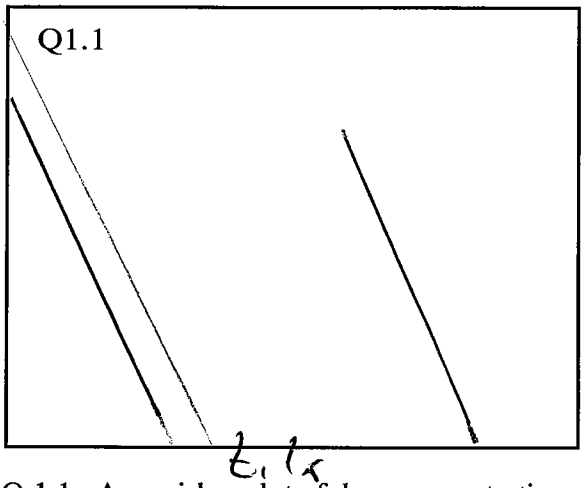
Name: KEY

(Legible please)

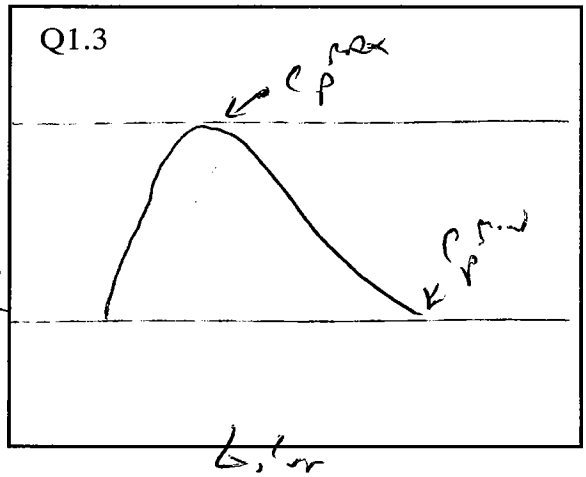
PHAR 7632 Spring 2004
Pharmacokinetics
OU HSC College of Pharmacy

Final Exam **22nd April 2004**

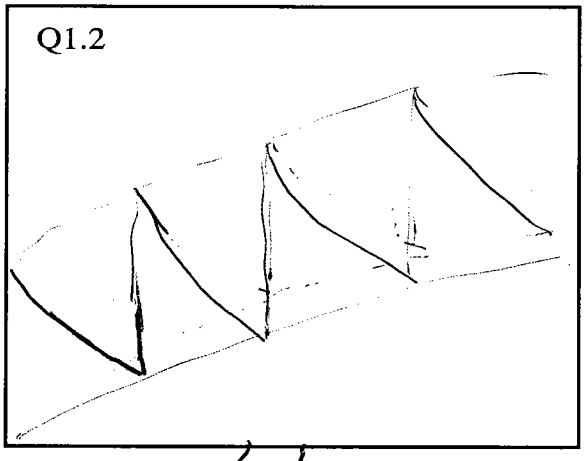
Section ONE. Sketch a Graph or Diagram—Sketch the graphs or diagrams requested in the space provided. Include any distinguishing characteristics. Assume that a linear one compartment model applies unless otherwise specified. **Include labels and units.** **4 x 6 = 24 points**



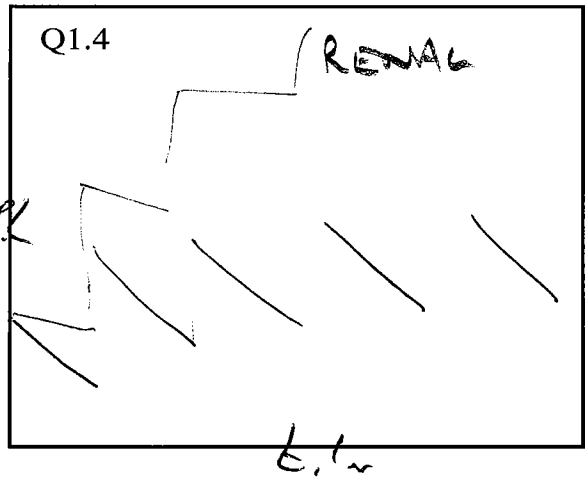
Q 1.1 A semi-log plot of drug concentration *versus* time after two independent IV bolus doses



