ABSORPTION AND ANTIDYSRHYTHMIC ACTIVITY OF ORAL DISOPYRAMIDE PHOSPHATE AFTER ACUTE MYOCARDIAL INFARCTION

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1 In a prophylactic, double-blind, randomized placebo-controlled trial of oral disopyramide phosphate, initiated within 12 h of suspected acute myocardial infarction (MI), antidysrhythmic effect was evaluated. The loading dose was 150, 200, or 300 mg followed 6 h later by 100, 150, or 200 mg every 6 h for patients assessed to weigh <55, 55–85, or >85 kg, respectively. After each loading dose and a maintenance dose on one of days 4–7, 2 and 6 h venous blood samples were obtained for determination of plasma disopyramide and mono-*N*-dealkylated disopyramide (MND) concentrations (expressed herein as levels), by a technique incorporating fluorescence photometry and thin layer chromatography. Of 121 patients entering the trial, 101 had confirmed acute MI and of these, 12 on active drug were recalled during convalescence and restudied after a loading dose.

2 In acute MI patients on disopyramide phosphate, an important degree of antidysrhythmic effect was observed (on active drug and placebo, 19% v 37%, respectively ($P = 0.047$), received lignocaine for 'warning arrhythmias'), even though in the first 6 h post-loading dose, disopyramide and MND levels were low and variable.

3 Disopyramide levels 2 h post-loading dose were lower in acute MI than in non-MI patients ($P = 0.004$), and similarly in the limited within patient study corresponding levels after acute MI were lower than during convalescence ($P = 0.013$). At 6 h post-loading dose, the levels had increased in acute MI patients but decreased in non-MI patients, this change being significantly different ($P = 0.048$). A similar significant difference existed in the limited within patient data available during acute MI and convalescence ($P = 0.002$).

4 Acute MI patients on active drug developing 'warning arrhythmias' had lower post-loading dose, 2 and 6 h levels than in those without 'warning arrhythmias' ($P = 0.012$ and $P = 0.0002$, respectively).

5 One patient who developed renal insufficiency developed excessive disopyramide levels.

6 On any given dose, there was no significant correlation between disopyramide level and body weight.

7 In acute MI patients given oral disopyramide phosphate (a) there was marked interindividual variation in the ensuing drug and metabolite levels, (b) absorption of disopyramide into the circulation was delayed, (c) prophylactic antidysrhythmic activity was present at levels of about 1.5 mg/l which is about half the minimal level recommended hitherto, (d) disopyramide accumulated in renal insufficiency, (e) elaborate dosage adjustments based on body weight are not useful.

Introduction

The absorption of orally administered drugs and the way in which they are subsequently handled, and consequently their effects on the body, may be altered in acute myocardial infarction (MI). This appears to be the case for procainamide (Shaw *et al.*,

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1974) and digoxin (Korhonen *et al.*, 1979), the absorption of which are sometimes delayed, especially in patients with heart failure. Such pharmacokinetic alterations can be ascribed to gastrointestinal circulatory changes (including poor perfusion or congestion from right heart failure), nausea and vomiting, and/or coexistent treatment predisposing to gut stasis (e.g. morphine or atropine). This investigation evaluated the absorption and antidysrhythmic activity of orally administered disopyramide phosphate under such circumstances.

Methods

(a) Plasma disopyramide and mono-*N*-dealkylated disopyramide concentration after acute MI

Patients (21–70 years) were entered into a randomized, placebo-controlled double-blind trial (Kumana *et al.*, 1982) in order to evaluate oral disopyramide phosphate in the prophylaxis of dysrhythmias occurring after acute MI. None of the patients had overt heart failure, systolic blood pressures < 100 mm Hg, or contraindications to anticholinergic drug effects. Trial medication (active drug or placebo) was continued for 7 days unless the patients developed (a) 'warning arrhythmias', which were treated with lignocaine, (b) significant complications of acute MI, or (c) significant possible anticholinergic side effects. Oral disopyramide phosphate therapy was initiated within 12 h of sustaining chest pain from acute MI, and involved administration of a loading dose, and after 6 h, every 6 h maintenance dosing was commenced as follows:

Assessed weight (kg)	Loading dose (mg)	Maintenance dose (mg)
< 55	150	100
55–85	200	150
> 85	300	200

Venous blood samples were drawn 2 and 6 h after the loading dose, and again at 2 and 6 h after a regular maintenance dose on one of days 4–7, as by Day 4 a steady state disopyramide concentration was expected to have been achieved. In some patients, including 6 later determined to have received active drug, additional blood sampling was also carried out 2 and 6 h after a regular maintenance dose on day 2 (approximately 24 h after initiating treatment).

