PHARMACOKINETICS OF ORAL DISOPYRAMIDE PHOSPHATE IN PATIENTS WITH RENAL IMPAIRMENT

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- 1 The pharmacokinetics of disopyramide were studied after the oral administration of a 300 mg dose to 11 patients with stable chronic renal impairment (creatinine clearance 2–53 ml min⁻¹).
- 2 Absorption half-life and volume of distribution were similar to those seen in normal subjects.
- 3 Mean plasma elimination half-life in these patients was 12.7 h, which is substantially greater than that reported for normal subjects. Elimination half-life tended to increase as creatinine clearance fell, and renal clearance of disopyramide correlated significantly ($r=0.814$; $P < 0.001$) with creatinine clearance.
- 4 From these results, we have calculated that patients with renal impairment should be started on a dose of disopyramide 1.5 mg kg⁻¹ thrice daily and the regimen subsequently altered according to plasma concentrations of the drug. However, further studies are needed to define the handling of the metabolites of disopyramide.

Introduction

Disopyramide, a class 1 anti-arrhythmic drug (Vaughan Williams, 1970), is effective in the prophylaxis and treatment of cardiac arrhythmias (Heel, Brogden, Speight & Avery, 1978). The most common unwanted effects of disopyramide are due to its anticholinergic action: dry mouth, blurred vision, constipation, difficulty in micturition, and even impotence (Ward & Kinghorn, 1976; McHaffie, Guz & Johnston, 1977). Myocardial depression and drug-induced arrhythmias are seen less commonly, but all these adverse effects seem more likely to occur when plasma concentrations of the drug are too high.

Disopyramide is eliminated predominantly in the urine; after a single intravenous dose, 77% is excreted as the parent drug and the mono-N-dealkylated metabolite (Hinderling & Garrett, 1976). Dealkylation is the most important metabolic pathway; ring hydroxylation and conjugation account for only a small proportion of a given dose, and the cyclic metabolites which have been reported are probably analytical artefacts (Karim, Kook, Campion & Doherty, 1977). Because the elimination of disopyramide appears to depend on urinary excretion, we have studied its pharmacokinetics in patients with renal impairment in order to allow prediction of appropriate dosage of the drug in this group. This is of some importance, since patients with renal failure are prone to hypertensive and coronary heart disease, and not uncommonly need treatment with anti-arrhythmic drugs.

Methods

Eleven patients with stable chronic renal impairment (creatinine clearance between 2 and 53 ml min⁻¹) gave their informed consent to take part in the study, which was approved by the Ethical Committee of St Bartholomew's Hospital. Each patient received a 300 mg oral dose of disopyramide base, as the phosphate (2 Norpace capsules; Searle Laboratories) 2 h after a light breakfast; they fasted for 3 h after drug administration. Venous blood samples were drawn at 0, 15, 30, 45, 90, 120, and 150 min and 3, 4, 6, 8, 10, 12, 15, 24, 28, 30, 35, 48, 52, and 56 h after disopyramide was given. The early samples were taken through an indwelling cannula, which was flushed with heparinized saline after each one. All urine passed was collected and pooled between 0 and 24, and 24 and 48 h; 15 complete 24-h specimens were obtained for estimation of disopyramide. Twenty-four hour creatinine clearances were also obtained during the study. Disopyramide was estimated in these samples using a specific gas chromatographic method (Johnston & McHaffie, 1978). The assay was capable of estimating concentrations of 500 µg l⁻¹ with a coefficient of variation of approximately 5%.

The blood level data were analysed by a reiterative curve fitting technique using a digital computer. Both one and two compartment extravascular models were fitted to the data and the model chosen for each individual's results was decided on the basis of the best fit of the computer-predicted curves to the measured plasma levels. Pharmacokinetic parameters

were calculated using standard techniques (Ritschel, 1976).

Results

The clinical details of the patients are shown in Table 1. No unwanted effects of disopyramide were noticed by either the patients or the investigators.

The plasma disopyramide concentration results from seven patients were best fitted by a monophasic blood level decay curve, based on a one compartment open model, while the data from the other four patients were best fitted by a biphasic curve, that is a two compartment open model.

