PAPERS

Oral disopyramide after admission to hospital with suspected acute myocardial infarction

U. K. RYTHMODAN MULTICENTRE STUDY GROUP†

Summary

A multi-centre double-blind randomized study is reported in which the effect on mortality of oral disopyramide (300 mg loading dose, then 100 mg qds) was compared with placebo in 1985 patients entering hospital with suspected acute myocardial infarction. Treatment was commenced with 24 hr of onset of symptoms (mean time to first dose 9 hr) and continued until discharge from hospital or 14 days, whichever came first. Nine-hundred and ninety-five patients were allocated to disopyramide and 990 to placebo. The overall mortality, calculated on an intention-to-treat basis, was 7.2% for the disopyramide and 5.6% for the placebo patients. Among those patients with proven infarction mortality was 9.5% of 687 on disopyramide and 7.4% of 716 on placebo. These differences are not statistically significant. Patients with cardiac failure or hypotension at entry did not fare worse on disopyramide, but those with a conduction defect did. Reinfarction was not significantly influenced by disopyramide. The prophylactic use of disopyramide in patients with suspected acute myocardial infarction does not reduce mortality or the incidence of early reinfarction.

KEY WORDS: cardiac arrhythmias, hypotension, dysuria, reinfarction; prophylaxis, cardiac failure.

Introduction

Arrhythmias contribute substantially to the mortality of acute myocardial infarction (AMI), especially in the first 24 hr (Engler and LeWinter, 1982). Disopyramide is a proven anti-arrhythmic agent (Koch-Weser, 1979) and there have been four studies of its effect on survival after AMI (Jennings *et al.*, 1976; Zainal *et al.*, 1977; Nicholls, Haybyrne and Barnes, 1980; Wilcox *et al.*, 1980). In the first study

(Jennings *et al.*, 1976) of 95 patients with proven AMI admitted to a Coronary Care Unit, there was evidence of an anti-arrhythmic effect but no significant difference in mortality with disopyramide compared with placebo. Another small study (Zainal *et al.*, 1977) with patients treated in an open ward showed a dramatic reduction in mortality with 18 deaths on placebo compared with one on disopyramide. This study was strongly criticized (Dollery, Krikler and Shillingford, 1977; Greenbaum, 1977; Julian, 1977; Pottage, Pickens and Robson, 1977a, b) and there were calls (Anonymous, 1977; Julian, 1977; Goldman and Inglefinger, 1978) for a larger and better designed study.

Since the inception of our trial, two studies (Nicholls *et al.*, 1980; Wilcox *et al.*, 1980) have been published which failed to confirm the earlier findings but we believe from our calculations that these were much too small, as acknowledged by Nicholls *et al.* (1980). Our large multi-centre trial of oral disopyramide given to patients admitted to hospital with suspected AMI was designed to determine whether disopyramide can reduce mortality in this situation. The number of patients required was estimated.

Patients and methods

Between October 1978 and December 1980, investigators at 16 hospitals in England, Scotland and Wales entered 1985 patients with suspected AMI. The approval of local research ethics committees had been obtained. Patients under 70 years of age, of either sex, with symptoms of less than 24 hr duration were eligible for entry.

Exclusion criteria were:

- (1) Informed consent not available.
- (2) Unable to take oral medication.
- (3) Second or third degree atrioventricular block.
- (4) Presence of a condition in which the anticholinergic effect of disopyramide would be undesirable, e.g. glaucoma.
- (5) Already on treatment with disopyramide.

Also, patients in whom a pattern of crescendo

†Correspondence: Dr Alasdair D. Malcolm, Airedale General Hospital, Keighley, West Yorkshire BD20 6TD.

angina was recognised were excluded for it was felt that many physicians would wish to treat them differently.

Eligible patients were randomly allocated either to active disopyramide, 100 mg, or placebo capsules. Each patient received an immediate oral dose of three capsules on entry to the study and thereafter one capsule every 6 hr until discharge from hospital, or until 14 days after entry to the trial, whichever came first.

Basic information was recorded at entry together with relevant clinical and electrocardiographic findings. Throughout the trial the major events of death, reinfarction, development of heart failure, hypotension or shock, supposed side effects of trial treatment, and withdrawal of trial treatment were recorded.

Patients were judged to have sustained AMI if at least two of the following criteria were satisfied:

- (1) typical history.
- (2) characteristic electrocardiographic changes.
- (3) transient serum enzyme elevation, exceeding twice the upper limit of normal for the particular hospital's laboratory.

Where the electrocardiographic evidence suggested subendocardial infarction, it was deemed necessary that the enzymatic criteria should also be satisfied. Clear necropsy evidence of recent AMI or coronary arterial occlusion was accepted as evidence of myocardial infarction for the purposes of this study, regardless of whether the aforementioned criteria were satisfied. The diagnosis of reinfarction rested on the same criteria as those used for the initial infarction.

