

PHARMACOLOGY LABORATORY 2

PHARMACOKINETIC LABORATORY

OBJECTIVES:

1. Reinforce the different concepts of pharmacokinetics which were presented in lecture using computer simulation of one and multiple compartment models.
2. Scrutinize the concept of 4-5 halfives to steadystate concentration and to complete drug elimination.
3. Review how changing the dose and/or dose interval changes the concentration at steady state; inspect the difference between rapidly absorbed and slowly absorbed drugs.
4. Determine how reduced renal function alters steady state drug concentrations.
5. Review the concept of loading and maintenance doses and how changes effect concentrations at steady state.
6. Investigate the complexities of two compartment modeling.

INTRODUCTION:

This laboratory utilizes the computer software Kinetics/DOS or MacKinetics (Dept. Pharmacology, Uniformed Services University) to reinforce the pharmacokinetic concepts from lecture. You can determine the changes in blood levels of drugs after administration of different doses. Initially, the simulations will be simplified and involve one compartment modeling. The software will allow you to set up the concentration (y -axis) and time (x axis) after administering the dose by different routes (oral or intramuscular, intravenous bolus or infusion) for different dosing intervals. The other models that are available with this software are that of one compartment saturation kinetics (Michaelis-Menten) and two - compartment modeling.

There are several formulas which pertain to these exercises:

$$t_{1/2} = 0.693 / K_e$$

$$V_D = \text{dose} / [\text{plasma}]$$

$$Cl = (0.693) V_D / t_{1/2}$$

$$C_{ss} = \frac{\text{dose} * t_{1/2} * \text{Bioavailability}}{\text{interval} * (0.693) * V_D}$$

$$\text{Loading Dose} = C_{ss} * V_D / F$$

$$\text{Maintenance Dose} = C_{ss} * Cl / F$$

It may be helpful for some of you to calculate the parameters using these formulas and compare the numbers with those from computer simulation. For some of the problems below, you will need to use the correct formula to enter data into the computer.

INSTRUCTIONS FOR THE PC Kinetics/DOS PROGRAM:

Put the disc in the appropriate drive (usually drive A) of your computer or turn on computer. Open the A drive directory or the Kinetics folder and double click on the kinetics.exe icon. On the computers in the computer lab, select the LABS folder in Windows 95. Click on the shortcut to Pharmacology folder. In that folder, select KINETICS. In the NEFF computer lab, insert your disc into the floppy disc drive A and work from the disc. You may download the disc contents to the hard drive, but it is not necessary. **In working through the problems, remember that some action must be taken at the end of each dose interval.** A bell will sound or some alert given that you have completed a dose interval and another action is required. In the first problem, you make the following initial choices:

(1) One compartment model (2) Linear plot (3) hours time scale, 24 (4) maximum plasma conc = 100 (5) maximum safe conc = 40 (6) minimum effective conc = 20 (7) oral dose, 250 mg (8) dose interval of 8 hrs (9) volume of distribution, 10.5 liters (10) elimination half-life, 8 hrs (11) absorption half-life, 1.5 hrs. **These parameters are also contained as Prob1 which can be loaded automatically at the start screen by choosing <R> RETRIEVE SAVED DATA.**

After data entry, the screen will clear, a graph will be presented and plotting begins. At 8 hrs (dosage interval), plotting ceases and an alert will sound. Repeat the dose, using the appropriate command in these choices at the bottom of the graph:

<R> : repeat dose <O>: overlay graph (re-plot over old graph)
<D>: change dose <K>: change kinetics parameters
<T>: test report <P>: print report
<S>: save data <N>: new graph (start over with clean slate)
<Esc> quit

If you happen to goof and the computer locks, ask for assistance! If you are thrown out of the program, type control C or answer Yes in the Windows fix dialogue that appears.

INSTRUCTIONS FOR THE MacKinetics PROGRAM:

The MacKinetics program allows either the mouse or keyboard commands to be used. Turn on the computer and click on the PHARM folder, then on MacKinetics. In working through the problems, remember that some action must be taken at the end of each *dose interval*. Use the pull down menu *Model* to select *one compartment*, and the menu *Action* to select *enter data*. In the first problem, you make the following initial choices:

(1) 96 hr time scale (2) Linear plot (3) maximum plasma conc = 100 (4) maximum safe conc = 40 (5) minimum effective conc = 20 (6) oral dose, 250 mg (7) dose interval of 8 hrs (8) volume of distribution, 10.5 liters (9) elimination half-life, 8 hrs (10) absorption half-life, 1.5 hrs.