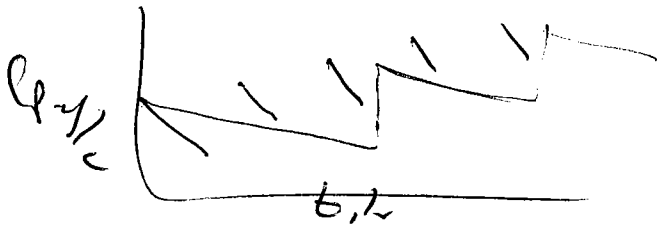
Q 1.3 A linear plot of Cp *versus* time for multiple oral doses showing Cp_{max} and Cp_{min}

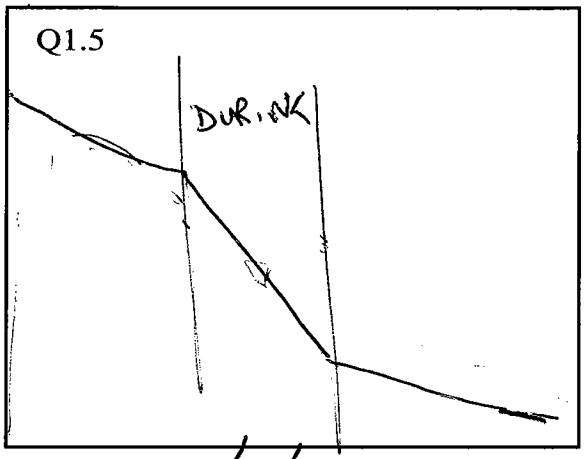


Q 1.2 A linear plot of Cp *versus* time showing doses every six hours, $t_{1/2}$ = 6 hr

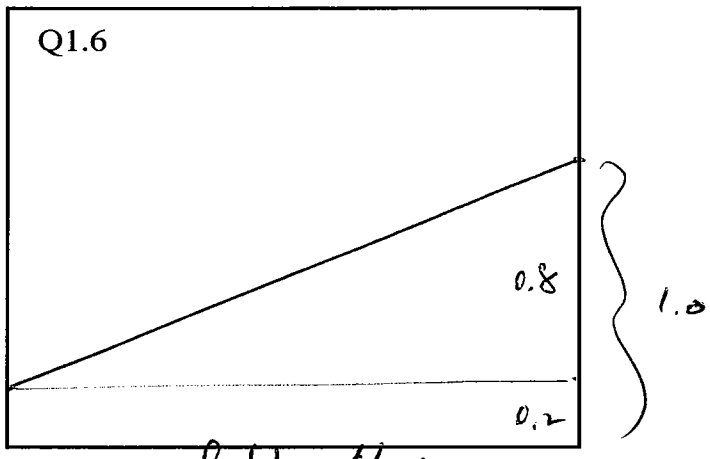


Q 1.4 A semi-log plot of Cp *versus* time after multiple IV bolus doses to two patients. One with normal renal function and one with poor renal function. Label each.

