The modelling of drug response

B. WHITING1 AND A. W. KELMAN2

1 Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow, and 2 West of Scotland Health Boards, Department of Clinical Physics and Bio-Engineering, Glasgow, Scotland, U.K.

Introduction
The mathematical description of drug disposition (pharmacokinetics) has laid the foundation for the rather more complex task of modelling drug response (pharmacodynamics). Several studies have now shown that kinetic and dynamic data can be integrated to produce unified models which describe the data well and which may form the basis of a useful forecasting system. For example, changes in systolic time intervals after cardiac glycosides (Kramer, Kolibash, Lewis, Bathala, Visconti & Reuning, 1979; Kelman & Whiting, 1980), prolongation of the electrocardiographic QT interval in response to disopyramide (Whiting, Holford & Sheiner, 1980a), reduction in the number of ectopic beats after tocainide (Meffin, Winkle & Blaschke, 1977), change in the force of muscle contraction after the administration of D-tubocurarine (Sheiner, Stanski, Vozeh, Miller & Ham, 1979a) and increase in ventilatory function after theophylline (Whiting, Kelman, Barclay & Addis, 1980b) have all provided effects that could be related to the pharmacokinetic properties of these drugs. The aim of modelling, therefore, must be to describe, and hopefully predict, the pharmacological effects of drugs on the individual subject.

Pharmacokinetics
In pharmacokinetics, the disposition of a drug throughout the body is represented by some form of model. Although purely mathematical models can be used, it is more usual to view the body in terms of a series of compartments (Fig. 1a), where the rates of transfer of drug from one compartment to another are governed by first-order processes defined by equations of the form shown in eqn. (1)

\[
\frac{dX_i}{dt} = k_{12}X_C - k_{21}X_S
\]

where the \(X_i\) represent the amount of drug in the \(i^{th}\) compartment, and the \(k_{ij}\) are the appropriate intercompartmental first-order rate constants.

![Diagram of three-compartment pharmacokinetic model](image)

Correspondence: Dr B Whiting, Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW, Scotland, U.K.
The parameters which characterize the model are determined by fitting plasma concentration versus time data to equations which define the model, so that the amount of drug in the central compartment (compartment C, Fig. 1) mirrors that actually measured in the plasma. The central compartment therefore corresponds to the plasma, but the other compartments probably have little physiological significance, and indeed, the model chosen need not be unique. However, if it can be shown that its application successfully describes the data then it is considered to be acceptable.

Solutions to equations of this type (eqn. 1) lead to the amount of drug in the $i^{th}$ compartment, $X_i$, at any time $t$ being described as the summation of a series of exponential terms, eqn. (2)

$$X_i = \sum A_i e^{-\alpha_i t}$$

where $A_i$ is the $i^{th}$ coefficient (which may be positive or negative) and $\alpha_i$ is the exponent of the $i^{th}$ exponential term. The $A_i$ and $\alpha_i$ are complex functions of the intercompartmental rate constants, $k_{ij}$ (see eqn. 1).

The disposition characteristics of any particular drug will essentially determine the most appropriate pharmacokinetic model. Digoxin, for example, is well described by a three-compartment model (as in Fig. 1: Sumner, Russell & Whiting, 1976) whereas two-compartment models suffice for theophylline (Mitenko & Ogilvie, 1973; Powell, Vozeh, Hopewell, Costello, Sheiner & Riegelman, 1978) and disopyramide (Hinderling & Garrett, 1976; Bryson, Whiting & Lawrence, 1978). Again these models may not be unique, and will depend, to a certain extent, on the type and quality of data available. The compartmental characteristics of a drug are most obvious after intravenous bolus injection; after oral administration, with the relatively slow input from the gut, there may be less information about disposition and the data may then be adequately described by a simpler model (Bryson et al., 1978).

For some drugs, e.g. phenytoin, eqn. (1) does not hold, and the kinetics are not governed by first-order processes, but rather by some form of capacity-limited enzyme system where the following eqn. (3) applies (Michaelis–Menten equation)

$$\frac{dC(t)}{dt} = \frac{V_{\text{max}} C(t)}{K_m + C(t)}$$

where $dC(t)/dt$ represents the rate of change of plasma concentration of a drug at time $t$, $C(t)$ is the concentration of a drug at time $t$, $V_{\text{max}}$ is the maximum velocity of the enzyme reaction (indicative of the capacity of the system), and $K_m$ is the Michaelis constant, equivalent to the concentration when the velocity of the reaction is half $V_{\text{max}}$.

But returning to the less complex linear situation represented by eqn. (2), the values of the parameters $A_i$ and $\alpha_i$ can be estimated by comparing the measured plasma concentrations with those predicted by the model by non-linear least-squares regression analysis. This type of analysis is readily available on many computers in the form of the NONLIN programme (Metzler, Elfring & McEwen, 1974), the SAAM programme (Berman & Weiss, 1969) and as an integral part of standard packages such as BMDP (Dixon & Brown, 1977). Excellent discussions on the principles of pharmacokinetics are given by Wagner (1975) and Gibaldi & Perrier (1975).

