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DISOPYRAMIDE PHARMACOKINETICS DURING RECOVERY FROM MYOCARDIAL INFARCTION

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1 Previous pharmacokinetic studies of disopyramide in patients with ischaemic heart disease include unexplained reports of poor bioavailability and extremely long elimination half-lives which undermine accepted dosage recommendations.

2 Disopyramide pharmacokinetics were investigated after intravenous and oral administration to nine such patients.

3 Mean elimination half-life (6.82 h) and bioavailability (79.8%) were consistent with findings from a previous study in young healthy volunteers.

4 Volume of distribution was reduced by 25%: the mean ± s.d. value was 0.61 ± 0.17 l/kg. Total body clearance was significantly reduced: the mean ± s.d. value was 1.02 ± 0.16 ml min^{-1} kg^{-1}.

5 These figures indicate that, in this patient group, if renal function is not significantly impaired, a standard loading dose of 2 mg/kg should be followed by the appropriate maintenance dose administered three or four times daily.

Introduction

Disopyramide is a quinidine-like antiarrhythmic drug, useful in the prevention and treatment of cardiac arrhythmias associated with ischaemic heart disease. Individualisation of dosage is advisable if optimum therapy is to be achieved and measurement of the plasma concentration is a valuable guide to dosage adjustment: the accepted therapeutic range is 2–7 μg/ml (Niarchos, 1976). Side effects are primarily related to anticholinergic activity but disopyramide also exhibits negative inotropic activity and must therefore be used with great caution in patients with incipient cardiac failure.

A previous pharmacokinetic study in normal, young, healthy male volunteers (Bryson *et al.*, 1978) showed that disopyramide total body clearance is of the order of 95 ml/min and that the elimination half-life ranges from 6–10 h. The parent drug is excreted unchanged by glomerular filtration and approximately 25% of a dose is metabolised to mono-*N*-dealkyldisopyramide. The plasma protein binding is saturable and depends on both parent drug and metabolite concentrations (Hinderling *et al.*, 1974).

The disposition of antiarrhythmic drugs has been shown to be altered in patients following myocardial infarction; the absorption of procainamide (Koch-Weser, 1971), aprindine (Hagemeijer, 1975) and mexilitine (Pottage *et al.*, 1978) may be impaired and the elimination half-life of aprindine is significantly prolonged (Hagemeijer, 1975). The present study was designed to investigate whether or not similar changes in the pharmacokinetics of disopyramide occur in patients with ischaemic heart disease and whether or not there are any changes in bioavailability in clinical practice.

Methods

Patients

Nine patients (seven males and two females) were included in the study. Clinical details are listed in Table 1. All patients had sustained an acute myocardial infarction and were receiving disopyramide for the treatment or prophylaxis of ventricular or supraventricular tachyarrhythmias. Ages ranged from 43–73 years (mean 60 years) and weights ranged from 46–82 kg (mean 68 kg). Patients were studied between 3 and 14 days after myocardial infarction. All patients had moderate to good renal function (creatinine clearance > 30 ml/min) estimated from serum creatinine values by the method described by Mawer (1976).

The study did not interrupt normal ward routine;

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Table 1 Clinical details of the patients studied

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Cl_{cr} (ml/min)*	*Diagnosis*	*Time after MI (days)*	*Concurrent therapy*
1	59	M	73.3	71.7	AMI	6	Frusemide, chlordiazepoxide
2	70	F	81.5	57.0	IMI	2	Isosorbide dinitrate, frusemide, GTN
3	65	M	45.5	48.5	IMI	4	Salbutamol, temazepam, co-trimoxazole
4	43	M	72.3	73.3	IMI	13	Oxprenolol, frusemide, pentazocine, nitrazepam
5	59	F	73.5	80.2	IMI	7	—
6	47	M	54.9	47.5	IMI	14	Bendrofluazide, temazepam, Dorbanex.
7	73	M	66.0	38.6	AMI	5	Frusemide, paracetamol, dihydrocodeine, nitrazepam
8	70	M	64.2	59.3	IMI	8	Frusemide
9	54	M	80.0	84.5	AMI	6	Methyldopa, nitrazepam, bendrofluazide

AMI—anterior myocardial infarction
IMI—inferior myocardial infarction

diet and activity were dictated by clinical progress and no other drugs were withheld. Approval for the study was sought and obtained from the Research and Ethics Committee, Stobhill General Hospital. The purpose of the investigation was explained to each patient and written informed consent was obtained.

