Practical schedule and self marking scheme

Year 2 Medical Students

SCHEDULE : PHARMACOKINETICS SIMULATION.

Objectives.
To illustrate the basic pharmacokinetic parameters of:
1. plasma half life;
2. steady state and its dependence on dosage regimen;

Requirements. Use the simulation available from the pharmacology departmental software section (pharmacokinetic simulation). You are required to:
- carry out the set schedule using the simulation recording appropriate data;
- produce a write-up presenting data you have derived from the simulation;
- explain the form the data takes;
- produce written answers to the questions which are to be found at the end of each piece of work.

Note that the information you need to answer these questions may have to be obtained from reference sources in the library. Standard text books (which may contain useful references) are always a good starting point. Index Medicus will also provide a ready source of references (search in the pharmacokinetics section under each drug name). Martindale, The Extra Pharmacopoeia published by the Pharmaceutical Press contains a great deal of useful information; The National Formulary and Goodman & Gilman's The Pharmacological Basis of Therapeutics may also be helpful.

THE COMPUTER MODEL
The computer model allows you to generate data relating the plasma concentration of drugs to the time after administration.

These data can be obtained:-
as a screen display using linear arithmetic concentration (y) and time (x) axes
or as a screen display using a $\log_{10}$ concentration (y) and arithmetic time (x) axes.

Measurements can be taken directly from the screen displays which are largely self-explanatory. Note the scale and units on the concentration axis. The program chooses an appropriate scale on which to plot the graphs. Do not worry about the difficulty of making highly accurate measurements from a curved screen. Make the best estimate you can. **Marks will NOT be lost for small inaccuracies of measurements.**

The upper (maximum therapeutic) and lower (minimum effective) plasma concentrations for each drug are displayed numerically at the top of the screen display. If these upper and lower concentrations fall within the scale of the graphical presentation they are also displayed as lines across the screen at the appropriate concentration level. These are guide-line concentrations only and in the program, these concentrations have fixed values. In practise they will vary from subject to

subject and will also depend ON THE THERAPEUTIC USE OF THE DRUG. For example the minimum effective concentration of aspirin depends on whether it is being used as a minor analgesic (headache) or as an anti-inflammatory agent (rheumatoid arthritis). For antibacterial drugs like ampicillin the effective concentration will depend on the sensitivity of the organism. In vitro minimum inhibitory concentrations may be as low as 0.02 microg/ml (strep. pneumoniae) or as high as 500 microg/ml (beta lactamase producing H. influenzae).

What is regarded as a toxic level may depend on: the duration for which tissues are exposed to a concentration of the drug; the nature and seriousness of the toxic effect in relation to the likely benefits of treatment; the particular aspect of toxicity considered, and, the proportion of patients that experience toxicity. Gentamicin for example can produce vestibular damage (tinnitus, vertigo), deafness (less often) or nephrotoxicity. The proportion of patients exhibiting these effects at a plasma concentration of say 15 microg/ml is different and depends on duration of exposure to the drug.

Toxicity can also be affected by the degree of protein binding (reduced in hypoalbuminaemia, uraemia or by interactions with other drugs). Allergic reactions can occur at any concentration of drug. The effective and toxic concentrations shown are therefore GUIDE-LINES only.

The model assumes that all drugs given by intravenous injection are administered as a bolus over a few seconds. This will produce a very high initial peak plasma concentration. In practice many drugs are given iv by a slow injection over 2-3 minutes and this produces a lower initial plasma concentration. Note also that oral dosage forms may be available which release the drug slowly, quickly or over a sustained period. Clearly the characteristics of the particular dosage form used will influence the shape of the plasma concentration-time plot.

The program will ask you for certain information about the subject in whom the measurements are being made (e.g. normal? liver failure?) and about the dosage regimen (e.g. size of dose? frequency of dosing?). These can be set as you wish or according to the instructions you have been given. Note that the duration of the investigation specifies the time period (hours; maximum 300) over which measurements of plasma concentration of drug will be taken. Allow sufficient time for steady-state to be established if using multiple dose regimens or for plasma concentrations to fall to low levels if single doses are used.

(1) PLASMA HALF-LIFE.

Generate a **plasma concentration-time plot** of 2 hours duration for a single iv dose of 1000mg ampicillin. Estimate the concentration in the plasma at 0, 0.25, 0.5, 0.75 and 1 hour after dosing and from the graph determine the length of time required for the plasma concentrations at these times to fall to half their value.

1.a). Tabulate these data.

1.b). Why are the times required for the plasma concentration to fall to half the value different? Which is the best estimate of plasma half life?

Generate a **LOG plasma concentration-time plot** of 12 hours duration for a single iv doses of 1000mg ampicillin.

1.c). Calculate the slope of the line in the elimination phase, Kel and the half life and

tabulate these values.
1.d). How does this value of half-life relate to those obtained above? Which is correct?