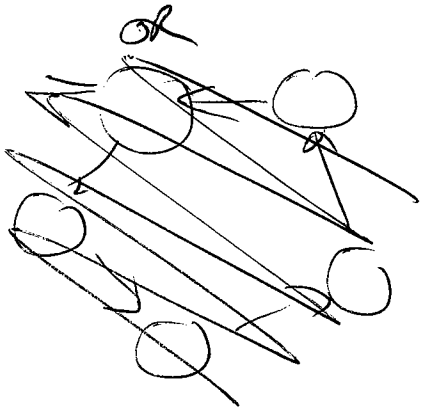


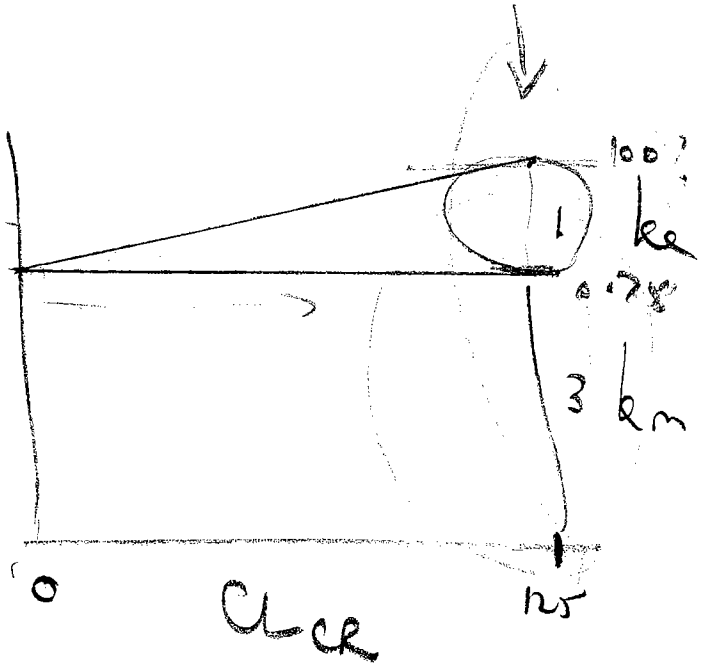


Q 1.5 A plot illustrating Cp before, during and after hemodialysis



Q 1.6 Draw a Dettli plot for a drug where fe = 0.8





Section TWO. True/False—Check the Correct Response. **8 x 2 = 16 points**

Q 2.1 The sublingual ROA is convenient for larger doses

True ☐ False ☒

Q 2.2 The time it takes for plasma concentrations to reach steady state after repeated IV doses is dependent on the dosing interval and not on any characteristic of the drug such as volume of distribution or elimination rate constant

True ☐ False ☒

Q 2.3 At steady state (during equal dose, equal interval multiple dose administration) accumulation stops because the amount of drug eliminated during the dosing interval is the same as the dose given at each dose time

True ☒ False ☐

Q 2.4 If you double the dose AND the dosing interval the calculated average drug concentration will be unchanged

True ☒ False ☐

Q 2.5 The average plasma concentration calculated at steady state after a large number of uniform oral doses given with uniform dosing interval is dependent of the elimination rate constant

True ☒ False ☐

Q 2.6 Two properties of a drug which will improve the extent of removal by hemodialysis are good water solubility and a small apparent volume of distribution

True ☒ False ☐

Q 2.7 A Dettli plot that passes through the origin indicates that the drug is excreted entirely as metabolized drug

True ☐ False ☒

Q 2.8 Appropriate units for the apparent volume of distribution are L/hr

True ☐ False ☒

-----OOOOO-----

Section THREE Calculations **This section = 60 points**

Show all your work for full credit. All material not deleted or crossed-out will be considered for grading. **Put labels and units on all requested graphs.**

Q 3.1 (16 points) A potent drug is to be given by multiple IV bolus injections. On consideration of the patient's clinical condition it is decided that drug concentrations should be maintained close to but below 15 and 2 mg/L. Assume a one compartment linear model applies to this drug in this concentration range. The kel and V for this drug in this patient (74.7 kg) are 0.231 hr^{-1} and 0.68 L/kg, respectively. Calculate the dosing interval which will exactly achieve this concentration requirement. Round this dosing interval to the nearest, appropriate multiple of 2 hour. Recalculate the accumulation factor (R') and estimate an appropriate loading and maintenance dose (rounding to the nearest appropriate 10 mg). Finally, check your answer by estimating Cp_{max} and Cp_{min}.