The full pharmacokinetic data from our series of patients are shown in Table 2. The mean absorption half-life of disopyramide was similar (36 min) in these patients to that recorded in normal subjects (Hinderling & Garrett, 1976). The mean elimination half-life ($T_{1/2}$) calculated using the formula $T_{1/2} = 0.693/K_{el}$ which yields a value which is independent of the number of phases of elimination, was 12.7 h, which is substantially greater than the figure of 6.1 h reported by Hinderling & Garrett (1976) in their study of healthy volunteers.

Renal clearance of disopyramide correlated significantly ($r=0.814$, $P<0.001$) with renal function as measured by creatinine clearance (Figure 1). Log disopyramide $T_{1/2}$ tended to increase as

Figure 1 Correlation of renal clearance of disopyramide with creatinine clearance. Fifteen values were obtained for the eight patients from whom satisfactory 24 h urine samples were available ($r=0.814$, $P<0.001$).

Table 1 Clinical details of the patients studied.

Subject	Age (years)	Sex	Weight (kg)	Creatinine clearance (ml min^{-1})	Aetiology of renal failure	Other illnesses	Concurrent medication
1	76	F	52	2.4	Unknown	None	Frusemide, ferrous sulphate, folic acid, multivitamins
2	66	M	58	6.7	? Obstructive uropathy	Diabetes mellitus	Sodium fusidate, co-trimoxazole, Distalgesic
3	33	M	93	5.4	Hypercalcaemia	Hypertension	Clonidine, frusemide, methyldopa, multivitamins, thyroxine, ferrous sulphate
4	48	M	68	9.9	Amyloidosis	Bronchiectasis	Frusemide, prednisolone, salbutamol, multivitamins
5	65	F	55	17.5	Analgesic nephropathy	Hypertension	Atenolol
6	15	M	35	26.5	Chronic glomerulonephritis	None	Senokot, Squill linctus
7	64	M	63	36.0	Chronic glomerulonephritis		
8	55	M	70	38.7	Shunt glomerulonephritis	Left ventricular failure	Bumetanide, Slow K, digoxin, bethanidine
9	55	M	57	25.3	Papillary necrosis	Epilepsy	Phenytoin, primidone, folic acid
10	59	F	76	52.6	Hypertension	Diabetes mellitus	None
11	56	F	73	21.5	Nephrotic syndrome	None	Propranolol, Navidrex-K, clonidine, hydralazine

creatinine clearance fell, but this correlation was not statistically significant ($r=0.248$, $P < 0.5$); there was a better correlation between log disopyramide $T_{1/2}$ and the reciprocal of serum creatinine ($r=0.529$, $P < 0.1$). A weak negative correlation was found between log disopyramide $T_{1/2}$ and disopyramide renal clearance ($r=0.568$, $P < 0.2$).

Mean volume of distribution was similar in our patients (0.62 l kg^{-1}) to that in normal subjects (Heel *et al.*, 1978), but the range of values obtained was large.

Discussion

In healthy individuals, renal excretion is the most important route of elimination of disopyramide and its major metabolite. Renal impairment would therefore be expected to cause slower elimination of the drug, and our findings confirm this expectation. Prolongation of the elimination half-life would lead to higher plasma concentrations after repeated doses, but some of our subjects had high peak concentrations (up to 9 mg l^{-1}) after only a single 300 mg dose. Nevertheless, the mean volume of distribution of disopyramide in this study is similar to that found by others (Heel *et al.*, 1978), and the cause of these high levels was probably the low body weight of some of the patients.

Although disopyramide elimination half-life clearly tends to increase as creatinine clearance falls, we failed to show a statistically significant correlation between these two variables. This seems to be due to marked intersubject variability in handling of disopyramide, which in turn may be due to differences in the extent of protein binding, tissue

binding, and non-renal elimination of the drug. Such variability is important since it makes difficult the prediction of correct drug dosage for a patient with a known degree of renal impairment. It is of course possible that the lack of significant correlation between log disopyramide $T_{1/2}$ and creatinine clearance is due to errors in the collection of urine, which is notoriously difficult to perform accurately, especially in ill patients. In fact, the reciprocal of serum creatinine correlated better ($r = 0.529$) with log disopyramide elimination half-life than did creatinine clearance ($r=0.248$), which suggests that the determination of urinary creatinine excretion may have been an important source of variability in creatinine clearance.

