A trial of prophylactic mexiletine in home coronary care

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SUMMARY A double blind randomised study was undertaken comparing the effects of oral mexiletine and placebo given by general practitioners at home in the early stages of suspected acute myocardial infarction, and continued for six weeks. The study comprised 216 patients. In 59 the diagnosis of acute myocardial infarction was not confirmed. Of the 72 patients with confirmed myocardial infarction treated with mexiletine, 11 (15.3%) died, compared with 19 (22.4%) of the 85 patients given the placebo, and significantly fewer of the former compared with the latter had frequent ventricular ectopics or ventricular tachycardia recorded on 24 hour electrocardiograms. Numbers of patients transferred to hospital or withdrawn from the trial because of arrhythmia or heart failure were similar in the two treated groups. Ten (13.9%) of the patients taking mexiletine had the drug withdrawn because of side effects attributed to it, compared with three (3.5%) of the group taking the placebo. A further five patients (all on mexiletine) also had treatment withdrawn because of side effects but infarction was not later confirmed. The results indicate that oral mexiletine can be given safely to patients with suspected myocardial infarction at home by their general practitioners in the absence of a positive electrocardiographic diagnosis. The frequency of ventricular tachycardia is significantly reduced; but there is no evidence of reduced mortality.

Precise figures are not available for the proportion of patients with acute myocardial infarction cared for at home in the UK. There is no reason to believe that the proportion of one-third found in the Teesside survey in 1976¹ is unusual. Sudden unexpected death from ventricular fibrillation occurs in patients looked after at home just as it does in hospital.

Apart from one study² using intramuscular lignocaine prophylactically for prehospital coronary care, there have been no studies on prophylactic antiarrhythmic therapy at home. General practitioners are reluctant to use drugs usually reserved for the controlled conditions of a coronary care unit. Lignocaine can be used but its parenteral route of administration poses insuperable problems in patients for whom continued home care is proposed.

We have investigated the feasibility of preventing ventricular fibrillation at home. This study was designed to determine the practicability of general practitioners giving a prophylactic antiarrhythmic agent to patients with suspected acute myocardial infarction and to determine the effects on cardiac arrhythmias and mortality. Mexiletine was chosen as

being a class I antiarrhythmic agent rapidly absorbed orally with few side effects which has been shown to reduce the prevalence of ventricular arrhythmias after acute myocardial infarction.^{3 4}

Method

The West Berkshire Health District centred on Reading has a mixed urban and rural population of 450 000 patients served by 202 general practitioners. One hundred and seventy-four of these general practitioners agreed to participate in the trial and they were specifically asked not to change their usual criteria for deciding what to do with patients with suspected acute myocardial infarction. If they decided to look after a patient at home they were invited to enter the patient into the trial and to use the diagnostic facilities offered. Management of the patients remained in the general practitioners' control unless a problem arose while the research registrar was with the patient. Consent for the trial was obtained from the local ethical committee.

Patients seen more than 36 hours after the onset of symptoms and those unlikely to comply with treatment were excluded, as were those who were aged over 75, or were shocked, or comatose, or who had a heart rate of less than 50 beats per minute.

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Supplies of identical active and placebo capsules in computer randomised blocks of two were distributed to all general practitioners at the onset of the trial and subsequently as the usage dictated, with the recommendation they carry them with them when on duty. Prior informed consent was obtained verbally from the patients. After recording the basic details of pulse rate, blood pressure, analgesia given, and starting the patient double blind on a six week course of mexiletine (400 mg at once and then 200 mg eight hourly) or placebo, the general practitioner registered the patient by telephone with the Coronary Care Unit at Battle Hospital, Reading.

Each day a full time research registrar (JMT) or one of her deputies (NJCS, JRI) visited any patients registered over the previous 24 hours. The history was confirmed, details of analgesia and other cardiac drugs documented, the patient examined, a 12 lead electrocardiogram recorded, and blood taken for the measurement of both cardiac enzymes and mexiletine concentrations. In those patients in whom it was practicable, an Oxford Instruments Medilog 424 electrocardiograph recorder was connected. Relevant results were telephoned to the general practitioner at this stage and subsequently. A further visit was made the next day to repeat the observations and remove the recorder. An appointment was made for a final visit at six weeks when the patient was questioned about side effects, blood was taken for a final mexiletine concentration, and the number of capsules remaining was counted.