$R = \frac{2}{15} = 0.1333 = e^{-kel.\tau} = e^{-0.231 \times \tau}$

$V = 0.68 \times 74.7 = 50.80$ L

$-2.015 = 0.231 \times \tau$

$\tau = 8.72$ hr

$\tau' = 10$ hr

$R' = e^{-0.231 \times 10}$

$= 0.09926$

$LD = Cp^{max} \times V$

$= 15 \times 50.80$

$= 762$ mg

$LD' = 760$ mg

$Cp^{max} = 14.96$ mg/L $= \frac{LD}{V}$

$\simeq 15$ g/L

$MD = Cp^{max} . V . (1 - R)$

$= 15 \times 50.8 \times (1 - 0.09926)$

$= 686$ mg

$MD' = 680$ mg

$Cp^{max} = \frac{680}{50.8 \times (1 - 0.09926)}$

$= 14.86$ g/L ✓

$Cp^{min} = Cp^{max} \times R$

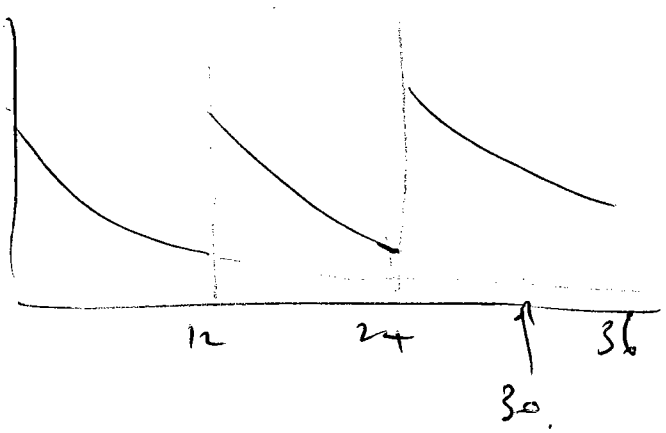
$= 1.475$ g/L ✓

Post Answer (-2)

BAD Rounds (-2)

CALCN (-1)

Q 3.2 (10 points) A patient is started on a drug at an IV bolus dose of 500 mg every 12 hours. Assume a one compartment linear model applies to this drug in this concentration range. The half-life and V for this drug in this patient (84.6 kg) are 1.6 hr and 0.56 L/kg, respectively. Calculate the expected drug concentration 30 hours after the first dose.



$V = 47.38\,L$

$k_{el} = 0.4332\ h^{-1}$

$n = 3 \qquad t = 6$

$\tau = 12$

$t = 30$

0.000023 ✗

$$C_p = \frac{Dose}{V}\left[\frac{1-e^{-n.k_{el}.\tau}}{1-e^{-k_{el}.\tau}}\right]e^{-k_{el}.t}$$

$$= \frac{500}{47.38}\left[\frac{1-e^{-3\times 0.4332\times 12}}{1-e^{-0.4332\times 12}}\right]e^{-0.4332\times 6}$$

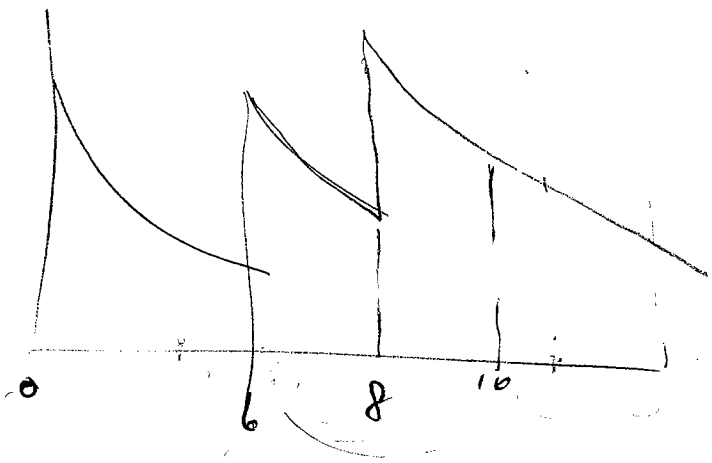
$$= 10.55 \times \frac{1.0}{0.9945} \times 0.07433$$

$$= 0.789\ mg/L$$

Q 3.3 (10 points) A patient is started on a drug at an IV bolus dose of 25 mg every 4 hours. Assume a one compartment linear model applies to this drug in this concentration range. The half-life and V for this drug in this patient (90.5 kg) are 2.7 hr and 0.26 L/kg, respectively. Calculate the expected drug concentration 10 hours after the first dose if the second dose was given at 6 hours instead of the scheduled dose time.