Four of our subjects had biphasic plasma level decay curves. This may be due to the concentration-dependent protein binding of disopyramide (Meffin, Robert, Winkle, Harapet, Peters & Harrison, 1979); the proportion of free drug is greater when the total drug levels are higher, so that more drug is available for elimination by metabolism or renal excretion. If this were the case, biphasic plasma level decay curves might have been expected in those patients who had higher peak plasma levels of disopyramide and/or low plasma protein concentrations. In fact, peak disopyramide and plasma albumin concentrations were similar in patients with biphasic and monophasic curves. We cannot exclude the possibility that the heparinized saline with which the i.v. cannulae were flushed might have altered the protein binding of disopyramide; this effect has been shown in the case of propranolol (Wood, Shand & Wood, 1979), warfarin (Routledge, Bjornsson, Kitchell & Shand, 1979), digoxin (Storstein & Janssen, 1976) and quinidine (Nilsen, Storstein & Jacobsen, 1977) but not as yet for disopyramide.

Table 2 Pharmacokinetic parameters for disopyramide in patients with chronic renal impairment. Values for disopyramide clearance are missing for patients 1, 2 and 9 because of inadequate urine collection. Subjects 2, 3, 5, 6, 7, 10 and 11 had monothesic plasma level decay curves, and therefore no value for α and β rate constants are presented in these cases.

Subject	Renal clearance (ml min^{-1})		Rate constants (h^{-1})				Half-lives		$V_d (\text{l kg}^{-1})$ (assuming 80% bioavailability)
	Creatinine	Disopyramide	K_a	α	β	K_{el}	Absorption (min)	Elimination (h)	
1	2.4	—	1.22	-0.1402	-0.0364	-0.0702	34	9.9	0.40
2	6.7	—	1.10	—	—	-0.0382	38	18.14	0.57
3	5.4	2.4	1.41	—	—	-0.0347	29	20.0	0.60
4	9.9	2.1	0.8	-0.1047	-0.0239	-0.0488	51	14.2	0.46
5	17.5	4.0	0.46	—	—	-0.0574	90	12.1	0.81
6	26.5	13.6	1.65	—	—	-0.0568	25	12.2	1.02
7	36.0	12.0	1.84	—	—	-0.0479	23	14.5	0.42
8	38.7	7.3	2.88	-0.1247	0.0110	-0.0652	14	10.6	0.98
9	25.3	—	5.9	-0.205	-0.0598	-0.1122	7	6.2	0.57
10	21.5	14.8	1.77	—	—	-0.0744	23	9.3	0.41
11	52.6	11.7	1.80	—	—	-0.0546	23	12.7	0.57
Mean			1.90	-0.1437	-0.0328	-0.0600	36	12.7	0.62

Since the elimination half-life in subjects with impaired renal function is clearly prolonged, a reduction in dose should be made when the drug is administered therapeutically. From the mean values of the data obtained from all the subjects in this study we have calculated an ideal dosage regime using the formula devised by Wagner, Northam, Alway & Carpenter (1965):

$$\text{Dose} = \frac{\text{Dosage interval} \times V_d \times K_{el} \times \text{desired average plasma level}}{\text{Bioavailability}}$$

Taking the dosage interval as 8 h, the desired average plasma level as 4 mg l^{-1} (Heel *et al.*, 1978), and the bioavailability of disopyramide as 0.8 (Bryson, Whiting & Lawrence, 1978), and substituting our own values for V_d and K_{el} :

$$\text{Dose} = \frac{8 \text{ h} \times 0.62 \text{ l kg}^{-1} \times 0.06 \times 4 \text{ mg l}^{-1}}{0.8} \\ = 1.5 \text{ mg kg}^{-1} \text{ every 8 h.}$$

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