Nitrates in myocardial infarction: influence on infarct size, reperfusion, and ventricular remodelling

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Abstract

Objective—To assess the possible benefits of intravenous isosorbide dinitrate in acute myocardial infarction and oral isosorbide mononitrate in subacute myocardial infarction.

Methods—316 patients presenting with acute myocardial infarction were entered into double blind placebo controlled clinical trials assessing infarct size by enzyme release, ventricular size and function by echocardiography, reperfusion by continuous 12 lead ST segment monitoring and late potentials by high resolution electrocardiography.

Results—301 patients, of whom 292 (97%) received thrombolytic treatment, were randomised on admission to intravenous isosorbide dinitrate or placebo. Overall, there was no significant effect of treatment on infarct size, ST segment resolution, ventricular remodelling, or late potentials at day 3. A trend was observed towards a reduction in infarct size in patients with non-Q wave infarction treated with isosorbide dinitrate. Heterogeneity of nitrate effect was observed in relation to the degree of ST segment elevation on presentation with a clear benefit of isosorbide dinitrate in patients with moderate ST segment elevation (472 U/l v 704 U/l, $P = 0.003$) and a trend towards a deleterious effect in patients with marked ST segment elevation (1152 U/l v 1058 U/l, $P = 0.2$). ST segment re-elevation was more common among patients receiving nitrate treatment than in those assigned to placebo (29 v 16, $P < 0.05$). Some 160 patients underwent a further randomisation to sustained release isosorbide mononitrate or placebo on day 3. Echocardiographic volumes after 6 weeks of treatment were similar in the two groups.

Conclusions—No benefit was observed with administration of nitrates in the treatment groups as a whole for either acute or subacute infarction. There was, however, evidence of heterogeneity of effect in the different subgroups of acute infarction, and the possibility that nitrates may have differing actions in different groups of patients should be considered.

Keywords: myocardial infarction; isosorbide dinitrate; isosorbide mononitrate

Intravenous nitrates are commonly used in the management of acute myocardial infarction. Meta-analysis of randomised studies of intravenous nitrate treatment has suggested a statistically significant reduction in mortality.¹ This analysis was, however, based on studies predating the thrombolytic era and its applicability to patients undergoing thrombolysis remains uncertain.

Two recent multicentre randomised studies have failed to demonstrate an overall benefit of nitrates in the acute and subacute phases of infarction (GISSI-3² and the 4th international study of infarct survival (ISIS-4), American Heart Association 66th Scientific Session, Atlanta, 1993). The overall negative conclusions from these investigations do not, however, exclude the possibility that subgroups of patients may still benefit from nitrates. It is of value, therefore, to assess potential mechanisms of nitrate benefits as possible pointers to subgroups of patients in whom nitrates may be of value.³

There are a number of mechanisms whereby nitrates may favourably influence myocardial infarction.⁴ They may reduce infarct size through haemodynamic effects^{5,7} and increased collateral flow.⁸ They may interact with thrombolytic treatment to accelerate or stabilise reperfusion.⁹ Finally, they may prevent adverse remodelling in those patients who fail to reperfuse.¹⁰

The present study was designed to assess the effect of intravenous nitrate treatment on infarct size, reperfusion status, and early ventricular dilatation in the acute phase of infarction and the effects of oral nitrates on ventricular dilatation in the subacute phase of infarction.

Patients and methods

The study was divided into two parts, encompassing the acute and subacute phases of infarction. In the acute phase (days 1-3) patients with suspected acute myocardial infarction were randomised at presentation to intravenous isosorbide dinitrate or placebo in a double blind fashion. The primary trial end point was enzymatic infarct size. Secondary objectives were the non-invasive assessment of reperfusion status by continuous 12 lead ST segment monitoring, measurement of left

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ventricular dimensions by echocardiography, and assessment of late potential status using high resolution electrocardiography.

In the subacute phase (days 3–42) patients with proven myocardial infarction who were good echocardiographic subjects were randomised in a double blind fashion to treatment with oral isosorbide mononitrate or placebo for six weeks. The primary end point was the change in end diastolic volume between day 3 and day 42 with secondary end points of changes in end systolic volume and ejection fraction. Because it was anticipated that there would be a substantial drop out of patients between the acute and subacute phases, a two-by-two study design was considered inappropriate and treatment in the subacute phase was allocated by a second, independent randomisation.

The study was approved by the hospital ethics committee and informed consent was obtained from all participating patients.

ACUTE PHASE

Inclusion and exclusion criteria

Patients were considered eligible for the acute study if they presented within 24 h of the onset of symptoms, with a history of chest pain lasting longer than 30 min unrelieved by sublingual nitrates, and with ST elevation exceeding 1 mm in two limb leads or exceeding 2 mm in two contiguous precordial leads. Patients with severe hypertension (blood pressure > 200/110 mm Hg) or hypotension (systolic blood pressure < 110 mm Hg) were excluded. Patients were also excluded if they had significant left ventricular failure which, in the opinion of the attending physician, necessitated immediate treatment with nitrates, significant valvular or myocardial conditions limiting cardiac output (mitral stenosis, aortic stenosis, or hypertrophic obstructive cardiomyopathy), or were receiving either oral nitrate treatment which could not be discontinued, or angiotensin converting enzyme (ACE) inhibitor medication.

