Br. J. clin. Pharmac. (1978), **6**, 409–419

DISOPYRAMIDE SERUM AND PHARMACOLOGIC EFFECT KINETICS APPLIED TO THE ASSESSMENT OF BIOAVAILABILITY

S.M. BRYSON

Department of Pharmacy, Stobhill General Hospital, Glasgow G21 3UW

B. WHITING & J.R. LAWRENCE

Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow G21 3UW

1 Serum, urine and pharmacologic effect (prolongation of the QT interval) kinetics of the antiarrhythmic disopyramide have been investigated in eight volunteers after intravenous administration (2 mg/kg) and oral administration (300 mg) of the two commercially available preparations, Rythmodan (Roussel Laboratories) and Norpace (Searle Laboratories).

2 An open one compartment body model adequately described the kinetics of disopyramide in serum and urine.

3 After intravenous administration, the following average pharmacokinetic parameters were found: biological half-life, 7.8 h; total clearance, 95 ml/min; renal clearance, 54 ml/min; apparent volume of distribution, 60 litres.

4 After oral Rythmodan and Norpace, serum concentration profiles and urinary excretion data revealed significant differences in rates of absorption, times required to achieve peak serum concentrations and biological half-lives. These differences were largely due to the relatively slow absorption characteristics of Norpace.

5 The absence of hysteresis in plots of QT prolongation against disopyramide serum concentration after oral administration indicated that serum and pharmacologic effect kinetics were indistinguishable within a kinetically equivalent compartment.

6 Analysis of both serum and urine data showed that while Norpace had a significantly higher degree of bioavailability ($P < 0.005$), the 5–15% difference between the two formulations should not normally be of any clinical significance.

Introduction

Disopyramide (4-diisopropylamino-2-phenyl-2(2-pyridyl) butyramide) is a relatively new antiarrhythmic agent which is finding an established role in the prevention of post-myocardial infarction ventricular arrhythmias (Jennings, Model, Jones, Turner, Besterman & Kidner, 1976; Kidner, 1977). In addition, it has been used successfully in the treatment of a variety of arrhythmias (Härtel, Louhija & Konttinen, 1974; Mizgala & Huvelle, 1976; Niarchos, 1976). It acts principally by slowing conduction in the His–Purkinje system and by increasing the effective refractory period of the atria and ventricles (Spurrell, Thorburn, Camm, Sowton & Deuchar, 1975). Recent work has indicated a dual effect on atrial and atrioventricular conduction and refractory periods (Birkhead & Vaughan Williams, 1977).

Previous pharmacokinetic studies in man (Karim, 1975; Hinderling & Garrett, 1976a) indicate that disopyramide has a biological half-life of about 6 h in healthy volunteers, and that it is excreted predominantly unchanged in the urine by glomerular filtration. Approximately 25% of the dose is metabolized and the principal metabolite in man has been identified as the mono-N-dealkylated derivative (Karim, 1975). The extent to which the drug is bound to plasma proteins has been estimated to be of the order of 27%, (Chien, Lambert & Karim, 1974), but the binding process is saturable and this figure is dependent on both the plasma disopyramide and metabolite concentrations (Hinderling, Brès & Garrett, 1974).

Two oral preparations of the drug are available for

clinical use—disopyramide *base*, marketed as Rythmodan (Roussel Laboratories) and disopyramide *phosphate*, marketed as Norpace (Searle Laboratories). The phosphate is also available for intravenous use, marketed as Rythmodan (Roussel Laboratories). As generic inequivalence may have an important bearing on clinical practice, it was decided to assess the comparative bioavailabilities of the two oral forms of disopyramide, using the intravenous preparation as a reference standard. Although pharmacokinetic differences *per se* would be of considerable interest, the study was also designed to investigate the relationship between the pharmacokinetics and one measure of pharmacological effect of the drug, namely prolongation of the QT interval (Hinderling & Garrett, 1976b).

This paper is based on a project presented by S.M. Bryson to the University of Strathclyde for the degree of MSc (Clinical Pharmacy).

Methods

Subjects

Eight normal healthy male volunteers were used for the study. All were of similar age (21–31 years, mean 25 years) and weight (62–92 kg, mean 75 kg). They were instructed that no drugs should be taken for 1 week prior to the date of each disopyramide administration and that no alcohol was permitted over the entire study period. Food and fluid intake was standardized on study days and volunteers remained supine for the first 4 h post-drug administration period. During the remainder of the day, they were advised not to engage in any strenuous or athletic activities which might influence the kinetics of the drug.

Approval for the study was sought and obtained from the Research and Ethics Committee of Stobhill General Hospital.

Drug administration schedule

At intervals of not less than 1 week, each volunteer received three single doses of different preparations of disopyramide, following a Latin Square crossover design to ensure that the sequence was randomized. The three preparations were:

(a) oral Rythmodan, 3 x 100 mg capsules
(b) oral Norpace, 2 capsules, each containing the phosphate salt equivalent to 150 mg disopyramide base
(c) intravenous disopyramide, 2 mg/kg body weight, given as a bolus over 2 min.

One batch of each preparation was used throughout the study to avoid the possibility of inter-batch variation influencing the results.

Sample collection

Blood samples (10 ml into plain glass tubes) were withdrawn through an indwelling 'Venflon' cannula, previously inserted into an antecubital vein, at the following times: pre-dose (control), 2, 3, 5, 7, 10, 15, 20, 30, 45, 60 and 90 min and at 2, 3, 4, 6, 8, 10, 12, 24, 32 and 48 h after intravenous administration and at pre-dose (control), 10, 20, 30, 45, 60 and 90 min after oral administration and then at the same intervals as shown for the intravenous experiment. The indwelling cannulae were flushed regularly with small quantities of heparinized saline and an initial 2 ml blood was discarded at each sampling time to ensure no dilution effect. After clotting, serum was separated by centrifugation and stored at −20°C until required for analysis.