Protocol

Disopyramide (Rythmodan, Roussel Laboratories) was given orally for at least 48 h to ensure that steady state had been achieved. Five of the group had previously received intravenous loading doses or infusions while in the coronary care unit. Dosage requirements for the individual patients were selected at the discretion of the attending physicians. A schematic representation of the experimental protocol is illustrated in Figure 1. The plasma concentration *v* time profile following the first oral dose on the first study day was determined, and 24 h later, a similar profile was determined following a short 5 min infusion.

Sample collection

Venous blood samples (5 ml in plain tubes) were withdrawn through a 'Venflon' indwelling i.v. cannula (inserted into an antecubital vein) at the

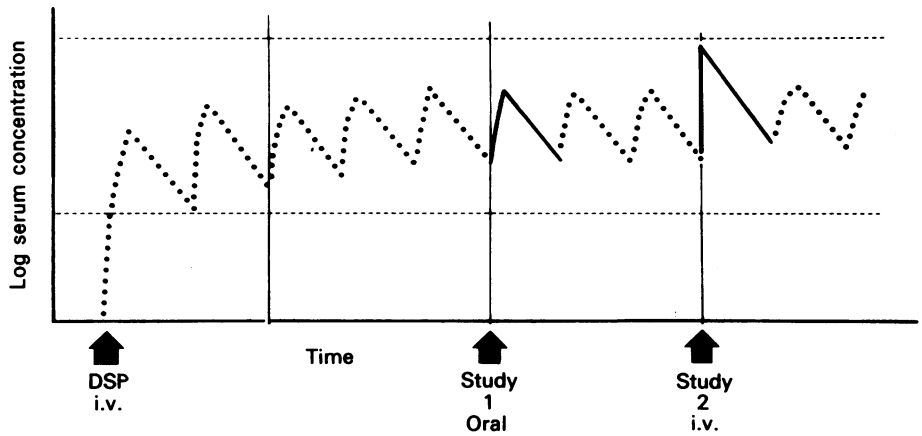

Figure 1 Schematic representation of experimental protocol; DSP disopyramide.

following times: zero (trough) and then hourly throughout the dosing interval. Heparinised saline, 100 units/ml, was used to prevent clotting in the cannula and an initial 1 ml of blood was discarded at each sampling time to ensure no dilution effect. After collection, the blood was allowed to clot and the serum was separated by centrifugation and stored at −20°C until required for analysis.

Drug analysis

A modification of a sensitive and specific gas liquid chromatographic method for the quantitation of disopyramide in body fluids was utilised (Duchateau *et al.*, 1975). This employed a Perkin Elmer F33 gas liquid chromatograph equipped with a Perkin Elmer nitrogen/phosphorus detector. Details of the extraction procedure, operating conditions, and assay precision have been published previously (Bryson *et al.*, 1978).

Pharmacokinetic analysis

The disposition of disopyramide in humans has been described by an open 2 compartment model. However, it has been shown that drug distribution is extremely rapid (Hinderling & Garrett, 1976); the distribution half-life is short (of the order of 2–3 min) and the contribution of the distribution component (α) to the total area under the serum concentration v time curve (AUC) is extremely small. For these reasons, a one compartment model was considered adequate for the pharmacokinetic data analysis.