Trial treatment

The trial infusion (0.1% isosorbide dinitrate (Isoket, Schwarz Pharma, Mannheim, Germany) or matching placebo) was commenced within 90 min of the start of thrombolytic treatment or immediately in the small minority of patients in whom thrombolytic treatment was contraindicated. The initial infusion rate was 1 mg/h in patients with anterior infarction, with a systolic blood pressure at the time of randomisation > 125 mm Hg. The infusion was started in all other patients at a rate of 0.5 mg/h. Blood pressure and heart rate were measured using an automatic sphygmomanometer every 15 min and the trial infusion rate was titrated to reduce systolic blood pressure by 10%. The infusion rate was increased by 1 mg/h/30 min to a maximum infusion rate of 6 mg/h or until a target 10% reduction in systolic pressure was achieved. The initial titration step in patients starting at 0.5 mg/h was to 1 mg/h and each step thereafter was 1 mg/h. The infusion rate

was reduced if the decrease in systolic blood pressure > 30 mm Hg and discontinued if it fell below 95 mm Hg.¹¹ The infusion was restarted two steps back in the titration protocol on recovery of systolic pressure to the target value. The trial infusion was continued for a minimum of 24 h and discontinued between 6 00 pm and midnight of the day after randomisation (day 2).

Infarct size

Blood samples were drawn on admission, every 12 h on days 1 and 2, and daily on days 3, 4, and 5. Samples were analysed for α hydroxybutyrate dehydrogenase activity (α HBDH) at 25°C (Boehringer optimised standard method). The cumulative release of α HBDH was calculated using a two compartment model for enzyme release up to 72 h.^{12–14} This method has been shown experimentally to correlate with a high degree of accuracy with the amount of myocardial necrosis occurring after coronary occlusion.^{15–17}

Echocardiography

Echocardiograms were performed in all patients on day 3, at least 12 h after the discontinuation of trial medication and other cardioactive preparations. An echocardiogram was also recorded on day 1 before study randomisation when this could be achieved without delaying the start of the trial infusion. Echocardiograms were recorded (Hewlett Packard Sonos 500) on Super-VHS tape for subsequent off line analysis.¹⁸ Apical four chamber and two chamber long axis views were recorded with the patient semirecumbent and lying on the left side. The position of the probe was documented to ensure comparability of subsequent recordings. Recordings were rejected if less than 90% of the endocardium was visible. Off line analysis was performed using a custom built video overlay system in which the endocardial outline could be traced using a digitiser while the video image was replayed in real time. The endocardial outlines were traced at end diastole and end systole and the ventricular volumes calculated using a biplane disc method.^{19,20} Two beats were analysed for each echocardiographic view and the results averaged. The resulting volumes were corrected for body surface area.

Repeatability of the echocardiographic measurements was assessed in 15 patients. The standard deviation of repeated measurements of end diastolic volume index was 4.6 ml/m².¹⁸

Infarct artery patency

Infarct artery patency was assessed non-invasively by speed of resolution of ST segment elevation.^{21–23} On admission to the coronary care unit patients were attached to a continuous 12 lead electrocardiograph monitor (Mac 15, ST Guard; Marquette Electronics, Milwaukee). This machine sampled each lead every 30 s and measured and stored the elevation of the ST segment 60 ms after the J point. A change in ST elevation of 0.15 mV in a single lead or 0.1 mV in two or more leads

triggered the automatic recording of a 12 lead electrocardiogram (ECG). In addition, 12 lead ECGs were routinely recorded every 15 min. Recorded ECGs were stored on floppy disk for subsequent analysis. Each ECG was visualised during analysis and recordings rejected if there was excessive noise, left bundle branch block, or ventricular arrhythmia. All satisfactory ECG recordings were used to construct a trend of ST segment elevation at 60 MS after the J point against time.

Early reperfusion was defined as a decrease in ST segment elevation to less than 50% of its peak value within 90 min of starting thrombolytic therapy.²⁴ ST segment re-elevation suggesting reocclusion was considered significant if, after 50% resolution had occurred, there was an increase in ST elevation of 0.2 mV in a single lead or 0.15 μ V in multiple leads occurring within 1 h of the previous nadir and lasting for more than 1 min.^{25 26}

Late potentials

All patients without previous infarction had a signal averaged ECG recorded on day 3 and after six weeks (Predictor II; Corazonix Corporation, Oklahoma City). 300 beats were averaged and the recording rejected if the noise level was in excess of 0.7 μ V. The presence of late potentials was assessed using two of three standard criteria: filtered QRS duration of > 114 ms, root mean square energy of the terminal 40 ms < 20 μ V, and low amplitude (< 40 μ V) signal duration of > 38 ms.²⁷

SUBACUTE PHASE

Inclusion and exclusion criteria

Patients were excluded from entering the oral phase of the study if they did not have definite myocardial infarction based on two of three criteria: history consistent with myocardial infarction, new Q waves on the ECG, and an increase in creatine kinase levels to greater than three times the upper limit of normal. They were also excluded if they were inadequate echocardiographic subjects—that is, if less than 90% of the endocardium was adequately visualised. Patients with postinfarct angina or heart failure requiring nitrate treatment were not included in the subacute study. This exclusion was necessary on ethical grounds but eliminated from the study a group of patients with early heart failure who have recently been shown to benefit from pharmacological intervention to reduce ventricular dilatation.²⁸ Finally, patients with a systolic blood pressure < 105 mm Hg on day 3 were excluded.

