Diazepam in immediate post-myocardial infarct period

A double blind trial

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SUMMARY One hundred and thirty-one male patients admitted to a coronary care unit with myocardial infarction, later confirmed, were randomly allocated to receive either 10 mg diazepam every six hours, or a matched placebo, for 48 hours. During this period, no differences were found between the treatment groups in the incidence of fatal or non-fatal tachyarrhythmias even when account was taken of differences in the severity of the initial infarct. Monitored blood pressure and heart rate data were comparable as were the patients' self-assessed anxiety levels and symptoms, except that drowsiness was more common in the patients treated with diazepam.

Routine sedation of patients has been recommended for many years after coronary thrombosis and indeed it has been suggested that patients are under-sedated in the early post-infarct period.¹ Diazepam is a widely prescribed and safe drug which has been used in the management of the early convalescent phase of myocardial infarct.² *A priori*, it seems to be a desirable agent for four reasons.

Firstly, it should help the patient through an emotionally traumatic experience,³ at the same time allowing him to rest more completely.

Secondly, a direct antiarrhythmic action has been attributed to the compound in animal experiments and in man.^{4 5}

Thirdly, direct coronary artery vasodilatation by diazepam has been suggested.^{6 7}

Fourthly, by relieving anxiety, there should be a reduction of circulating catecholamine levels and sympathetic autonomic discharge thus reducing the risk of arrhythmias being caused indirectly through these mechanisms.

A double blind controlled prophylactic trial of oral diazepam versus placebo was therefore carried out to determine whether an oral dose of 10 mg qds would reduce the incidence of death or of those tachyarrhythmias defined as requiring treatment.

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Patients and methods

One hundred and seventy-two consecutive male patients with suspected myocardial infarction, and without arrhythmias on admission to the coronary care unit at Sheffield Royal Infirmary, were admitted to the trial. Patients too ill to take oral therapy or those having taken tranquillising drugs routinely over the previous month were excluded. Subsequent confirmation of the diagnosis of myocardial infarction depended upon: (1) the development of Q wave or T wave inversion in daily electrocardiograms; and (2) transient rise in the serum creatine kinase (CK) or aspartate transaminase (AST) above hospital normal values.

After random allocation (stratifying according to the time interval from the onset of pain) patients received either a white 10 mg tablet of diazepam or a placebo tablet matched for appearance. The first tablet was given on admission and treatment was then continued every six hours before meals for 48 hours when the trial terminated. Other treatment was given as clinically indicated over this time (see Table 6) but day-time sedation other than necessary analgesics or antiemetics was to be avoided.

Over the 48-hour period of assessment the following observations were recorded.

(1) MONITORING

Nursing staff took readings periodically and these were later summarised for each of the four 12-hour

periods by noting each type of arrhythmia and calculating the average of the following:

From central monitoring oscilloscope (readings lasting one minute in every 15 minutes)—frequency of ventricular extrasystoles and heart rate; and by auscultation (hourly)—lying systolic blood pressure, and lying diastolic blood pressure (stage 4 measurement).

(2) URINARY CATECHOLAMINES

Two 24-hour urine samples beginning on admission were analysed for each patient by a modification⁸ of the method of Weil-Malherbe and Bone.⁹

(3) DAILY ELECTROCARDIOGRAM

The electrocardiogram and plasma urea, electrolytes, full blood counts, and ESR to detect patients with other serious disease were recorded, particularly renal abnormalities. (No such patients were encountered.)

(4) TRANSAMINASES (AST, CK, HBD)

Daily measurements were made, and for each patient the maximum value for each enzyme was used. CK was regarded as the best measure of initial infarct size.¹⁰

(5) PATIENTS' SELF-ASSESSMENT OF SYMPTOMS AND ANXIETY

Patients were asked on day 1 and again on day 2 to indicate by a cross on a continuous line their feelings about the opposites represented by the ends of the lines (see Table 6). For analysis the distance in inches of the cross from that end denoting mild (or no) symptom or anxiety was measured; this gave a score ranging from 0 to 6 inches (to the nearest tenth of an inch) corresponding to mild and severe symptoms, respectively. Two questions (Q10 relating to double vision and Q11 to pain in the fingers and toes) were used in combination to identify patients who were unlikely to report their symptoms reliably. Question 3 (chest pain) is a measure both of a physical symptom and of the patient's anxiety about it, and the two aspects are inextricably linked.

(6) DIAZEPAM AND ITS METABOLITES

Serum for diazepam and desmethyldiazepam, its active metabolite, was taken at the end of the first 24-hour period.