Individual kinetic parameters were calculated using standard techniques. The elimination rate constant (k_e) was determined from the slope of the ln serum concentration versus time profile. The volume of distribution (V_d) was calculated from the following equation after i.v. administration:

$$V_d = \frac{X_o}{(Cp' - Cp_t)}$$

where X_o is the dose, Cp′ is obtained by extrapolation of the ln serum concentration versus time line to time zero, and Cp_t is the trough concentration measured immediately before injection. The area under the concentration v time curve after oral administration (AUC_o) was determined during a dosage interval at steady state by application of the trapezoidal rule. However, administration of the intravenous dose disrupted the steady state conditions and the resultant AUC ($AUC_{i.v.}$) was determimed from the following equation:

$$AUC_{i.v.} = \frac{Cp' - Cp_t}{k_e}$$

Total body clearance of disopyramide (Cl) was calculated from the equation:

$$Cl = \frac{X_o}{AUC_{i.v.}}$$

Disopyramide bioavailability (F) was determined from the relationship:

$$F = \frac{AUC_o}{AUC_{i.v.}} \times \frac{X_{o\,(i.v.)}}{X_{o\,(oral)}} \times 100$$

Results

Individual pharmacokinetic parameters for the nine patients are listed in Table 2. The mean ± s.d. k_e was found to be 0.110 ± 0.03 h^{-1}; the mean ± s.d. elimination half-life ($T_{1/2}$) was 6.85 ± 1.87 h, with a range of 4.64–9.65 h. Large interindividual differences were found in V_d: the mean ± s.d. value was 38.80 ± 11.35 l (or 0.61 ± 0.17 l/kg body weight), with a range of 28.21–64.52 l. The mean total body clearance (Cl) was 65.8 ± 14.2 ml/min (or 1.02 ± 0.16 ml min^{-1} kg^{-1}), with a range of 47.5–85.3 ml/min. Although there appeared to be a linear relationship between disopyramide and creatinine clearance, the amount of data available was insufficient to provide a

Table 2 Pharmacokinetic parameters determined after intravenous administration of disopyramide

Patient	k_e (h^{-1})	$T_{1/2}$ (h)	V_d (l/kg)	*AUC* ($\mu g\,ml^{-1}\,h$)	*Cl* ($ml\,min^{-1}\,kg^{-1}$)
1	0.132	5.23	0.52	19.52	1.16
2	0.074	9.33	0.79	20.88	0.98
3	0.072	9.65	0.87	17.56	1.05
4	0.119	5.82	0.44	26.24	0.88
5	0.143	4.83	0.41	23.21	0.98
6	0.102	6.78	0.78	28.48	1.30
7	0.092	7.53	0.60	16.59	0.77
8	0.142	4.64	0.44	47.58	1.09
9	0.089	7.81	0.63	44.24	0.93
Mean	0.110	6.85	0.61		1.02
s.d.	0.03	1.87	0.17		0.16

significant correlation at the 5% level ($Cl = 40.5 + 0.4\ Cl_{cr}$, $r = 0.56$).

After oral administration relatively rapid absorption was observed (peak plasma concentrations were achieved within 1–3 h) and the terminal elimination phase was found to be similar to that after i.v. administration (mean $T_{½}$ values were 6.80 and 6.85 from the oral and i.v. profiles respectively). The mean ± s.d. bioavailability was 79.8 ± 9.5%, with a range of 65.0–91.9%. Details of the pharmacokinetic parameters determined after oral administration are listed in Table 3.

Table 3 Pharmacokinetic parameters after oral administration of disopyramide to ten patients with ischaemic heart disease.

