QUANTITATIVE ANALYSIS OF THE DISOPYRAMIDE CONCENTRATION-EFFECT RELATIONSHIP

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- 1 A combined pharmacokinetic-pharmacodynamic model has been used to analyse the relationship between QT prolongation and changes in plasma concentration which occurred after disopyramide was given intravenously and orally to eight healthy subjects.
- 2 The pharmacokinetic models appropriate to intravenous and oral disopyramide have been extended by an 'effect compartment' which has no influence on the predetermined mass of drug in the body.
- 3 The model incorporates an adjustment for lag of effect behind any rapid changes in plasma concentration such as occur in the early distributive phase following intravenous administration. This permits calculation of the proportionality constant relating plasma concentration to effect.
- 4 Irrespective of the route of administration the mean ($\pm$ s.d.) prolongation of the QT interval was 14.5 ± 6.5 ms/ μ g ml⁻¹.
- 5 There was no evidence that metabolite produced during first pass after oral administration made any significant contribution to effect.
- 6 This modelling technique should be applicable to the study of the concentration-effect relationship of a number of other drugs, both in health and in disease.

Introduction

A recent paper on the assessment of disopyramide bioavailability (Bryson, Whiting & Lawrence, 1978) presented pharmacodynamic data which suggested that prolongation of the QT interval after oral administration was directly proportional to the plasma disopyramide concentration. Effect and concentration were plotted against each other on linear axes and the degree of hysteresis, i.e. the presence or absence of a loop when the points were connected in time order, was determined. For both oral preparations studied (Rythmodan, Roussel Laboratories Ltd, and Norpace, Searle Laboratories Ltd), the area included within the loop was not significantly different from zero, confirming that pharmacological-effect kinetics were apparently perfectly in phase with plasma concentration kinetics at all times.

To determine the bioavailability of the oral preparations, disopyramide was also administered intravenously, but the concentration-effect relationship following intravenous administration was not

examined. It was clear from the hysteresis plots that after oral administration prolongation of the QT interval could be directly related to concentrations of drug in the plasma. This implied a state of equilibrium between plasma and relevant receptor site concentrations at all times, a concept not inconsistent with the one-compartmental characteristics of the drug after oral administration. Intravenous administration, however, presents an initial disequilibrium period when plasma concentration and effect may be out of phase. This has been demonstrated by Galeazzi, Benet & Sheiner (1976) who found a distinct time lag in QT prolongation relative to plasma concentration after rapid intravenous infusion of procainamide. Thus to model pharmacodynamics satisfactorily, two essential components of the concentration-effect relationship must be specified,

- (a) a proportionality constant relating equilibrium plasma (or tissue) concentrations to effect (sensitivity component) and
- (b) a time-related factor which accounts for any lag of effect behind changes in plasma concentration during periods of disequilibrium (temporal component).

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This paper re-examines the relationship between disopyramide plasma concentration and pharmacological effect after both oral and intravenous administration and seeks to quantitate its sensitivity and temporal components.

Methods

Details of the experimental protocol, drug administration schedules, ECG recording and disopyramide assay have been published previously (Bryson *et al.*, 1978). Eight normal healthy male volunteers were given three single doses of different preparations of disopyramide in a randomized sequence. The preparations were:

- oral Rythmodan (disopyramide base) 3×100 mg capsules
- oral Norpace, 2 capsules, each containing the phosphate salt equivalent to 150 mg disopyramide base
- intravenous disopyramide phosphate, 2 mg/kg body weight, administered as a short 2 min infusion.

For 8–10 h after drug administration, frequent blood samples were withdrawn along with recordings of the QT interval. At each time point 20–30 consecutive ECG complexes were recorded on a Cardiostat-T Electrocardiograph running at a speed of 25 mm/s with standard lead II limb leads. Twenty consecutive QT intervals were measured on each strip and their mean was determined. Control strips recorded before drug administration gave QT values which were used to determine the slope of the linear regression relationship between QT interval and heart rate in individual subjects over the 50–100 beats/min range. This was used to correct any observed post-drug administration QT changes for variations in heart rate according to the following relationship:

$$QT_p = b + mHR$$

where QT_p is the predicted QT interval,
 b is the zero intercept on the QT axis,
 m is the (negative) slope of the linear regression, and
 HR is the mean heart rate determined from measurement of 20 consecutive R-R intervals.