In both intravenous and oral experiments, urine was collected at the following times: pre-dose (control), 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–48 and 48–72 h after drug administration. Total volumes were measured and 10 ml aliquots subsequently stored at −20°C until required for analysis.

Assay procedure

Extraction Disopyramide is a weak base (pK_a 9.2), and was extracted from serum or urine as follows (Holt, personal communication). 100 µl internal standard solution (*p*-chlorodisopyramide in chloroform, 50 µg/ml) was evaporated to dryness, and 1 ml serum (blank, standard or sample) or 1 ml of a 1 : 10 dilution of urine was added. To this, 200 µl 2 M NaOH followed by 5 ml diethyl ether were added. After vortex mixing for 30 s and centrifugation at 3000 rev/min for 4 min the ether layer was removed, acidified with 1 ml 0.05 M H_2SO_4, and similarly vortex mixed and centrifuged. The organic layer was removed by aspiration and any residual ether eliminated by a stream of air. Alkalinization was then effected by adding 600 µl 2 M NaOH and the extraction completed by the addition of 100 µl chloroform. The organic layer was again separated by centrifugation after vortex mixing for 30 s. Up to 5 µl of the chloroform layer was injected onto the gas chromatograph.

Gas liquid chromatography The instrument used was a Perkin Elmer F33 gas chromatograph equipped with a nitrogen/phosphorus detector. Operating conditions were similar to those described by Duchateau, Merkus & Schobben (1975). The column was a 1 m pyrex glass coil, internal diameter 3 mm, packed with 3% w/w OV–17 on Gaschrom Q support. The oven was maintained at a temperature of 270°C, with an injector/detector temperature of 300°C. The nitrogen detector bead heating voltage was 600 mv. Carrier gas was nitrogen at 30 psi.

Hydrogen and air were supplied at 15 and 22 psi respectively.

The limit of detection was 0.1 μg/ml (plasma) and the extraction efficiency from plasma at 5 μg/ml was 85.5%. Quality control experiments showed satisfactory reproducibility with a coefficient of variation of 4.1% at the 5 μg/ml level and 4.67% at the 0.5 μg/ml level.

Electrocardiography

After administration of all three forms of the drug, the effect of disopyramide on the rate of impulse conduction through the AV node and His-Purkinje system was assessed by measurement of the change in the electrocardiographic QT interval with time (Hinderling & Garrett, 1976b) in parallel with the pharmacokinetic study. At each time point, 20–30 consecutive ECG complexes were recorded by means of a Cardiostat-T Electrocardiograph with standard lead II chest leads. Three control strips were recorded in the half hour before drug administration, then at 2 min intervals to 20 min, 10 min intervals to 60 min, and at 75, 90, 105, 120, 150, 180, 210, 140, 300, 360, 420, 480 and 600 min after intravenous disopyramide, and at 10 min intervals after oral disopyramide to 60 min, then as for the intravenous study. Whenever possible, blood samples were taken at the mid time points of ECG recordings. Twenty consecutive QT intervals were measured on each strip and their mean and standard deviation determined. The coefficient of variation of these measurements was always within 1–2%.

As has been pointed out recently by Galeazzi, Benet & Sheiner (1976), correction of QT intervals for heart rate by the standard square-root correction (Bazett, 1920) proved unsatisfactory as it actually magnified drug and heart-rate related effects. The approach adopted by Galeazzi *et al.* (1976) was therefore followed and a linear regression of QT interval on heart rate was determined for all subjects, the mean slope being -1.7 ms beat min^{-1}, over a range of heart rates from 50–100 beats min^{-1}. Heart rate correction was obtained from the equation

$$cQT = QT + mHR \quad \ldots\ldots \quad \text{Equation 1}$$

where cQT is the corrected QT interval,
QT is the measured QT interval,
m is the slope of the linear regression line,
and HR is the mean heart rate determined from measurement of 20 consecutive R–R intervals.

Placebo injections of normal saline administered to two volunteers on a separate occasion showed that this approach was valid and that the cQT value was uninfluenced by variations in heart rate. All cQT values subsequent to drug administration were expressed as a percentage of control values, or ΔQT%.

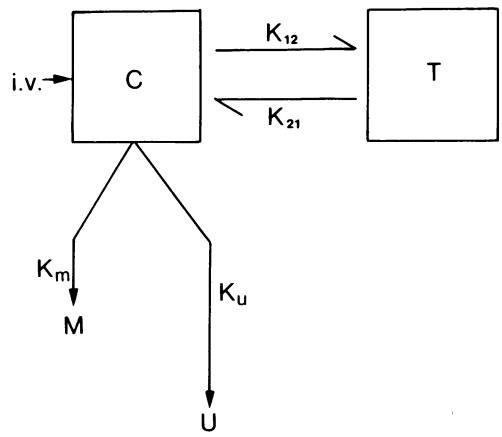

Figure 1 Open two compartment body model used initially to fit intravenous disopyramide data. C and T are the central and peripheral compartments respectively; U represents drug excreted in the urine and M represents metabolic conversion in the liver. K_{12}, K_{21}, K_u and K_m are corresponding first order rate constants.

