TITLE: PERSONAL COMPUTER SPREADSHEET - A TEACHING TOOL FOR DRUG KINETICS

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Introduction Residents find conventional lectures on pharmacokinetics, drug uptake and distribution rather difficult material. Today many residents possess a portable programmable computer and they are anxious to learn how to utilize the power of their personal computers. This paper capitalizes on this positive computer attitude and describes how the teaching of drug kinetics may be enhanced by the use of personal computers.

Methods This work is concerned with the use of the LOTUS spreadsheet with a portable personal computer, the Toshiba T1100. This system was chosen for this particular effort because our department subsidizes the cost of these small, laptop computers for our residents and attending anesthesiologists. Other microcomputers and spreadsheets could be used just as well. As an initial approach to the problem, the drug kinetic model is described in terms of straightforeward, finite difference equations. Time is the independent variable and concentrations in the various compartments (e.g. central compartment, tissue compartment) are the dependent variables. There are then a number of fixed or time dependent parameters corresponding to rate constants, volumes of distribution, clearances, bolus injections and continuous infusions. Equations for the model are entered directly into the appropriate cells of a LOTUS spreadsheet. For a two compartment model only two equations must be entered. By use of a combination of absolute and relative addressing, the equations are written in a form such that the COPY command can be used to generate the appropriate formula in succeeding cells of the same column or row. Column orientation of the spreadsheet is preferable because LOTUS provides only 256 columns, but permits 2,048 rows). Once the initial conditions and the kinetic parameters have been entered appropriately, a manual recalculation command can be given. Then with a few simple menu commands, the student can obtain plots of one or more of the dependent variables as a function of time. By changing the model parameters it is possible quickly to determine the effect of changes in drug infusion rate, the effect of multiple bolus injections or any imaginable combination of the above. It is even possible to alter the kinetic parameters at different time steps. The effect of varying the size of the time steps can be seen easily by simply changing the time increment and recalculating the spreadsheet.

Results & Discussion This approach to pharmacokinetics has been well received by the residents of our department. Table I presents a portion of the printout from the LOTUS spreadsheet for a simple, two compartment model. Figure 1 shows the results of the model for a fentanyl infusion of 1 microgram/minute during the time interval from 5 to 20 minutes. The large peak followed by the exponential decline is the concentration in the central compartment and the other curve is the deep or tissue compartment. The difference between Figs. 2 and 3 are the size time steps involved. Fig. 1 has a one minute increment while Fig. 2 has a 4 minute step size.

This LOTUS-finite difference approach has a number of advantages. Perhaps the foremost is that it initially avoids the use of calculus. However, students can readily appreciate the limitations of the finite difference approximations by varying the step size. At a later stage in their education students then can learn how taking the limit of the finite difference (time step → zero) leads to the differential equations which describe the model. The analytical solution for the differential equations can then be programmed into the spreadsheet so as to compare directly the calculus-differential equation solutions with the simpler finite difference models proposed here. Less capable residents can avoid all of the above complications by copying a preprogramed LOTUS disc into their system. It is then very easy to simply "play" with the model.

The principal advantage of utilizing the LOTUS spreadsheet is its graphical capabilities. The student is relieved from the details of the graphing software so he or she can concentrate on proper entry of the equations, injections, infusions, and kinetic parameters. This approach also differs from larger, commercially available training systems in that the student can independently handle all the detials going from the basic mathematical model through input of the equations to examination of the final results in graphical or tabular form. This fosters more confidence on the part of the resident as to the validity of the results he is obtaining from a mathematical model.

TWO COMPARTMENT MODEL

TIME	MCG/L C1	MCG/L C2	MCG INJ	MCG/MIN INF		
0	0	0	0	0	V1DOT	91 L/HR
1	0	0		0	V2DOTR	370 L/HR
2	0	0		0	V2DOTL	370 L/HR
3	0	0		0	V1	60 LITER
4	0	0		0	V2	275 LITER
5	0	0		1	DELTA T	1 MIN
6	0.016666	0		1		
7	0.031199	0.000373		1		
8	0.043908	0.001064		1		
9	0.055062	0.002025		1		
10	0.064886	0.003215		1		
11	0.073574	0.004597		1		
12	0.081291	0.006144		1		
13	0.088180	0.007829		1		
14	0.094359	0.009631		1		
15	0.099932	0.011531		1		
16	0.104907	0.013513	0	1		
17	0.109599	0.015565		1		
18	0.113830	0.017673		1		
19	0.117737	0.019830		1		
20	0.121365	0.022025		1		
21	0.124754	0.024253				

TABLE 1

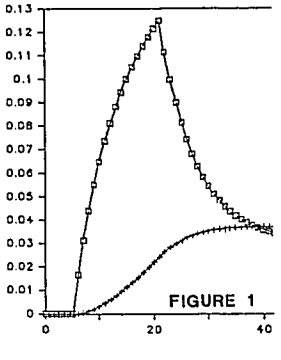

FIGURE 1

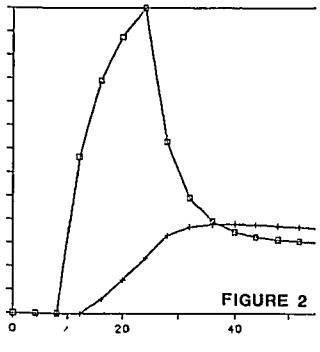

FIGURE 2