Prophylaxis against ventricular arrhythmias in suspected acute myocardial infarction: a comparison of tocainide and disopyramide

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1 Five hundred and seventy one patients admitted to a coronary care unit with suspected acute myocardial infarction were considered for entry into a double-blind study. Two hundred and eighty-three patients were excluded, mainly because of recent treatment with β -adrenoceptor blocking agents, life threatening arrhythmias requiring specific treatment and left ventricular failure presenting with hypotension or pulmonary oedema. Two hundred and eighty-eight entered the trial of whom 202 were subsequently confirmed to have had myocardial infarction.

2 The effects of tocainide and disopyramide on ventricular arrhythmias were compared with placebo over the first 48 h period. The three treatments were given by a combination of intravenous infusion and oral administration. The doses used were tocainide 500 mg intravenously over 30 min plus 2800 mg orally over 48 h and disopyramide 150 mg intravenously over 30 min plus 1050 mg orally over 48 h.

3 As judged by counts of ventricular premature beats, tocainide and disopyramide exerted a similar and significant antiarrhythmic effect. The median number of ventricular premature beats over the first 24 h of treatment was 58 on placebo compared with 30 on tocainide ($P < 0.05$) and 19 on disopyramide ($P < 0.05$). The corresponding figures for the second 24 h were 9, 6 and 2, respectively.

4 There were eight deaths and three episodes of ventricular fibrillation with no significant differences between the three treatment groups. Sustained ventricular tachycardia was observed in one patient in the tocainide group.

5 Apart from the occurrence of urinary retention in 10 of the 96 patients treated with disopyramide, both active treatments were well tolerated.

6 The population of patients entering the trial was clearly at low risk from serious cardiac arrhythmias. The presence or absence of a prophylactic effect of either drug against serious arrhythmias could therefore not be assessed.

Keywords tocainide disopyramide myocardial infarction

Introduction

Lignocaine is well established in both the treatment and prophylaxis of ventricular arrhythmias after myocardial infarction (Jewitt *et al.*, 1968). However, it can only be given

intravenously, has a short half-life and blood levels vary widely (Lie *et al.*, 1977).

Tocainide, a new structural analogue of lignocaine with similar electrophysiological

properties (Holmes *et al.*, 1983; Anderson *et al.*, 1978b) has been shown to be as effective as lignocaine in suppressing ventricular arrhythmias in acute myocardial infarction (McDevitt *et al.*, 1976) but in contrast to lignocaine has high oral bioavailability and a long half-life (Graffner *et al.*, 1980; Graffner & Lundborg, 1978; Lalka *et al.*, 1976; Winkle *et al.*, 1976).

Disopyramide is a well established drug with quinidine-like electrophysiological properties (Anderson *et al.*, 1978a; Vismara *et al.*, 1974). It has also been used in acute myocardial infarction (Jennings *et al.*, 1976; Nicholls *et al.*, 1980; Wilcox *et al.*, 1980; Zainal *et al.*, 1977). Although both disopyramide and tocainide have been shown to be effective antiarrhythmic agents in a variety of clinical situations there have been no studies comparing their effects in acute myocardial infarction.

The aim of this study was therefore to compare the effects of intravenous and oral regimens of disopyramide and tocainide against placebo in the prophylaxis of ventricular arrhythmias in patients with suspected acute myocardial infarction.

Methods

The study protocol was approved by the ethical committee of the Bristol and Weston Health District (Teaching). The study was designed to run for a period of 18 months. Five hundred and seventy one successive patients admitted to the coronary care unit (C.C.U) of the Bristol Royal Infirmary between 16 June 1980 and 29 December 1981 with a suspected acute myocardial infarction were considered for entry into the study.