Pharmacodynamics

Data for pharmacokinetic studies are fairly easy to obtain but it is only with the development of non-invasive techniques that the possibility of acquiring comparably reliable 'effect' data has been realized.

The fact that drug response ($E$) cannot increase indefinitely as the amount of drug in the body increases is embodied in the Hill equation, shown by eqn. (4)

$$E = \frac{E_{\text{max}} C^\gamma}{C(50)^\gamma + C^\gamma}$$

where $E_{\text{max}}$ is the maximum effect possible, $C$ is the concentration of drug in plasma, $C(50)$ is the concentration required to produce 50% of $E_{\text{max}}$, and $\gamma$ is a positive number (not necessarily an integer) that allows sigmoidicity of the concentration–effect relationship. The simpler Langmuir-type function (where $\gamma = 1$) can also be used, shown by eqn. (5).

$$E = \frac{E_{\text{max}} C}{C(50) + C}$$

Meffin, Winkle & Blaschke (1977) used eqn. (4) to describe the reduction in ectopic activity produced by the antiarrhythmic agent tocainide during multiple oral dosing. Pharmacokinetic parameters relevant to a one-compartment model were first determined and then used to obtain the values of $E_{\text{max}}$, $C(50)$ and $\gamma$. The parameters were then used to simulate antiarrhythmic effect at various doses with a view to optimizing
Modelling drug response

Unfortunately, the degree of intrasubject variability in response was so great that precise dosage adjustment was impractical.

Kramer et al. (1979) studied the inotropic response to digoxin in 12 normal male volunteers after a single intravenous bolus dose. Response was assessed by measuring the shortening of the QS2 interval (the time of total electromechanical systole) and was related to drug concentrations by the Langmuir equation (eqn. 5). Kramer's hypothesis was that the inotropic response would be mediated by the amount of digoxin in one of the three compartments defined by the appropriate pharmacokinetic model (Fig. 1a). When the mean data from the 12 subjects were used, statistical analysis showed that the response was most closely related to the amount of drug in the 'deep' tissue compartment (the word 'deep' has no significance other than to distinguish this compartment from the shallow compartment on the basis of the relative magnitudes of the intercompartmental rate constants). Although concentration and effect were also fitted simultaneously to the model, i.e. kinetic and dynamic parameters were determined simultaneously, there was no distinct advantage in doing this because it did not improve the goodness of the fits. The clear relationship established with the mean data could not be substantiated when individual data sets were analysed, suggesting, perhaps, that there was too much random 'noise' associated with these data or that the process of averaging masked the unique features of the individual data sets.

Contrary to Kramer's hypothesis, one of the most interesting features of pharmacodynamic modelling is illustrated in Fig. 2, which is representative of the type of data that can be obtained after intravenous digoxin. The response curve (E) is clearly not in phase with the amount of drug in any of the predetermined kinetic compartments, whose profiles are represented by curves C, S and D (central, shallow and deep compartments respectively). Curve E, for example, could reflect shortening of the QS2 interval or reduction in the left ventricular ejection time.

An approach which recognizes and models the fact that response may not be in phase with drug concentrations in any particular kinetic compartment has been presented by Sheiner, Stanski, Vozeh, Miller & Ham (1979a). This approach involves extending the classical pharmacokinetic model (e.g. Fig. 1a) by an explicitly defined 'effect' compartment (Fig. 1b) in such a way that this modification does not influence the pharmacokinetic parameters defined by the original model. The amount of drug, $X_e$, in the effect compartment is described by an equation of the form shown by eqn. (6)

$$\frac{dX_e}{dt} = k_{1e} X_1 - k_{eq} X_e$$  (6)
where $X_i$ is the amount of drug in the central compartment and $k_{re}$ and $k_{eq}$ are first-order rate constants. The response is then described as a function of drug concentration, $C_e$, in the effect compartment, shown by eqn. (7).

$$E = f(C_e)$$

(7)

where $f$ can be linear or sigmoid, as defined by the Hill or Langmuir equations. This approach was first used to model changes in the force of muscle contraction induced by $\beta$-tubocurarine during general anaesthesia (Sheiner et al., 1979a). The effect function, $f(C_e)$, was that defined by the Hill equation and the kinetic and dynamic data were fitted both separately (for individual subjects) and simultaneously (for a group of subjects). The analysis indicated a good agreement between the observed responses and those predicted by the model. These authors were fortunate in being able to apply their model over the entire range of observable effect (i.e. approaching $E_{\text{max}}$), so that data were available to confidently estimate $E_{\text{max}}$, $C(50)$ and $\gamma$ (eqn. 4). The relatively simple Langmuir-type function was rejected for the more general form of the effect relationship because it was shown that $\gamma$ was not equal to one.