Trial treatment could be withdrawn at any time at the discretion of the local investigator and the timing and reason for all such withdrawals were recorded. Patients were to be withdrawn from the study if the diagnosis of AMI was not confirmed, if hypotension (systolic blood pressure ≤ 70 mmHg) developed with evidence of low cardiac output, or if apparent side effects from the trial medication were troublesome.

Trial design

The primary objective of the study was to evaluate the prophylactic effect of oral disopyramide on mortality in patients with AMI managed in hospital. It was a double-blind, placebo-controlled multi-centre study and at each centre treatment was randomly allocated in pairs (one patient of the pair receiving disopyramide and the other placebo) in order to balance the number of patients receiving each form of treatment at each hospital. The patients remained in the trial until one of the pre-determined end-points was reached and these were death, discharge from hospital, or 14 days after entry to the

trial. Withdrawal of treatment, although recorded, was not an end-point.

With symmetrical error rates at 5% significance and 95% power, a reduction in mortality from 17.0% to 8.5% would need 390 subjects per treatment group. If the error rates are tightened up to 1% significance and 99% power the numbers per treatment group are approximately doubled. On statistical advice a minimum inclusion of 1,000 patients with confirmed AMI was proposed and a modification of the group sequential block design of Pocock (1977) adopted in which the initial significance test was performed when 1,000 patients had been entered and subsequent tests performed at the completion of every additional block of 100 patients up to a maximum of 2,000 patients. Mortality in the active and placebo groups was compared using the chi-square test of the 2-by-2 contingency table and the nominal significance level to be used in the repeated significance tests (McPherson, 1974) derived by computer simulation. Additional comparisons of demographic and clinical features of the two treatment groups were also performed using the chi-square test with Yates' correction for continuity. A P value < 0.05 was considered significant.

Results

General data

A total of 1985 patients with suspected AMI entered the trial; 995 received disopyramide and 990 placebo. The mean interval between onset of symptoms and first dose of trial medication was 9 hr. Myocardial infarction was confirmed in 687 patients receiving disopyramide and 716 receiving placebo, with average duration of stay in hospital for these patients of 10.1 and 10.7 days respectively. The remaining 308 patients in the disopyramide group and 274 patients in the placebo group in whom AMI was not confirmed stayed in hospital for an average of 6.5 and 6.6 days respectively. If the average length of stay in hospital is calculated only for survivors, the figures are 10.7 and 11.1 days for disopyramide and placebo patients who sustained AMI and 6.6 days for both treatment groups in patients who did not sustain AMI.

Comparability

The characteristics at entry are set out in Table 1. These groups are broadly similar apart from significantly more disopyramide patients having been on a diuretic prior to entry ($P < 0.01$), significantly more placebo patients having ventricular arrhythmia at entry ($P < 0.01$), and significantly more disopyramide patients with an interval of more than 8 hr between onset of symptoms and first dose of trial medication ($P < 0.05$).

TABLE 1. Characteristics of 1985 randomised patients before treatment and time to first dose [actual number (%)]

Characteristic	Treatment group	
	Disopyramide (n = 995)	Placebo (n = 990)
Sex		
Men	772(77.6)	782(79.0)
Women	223(22.4)	208(21.0)
Age		
≤60 years	669(67.2)	694(70.1)
>60 years	326(32.8)	296(29.9)
Mean age (years)	55.7	55.3
Clinical history		
Previous infarction	243(24.4)	232(23.4)
Angina	487(48.8)	448(45.3)
Hypertension	177(17.8)	151(15.3)
Diabetes	42 (4.2)	45 (4.5)
Smoking	607(61.0)	577(58.3)
Therapy before admission		
Digoxin	37 (3.7)	31 (3.1)
Diuretic	187(18.7)	136(13.7)*
Oral nitrate	187(18.7)	189(19.1)
Beta blocker	154(15.5)	168(17.0)
Clinical findings		
Overweight	320(32.2)	318(32.1)
Evidence of heart failure	266(26.7)	255(25.8)
Heart rates		
≤60 beats/min	149(15.0)	161(16.3)
≥100 beats/min	133(13.7)	143(14.4)
Systolic blood pressure ≤100 mmHg	79 (7.9)	79 (8.0)
Rhythm or conduction disturbances		
Supraventricular arrhythmia	89 (8.9)	86 (8.7)
Ventricular arrhythmia	60 (6.0)	92 (9.3)*
Conduction defect	45 (4.5)	42 (4.2)
Time to first dose from onset of symptoms		
≤4 hr	298(29.9)	318(32.1)
4-8 hr	284(28.5)	312(31.5)
>8 hr	413(41.5)	360(36.4)†
Mean time to first dose from onset of symptoms (hr)	9.36	8.56

* $P < 0.01$; † $P < 0.05$.