On completion of the data entry, click on the *okay* button at the bottom panel and a graph will be plotted. At 8 hrs (dosage interval), plotting ceases. To repeat or alter the dose, either choose from the menu under *Action* or use a keyboard command from these choices:

[≡ R] : repeat dose [≡ O]: overlay graph (re-plot over old graph)
[≡ D]: change dose [≡ K]: change kinetics parameters
[≡ U]: undo last dose [≡ P]: print report
[≡ Q] quit

If you happen to goof and the computer locks, ask for assistance!

PROBLEMS:

(1) A patient who weighs 70 kg is instructed to take 250 mg of a drug orally every 8 hours (3 X daily). The drug distributes in extracellular water (15% X 70 kg = 10.5 L), the maximum safe conc is 40 $\mu\text{g/ml}$, the minimum effective conc is 20 $\mu\text{g/ml}$, the absorption half-life is 1.5 hr and the elimination half-life is 8 hrs. You will need to repeat the dose multiple times. Estimate the following numbers from your plotted graph and compare them to calculated numbers.

Estimate min and max conc at steady state? _____ $\mu\text{g/ml}$ _____ $\mu\text{g/ml}$
Why doesn't the formula give an accurate estimate? _____
How long to steady state levels? _____ hr How long to therapeutic conc? _____ hr

Examine the profile when a priming dose (250 mg) is given as an IV bolus over 5 seconds (.001 hr) and then 250 mg is given every 8 hours? (**HINT: The results may not be seen against the y axis so change the dose to 250 mg oral / 8 hr before hitting <R>**). Do not clear display, but choose <O> (PC) or [= O] to overlay the second graph for comparison; change the dose (250) to IV and interval 6 min (0.1 hr); plot it and then change dose (250) oral and interval (8). Repeat the dose multiple times. Examine the curve shape if the 250 mg is given as an IV bolus every 8 hours. What explains the difference in shape? _____

The patient's condition has deteriorated and the reduced renal function is such that the elimination half-life becomes 16 hours. What is the effect of continuing drug administration at the rate of 250 mg every 8 hours? _____
How long is required to achieve a new steady - state? _____
Max and min blood levels at new steady state? _____ $\mu\text{g/ml}$ _____ $\mu\text{g/ml}$

(2) A manufacturer has developed a new formulation of a well known drug that is more slowly absorbed when taken orally than the standard preparation. The claimed advantage of the slow - absorbing preparation is that it need be taken only once daily, instead of the usual 3 times daily, in order to maintain adequate blood levels., Based on the information given below, is the manufacturer's claim valid? [bioavailability x dose = actual amount absorbed, either 85 or 260 mg entered for dose in program] Set the X axis for 48 hrs and y axis maximum at 5 mg/L. (Use overlay to plot both formulations on same graph.)

	<u>Standard Prep</u>	<u>New Formulation</u>
Bioavailability	85%	65%
V_D (total body water)	50 L	50 L
Recommended oral dose	100 mg	400 mg
Dose interval	3 X daily	1 X daily
Elimination half-life	7 hours	7 hours
Absorption half-life	0.8 hours	6 hours
Maximum safe conc	3 mg / L	3 mg / L
Minimum effective conc	1 mg / L	1 mg / L

Is the claim valid? _____
What are the maximum and minimum blood conc of these two dosage regimens when given at the recommended dosage?
Standard prep: _____ mg/L _____ mg/L
New Formulation: _____ mg/L _____ mg/L

What question should you ask about this new preparation (hint: where is max safe conc and what effects it? What population used for dosages determinations?)

- a. _____
- b. _____

(3) An intravenous infusion of an antibiotic is started. It has a maximum safe concentration of 25 mg/L and a minimum effective conc of 15 mg/L, and it is important to achieve therapeutic blood levels of the drug quickly (within the first hour). The drug distributes in a V_d of 20 L (approximately extracellular water) and has an elimination half-time of 4 hours.

What rate of drug infusion (mg/hr) will achieve a steady-state level of approximately 20 mg/L?

How long to steady-state after starting the infusion if no bolus drug were given?

What is an appropriate bolus dose to achieve an immediate blood level of approximately 20 mg/L? _____

What is the bolus dose, and intravenous infusion rate necessary to rapidly achieve and hold at 20 mg/L? _____

(4) Theophylline follows a one-compartment kinetic model. The minimum effective conc (MEC) is 5 mg/L, the maximum safe conc (MSC) is 20 mg/L, and the maximum plasma conc (MPC) should be set for 40 mg/L. Your patient has a volume of distribution of 28.5 L, elimination half-time of 8 hours, absorption half-time of 1.5 hour.

a. Give a 480 mg iv infusion over 30 min and follow the blood die-away curve for the next 23.5 hours. (Since infusion can only be given in mg/hr in program, use 480 mg/hr for 0.5 hrs, then change the dosage to zero for 23.5 hrs.)