Pharmacokinetic analysis

Serum data: intravenous administration Hinderling & Garrett (1976a) showed that the disposition of disopyramide in humans can be described by an open two compartment model (Figure 1). Thus concentrations of disopyramide in the serum after intravenous administration were analysed according to the following equation

$$C_p^t = A\,e^{-\alpha t} + B\,e^{-\beta t} \quad \ldots\ldots \quad \text{Equation 2}$$

where C_p^t is the total serum disopyramide concentration at time t, A and B are the extrapolated zero intercepts on a semilogarithmic plot of concentration vs time and α amnd β represent distribution and elimination rate constants respectively. Initial graphical estimates of these parameters and corresponding serum concentration vs time data were analysed by a non-linear least squares fitting programme on an IBM 360/370 digital computer. An accurate prediction of serum concentration profiles was obtained, together with the dimensions of the two compartment model and a precise estimate of the total area under serum concentration vs time curves (AUC_{iv}). Total clearance (Cl_{tot}), defined as the constant fraction of the volume of distribution from which drug is eliminated in unit-time, and expressed in ml/min, was derived from the relationship

$$Cl_{tot} = \frac{\text{Dose}}{AUC_{iv}} \quad \ldots\ldots \quad \text{Equation 3}$$

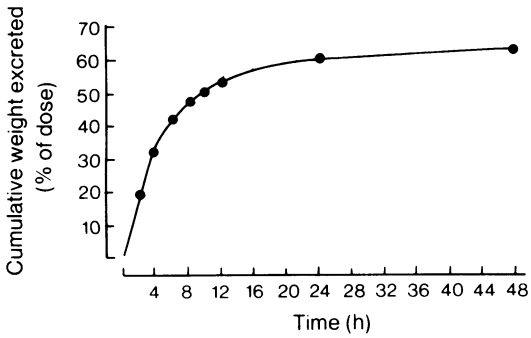

Figure 2 Cumulative urinary excretion profile of disopyramide after intravenous administration (164 mg, volunteer PM).

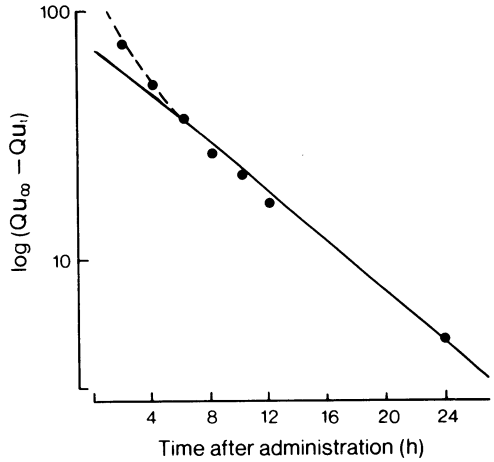

Figure 3 The Sigma-minus plot, where ($Qu_\infty - Qu_t$) represents the sum (Sigma) of the amounts of disopyramide excreted until such time as excretion is considered to be complete (Qu_∞), minus the cumulative amount excreted to any time t (Qu_t). (Volunteer PM, 164 mg intravenously).

Analysis of intravenous data based on the two compartment model showed that in all subjects, the intravenous distribution half-life ($\alpha T_{\frac{1}{2}}$) was extremely short (mean ± s.d., 3.0 ± 1.0 min) and relatively high values for K_{12} (mean ± s.d., 9.104 ± 3.52 h^{-1}) and K_{21} (mean ± s.d., 5.936 ± 1.497 h^{-1}) indicated rapid equilibrium between 'central' and 'peripheral' compartments. These observations suggested that a one compartment model would be adequate to describe disopyramide kinetics. Moreover, on the assumption that pseudo distribution equilibrium is attained when the α term in equation 2 contributes less than 1% to the total plasma concentration (Hinderling & Garrett, 1976a) this state was always attained within approximately 20 min of intravenous administration. It was therefore highly unlikely that significant amounts of drug were slowly equilibrating with poorly perfused tissues in the 'peripheral' compartment and it was decided that all pharmacokinetic analysis could be based on the simpler one compartment model.

Serum data: oral administration Concentration v time data after oral administration were analysed according to the following equation, which describes absorption and elimination from a one compartment model

$$C_p^t = A_0[e^{-\beta(t_{lag})} - e^{-Ka(t-t_{lag})}] \quad \text{Equation 4}$$

where C_p^t is the total serum disopyramide concentration at time t, A_0 is the extrapolated β phase intercept on the Y axis of a semilogarithmic concentration v time plot, β is the slope of the terminal elimination phase, 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. Initial graphical estimates of these parameters and corresponding serum concentration v time data were analysed by a non-linear least squares fitting programme as before, and computed parameters were used to determine the area under the oral serum concentration v time curve (AUC_{oral}), the time at which peak plasma concentrations occurred (T_{max}) and peak serum concentrations (Cp_{max}). Bioavailability of both oral forms was determined with reference to the intravenous dose (representing 100% absorption) by comparison of the respective areas under the concentration v time curves.

Thus apparent availability (%)

$$= \frac{\int_0^\infty C_p^t\,dt(\text{oral})}{\int_0^\infty C_p^t\,dt(\text{i.v.})} \times 100 \quad \text{Equation 5}$$

Urinary excretion data The amount of disopyramide excreted unchanged in the urine over each time period was determined. Total recovery was estimated by plotting these amounts cumulatively as per cent dose against time (Figure 2). Biological half-lives were also estimated from urinary data by plotting the log of the amount of drug not yet excreted against time (Figure 3, 'Sigma–Minus' plot). The slopes of the terminal phases of these plots gave an alternative estimate of the biological half-life, as follows

$$\log(Qu_\infty - Qu_t) = -\frac{\beta}{2.303} + \log Qu_\infty \quad \text{Equation 6}$$

where Qu_∞ is the amount of unchanged disopyramide eliminated in the urine over an infinite period of time