In Table 2 the diagnostic categories are listed for the two treatment groups. Again, a similar pattern is evident in the two groups with only slight differences in terms of the site of infarction, diagnosis where AMI was not confirmed, and in the ratio of confirmed to non-confirmed AMI.

Mortality

Analysis proceeded according to the modified Pocock design from entry of 1,000 patients onwards. When 1,300 patients with confirmed AMI had been entered, 63 of 635 disopyramide patients and 51 of 665 placebo patients were found to have died; this represented mortality rates of 9.92% and 7.67% respectively, a difference of 2.25% in favour of placebo. This difference has a 95% confidence interval from 0.83% in favour of disopyramide to 5.33% in favour of placebo. The difference was not statistically significant at the 5% level, and the best

result in favour of disopyramide consistent with these data was a mere 0.83% improvement in mortality. To confirm this possibility with type I and II error rates of 5% would have required over 30,000 patients per group. It was therefore decided to discontinue the trial at this stage, especially as the balance of probability was in favour of placebo. The numbers finally available for analysis were slightly increased because of recruitment to the study whilst analysis was being carried out, before the investigators were advised to cease entry of further patients.

The final analysis is presented in Fig. 1 in the format advocated by Hampton (1981), distinguishing between the patients with and without confirmed AMI. It should be noted that treatment was usually withdrawn in the cases where AMI was not confirmed and these patients generally had a shorter stay in hospital as they tended to be discharged once the investigator had established that they had not suffered AMI.

TABLE 2. Diagnostic categories [actual number (%)]

	Disopyramide (n=995)	Placebo (n=990)
Acute myocardial infarction confirmed		
Site: anterior	327(32.9)	344(34.7)
inferior	290(29.1)	286(28.9)
anterior and inferior	18 (1.8)	24 (2.4)
other or uncertain	52 (5.2)	62 (6.3)
Total	687(69.0)	716(72.3)
Acute myocardial infarction not confirmed		
Ischaemic cardiac pain	161(16.2)	148(15.0)
Chest pain of unknown cause	39 (3.9)	33 (3.3)
Other	108(10.9)	93 (9.4)
Total	308(31.0)	274(27.7)

FIG. 1. Mortality data. AMI=acute myocardial infarction confirmed. Non-AMI=acute myocardial infarction not confirmed. *Five disopyramide and one placebo case died with insufficient data to confirm infarction.

The final overall mortality in the two groups was 7.2% for disopyramide and 5.6% for placebo treatment, and among cases with confirmed AMI 9.5% and 7.4% respectively. Six of the deaths among patients in whom AMI was not confirmed were clinically believed to be due to myocardial infarction but the patients died before sufficient data could be accumulated to establish infarction according to trial criteria and conclusive necropsy evidence was lacking. Because of this and the small numbers in these groups, percentage mortality rates were not calculated as these might be misleading. The greater

mortality among patients in whom treatment was withdrawn, both for disopyramide and for placebo groups, would be anticipated because indications for withdrawal included certain clinical developments which signal a worsening situation.

The time of death after commencement of treatment was similar for the two treatment groups (Table 3), with the greatest mortality occurring as expected during the first 24 hr.

The causes of death are presented in Table 4, and the spectrum of clinical events is that which would be expected in patients admitted to hospital with sus-

TABLE 3. Day of death

Day	Treatment group	
	Disopyramide (n = 72)	Placebo (n = 55)
1 (≤6 hr)	25(6)	22(12)
2	14	8
3	3	7
4-6	12	6
7-10	15	5
11-14	3	7

pected AMI. There were no significant differences for any one cause between disopyramide and placebo treatment groups. More patients on disopyramide suffered terminal bradycardia or asystole (20.8% v. 12.7%) but fewer patients on disopyramide suffered terminal cardiac failure (36.1% v. 43.6%) and the numbers dying in ventricular fibrillation were virtually the same for the two treatments (18.1% v. 18.2%).

The overall mortality data and retrospective subgroup analysis shown in Table 6 permits assessment of which, if any, groups might do better or worse on active drug or placebo treatment. This type of subgroup analysis must be interpreted with caution, because occasional statistically significant differences would be expected to arise by chance and the more subgroup comparisons which are made the greater the chance of finding a significant difference. From Table 5 the only subgroups which appear to fare significantly worse on disopyramide are those with anterior infarction and those with conduction defect at entry.

Because of concern over cardiac failure with the use of disopyramide we examined the possible association between cardiac failure and the highest risk factor identified in the subgroup analysis, namely conduction defect on entry. The results are presented in Table 6 and show that where patients with cardiac failure at entry were treated with disopyramide the excess mortality compared with placebo treatment is attributable to the additional presence of conduction defect.