The collated results from the first two visits were assessed blind by one person (JMT), and on the basis of the clinical findings, the electrocardiogram, and the cardiac enzymes all patients were assigned into one of four categories.

(1) *Definite myocardial infarction*: Good clinical history *plus*: electrocardiographic changes (including left bundle-branch block or subendocardial infarction), *plus* a pronounced rise in enzymes ($\geq 50\%$ above the upper limit of normal).

(2) *Probable myocardial infarction*: Good clinical history *plus*: an electrocardiogram showing new Q waves or typical subendocardial changes *and/or* a rise in enzymes above the upper limit of normal.

(3) *Ischaemic heart disease*: A good previous history of ischaemic heart disease but no evidence for fresh myocardial infarction.

(4) *Other*

For the purposes of this study, patients in categories 1 and 2 were considered as having suffered an acute myocardial infarction and this was assumed in those

dying at home after taking the trial tablets but before the visit of the trial doctor. Patients in categories 3 and 4 were withdrawn from treatment as were those transferred to hospital, those with arrhythmias requiring treatment, and those with shock, coma, severe intercurrent illness, unacceptable side effects, or who were otherwise unable to take drugs orally. All such patients withdrawn from treatment were questioned at six weeks about side effects and were included in the analysis of results. Details concerning the patients who died during the six week study period were obtained from the general practitioner or occasionally the relatives. Deaths were classified as being either sudden or occurring in the context of a gradual deterioration.

Serum cardiac enzyme concentrations were estimated in the Department of Clinical Chemistry, Royal Berkshire Hospital, with upper limits of normal of 40 U (AST) and 250 U (LDH). Plasma mexiletine concentrations were measured using a specific gas-liquid chromatographic technique.⁵ Twenty-four hour tape recordings were analysed on a Reynolds High Speed ECG Analyser by a trained observer who did not know which patients had been treated. Tapes with less than eight hours' analysable electrocardiogram were rejected. Ventricular arrhythmias were classified as ventricular extrasystoles (aberrant beats not preceded by P waves), frequent ventricular extrasystoles (>30 per hour), R on T ($RR/QT \leq 0.85$), multifocal (two or more morphologies in any hour), couplets (two consecutive ventricular beats separated by not more than 400 ms), ventricular tachycardia (three or more consecutive ventricular beats at a heart rate more than 150 beats a minute), prolonged ventricular tachycardia (more than 10 beats a salvo), and frequent ventricular tachycardia (more than three runs in any tape). A pause was defined as a gap of 1500 ms separating two consecutive beats.

Significance testing for the differences in mortality, additional treatment received, incidence of arrhythmias, and side effects in the two groups was done using the χ^2 test, with Yates' correction. The Mann-Whitney U test was used for testing the significance of the differences in numbers of extrasystoles and enzyme levels between the two groups. Simple linear regression was used to test the correlation of blood levels with age.

Results

Over a 22 month period (November 1978 to August 1980), 222 patients were referred and 216 complied with the entry criteria (five had histories longer than 36 hours and one was aged over 75). Seventy-two of 103 patients allocated to mexiletine and 85 of 113 patients allocated to placebo had confirmed myocar-

Table 1 Classification of entrants

Entrants	Placebo		Mexiletine		Total
	No.	%	No.	%	
	113	100	103	100	216
Definite myocardial infarction	66	58	52	50	118
Probable myocardial infarction	19	17	20	19	39
Ischaemic heart disease	14	12	12	12	26
Other	14	12	19	18	33

dial infarction.

Table 1 shows the classification of the trial entrants according to our four diagnostic categories. Table 2 shows the baseline clinical details of the patients with myocardial infarction according to treatment group. Table 3 shows the electrocardiographic details and median peak cardiac enzymes in the two treatment groups. There were no significant differences between the two treatment groups for any of these criteria, and, other than oral analgesics which were given more frequently ($p < 0.05$) within three hours of the loading dose to patients taking mexiletine, there were no differences in concurrent drug administration. Apart from beta blockers being taken by 12 out of 113 (10.6%) having placebo and 10 out of 103 (9.7%) having mexiletine, no patients were receiving any other antiarrhythmic drug. Table 4 shows the outcome for all patients.