Any change in QT interval (ΔQT s) was then expressed as the absolute difference between observed and predicted QT values.

Pharmacokinetic analysis

Following intravenous administration, the disposition of disopyramide can be described by an

open two compartment model according to the following equation

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C_p^t is the total plasma disopyramide concentration at time t , A and B are the extrapolated zero intercepts on the Y axis of a semilogarithmic concentration v time plot and α and β are the rapid and slow disposition rate constants respectively. Analysis of the intravenous data based on this model showed that in all subjects, equilibrium between central and peripheral compartments was established within 20 min of intravenous administration.

Following oral administration, kinetic analysis revealed no discernible two compartmental characteristics, the data being adequately described by an open one compartment model according to the following equation

$$C_p^t = A_0 [e^{-k_{10}(t-t_{lag})} - e^{-k_a(t-t_{lag})}] \quad (2)$$

where C_p^t is the total plasma disopyramide concentration at time t , A_0 is the extrapolated mono-exponential terminal phase intercept on the Y axis of a semilogarithmic concentration v time plot, k_{10} is the elimination rate constant, k_a is the apparent first order absorption rate constant and t_{lag} is the lag time, included to account for the delay between drug administration and its first appearance in the blood. After initial graphical estimates of the coefficients of all exponential terms, plasma concentration v time data were analysed by a nonlinear least squares fitting program on an IBM 360/370 digital computer to yield the mean kinetic parameters shown in Table 1.

Pharmacodynamic model

The kinetic parameters can then be incorporated into a model which characterizes the relationship between plasma concentration and effect. Sheiner, Stanski, Vozech, Miller & Ham (1979) have postulated that changes in pharmacological effect can be related to plasma concentrations by a first order process. The analytical technique involves extending the classical pharmacokinetic models shown in the upper part of Figure 1 by a hypothetical 'effect compartment' whose input and output functions *do not influence* the formal pharmacokinetic solution for mass of drug in the body. In other words, the established pharmacokinetics are unaffected by the minute 'loss' from the central compartment. Effect is then considered to be proportional to hypothesized changes in effect compartment concentrations and k_{eq} is the first order rate constant which expresses the discrepancy between events in the plasma (changes in concentration) and events in the effect compartment (changes in pharmacological effect). The *volume* of the effect compartment is considered to be negligible in relation

Figure 1 Pharmacodynamic and pharmacokinetic models: intravenous and oral disopyramide. See text for explanation of symbols.

to the total volume of distribution of the drug, and the input rate constant, k_{1e} , is extremely small compared with k_{eq} or any other rate constant in the pharmacokinetic model. It is important to note that it is not necessary to visualize the effect compartment in classical mammillary terms with a reversible component (' k_{e1} ') because, by definition, this compartment serves only to model the exponential process relating concentration to *effect*, and it in no way contributes to changes in the amount of drug in the rest of the model. In mathematical terms, a reversible component would only be credible if it contributed to another exponential in equations (1) and (2). As this is clearly inappropriate, k_{eq} ought not to be thought of in terms of ' k_{e1} '.

The following equation describes the change in amount of drug in the effect compartment with time:

$$\frac{dA_e}{dt} = k_{1e}A_1 - k_{eq}A_e \quad (3)$$

where A_e is the (hypothetical) amount of drug in the effect compartment and A_1 is the amount of drug in the central compartment.

After oral administration, the following equation describes the change in amount of drug in the body (A_{oral}) with time:

$$A_{oral} = \frac{k_a FD}{k_{10} - k_a} [e^{-k_a t^*} - e^{-k_{10} t^*}] \quad (4)$$

where F is the bioavailability factor, D is the dose, k_a and k_{10} are as previously defined and $t^* = t - t_{lag}$. Using Laplace transforms to solve for the corresponding amount in the effect compartment ($A_e(oral)$),

$$A_e(oral) = k_a k_{1e} FD \left[\frac{e^{-k_{1e} t^*}}{(k_{10} - k_a)(k_{eq} - k_{1e})} + \frac{e^{-k_{10} t^*}}{(k_a - k_{10})(k_{eq} - k_{10})} + \frac{e^{-k_{eq} t^*}}{(k_a - k_{eq})(k_{10} - k_{eq})} \right] \quad (5)$$