Withdrawals

Reasons for withdrawal are given in Table 7. The majority of patients in whom AMI was not confirmed had their treatment withdrawn as specified in the trial protocol, and of these 8.1% who had been taking disopyramide and 6.9% who had been on placebo left hospital immediately.

In 17 cases in the disopyramide group and nine in the placebo group an adverse effect occurred which resulted in withdrawal of trial therapy, regardless of the fact that AMI was not subsequently confirmed. Among the group with confirmed AMI 119 patients (17.3%) in the disopyramide group and 106 (14.8%) in the placebo group had their treatment withdrawn.

The only significant differences between disopyramide and placebo treatment in terms of reasons for withdrawal were in respect of heart block and urinary retention among patients with confirmed AMI ($P < 0.05$ in both cases). Cardiac failure and cardiogenic shock were slightly, but not significantly, less of a problem in patients treated with disopyramide than in patients treated with placebo where AMI was confirmed and, as might be expected, such haemodynamic disturbances hardly featured in the reasons for withdrawal among patients in whom AMI was not confirmed.

Events other than death during the trial (Table 8)

The most significant difference between the treatment groups was in respect of arrhythmias other than ventricular fibrillation, ventricular tachycardia, and asystole in patients with confirmed AMI ($P < 0.01$, in favour of disopyramide). Although ventricular fibrillation and ventricular tachycardia occurred less frequently in patients with confirmed AMI treated with disopyramide, the difference was not significant; however, ventricular arrhythmias were also less common in the disopyramide group at entry (Table 1). Disopyramide treatment in patients with confirmed AMI showed a lower incidence of development of cardiac failure compared with placebo.

TABLE 4. Cause of death [actual number (%)]

	Treatment Group	
	Disopyramide (n = 72)	Placebo (n = 55)
Terminal bradycardia or asystole	15(20.8)	7(12.7)
Ventricular fibrillation	13(18.1)	10(18.2)
Cardiac failure	26(36.1)	24(43.6)
Sudden, rhythm not documented	12(16.7)	9(16.4)
Respiratory arrest	1 (1.4)	1 (1.9)
Cardiac rupture	4 (5.6)	4 (7.3)
Renal failure	1 (1.4)	—

TABLE 5. Analysis of mortality according to certain retrospectively formed subgroups [actual number (%)]

	Number of deaths/number of patients in that subgroup	
	Disopyramide (n=995)	Placebo (n=990)
Males	55/772 (7.1)	41/782 (5.2)
Females	17/223 (7.6)	14/208 (6.7)
Age ≤60 years	31/669 (4.6)	31/694 (4.5)
Age >60 years	41/326(12.6)	24/296 (8.1)
Time to first dose		
≤6 hr	31/669 (4.6)	31/694 (4.5)
>6 hr	41/326(12.6)	24/296 (8.1)
Previous history		
Angina	33/487 (6.8)	41/448 (9.2)
Previous M.I.	22/243 (9.1)	15/232 (6.5)
Raised blood pressure	12/177 (6.8)	15/151 (9.9)
Diabetes	4/42 (9.5)	4/45* (8.9)
Cigarette smoking	33/607 (5.4)	22/577 (3.8)
Non-smoker	39/388(10.1)	33/413 (8.0)
Clinical findings on admission		
Overweight	19/320 (5.9)	22/318 (6.9)
Systolic blood pressure ≤100 mmHg	11/79 (13.9)	13/79 (16.5)
Supraventricular arrhythmia	2/89 (2.2)	3/86 (3.5)
Ventricular arrhythmia	7/60 (11.7)	5/92 (5.4)
Conduction defect	21/48 (43.8)	7/45 (15.6)*
Cardiac failure	38/260(14.6)	26/255(10.2)
Diagnosis		
Confirmed AMI		
Anterior	42/327(12.8)	24/344 (7.0)†
Inferior	17/290 (5.9)	23/286 (8.0)
Anterior and inferior	2/18 (11.1)	2/24 (8.3)
Other or unknown	4/52 (7.7)	2/26 (3.2)
AMI not confirmed§	7/308 (2.3)	4/274 (0.7)

AMI=acute myocardial infarction; * $P<0.01$; † $P<0.05$;§five disopyramide and one placebo patient died with insufficient data to confirm infarction.

TABLE 6. Influence of cardiac failure and conduction defect on mortality [actual number (%)]

		Number of deaths/number of patients in that subgroup	
		Disopyramide (n=995)	Placebo (n=990)
Cardiac failure	Conduction defect		
Present	Present	17/27 (62.9)	6/23 (26.1)
Present	Absent	21/233 (9.0)	20/232 (8.6)
Absent	Present	4/21 (19.0)	1/22 (4.5)
Absent	Absent	30/714 (4.2)	28/713 (3.9)

treatment (9.8% v. 11.6%), but again this difference was not significant.