The size of the trial (60 to 70 patients per treatment group) was to be sufficiently sensitive to have a 50 per cent chance of detecting a halving of the real 48-hour incidence of tachyarrhythmias (assumed to be around 30%), if significance at the 5 per cent level is used; or an 80 per cent chance

of detection at the same significance level if the real incidence in actively treated patients is reduced to one-third that of placebo treated patients.¹¹ "Real" in this context refers to large populations of patients of the designated type from which the trial samples are assumed to have been randomly selected.

Results

Of 172 patients admitted to the trial, 11 were subsequently excluded because they did not fulfil the entry criteria, and another 30 because neither the daily electrocardiograms nor the transaminase levels were confirmed; 131 valid participants remained. The treatment groups were comparable on admission in age, body weight, blood pressure, time from infarct to trial admission, Peel index,¹² site of infarct by electrocardiogram, proportion with heart failure, and past medical history (Table 1). The maximum of the three daily CK levels gave a higher mean for the diazepam patients (389 IU/l) than for those on placebo (319 IU/l), but this difference does not reach significance at

Table 1 Comparability of treatment groups

	Diazepam		Placebo	
<i>On admission</i>				
Mean age (y)	57	(67)	55	(63)
Age range (y)	37-80	(67)	36-69	(63)
Mean body weight (kg)	71	(58)	71	(53)
Mean systolic blood pressure (mmHg)	144	(62)	142	(58)
Mean diastolic blood pressure (mmHg)	92	(62)	90	(57)
Time from onset of attack to admission to trial (no. of patients)				
Less than 6 h	45	} (68)	40	} (63)
6-23h	18		16	
24-48 h or not known	5		7	
Peel index (mean $\pm$ SEM)	20.4 $\pm$ 1.6	(60)	19.7 $\pm$ 1.6	(55)
Max CK (IU/l) (of daily measurements over three days): mean $\pm$ SEM	389 $\pm$ 29	(61)	319 $\pm$ 23	(57)
Site of infarct: anterior	29	} (61)	27	} (55)
inferior	27		22	
patients) other	5		6	
Heart failure clinically or radiologically (no. of patients)	19	(62)	22	(58)
<i>Previous medical history (no. of patients):</i>				
No. of previous infarcts: 0:	46	} (62)	37	} (58)
1:	11		13	
2+:	5		8	
Angina none:	26	} (62)	23	} (58)
for 2 weeks or less:	8		4	
for more than 2 weeks:	28		31	
Hypertension	3	(62)	9	(58)
Diabetes	2	(61)	2	(58)
No. of valid participants	68		63	

Note: Numbers of patients on which indices are based shown in parentheses; information not known for the remainder.

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the 5 per cent level whether a normal or a lognormal distribution is assumed (Student's *t* test).

Similar numbers of patients in each treatment group died or were withdrawn from the trial during the 48 hours of trial treatment (Table 2).

Table 2 *Reasons for not completing 48-hour treatment*

	No. of patients on:	
	Diazepam	Placebo
<i>Death (time in parentheses) after:</i>		
Cardiogenic shock	—	2 (3,18 h)
Primary asystole	1 (4 h)	—
Ventricular fibrillation	—	1 (15 h)
<i>Other reasons (time of event in parentheses):</i>		
Early discharge	2 (17,25 h)	1 (40 h)
Cerebrovascular accident	—	1 (6 h)
Depressed respiration	1 (time unknown)	—
Total no. not completing treatment	4	5

ARRHYTHMIAS

The groups were also similar in the numbers of patients suffering arrhythmias in this period, and in the distribution of types of arrhythmia (Table 3). Arrhythmias tabulated are those for which treatment is customarily given; the ventricular extrasystoles were those of 6 beats per minute or more suggested by Lown *et al.*¹³ as requiring treatment.

Table 3 *Tachyarrhythmias normally requiring treatment: patients validly completing 48-hour treatment*

'Main' arrhythmia*	No. of patients on:	
	Diazepam	Placebo
Primary ventricular fibrillation	2	1
Ventricular tachycardia	6	7
Ventricular extrasystoles (6 beats/min or more)	8	2
Supraventricular tachycardia	6	8
Total no. of patients completing treatment but developing tachyarrhythmia(s)	22	18

* Where more than one type occurred, the patient is counted in the highest applicable row of the table.