Trial treatment

Patients eligible for phase two were randomised on day 3 to 50 mg slow release isosorbide mononitrate once daily (Elantan LA50) or matching placebo. Medication in patients experiencing symptomatic hypotension or troublesome side effects was reduced, at the discretion of the investigator, to a dose of 25 mg daily, once again with matching placebo. Trial medication in phase

two was continued for six weeks. Patients were reassessed 48 h after discontinuation of study medication.

STATISTICAL ANALYSIS

Data were analysed on an intention to treat principle and a two tailed probability of < 0.05 was considered significant for major predefined end points. Normally distributed data are presented as means (SE) and between group comparisons were made with the Student's *t* test. Data with a non-normal distribution (infarct size, time intervals to treatment) are presented as medians (inter-quartile range) and comparisons were made with the Mann-Whitney U test. Discrete variables were compared using the χ^2 test or Fisher's exact test for very small numbers.

Some subgroups were defined prospectively for the acute study: site of infarction, presence or absence of Q waves on admission, randomisation within 4 h of onset of symptoms, and successful early reperfusion (defined as 50% reduction in ST elevation within 90 min of the onset of thrombolytic treatment). A two tailed probability of < 0.01 was considered significant in assessing the effects of nitrates in these subgroups.

Power calculations

The acute study was designed to have an 80% chance of finding a decrease of 20% in infarct size in the nitrate treated group compared with that of those who received placebo, with $\alpha = 0.05$. In the subacute phase there was an 80% chance of finding a difference of 5 ml/m² (approximately 8%) in the change in end diastolic volume index between active and placebo groups, with $\alpha = 0.05$. Analyses for secondary end points were considered exploratory.

Results

A total of 301 patients with suspected acute myocardial infarction were enrolled in the acute study between 7 May 1991 and 10 January 1993 (fig 1). Acute myocardial infarction was confirmed in 281 patients (93%). Of the remaining 20 patients, 18 were considered to have myocardial ischaemia and two pericarditis.

Of the 281 patients with confirmed infarction, 10 died in the first 3 days and one underwent emergency coronary artery bypass surgery. Some 125 of the 270 remaining patients who were eligible for randomisation in the subacute study were excluded. The reasons for exclusion were a technically poor echocardiogram ($n = 59$), continuing angina ($n = 17$), heart failure requiring open nitrates or an ACE inhibitor ($n = 24$), atrioventricular block ($n = 2$), hypotension ($n = 8$), and refusal or inability to give consent ($n = 15$).

An additional 15 patients who had been ineligible for the initial randomisation were randomised into the subacute study. The reasons for earlier exclusion from the acute study included non-diagnostic ECG on presentation ($n = 6$), hypotension on presentation

Figure 1 Patient numbers in the acute and subacute phases of the investigation. Reasons for exclusion of patients from each phase of the investigation are described in the text.

($n = 2$), hypertension on presentation ($n = 1$), heart failure on presentation ($n = 1$), ACE inhibitor medication on admission ($n = 1$), and inability to begin the trial infusion within 90 min of the start of thrombolytic treatment ($n = 4$).

ACUTE STUDY

Patient demographics

Table 1 gives the baseline demographics for the 301 patients randomised in the acute study. The groups were well matched in their baseline characteristics, with the exception of a slight excess of anterior infarcts in the nitrate treated group.

Table 1 Baseline characteristics of patients in the acute study

	ISDN ($n = 150$)	Placebo ($n = 151$)
Age (years)	65.4 (56–72)	63.0 (54–71)
No of patients who received thrombolytic treatment	146 (97%)	146 (97%)
Time from onset of symptoms to thrombolysis (min)	230 (143–404)	230 (135–393)
Time from onset of symptoms to trial infusion (min)	290 (200–480)	285 (190–460)
Time from thrombolysis to trial infusion (min)	50 (39–65)	50 (35–69)
Male	111 (74%)	111 (74%)
Anterior myocardial infarction	84 (56%)	63 (42%)
Previous history		
Previous myocardial infarction	25 (17%)	25 (17%)
Angina	36 (24%)	35 (23%)
Hypertension	35 (23%)	37 (25%)
Heart failure	2 (1%)	2 (1%)
Diabetes mellitus	4 (3%)	8 (5%)
Current smoking	66 (44%)	67 (44%)
Therapy on admission		
Aspirin	24 (16%)	22 (15%)
β blocker	22 (15%)	32 (21%)
Calcium T antagonist	27 (18%)	16 (11%)
Nitrate	20 (13%)	11 (7%)
Diuretic agent	16 (11%)	17 (11%)

Continuous variables are presented as medians (interquartile range). ISDN, isosorbide dinitrate.

