50/ (0.40+020+0.01+0.50) = 0.50/1.11 =0.4505 10 millimoles x 0.4505 = **4.50 millimoles**	Feces

[2] (ii) The Half-life of selegiline averages ____0.62 _± 5.0____ hr in the population studied.
The overall K value for selegiline is (0.40 + 0.20 + 0.01 + 0.50) = 1.11 hr-1. This translates into a half-life of 0.624 hrs.

[2] (iii) The terminal elimination half-life of M4 is: _0.8349_ ± 0.0051__ hr.
The rate limiting step of M4 into the feces is the smaller of the K (1.11) and kme (0.83). Therefore kme rate limits the process producing a terminal elimination half-life of 0.8349 hrs

[2] (iv) At 4 hours after an IV dose, which compound(s) are present in plasma?
More than 90% of the amount of M1 and M2 formed would still be in plasma at 4 hours. **1 mark for each of these compounds.** Only about 1% of the initial concentration of selegiline would be present. No marks for selegiline. M3 & M4 are excreted rapidly once formed and so it is likely that either is never detected in plasma. No marks for M3 or M4. If a student lists four or all compounds … they should be awarded only 1 mark (1 each for M1 & M2 less ½ for each of 2 others).

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QUESTION 4 (15 marks)

200-mg of ketoconazole, an antifungal agent of the imidazole class, was administered to 20 healthy volunteers under 3 different conditions. Each condition (treatment) was separated by 1 week. The three conditions/treatments were;

(i) A single 200-mg dose administered by rapid IV bolus. Blood samples were drawn following the dose and for the next 8 hours (0-8 hrs).

(ii) Following an overnight fast, 200 mg was administered orally with 250 mL of water every eight hours. Four doses were administered. Blood samples were drawn following the dose administered at 24 hours and the concentrations determined over the following 8-hour period. (24-32 hrs)

(iii) Following an overnight fast, 200 mg was administered orally with 250 mL of a cola beverage every eight hours. Four doses were administered. Blood samples were drawn following the dose administered at 24 hours and the concentrations determined over the following 8-hour period. (24-32 hrs)

Blood samples drawn during the study were analysed and the serum ketoconazole concentration determined. Mean pharmacokinetic parameters calculated from the 20 subjects for each dose are provided in the table below. You may assume a 1-compartment model with first order elimination for all doses and first order absorption for all oral doses.

Average pharmacokinetic results following 200-mg doses of ketoconazole.

	200-mg single Dose IV Bolus	**200-mg oral Capsule – Fasting with 250 mL water Data Following 4th dose**	**200-mg oral Capsule – Fasting with 250 mL Cola Data Following 4th dose**
Cmax (mg/L)	13.33	4.42	7.55
Tmax (hr)	0.01	2.50	1.5
Half-life (hr)	2.0	2.0	2.0
AUC_{0-8} (mg*hr/L)	36.06	28.84	34.57
$AUC_{0-\infty}$ (mg*hr/L)	38.48	Not reported	Not reported
ka (hr-1)	na	0.25	1.14

[2] **(i)** Based on the IV data, the total clearance of ketoconazole is __5.20_ ± 0.01_ L/hr.
Clearance for IV data can be calculated from Dose/AUC
Cl = 200-mg/38.48-mg*hr/L =5.198 L/hr
1 mark for the correct formula and **1** mark for the correct answer

[3] **(ii)** The absolute bioavailability (%) of ketoconazole when administered with 250 mL of **water** is: __74.95_ ± 0.10_ %
Bioavailability can be calculated from a comparison of AUC_{0-inf} following singles doses, or a comparison of AUC_{0-J} (where J is the dosing interval) at steady state. Since AUC_{0-J} at steady state and AUC_{0-inf} following a single dose are equal, then bioavailability may also be calculated based on a comparison of AUC_{0-J} at steady state and AUC_{0-inf}.
Therefore, F= 28.84/38.48 = 0.7495 or 74.95%
3 marks for the correct answer or **1** mark for using AUC for each of the water and IV treatments.

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[3] **(iii)** The relative bioavailability (%) of ketoconazole administered with 250 mL of water relative to 250 mL of **COLA** is: 83.42 ± 0.10 or 119.87 ± 0.10 %

Bioavailability can be calculated from a comparison of AUC_{0-J} (where J is the dosing interval) at steady state.

Therefore, F= 28.84/34.57 = 0.8342 or 83.425%

Since the question could be interpreted or calculated as the inverse F= 34.57/28.84 = 1.1987 or 119.87%

3 marks for the correct answer or **1** mark for using AUC_{0-J} for each of the water and cola treatments.