$V = 23.53\ L$

$k_{el} = 0.2567\ h^{-1}$



NO THIRD DOSE
(-4)
EXPLANATION
(-2)

$$C_p = C_{p_1}^{10} + C_{p_2}^{4} + C_{p_3}^{2}$$

$$= \frac{25}{23.53} \times e^{-0.2567 \times 10} = 0.08156$$

$$+ \frac{25}{23.53} \times e^{-0.2567 \times 4} = 0.3805$$

$$+ \frac{25}{23.53} \times e^{-0.2567 \times 2} = 0.6358$$

AFTER THIRD DOSE @ 10 HR
(-4) & Ex (-2)
UNIFORM EX
-8

$$C_p = 0.08156 + 0.3805 + 0.6358$$

$$= 1.098\ \mu g/L$$

Q 3.4 (14 points) A female patient is to receive Drug8 and it is know that the elimination of this drug depends on renal function. This patient is 50.7 kg (111.5 pound), 145 cm (57.1 inches) height and 45 years old. The measured serum creatinine was 1.08 mg/dl. Calculate the creatinine clearance for this patient using the Cockcroft and Gault equation. (Note: Use ideal body weight if less than actual body weight). Once you have calculated the creatinine clearance for this patient estimate the expected elimination rate constant for Drug8 in this patient.

A previous study with Drug8 resulted in the following data.

k_el	$t_{1/2}$ (hr)	Creatinine Clearance (ml/min)
0.093	7.47	10
0.252	2.75	50
0.529	1.31	120

$$IBW = 45.5 + 2.3 \times (57.1 - 60)$$

$$= 38.83 \text{ kg}$$

$$Cr\,Cl = \frac{(140 - 45)\,38.83}{72 \times 1.08} \times 0.85$$

$$= 40.3 \text{ ml/min}$$

k_el

$$= 0.212 \text{ hr}^{-1}$$

Q 3.5 (10 points) A drug is to be given by multiple oral doses every 12 hr. After consideration of the patient's clinical condition it is decided that the average drug concentrations should be maintained at 6 mg/L. Assume a one compartment linear model applies to this drug in this concentration range. For this dosage form and patient the bioavailability is 0.88 and the absorption rate constant is 1.41 hr^{-1}. The half-life and V for this drug in this patient are 5.9 hr and 48 L, respectively. Calculate the dose which will achieve this average concentration of 6 mg/L.