Table 2 Reasons for withdrawal of trial infusion

Reason for withdrawal	ISDN	Placebo
Hypotension	13	10
Recurrent angina	11	9
Reinfarction	2	3
Left ventricular failure	7	6
Cardiogenic shock	2	0
Hypertension	0	1
Patient's request	1	0
Cerebrovascular accident	2	0
Death	1	3
Total	39	32

ISDN, isosorbide dinitrate.

Trial infusion and blood pressure

A total of 71 patients (24%) had their trial infusion withdrawn. Of these 39 were allocated to isosorbide dinitrate and 32 to placebo ($P < 0.25$). Table 2 summarises the reasons for withdrawal. Dose reduction because of hypotension was more common in the nitrate treated group (52 patients (35%)) than the placebo (33 (22%)), ($P < 0.02$). The median (interquartile range) duration of infusion was 26.0 (24.0–30.4) h in the nitrate treated group and 26.9 (24.0–31.1) h in the placebo ($P = 0.2$). A stable infusion rate after titration was achieved earlier in patients treated with nitrate than in those given placebo (75 (30–158) min *v* 150 (30–210) min) ($P = 0.002$); and the median (interquartile range) stable infusion rate was lower in those receiving nitrate (3 (1–4) ml/h *v* 4 (1–6) ml/h, $P = 0.001$).

Blood pressure decreased initially in each group (fig 2). A statistically significant divergence in systolic pressures was apparent in the two groups by 120 min, with a greater reduction in the nitrate treated group. Significant hypotension (defined as a systolic blood pressure < 90 mm Hg, a diastolic blood pressure < 50 mm Hg, or $> 30\%$ decrease in systolic blood pressure) was observed in 27 (18%) patients receiving isosorbide dinitrate and 19 (13%) receiving placebo ($P > 0.1$). Hypotension was sustained (lasting for 30 min or more) in 12 patients (8%) treated with nitrate and in eight (5%) given placebo ($P > 0.25$).

A significant reduction in systolic blood

Figure 2 Systolic blood pressure for the first 24 h of the trial infusion. Time 0 is the time at which trial medication started. Values are means (SEM).

Figure 3 Distribution of infarct size among the patients included in the acute phase of the study in patients randomised to nitrate or placebo.

pressure in the nitrate group was still present 24 h after the start of the trial infusion (107 (1.5) mm Hg *v* 113 (1.2) mm Hg; $P = 0.005$).

Diagnosis of infarction

A diagnosis of myocardial infarction was confirmed in 137 patients randomised to nitrate treatment (91%) and 144 randomised to placebo (95%). The slightly increased representation in the nitrate treated patients with confirmed ischaemia who failed to evolve enzymatic or electrocardiographic criteria of infarction (nitrate 12, placebo six) did not achieve significance ($P = > 0.1$). The incidence of Q wave infarction was similar in the two groups (nitrate 102 (68%) *v* placebo 98 (65%); $P > 0.5$).

Enzymatic infarct size

There was insufficient data to assess the cumulative release of α HBDH in 12 patients

All patients ($n = 289$)

Anterior MI ($n = 140$)

Inferior MI ($n = 149$)

Q wave on admission ($n = 137$)

No Q wave on admission ($n = 152$)

Early treatment ($n = 142$)

Late treatment ($n = 147$)

Early reperfusion ($n = 168$)

Late or no reperfusion ($n = 83$)

Figure 4 Difference in infarct size between nitrate and placebo treated patients in predefined subgroups. The difference in infarct size between the nitrate and placebo treated groups given is the Mann-Whitney point estimate and 99% confidence interval (CI). Early treatment is defined as patients receiving thrombolytic agents within 4 h of the onset of continuous symptoms. Early reperfusion is defined as a reduction to $< 50\%$ of peak ST segment elevation within 90 min of the onset of thrombolytic treatment. α HBDH, α hydroxybutyrate dehydrogenase.

(six of each group) because of death (11 patients, 10 during the acute phase and one subsequent to the acute phase on day 3) or emergency surgery (one). These patients were excluded. Figure 3 shows the distribution of infarct size among the remaining 289 patients. Median infarct size was lower in the nitrate treated patients than in those given placebo by 47 U/l, but this difference did not achieve significance (95% confidence interval - 169 to 83 U/l, $P = 0.45$).

The effect of nitrate on infarct size was also considered in the predesignated subgroups (fig 4). Nitrate had no effect on infarct size in relation to the site of infarction, the time of starting trial treatment, or reperfusion status. There was, however, a trend towards a reduction of infarct size among patients without Q waves before randomisation (median infarct size was 397 U/l for the nitrate treated group, and 604 U/l for those given placebo, $P = 0.08$). On the basis of the presence or absence of Q waves on day 3, post-randomisation stratification demonstrated that the trend to smaller infarct size was stronger in the non-Q wave group (median infarct size was 279 U/l for the nitrate group, and 492 U/l for the placebo, $P = 0.02$).

