Wellcome Film Project

Pharmacokinetics, Part 2: Intravenous Dosing and the Two Compartment Model

Presented by Professor Leonard Saunders, The School of Pharmacy.

University of London Audio-Visual Centre, 1976.

Produced by David Clark and Michael Tomlinson.

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Black and White
Duration: 00:27:40:03

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<**Opening credits**>

<**Intertitle**>

> **Part 1: the Mechanism.**
> **Presented by Professor Leonard Saunders, The School of Pharmacy**

<**Professor Leonard Saunders to camera, then over graphs, animated diagrams and tables of differential equations showing how intravenous drug doses function in a two compartment model**>

In the first programme of this series, a model of drug disposition was examined which was simple first order. The characteristic feature of this model is the linearity of the log concentration versus time plot. Experimental errors scatter the points about a straight line. However, for many drugs this is not the case. The best line through these points with a similar scatter is a curve. This means that the simple one

compartment disposition model cannot be applied. The curvature of the log plot suggests that the elimination rate gets less and less rapid as time passes, in comparison with the simple one compartment model.

This can happen if there is a reservoir or second compartment from which elimination does not take place. For example, compartment one might be the plasma and all the tissue fluids that equilibrate rapidly with it. And compartment two, all other tissue fluids accessible to the drug. Then there will be a reversible transfer of drug between one and two. If the rates of transport are appropriate, compartment two will act as a reservoir. It will fill at high concentrations in compartment one in competition of excretion and return drug to compartment one as excretion reduces the concentration in the system. The intravenous administration of a dose of drug represents the rapid filling of compartment one. And as time passes, the drug disposes itself between the two compartments at the same time as being excreted. See how compartment two fills rapidly then slowly empties. The concentration of drug is always less than in compartment one. The amount of drug may be greater because of the larger volume of compartment two.

We can examine the kinetics of this system. The disposition of the drug is characterised by three first order rate constants. k_e, the rate constant for excretion; K_1, the rate constant for absorption into the reservoir and k_2 the constant for the return from the reservoir. These give rates of depletion of C_1 as

$$dC_1/dt = -k_e C_1 - k_1 C_1 + k_2 C_2 \ .$$

The rate of this process depends on the concentration in C_2. Because the volumes of compartments one and two are different, the same number of drug molecules leaving two, represents in C_1, v_2/v_1 times the concentration in C_2. So the contribution to compartment one from C_2 is $k_2 C_2 v_2$ divided by v_1.

The change in C_1 and C_2 looks like this. This dotted curve represents just first order excretion with the same k_e value. C_1 decreases more rapidly at high C_1, because of the filling of the reservoir, and decreases more slowly at low C_1 because the reservoir is empty. At all stages in the process, the total number of drug molecules is constant.

This can be expressed by writing $x_0=x_1+x_2+x_e$. That is to say, the initial dose is either in C_1, C_2 or excreted.

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So the term $C_2\, v_2/v_1$ can be expressed as

$$C_2\, v_2/v_1 = v_2/v_1 \times x_2/v_2 = 1/v_1\,(x_0-x_1-x_e).$$

And since x_1/v_1 is C_1, the right-hand side of the equation becomes

$$(x_0/v_1)-C_1-(x_e/v_1).$$

This means that the kinetic equation for the model can be written in terms of C_1 and x_e.

The elimination process can be considered separately. The quantity of drug eliminated to a given time, x_e, represents a loss of C_1 of x_e/v_1 concentration units. If this elimination process is first order, then

$$d/dt\,(x_e/v_1)=k_eC_1.$$

This is a relation between x_e and C_1. These three equations are sufficient to express C_1 in terms of t and the constants of the model. To make use of the third relation it is easiest to differentiate a second equation. Note that the term in x_0 disappeared; the derivative of a constant is zero. Substituting the third equation into the second gives

$$k_2\,(v_2/v_1) \times dC_2/dt = k_2\,(-dC_1/dt - k_eC_1).$$

To make use of the second equation differentiate the first with respect to time which gives

$$d_2C_1/dt^2 = (-k_e+k_1) \text{ into } dC_1/dt + k_2\, v_2/v_1 \times dC_2/dt.$$

And substituting for the last term gives

$$d_2C_1/dt^2 = -\,(k_e+k_1+k_2) \times dC_1/dt - k_2k_eC_1.$$

Rearranging, this gives a well-known second order differential equation.

$$d^2C_1/dt^2 + (k_e+k_1+k_2)\, dC_1/dt + k_2k_eC_1 = 0.$$

This equation has exponential solutions and if $C_1 = Ae^{-mt}$, the two derivatives

$$dC_1/dt = -mC_1; \text{ and } d_2C_1/dt^2 = m^2C_1.$$

When substituted into the differential equation give

$$m^2C_1 – (k_e+ k_1+ k_2)mC_1 + k_ek_2C_1 = 0.$$

The C_1 cancels. This is the proof that the exponential is a solution and there are two possible values for m, the roots of the quadratic equation. If these are α and β, that is to say, the quadratic is

$$(m-\alpha)(m-\beta)=0 \text{ or } m^2 –(\alpha+\beta)m + \alpha\beta = 0.$$

A comparison with the original equation for m gives

$$\alpha+\beta = k_e+ k_1+ k_2; \alpha\beta = k_ek_2.$$

The complete solution involves both possibilities and is

$$Ae^{-\alpha t} + Be^{-\beta t}$$

where A and B are the two arbitrary constants that arise from the solution of the second order differential equation. We can now follow the whole course of the disposition of excretion of a drug by this model.