In Table 4 the incidence of tachyarrhythmias is compared between the two treatment groups, stratifying according to two factors thought likely to influence this incidence, that is the maximum of the three daily values of CK and the time from infarction to admission to the trial. The diazepam group contained a higher proportion than the placebo group of patients with a maximum value of CK of 600 IU/l or more (who had a high risk of tachyarrhythmia). The data as laid out in this Table may be used to compare the incidence

between the two treatment groups, taking account of the CK and time to admission, by means of Cochran's test,¹⁴ and there is no significant difference (critical ratio = 0.27: $p > 0.05$).

MONITORING

In Table 5, a summary of the monitoring data is given, excluding the four patients who died after only a few hours of monitoring (see Table 2). For brevity, heart rate and blood pressure data are summarised for the first 12 hours and for the last 12 hours of the 48-hour period of the trial.

Bearing in mind the sizes of the standard errors of the mean in Table 5 there are no remarkable contrasts, other than in the higher CK and aspartate transaminase levels in the diazepam group. Some of the catecholamine data are not available for analysis, for technical reasons or because there were doubts about the completeness of the "24-hour urine" sample from which they were obtained.

If Table 5 is subdivided (not shown) according to the maximum CK level attained, then among patients with maximum values in the range 0 to 299 IU/l, the mean systolic and mean diastolic blood pressures during the first 12 hours were each significantly higher* for 25 such diazepam patients (149/95 mmHg) than for the same number of controls (133/87 mmHg). However, further analysis shows that these figures simply reflect mean blood pressures on admission which were higher among these 25 diazepam patients.

SYMPTOMS AND ANXIETY LEVELS

For 53 patients on diazepam and 50 on placebo, suitable records of self-assessment of symptoms and anxiety were available (Table 6). Among the records excluded were those of three patients on diazepam who were too drowsy to complete them and those of three further patients (also on diazepam) who claimed double vision (Q10) and pain in their fingers and toes (Q11). As Table 6 shows, these two symptoms were unimportant (regardless of treatment group or day), as indicated by the small numbers of patients reporting them (five to 10) and the low median scores (0.7 to 1.3) among those few patients. Palpitation (Q2) was not common in either treatment group though when reported it was severe on day 1. Most symptoms were less common and/or less severe on day 2 than on day 1. Among the placebo patients, however, 10 more were pre-occupied with their heart (Q4) on day 2 (42) than on day 1 (32), and among the diazepam patients it was the same number (31) on the two days. In each treatment group on each day over three-

* Student's two-sample *t* tests: systolic BP: $t = 3.14$, $df = 48$, $p < 0.01$; diastolic BP: $t = 2.69$, $df = 48$, $p < 0.05$.

Table 4 Incidence of tachyarrhythmias

Risk factor	Diazepam			Placebo		
	Total	Tachyarrhythmias (No.)	(%)	Total	Tachyarrhythmias (No.)	(%)
(1) CK ≥ 600 IU/l and time from onset < 6 h	4	2	50.0	3	1	33.3
(2) CK ≥ 600 IU/l and time from onset ≥ 6 h	7	6	85.7	1	—	—
(3) CK 300–599 IU/l and time from onset < 6 h	18	8	44.4	18	7	38.9
(4) CK 300–599 IU/l and time from onset ≥ 6 h	7	3	42.9	6	1	16.7
(5) CK < 300 IU/l and time from onset < 6 h	14	3	21.4	17	7	41.2
(6) CK < 300 IU/l and time from onset ≥ 6 h	11	—	—	10	2*	20.0
(7) Time from onset or CK value not known	7	—	—	8	1	12.5
Total	68	22	32.4	63	19*	30.2

* Includes one patient who died in ventricular fibrillation.

quarters of the patients were worried about what had happened (Q5), about a third admitted to being frightened (Q6), and about half were tense (Q7).

Chest pain (Q3) was reported on day 1 by half the placebo group and two-thirds of the diazepam group; on day 2 fewer patients reported the symptom and it was less severe, and for the diazepam group there were significantly more patients whose chest pain improved than whose pain deteriorated ($p < 0.01$). In both treatment groups drowsiness (Q9) was reported by over two-thirds of patients on each day but was more severe in the diazepam patients: when the entire groups were compared by the Mann-Whitney test,¹⁵ the distribution of drowsiness scores was significantly more severe in the diazepam group, both on day 1 ($p < 0.05$) and even more so on day 2 ($p < 0.001$). In the placebo group significantly more patients became less sleepy

on day 2 than became more sleepy ($p < 0.05$), and there was also a significant difference between the treatment groups in the distribution of patients among the three categories—"improved", "deteriorated", "unchanged" ($\chi^2 = 6.03$; $p < 0.05$), indicating less rapid recovery with diazepam.