Generate a **LOG plasma concentration-time plot** of 24 hours duration for a single iv doses of 1000mg ampicillin in a patient with severe renal failure.
1.e). Calculate the slope of the line in the elimination phase, Kel and the half life and tabulate these values. Tabulate the data in the same table as above.
1.f). Why is the value different in the patient with renal failure?

(2) STEADY STATE and DOSE REGIMEN

2.1 Generate plasma concentration-time plots of 240 hr duration for 0.05, 0.1, 0.25, 0.5 and 1.0 mg digoxin given orally every 6 hours.

For each dose regimen tabulate:
2.1.1 The steady state plasma concentration achieved
2.1.2 The time required for steady state to be achieved
a. Plot steady state plasma concentration against dose. Explain the form the graph takes.
b. What is the relationship between the dose administered and the time required to reach steady state. Explain why this is so.
2.1.3 Are any of these dosage regimens satisfactory? Specify the criteria for a satisfactory you are using to make this judgement.
2.1.4. Change the dosage regimen and discover what you would define as a satisfactory dosage regimen. Specify what regimen you have chosen.
a. How is it different from those used in 2.1?
b. Under what circumstances might the regimen you have chosen for a normal patient be or become unsatisfactory?

Hand in the write-up by the deadline published in the timetable.

PHARMACOKINETICS SELF-MARKING SCHEDULE. FEBRUARY, 2000

Only if you are able to be critical of your own work and see how you could have done it better will you be able to improve and develop your abilities. In the real world there is not always somebody telling you where you could improve - you have to manage this task for yourself and develop appropriate self critical abilities. This marking scheme helps you in this process by providing experience of assessing your own work against a set of requirements. You will not find this easy in some circumstances. In this exercise you must reach your own decision as to what marks to award; you must decide how to interpret the requirements; members of staff will not help with this decision.

Hand in BOTH your write-up AND the named marking schedule with the marks you have awarded yourself written in the appropriate space - don't forget to provide a total. Staff will check mark a proportion of scripts - grossly overmarked scripts will be given zero.

In all this schedule numerical agreement between the students answers and those given here may not be exact. This should not result in a loss of marks as there is a fair margin for error reading concentrations from the screen. Penalise incorrect maths or incorrect methods and concepts not simply small differences from the answers given below. Write comments and corrections on the writeup or circle this marking schedule and attach to returned write-up.

General

The marks in parentheses represent the maximum number available for each point for a perfect answer. Answers which cover only part of the point or are unclear should be marked down substantially.

Is it dated. All work should be. **(1)(....)**
Is it named. **(1)(....)**
It should have a title **(1)(....)** and a heading of introduction **(1)(....)**. Does the introduction specify the aims:
To illustrate the basic pharmacokinetic parameters of:
plasma half life; apparent volume of distribution; steady state and its dependence on dosage regimen; bioavailability.**(5)(....)**

(1) PLASMA HALF-LIFE.

*Generate a **plasma concentration-time plot** of 2 hours duration for a single iv dose of 1000mg ampicillin. Estimate the concentration in the plasma at 0, 0. 25, 0.5, 0.75 and 1 hour after dosing and from the graph determine the length of time required for the plasma concentrations at these times to fall to half their value.*

1.a. Tabulate these data.

There must be a properly constructed table of data with ruled lines **(2)(....)**; units for each column **(10)(....)** neatly laid out **(5)(....)** with all the data present **(10)(....)**.

OBSERVATIONS

time (hrs)	plasma conc (ug/ml)	hours to half value
00	87	0.3
0.25	50	0.35
0.5	30	0.4
0.75	20	0.5
1.0	15	0.5

Note: Your values may not numerically be the same as these. This is because the simulation draws data from individual patients at each run.

1. b. Why are the times required for the plasma concentration to fall to half the value different? Which is the best estimate of elimination half life?
Because the drug is still in a distribution phase. Initially some drug is removed by excretion and some by distribution to other body compartments and the drug disappears from plasma faster than would be expected (shorter half-life) because both distribution and excretion are operating. Once distribution is effectively complete the drug is in the elimination phase and will disappear at a constant rate the from the body. The later values are better as they are obtained when the distribution phase is more complete. **(10)(....)**

*Generate a **LOG plasma concentration-time plot** of 12 hours duration for a single iv doses of 1000mg ampicillin.*
1.c). Calculate the slope of the line in the elimination phase, Kel and the half life and tabulate these values.

	slope	Kel (hr_{-1})	half-life
normal patient	-0.25	0.57	1.2 hr
severe renal failure	-0.04	0.095	10.2 hrs

The elimination phase is the straight line part of the log graph when distribution is complete. The slope is y/x = about -1/4.0 = -.25. This is a LOG graph so -Kel is slope x 2.303 (about 0.57) and half life is 0.693/Kel (about 1.2 hr). **(15)(....)** This is a better value than those above since the drug is past the distribution phase the value is obtained from a straight line relationship determined by several points which allows errors to average out. **(6)(....)**
(A more complicated way is to read off the log values, antilog them, convert to loge and subtract. Divide by delta t and you have Kel).

