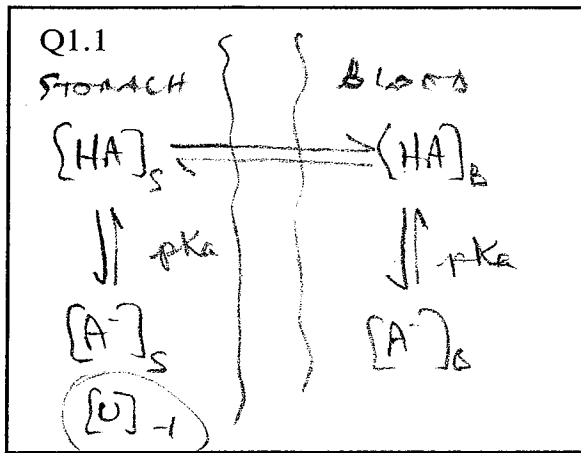


PHAR 7632 Spring 2005
Pharmacokinetics
OU HSC College of Pharmacy

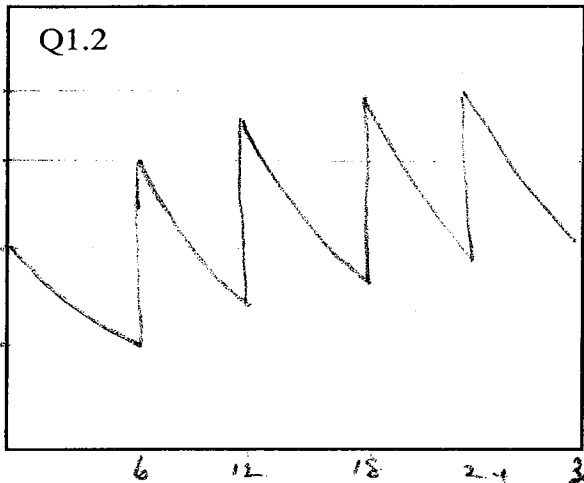
Final Exam

28th April 2005

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



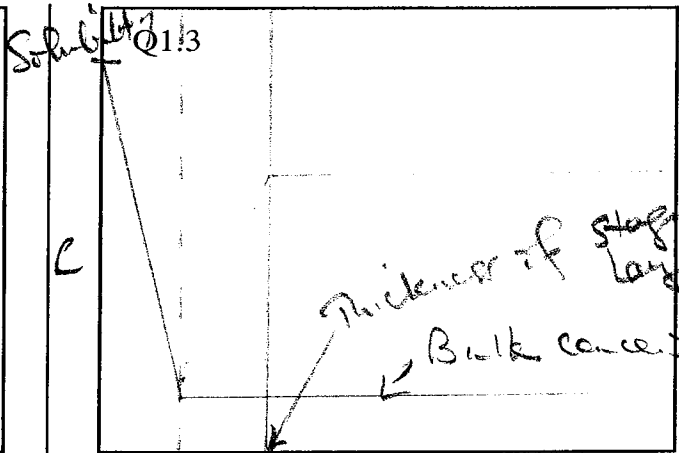
Q 1.1 A diagram illustrating the species involved in the passive transfer of a weakly acidic drug between the stomach and the blood stream



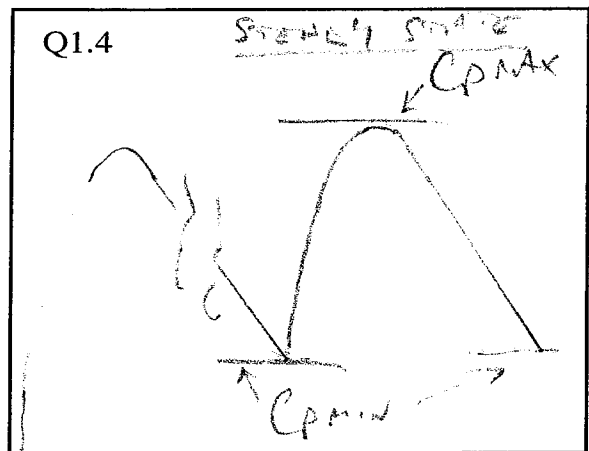
Q 1.2 A linear plot of C_p versus time showing doses every six hours, $t_{1/2} = 6$ hr