[2] **(vi)** The observed terminal half-life following the oral dose administered with 250 mL of water is : 2.77 ± 0.01 hr.

The half-life of ketoconazole is 2 hours. This corresponds to a K value of 0.3465 hr-1. In the "with water only fasting treatment", the ka is reported as 0.25 hr-1. This is smaller that 0.3465 hr-1, indicating that in this treatment the concentration – time profile is rate limited by absorption. Therefore, the terminal phase exponential will have a value of 0.25 hr-1 which corresponds to a half-life of 2.772 hours.

2 marks for the proper half-life. If half-life is wrong, **1** mark can be awarded for using ka as the terminal phase exponential.

[2] **(viii)** If a patient was counseled to ingest all doses of ketoconzaole with 250 mL of COLA rather than WATER, Relative to an ketoconazole dose administered with 250 mL of water, explain the effect on the rate and extend of ketoconazole absorption when it is administered with a cola beverage.

Administration of ketoconazole with COLA increases both the rate (as measured by ka or Cmax) and extent (as measured by AUC) of absorption.

0.5 mark for indicating that COLA increases RATE and **0.5** marks for indicating that is explained by an increase in Cmax or an increase ka

0.5 mark for indicating that COLA increases EXTENT and **0.5** marks for indicating that is explained by an increase in AUC.

[3] **(viii)** If a patient was counseled to ingest all doses of ketoconzaole with 250 mL of COLA rather than WATER, Relative to an ketoconazole dose administered with 250 mL of water, what effect would likely be encountered in the Peak-Trough fluctuation?

Administration of ketoconazole with COLA increases both the rate (as measured by ka or Cmax) and extent (as measured by AUC) of absorption. Tmax also occurs earlier such that the higher observed peak (Cmax = 7.55 mg/L) occurs 1 hour earlier than the lower peak of 4.42 mg/L. Assuming linear decline in concentration from the peak, the COLA treatment would then have 6.5 hours with a half-life of 2 hours before the end-of-interval trough concentration was obtained (~0.8 mg/L … in reality 1.10 mg/L). However, ketoconazole administered with water has a peak of 4.42 mg/L at 2.5 hours and the terminal phase is rate limited by absorption, such the end of interval concentration could be estimated to be 0.657 (in reality 2.3 mg/L). The absolute Peak Trough Fluctuation is lower for ketoconazole administered with water.

1 mark for indicating that COLA peaks sooner and/or has a greater amount of time to fall to the trough. **1 mark** for indicating that water has a slower terminal phase and less time to fall to the trough and **1 mark** for indicating that the peak trough fluctuation would be lower for ketoco0nazole administered with water.

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QUESTION 5 (14 Marks)

A 40-mg single oral dose of nifedipine PA (Adalat®) is given to a patient. Blood samples were drawn and the plasma concentrations are shown below.

Time (hr)	Concentration (ng/mL)
0	0.000
0.25	10.13
0.5	19.92
0.75	29.38
1	38.51
1.5	55.85
2	72.03
3	62.71
4	54.59
5	47.53
6	41.38
8	31.36
12	18.01
16	10.35
24	3.41
32	1.13

[2] **(i)** On the next page, a piece of 2 – cycle semi-log paper can be found. Graph data on this paper. Label each axis appropriately.

0.5 marks for indicating a y-axis label of "ng/mL" or "concentration ng/mL" and **0.5 marks** if the x-axis label is marked "time", "hours" or time in hours" or equivalent. **1 mark** for accurately plotting the graph. **No marks** deducted if the 32 hr concentration is not plotted as it will not affect the graph. Graph should show a single terminal phase (straight line) from 2 hours and a concentration of 72 ng/mL. *If the line is not straight, concentrations from 10-100 are plotted on the same cycle as 1-10, this mark will not be awarded.*

[2] **(ii)** **ON THE GRAPH**, label the back-extrapolated time zero concentration clearly. Print "time zero concentration is 95.03 ng/mL" and with an arrow show how your back extrapolated line runs through this concentration. The intercept is 95.03. Award 1 mark for a straight line, super-imposed on the terminal phase and extending back to the y-axis and a second mark if this line intersects the axis anywhere between 90 – 100 ng/mL

[3] **(iii)** Describe, in words, a model that appears to satisfy the concentration-time profile.
This appears to be a 1 compartment model with zero order input and first order elimination.
1 mark for 1 compartment model **1 mark** for zero order input and **1 mark** for first order elimination.

[1] **(iv)** The terminal phase half-life observed for nifedipine is: 5.0 ± 0.20 hr.