The greater number of patients developing urinary difficulties on disopyramide treatment was expected, in view of the anti-cholinergic properties of the drug (Koch-Weser, 1979), but the difference achieved statistical significance only in the patients with confirmed AMI (4.5% with disopyramide v. 2.4% with placebo, $P<0.05$). Only one other clinical feature proved statistically significant between the treatment groups, and that was the occurrence of thromboembolic problems in patients with confirmed AMI

(3.1% with disopyramide v. 1.3% with placebo, $P<0.05$).

Discussion

In this study of 1985 patients admitted to hospital with suspected AMI, and fulfilling certain criteria, there was no demonstrable difference in mortality with routine use of oral disopyramide compared with placebo. It appears that the active and placebo treatment groups were fairly well matched in terms of characteristics before treatment (Table 1), the pro-

TABLE 7. Withdrawals [actual number (%)]

Reason	AMI confirmed		AMI not confirmed	
	Disopyramide (n=687)	Placebo (n=716)	Disopyramide (n=308)	Placebo (n=274)
Arrhythmia requiring treatment	33 (4.8)	40 (5.6)	8 (2.6)	4 (0.4)
Heart block	32 (4.6)	18 (2.5)†	2 (0.6)	0
Cardiac failure	3 (0.4)	8 (1.1)	1 (0.3)	0
Hypotension	5 (0.7)	1 (0.1)	1 (0.3)	0
Cardiogenic shock	8 (1.2)	13 (1.8)	0	0
Renal failure	0	2 (0.3)	0	0
Urinary retention	18 (2.5)	6 (0.8)†	2 (0.6)	0
Visual problems	1 (0.1)	2 (0.3)	0	0
Miscellaneous	24 (3.5)	17 (2.4)	3 (1.0)	5 (1.8)
AMI not confirmed	NA	NA	283(91.9)	255(93.1)
Total number of patients withdrawn	119(17.3)	106(14.8)	289(93.8)	255(93.1)

† $P<0.05$. AMI=acute myocardial infarction; NA=not applicable.

TABLE 8. Events other than death during trial period [actual number (%)]

	AMI confirmed		AMI not confirmed	
	Disopyramide (n=687)	Placebo (n=716)	Disopyramide (n=308)	Placebo (n=274)
Cardiovascular				
Reinfarction	17(2.5)	21(3.1)	NA	NA
Later infarction	NA	NA	2(0.6)	4(1.5)
Ventricular fibrillation	13(1.9)	22(3.1)	1(0.3)	—
Ventricular tachycardia	18(2.6)	24(3.4)	1(0.3)	—
Asystole	7(1.0)	6(0.8)	—	—
Other arrhythmia	40(5.8)	70(9.8)*	5(1.6)	6(2.2)
Conduction disturbance	46(6.7)	46(6.4)	1(0.3)	—
Cardiogenic shock	23(3.3)	21(2.9)	—	2(0.7)
Cardiac failure developed	67(9.8)	83(11.6)	7(2.3)	4(1.5)
Hypotension	6(0.9)	6(0.8)	—	—
Embolism/deep vein thrombosis	21(3.1)	9(1.3)†	1(0.3)	—
Other cardiocirculatory problems	34(4.9)	45(6.3)	4(1.3)	1(0.4)
Other				
New urinary difficulties	31(4.5)	17(2.4)†	3(1.0)	1(0.4)
Other anticholinergic drug effects	7(1.0)	8(1.1)	—	—
Nausea or other gastrointestinal problems	4(0.6)	—	1(0.3)	—

These are patients who failed to satisfy the criteria for infarction at entry, but later developed myocardial infarction. NA=not applicable. * $P<0.01$; † $P<0.05$.

portion of the group in whom AMI was confirmed and the site of infarction (Table 2). We believe that the results of this large study effectively and authoritatively negate the findings in the two earlier smaller studies (Jennings *et al.*, 1976; Zainal *et al.*, 1977). This reinforces the point that small studies, especially where flaws have been identified in the design or execution, should never be taken as the basis for the major change in prescribing habits such as starting to use a drug routinely for prophylaxis. Not only did we fail to confirm the observation that disopyramide was associated with a significant reduction in mortality (Zainal *et al.*, 1977), but also we failed to confirm (Table 8) the reported significant reduction in early reinfarction (Jennings *et al.*, 1976; Zainal *et al.*, 1977). The previously reported significant reduction in ventricular arrhythmias (Jennings *et al.*, 1976; Zainal *et al.*, 1977) and all types of atrioventricular block

(Jennings *et al.*, 1976) could not be confirmed in the defined categories of ventricular fibrillation, ventricular tachycardia, asystole and conduction disturbance in our study (Table 8). In our group with confirmed AMI ventricular fibrillation occurred in 1.9% of patients on disopyramide and 3.1% on placebo; these differences were not significant and it must be remembered that ventricular arrhythmias were more common in the placebo group at entry. However, we did find that other arrhythmias were less common in the disopyramide-treated group with confirmed AMI (5.8% on disopyramide v. 9.8% on placebo, $P<0.01$).