Similarly, for a bolus injection into the central compartment,

$$A_1 = D \left[\frac{k_{21} - \alpha}{\beta - \alpha} e^{-\alpha t} + \frac{k_{21} - \beta}{\alpha - \beta} e^{-\beta t} \right] \quad (6)$$

and the corresponding solution for the effect compartment is given by

$$A_e(i.v.) = k_{1e} D \left[\frac{k_{21} - \alpha}{(\beta - \alpha)(k_{eq} - \alpha)} e^{-\alpha t} + \frac{k_{21} - \beta}{(k_{eq} - \beta)(\alpha - \beta)} e^{-\beta t} + \frac{k_{21} - k_{eq}}{(\alpha - k_{eq})(\beta - k_{eq})} e^{-k_{eq} t} \right] \quad (7)$$

If we assume, as usual, that the partition coefficient between V_1 and V_e is 1, then

$$V_e = V_1 \cdot \frac{k_{1e}}{k_{eq}} \quad (8)$$

and as k_{1e} is extremely small compared with k_{eq} , V_e is negligible in relation to V_1 . Whereas the concentration in the effect compartment (C_e) is theoretically the amount of drug in that compartment divided by its steady state volume, or

$$C_e = \frac{A_e}{V_e} \quad (9)$$

C_e can also be derived in terms of the steady state volume of the central compartment by substituting the expression for V_e from equation (8) into equation (9), thus

$$C_e = \frac{A_e}{V_1} \cdot \frac{k_{eq}}{k_{1e}} \quad (10)$$

Now if $A_e(i.v.)$ from equation (7) is substituted into equation (10), k_{1e} cancels out giving a final expression for 'steady state equivalent' concentration of drug in the effect compartment. Thus after intravenous administration of disopyramide,

$$C_e(i.v.) = \frac{k_{eq}D}{V_1} \left[\frac{k_{21}-\alpha}{(\beta-\alpha)(k_{eq}-\alpha)} e^{-\alpha t} + \frac{k_{21}-\beta}{(k_{eq}-\beta)(\alpha-\beta)} e^{-\beta t} + \frac{k_{21}-k_{eq}}{(\alpha-k_{eq})(\beta-k_{eq})} e^{-k_{eq}t} \right] \quad (11)$$

Similarly after oral administration,

$$C_e(oral) = \frac{k_{eq}FDk_a}{V} \left[\frac{e^{-k_a t^*}}{(k_{10}-k_a)(k_{eq}-k_a)} + \frac{e^{-k_{10} t^*}}{(k_a-k_{10})(k_{eq}-k_{10})} + \frac{e^{-k_{eq} t^*}}{(k_a-k_{eq})(k_{10}-k_{eq})} \right] \quad (12)$$

Having derived an expression for C_e with only one unknown parameter, k_{eq} , substitution can then be made into a model which relates observed pharmacological effect to predicted concentrations in the effect compartment. The simplest possible model, a linear one, was tried, viz.:

$$E = mC_e + i \quad (13)$$

where E is the effect corresponding to a concentration, C_e , m is the slope and i is the intercept of the linear regression relationship. Preliminary testing of this model indicated that there was no advantage to be gained from using the more traditional effect v log concentration plot and all subsequent analyses were based on the linear model.

The full equations (11 and 12 substituted into 13) relating QT prolongation to concentrations of disopyramide in the effect compartment (or 'equivalent' steady state plasma concentrations) contain three unknown parameters, m (slope), i (intercept) and k_{eq} . Using the change in QT interval with time as

input, these parameters were estimated by a nonlinear least squares fitting program with unit weighting on PROPHET (a computer facility developed specifically as a data-handling tool for biomedical scientists, by Bolt, Beranek and Newman Inc., Cambridge, Mass., under the sponsorship of the N.I.H. Division of Research Resources). Values based on previous pharmacokinetic analysis were assigned to all other parameters. As three sets of data were available per individual (from one intravenous and two oral studies) the three corresponding equations could be solved separately or simultaneously, the former approach (referred to below as the *full* or *unrestricted* model) giving estimates for nine parameters—three slopes, three intercepts and three k_{eq} values. The latter approach led to a reduction in the number of parameters (*reduced* or *restricted* models) as discussed further below.

Before fitting data from individual subjects, an attempt was made to choose the most appropriate model (or models) using the pooled data from all subjects. The mean values for previously determined kinetic parameters (Table 1) were substituted into equation (13). A cubic spline interpolation procedure (INTERPOL in PROPHET) was used to adjust individual QT prolongation values to standardized times and the mean value at each time was used as input to the least squares fitting program.