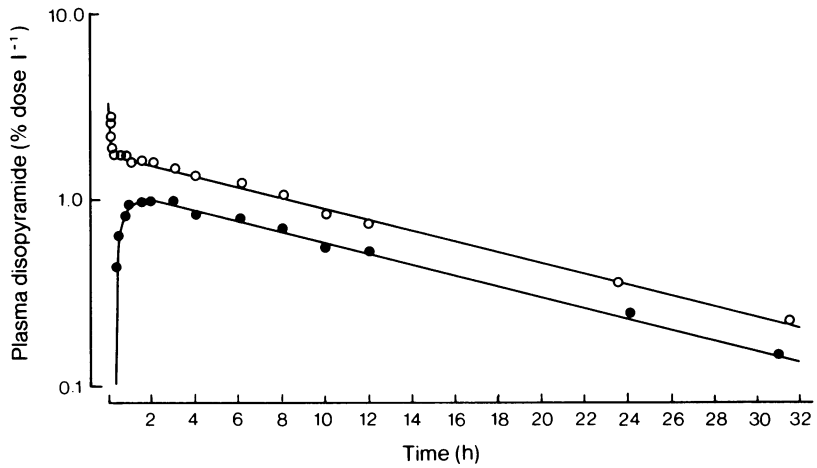

Figure 4 Semi-logarithmic serum concentrations *v* time plots after 164 mg intravenous (○) and 300 mg oral (●) disopyramide (Volunteer PM). The computed least squares fit is shown by the line drawn through the data points

and Qu_t is the cumulative amount of drug excreted unchanged up to any time, t. Renal clearance (Cl_r) was determined from the quotient of Qu_∞ and the corresponding area under the serum concentration *v* time curve, as follows:

$$Cl_r = \frac{Qu_\infty}{\int_0^\infty C_p^t \, dt} \quad \text{. . . . . Equation 7}$$

The difference between total and renal clearance after intravenous administration gave an estimate of non-renal clearance, Cl_{nr}.

Results

Serum pharmacokinetics: intravenous administration

Unless otherwise specified, all results are expressed as mean ± s.d. and statistical significance is based on the Student's paired *t*-test.

A typical semilogarithmic concentration *v* time curve is shown in Figure 4. After an initial rapid fall in concentration, characterized by the α distribution constant, the intravenous plot followed a log-linear decline (β phase). Associated computed kinetic parameters and calculated values for apparent volume of distribution (V_d), AUC_{IV} and Cl_{tot} are shown in Table 1. The mean biological half-life was 7.79 ± 1.55 h with a range of 5.96 h (WS) to 10.49 h (GT). The mean apparent volume of distribution was 59.97 ± 20.74 litres. With the exception of WS, V_d values fell within the range 40–70 l. The mean total clearance was 95.09 ± 50.28 ml/min. Again with the exception of WS, clearance values varied within the range 60–120 ml/min. Pseudo-distribution equilibrium, based on a value of $f\alpha \leqslant 0.01$ in the ratio

$$f\alpha = \frac{A\,e^{-\alpha t}}{A\,e^{-\alpha t} + B\,e^{-\beta t}} \quad \text{. . . . . Equation 8}$$

was attained at a mean of 21.3 ± 6.6 min after intravenous administration.

Serum pharmacokinetics: oral administration

A typical semilogarithmic concentration *v* time plot after the oral administration of Rythmodan or Norpace is shown in Figure 4. Tables 2 and 3 illustrate the important similarities and differences in serum profiles and areas under the curves. Lag times (Rythmodan 14.3 ± 5.6 min, Norpace 13.1 ± 7.7 min) and peak serum concentrations (Rythmodan 1.00 ± 0.25% dose/litre; Norpace 1.01 ± 0.26% dose/litre) were very similar. However, the rate of absorption of Rythmodan was significantly faster than that of Norpace (absorption half-lives were 18.2 ± 7.0 min and 38.9 ± 13.3 min respectively: $P < 0.02$), and this was associated with a significantly shorter time to achieve peak serum concentrations (Rythmodan 1.69 ± 0.49 h; Norpace 2.80 ± 0.66 h: $P < 0.02$). The decline in serum concentrations as reflected by half-lives after Rythmodan and intravenous disopyramide was very similar, 7.96 ± 1.45 h and 7.79 ± 1.55 h respectively, but both these values differed significantly from the half-lives found with Norpace, mean 8.91 ± 1.60 h (intravenous disopyramide *v* Norpace, $P < 0.05$; Rythmodan *v* Norpace, $P < 0.02$). Mean comparative bioavailability

results are presented in Table 4. The availability of Norpace (81.76 ± 17.9%) was higher than that of Rythmodan (66.88 ± 10.99%, $P < 0.005$), although Norpace showed slightly more variation in the consistency of absorption, with a coefficient of variation of 22% compared with 16% for Rythmodan.

Urine Pharmacokinetics

Figure 2 shows the typical urinary excretion profile of disopyramide after intravenous administration. Renal excretion was almost complete within 24 h and 58.13 ± 6.42% of the intravenous dose was excreted as

Table 1 Computed kinetic parameters and clearance values after intravenous disopyramide administration (2 mg/kg) to eight volunteers. (For explanation of symbols, see text).

	Subjects								
	SB	*AT*	*WS*	*PM*	*CC*	*DG*	*GT*	*MC*	*Mean* ± s.d.
A (% dose/l)	2.63	2.98	2.13	1.78	4.05	5.42	2.00	1.69	2.84 ±1.30
α (h^{-1})	12.69	16.77	15.47	8.76	20.97	19.09	18.34	9.41	15.19 ±4.51
$T_{\frac{1}{2}}\alpha$ (min)	3.3	2.5	2.7	4.7	2.0	2.2	2.3	4.4	3.0 ±1.0
B (% dose/l)	1.98	1.92	0.93	1.45	2.07	2.31	1.79	1.90	1.79 ±0.43
β (h^{-1})	0.074	0.095	0.116	0.105	0.079	0.096	0.066	0.101	0.091 ±0.017
$T_{\frac{1}{2}}\beta$ (h)	9.28	7.30	5.96	6.55	8.72	7.21	10.49	5.81	7.79 ±1.55
AUC (% dose/l.h)	26.46	20.17	7.97	13.67	26.06	24.01	27.07	18.68	20.51 ±6.85
V_d (l)	50.58	52.17	107.87	69.14	48.27	43.33	55.89	52.57	59.97 ±20.74
Cl_{tot} (ml/min)	62.97	82.61	209.11	121.93	63.95	69.40	61.57	89.20	95.09 ±50.28
Cl_r (ml/min)	38.79	47.88	96.93	77.67	41.73	43.2	32.19	50.90	53.65 ±22.12

Table 2 Absorption and elimination characteristics of Rythmodan (For explanation of symbols, see text)