Decreased mortality with use of β -blocker drugs as secondary prophylaxis after AMI has been demonstrated over study periods ranging from 3 to 48 months in a number of placebo-controlled trials published in the last decade (Staessen *et al.*, 1982).

Two of these trials which recently received considerable attention were the timolol trial from Norway (Norwegian Multicentre Study Group, 1981) and the propranolol trial from the United States (β -blocker Heart Attack Study Group, 1981); both showed significant reduction in mortality for the groups receiving the β -blocker but entry to the trials was not until 5 to 28 days postinfarction and the influence on mortality was measured over an average follow-up of 17 months (timolol) and 25 months (propranolol). Thus, in comparison to our disopyramide study they represent later starts and very much longer study periods. There has, however, been one β -blocker trial with a very early start and that was the Göteborg study in which intravenous metoprolol or placebo was given at a mean interval of 11 hr from onset of pain, and the patients then continued on oral treatment for 90 days (Hjalmarson *et al.*, 1981). Among 1395 patients there were 40 deaths in the metoprolol group (5.7%) and 62 deaths in the placebo group (8.9%), a difference of 36% ($P < 0.03$). At 10 days, which was the average duration of treatment in our study, there appear to have been 22 deaths in the metoprolol-treated and 31 in the placebo-treated groups (Fig. 1 of Hjalmarson *et al.*, 1981). The difference between the groups appeared and widened gradually between day 5 and day 40, after which the mortality plots for both groups remained roughly parallel. Therefore it is possible that reduction in mortality after AMI may not be very impressive in early-phase short-term trials, such as ours, even when drugs which confer benefit over longer-term administration are used.

Our failure to reduce mortality among the patients receiving disopyramide prompts consideration of whether our patients had adequate plasma levels of the drug, particularly in the early phase when mortality is greatest. We based our dosage on the recommendation of Ward and Kinghorn (1976) who had studied the kinetics of disopyramide in AMI and suggested a loading dose of 300 mg, but subsequent reports have cast some doubt on the adequacy of this (Ilett, Madsen and Woods, 1979; Weissberg *et al.*, 1981).

Of concern during our study was the report from the United States of frequently encountered precipitation of new congestive cardiac failure or aggravation of pre-existing cardiac decompensation with disopyramide (Podrid, Schoeneberger and Lown, 1980). If cardiac failure had occurred in the past, there was a substantial risk of recurrence with disopyramide. The Nottingham group had also reported in their 6-week post-infarction study that there were significantly more withdrawals from the disopyramide phosphate-treated group for heart failure (Wilcox *et al.*, 1980). Our own results, like those of the Salford group (Nicholls *et al.*, 1980), indicate

that disopyramide is not associated with the hazard suggested by the group from the United States (Podrid *et al.*, 1980).

The data on cardiac failure have been considered in some detail because of the obvious clinical importance of our experience in almost 2,000 patients. Cardiac failure was given as a reason for withdrawal in only four of the patients treated with disopyramide compared with eight on placebo treatment; corresponding figures for hypotension and cardiogenic shock are 14 patients receiving disopyramide and 14 patients receiving placebo (Table 7). Deaths among patients with evidence of cardiac failure at entry to the study (Table 5) were slightly, but not significantly, higher in the disopyramide group and the difference is accounted for almost entirely by the further subgroups with co-existing conduction defect in which the mortality was 62.9% on disopyramide compared with 26.1% on placebo. Our data do not allow identification of the mechanism underlying increased mortality when disopyramide was given to patients with both cardiac failure and conduction defect but, as already suggested by Desai *et al.* (1981), disopyramide could be exerting a diffuse toxic effect on both sinus node and junctional automaticity and on conduction in both the specialized cardiac conduction system and the ventricular muscle. We disagree strongly with the blanket condemnation (Podrid *et al.*, 1980) of disopyramide treatment in patients with past or present cardiac failure and would not wish to see this generally useful anti-arrhythmic drug (Heel *et al.*, 1978; Koch-Weser, 1979) unnecessarily withheld from patients, especially where there are serious rhythm disturbances which have already proven refractory to other therapy (Vismara *et al.*, 1977). Rather, we would urge recognition of the evident hazard of using disopyramide in patients with conduction defect, whether or not cardiac failure is present (Table 6).