The subgroups of patients with and without Q waves on day 3 were retrospectively examined to determine whether any differences in baseline characteristics might help to identify patients who would benefit from nitrate treatment. On admission the groups were well matched for age, site of infarction, previous history of angina, history of hypertension, heart failure, current medication, presenting blood pressure, and time from onset of symptoms to thrombolysis. Three characteristics differed significantly between the two groups: male sex was more common among patients with Q wave infarction (159/205 patients (78%) *v* 60/92 (65%), $P = < 0.03$), previous infarction was more common in patients with non-Q wave infarction (24/92 (26%) *v* 30/205 (15%), $P < 0.02$), and extent of ST elevation was greater among patients with Q waves (0.39 (0.02) mV) than in those with non-Q wave infarction (0.30 (-0.03) mV), ($P = 0.008$).

Further subgroup analyses were therefore performed, dividing the patients on the basis of sex and history of previous infarction. There was no significant difference in the median infarct size in the nitrate and placebo treated groups between males (669 U/l *v* 731 U/l, $P = 0.3$) and females (710 U/l *v* 627 U/l, $P = 0.8$), or between patients with previous infarction (530 U/l *v* 681 U/l, $P = 0.3$) and those with first infarction (740 U/l *v* 705 U/l, $P = 0.7$). To assess the possibility that nitrate benefits might vary in relation to extent of ST elevation, an analysis of covariance was performed for the influence of prerandomisation ST segment elevation and treatment on infarct size, including a term for the interaction of these two variables. This analysis demonstrated a significant interaction between nitrate treatment and the extent of ST elevation ($P = 0.04$). The study

Figure 5 Difference in infarct size between nitrate and placebo treated patients for subgroups defined by the extent of ST segment elevation on admission (Mann-Whitney point estimate of the difference and 99% confidence interval (CI)). α HBDH, α hydroxybutyrate dehydrogenase.

population was divided into three roughly equal groups defined on the basis of the extent of ST elevation on presentation to illustrate this interaction (fig 5). Nitrates did not significantly influence infarct size in the group with minimal ST segment elevation (< 0.2 mV). A highly significant reduction in infarct size was observed in the group with moderate ST segment elevation ($0.2\text{--}0.4$ mV), (median infarct size 427 U/l for patients receiving nitrate treatment *v* 704 U/l for those given placebo, $P = 0.003$). In the group with greatest ST elevation (> 0.4 mV), however, a trend was observed towards an increased infarct size in the nitrate treated group (1152 U/l *v* 1058 U/l, $P = 0.2$).

Left ventricular function

A total of 224 patients were good echocardiographic subjects and had technically satisfactory echocardiograms recorded on day 3. An echocardiogram was recorded before randomisation in 122 of these patients (54%). Table 3 gives ejection fraction, end diastolic volume, and end systolic volume on day 3. No significant differences were observed between the nitrate treated and placebo groups. The subgroup of patients with prerandomisation echocardiograms was considered separately to compare changes in ejection fraction and ventricular volumes between echocardiograms recorded before prerandomisation and on day 3 in each patient (table 3). There were no statistically significant differences between the two groups.

Reperfusion status

Technically satisfactory continuous 12 lead ECG recordings were achieved in 236

Figure 6 Pattern of resolution of ST segment elevation (mean (SE)). The ST segment elevation on admission is not included on the linear x axis as the time from admission to starting trial infusion varied among patients. Time 0 is the start of the trial infusion.

patients (78%) (120 nitrate, 116 placebo). The median time delay between starting thrombolytic treatment and ST recording was 9 min. ST trend recording was started at a median of 34 min before the trial infusion and the median (interquartile range) duration of recording was 463 (281–712) min.

Figure 6 shows ST elevation on presentation and for the first 5 h after starting trial treatment. There was no significant difference in the rate of ST segment resolution between the two groups.

Significant re-elevation of the ST segment was seen on 93 occasions in 54 patients (fig 7). Twenty one of these episodes occurred before starting trial treatment. Episodes occurring after the start of trial treatment were seen in 45 patients (29 nitrate, 16 placebo, $P < 0.05$). Some 47 episodes of ST segment re-elevation were observed in the nitrate treated

Figure 7 Continuous ST segment monitoring in an individual patient with acute infarction. ST elevation in a single lead is presented. About 1 h after starting thrombolytic treatment, substantial resolution of ST segment elevation occurred. Marked ST segment elevation is again evident at 3 h, with subsequent ST segment oscillation for the next 2 h.

Table 3 Left ventricular volumes in the acute phase

	Isosorbide dinitrate	Placebo	P value
Day 3	(n = 113)	(n = 111)	
Ejection fraction (%)	43.8 (1.1)	44.5 (1.2)	0.63
End systolic volume (ml/m ²)	37.9 (1.7)	36.3 (2.0)	0.53
End diastolic volume (ml/m ²)	65.2 (1.8)	62.4 (2.2)	0.33
Change from day 1	(n = 60)	(n = 62)	
Ejection fraction (%)	+ 0.5 (1.0)	+ 1.4 (1.1)	0.20
End systolic volume (ml/m ²)	-0.3 (1.2)	+ 0.5 (1.3)	0.64
End diastolic volume (ml/m ²)	-0.3 (1.7)	-1.1 (1.4)	0.71

Values are mean (SD).