	Subjects								
	SB	*AT*	*WS*	*PM*	*CC*	*DG*	*GT*	*MC*	*Mean* ± s.d.
K_a (h^{-1})	2.58	4.96	2.78	1.63	1.83	4.49	1.81	1.55	2.70 ±1.33
Absorption $T_{\frac{1}{2}}$ (min)	16.1	8.4	14.9	24.4	22.7	9.2	23.0	26.8	18.2 ±7.0
β (h^{-1})	0.081	0.085	0.118	0.102	0.076	0.076	0.068	0.108	0.090 ±0.017
$T_{\frac{1}{2}}\beta$ (h)	8.56	8.12	5.88	6.80	8.69	9.06	10.13	6.44	7.96 ±1.45
t_{lag} (min)	16.5	8.2	12.5	15.2	20.8	10.7	22.9	7.7	14.3 ±5.6
T_{max} (h)	1.66	0.97	1.39	2.06	2.14	1.10	2.26	1.97	1.69 ±0.49
$C_{p\,max}$ (% dose/l)	0.84	1.19	0.62	0.77	1.29	1.29	1.01	1.02	1.00 ±0.25
AUC_{oral} (%dose/l.h)	11.61	14.95	6.04	9.10	19.58	18.09	16.88	11.56	13.48 ±4.69
Cl_r (ml/min)	58.8	62.33	116.67	95.91	57.69	48.59	57.86	58.87	69.59 ±23.64

unchanged disopyramide over an infinite time period (approximating to 72 h). Corresponding percentages after oral administration were Rythmodan, 51.07 ± 8.90% and Norpace, 54.80 ± 9.83%.

Figure 3 illustrates the 'Sigma–Minus' method for estimating the biological half-life from urinary data. After intravenous administration, individual $T_{\frac{1}{2}}\beta$ estmations determined from urinary data (7.36 ± 1.31 h) agreed very well with those from serum data, (7.79 ± 1.5 h). Good agreement was also obtained after oral Rythmodan (urinary data, 7.96 ± 1.45 h; serum data 7.98 ± 0.85 h) but it was not possible to show the same correlation for Norpace (urinary data, 7.39 ± 1.27 h; serum data 8.91 ± 1.59 h).

Table 5 shows the mean urinary disopyramide excretion rates with respect to time after administration of both oral preparations. Significant differences ($P < 0.05$) in excretion rates were found at two time periods, 0–2 and 6–8 h. The rate of Norpace excretion was slower than that of Rythmodan initially, but faster during the 6–8 h time period.

Bioavailability calculated on the basis of comparison of the total amounts of intact drug excreted in the urine following oral and intravenous administration yielded higher values than those obtained from comparison of the areas under the oral and intravenous serum concentration time curves (Table 4). From urinary data, mean bioavailability of Rythmodan was 87.68 ± 14.40% and that of Norpace, 94.98 ± 13.83%. Again, the availability of Norpace was significantly higher than that of Rythmodan ($P < 0.005$).

Clearance

Individual variations in clearance were observed after intravenous disopyramide, (Table 1) with values ranging from 61.57 to 209.11 ml/min for total clearance (equation 3) and 32.19 to 96.93 ml/min for renal clearance (equation 7). Differences in renal clearance after the two oral preparations (Tables 2 and 3) were generally small (Rythmodan, 69.59 ± 23.64 ml/min, Norpace 61.22 ± 19.19 ml/min) and the mean renal clearance determined in each subject after both oral drugs was consistently higher than corresponding intravenous values ($P < 0.01$).

Table 3 Absorption and elimination characteristics of Norpace (For explanation of symbols, see text)

	SB	*AT*	*WS*	*PM*	*CC*	*DG*	*GT*	*MC*	*Mean* ± s.d.
κ_a (h^{-1})	0.95	1.47	0.99	0.80	1.32	0.70	2.35	1.12	1.21 ±0.52
Absorption $T_{\frac{1}{2}}$ (min)	43.6	28.2	42.0	51.6	31.4	59.7	17.7	37.2	38.9 ±13.3
β (h^{-1})	0.082	0.069	0.094	0.089	0.063	0.074	0.065	0.104	0.080 ±0.015
$T_{\frac{1}{2}}\beta$ (h)	8.45	9.99	7.36	7.80	11.00	9.42	10.66	6.64	8.91 ±1.60
t_{lag} (min)	8.0	–	13.8	24.6	18.0	11.4	9.0	19.7	13.1 ±7.7
T_{max} (h)	2.95	2.18	2.86	3.48	2.71	3.8	1.72	2.67	2.80 ±0.66
Cp_{max} (% dose/l)	0.85	1.12	0.59	0.75	1.37	1.23	1.00	1.19	1.01 ±0.26
AUC_{oral} (% dose/l.h)	13.10	18.82	8.05	11.08	25.42	21.83	17.08	14.51	16.24 ±5.72
Cl_r (ml/min)	61.00	47.34	93.21	88.04	48.83	41.73	58.47	51.15	61.22 ±19.19

Table 4 Comparative bioavailabilities of Rythmodan and Norpace derived from serum data (mean ± s.d. eight volunteers).