bolus oral

t, hr

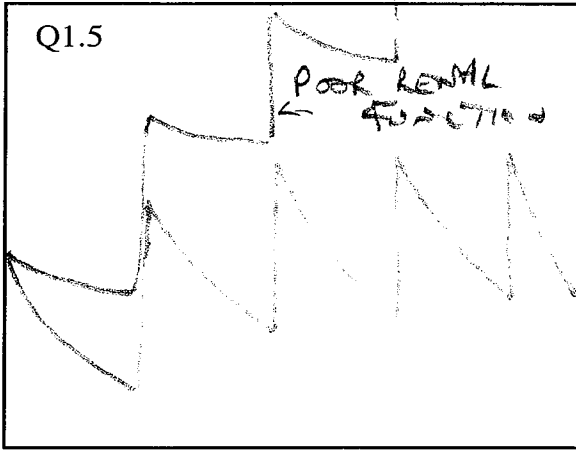


Q 1.3 Plot of concentration versus distance for dissolution into a reactive medium



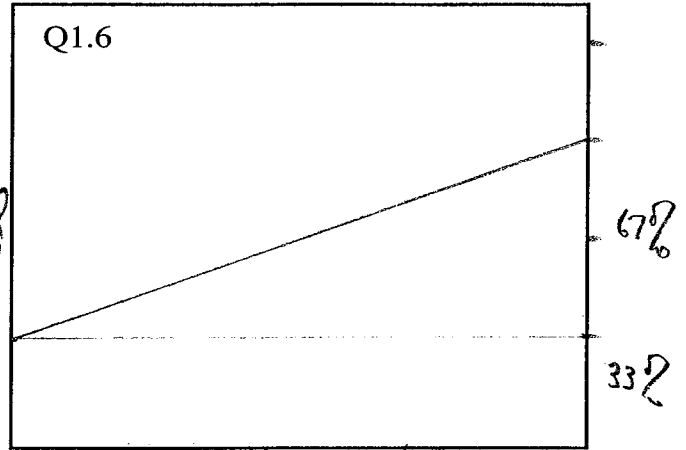
Q 1.4 A semi-log plot of C_p versus time for multiple oral doses showing C_{pmax} and C_{pmin}

C_p
mg/L



Q 1.5 A linear plot of C_p versus time after multiple IV bolus doses to two patients. One with normal renal function and one with poor renal function. Label each

Cl_{CR}
ml/min



Q 1.6 Draw a Dettli plot for a drug where $f_e = 0.67$

Section TWO. True/False—Check the Correct Response.

8 x 2 = 16 points

Q 2.1 The calculated Brodie D value is higher for a weak base ($pK_b = 5.4$) in the stomach ($pH = 3.4$) compared with the value for the small intestine ($pH = 6.4$)

True False

Q 2.2 Enteric coated tablets are designed to resist dissolution in the stomach since some drugs are not stable in low pH solutions

True False

Q 2.3 Tablet dissolution produces granules or fine particles

True False

Q 2.4 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 2.5 The average plasma concentration calculated at steady state after a large number of uniform oral doses given with uniform dosing interval is independent of the absorption rate constant

True False

Q 2.6 A drug will be efficiently removed by hemodialysis if it has good water solubility, very little protein binding and a small apparent volume of distribution

True False

Q 2.7 One type of metabolism pathway is oxidation. Oxidation results in the removal of an oxygen atom or the addition of a hydrogen atom to the drug molecule

True False

Q 2.8 Drug which undergo capacity limited metabolism in the liver tend to have high first-pass metabolism

True False

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 (12 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 20 and 10 mg/L. Assume a one compartment linear model applies to this drug in this concentration range. The k_{el} and V for this drug in this patient (74.7 kg) are 0.071 hr^{-1} and 0.38 L/kg , respectively. Calculate the dosing interval that 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).

$$C_{p\max} = 20 \text{ mg/L} \quad k_{el} = 0.071 \text{ hr}^{-1}$$

$$C_{p\min} = 10 \text{ mg/L} \quad V = 28.386 \text{ L}$$

$$R = \frac{10}{20} = 0.5 = e^{-k_{el} \cdot T} = e^{-0.071 \cdot T}$$

$$-0.693 = -0.071 \cdot T$$

$$T = \underline{9.76 \text{ hr}}$$

$$\rightarrow T = \underline{10 \text{ hr}}$$

$$R = e^{-0.071 \times 10}$$

$$= 0.4916$$

$$L.D. = C_{p\max} V$$

$$= 20 \times 28.386$$

$$= \underline{567.7 \text{ mg}}$$

$$\rightarrow L.D. = \underline{560 \text{ mg}}$$

$$C_{p\max} = \frac{560}{28.386} = \underline{19.7 \text{ mg/L}}$$

$$M.D. = C_{p\max} \cdot V \cdot (1 - R)$$

$$= 20 \times 28.386 \times (1 - 0.4916)$$

$$= \underline{288.6 \text{ mg}}$$

$$\underline{M.D.} = \underline{280 \text{ mg}}$$

$$C_{p\max} = 19.4 \text{ mg/L}$$

$$C_{p\min} = 9.54 \text{ mg/L}$$

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 4.6 hr and 0.46 L/kg, respectively. Calculate the expected drug concentration 30 hours after the first dose.