Table 4 Baseline characteristics of patients in the subacute study

	ISMN (n = 80)	Placebo (n = 80)
Age (years)	58.4 (52.3–68.8)	60.8 (51.7–68.7)
No of patients who received thrombolytic treatment	78 (98%)	73 (91%)
Early ST resolution	49/66 (74%)	51/64 (80%)
Infarct size (U/l α HBDH)	645 (394–1098)	758 (394–1155)
Male	66 (83%)	62 (78%)
Q wave myocardial infarction	56 (70%)	63 (79%)
Anterior myocardial infarction	41 (51%)	32 (40%)
History before admission		
Previous myocardial infarction	6 (8%)	11 (14%)
Angina	8 (10%)	16 (20%)
Hypertension	21 (26%)	19 (24%)
Heart failure	1 (1%)	0 (0%)
Diabetes mellitus	3 (4%)	0 (0%)
Current smoker	42 (53%)	38 (48%)
Treatment on day 3		
β -blocker	47 (59%)	54 (68%)
Calcium antagonist	2 (3%)	8 (10%)
Diuretic agent	15 (19%)	17 (21%)
Aspirin	79 (99%)	79 (99%)

ISMN, isosorbide mononitrate.

Continuous variables are presented as medians (interquartile range). α HBDH, α hydroxybutyrate dehydrogenase.

group compared with 25 in the placebo treated group. The mean (SE) duration of episodes of ST segment elevation was greater in patients receiving nitrate treatment than in those receiving placebo (39 (8) min *v* 19 (13) min, $P = 0.2$). Patients showing re-elevation had similar initial ST segment elevation (0.29 mV *v* 0.28 mV, $P = 0.5$) and infarct size to those without re-elevation (median 713 U/l *v* 709 U/l, $P = 0.8$). ST segment re-elevation was not associated with an increased incidence of hypotension. Among patients with satisfactory ST segment and haemodynamic monitoring, transient hypotension was observed in 12 of 52 (23%) patients demonstrating ST re-elevation and 22 of 149 (15%) without re-elevation ($P < 0.2$). Hypotension was sustained in four patients (8%) with ST re-elevation and in nine (6%) of those without re-elevation ($P > 0.5$).

Late potentials

Of 291 patients surviving to day 3 243 had no previous history of infarction. Of these, 205 patients (104 isosorbide dinitrate, 101 placebo) had technically satisfactory signal averaged electrocardiograms. Late potentials were present on day 3 in 28 patients (27%) randomised to nitrate and 25 (25%) randomised to placebo ($P > 0.5$).

SUBACUTE STUDY

Patient demographic data

Table 4 summarises the baseline characteristics of patients entering the subacute study. The groups were well matched.

Study medication and withdrawal

During the subacute phase there was no significant difference in the rate of withdrawal of trial medication between active and placebo groups (nitrate 11, placebo 10). The most common reason for withdrawal was recurrent chest pain requiring open nitrate treatment (six nitrate, nine placebo). Three patients in the nitrate group had headache leading to withdrawal. One patient in the placebo group was withdrawn for dizziness and four (three nitrate, one placebo) were withdrawn at their own request. Dose reductions were more common in isosorbide mononitrate treated patients, principally because of headache. Eight patients in the isosorbide mononitrate group had their dose of medication reduced because of headache compared with only one in the placebo group. One patient in each group had their dose reduced for dizziness.

Clinical effects

Patients were assessed at six weeks, 48 h after discontinuation of study medication. There was clinical evidence of left ventricular failure in 10 patients (two nitrate, eight placebo, $P = 0.04$ by Fisher's exact test). Treatment for heart failure was almost identical in the two groups with 18 patients in the nitrate group and 17 in the placebo receiving diuretic agents and four in each group an ACE inhibitor.

There was one death in the placebo group and none in the nitrate group. Recurrent myocardial infarction was more common among patients randomised to placebo (five of 80 *v* none of 80, $P = 0.03$ by Fisher's exact test).

Effects on left ventricular function

Some 150 patients had technically satisfactory echocardiograms on days 3 and 42. No difference was observed between the groups treated with isosorbide dinitrate and placebo (table 5). Significant left ventricular expansion, arbitrarily defined as an increase in end diastolic volume of ≥ 10 ml/m² (two SDs of repeated measurements of end diastolic volume) occurred in 26 of 77 patients randomised to isosorbide mononitrate and in 24 of 73 patients randomised to placebo ($P > 0.5$).

Discussion

Studies predating the thrombolytic era have suggested that intravenous nitrates may have beneficial effects on infarct size,^{6,7} ventricular function,¹⁰ and mortality.¹ The current study was undertaken to assess whether similar benefits can be demonstrated when intravenous nitrates are added to contemporary treatment, including thrombolytic agents. Some 97% of our patient population received thrombolytic treatment.