By fitting i.v. and oral data sets simultaneously, the effect of combining or eliminating parameters could be tested (Table 2). Reduced models IV and VI were chosen to fit the data from individual subjects on the basis of the F statistic computed from the ratio of the model variances using the General Linear Test (Neter & Wasserman, 1974).

QT prolongation was also modelled as a linear function of the plasma disopyramide concentration (model V) where appropriate central or body

Table 1 Mean kinetic parameter values ($\pm$ s.d.) used in equation (13)

Parameter	Oral disopyramide		
	Intravenous disopyramide	Rythmodan	Norpace
$\frac{Dose}{V_1}$ ($\mu\text{g ml}^{-1}$)	6.8450 (± 2.1035)	—	—
$\frac{k_a FD}{V_d}$ ($\mu\text{g ml}^{-1} \text{ min}^{-1}$)	—	0.1448 (± 0.1103)	0.0868 (± 0.0403)
k_{21} (min^{-1})	0.0990 (± 0.0250)	—	—
α (min^{-1})	0.2531 (± 0.0751)	—	—
β (min^{-1})	0.0015 (± 0.0003)	—	—
k_a (min^{-1})	—	0.0397 (± 0.0174)	0.0202 (± 0.0088)
k_{10} (min^{-1})	—	0.0015 (± 0.0003)	0.0013 (± 0.0002)
lag (min)	—	14.3 (± 5.6)	13.1 (± 7.7)

Table 2 Pharmacodynamic models: combination of parameters and General Linear Test results

Model	Number of parameters	General Linear Test				P value
		k_{eq}	Slopes	Intercepts	SSQ*	F relative to Model I
I	9	i.v.	RYT	RYT	1077	—
II	7	i.v.	Common oral	RYT	1079	0.058
III	7	i.v.	RYT	RYT	1156	2.110
IV	6	i.v.	Common	RYT	1097	0.354
V	6	Nil	Common oral	RYT	6049	89
VI	5	Common	RYT	RYT	1194	1.565
VII	4	Common	Common	RYT	1491	4.455
VIII	3	Common	RYT	0	1699	5.577
IX	2	Common	Common	Common	1937	6.611

*SSQ = Sum of squared deviations from the best fit associated with each model.
RYT, Rhythmodan; NOR, Norpace.

compartment values were generated from equations (1) and (2) respectively and substituted into equation (13), thus

$$E = mC_p^i + i \quad (14)$$

Results

The full model (I) and reduced models (II–IX) are presented in Table 2, together with the effect of combining or eliminating various parameters. At the 5% level, the General Linear Test showed that models II, III, IV and VI provided fits which were entirely consistent with the full model. Reductions presented by the other models, however, resulted in fits which were significantly worse than that of the full model (VII, VIII and IX, $P < 0.05$; V, $P < 0.005$). The worst fit was given by the model which lacked the k_{eq} parameter (Model V) and this served to emphasize the need for its inclusion.

Final estimates of k_{eq} and the slope parameters appropriate to the full model and reduced models IV and VI are shown in Tables 3 and 4. Models IV and VI were chosen to fit individual data sets on the basis that VI was the simplest model consistent with the full model and IV permitted separate identification of i.v. and oral slopes.

The General Linear Test applied to the pooled data showed that only when intercepts were parameterized separately, were fits obtained which were consistent with the full model. It was clear, however, that as the intercepts were consistently close to zero, they were of *no pharmacological significance* and probably represented small intraindividual day-to-day shifts in baseline QT observations.

Parameter values derived from individual data with models IV and VI are presented in Table 5. Model IV gave k_{eq} values which ranged from 0.2907 to 0.7115 min^{-1} with a mean ($\pm$ s.d.) of $0.4580 \pm 0.1636 \text{ min}^{-1}$. As each value represented a rate constant, it could also be expressed in terms of the half-life of equilibration of drug effect following a sudden shift in plasma concentration. Thus corresponding 'equilibration' half-lives ($T_{1/2eq}$) ranged from 2.4 to 0.97 min, with a mean ($\pm$ s.d.) of $1.7 \pm 0.6 \text{ min}$.