(b) Plasma drug concentrations during acute MI and convalescence

Twelve of the above acute MI patients who had received the intermediate dose of disopyramide phosphate were recalled for study at least 6 weeks post-MI, when they were either convalescing well at home

or already back at work. Of these, 5 were selected because of very low plasma disopyramide concentrations noted during the first 6 h after their initial loading dose during the trial. At the time of re-evaluation, no patient had congestive heart failure or acute electrocardiographic changes. After informed consent was obtained, each patient received a single 200 mg oral dose of disopyramide phosphate (i.e. a loading dose equal to that received in the acute phase of their MI). Using a butterfly needle and heparinised saline to flush the system, venous blood samples were obtained from each patient before, and at 2 and 6 h after dosing.

All blood samples (10 ml) were collected in heparinized tubes. The plasma was separated and frozen for later analysis of disopyramide and mono-*N*-dealkylated disopyramide (MND) concentrations using a technique incorporating fluorescence photometry and thin layer chromatography (Gupta *et al.*, 1979). Concentrations of the latter two substances in plasma are referred to henceforth as 'levels'. Only the levels from appropriately timed blood samples (deviation of less than 15 min in dosing or blood sampling) are reported. The results were analysed using Student's *t*-test for group means, paired or unpaired as appropriate. For acute MI patients receiving any given dosage of disopyramide phosphate (large or intermediate) correlations between body weight and disopyramide levels 2 and 6 h post-loading dose and 2 and 6 h post-maintenance dose on one of days 4–7, were determined by linear regression. The resulting correlation coefficients were referred to a 2-tailed *t*-distribution for significance testing.

Results

After the loading dose, of the 47 patients with acute MI receiving disopyramide phosphate, both 2 and 6 h levels were available from 39. Similarly, in 21 of 23 patients remaining on the drug long enough to have post-maintenance dose sampling (on one of days 4–7) there were both 2 and 6 h levels. In addition, 2 and 6 h levels were available from 10 patients later recognized not to have acute MI. The mean disopyramide levels (and ranges) observed in different categories of patients entering the trial, are recorded in Table 1. The mean disopyramide and MND levels are illustrated in Figure 1. During the first 6 h post-loading dose, MND levels were very low or undetectable, irrespective of disopyramide levels. The MND/disopyramide plasma level ratio varied markedly (0–0.7). In general, this ratio tended to be greater after 4–7 days of maintenance therapy than after the loading dose. The mean disopyramide levels in the limited within patient study of oral disopyramide phosphate in acute MI and convalescence, are shown in Figure 2. The outcome of statistical analysis

Table 1 Plasma disopyramide concentrations in acute myocardial infarction (MI) patients entering the trial who had approximately timed blood sampling at both 2 and 6 h.

Dosage category	Non-MI				Acute MI						
	Loading dose			All	Loading dose			All	Maintenance dose (Day 4-7)		
	All	Intermediate	Large		Small	Intermediate	Large		Small	Intermediate	Large
Number of patients	10	9	2	39	2	25	12	21	1	13	7
Mean plasma disopyramide concentrations, (mg/l) (Range*):											
2 h	2.3 (0.5-3.2)	2.2 (0.5-2.8)	3.2	1.2 (0-3.4)	0.2 (0-0.4)	1.2 (0-3.4)	1.4 (0-3.3)	4.1 (2.0-9.2)	3.3 (—)	3.9 (2.6-6.0)	4.4 (2.0-9.2)
6 h	2.0 (0.8-3.2)	1.9 (0.8-3.2)	2.7	1.6 (0-3.9)	0.6 (0.5-0.6)	1.6 (0-3.9)	1.6 (0-2.6)	3.9 (1.7-7.9)	2.6 (—)	3.8 (2.6-6.1)	4.1 (1.8-7.9)
Small dosage (body weight < 55 kg)	Small dosage (body weight < 55 kg)			Loading = 150 mg			Maintenance = 100 mg every 6 h				
Intermediate dosage (body weight 55-85 kg)	Intermediate dosage (body weight 55-85 kg)			Loading = 200 mg			Maintenance = 150 mg every 6 h				
Large dosage (body weight > 85 kg)	Large dosage (body weight > 85 kg)			Loading = 300 mg			Maintenance = 200 mg every 6 h				