	Rythmodan	*Norpace*	P *value paired* t-*test*
$AUC_{oral_{0-\infty}}$ (% dose)	13.48 ± 4.69	16.24 ± 5.72	<0.005
Availability (%) (Equation 5)	66.88 ± 10.99	81.76 ± 17.90	<0.005

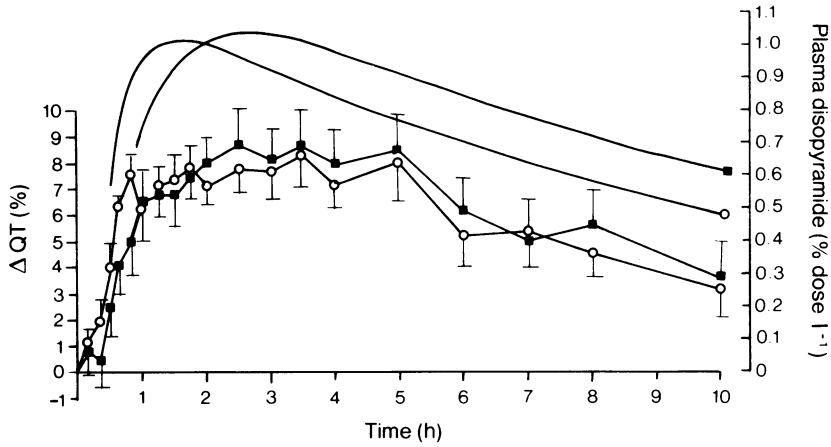

Figure 5 Plot of (i) mean ± s.e. mean ΔQT (%) after the oral administration of Rythmodan (○) and Norpace (■) and (ii) corresponding mean predicted disopyramide serum concentrations *v* time for all volunteers. (The lower pair of lines simply connect ΔQT (%) points).

Electrocardiographic data

The average ± s.e. mean maximum ΔQT% which occurred within 2–12 min of intravenous administration was 9.1 ± 0.76%, and thereafter declined in parallel with disopyramide serum concentrations ($r = 0.92$, $P < 0.001$).

The mean ΔQT% values (±1 s.e. mean) at all recorded times up to 10 h after oral drug administration for all subjects are shown in Figure 5, together with the mean predicted serum concentration *v* time profiles, derived from substitution of mean kinetic parameters in equation 4. There was a definite tendency for QT changes to mirror differences in the serum profiles, but at no time was there any statistically significant difference between Rythmodan and Norpace as reflected by ΔQT%. Using the *t*-test, the highest *t* values were found at 40 and 50 min (1.9649 and 1.9426 respectively) which only attained the 10% significance level.

The relationship between QT prolongation and serum concentration after oral administration was examined further by plotting these variables against each other (Figure 6) and determining the degree of hysteresis, i.e. the presence or absence of a loop in the graph when the points are connected in time order. For both Rythmodan and Norpace, the area included in the loop was not significantly different from zero. This was determined by subtracting the total area under the lower limb from that under the upper limb, and computing the significance of the deviation of the difference in areas from zero by the *t*-test (Galeazzi *et al.*, 1976). The absence of hysteresis confirmed that the kinetics of the pharmacological effect are closely related to those of the drug in the serum.

Table 5 Urinary excretion rates of disopyramide with respect to time after oral administration of Rythmodan or Norpace (mean ± s.d: eight volunteers).

Time (h)	*Excretion rate (mg/h)* *Rythmodan*	*Norpace*
0–2*	13.48 ± 4.16	8.60 ± 2.85
2–4	14.74 ± 2.07	13.61 ± 1.68
4–6	13.63 ± 2.95	16.20 ± 3.47
6–8*	8.71 ± 3.16	11.75 ± 4.80
8–10	5.82 ± 2.19	6.48 ± 1.67
10–12	4.56 ± 2.17	4.89 ± 1.21
12–24	1.62 ± 0.46	2.02 ± 0.71
24–48	0.42 ± 0.19	0.46 ± 0.21
48–72	0.08 ± 0.05	0.09 ± 0.04

* $P < 0.05$, Student's paired *t*-test

Discussion

This study, designed to assess the comparative bioavailabilities of two oral forms of disopyramide used Dost's law of corresponding areas (Dost, 1962; 1968) and measurement of cumulative amount of unchanged drug excreted in the urine to estimate the extent of absorption. Since the biological half-life of disopyramide was of the order of 8 h, two important bioavailability criteria were fulfilled. Firstly, serum concentration measurements extended over what was

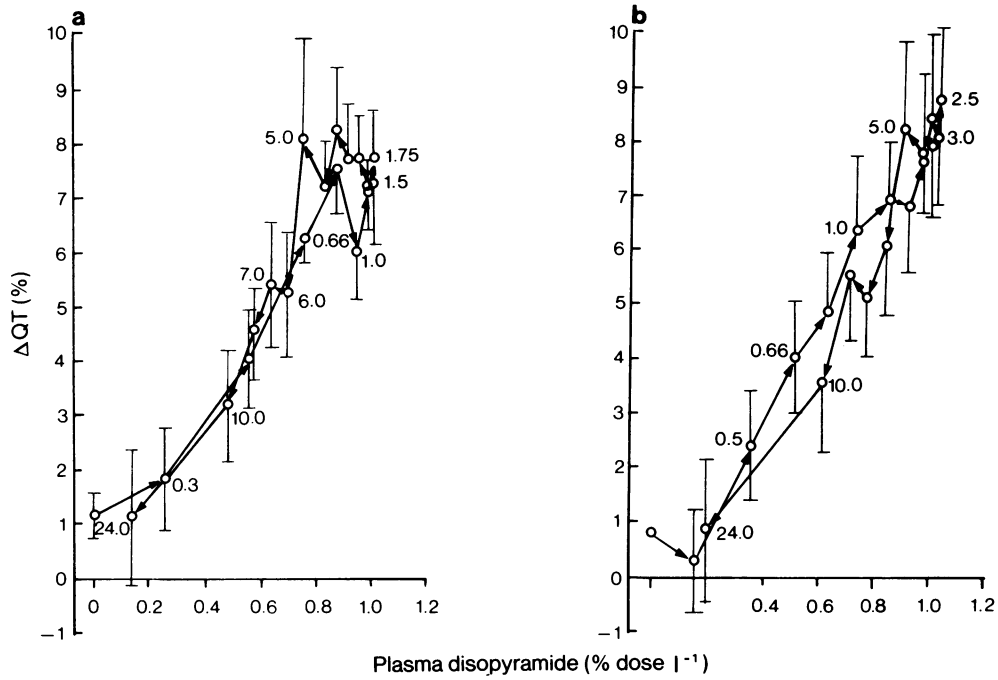

Figure 6 Hysteresis loops for ΔQT (%) plotted against simultaneously predicted serum disopyramide concentrations after the oral administration of (a) Rythmodan and (b) Norpace. The points are mean values (± s.e. mean) for all studies in all volunteers and are connected in time order by arrows. Time (h) is shown by figures next to some of the points. The area in each hysteresis loop is not significantly greater than zero.