1.d). How does this value of half-life relate to those obtained above? Which is correct? This value is larger than those obtains above since the distribution phase is complete and the fall in plasma concentration is due only to elimination. As a measure of elimination this is the better value **(5)(....)**.

*Generate a **LOG plasma concentration-time plot** of 24 hours duration for a single iv doses of 1000mg ampicillin in a patient with severe renal failure.*
*1.e). Tabulate the data (see Table above).***(5)(....)**
1.f). Why is the value different in the patient with renal failure?
Since 82% of ampicillin is removed by renal excretion so renal damage can significantly affect pharmacokinetics of this drug. Note damage to a system which eliminates a drug
will only be of pharmacokinetic significance if an appreciable about of the drug is eliminated by the damaged system. Renal damage does NOT potentiate all drug action.**(10)(....)**

2. STEADY STATE

2.1 Generate plasma concentration-time plots of 240 hr duration for 0.05, 0.1, 0.25, 0.5 and 1.0 mg digoxin given orally every 6 hours.

*For each dose regimen tabulate: (there must be a table of data) **(10)(....)***
2.1.1 The steady state plasma concentration achieved
2.1.2 The time required for steady state to be achieved

dose	steady state	time to steady state
0.05	0.53ng/ml	200 hr
0.1	1.1ng/ml	200 hr
0.25	2.1ng/ml	200 hr
0.5	5.1ng/ml	200 hr
1.0	11.0ng/ml	200 hr

a. *Plot steady state plasma concentration against dose.* Must be a graph. Graph must have axes labelled with units, neatly drawn, points shown, title to explain what it shows. **(10)(....)** Explain the form the graph takes.
The graph is a straight line. Steady state is directly related to dose. Biotransformation and excretion are first order processes the rate of which is directly related to the concentration presented to the mechanisms involved.**(10)(....)**

b. *What is the relationship between the dose administered and the time required to reach steady state. Explain why this is so.*
Achievement of steady state is independent of dose. This is because the processes involved are first order and a constant fraction of the drug will be eliminated independent of the amount present. **(10)(....)**

2.1.3 *Are any of these dosage regimens satisfactory? Specify the criteria you are using to make this judgement.*
NO. **(5)(....)** all fail on one or more of the following criteria :
-- is steady state above therapeutic threshold?; is it below toxic threshold? ie.e is

it within the therapeutic window? **(5)(....)**
-- is an effective level achieved quickly? **(5)(....)**
-- are the fluctuations with each dose acceptably small? **(5)(....)**
-- are the number and timing of doses conducive to promote compliance?**(10)(....)**
-- can be doses be given with available tablets? **(15)(....)**

2.1.4. *Change the dosage regimen and discover what you would define as a satisfactory dosage regimen. Specify what regimen you have chosen.*
e.g. 1 mg loading; 0.25 mg every 12 hours. **(10)(....)**
a. How is it different from those used in 2.1? It now achieves all the criteria, has a loading dose and longer interval between doses.
(Note that a 6 hourly dosing schedule is less good as patients comply less. Digoxin comes in 0.0625, 0.125 and 0.25 mg tablets so anybody using doses not available by a combination of these values is marked down).**(-15)(-....)**

(Note that the option is not given in the program but anybody who suggest the loading dose should be divided (e.g. 0.5 followed by 0.5 gets **10 extra (....)**).

b. *Under what circumstances might the regimen you have chosen for a normal patient be or become unsatisfactory?*
-- Deterioration of the disease - may need higher dose. **(10)(....)**
-- Development of other problem e.g. renal failure which will affect the major route of elimination of digoxin.**(10)(....)**
-- Administration of other drugs e.g. thiazide diuretics which tend to produce hypokalaemia which potentiates the effects of the cardiac glycosides like digoxin.**(10)(....)**
-- Switching to another manufacturers brand of tablet since not all digoxin tablets are bioequivalent (differences in bioavailability) though this is much less of a problem now than it used to be.) **(10)(....)**.

Hand in BOTH your write-up AND the named marking schedule with the marks you have awarded yourself written in the appropriate space - don't forget to provide a total. Staff will check mark a proportion of scripts - overmarked scripts will be given zero.

Total available 222
Grades: put the grades and the percentage mark on the FRONT of the script.
Medical students: A>70%; B=60-69%; C=55-59%; D=50-54%; E=45-49%; F=40-44%; G<40%
Medical Science students: I>70%; II(i)=60-69%; II(ii)=50-59%; III=40-49%; Pass = 37-39%; Fail = <37%

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