OTHER FINDINGS

Serum levels of diazepam and of its active metabolite desmethyldiazepam were measured in a randomly selected subgroup of 24 of the patients on diazepam. The mean level of diazepam was 149 ng/ml and the mean level of desmethyldiazepam 88 ng/ml.

Although the trial procedure requested that sedatives should not be prescribed, about half the patients on diazepam and on placebo were given a sedative (Table 7), usually prochlorperazine, as an antiemetic, and/or nitrazepam at night. If anything,

Table 5 Monitoring data: patients surviving 48 hours

		Diazepam	Placebo
Peel index (mean $\pm$ SEM)		20.4 $\pm$ 1.6 (60)	19.5 $\pm$ 1.7 (54)
Transaminases (mean of max values in IU/l, $\pm$ SEM):			
	CK	389 $\pm$ 29 (61)	321 $\pm$ 23 (55)
	AST	246 $\pm$ 25 (61)	180 $\pm$ 18 (55)
	HBD	755 $\pm$ 53 (61)	685 $\pm$ 55 (55)
Urinary catecholamines (μ g/24 h)			
Mean adrenaline $\pm$ SEM:	day 1	26.8 $\pm$ 2.7 (45)	31.2 $\pm$ 5.6 (43)
	day 2	22.5 $\pm$ 3.7 (45)	19.4 $\pm$ 3.1 (43)
Mean noradrenaline $\pm$ SEM:	day 1	98.7 $\pm$ 8.9 (48)	101.8 $\pm$ 10.8 (43)
	day 2	108.7 $\pm$ 8.8 (48)	119.3 $\pm$ 9.9 (43)
Heart rate (12 hourly means, beats/min, $\pm$ SEM):	0–12 h	80.0 $\pm$ 1.7 (61)	80.5 $\pm$ 2.1 (54)
	36–48 h	88.9 $\pm$ 2.9 (58)	82.1 $\pm$ 3.1 (53)
Blood pressure (12 hourly means, mmHg, $\pm$ SEM):			
	Systolic: 0–12 h	140.3 $\pm$ 3.6 (62)	134.1 $\pm$ 3.0 (55)
	Diastolic: 0–12 h	92.4 $\pm$ 1.7 (62)	89.3 $\pm$ 1.8 (55)
	Systolic: 36–48 h	125.6 $\pm$ 2.4 (59)	125.2 $\pm$ 2.5 (54)
	Diastolic: 36–48 h	81.9 $\pm$ 2.4 (57)	79.3 $\pm$ 2.3 (54)
Total no. of patients surviving 48 hours		67	60

SI units conversion factors for adrenaline 1 μ g $\approx$ 0.0055 μ mol; for noradrenaline 1 μ g $\approx$ 0.0059 μ mol.

Note: numbers of patients on which indices are based are shown in parentheses: data missing for remaining patients.

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Table 6 Self-rating symptom and anxiety scores
For each symptom, scores range from 0.0 (mild) to 6.0 (severe)

Symptom, etc. (labelling of ends of line shown n parentheses)		No. with scores ≥ 0.5 , and, in parentheses, median scores for these patients				Patients improving (scoring at least 0.5 less on day 2 than on day 1) as proportion of all patients showing a change in either direction of at least 0.5	
		Day 1		Day 2			
		Diazepam (n=53)	Placebo (n=50)	Diazepam (n=53)	Placebo (n=50)	Diazepam	Placebo
Q 1	Nausea and vomiting (vomited a good deal/ not nauseated)	20 (1.2)	18 (1.5)	8 (2.0)	11 (1.7)	15/20	12/18
Q 2	Palpitation (yes/no)	7 (3.6)	13 (3.2)	6 (1.2)	10 (1.0)	4/7	8/13
Q 3	Chest pain (severe/none)	34 (2.0)	24 (2.1)	26 (1.5)	19 (1.8)	25/32§	16/23
Q 4	Think about heart (most of time/never)	31 (2.8)	32 (2.7)	31 (2.8)	42 (2.3)	18/32	16/34
Q 5	Worried about what has happened (very/not bothered at all)	46 (2.9)	45 (3.6)	42 (2.9)	42 (3.2)	20/37	19/31
Q 6	Frightened (very/not at all)	21 (2.0)	21 (1.6)	18 (1.6)	14 (1.9)	13/21	14/20
Q 7	Tension (tense/relaxed)	29 (2.3)	23 (1.8)	29 (1.6)	25 (1.8)	18/30	12/25
Q 8	Irritability (easily irritated/completely calm)	25 (2.8)	26 (1.5)	21 (1.9)	18 (1.0)	13/19	19/24‡
Q 9	Drowsiness (wide awake/sleepy)	42 (5.4)*	37 (3.8)	42 (5.2)†	34 (2.7)	15/31	26/36‡
Q10	See two of everything (yes/no)	5 (0.9)	6 (0.9)	7 (0.7)	6 (0.8)	2/5	4/6
Q11	Pain in fingers and toes (yes/no)	6 (1.3)	10 (1.2)	5 (1.0)	5 (0.7)	5/7	7/9