Two hundred and eighty-three patients were excluded for the following reasons:

1. β -adrenoceptor blocking drugs taken within the previous 48 h (135 patients).
2. Antiarrhythmic agents including digoxin taken within 48 h (37 patients).
3. Left ventricular failure diagnosed clinically or radiologically or systolic blood pressure less than 90 mm Hg (36 patients).
4. Cardiac arrest either ventricular fibrillation (17 patients) or asystole (two patients) prior to arrival on the coronary care unit; other tachyarrhythmias requiring immediate treatment (three patients).
5. Complete or second degree (Mobitz type 2) atrioventricular block or persistent bradycardia (13 patients).
6. Clinical diagnosis overturned by attending physician (13 patients).
7. Main episode of chest pain more than 48 h previously (four patients).

8. Previous history of glaucoma (three patients).

9. Inadequate reason (18 patients).

Some patients had more than one reason for exclusion. Two hundred and eighty-eight patients were therefore available for randomisation. Patients were randomised in blocks of 12 to one of three treatments. Medical staff, nursing staff and patients were unaware of the treatment given.

The three treatment regimes were as follows:

1. Disopyramide 150 mg by constant intravenous infusion over 30 min plus a 150 mg disopyramide capsule at the start of the infusion, at 2 h and 8 hourly for five doses.
2. Tocainide 500 mg by intravenous infusion over 30 min plus a 400 mg tocainide tablet at the start of the infusion, at 2 h and 8 hourly for five doses.

3. Placebo infusion, tablets and capsules given at the same time as in the active treatment groups.

A double dummy technique was used so that each patient received an infusion 1.0 m two ampoules followed by a capsule and a tablet at each dosage interval.

Doses were chosen on the basis of a pilot study which indicated that the above regimens achieved drug levels within the accepted therapeutic range in the majority of patients (Anderson *et al.*, 1978a).

Blood pressure was monitored automatically at 2 min intervals during the intravenous infusion using a Dinamapp recorder (Applied Medical Research Corporation). Venous blood samples were taken at 30 min, and at 8, 24 and 48 h after the start of the infusion for the estimation of plasma drug concentrations. Tocainide concentration was measured by gas chromatography with nitrogen-selective detection after Schiff base formation (Johansson & Vessman, 1982) and disopyramide by EMIT homogenous enzyme immunoassay.

Electrocardiograms were monitored continuously for arrhythmias requiring intervention. Permanent records were made independently on Medilog tape recorders from 0 to 24 h and 24 to 48 h. Tapes were analysed for rhythm disturbance on a Reynolds 'Pathfinder' rhythm analyser without knowledge of the patients' treatment group or diagnosis. Ventricular tachycardia was defined as three or more consecutive ventricular premature beats (VPB) at a rate greater than 100/min.

The criteria for withdrawal from the trial were: ventricular fibrillation, other arrhythmias requiring specific treatment, refractory pulmonary oedema and development of hypotension (systolic blood pressure below 90 mm Hg). Patients who developed intolerable side effects attributable to treatment were also

withdrawn. On withdrawal from the trial, the treatment code was only broken if the patient had developed a ventricular arrhythmia requiring specific treatment.

The final diagnosis of acute myocardial infarction, acute ischaemic episode or undiagnosed chest pain was made by one physician (DWB) unaware of the treatment group. Myocardial infarction was diagnosed when at least two of the following criteria were fulfilled:

1. A typical history
2. Diagnostic ECG changes
3. Rise in either cardiac enzyme—hydroxybutyrate dehydrogenase (HBD) or aminoaspartate transferase (AAT)—to more than twice the upper limit of normal.

'Acute ischaemic episode' was diagnosed in those in whom there had been central chest pain and ECG or other evidence of ischaemic heart disease; 'undiagnosed chest pain' in those who did not fulfil the criteria for either acute myocardial infarction or acute ischaemic episode.

Statistical methods

The patient entry characteristics were compared by analysis of variance and Chi squared tests. Comparison of the ventricular premature beat count in each group was by non-parametric analysis of variance (Kruskal-Wallis followed by Nemenyi tests) (Miller, 1981).

Results

Of the 288 patients included in the study, 202 had had a definite myocardial infarction (Figure 1).