$\tau = 12\ hr$

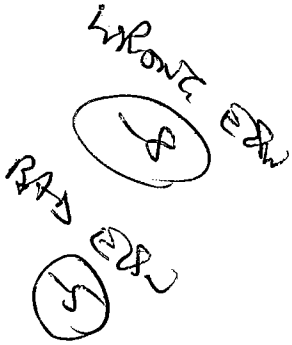
$\bar{C}_p = 6\ mg/L$

$F = 0.88$

$k_a = 1.41\ hr^{-1}$

$k_{el} = 0.1175\ hr^{-1}$

$V = 48\ L$

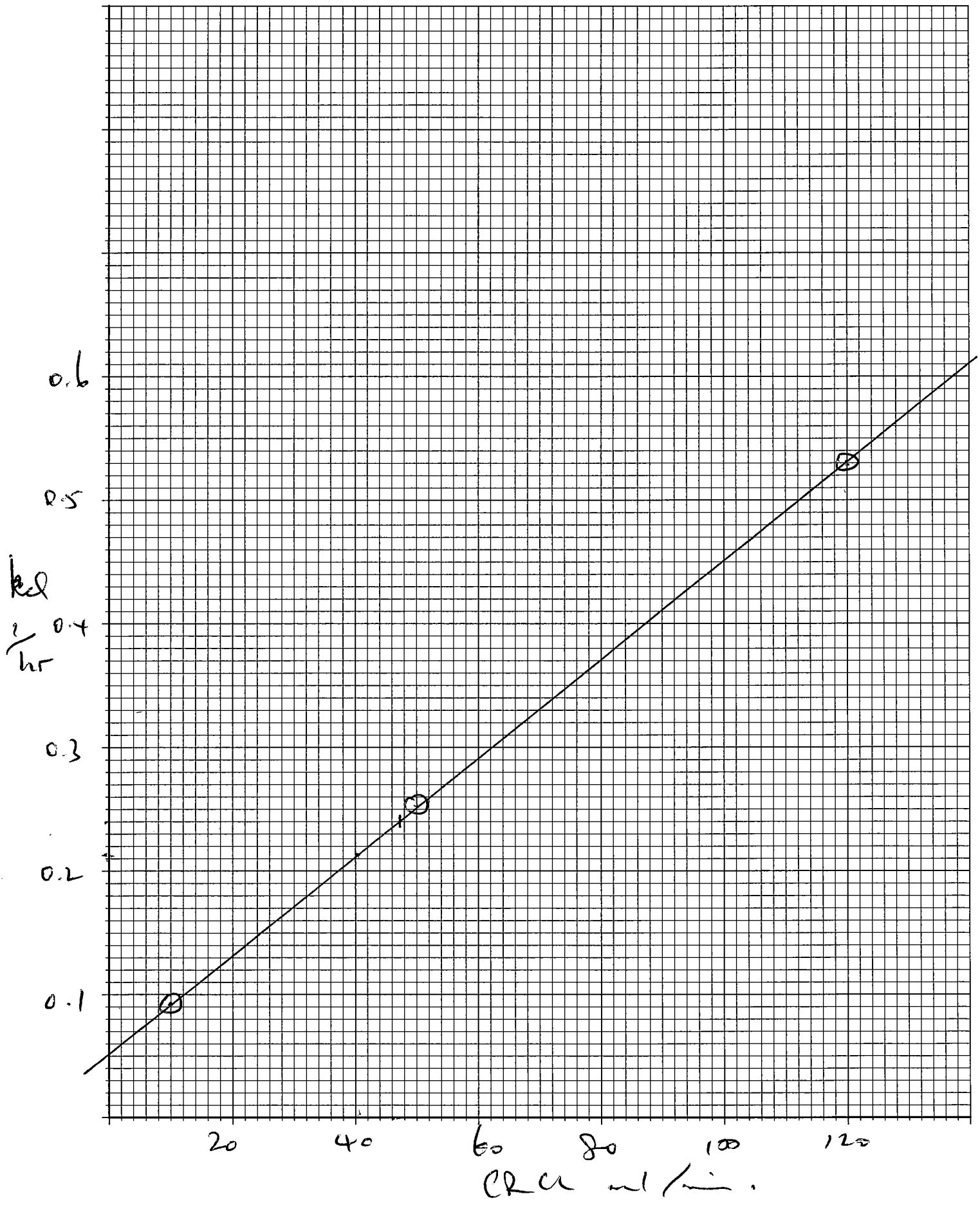


$$\text{Dose} = \frac{\bar{C}_p \cdot k_{el} \cdot V \cdot \tau}{F}$$

$$= \frac{6 \times 0.1175 \times 48 \times 12}{0.88}$$

$$= 461\ mg$$

Linear inch



The Equations

$$Cp = \frac{Dose}{V} \cdot e^{-kel \cdot t}$$

$$Cp = \frac{k0}{kel \cdot V} \cdot \left[1 - e^{-kel \cdot T}\right] \cdot e^{-kel \cdot (t-T)}$$

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[e^{-kel \cdot t} - e^{-ka \cdot t}\right]$$

$$t_{max} = \frac{1}{ka - kel} \cdot \ln \frac{ka}{kel}$$

$$\frac{A}{V} = Cp + kel \cdot \int_0^t Cp \cdot dt$$

$$AUMC^{last} = \frac{Cp^{last} \cdot t^{last}}{k} + \frac{Cp^{last}}{k^2}$$

$$pKa - pH = \log \frac{[HA]}{[A^-]}$$

$$\frac{F^A}{F^B} = \frac{Dose^B \cdot kel^A \cdot V^A \cdot AUC^A}{Dose^A \cdot kel^B \cdot V^B \cdot AUC^B}$$

$$kel = knr + a \cdot CL_{CR}$$

$$D = \frac{\text{Total in blood}}{\text{Total in GI tract}}$$

$$CL_{CR} = \frac{(140 - age) \cdot Wt(kg)}{72 \cdot S_{CR}} \cdot 0.85$$

$$Slope = \frac{\ln Cp_1 - \ln Cp_2}{t_1 - t_2} \quad \left| \quad \tau = \frac{Dose \cdot F}{\overline{Cp} \cdot V \cdot kel} \right.$$