*Range rather than standard deviation was included because values were not distributed normally.

Figure 1 Representation of mean disopyramide (▨) and mono-*N*-dealkylated disopyramide (MND) (■) levels in acute myocardial infarction (MI) and non-MI patients. In non-MI patients, post-loading (LD) levels decreased between 2 and 6 h. In acute MI, post-LD levels were very low and increasing between 2 and 6 h, compared to those occurring after maintenance doses on day 2 and days 4–7. MND levels were about 1/10–1/15 the disopyramide levels.

Figure 2 Mean disopyramide levels 2 and 6 h after loading doses: in acute myocardial infarction (MI), levels were low and increasing between 2 and 6 h, (a); in contrast to much higher decreasing levels expected in healthy volunteers (Karim, 1975) (b). Twelve acute MI patients who were convalescing had relatively high and decreasing levels (bottom right) as expected in healthy volunteers. During acute MI the same 12 patients had low and increasing levels (bottom left). The results in acute MI are consistent with delayed disopyramide absorption.

comparing disopyramide levels in different categories of patients at different times is listed in Table 2.

Six patients receiving disopyramide phosphate had to discontinue medication because of urinary retention. Their mean 2 and 6 h post-loading dose disopyramide levels were 1.3, and 1.5 mg/l, respectively, and their MND levels were 0.05 and 0.04 mg/l, respectively.

Amongst patients receiving active drug, those given lignocaine had post-loading dose 2 and 6 h mean disopyramide levels of 0.3 and 0.5 mg/l, respectively, and the corresponding levels in the remaining patients not requiring lignocaine were 1.4 and 1.8 mg/l, respectively (Figure 3). Respective differences between corresponding values were significant ($P = 0.012$; $P = 0.0002$).

One patient with non-anterior MI (who received the large dosage of disopyramide phosphate according to body weight) had excessive disopyramide levels 2 and 6 h after the maintenance dose on day 5 (9.2 and 7.9 mg/l respectively), but corresponding MND levels were not excessive (1.6 and 1.5 mg/l, respectively). He had a history of untreated hypertension and

passage of renal calculi. While in hospital he developed fever, chills, and a haematuria (urine culture negative) and on completing the course of his trial medication it became evident that he had developed a bout of renal insufficiency (BUN and plasma creatinine increased from 13 to 64 and 1.5 to 3.2 mg/100 ml, respectively, while haemoglobin decreased from 14.7 to 10.5 g/100 ml). This patient developed minimal heart failure, but no urinary retention occurred.

In acute MI patients on the intermediate dosage, respective correlation coefficients (between body weight and disopyramide levels) 2 and 6 h post-loading dose and 2 and 6 h post-maintenance dose on one of days 4–7, were 0.043, 0.006, 0.230, and 0.392. On the large dosage corresponding correlation coefficients were 0.330, 0.234, 0.141, and 0.201. None of these were statistically significant.

Discussion

Disopyramide phosphate doses chosen for this study were slightly greater than those used in early trials with oral disopyramide in acute MI in which favourable outcomes with safety were reported (Jennings *et al.*, 1976; Zainal *et al.*, 1977). Dosages were not selected to achieve any predetermined range of disopyramide concentration, since grounds for defining such limits based on the available data (Table 3) were tenuous. Moreover, in one of the aforementioned trials (Zainal *et al.*, 1977) in which drug concentrations were recorded (though detailed results were not provided), disopyramide concentrations were reported not to correlate with dysrhythmias or side effects. Indeed, the authors admitted (Carmichael *et al.*, 1977) that 'therapeutic concentrations' were only encountered after the first day.