Patients with confirmed acute myocardial infarction

Comparability The treatment groups were well matched in number and in the patient characteristics examined (Table 1). There were no significant differences between the groups in site or size of infarction as indicated by plasma cardiac enzyme levels.

Arrhythmia detection The occurrence of ventricular fibrillation and sustained ventricular tachycardia was detected from the bed side monitor. All 202 patients with acute myocardial infarction were included in the study population. However for the purpose of measuring the numbers of ventricular premature beats and detection of non-sustained ventricular tachycardia only the 24 h tapes were used. For technical reasons not all tapes were suitable for analysis. Only tapes with greater than 20 h

Figure 1 Patient flow diagram

'Total deaths' refer to deaths before discharge from hospital. Numbers in parenthesis refer to deaths within 48 h of entry to study.

AMI: acute myocardial infarction.

Table 1 Patient characteristics

	Placebo	Tocainide	Disopyramide
Number of patients	69	64	69
Male	56	57	55
Female	13	7	14
Mean age (years)	58 ± 1	57 ± 1	55 ± 1
<i>Risk factors (patients)</i>			
Hypertension only	15	14	12
Diabetes only	4	4	1
Hypertension and diabetes	2	2	1
Previous AMI	10	9	11
<i>At entry to study</i>			
Mean delay time (h)	8.2 ± 0.69	8.66 ± 0.73	7.59 ± 0.64
Delay time > 1 h ≤ 3 h	6	4	3
> 3 ≤ 6	28	31	36
> 6	35	29	30
Mean heart rate (beats/min)	77 ± 1.7	80 ± 1.9	80 ± 1.7
Mean systolic BP (mm Hg)	141 ± 3.3	136 ± 3.2	135 ± 3.1
Mean diastolic BP (mm Hg)	88 ± 1.9	86 ± 1.6	87 ± 1.6
<i>Site of AMI</i>			
Anterior	38	34	27
Inferior	30	29	42
Indefinite	1	1	0
<i>Peak enzymes (iul)</i>			
Amino aspartate transferase	112 ± 8	104 ± 8	131 ± 16
Hydroxybutyrate dehydrogenase	613 ± 37	591 ± 39	652 ± 53

Means are expressed ± s.e. mean

Delay time = onset of pain to start of infusion

interference-free recording were analysed. There were 43 from patients taking placebo, 47 taking tocainide and 48 taking disopyramide in the first 24 h and 39 taking placebo, 46 taking tocainide and 38 taking disopyramide in the second 24 h period. Exclusion of patients without validated tapes did not alter the comparability of the three groups in terms of their entry characteristics and there was no evidence that the treatment *per se* affected the likelihood of satisfactory Medilog recording.

Ventricular premature beats The ventricular premature beat count (Table 2) over the first 24 h was significantly reduced in the tocainide and disopyramide groups compared with placebo ($P < 0.05$). There was no significant difference between the two treatment groups. In the second 24 h the number of ventricular premature beats was lower in all three groups and was significantly lower than placebo only in the case of disopyramide ($P < 0.05$).

Ventricular tachycardia In the first 24 h, episodes of non-sustained ventricular tachy-

cardia (VT) (less than 10 s duration) were recorded on 18 of the 43 tapes in the placebo group, 13 out of the 47 in the tocainide group and 13 out of the 48 in the disopyramide group. The differences between the groups were not statistically significant. The incidence of non-sustained VT during the second 24 h period was lower (six on placebo, five on tocainide and one on disopyramide, NS).

Ventricular tachycardia sustained for more than 10 s was recorded in one patient in the tocainide group 42 h after entering the study. This episode which was of 3 min duration was converted to sinus rhythm by 100J direct current shock. The patient was later discharged home.

