Diazepam in acute myocardial infarction

Clinical effects and effects on catecholamines, free fatty acids, and cortisol

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Diazepam is a valuable drug in cases of acute myocardial infarction. The 10 mg intravenous loading dose and the subsequent 15 mg oral dose of diazepam administered three times daily produced safe, pleasant sedation, and reduced the need for analgesics. A much reduced excretion of catecholamines was recorded. It is presumed that diazepam causes a lower stress reaction, which is beneficial in diminishing the incidence of malignant arrhythmias and preventing the existing myocardial injury from spreading.

Acute myocardial infarction represents a stress situation regularly accompanied by raised plasma concentrations of catecholamines, free fatty acids, and cortisol (Vetter *et al.*, 1974), which are among the factors held responsible for the occurrence of such serious complications as malignant arrhythmias, left ventricular failure, and cardiogenic shock (Jewitt *et al.*, 1969). Since the changes are also influenced to a great extent by emotional stress produced by pain and anxiety, a study was performed to measure the effect of sedation in the early phase of myocardial infarction. Diazepam was chosen for this purpose, as we have previously shown that this drug produces safe sedation, with no adverse respiratory or circulatory reactions. Oral and intravenous administration of diazepam was found to be superior to intramuscular injection (Hillestad *et al.*, 1974a); Hillestad, Hansen, and Melsom, 1974b).

This report describes the clinical effects of diazepam in myocardial infarction on the incidence

of malignant arrhythmias, size of infarct, and sedation, and its effect on catecholamines, free fatty acids, and cortisol.

Subjects and methods

Thirty-eight male patients aged 35 to 70 with proven acute myocardial infarction (admission less than 24 hours from the onset of pain) were diagnosed by means of WHO electrocardiographic criteria and by elevation of plasma aspartate aminotransferase (AST) levels. On admission the patients were randomly divided into a diazepam group and a control group, which later proved to be fairly comparable (Table 1). Patients who had previously been taking drugs that might influence the values (diazepam and diazepam-related compounds, corticoids, ataractics, and methyl dopa) were not included in the trial, neither were patients with serious complicating diseases (renal failure, liver cirrhosis) that might interfere with the metabolism of diazepam. Patients who were in cardiogenic shock or in pulmonary oedema on admission were also excluded from the trial.

On admission patients in the diazepam group immediately received 10 mg diazepam (Stesolid) intravenously. One hour later they received an oral dose of 15 mg diazepam and this dose was repeated every 8 hours for three days. Blood samples for determination of plasma-cortisol concentrations (Mattingly, 1962) and free fatty acids (Dole, 1956)

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TABLE 1 Clinical data of 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls)

		Diazepam group	Control group
Mean age (y)		56 ± 6* (range: 47-69)	57 ± 7* (range: 46-67)
Duration of pain before admission (no. of patients)	<div> <div>0- 3 h</div> <div>3- 6 h</div> <div>7- 24h</div> </div>	<div> <div>9</div> <div>4</div> <div>6</div> </div>	<div> <div>5</div> <div>7</div> <div>7</div> </div>
Mean duration of pain before admission (h)		6.5	6.6
No. of patients with:			
No previous illness		9	6
Coronary heart disease		7	10
Hypertension		3	1
Obliterative atherosclerosis		0	2
Mean maximum plasma aspartate aminotransferase (AST) (IU)		410	514
Localization of infarct (no. of patients)	<div> <div>Anterior</div> <div>Diaphragmatic</div> <div>Posterior</div> </div>	<div> <div>10</div> <div>9</div> <div>0</div> </div>	<div> <div>6</div> <div>10</div> <div>3</div> </div>

*Standard deviation.

were drawn on hospital admission, and thereafter every 12 or 24 hours for 72 hours. In addition, because of the rapid lowering of free fatty acids reported after acute myocardial infarction (Vetter *et al.*, 1974), blood samples were drawn for estimation 4 hours after admission.

The urinary output was collected over 24 hours for each of three consecutive days. Ten ml 10 per cent hydrochloric acid solution were added to the samples from which, after thorough mixing, 100 ml were withdrawn and deep-frozen for later determination of adrenaline, noradrenaline, and dopamine concentrations (Takahashi and Gjessing, 1972).