(v) **The concentration** that would be observed at the end of a dosing interval, when doses are administered every eight hours and only:

[3] 3 doses have been given is 45.12 ± 0.20 ng/mL. (2 decimal places).
Concentrations contributing to the end of interval trough concentration are the 8, 16 & 24 hour concentration [31.36 + 10.35 + 3.41 = 45.12 ng/L]

[3] 4 doses have been given is 46.25 ± 0.20 ng/mL. (2 decimal places).
Concentrations contributing to the end of interval trough concentration are the 8, 16, 24 & 32 hour concentration [31.36 + 10.35 + 3.41 + 1.13 = 46.25 ng/mL]

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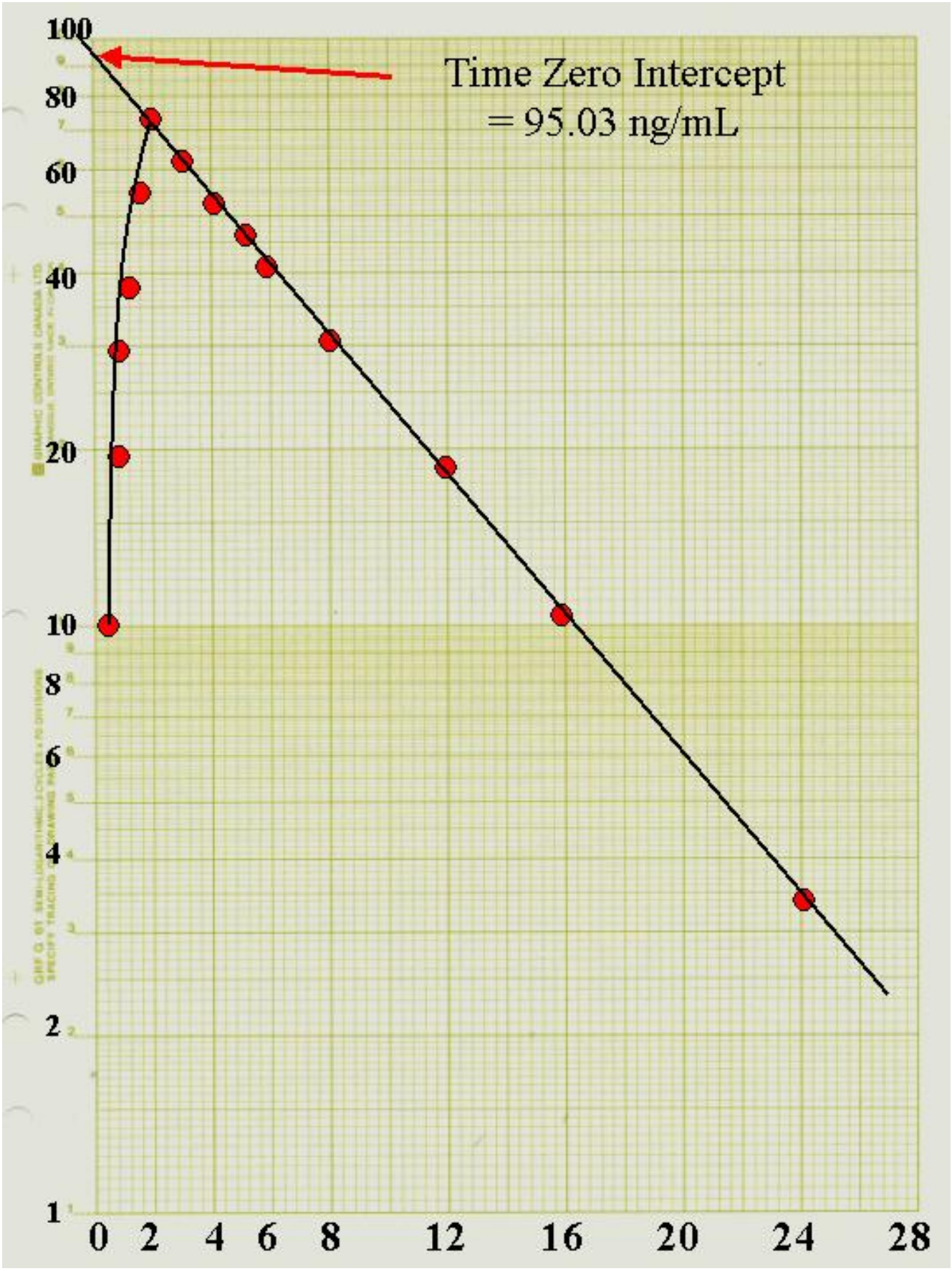

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