Patient	k_e (h^{-1})	$T_{½}$ (h)	*AUC* ($\mu g\ ml^{-1}\ h$)	*F* (%)
1	0.132	4.82	17.01	87.2
2	0.127	5.46	20.88	68.3
3	0.066	10.44	26.48	75.4
4	0.127	5.46	20.47	78.0
5	0.126	5.50	30.85	86.8
6	0.098	7.07	26.18	91.9
7	0.085	8.12	25.46	76.6
8	0.116	5.98	15.46	65.0
9	0.083	8.36	39.99	89.0
Mean	0.110	6.80		79.8
± s.d.	0.02	1.85		9.48

Discussion

Much of the previous work on the pharmacokinetics of disopyramide has been carried out in normal healthy volunteers. Drug disposition in patients who have sustained a myocardial infarction may differ for several reasons. They are usually considerably older than volunteers and cardiovascular status, as well as hepatic and renal status may be compromised. Moreover, administration of narcotic analgesics and antiemetics may interfere with drug absorption.

The disopyramide elimination half-life values found in patients recovering from myocardial infarction in this study were not significantly different from values found in single dose studies in normal volunteers (Bryson *et al.*, 1978; Karim, 1975). This observation is consistent with some previous reports (Rango *et al.*, 1976; Ward & Kinghorn 1976), but does not agree with the conclusions of Ilett *et al.* (1979) who reported an extremely long mean disopyramide half-life (38.0 ± 3.7 (s.e. mean) h) in a group of similar patients who had no renal impairment.

Despite the fact that elimination half-life does not seem to be influenced by a recent myocardial infarction (or incidentally, by age), mean ± s.d. total body clearance of disopyramide is significantly reduced when compared with volunteers (1.02 ± 0.16) and 1.30 ± 0.70 ml min^{-1} kg^{-1} respectively; Student's *t*-test, $P < 0.05$). Presumably this reflects the reduction in both creatinine and renal disopyramide clearances which occur with advancing age. A further reduction (mean ± s.d. value 0.467 ± 0.215 ml min^{-1} kg^{-1}) was found recently in a group of patients with imminent to moderate cardiac failure (Landmark *et al.*, 1981). In the present study, one patient (No. 3) had acute left ventricular failure which responded successfully to treatment before the institution of disopyramide and good evidence of mild, transient congestive cardiac failure was present in only one other patient (No. 8). The other four who received frusemide had evidence of chest infection and/or chronic obstructive airways disease.

The mean ± s.d. volume of distribution found in the present study (0.61 ± 0.17 l/kg) was identical to that found by Landmark *et al.* (1981) in patients with cardiac failure (0.61 ± 0.14 l/kg) but was considerably lower than that previously reported by Bryson *et al.* (1978) following single doses given to normal subjects (0.78 ± 0.26 l/kg). This discrepancy may be a reflection of altered tissue perfusion in such patients.

The results of a previous investigation (Ward & Kinghorn, 1976) suggested that, after oral administration, disopyramide serum levels were, on average, lower in patients recovering from myocardial infarction than in healthy volunteers. This was thought to be related to poor bioavailability or high first pass metabolism but no data was presented to substantiate this. In the present study, therapeutic serum levels were achieved in all patients and mean bioavailability at steady state was comparable with figures reported in a previous, single dose, volunteer study (79.8 and 66.9% respectively; Bryson *et al.*, 1978). Disopyramide does not undergo any significant degree of first pass metabolism and the low serum levels observed by Ward & Kinghorn (1976) are more likely to be a consequence of reduced absorption due to concurrent therapy with narcotic analgesics and antiemetics.

Information about the absorption and disposition of disopyramide in patients with ischaemic heart disease is sparse and conflicting. Of particular concern are the unexplained observations of poor bioavailability and extremely long biological half-lives. In comparison to normal volunteers, the results of this study show that bioavailability and half-life are apparently unchanged by ischaemic heart disease (and age). The latter observation indicates that the

dosage interval for oral disopyramide should not exceed 8 h.

These patients did exhibit changes in disopyramide disposition. Volume of distribution was reduced by 25%, possibly due to decreased tissue perfusion. A reduced clearance was also observed and may be explained by a combination of decreased tissue perfusion and age related reductions in renal function. Nevertheless, these changes are not of a sufficient degree to warrant any alteration in the accepted dosage recommendations: 2 mg/kg (loading), 300–800 mg daily (maintenance).

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