All patients were treated in a 6-bed intensive coronary care unit. This unit was connected to a 6-channel central oscilloscope which was placed in a separate room. The oscilloscope was constantly supervised by a trained nurse and all arrhythmias seen on the oscilloscope were recorded.

The patients were observed several times a day, and their mental state was rated according to the

criteria listed in Table 2. Particular attention was paid to signs of diazepam intoxication, such as ataxia, confusion, and euphoria. The need for analgesics was registered as numbers of injections given, either 10 mg morphine or equivalent doses of similar drugs. Blood samples for determination of concentrations of diazepam and its metabolite, N-desmethyldiazepam, were drawn on hospital admission, and 4, 24, 48, and 72 hours after admission (Arnold, 1975). Plasma aspartate aminotransferase (AST) levels were determined on admission, and several times during the next 2 weeks.

The statistical analysis was done by the χ^2 -test and Wilcoxon's non-parametric rank test.

Results

It appears from Fig. 1 that administration of diazepam as described caused a distinct accumulation of diazepam and its metabolite, N-desmethyldiazepam, and the same basic pattern was seen as already discussed by Hillestad *et al.*, (1974b). Continued diazepam treatment had a conspicuously beneficial effect on these patients as compared with the control group (Table 2). It reduced signs of unrest and anxiety ($P < 0.01$). Psychoemotional disturbances were seen in the diazepam group only during the first 24 hours of the trial when the serum diazepam concentrations were below 250 ng/ml. At the end of the trial, mean diazepam concentrations of 510 ± 215 ml (SD), and N-desmethyldiazepam concentrations of 281 ± 110 ng/ml (SD) were determined. At this time about 70 per cent of the patients in the diazepam group had no memory of the first 24 hours in the coronary unit.

Very few adverse reactions were observed after

TABLE 2 Mental state and need for analgesics in 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)

	Diazepam group	Control group
No signs of unwanted psychical reactions	15	7
Obvious signs of unrest and anxiety	3	6
Severe psychical reactions	1	6
Daily need for analgesics*	3.7	5.0

*Number of injections, 10 mg morphine ore equivalent doses of similar drugs.

FIG. 1 Mean plasma concentrations of diazepam and N-desmethyldiazepam in 19 patients with acute myocardial infarction treated with diazepam. (A loading dose of 10 mg i.v., followed by a 15 mg oral dose three times daily for three days.)

diazepam administration. Some patients showed signs of slight ataxia, and a 69-year-old patient became confused and agitated when the serum concentrations of diazepam and N-desmethyldiazepam were 248 ng/ml and 61 ng/ml, respectively. These adverse reactions quickly abated and disappeared 12 hours after diazepam was discontinued. Otherwise, no adverse reactions were seen—in particular no haemodynamic effects.

Fewer analgesics were needed by patients in the diazepam group as compared with the patients of the control group (Table 2). In comparison with the control group the diazepam group had a lower mean aspartate aminotransferase (AST) level (Fig. 2)

FIG. 2 Mean plasma aspartate aminotransferase (AST) levels in 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls).

TABLE 3 Incidence of severe cardiac arrhythmias requiring treatment amongst 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)

	Diazepam group	Control group
No. of patients requiring treatment	10	9
Supraventricular arrhythmias	8	5
Ventricular ectopic beats (more than 6/min)	6	5
Third degree heart block	0	1
Ventricular tachycardia	0	2
Ventricular fibrillation	0	1

and a lower mean maximum AST value (Table 1), the differences, however, being statistically insignificant ($P > 0.10$).

Malignant arrhythmias (ventricular tachycardia, third degree heart block, ventricular fibrillation) were seen only in the control group (Table 3). In the diazepam group, ventricular ectopic beats (more than 6 per minute) occurred only during the initial 12 hours after hospital admission (6 patients), whereas this arrhythmia was observed throughout the whole trial period in the control group (5 patients). No difference was seen between the groups in the incidence of heart failure, hypotension, and cardiogenic shock.