Mann-Whitney U test (Siegel¹⁵, p 116 ff) for comparison of *entire* diazepam group with the *entire* placebo group on same day:

*, $p < 0.05$. †, $p < 0.001$.

Sign test (Siegel¹⁵, p 68 ff) for comparison *within one treatment group only* of observed proportion against an 'expected' proportion of 0.5: ‡, $p < 0.05$. §, $p < 0.01$.

χ^2 test for comparison of numbers of diazepam patients in 'improved', 'deteriorated', 'unchanged' categories with corresponding number of placebo patients: ||, $\chi^2_1 = 6.03$, $p < 0.05$.

a higher proportion of patients on diazepam took these sedatives as well as dihydrocodeine which has sedative properties. The proportions of patients requiring any analgesics and those requiring any drugs to treat heart failure were each comparable between the two treatment groups. However, diuretics (mainly bendroflumazide and frusemide) were taken by a higher proportion of those on placebo than of those on diazepam.

Discussion

Melsom *et al.*¹⁶ claimed that "obvious signs of unrest and anxiety" and the need for analgesia were reduced by diazepam in the immediate post-infarct period. Their trial, however, was not reported as double blind and the numbers were smaller than in the present study. We have obtained subjectively scored symptoms and anxiety levels of patients, including those specifically related to their myocardial infarction. Sedation occurred more frequently in those on diazepam than in those on placebo, but anxiety levels as such were comparable in the two groups throughout.

Slightly higher proportions of the patients on diazepam than of the controls were given other drugs which have sedative action. Whatever the cause of sedation, we have been unable to demonstrate that diazepam is more effective than placebo in relieving the patient's anxiety or awareness of pain. In assessing a patient's level of anxiety, observers may be misled into assuming that a

drowsy patient is not an anxious one, a conclusion that is not supported by these results. It is, however, possible that sedation may blunt subsequent memory of the events though we have not attempted to assess this in the present study. It is common to draw a distinction between the somatic and psychological components of anxiety. In the circumstances of this study anxiety may have been somatic in

Table 7 Associated drug treatment

	No. of patients on:	
	Diazepam	Placebo
Drug records mislaid	6	5
Analgesics		
Dihydrocodeine	38	30
Diamorphine	40	35
Any drug*	53	46
Sedatives		
Nitrazepam	11	4
Prochlorperazine	29	22
Any drug*	37	24
Antiarrhythmic agents		
Lignocaine	11	5
Any drug*	17	11
Drugs used to treat heart failure		
Diuretics	22	33
Digoxin	6	8
Any drug*	26	35
Other drugs	10	8
Total no. of patients	68	63

* Including those listed.

origin and therefore less accessible to a central psychotropic action.

There was a suggestion from the maximum CK and AST levels attained that the two groups may not have been comparable in the severity of their infarcts on admission to the trial, but corrections were made for this in the analysis.

Other monitored data including heart rate, blood pressure, and tachyarrhythmias showed no consistent differences (though the one minute in 15 sampling procedure is likely to underestimate the number of tachyarrhythmias, to the same extent in each treatment group, in contrast to the semi-automated analysis of continuous recordings for which equipment is now commercially available). On the whole, therefore, the treatment groups were similar in the monitored physiological and biochemical data.

The important difference between this study and that of Melsom *et al.*,¹⁶ apart from the use of double-blind controls, is that they used an intravenous loading dose of diazepam, while we did not. It is difficult to compare serum levels of diazepam and of its active metabolite between the studies since they took repeated blood samples over 72 hours (finding accumulation over this time), whereas in this study serum was taken at the end of the first 24-hour period only for a random sample of 24 patients.

Thus, apart from the possibility that diazepam could be responsible for small increases in CK levels, we did not observe any major unwanted side effects. However, it seems unlikely that any major beneficial effect other than sedation accrues from the use of diazepam in the post-myocardial infarction state. In particular, the half to two-thirds reduction in the incidence of tachyarrhythmias which the trial was capable of detecting was not found.

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