Ventricular fibrillation There were three episodes of ventricular fibrillation prior to withdrawal (two in patients given placebo and one tocainide). One patient on placebo, admitted to the trial 11 h after the onset of pain developed ventricular fibrillation 19 h after inclusion. The arrhythmia was successfully converted to sinus rhythm and the patient was later discharged. The second patient on placebo was

Table 2 Total ventricular premature beat counts for 24 h period in patients with confirmed myocardial infarction

Treatment group	Day 1				Day 2			
	Mean	Median	Range	n	Mean	Median	Range	n
Tocainide	140	30	0-3045	47	38	6	0-507	46
Disopyramide	110	19	0-2692	48	57	2	0-1723	38
Placebo	162	58	0-1272	43	89	9	0-760	39

admitted to the trial 8 h after the onset of chest pain and was withdrawn 55 min later with ventricular fibrillation and subsequently resuscitated. However, this patient had a second episode of ventricular fibrillation from which he could not be resuscitated and died 2.5 h after inclusion in the study.

The patient in the tocainide group was admitted 17 h after the onset of chest pain and developed ventricular fibrillation 20 h after inclusion. A sharp blow on the chest converted his arrhythmia to sinus rhythm. This patient was discharged home. The tocainide level was within the therapeutic range at the time ventricular fibrillation developed.

Deaths All the deaths are indicated in Figure 1. Total deaths during hospitalisation were five in each group. Within the first 48 h of the study two patients receiving tocainide, three on disopyramide and three on placebo died.

Plasma drug concentrations A summary of the plasma concentrations of disopyramide and tocainide is given in Table 3. The concentrations of disopyramide both at the end of the infusion and at the end of the dosing interval were above the minimum therapeutic level (Kumana *et al.*, 1982) in the majority of patients. The median tocainide level at the end of the infusion was at the lower end of the therapeutic range (Anderson *et al.*, 1978a) but therapeutic concentrations were present at the end of each dosing interval in the majority of cases.

Patients without confirmed myocardial infarction

Acute myocardial infarction was not confirmed in 86 patients (Figure 1). The incidence of arrhythmias in this group of patients was low. Ventricular fibrillation did not occur and there were no deaths.

Adverse reactions in all trial patients

There were no effects on heart rate or blood pressure during or after the infusion except for a slight increase in heart rate towards the end of the disopyramide infusion. A summary of the adverse events and reasons for withdrawal are shown in Table 4. The only significant difference between the groups lay in the incidence of urinary retention.

Discussion

When assessing new antiarrhythmic agents in acute myocardial infarction, certain groups of patients must be excluded. These are those who might be harmed by negative inotropic effects, those at risk from inadequate treatment and those in whom other treatments might confuse the conclusions of the study. In this study this resulted in the exclusion of large numbers of patients due to prior β -adrenoceptor blockade and left ventricular failure. Seventeen patients suffered a cardiac arrest in hospital prior to arrival in the coronary care unit. The study

Table 3 Median (range) drug concentrations in patients with proven myocardial infarction

Concentration (mg/l)	Disopyramide	Tocainide
End of infusion	4.11 (1.82-12.66) <i>n</i> = 58	3.50 (1.1-16.3) <i>n</i> = 51
Pretreatment		
8 h	3.03 (1.39-8.8) <i>n</i> = 54	4.44 (2.34-8.38) <i>n</i> = 48
24 h	2.83 (0.62-8.25) <i>n</i> = 54	4.86 (2.13-9.90) <i>n</i> = 48
48 h	3.04 (1.06-7.26) <i>n</i> = 54	5.21 (2.45-8.85) <i>n</i> = 48

Therapeutic range for disopyramide: > 1.5 mg/l

Therapeutic range for tocainide: 3.5-9 mg/l

Table 4 Summary of adverse events and withdrawals

	Tocainide		Disopyramide		Placebo	
	AMI	Non AMI	AMI	Non AMI	AMI	Non AMI
Ventricular fibrillation	1[1]	0	0	0	2[2](1)	0
Ventricular tachycardia	1[1]	0	0	0	0	0
Complete heart block	1[1]	0	2[2]	0	0	0
Asystole	11	0	11	0	11	0
Atrial fibrillation needing treatment	1[1]	0	0	0	2[2]	0
Supraventricular tachycardia	2[2](1)	0	0	0	0	0
Septal perforation	0	0	11	0	11	0
Hypotension	2	1	1	2	7	0
Mild left ventricular failure	0	0	2	0	1	0
Urinary retention	1	0	7[4]	3[3]	2	0
Vomiting	14[1]	11[1]	24[2]	2[1]	15[2]	1
Sweating	6	3	8	2	14	1
Tremor	0	1	1	0	0	0
Protocol violation	1[1]	1[1]	1[1]	0	2[2]	1[1]
Invalid reason	0	0	3[3](1)	2[2]	1[1]	1[1]
Total withdrawals	9	2	14	6	11	2