The changes in each compartment follow the mathematical model and the values of C_1, C_2 and x_e, the amount excreted, approach the limiting values of 0,0 and X_0 at long times.

<**Saunders to camera**>

The next programme examines the best ways in which kinetic parameters may be derived from a biological system which is represented by this model.

<**End of first programme**>

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<**Intertitle**>

Part 2: Obtaining Kinetic Parameters

Presented by Leonard Saunders, The School of Pharmacy

<**Saunders over animated graphs and diagrams of differential equations showing how intravenous drug doses function in a two compartment model**>

The two compartment model of drug disposition is described by an equation with two exponential turns. In the preceding programme, the concentration C_1 as a function of time was deduced as

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t}$$

where α and β depend on the rate constants k_e, k_1 and k_2. It is conventional to take α as numerically the larger of the two and refer to it as the fast disposition constant; β is the slow disposition constant. This suggests a way of determining α and β. Long times, $e^{-\alpha t}$ will be very small in comparison with $e^{-\beta t}$. And so the decay at long times is dominated by the slow disposition constant. The log C_1 versus t plot at late times tends to a straight line whose slope is $-\beta/2.3$. The differences between the two lines in terms of the numerical values on the vertical axis are the residuals, γ. As C_1 is $Ae^{-\alpha t} + Be^{-\beta t}$ the residuals are just $Ae^{-\alpha t}$. The log plot of these residuals should be linear. This residual at t = 1 hour is given by 20.8, the value of C_1 – 11.0 from the extrapolated line. So $\gamma = 9.8$ which we can plot on the same graph. Similarly with the other points which lie on a reasonable straight line. From the graph the values of B, β, A and α can be read off as B = 19.0mg per litre, $\beta = 0.124$ hour^{-1}, A = 14.3mg per litre, $\alpha = 1.15$ hour^{-1}.

This graphical method is known as feathering. These values are liable to considerable error when the points are scattered. This is especially true for A and α since they depend on an extrapolation of a line based on the least accurate of the readings, the small long time values of C_1.

<**Saunders to camera then over table showing computer programme model of equations**>

A better method of extracting these values from the data is the computer method of non-linear least squares. The least squares regression analysis developed in the previous programme, was for a straight line. Values of A and B that gave a best fit were found by minimising the quantity Q, the sum of the squares of the differences between each value of y and the point on the line at the same x. This can be extended to any calculable function instead of a straight line. When Q becomes the sum over all points of observed value of the function minus calculated value squared. However, the partial derivatives of Q, with respect to the fitting parameters, in our case A, α, B and β give equations that are not so simply solved. The easiest way is to use a computer programme especially designed to give a numerical solution.

A typical programme is in the Biomedical Library published by University of California. This programme minimises the fit of a given function at F with respect to the parameters. In this case, the programme requires expressions for the four derivatives D_1 to D_4. For this problem

$$F = P_1e^{-P2x} + P_3e^{-P4x}.$$

And for example, D_2 is $-P_1xe^{P2x}$.

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The programme starts with given initial parameters and ends with values for them that minimise the squares of the differences between the observed value y and the value of the chosen function F at the same x for all points.

<**Saunders over computer output data, a table comparing results, tables showing differential equations, then to camera**>

This is the computer output from our data. The starting values were guesses and here are the values of the parameters that minimise the sum of the squares of the differences together with their standard deviations. As a check, this table is a comparison of the observed and best fit calculated points. The calculation fails if the points are too scattered or the function F is unsuitable for the data. You can tell that

this has happened when the standard deviations at some of the parameters are either zero or unreasonably large.

As with the simple first order analysis, the least squares and graphical methods usually give us different answers.

These are the computed results together with the graphical results obtained by the feathering method. The limits shown are the standard deviations from the programme. Only α in the last column is within one standard deviation from the least squares value. The values of the rate constants for the kinetic processes can be obtained from these values of the fitting parameters as follows.

The mathematical analysis in the preceding programme gave two relationships between $\alpha\beta$ and $k_1k_2k_e$. These are

$$\alpha + \beta = k_e+k_1+k_2 \text{ and } \alpha\beta = k_ek_2.$$

Since there are three rate constants to determine, one further equation is required which may be developed from the excretion expression assumed to be first order. This can now be integrated since C_1 is a known function of t. $x_e/v_1 = k_e$ times the intergral from 0 to t $(Ae^{-\alpha t} + Be^{-\beta t})dt$. After a long enough time x_e is equal to x_0 the initial dose so the relationship on setting the upper limit of the integral to infinity becomes

$$x_0/v_1 = k_e(A/\alpha + B/\beta).$$

x_0/v_1 is the initial concentration C_0. From the boundary conditions that's $C = C_0$, at t = 0. At t = 0 the exponential terms in the equation for C_1 become 1. So $C^0 = 1$, giving $C_0 = A+B$.

These equations can be combined by eliminating x_0/v_1 between them to give

$$k_e = \alpha\beta(A+B / A\beta + B\alpha).$$

The second equation then gives

$$k_2 = \alpha\beta/k_e.$$

And finally from the first equation

$$k_1 = \alpha+\beta-k_e -k_2.$$

The least squares values of the parameters give k_e = 0.178 hours^{-1}, k_1 = 0.394 hours^{-1}, k_2 = 0.536 hours^{-1}.

This programme completes the consideration of results following intravenous injection. In the next programme we shall consider the kinetics after oral dosing.

<**End credits**>