Based on the paired *t*-test at the 5% level, there was no significant difference between intravenous and common oral slopes when they were parameterized separately (Model IV). When they were combined, model VI gave k_{eq} values which ranged from 0.265 to 0.9768 min^{-1} ($T_{1/2eq}$ 2.8 to 0.71 min) with a mean ($\pm$ s.d.) of $0.5205 \pm 0.2477 \text{ min}^{-1}$ ($T_{1/2eq}$ $1.6 \pm 0.7 \text{ min}$). Slopes varied from 22.27 to 7.78 $\text{ms}/\mu\text{g ml}^{-1}$ with a mean ($\pm$ s.d.) of $14.52 \pm 6.47 \text{ ms}/\mu\text{g ml}^{-1}$. Standard errors of parameter estimates are included in Tables 3, 4 and 5 to illustrate the accuracy associated with each estimate.

The linear form of the concentration-effect relationship given by equation (13) is shown in Figures 2 to 5. Pooled data were used to construct Figures 2 and 3; data from one individual (Subject 2) were used to construct Figures 4 and 5. Both observed changes in the QT interval and the predicted form of the relationship are illustrated.

Discussion

The quantitative analysis of the disopyramide concentration-effect relationship presented in this paper confirms the earlier impression that after *oral* administration, plasma concentration and pharmacological-effect kinetics are essentially in phase at all

Table 3 Final parameter estimates from pooled data: k_{eq}

Model	Number of parameters	$k_{eq} (min^{-1})$			
		Common	i.v.	Oral	
				<i>RYT</i>	<i>NOR</i>
I	9	—	0.3909 (1.8600)	0.8470 (137.1)	21.06 (1.04)
IV	6	0.3992 (0.0433)	—	—	—
VI	5	0.4491 (0.0564)	—	—	—

Values are given with standard error of estimates in parentheses.

Table 4 Final parameter estimates from pooled data: slopes

Model	Number of parameters	Slopes ($ms/\mu g\ ml^{-1}$)				
		Common	i.v.	Oral		
				Common	<i>RYT</i>	<i>NOR</i>
I	9	—	16.55 (1.19)	—	13.78 (2.52)	13.97 (3.35)
IV	6	—	13.45 (2.02)	16.46 (2.13)	—	—
VI	5	14.5 (1.84)	—	—	—	—

Values are given with standard error of estimates in parentheses.

Table 5 Final parameter estimates from individual data: Models IV and VI

Subject	$k_{eq} (min^{-1})$		Slopes ($ms/\mu g\ ml^{-1}$)		
	Model IV	Model VI	Model IV		Model VI
			i.v.	common oral	common
1	0.3778 (0.0572)	0.6634 (0.3492)	36.45 (2.68)	12.25 (1.80)	20.26 (1.95)
2	0.3303 (0.0614)	0.3491 (0.0674)	18.02 (1.57)	16.29 (1.26)	16.96 (0.97)
3	0.6701 (0.2588)	0.9768 (0.6104)	11.80 (1.27)	7.70 (0.91)	9.11 (0.76)
4	0.4764 (0.1472)	0.4787 (0.1435)	22.06 (2.84)	21.85 (2.84)	21.96 (1.99)
5	0.3010 (0.1286)	0.2465 (0.0800)	7.88 (1.79)	9.94 (0.87)	9.57 (0.78)
6	0.5060 (0.2564)	0.3597 (0.1225)	5.77 (1.26)	9.75 (1.01)	8.24 (0.82)
7	0.2907 (0.0594)	0.3611 (0.0971)	10.57 (1.31)	7.02 (0.66)	7.78 (0.60)
8	0.7115 (0.1798)	0.7289 (0.1836)	23.06 (2.13)	21.94 (1.36)	22.27 (1.14)

Values are given with standard error of estimates in parentheses.

Figure 2 Plasma concentration-effect relationship after intravenous disopyramide. Each point represents the mean ΔQT observed in eight subjects at concentrations generated from mean i.v. kinetic parameters (Table I). The predicted form of the relationship according to Model VI is shown by the continuous line: arrows denote the time sequence.

Figure 4 Plasma concentration-effect relationship after 150 mg disopyramide intravenously: subject 2. Each point represents the ΔQT value observed at concentrations generated from individually fitted kinetic parameters. The predicted form of the relationship according to Model VI is shown by the continuous line: arrows denote the time sequence.

Figure 3 Plasma concentration-effect relationship after oral disopyramide. Each point ($\circ$, Rythmodan; $\bullet$, Norpace) represents the mean ΔQT observed in eight volunteers at concentrations generated from mean oral kinetic parameters (Table I). The predicted form of the relationship according to Model VI is shown by the continuous (Rythmodan) and interrupted (Norpace) lines: anticlockwise arrows denote the time sequence.