MORTALITY

The overall mortality rate was lower in the mexiletine group (12 out of 103, 11.7%) than in the placebo group (20 out of 113, 17.7%) (NS). Two patients with unconfirmed myocardial infarction died, one one day after withdrawal from a dissecting aneurysm, and one suddenly 14 days after treatment was withdrawn. For patients with confirmed myocardial infarction, the mortality during the six week trial period was again

lower in the mexiletine group (11 out of 72, 15.3%) compared with the placebo group (19 out of 85, 22.4%) (NS). Thus 30 deaths occurred in the confirmed infarct group. Of these, 13 patients were withdrawn before death and in only two of this group had mexiletine been taken within 24 hours of death.

Eleven patients (seven placebo, four mexiletine) with assumed myocardial infarction died suddenly after entry but before being seen by the project doctor. In one of these an electrocardiogram taken by the general practitioner showed early changes of infarction, but the remaining 10 patients had no electrocardiographic or enzyme evidence collected before sudden death after a story of typical chest pain.

No patients died between the project doctor's two visits while on the 24 hour electrocardiograph recorder. Six patients died after the project doctor's second visit while still in the trial, three suddenly (two taking placebo, one taking mexiletine) and three after gradual deterioration with heart failure (one taking placebo, two taking mexiletine). Of the withdrawals, nine patients with confirmed infarction on placebo died during the six week period (four suddenly and five in heart failure), compared with four on mexiletine (two suddenly and two in heart failure). Fourteen patients died suddenly while taking treatment (nine taking placebo and five taking mexiletine) (NS).

WITHDRAWALS

Forty-three (27%) patients with confirmed myocardial infarction were withdrawn for reasons given in Table 5. Twenty-four of these (14 taking placebo, 10 taking mexiletine) were transferred to hospital, mostly because of continuing chest pain or heart failure (10 taking placebo, eight taking mexiletine) and none solely because of side effects.

SIDE EFFECTS

By the second day of the trial doctor's visit 37 of 216

Table 2 Baseline details in patients with confirmed myocardial infarction

Total	Placebo 85	Mexiletine 72	Total 157
(1) Sex:			
Male	72 (85%)	57 (79%)	129
Female	13 (15%)	15 (21%)	28
Mean age $\pm$ SD (y)	61.3 (8.5)	61.0 (9.4)	61.1 (8.9)
Relevant past medical history			
Nil	40	34	74
Infarct	23	19	42
Angina	21	21	42
Diabetes	3	4	7
Hypertension	18	11	29
Heart failure	5	3	8
(2) Median time between onset of symptoms and initial dose of trial drug (h)	5.17	6.14	5.85
(3) Initial pulse rate (beats/min (mean))	77.9	79.6	
Initial systolic BP (mean)	146.5	143.6	
Initial diastolic BP (mean)	87.6	87.8	

Table 3 Classification of infarcts and enzyme results

	Placebo		Mexiletine	
	No.	Probable	No.	Probable
Total number of patients	85		72	
Median peak AST	128		161	
Median peak LDH	360		535	
Electrocardiographic pattern	Definite	Probable	Definite	Probable
Anterior full thickness	16	3	12	1
Anterior full thickness + right bundle-branch block and/or left axis deviation (-30°)	6	1	6	1
Inferior full thickness	17	3	20	0
True posterior	2	1	1	0
Left bundle-branch block	2	0	1	0
Subendocardial infarct	16	6	9	16
No definite electrocardiographic change of infarction	0	5	0	2
Electrocardiogram not recorded before patient died at home	7	0	3	0

Table 4 Outcome for all patients admitted to study

	Placebo		Mexiletine	
	No.	%	No.	%
Patients in study	113	100	103	100
Infarction not confirmed so withdrawn from study*	28	24.8	31	30.1
Withdrawn for other reasons† (see Table 5)	20	17.7	23	22.3
Died while taking trial drug	10	8.8	7	6.8
Completed 42 days on treatment	55	48.7	42	40.8

* Two patients died subsequently during the six week study period (see text).

† Thirteen patients died after withdrawal but during the six week study period (see text).

patients (15 taking placebo, 22 taking mexiletine) had developed possible side effects of treatment, nausea being the most common (six taking placebo, 11 taking mexiletine). In 18 patients (15 taking mexiletine, three taking placebo), unacceptable side effects alone caused withdrawal of treatment, and in five of these (all taking mexiletine) the diagnosis of myocardial infarction was not subsequently confirmed. Nineteen (45%) of the 42 patients taking mexiletine completing the trial volunteered side effects, mainly gastrointestinal upset and dizziness, compared with 12 of 55 (22%) taking the placebo ($p < 0.05$). No patient started on mexiletine and subsequently withdrawn because the diagnosis was not confirmed had any symptoms six weeks later.