Protocol violation = patients subsequently found to have one of the defined reasons for exclusion

Invalid reason = withdrawn for reasons other than specified in the protocol

[] = withdrawals

() = deaths

population was therefore a selected low risk group.

Disopyramide was chosen because although it has been shown to have antiarrhythmic activity (Kumana *et al.*, 1982) its value for the prophylaxis of life threatening arrhythmias in acute myocardial infarction is controversial (Dollery *et al.*, 1977; Jennings *et al.*, 1976; Nicholls *et al.*, 1980; Wilcox *et al.*, 1980; Zainal *et al.*, 1977). Jennings *et al.* (1976) and Zainal *et al.* (1977) showed that oral disopyramide was effective in the prevention of serious ventricular arrhythmias following myocardial infarction. However Wilcox *et al.* (1980) concluded that it was not beneficial. In these studies only oral treatment was given and so adequate blood levels might not have been present for several hours. We felt that improved results might be obtained by combining intravenous and oral administration, although Nicholls *et al.* (1980) showed that a combination of intravenous and oral disopyramide produced no significant advantage.

Tocainide has been shown to be more effective than placebo in the suppressing ventricular arrhythmias after myocardial infarction (Campbell *et al.*, 1979; Swedberg & Holmberg, 1981) and its efficacy is comparable to that of lignocaine (Rehnqvist *et al.*, 1983). Lignocaine has been shown to reduce the incidence of ventricular fibrillation if given early after the

onset of chest pain (Lie *et al.*, 1977) but at the dosage required it causes a high incidence of side effects. The drug is frequently commenced when 'warning arrhythmias' occur. However, the value of these as predictors of ventricular fibrillation has been questioned. It has been suggested that they are as common in patients who do not progress to ventricular fibrillation as in those who do (Dhurandhar *et al.*, 1971; El-Sherif *et al.*, 1976; Lie *et al.*, 1975). Also, although there is a relationship between 'R on T' ventricular ectopic complexes and the development of primary ventricular fibrillation (Campbell *et al.*, 1981) it has no practical value. A safe and effective drug that could be given intravenously and orally for prophylactic use in all patients with suspected acute myocardial infarction would therefore be useful.

Both tocainide and disopyramide are shown in this study to exert a significant and similar effect in suppressing ventricular ectopics in the immediate post myocardial infarction period. The effect on sustained ventricular tachycardia could not be assessed as this only occurred in one patient. Similarly prophylaxis against ventricular fibrillation could not be assessed there being only three cases during the trial period.

The intravenous infusion was completed in all cases with no important falls in blood pressure and withdrawals from treatment were few. The most common reason for withdrawal

from treatment was rhythm disturbance requiring definitive treatment. The high incidence of urinary retention in the disopyramide group was to be expected in view of the drug's known anticholinergic properties (Mokler & Hillman, 1972). Acute urinary retention with its attendant anxiety and need for urinary catheterisation is clearly undesirable in patients in the immediate post infarction period and this adverse effect is a disadvantage to the use of disopyramide.

In conclusion this study has shown that tocainide is well tolerated in patients with suspected acute myocardial infarction but it has failed to show any beneficial prophylactic effect against serious ventricular arrhythmias with

either drug. Nevertheless the significant reduction in ventricular premature beats is evidence of the drugs' antiarrhythmic effects in this situation and the absence of prophylaxis may reflect small numbers and the low risk state of the patients studied. Tocainide is without the unwanted anticholinergic effects of disopyramide and this may be an advantage.

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