Figure 5 Plasma concentration-effect relationship after 300 mg disopyramide orally: subject 2. Each point ($\circ$, Rythmodan; $\bullet$, Norpace) represents the ΔQT value observed at concentrations generated from individually fitted kinetic parameters. The predicted form of the relationship according to Model VI is shown by the continuous (Rythmodan) and interrupted (Norpace) lines: anticlockwise arrows denote the time sequence.

times (Hinderling & Garrett, 1976b; Bryson *et al.*, 1978). The pharmacodynamic model now proposed is capable of defining the essential components of this relationship in quantitative terms. Disequilibrium between plasma concentration and effect can be described by a first order rate constant which allows pharmacodynamics to be modelled as a function of plasma concentration irrespective of the disposition characteristics of the drug. Figures 3 and 5 show that after oral administration, the linear form of the relationship chosen to describe the data was

appropriate for the range of values studied. In keeping with previous hysteresis plots, predicted changes in QT (continuous and broken lines in Figures 3 and 5) showed no significant lag behind changes in concentration. The extremely small anticlockwise hysteresis which is apparent is merely a reflection of the equilibration half-life which was computed from simultaneously fitted intravenous data. When oral data were fitted separately, as in the full model, the relatively large estimates for k_{eq} indicated that almost instantaneous equilibrium was

achieved between concentration and effect at all plasma levels. In other words, these data showed that after oral administration, the k_{eq} parameter was essentially redundant and the pharmacodynamic model reduced to the linear relationship expressed by equation (14), where effect is modelled as a linear function of the plasma (or single compartment) concentration.

After intravenous administration however, the form of the *plasma* concentration-effect relationship cannot be modelled satisfactorily without accommodating the disequilibrium between plasma concentration and effect which occurs during the early distributional phase. Figures 2 and 4 show the form of this relationship. The point of inflexion, P, between the curved component and the straight line is the point at which *pseudodistribution equilibrium* is attained. Above this point the model predicts the curvilinear relationship which clearly expresses the disequilibrium between concentration and effect. Below this point the linear segment characterizes the phase when concentration and effect *are* in equilibrium.

The lack of any significant difference between the oral and intravenous slopes is good evidence that as far as QT prolongation is concerned, sensitivity to disopyramide is not influenced by route of administration. First pass metabolism of up to 16% of an orally administered dose has been reported by Hinderling & Garrett (1976a) but the present analysis finds no evidence for active metabolites. These would tend to steepen and shift the oral slopes to the left.

Some impression as to where the site of action or biophase is in relation to established pharmacokinetic compartments can be gained from examination of the relative values of k_{eq} and k_{21} . When k_{eq} is equal to k_{21} the effect parallels changes in concentration in the peripheral compartment of a two compartment model. When k_{eq} is greater than k_{21} , as exemplified in the present study, the biophase is 'closer' to the central compartment, i.e. the biophase is kinetically shallower than the peripheral compartment. When k_{eq} is less than k_{21} the biophase exists in a compartment which is kinetically 'deeper' than that allowed by the peripheral compartment. It is possible, therefore, to visualize effect as the result of changes in the amount of drug in the whole kinetic model rather than to relate it to one or other specific compartments.

As well as providing an accurate prediction of the concentration-effect relationship as shown in

Figure 6 Comparison of profiles of predicted concentration *v* time (continuous line—two compartment pharmacokinetic model) and effect *v* time (interrupted line—pharmacodynamic Model VI) in one subject (2) after 150 mg disopyramide intravenously.

Figures 2 to 5, the model can also generate a predicted effect-time profile as shown in Figure 6, here contrasted with the more traditional concentration-time profile after intravenous administration. The precise relationship between plasma concentration and effect as time progresses is clearly demonstrated.

It is difficult to say whether or not QT prolongation induced by disopyramide closely reflects antiarrhythmic activity, but the analytical technique presented in this paper gives some insight into the relationship between drug concentrations as they appear in the plasma, and one of their important electrophysiological effects. More generally, this modelling technique should find useful application in the accurate definition and prediction of pharmacological effect in response to changes in the plasma concentration of a number of other drugs. It should also facilitate the study of the relationship between altered pharmacokinetics and sensitivity to drugs in disease states.

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