24 HOUR ELECTROCARDIOGRAPHIC ANALYSES

Fifty patients with confirmed myocardial infarction taking placebo and 38 patients with confirmed myocardial infarction taking mexiletine had readable tapes with median tape lengths of 23 and 22 hours,

Table 5 Reasons for withdrawal of patients with confirmed myocardial infarction

	Placebo	Mexiletine
Heart failure	6*	6
Side effects	3	10
Chest pain	5	2
Arrhythmias	4	2
Other	2	3

*Includes one patient not transferred to hospital.

Table 6 24 hour electrocardiographic abnormalities

	Placebo No. %	Mexiletine No. %
No. of electrocardiograms analysed (≥ 8 hours)	50 (100)	38 (100)
No. with atrial ectopics	33 (66)	21 (55)
No. with supraventricular tachycardia	12 (24)	8 (21)
No. with atrial fibrillation*	7 (14)	2 (5)
No. with pauses	1 (2)	0 (0)
No. with ventricular extrasystoles	47 (94)	36 (95)
(a) frequent ventricular extrasystoles***	20 (40)	4 (11)
(b) R on T	1 (2)	1 (3)
(c) multifocal	38 (76)	28 (74)
(d) couplets	26 (52)	15 (39)
(e) ventricular tachycardia**	12 (24)	2 (5)
(f) frequent ventricular tachycardia	4 (8)	1 (3)
(g) prolonged ventricular tachycardia	2 (4)	1 (3)
(h) ventricular fibrillation	0 (0)	1 (3)

*** $p < 0.01$

** $p < 0.05$

* $p < 0.325$

respectively. The median delay between the onset of symptoms to the start of the tapes was 26 hours for the placebo group and 29 hours for the mexiletine group. The abnormalities found on the 24 hour electrocardiogram are shown in Table 6.

Patients with confirmed myocardial infarction taking mexiletine had fewer ventricular extrasystoles than those taking placebo (median ectopic count per hour 2.63 versus 6.09, $p < 0.05$). Serious ventricular arrhythmias, including frequent ventricular extrasystoles and ventricular tachycardia, were seen more frequently in patients in the placebo group. No differences were seen between the two groups in the incidence of pauses or supraventricular arrhythmias including atrial fibrillation. The median number of ventricular extrasystoles per hour in the 12 of the 50 patients taking placebo who had ventricular tachycardia was 14.34 compared with 3.02 in the other 38 who did not have this arrhythmia ($p < 0.01$). Similarly, in the former, frequent ventricular extrasystoles (nine out of 12 compared with 11 out of 38, $p < 0.05$) and couplets (12 out of 12 compared with 14 out of 38, $p < 0.001$) were seen more frequently. Of the 12 patients on placebo who had ventricular tachycardia, seven completed the six week study, three died during the trial, and two were withdrawn because of heart failure, one to die subsequently.

DRUG PLASMA LEVELS

The mean mexiletine concentrations for patients with confirmed myocardial infarction on days 1, 2, and 42 were 0.69 $\mu\text{g/ml}$, 1.00 $\mu\text{g/ml}$, and 0.82 $\mu\text{g/ml}$, respectively. Two patients supposedly taking mexiletine had an undetectable level on day 42 (lower limit of sensitivity for the assay 0.01 $\mu\text{g/ml}$). No significant correlation was found in patients with confirmed myocardial infarction between age and blood levels on day 1, 2, or 42.

There was no significant difference in the median number of extrasystoles per hour for patients with mexiletine concentrations (mean of day 1 and day 2 concentration) of at least 0.75 $\mu\text{g/ml}$ compared with those with concentrations of less than this for patients with or without confirmed myocardial infarction. The mean drug levels on day 2 in those patients subsequently withdrawn because of side effects was not significantly different from that in other patients on day 2.

Discussion

The prime function of coronary care remains the prevention and treatment of ventricular fibrillation. Lown's original prediction⁶ that the detection and treatment of warning arrhythmias would reduce the frequency of ventricular fibrillation has not stood the test of time.⁷ An argument can be made for effective prophylactic antiarrhythmic therapy, since significant reduction in the mortality of acute myocardial infarction will only be achieved by early intervention. Prophylactic antiarrhythmic therapy given at home has the advantage that treatment is started at the earliest opportunity and a reduction in ventricular fibrillation ought to be paralleled by a reduction in mortality.