Considering the patient population as a whole, intravenous isosorbide dinitrate failed to influence infarct size, reperfusion status, or ventricular function in acute infarction. Similarly, oral isosorbide mononitrate failed to influence ventricular function in the subacute phase after infarction. These results are

Table 5 Change in ventricular volumes and function from day 3 to 6 weeks in the subacute study

	ISMN (n = 77)	Placebo (n = 73)	<i>p</i> value
Ejection fraction (%)	+ 1.1 (1.0)	+ 2.5 (0.9)	0.27
End systolic volume (ml/m ²)	+ 1.3 (1.4)	+ 0.3 (1.2)	0.59
End diastolic volume (ml/m ²)	+ 4.2 (1.7)	+ 3.9 (1.6)	0.80

Values are means (SE). ISMN, isosorbide mononitrate.

consistent with the recent demonstrations in the ISIS-4 and GISSI-3 investigations that nitrate treatment started in acute infarction and continued into the subacute phase had no significant effect on overall mortality. The ESPRIM study has shown a similar lack of effect on mortality for the nitrate analogue, molsidomine.²⁹

NITRATES AND CORONARY PATENCY

Evidence concerning the effects of nitrates on reperfusion is limited to invasive studies in which nitrates have been administered by direct intracoronary infusion. Hackett and coworkers⁹ found that intracoronary nitrates given before streptokinase in 45 patients did not facilitate reperfusion. By contrast, when reocclusion occurred after either streptokinase induced or spontaneous reperfusion, intracoronary isosorbide dinitrate was associated with the restoration of reperfusion within 1–2 min on 14 of 28 occasions. No information was provided on restoration of perfusion in the absence of nitrates and it was therefore uncertain whether nitrates had contributed to the restoration of flow.

In a larger study by Rentrop and coworkers,³⁰ 393 patients were randomly assigned to intracoronary streptokinase, nitroglycerin, their combination, or neither. The combination of nitroglycerin and streptokinase did not increase the proportion of patients achieving reperfusion compared with that receiving streptokinase alone.

The study by Rentrop *et al*³⁰ also considered the effect of streptokinase and nitroglycerin on change in ejection fraction measured by nuclear ventriculography before and 10–14 days after intervention. Overall, a significant improvement in ejection fraction occurred only in patients treated with the combination of intracoronary streptokinase and nitroglycerin. The benefits of the nitroglycerin-streptokinase combination were seen in patients with total occlusion and confined to patients with collaterals. The authors suggested that the beneficial effect of nitrate in the presence of collaterals was to prolong the time window during which streptokinase induced reperfusion can successfully achieve myocardial salvage. This hypothesis is indirectly supported by the study of Sabia *et al*³¹ which showed that successful late reperfusion of an occluded infarct related artery 2–35 days after the acute infarct significantly improved regional wall motion in patients with substantial collateral flow compared with that in those without collateral flow. The presence of collaterals per se has also been shown to reduce infarct size and left ventricular dysfunction in the absence of successful reperfusion.^{32 33} Nitrate induced improvement in collateral flow might therefore benefit patients achieving reperfusion and those with persistent occlusion.

In the present investigation we were unable to demonstrate a benefit of intravenous nitrates on the overall speed of ST resolution. These results are consistent with the conclusion of Rentrop *et al*³⁰—that is nitrates do not accelerate reperfusion. Our study design,

however, imposed the limitation that nitrate infusion was not started until after completion of a streptokinase infusion. This design was selected to avoid the confounding issue of streptokinase induced hypotension. It remains possible that earlier administration of nitrates, concurrent with thrombolysis, might still accelerate reperfusion.

NITRATES AND INFARCT SIZE

The most immediate benefit of early reperfusion is reduction of infarct size, a powerful determinant of long-term outcome.^{34 36} Several studies have reported that intravenous nitrates can reduce infarct size in dogs⁸ and in patients not subjected to thrombolysis.^{6 7 10} There has been little previous information on the effects of nitrates in patients given thrombolytic treatment. In a study of 100 patients given streptokinase for acute myocardial infarction Hildebrandt *et al*³⁷ demonstrated no significant benefit of isosorbide dinitrate in the patient group overall, but in a small subgroup of 25 patients, who were judged on the rate of initial release of creatine kinase MB not to have reperfused, a beneficial effect on infarct size was observed. Nitrates had no significant effect on infarct size in the subgroup of patients in the present study, who were judged not to have reperfused on grounds of ST segment resolution ($n = 83$). The effects of nitrate were similarly negative in relation to site of infarction and timing of treatment.

In the predesignated subgroup defined by the absence of Q waves on the admission ECG, however, a trend was observed towards a significant reduction of infarct size with nitrate treatment. This group comprises patients destined to evolve Q waves together with patients who will continue to be designated as non-Q wave infarction. When analysis of infarct size was confined to the latter group, defined as the continuing absence of Q waves on day 3, this trend verged on statistical significance ($P = 0.02$).