Our data, like those from the recent smaller studies (Nicholls *et al.*, 1980; Wilcox *et al.*, 1980), indicate that disopyramide does not reduce mortality among patients admitted to hospital with suspected AMI. Even if the high-risk subgroup of patients with cardiac failure and conduction defect were to be excluded we do not have convincing evidence for using disopyramide prophylactically in this situation.

Acknowledgments

We thank the nursing, pharmacy and secretarial staff and our medical colleagues at the participating hospitals for their assistance in this study. The help given by Dr D. F. Woodings in planning the study is acknowledged. Supplies of trial medication were prepared by staff of Roussel Laboratories Ltd who also provided computer facilities for data storage and processing. The study was funded by Roussel Laboratories Ltd.

References

- ANONYMOUS (1977) Disopyramide for arrhythmias. *Drug and Therapeutics Bulletin*, **15**, 75.
- β -BLOCKER HEART ATTACK STUDY GROUP (1981) The β -blocker heart attack trial. *Journal of the American Medical Association*, **246**, 2073.
- DESAI, J.M., SCHEINMAN, M.M., HIRSCHFELD, D., GONZALEZ, R. & PETERS, R.W. (1981) Cardiovascular collapse associated with disopyramide therapy. *Chest*, **79**, 545.
- DOLLERY, C.T., KRIKLER, D.M. & SHILLINGFORD, J.P. (1977) Disopyramide in myocardial infarction [Letter to the editor]. *Lancet*, **ii**, 1185.
- ENGLER, R.L. & LEWINTER, M.M. (1982) Ventricular arrhythmias: diagnosis, treatment, and prognosis. In: *Coronary Care* (Eds J. S. Karliner and G. Gregoratos), p. 367. Churchill Livingstone, New York.
- GOLDMAN, P. & INGLEFINGER, J.A. (1978) Therapy with antiarrhythmic drugs [Editorial]. *New England Journal of Medicine*, **298**, 1193.
- GREENBAUM, R. (1977) Disopyramide in myocardial infarction [Letter to the editor]. *Lancet*, **ii**, 1362.
- HAMPTON, J.R. (1981) Presentation and analysis of the results of clinical trials in cardiovascular disease. *British Medical Journal*, **282**, 1371.
- HEEL, R.C., BROGDEN, R.C., SPEIGHT, T.M. & AVERY, G.S. (1978) Disopyramide: a review of its pharmacological properties and therapeutic use in treating cardiac arrhythmias. *Drugs*, **15**, 331.
- HJALMARSON, Å., ELMFELDT, D., HERLITZ, J., HOLMBERG, S., MALEK, I., NYBERG, G., RYDÉN, L., SWEDBERG, K., VEDIN, A., WAAGSTEIN, F., WALDENSTRÖM, A., WALDENSTRÖM, J., WEDEL, H., WILHELMSSEN, L. & WILHELMSSON, C. (1981) Effect on mortality of metoprolol in acute myocardial infarction. *Lancet*, **ii**, 823.
- ILETT, K.F., MADSEN, B.W. & WOODS, J.D. (1979) Disopyramide kinetics in patients with acute myocardial infarction. *Clinical Pharmacology and Therapeutics*, **26**, 1.
- 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.
- JULIAN, D.G. (1977) Disopyramide in myocardial infarction [Letter to the editor]. *Lancet*, **ii**, 1362.
- KOCH-WESER, J. (1979) Disopyramide. *New England Journal of Medicine*, **300**, 957.
- MCPHERSON, K. (1974) Statistics: the problem of examining accumulative data more than once. *New England Journal of Medicine*, **290**, 501.
- NICHOLLS, D.P., HAYBYRNE, T. & BARNES, P.C. (1980) Intravenous and oral disopyramide after myocardial infarction. *Lancet*, **ii**, 936.
- NORWEGIAN MULTICENTER STUDY GROUP (1981) Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *New England Journal of Medicine*, **304**, 801.
- POCOCK, S.J. (1977) Group sequential methods in the design and analysis of clinical trials. *Biometrika*, **64**, 191.
- PODRID, P.J., SCHOENEGERGER, A. & LOWN, B. (1980) Congestive heart failure caused by oral disopyramide. *New England Journal of Medicine*, **302**, 614.
- POTTAGE, A., PICKENS, S. & ROBSON, R.H. (1977a) Disopyramide in myocardial infarction [Letter to the editor]. *Lancet*, **ii**, 1185.
- POTTAGE, A., PICKENS, S. & ROBSON, R.H. (1977b) Disopyramide in myocardial infarction [Letter to the editor]. *Lancet*, **ii**, 1362.
- STAESSEN, J., BULPITT, C., CATTART, A., FAGARD, R., VANHEES, L. & AMERY, A. (1982) Secondary prevention with beta-adrenoceptor blockers in post-myocardial infarction patients. *American Heart Journal*, **104**, 1395.
- VISMARA, L.A., VERA, Z., MILLER, R.R. & MASON, D.T. (1977) Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. *American Journal of Cardiology*, **32**, 1027.
- WARD, J.W. & KINGHORN, G.R. (1976) The pharmacokinetics of disopyramide following myocardial infarction with special reference to oral and intravenous dose regimens. *Journal of International Medical Research*, **4** (Suppl. 1), 49.
- WEISSBERG, P.L., MATENGA, J., HAYLER, A.M. & HOLT, D.W. (1981) Plasma disopyramide concentrations following a 300-mg oral loading dose in acute myocardial infarction. *Therapeutic Drug Monitoring*, **4**, 277.
- WILCOX, R.G., ROWLEY, J.M., HAMPTON, J.R., MITCHELL, J.R.A., ROLAND, J.M. & BANKS, D.C. (1980) Randomised placebo-controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. *Lancet*, **ii**, 765.
- ZAINAL, N., CARMICHAEL, D.J.S., GRIFFITHS, J.W., BESTERMAN, E.M.M., KIDNER, P.H., GILLHAM, A.D. & SUMMERS, G.D. (1977) Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards. *Lancet*, **ii**, 887.