A review of the published reports of prophylactic antiarrhythmic treatment after acute myocardial infarction suggests that treatment given early might reduce the frequency of ventricular fibrillation. Oral procainamide,⁸ mexiletine,³ and intravenous lignocaine⁹ have been variously shown to cause a reduction in ventricular tachycardia^{3,8} and ventricular fibrillation⁹ in hospital. Intramuscular lignocaine² given out of hospital has been shown to reduce mortality but the same dosage repeated in hospital caused no reduction in ventricular fibrillation.¹⁰ No clear conclusion is apparent. Studies with negative results are commoner than studies with positive results and all the latter have been extensively criticised for either design, patient selection, or interpretation. A carefully conducted trial recently published failed to show either significant reduction in serious arrhythmias or in six week mortality in patients treated with

prophylactic oxprenolol or disopyramide¹¹ compared with placebo.

The placebo mortality of 22.4% in the present study must be compared with a six week mortality of 24% in the Nottingham trial¹² where 50% of patients were seen within three hours of the onset of symptoms. In the Tees-side survey¹ the mortality in patients seen after three hours was 15% so our mortality falls between these two figures.

We have not shown a significant reduction in mortality in patients taking mexiletine; but the reduction in arrhythmias and the fewer sudden deaths in such patients are consistent with a therapeutic benefit. Furthermore, an analysis of the deaths, the 24 hour electrocardiographic recordings, and the reasons for withdrawal do not support the possibility that the patients were harmed by being given mexiletine. The reduction in frequency of ventricular ectopics and ventricular tachycardia in our study is in keeping with the known effects of mexiletine given after acute myocardial infarction.^{3,4} The effect of intravenous mexiletine on left ventricular function in normal man is slight^{13,14} and in our patients the oral dosage used did not precipitate heart failure. The proportion of patients in the treatment group dying from heart failure was no more than in the placebo group, and the same was true for withdrawals from treatment because of heart failure. Similarly, our results make it unlikely that patients with atrioventricular or intraventricular conduction defects were harmed by mexiletine and this finding would support the data of McComish *et al.*¹⁵ who reported shortening of the effective refractory period of the atrioventricular node and no effect on atrioventricular and His-Purkinje conduction time.

Published data suggest a minimum effective plasma concentration for mexiletine of 0.5 $\mu\text{g/ml}$ ¹⁶ while a range of 0.75 to 2.0 $\mu\text{g/ml}$ is associated with a low incidence of side effects.¹⁷ The mean plasma drug concentrations in our patients were satisfactory on days 1 and 2 and at completion. The lowest concentrations were recorded on day 1 and it is probable that in the first few hours some of our patients had subtherapeutic plasma concentrations of mexiletine. The fixed dose and loading regimen used ensured that in sick and elderly patients toxic levels were rarely found and our figures indicate that a larger loading dose could be given safely to patients at home not under observation.

The study demonstrates the problems of home coronary care. Our 216 patients were seen at a median time of five hours after the onset of symptoms. Undoubtedly, general practitioners referred patients seen earlier to hospital rather than enter them into the trial. The overall diagnostic accuracy of the general practitioners was high and 73% of patients referred

had myocardial infarction. Overall, 15% of patients with confirmed acute myocardial infarction for whom home care was intended had to be transferred to hospital.

The present study makes no attempt to compare the role of home versus hospital in coronary care. In rural communities and in cases where patients are seen initially a few hours after the onset of their symptoms, many general practitioners will elect to look after the patient at home. Though it may be premature to use prophylactic antiarrhythmic drugs in routine domiciliary practice, we cannot agree with Sloman's statement quoted recently in a leading article¹⁸ "it is inappropriate to use such drugs as disopyramide or mexiletine in an environment outside a Coronary Care Unit where drugs are being used which can interfere with conduction, and which may produce serious side effects". The mainly negative findings of previous studies in prophylactic antiarrhythmic therapy may not apply to home care, and now that we have shown it to be both practicable and safe further evidence should be sought with regard to the benefit from earlier prophylactic administration of mexiletine or a similar drug by general practitioners at home.

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