effectively an 'infinite' time period (0–48 h) so that AUC values did not depend on extrapolation from partial AUC measurements and secondly, 72 h urine collections ensured that more than 98% of the unchanged drug excreted into the urine was recovered. The results from both these methods indicated that up to 26% more disopyramide could be absorbed from Norpace (subject CC) but there were considerable inter individual differences, one subject (GT), for example, only absorbing 1–2% more. Notwithstanding these differences, the important question to ask is whether or not this kind of generic inequivalence is of any *clinical* significance. Bearing in mind the relatively wide therapeutic ratio associated with this drug—effective serum levels range from 2.8 to 7.5 μg/ml (Niarchos, 1976)—steady state serum concentrations can be predicted on the basis of bioavailability from the formula proposed by Wagner, Northolm, Alway & Carpenter (1965):

$$C_{ss} = \frac{F \cdot D}{K \cdot V_d \cdot T}$$

where F = bioavailability
D = dose
K = elimination rate constant
V_d = volume of distribution
T = dose interval

When this formula is applied to subject CC, where the difference between the two preparations was most marked, it is at once obvious that these differences are reflected by only small changes in steady state serum concentrations. A dose of 400 mg daily would result in serum concentrations of 3.0 μg/ml with Rythmodan and 4.0 μg/ml with Norpace. This difference would be of no clinical significance within the latitude allowed by the wide therapeutic margin but a change from one brand to another at higher doses might be associated with the onset of anticholinergic side effects, which have been reported to occur at a level of about 5.5 μg/ml (Niarchos, 1976). This consideration alone might well dictate that a patient stabilized on one brand should not be changed to another, but in the majority of cases, where the difference in bioavailability will only be of the order of 5–15%, such a change will be of no consequence. Indeed, the comparison of pharmacodynamic data presented in

Figure 5 illustrates that whereas there was a tendency for QT prolongation to mirror the different serum concentration profiles, at no time did differences in this measure of pharmacological effect attain statistical significance.

It is apparent that the parent compound from neither formulation is absorbed completely into the systemic circulation. Hinderling & Garrett (1976a) found that whereas almost 100% of an oral aqueous solution of disopyramide phosphate was absorbed, 16% was metabolised during first-pass through the liver, and this may explain part of the absolute reduction in bioavailability found in the present study. It is also likely that the solid excipients in Rythmodan and Norpace, rather than the different chemical forms, contribute further to this reduction in availability and to the observed differences in the absorption and elimination profiles.

An interesting discrepancy revealed by the results was the significant difference in the bioavailability fraction calculated from serum and from urinary excretion data, the latter giving higher values. This phenomenon has been reported previously in relation to digoxin bioavailability studies (Greenblatt, Duhme, Koch-Weser & Smith, 1974; Marcus, Dickerson, Pippin, Stafford & Bressler, 1976), and may be due to alterations in clearance which are dependent on the precise mode of administration. Marcus *et al.* (1976) reported that 21% more digoxin was excreted in the urine over 6 days after a 3 h intravenous infusion than after a 1 h infusion. Greenblatt *et al.* (1974) also observed this effect when they found a greater 6 day urinary excretion of digoxin after a 1 h infusion compared with a rapid intravenous injection. This suggests that the calculated availability of an orally administered drug may vary with the rapidity of injection of the intravenous reference preparation. In the present study the high initial disopyramide serum concentrations associated with intravenous administration may have produced atypical distribution and elimination kinetics because there were significant differences in overall renal clearance after administration by oral and intravenous routes. A much more detailed analysis of the kinetics during the initial stages of each experiment, including measurement of free and bound drug and metabolite(s) in body fluids would be required to make a full assessment of the situation.

The mean predicted serum concentration profiles shown in Figure 5 illustrate the principal differences in the absorption and elimination characteristics of the two formulations. These differences were reflected in rates of absorption, the time required to achieve peak serum concentrations, and biological half-lives (Tables 2 and 3). Urinary excretion results (Table 5) confirmed that the rate of absorption of Norpace was slower than that of Rythmodan. In general, the serum half-lives found for Rythmodan were similar to those found after intravenous administration (Tables 1 and 2) and any small differences were assumed to be due to minor changes in clearance between study days. The apparent lengthening of the Norpace half-lives was due to its relatively slow release characteristics which tended to maintain plasma concentrations during the elimination phase. The similarity in peak concentrations attained at different times (Rythmodan 1.7 h: Norpace 2.8 h) provided further evidence for the greater availability of Norpace. A reduction in the Norpace K_a value without any increase in the fraction absorbed would have led to delayed, *reduced* peak concentrations, but these were not observed.

The close relationship between serum disopyramide levels and QT prolongation shown by the absence of significant hysteresis supports the view expressed by Hinderling & Garrett (1976b) that after *oral* administration, serum and pharmacologic effect kinetics, reflected by QT changes, are indistinguishable. These authors proposed a two-compartment model, the central compartment having an apparent volume of distribution intermediate between the volume of plasma water (3.0 l) and the volume of the extra-cellular water (12 l). Their suggestion that the biophase may be equivalent to the central compartment is in keeping with the present findings because serum levels will reflect concentrations in this compartment. However, for reasons already outlined, it appears that the disposition of disopyramide can be analysed in terms of one compartment model (apparent volume of distribution of the order of 60 litres) and that after oral administration, drug concentration changes within this single compartment are directly related to QT changes.