Personnel and participating hospitals

- A. D. Malcolm, M.Sc., M.R.C.P., G. C. Oldfield, M.B., S. M. Crawford, M.R.C.P. and K. B. Naranjo, M.B., Airedale General Hospital, Keighley, West Yorkshire.
- O. P. Galpin, F.R.C.P., I. U. Haque, M.R.C.P. and M. S. Safdar, M.R.C.P., Llandudno General Hospital, Gwynedd.
- B. E. Taylor, M.D., F.R.C.P., Sharoe Green Hospital, Preston, Lancs.
- J. Pilcher, M.D., F.R.C.P. and S. M. Elhag, M.R.C.P., Walsgrave Hospital, Coventry.
- A. M. Hazell, M.R.C.P., Royal Naval Hospital, Haslar, Gosport, Hants.
- J. R. Dathan, M.D., F.R.C.P. and R. B. Naranjo, M.R.C.P., Royal South Hants Hospital, Southampton.
- T. Fyfe, M.D., F.R.C.P., A. Hutchinson, M.R.C.P. and G. Bailie, M.Sc., M.P.S., Southern General Hospital, Glasgow.
- D. Robson, M.R.C.P., Greenwich District Hospital, London SE10.
- J. E. F. Pohl, F.R.C.P. and T. Freedmont, M.R.C.P., The General Hospital, Leicester.
- A. A. H. Lawson, M.D., F.R.C.P., D. N. S. Malone, F.R.C.P., G. Sangster, M.R.C.P., E. Rodrigues, M.R.C.P. and R. Young, M.R.C.P., Milesmark Hospital, Dunfermline.
- R. Buckle, M.D., F.R.C.P. and S. Illingworth, M.R.C.P., Southampton General Hospital, Southampton.
- P. S. Freedman, M.R.C.P. and H. Murfet, A.S.C.T., Addenbrooke's Hospital, Cambridge.
- A. C. F. Kenmure, M.D., F.R.C.P. and N. A. Irvine, M.R.C.P., Aberdeen Royal Infirmary, Aberdeen.
- C. Gilbertson, F.R.C.P., R. Lewis, M.R.C.P., R. H. McCaig, M.B. and H. D. Fatah, M.R.C.P., Nevill Hall Hospital, Abergavenny, Gwent.
- K. Hollinrake, F.R.C.P., P. Grant, M.R.C.P., Goddard, M.B. and G. Mubwandarikwa, M.R.C.P., George Eliot Hospital, Nuneaton, Warwickshire.

D. B. Barnett, M.D., M.R.C.P., C. Gold, M.R.C.P., C. F. George, M.D., F.R.C.P. and A. H. Scales,
D. Walker, M.B. and S. Levine, M.B., Leicester M.R.C.P., Southampton General Hospital, South-
amptom.
Royal Infirmary, Leicester.

Co-ordinators: A. D. Malcolm, M.Sc., M.R.C.P., Airedale General Hospital, Keighley, West Yorks.
W. S. Atkin, B. Pharm., M.P.S., Roussel Laboratories Ltd, Wembley Park, Middlesex.

Statisticians: J. Poloniecki, D. Phil. }
V. Chestney, B.Sc. } Roussel Laboratories Ltd, Wembley Park, Middlesex.
A. Mattieu }
K. D. MacRae, Ph.D., Charing Cross Hospital Medical School, London W6.

(Accepted 21 June 1983)