In the diazepam group no patients died during their stay in hospital, whereas in the control group one patient died 28 days after admission.

Patients treated with diazepam slept during most of the trial period, but could easily be awakened.

FIG. 3 Mean dopamine excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 88 ± 22 µg/g creatinine.

FIG. 4 Mean adrenaline excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 6.1 ± 1.8 $\mu\text{g/g}$ creatinine.

On interview, they expressed feelings of pleasant relaxation and were less concerned about their disease and the future than the patients in the control group.

The administration of diazepam produced a striking effect on the urinary excretion of catecholamines: a high urinary dopamine excretion was seen in the control group, but in the diazepam group it was within the normal range, and the difference between the two groups was highly significant ($P < 0.01$) (Fig. 3).

In both groups the urinary adrenaline concentration was much above normal (Fig. 4). However, diazepam administration caused a significant reduction in adrenaline excretion ($P < 0.001$). The urinary noradrenaline concentration exceeded the

FIG. 5 Mean noradrenaline excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 20.5 ± 9 $\mu\text{g/g}$ creatinine.

TABLE 4 Incidence of heart failure, hypotension, and cardiogenic shock among 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)

	No. of patients	
	Diazepam group	Control group
Signs of pulmonary congestion on consultation	3	4
Pulmonary congestion in addition to peripheral oedema and/or gallop rhythm of heart	2	3
Pulmonary oedema	0	1
Hypotension	3	3
Cardiogenic shock	2	1
Died	0	1

FIG. 6 Mean plasma free fatty acid concentrations in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 400 to 800 $\mu\text{Eq/l}$.

normal value about fourfold, but no significant reduction ($P > 0.10$) in the excretion of this substance was observed after diazepam administration (Fig. 5). There seems to be an extreme individual variation in the noradrenaline excretion as compared with excretion of adrenaline and dopamine.

On admission, the mean plasma free fatty acid concentrations in both groups were considerably increased, the diazepam group having the highest level (Fig. 6). After diazepam administration, the free fatty acid concentrations of the diazepam group initially decreased more rapidly than those of the control group. After 4 hours, there was no difference between the control group and the diazepam group,

FIG. 7 Mean plasma-cortisol concentrations in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 6.3 to 30.0 µg/100 ml.

and after 24 hours, the values were within normal limits in both groups.

Diazepam administration did not affect the plasma-cortisol concentrations (Fig. 7). On admission, increased mean values were determined in both groups, showing a rapid decline during the first 12 hours and decreasing to normal range within the next 72 hours. No diurnal variation of plasma cortisol concentrations was seen during the trial.

Discussion

In most cases, acute myocardial infarction gives rise to serious anxiety (Hackett, Cassem, and Wishnie, 1969). Pain will, in any circumstances, increase every patient's anxiety reactions. The diazepam dosage used in this study provided patients in a serious condition with safe sedation, yet negligible adverse reactions on physical and mental functions.

Previous studies have suggested that orally administered diazepam proves less effective than intravenously administered diazepam, but significantly more effective than intramuscularly administered diazepam (Hillestad *et al.*, 1974a, b). A good correlation was seen between the clinical effect (sedation) and the serum concentration level. Using diazepam as the sedative in myocardial infarction, it was found appropriate, therefore, to initiate treatment with an intravenous injection of the drug (a loading dose) followed by oral diazepam administration.

The clinical effects of the main metabolite, N-desmethyldiazepam, have not yet been completely assessed, but apparently it does not possess any potency as a sedative (Hillestad *et al.*, 1974a, b).

With the exception of a few days' delay for N-desmethyldiazepam, the accumulation of diazepam

and N-desmethyldiazepam occurs mainly during the first week, after which a steady state between cumulation and elimination is maintained. To achieve better sedation a higher loading dose of diazepam should be given initially, and the subsequent oral doses should be reduced gradually to maintain the serum diazepam concentration below 500 ng/ml (Hillestad *et al.*, 1974a, b).