Absorption of oral disopyramide phosphate after acute MI

In this study the disopyramide levels obtained during the first 6 h post-loading dose (i.e. early after acute MI when the risk of dysrhythmic death was greatest (Fulton *et al.*, 1969)) showed wide interindividual variation and many had very low levels. The reason for these low initial levels cannot be determined with certainty, but the following evidence suggests that disopyramide absorption from the gut may have been delayed.

In acute MI, mean levels were low (Figure 1 and 2), the 2 h values being lower than in non-MI patients (Table 2a). The corresponding levels in the limited within patient study showed lower levels during acute MI than during convalescence (Table 2c). This indicates that during acute MI, absorption of disopyramide was either incomplete or delayed or that the

Figure 3 Mean disopyramide levels 2 and 6 h post-loading dose in acute myocardial infarction patients receiving disopyramide phosphate (a) in those given lignocaine for 'warning arrhythmias' (WAs), and (b) in those not given lignocaine (no WAs), during the trial. Bars = s.d.

Table 2 Comparison of plasma disopyramide concentrations (mg/l) from patients having appropriately timed blood sampling.

a. Between patient comparison	Acute MI		Non-MI		2-tailed P
	Mean	n	Mean	n	
1) 2 h post-LD	1.1	44	2.3	10	0.004**
2) 6 h post-LD	1.6	41	2.0	10	0.162
3) Difference 2 h–6 h	–0.5	39	0.3	10	0.048*
b. Within patient comparison	2 h		6 h		
	Mean		Mean		
1) Acute MI, post-LD (n = 37)	1.2		1.6		0.013*
2) Acute MI, post-MD (n = 21)	4.1		3.9		0.109
3) Non-MI, post-LD (n = 10)	2.3		2.0		0.133
c. Limited within patient comparison (n = 12)	Acute MI		Convalescent MI		
	Mean	n	Mean	n	
1) 2 h post-LD	1.3		2.6		0.013*
2) 6 h post-LD	1.5		2.0		0.288
3) Difference (2 h–6 h)	–0.2		0.6		0.002**
d. Between patient comparison	Lignocaine intervention		No lignocaine intervention		
	Mean	n	Mean	n	
1) 2 h	0.3	8	1.4	36	0.012*
2) 6 h	0.5	8	1.8	34	0.0002***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

LD loading dose, MD maintenance dose, MI myocardial infarction, n number of patients.

Table 3 Suppression of ventricular tachyarrhythmias (VTAs) and disopyramide concentrations in man.

Reference	Patients treated*	Treatment successful†	Route and frequency	Minimum disopyramide level (mg/l) suppressing VTAs
Hulting & Rosenhamer (1976)	20	19	i.v. bolus + single oral dose	2.4–4.5 (plasma),
Niarchos (1976)	9	8	O over 6 h or every 8 h	3.27–7.48 (serum)
Mizgala & Huvelle (1976)	38	33	i.v. bolus	3 ± 1 (mean $\pm$ s.d.) (serum)
Rangno <i>et al.</i> (1976)	6	6	i.v. infusion	4 (mean) (serum)
Sbarbaro <i>et al.</i> (1979)	14	14	i.v. infusion	4.36 ± 0.95 (mean $\pm$ s.d.) (blood)

* Considered to be given appropriate dose and who had disopyramide concentrations determined

† More than 50–90% reduction from pretreatment VTAs

(From Kumana (1981) Therapeutic Drug Monitoring—Antidysrhythmic Drugs, reproduced by permission of the Editors)
 The above minimum disopyramide concentrations were proposed from studies in patients with stable and unstable arrhythmias, dosed by different routes. The studies had no true controls, were non-blind, involved relatively small numbers of patients and included patients studied at variable periods after acute myocardial infarction. They were all concerned with established arrhythmias, not prophylaxis.