$$Cp_{max} = \frac{Dose}{V \cdot (1 - R)}$$

$$Cp_{min} = Cp_{max} \cdot R$$

$$Cp_n^t = \frac{Dose}{V} \cdot \left[\frac{1 - e^{-n \cdot kel \cdot \tau}}{1 - e^{-kel \cdot \tau}}\right] \cdot e^{-kel \cdot t}$$

$$Cp_{min} = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[\frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}}\right]$$

$$Cp_{min} = \frac{F \cdot Dose}{V} \cdot \left[\frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}}\right]$$

$$\frac{dM}{dt} = -\frac{D \cdot A \cdot (Ch - Cl)}{X}$$

$$CL_L = \frac{Q_L \cdot (Ca - Cv)}{Ca} = Q_L \cdot E$$

$$CL = \frac{Q \cdot fu \cdot CL_{int}}{Q + fu \cdot CL_{int}}$$

$$\alpha + \beta = kel + k12 + k21 \text{ and } \alpha \cdot \beta = kel \cdot k21$$

$$k21 = \frac{A \cdot \beta + B \cdot \alpha}{A + B} \quad \left| \quad kel = \frac{\alpha \cdot \beta}{k21} \right.$$

$$V_1 = \frac{Dose}{A + B} \quad \left| \quad V_{area} = \frac{Dose}{\beta \cdot AUC} \right.$$

$$Area = \left(\frac{C_1 + C_2}{2}\right) \times (t_2 - t_1)$$

$$V_{extrap} = \frac{Dose}{B} \quad \left| \quad AUC^{last} = \frac{Cp^{last}}{k} \right.$$

$$CL = \beta \cdot V_{area}$$

$$V_{ss} = V_1 \cdot \frac{k12 + k21}{k21}$$

$$MRT = \frac{AUMC}{AUC} \quad \left| \quad k = \frac{1}{MRT} \right.$$

$$CL = \frac{Dose}{AUC} \quad \left| \quad ka = \frac{1}{MAT} \right.$$

$$MAT = MRT(po) - MRT(iv)$$

$$R = \frac{Vm \cdot Cp}{Km + Cp} \quad \left| \quad CL = kel \cdot V_1 \right.$$

$$Cp = A * e^{-\alpha * t} + B * e^{-\beta * t}$$

$$R = e^{-kel \cdot \tau}$$

$$V_{ss} = CL \cdot MRT$$

$$pKa - pH = \log \frac{[I]}{[U]} = \log \frac{[HB^+]}{[B]}$$

$$pKa - pH = \log \frac{[U]}{[I]} = \log \frac{[HA]}{[A^-]}$$

$$\alpha = \frac{(kel + k12 + k21) + \sqrt{(kel + k12 + k21)^2 - 4 \bullet kel \bullet k21}}{2}$$

$$\beta = \frac{(kel + k12 + k21) - \sqrt{(kel + k12 + k21)^2 - 4 \bullet kel \bullet k21}}{2}$$

$$IBW(male)(Kg) = 50 + 2.3x(Ht(in) - 60)$$

$$IBW(female)(Kg) = 45.5 + 2.3x(Ht(in) - 60)$$

$$A = \frac{Dose \bullet (\alpha - k21)}{V_1 \bullet (\alpha - \beta)}$$

$$B = \frac{Dose \bullet (k21 - \beta)}{V_1 \bullet (\alpha - \beta)}$$

$$CL = kel \bullet V$$

$$k12 = \alpha + \beta - kel - k21$$

$$V_{area} = \frac{V_1 \bullet kel}{\beta}$$

$$Cp_{late} = B \bullet e^{-\beta \bullet t}$$

$$Vm = \frac{DR_1 \bullet DR_2 \bullet (C_2 - C_1)}{(DR_1 \bullet C_2 - DR_2 \bullet C_1)}$$

$$Km = \frac{Vm \bullet C_1 - DR_1 \bullet C_1}{DR_1}$$

$$CrCl = \frac{U_{Cr} \bullet Vu}{S_{Cr} \bullet t}$$