The amnesia produced by the diazepam treatment may be of special value in attenuating later psycho-emotional problems, such as nightmares and cardiac neurosis. Diazepam is reported to be without analgesic effect, so that the reduced need for analgesics during the diazepam treatment is probably the result of an increased tolerance to pain (Bepko, Lowe, and Waxman, 1965). This observation is important, because administration of strong analgesics may suppress respiration, thus causing associated undesirable metabolic effects.

The findings of this study, viz. increased urinary excretion of catecholamines and high plasma free fatty acids and plasma cortisol levels, clearly show that acute myocardial infarction is a stress situation. The well-known correlation between plasma and urinary concentration of catecholamines (Fluck, 1972; Videbaek, Christensen, and Sterndorff 1972) makes it probable that using diazepam to treat patients with acute myocardial infarction caused a decreased plasma level of catecholamines. This conclusion may be of considerable importance, since increased plasma levels of catecholamines may cause ventricular arrhythmias and cardiogenic shock (Jewitt *et al.*, 1969; Siggers, Salter, and Fluck, 1971), and potentiate platelet aggregation (Ardlie, Glew, and Schwartz, 1966).

Adrenaline seems to be more connected with stress than does noradrenaline (Edmondson, Roscoe, and Vickers, 1972; Fluck, 1972). This may explain the lack of effect of diazepam treatment on the noradrenaline excretion.

We believe, despite the fact that continuous 24-hour recording tapes were not used, that serious ventricular arrhythmias did not remain undiagnosed. Our observation that diazepam seems to diminish the incidence of ventricular arrhythmias is in accordance with previous publications (Muenster *et al.*, 1967; Van Loon, 1968; Papp, 1969; Cristea, Coeugnet, and Dobrescu, 1970). This diminution may be the result of the decreased plasma catecholamine level, though the anti-arrhythmic effect of diazepam should be borne in mind.

An increase in the number of incidents of arrhythmias may be the consequence of high plasma free fatty acid levels (Oliver, Kurien, and Greenwood, 1968; Rutenberg, Pamintuan, and

Soloff, 1969), and it has been shown that the myocardial oxygen requirement is intensified by free fatty acids. The advantage of the rapid decline in raised free fatty acid levels after diazepam treatment is, therefore, notable.

The diazepam group and the control group were comparable in age distribution and clinical data (Table 1), and the average duration of pain before admission was also similar. However, among the very early admissions, i.e. less than 3 hours' duration of pain, 9 patients were found in the diazepam group and only 5 patients in the control group. The majority of very early cases in the diazepam group may explain the higher initial concentration of free fatty acids in this group. On the other hand, for the same reason a higher incidence of ventricular arrhythmias would be expected in the diazepam group, since the incidence of ventricular arrhythmias is highest in the early stage of myocardial infarction, but this was not seen in the present study.

Previous investigations indicate that the adrenocortical response in myocardial infarction is influenced by the amount of myocardial injury and not only by the stress reaction (Bailey, Abernethy, and Beaven, 1967); Logan and Murdoch, 1966; Chopra *et al.*, 1972; Vetter *et al.*, 1974). This observation may explain the lack of effect of diazepam on the increased cortisol level.

Although the difference in the plasma aspartate aminotransferase levels between the control group and the diazepam group is insignificant, this may suggest another beneficial effect of the drug. It has been shown that diazepam produces coronary vasodilatation in dogs (Abel, Reis, and Staroscik, 1970), and the coronary dilating effect of diazepam in patients with and without coronary heart disease was reported by Ikram, Rubin, and Jewkes (1973).

We conclude that the serious anxiety reactions seen during the initial phase of acute myocardial infarction can be controlled safely by means of diazepam. In addition, administration of diazepam might reduce both the incidence of malignant arrhythmias and the extension of existing injury.

The present study also shows that diazepam may serve to counteract the occurrence of deleterious hormonal imbalance during myocardial infarction.

Seventy-two hours after admission, a reduced daily diazepam dose of 15 mg, or less, is recommended considering the accumulation of diazepam as shown in Fig. 1. The dosage of diazepam has to be adjusted when administered to patients previously treated with anxiolytic agents. It should also be remembered that old patients often show a reduced tolerance to diazepam.

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