b. Repeat simulation with iv dose twice as high [960 mg/ 0.5 hr] (Use overlay option to add additional data to existing graph). What effect on duration of action did the doubling dose have? _____

c. Using the initial dose above, what happens if the clearance of the drug decreases to 1.2 L / hr? _____ (Hint: Calculate clearance)

	Peak Theophylline Conc (mg/L)	Time above MEC
480 mg for 30 min	_____	_____
960 mg for 30 min	_____	_____
480 mg (renal failure)	_____	_____

Patient Simulation #1

It is 2 AM and you are the pediatric intern on call. The emergency room has paged you to see a 5 year old (16 Kg) known asthmatic who presents with a 3 day history of fever and worsening respiratory distress. His mother had stopped giving him his asthma medication 1 week ago because she ran out and did not have time to get a refill. She did give him some Pediazole® that she had left over in the house for his fever.

When you see him, you find a child with a pulse of 100, respiratory rate of 45, temperature of 101, and marked difficulty in breathing. He is using his accessory muscles of respiration (marked intercostal retractions) and is wheezing audibly. A blood gas on 3 l/min of O₂ reveals a pH of 7.39, pCO₂ of 39, and pO₂ of 70. You also note a dull, somewhat

immobile tympanic membrane on the left.

You correctly assess this child as having severe respiratory distress resulting from exacerbation of his asthma and left otitis media, and admit him to the pediatric intensive care unit. Because he is seriously ill, you want to achieve a therapeutic theophylline level as quickly as possible. You therefore want to give him a loading dose of IV theophylline (as Aminophylline) followed by a maintenance infusion.

What are the appropriate pharmacokinetic parameters?

$$V_D = 0.5 \text{ L/Kg} \times \text{body weight} \\ = 0.5 \times 16 = 8 \text{ liters}$$

$$\text{Clearance} = 0.096 \text{ L/Kg/hr} \times \text{body weight} \\ = 1.536 \text{ L/hr}$$

$$t_{1/2} = .693 \times V_D / \text{Clearance} \\ = 3.6 \text{ hrs}$$

You would like to achieve a steady state plasma theophylline concentration of 15 mg/L. What are the appropriate loading and maintenance doses of Aminophylline (Aminophylline is 85% theophylline)? (You want to give the loading dose intravenously over a 20 minute period, and the loading dose would be desired concentration times V_D divided by the fraction available, .85. The maintenance dose (mg/hr) would equal the concentration desired at steady state (15 mg/L) times clearance (L/hr) divided by fraction available.) maintenance: _____ mg/hr loading: _____ mg/hr Simulate this regimen for the first 8 hours as follows: Time axis 48 hours, maximum plasma concentration 30 mg/L, MSC 20, MEC 10, loading dose of 320 mg/hr for 0.3 hours, $V_D = 8 \text{ L}$, $t_{1/2} = 3.6 \text{ hrs}$. After 0.3 hrs, change to 27 mg/hr for 7.7 hrs.

At this point, you decide to get a theophylline blood concentration determination, even though the patient has responded well. The lab reports a concentration of 22 mg/L, higher than expected. After a little thought, you realize that you continued the patient on Pediazole (which contains erythromycin) for his otitis media. You recall from your pharmacology course that erythromycin reduces the clearance of theophylline by 25%. Re-run your simulation using a clearance value of 1.152 L/hr. Can this explain your higher-than-expected plasma concentration? _____ Is there any need to do anything about it? _____ What would the steady state level of theophylline be if you continued this regimen (27 mg/hr)? _____ mg/L Calculate a new infusion rate based on a clearance of 1.152 L/hr. _____ mg/hr For your actual patient, a wise course would be to stop the infusion after the 8 hrs at the high rate (27 mg/hr), hold it at 0 mg/hr for 2 hours, then go to the new, lower infusion rate for the next 16 hours. Simulate this regimen.

After 24 hours, the patient is doing well and you want to switch him from intravenous medication to oral therapy. You decide to place him on Theodur®, an extended release form of theophylline. Theodur has a bioavailability of 0.95 and a half-life of absorption of 1.5 hours. Calculate an appropriate maintenance dose (twice daily dosing, i.e. dose interval of 12 hours), assuming you will keep him on Pediazole for the time being. _____ mg/hr Plot the simulation. What will be the minimum and maximum blood levels? max _____ mg/L min _____ mg/L What happens when he comes off the Pediazole? _____ What correction in dosing regimen would be required? _____ Show the appropriate plot.

Patient Simulation #2

A 60 year old man is admitted to the cardiac care unit because of suspected acute

earlier?