Clearly such an analysis is open to criticism, for being both retrospective and using patient groups defined after randomisation. Nevertheless the suggestion of a subgroup benefit led us to undertake an additional subgroup analysis relating the effects of nitrate to the extent of infarction as defined by ST elevation in the presenting ECG. This analysis indicated an interaction between nitrate treatment and extent of initial ST elevation. A highly significant benefit was observed in the subgroup of patients with an intermediate degree of ST elevation. By contrast, in patients with more marked ST elevation a trend was observed towards an adverse effect of nitrates. Although analysis of covariance suggested a continuous relation between the effects of nitrates on infarct size and initial ST elevation, no significant benefit was observed among patients with slight ST changes on presentation. This may reflect the wide variance of infarct size in this group compared with the modest median infarct size of the group.

This retrospective subgroup analysis is clearly not definitive and merely serves as a pointer for either future investigations or comparison with existing data. Our results are consistent with a previous study of Flaherty *et al*³⁸ who found that intravenous nitroglycerin was of no benefit in the infarct population as a whole, but was associated with a significant improvement in thallium myocardial perfusion scintigraphy scores in those patients with small to moderate sized defects treated within 10 h.

Our results, therefore, suggest a hitherto unrecognised heterogeneity of nitrate action in relation to the nature and extent of infarction. It is of interest to speculate on potential mechanisms which might underlie such heterogeneity. We found no evidence of any beneficial effect on reperfusion status. One might anticipate that, if effects on systemic haemodynamics were responsible for a benefit of nitrates, benefits would be greatest among those patients with the largest infarcts. Clearly this was not the case. Our results would, however, be consistent with the suggestion from the study by Rentrop *et al*³⁰ that improvement in collateral flow may underlie any nitrate benefits in acute infarction, as the presence of collaterals would limit the extent of ST elevation on presentation and prevent Q wave formation.

That nitrates should benefit one group of patients and yet show no benefit in the patient population as a whole raises the possibility of adverse effects in some subgroups. In the present study a retrospective analysis showed a trend towards a disadvantageous effect on infarct size in the group of patients with most marked ST elevation on admission, suggesting the need for caution in the use of intravenous nitrates in patients with large infarcts. Once again, however, independent corroborative evidence from other studies is necessary to substantiate this trend. The increased incidence of reocclusion in nitrate treated patients suggests another possible adverse effect, although there was no evidence that this was associated with an increased permanent reocclusion rate or with an increase in infarct size.

NITRATES, VENTRICULAR FUNCTION, AND REMODELLING

The current investigation was designed to assess the effects of nitrates in the acute and subacute phases of ventricular infarction. In the acute phase, intravenous isosorbide dinitrate failed to influence left ventricular dimensions or ejection fraction at 48 h. The study design did not permit long-term assessment of the effects of early intravenous treatment on ventricular dimensions. It seems unlikely, however, that a subsequent difference would evolve. We have shown that late potentials on day 3 are strongly predictive of subsequent ventricular dilatation,¹⁸ perhaps reflecting the earliest stage of myocyte slippage with breakage of tight junctions. No difference was observed in the incidence of late potentials on day 3 between nitrate and placebo treated groups.

Our results are at variance with those of Jugdutt and Warnica,¹⁰ who observed a marked effect of nitrates on ventricular dilatation in patients not subjected to thrombolysis. The explanation for this difference is unclear, but may partly reflect the high uptake of thrombolytic treatment in the present study. The high uptake of thrombolytic treatment reflects the electrocardiographic and time criteria for study entry, which defined a population of patients in whom thrombolytic treatment was clearly indicated.

In the subacute phase, nitrates similarly failed to influence change in ventricular dimensions up to six weeks. Overall, only a very limited increase in ventricular volumes occurred. This result conceals considerable volume changes in individual patients. Fifty (33%) of the overall group showed significant ventricular dilatation defined as an increase in left ventricular end diastolic volume beyond two SDs of the repeatability of the echocardiographic method. This group of patients was offset by 20 (13%) who showed a significant decrease in ventricular dimensions, reflecting recovery of stunned myocardium. Nitrates did not influence the proportion of patients demonstrating either significant ventricular dilatation, or significant recovery of ventricular function.

This is the first substantive report of the effects of long-term nitrate treatment on ventricular dilatation after infarction. Our results are at variance with a preliminary report.¹⁰ The reasons for this difference are unclear. Patient selection may be a factor. In the present study, patients with any evidence of failure were excluded from entering the subacute investigation. This group may be at particular risk from adverse remodelling.²⁸ Similarly, patients with ongoing angina, patients too unwell to cooperate with echocardiography on day 3, and those already started on ACE inhibitor treatment were excluded and it is possible that some of these groups might benefit from nitrate treatment.

Conclusions

The current study is complementary to the results of the ISIS-4 and GISSI-3 investigations. When administered to all patients with suspected acute myocardial infarction, there is no evidence that nitrates are of benefit, whether considered in terms of infarct size, reperfusion status, and ventricular function, as in the present investigation, or in terms of mortality as in ISIS-4 and GISSI-3.

Our study indicates that there may be limitations in a global approach to myocardial infarction and that there may be heterogeneity of nitrate actions in different subgroups. Our findings suggest that patients without Q waves on admission or with limited ST elevation may still derive benefit from nitrate treatment. On the basis of these findings, we would suggest that the results of the ISIS-4 and GISSI-3 investigations should not lead to the rejection of nitrate treatment for acute infarction.

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