The QT prolongation produced by disopyramide has been analysed in terms of concentrations achieved after both intravenous and oral administration by the same analytical technique (Whiting et al., 1980a). In this case the concentration–response range was relatively restricted and the effect function, $f(C_e)$, was approximated by a linear equation of the form shown by eqn. (8):

$$E = f(C_e) = mC_e + i$$

(8)

A satisfactory description of both mean and individual data was obtained. Eqn. (8) reveals one of the most interesting features of this type of model, the emergence of a 'sensitivity' parameter, $m$ (eqn. 8). Now at steady state, when there is no net transfer of drug between compartments (i.e. $dX_i/dt = 0$) the concentration in the plasma ($C_{pss}$) is equal to the concentration in the effect compartment. Eqn. (8) therefore becomes eqn. (9)

$$E = mC_{pss} + i$$

(9)

and $m$ then expresses the change in drug response for a given change in steady-state plasma concentration. Similarly, if the more generalized Hill equation is used, $C_{pss}(50)$ is estimated as the sensitivity parameter.

Another novel approach has been offered by Kelman & Whiting (1980). This avoids the a priori assumption that effect is related to a single-compartment model, so that effect can be described by an equation of the form shown by eqn. (10)

$$E = \sum_{i=1}^{N} A_i X_i + B$$

(10)

where there are $N$ compartments. In the first instance, it was assumed that $f$ could be approximated by a linear equation over the restricted ranges usually available. Eqn. (10) therefore reduces to eqn. (11)

$$E = \sum_{i=1}^{N} A_i X_i + B$$

(11)

where the $A_i$ are partial regression coefficients, $B$ is the intercept and $X_i$ represents the amount of drug in the $i^{th}$ compartment (multiple linear-regression model). Statistical tests can then be carried out to determine which of the compartments make a significant contribution to the time course of pharmacological response.

This technique has been successfully applied to the analysis of data obtained after a single intravenous bolus dose of digoxin in six normal male volunteers (Kelman & Whiting, 1980). It was found that both the shallow and deep compartments were required to describe the effect data (shortening of the left ventricular ejection time) and final parameter estimates from individual data sets were remarkably consistent. In these analyses, pharmacokinetic parameters were first determined so that the amount of drug in the various body compartments could be predicted: only then was eqn. (11) applied. Simultaneous fitting of these data has not been carried out.

The effect model (Sheiner et al., 1979a) was also used to fit these data and it was concluded that neither model showed any statistical superiority. The multiple linear-regression technique was also used to fit the disopyramide data presented by Whiting et al. (1980a) with the same conclusion.

Under other experimental conditions which allow the acquisition of response data over a much wider range, it may be more appropriate to assign non-linear functions to the $f$ of eqn. (10).

Pharmacodynamic models can provide insight into the physiological or pathological mechanisms which underlie observed changes in concentration and response, but unless the model has a sound physiological basis, conjectures about pathophysiological processes can be very misleading. For example, it is tempting to see drug response as the result of drug–receptor interactions in kinetically defined compartments,
but this is naïve because such compartments rarely correspond to well-defined tissues. It must therefore be stressed that the models discussed here are only mathematical devices which assist in the description of biological events. They may, however, fulfill a very useful purpose in clinical practice. The physician is often faced with some uncertainty about the degree of response that can be expected from many drugs, notably inotropic agents, antiarrhythmics, antihypertensives and bronchodilators. Depending on well-defined kinetic principles, the attainment of steady state bronchodilators. Depending on well-defined kinetic principles, the attainment of steady state in terms of drug concentration throughout the body can be confidently predicted. This is of little intrinsic interest to the clinician (although it may go some way to explaining unexpected drug effects, or the lack of them) but, integrated with appropriate response data, useful predictions about the degree of response in individual patients can be obtained. When alternative drug strategies are available, some clinical circumstances may well dictate that this could be an important consideration. Anticipation of a satisfactory response may well mitigate against prolonged morbidity occasioned by unnecessary delays in establishing 'correct' therapy.

With this aim in mind, Sheiner, Beal, Rosenberg & Marathe (1979b) have proposed the use of Bayesian prediction methods to determine estimates of model parameters. As a prerequisite, large amounts of drug concentration data and other relevant patient information are required to determine average population parameter values by using a computer programme, NONMEM (Beal & Sheiner, 1979). These parameters characterize the prior distribution of the Bayesian method, and in the absence of any information about a particular patient, the appropriate model parameter values would be the population mean values. Taking digoxin as an example (Sheiner et al., 1979b), one concentration measurement would improve forecast precision for future concentrations by about 40% and two concentration measurements would improve it by 67%. After only two measurements, forecast accuracy and precision would be as good as theoretically possible. Moreover, Sheiner points out that information from concentration measurements is far more valuable for forecasting than that from all other observable patient features, e.g. sex, age, weight etc.; use of this kind of information does not improve accuracy and precision as much as only one concentration measurement. To date this technique has been applied only to kinetic parameters, but in the future it is hoped that it can be extended to include dynamic parameters, by using one of the modelling techniques previously described.

References