It is not surprising that the initial rapid decline (α phase) in serum concentrations following *intravenous* administration was not paralleled by QT changes. During this phase, which had a mean half-life of 3.0 ± 1.0 min, maximum QT prolongation was established within 2–12 min and a good correlation between serum concentrations and QT prolongation was established and maintained after about 20 minutes. This of course coincided with the attainment of pseudo-distribution equilibrium, or the point at which $f_\alpha \leqslant 0.01$ in equation 8. The early disparity between serum and pharmacologic effect kinetics clearly represents the time taken for drug dispersal throughout the vascular system and subsequent distribution. After 20 min, the effect on the QT interval decreased at a rate very similar to the decline in serum concentrations. After oral administration, serum and pharmacologic effect kinetics were analogous at all time periods, implying a kinetically equivalent compartment. As overall volumes of distribution in the present study were referenced to *total* serum disopyramide concentrations, the values found were somewhat smaller than those reported by Hinderling & Garrett (1976a), whose calculations

were based on unbound concentrations. The volumes, however, were always in excess of values expected for total body water, and this implies some degree of tissue penetration or binding. Nevertheless, it appears that the reversible process of uptake and release of disopyramide from tissues are rapid, and occur within a kinetically homogeneous compartment.

The authors are indebted to Dr David F. Woodings, Senior Research Physician of Roussel Laboratories Ltd, for generous support in setting up the disopyramide assay, and for many helpful discussions. Grateful thanks are also due to Dr David J. Sumner for guidance and help with the computing and to Mr Daniel McSharry and Mr Stephen Miller for technical assistance.

References

BAZETT, H.C. (1920). An analysis of the time relationship of the electrocardiogram. *Heart*, **7**, 353–360.

BIRKHEAD, J.S. & VAUGHAN WILLIAMS, E.M. (1977). Dual effect of disopyramide on atrial and atrioventricular conduction and refractory periods. *Br. Heart H.*, **39**, 657–660.

CHIEN, Y.W., LAMBERT, H.J. & KARIM, A. (1974). Comparative binding of disopyramide phosphate and quinidine sulphate to human plasma proteins. *J. pharm. Sci.*, **63**, 1877–1879.

DOST, F.H. (1962). Ein Verfahren zur Ermittlung des absoluten Transportvermögens des Blutes im Fliessgleichgewicht. *Klin. Wschr.*, **40**, 732–733.

DOST, F.H. (1968). *Grundlagen der Pharmacokinetik*, 2nd ed., Georg Thieme, Stuttgart.

DUCHATEAU, A.M.J.A., MERKUS, F.W.H.M. & SCHOBBEN, F. (1975). Rapid gas chromatographic determination of disopyramide in serum using a nitrogen detector. *J. Chromatog.*, **109**, 432–435.

GALEAZZI, R.L., BENET, L.Z. & SHEINER, L.B. (1976). Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clin. Pharmac. Ther.*, **20**, 278–289.

GREENBLATT, D.J., DUHME, D.W., KOCH-WESER, J. & SMITH, T.W. (1974). IV digoxin as a bioavailability standard: slow infusion and rapid injection. *Clin. Pharmac. Ther.*, **15**, 510–513.

HÄRTEL, G., LOUHIJA, A. & KONTTINEN, A. (1974). Disopyramide in the prevention of recurrence of artrial fibrillation after electro-conversion. *Clin. Pharmac. Ther.*, **15**, 551–555.

HINDERLING, P.H., BRÉS, J. & GARRETT, E.R. (1974). Protein binding and erythrocyte partitioning of disopyramide and its mono-dealkylated metabolite. *J. Pharm. Sci.*, **63**, 1684–1690.

HINDERLING, P.H. & GARRETT, E.R. (1976a). Pharmacokinetics of the antiarrhythmic disopyramide in healthy humans. *J. Pharmacokin. Biopharm.*, **4**, 199–230.

HINDERLING, P.H. & GARRETT, E.R. (1976b). Pharmacodynamics of the antiarrhythmic disopyramide in healthy humans: Correlation of the kinetics of the drug and its effects. *J. Pharmacokin. Biopharm*, **4**, 231–242.

JENNINGS, G., MODEL, D.G., JONES, M.B.S., TURNER, P.P., BESTERMAN, E.M.M. & KIDNER, P.H. (1976). Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction. *Lancet*, **i**, 51–54.

KARIM, A. (1975). The pharmacokinetics of Norpace. *Angiology*, **26**, suppl. 1, 85–98.

KARIM, A., RANNEY, R.E. & KRAYCHY, S. (1972). Species differences in the biotransformation of a new antiarrhythmic agent: disopyramide phosphate. *J. pharm. Sci.*, **61**, 888–893.

KIDNER, P.H. (1977). Prevention of ventricular arrhythmias after myocardial infarction. *J. Roy. Coll. Phycns.*, **11**, 352–362.

MARCUS, F.I., DICKERSON, J., PIPPIN, S., STAFFORD, M & BRESSLER, R. (1976). Digoxin bioavailability—formulations and rates of infusion. *Clin. Pharmac. Ther.*, **20**, 253–259.

MIZGALA, H.F. & HUVELLE, P.R. (1976). Acute termination of cardiac arrhythmias with intravenous disopyramide. *J. Int. Med. Res.*, **4** (Suppl 1), 82–85.

NIARCHOS, A.P. (1976). Disopyramide-serum level and arrhythmia conversion. *Am. Heart J.*, **92**, 57–64.

SPURRELL, R.A.J., THORBURN, C.W., CAMM, J., SOWTON, E. & DEUCHAR, D.C. (1975). Effects of disopyramide on electrophysiological properties of the specialised conduction system in man and on accessory atrioventricular pathway in the Wolff-Parkinson-White syndrome. *Br. Heart J.*, **37**, 861–867.

WAGNER, J.G., NORTHOLM, J.I., ALWAY, C.D. & CARPENTER, O.S. (1965). Blood levels of drugs at the equilibrium state after multiple dosing. *Nature*, **207**, 1301–1302.

(Received October 24, 1977)