apparent volume of distribution was increased. In acute MI, mean levels were greater at 6 than at 2 h (Figure 1 and 2), the difference being significant (Table 2b). By contrast, in non-MI patients and in the limited number of convalescent MI patients, the 6 h levels were generally lower than at 2 h (Table 2b and 2c). Moreover, the changes in level between 2 and 6 h in acute MI (generally a concentration increment) and the non-MI patients (generally a concentration decrement) revealed a significant difference (Table 2a). Similarly, there was a significant difference between the corresponding changes in level in the 12 patients for which there were results obtained during acute infarction and during convalescence (Table 2c). In acute MI, low mean levels that increased between 2 and 6 h suggest delayed absorption. In healthy individuals, after oral dosing, levels normally peak after about 2 h (Figure 2). Hence, the finding of higher levels at 6 than 2 h could be compatible with delayed absorption and/or impaired elimination (in which case absorption would continue to exceed elimination for a longer period). But in the latter event, both 2 and 6 h levels would be high. With delayed absorption, however, as in this trial, corresponding levels (especially at 2 h) would be low.

Although theoretically it was possible that delayed drug absorption could have resulted from coexistent treatment with agents such as morphine or atropine, in individual patients the lowest disopyramide levels were not necessarily associated with the use of these agents. Moreover, 5 of the 10 non-MI patients had also received morphine during their acute illness.

Using single oral doses of disopyramide, Ward & Kinghorn (1976) were the first to report lower levels in acute MI patients compared to controls, and attributed their findings to reduced bioavailability. Ilett *et al.* (1979) also gave oral disopyramide to acute MI patients and while reporting slower elimination rates and dose-dependent pharmacokinetics (disproportionately faster elimination occurring with higher drug dosage), they also found lower than predicted trough levels. Interestingly, they ascribed this phenomenon to an increased volume of distribution and not to a diminished absorption rate. These authors can be criticized for having assumed uniform bioavailability and unchanging pharmacokinetics, over a period 24 to 120 h after acute MI, during which they sampled blood to determine drug levels and calculate various pharmacokinetic constants.

MND concentrations

MND accumulation relative to the parent drug did not occur in the patient developing renal insufficiency. Although the anticholinergic side effects of the disopyramide moiety have been ascribed to MND (Baines *et al.*, 1976), the levels of the latter in this study were not remarkable in the six patients developing urinary retention.

Antidysrhythmic activity

With the doses used in this study and the ensuing disopyramide levels occurring in the acute MI

Figure 4 Lack of correlation between 6 h plasma disopyramide levels and body weight in acute myocardial infarction (MI) patients after a 200 mg loading dose (a) and a 150 mg maintenance dose (b), on one of days 4–7.

patients, an antidysrhythmic action was nevertheless evident. Thus, only 9 of 47 patients receiving disopyramide phosphate required lignocaine compared to 20 of 54 receiving placebo (19% v 37%; $P = 0.047$). Moreover, such activity was evident even though the disopyramide levels during the early, and presumably most vulnerable phase (i.e., first 6 h), were very much lower than those commonly recommended (though, due to a variety of reasons, strict comparison may not be valid, Table 3). This was also likely to have been the case in the trials (Jennings *et al.*, 1976; Zainal *et al.*, 1977) in which even smaller dosages were used. The patients requiring lignocaine had post-loading dose disopyramide levels about one-third those of patients not requiring lignocaine (Figure 3). Hence, with very low disopyramide levels, antidysrhythmic efficacy was diminished.

Consideration should therefore be given to attaining minimal disopyramide levels of about 1.5 mg/l rather than about 3.0 mg/l recommended hitherto (Table 3), especially in view of the possible increased risk of heart failure reported (Podrid *et al.*, 1980; Wilcox *et al.*, 1980) in some patients.

Influence of renal function

In keeping with previous work (Whiting & Elliott, 1977) the patient who developed renal insufficiency towards the end of his course of trial medication was the only patient to develop 'excessive' disopyramide

levels. It is of interest that a relatively greater excess of drug did not accumulate as MND, since drug metabolites are often more dependent on renal elimination than their parent compound. Moreover, despite the high disopyramide levels prevailing in this patient, side effects sufficient to warrant discontinuing the medication did not occur, even though there was some evidence of mild heart failure.

Influence of body weight

On any given dose, of drug, an inverse relationship between body weight and drug level was expected. However, as can be seen from the representative example in Figure 4, the correlation of plasma levels with body weight was poor. Hence, elaborate dosage adjustments based on body weight are unlikely to be useful.

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