$$n = \begin{matrix} 3 \\ 0 \end{matrix} \quad 12 \quad 24 \quad \begin{matrix} \uparrow \\ 30 \end{matrix} \quad 36 \quad k_{el} = 0.151 \text{ hr}^{-1}$$

$$t = 6 \text{ hr} \quad V = 38.9 \text{ L}$$

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

$$= \frac{500}{38.9} \left[\frac{1 - e^{-3 \times 0.151 \times 12}}{1 - e^{-0.151 \times 12}} \right] e^{-0.151 \times 6}$$

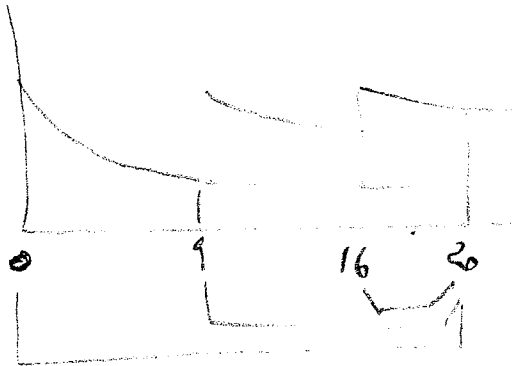
$$= 12.85 \times \frac{0.9956}{0.8361} \times 0.4049$$

$$= 6.20 \text{ mg/L}$$

Q 3.3 (10 points) A patient is started on a drug at an IV bolus dose of 25 mg every 8 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 5.7 hr and 0.36 L/kg, respectively. Calculate the expected drug concentration 20 hours after the first dose if the second dose was given at 9 hours instead of the scheduled dose time and the third dose was given at the scheduled time.

$$k_{el} = 0.122 \text{ h}^{-1}$$

$$V = 32.6 \text{ L}$$



$$C_p = \frac{25}{32.6} \times e^{-0.122 \times 20} + \frac{25}{32.6} e^{-0.122 \times 11} + \frac{25}{32.6} e^{-0.122 \times 4}$$

$$= 0.0674 + 0.2014 + 0.4718$$

$$= 0.741 \text{ mg/L}$$

Q 3.4 (14 points) A female patient is to receive Drug8 and it is known 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 50 years old. The measured serum creatinine was 1.38 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}
 0.093
 0.252
 0.529

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

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

$$= 38.83 \text{ kg}$$

$$CL_{CR} = \frac{(140 - 50) \times 38.83}{72 \times 1.38} \times 0.85$$

$$= 29.9 \text{ ml/min}$$

$$k_{el} \text{ from graph} = 0.175 \text{ hr}^{-1}$$

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 10 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 0.69 and the absorption rate constant is 2.41 hr^{-1} . The half-life and V for this drug in this patient are 7.9 hr and 48 L, respectively. Calculate the dose that will achieve this average concentration of 10 mg/L.

$$\begin{aligned} \text{Dose} &= \frac{\bar{C}_p \cdot k_{el} \cdot V \cdot \tau}{F} \\ &= \frac{10 \times 0.08774 \times 48 \times 12}{0.69} \\ &= 732 \text{ mg} \end{aligned}$$

Q 3.6 (4 points) A patient with poor renal function is to be given a new drug. The patient's creatinine clearance value was determined to be 20 ml/min, approximately 18% of normal. After searching the literature you find that the normal elimination rate constant is approximately 0.165 hr^{-1} . You also find that the drug is eliminated as unchanged drug into urine and as a metabolite and the total amount excreted as unchanged drug was 15%. Estimate the elimination rate constant in this patient.

$$k_{el}^N = 0.165 \quad k_e^N = 0.165 \times 0.15 = 0.02475$$

$$k_{Rn}^N = 0.14025$$

$$k_e^P = 0.004455$$

$$k_{el}^P = 0.004455 + 0.14025$$

$$= 0.145 \text{ hr}^{-1}$$

Linear inch

