The difference between the mean operative delays in the two groups was therefore 43 hours (95% confidence interval 41·35 to 44·45 h; $t=6·0$, 143 df; $p<0·0001$). Despite a slight difference in the median ages for groups A and B (80 (range 47-96) and 82 (range 69-93), respectively) age distributions were similar. Typical reasons for delay included operator fatigue, delay in diagnosis, lack of theatre time, industrial action, and lack of patient's consent.

Discussion

This retrospective study suggests that the longer an otherwise fit patient has to wait for her hip fracture to be treated the less she will progress after discharge, regardless of her social circumstances. Many hospitals use trauma list systems, patients admitted one day being held over to the next before undergoing surgery. Previous work has shown that delays of 13-48 hours are not necessarily detrimental to patients' wellbeing.[2] Such work, however, emphasises the delay between admission and surgery rather than between injury and operation, the two observations often being widely different. Some of our patients had languished at home for several days before being admitted to hospital; thus in these cases there was a short interval between admission and surgery but an unacceptable delay between injury and surgery.

Loss of independence is perhaps the most important social problem relating to patients with fractures of the femoral neck, resulting in blocked beds and overloading of social and primary care services. What then should be done to avoid this for the elderly patient who arrives in the accident and emergency department with a hip fracture? We believe that if she is otherwise fit every effort should be made for her to undergo surgery at the earliest opportunity. To include such patients in a standard trauma list system, however convenient it may be for surgeons, anaesthetists, and administrators, is to exacerbate a situation that is already out of control.

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Trial of early nifedipine in acute myocardial infarction: the Trent study

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Abstract

Over 30 months 9292 consecutive patients admitted to nine coronary care units with suspected myocardial infarction were considered for admission to a randomised double blind study comparing the effect on mortality of nifedipine 10 mg four times a day with that of placebo. Among the 4801 patients excluded from the study the overall one month fatality rate was 18·2% and the one month fatality rate in those with definite myocardial infarction 26·8%. A total of 4491 patients fulfilled the entry criteria and were randomly allocated to nifedipine or placebo immediately after assessment in the coronary care unit. Roughly 64% of patients in both treatment groups sustained an acute myocardial infarction. The overall one month fatality rates were 6·3% in the placebo treated group and 6·7% in the nifedipine treated group. Most of the deaths occurred in patients with an in hospital diagnosis of myocardial infarction, and their one month fatality rates were 9·3% for the placebo group and 10·2% for the nifedipine group. These differences were not statistically significant. Subgroup analysis also did not suggest any particular group of patients with suspected acute myocardial infarction who might benefit from early nifedipine treatment in the dose studied.

TRENT Study Group

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Introduction

Nifedipine is a substituted dihydropyridine with calcium channel blocking properties.[1] Compared with verapamil it has very little cardiac electrophysiological effect.[2] In experimental myocardial infarction in animals pretreatment with nifedipine in a dose carefully regulated to avoid a large fall in blood pressure and reflex tachycardia causes an increase in coronary blood flow in both normally perfused and ischaemic areas of the heart, delays the release of cytoplasmic enzymes and the intracellular accumulation of calcium, preserves intracellular stores of adenosine triphosphate, and reduces infarct size.[3-6] Nifedipine is active during periods of ischaemia and also during subsequent reperfusion.[3] This has led to speculation that the drug may have a "cardioprotective" action in man.

In angina nifedipine has been shown to increase coronary perfusion and decrease afterload with minimal decrease in contractility[7,8] and is thereby thought to stabilise the imbalance between oxygen supply and oxygen demand. Roberts and coworkers have shown that nifedipine produces similar haemodynamic effects in patients with acute infarction, suggesting that in this condition also the drug may be capable of improving a myocardial oxygen deficiency.[9] Nifedipine also inhibits coronary artery spasm[10,11] and exerts a mild antiaggregatory effect on platelets,[12] both effects that have been implicated in myocardial infarction.[13]

The study by Roberts *et al* also suggested that treatment with

nifedipine within 12 hours of an infarct is safe provided that the dose is judiciously regulated to prevent hypotension.[9] Of 17 patients examined, none developed increased chest pain or showed an increased incidence of ventricular arrhythmia. There was no sign of atrioventricular nodal blockade, which agrees with findings in dogs[14] and patients with angina.[2] Preliminary results from open trials including 164 patients with acute infarction in 11 different centres also indicated that early treatment (that is, within 24 hours) with nifedipine is safe.[15] Evidently patients with myocardial infarction tolerate nifedipine quite well, even when they have been receiving long term β blocker treatment.[16]

These data from animal and isolated heart models of myocardial ischaemia and the results of clinical pilot studies therefore suggest that controlled trials of early treatment with nifedipine in patients with suspected acute myocardial infarction are necessary. We describe the results of a large multicentre study of nifedipine in such patients.

Patients and methods

Patients of either sex aged between 18 and 70 who were admitted to the coronary care units of the nine participating hospitals within 24 hours of the onset of chest pain due to suspected acute myocardial infarction were considered for the trial. Criteria for exclusion were as follows: pregnancy or ability to become pregnant within the next four weeks; arterial blood pressure less than 100 mm Hg systolic or 50 mm Hg diastolic immediately before administration of the trial medication (see below); heart rate greater than 120/min immediately before administration of the trial medication (see below); severe heart failure requiring vasodilator or intravenous inotropic support; known serious renal or hepatic dysfunction; current treatment with calcium channel blocking drugs; and refusal to give consent or inability to attend for local follow up. Patients who initially had a low blood pressure or high pulse rate as described above were reassessed after a further two and four hours if still within the 24 hour time limit and included if the haemodynamic exclusion criteria were no longer present.

All patients excluded from the trial were fully documented and had their course in hospital and state at four weeks recorded. Throughout the trial a patient could receive only one documentation number.

Informed consent was obtained from all patients included in the trial after they had been given as much information as seemed individually appropriate by the admitting doctor after his clinical assessment. The trial was approved by the ethical committees of all the participating hospitals.

TREATMENT, STRATIFICATION, AND FOLLOW UP

Immediately after assessment in the coronary care unit eligible patients were randomised in a double blind manner to receive placebo or a 10 mg nifedipine capsule. The first capsule was given sublingually and the patient reassessed at four hours. If at that time the systolic blood pressure exceeded 90 mm Hg and the heart rate was less than 120 beats/min a second sublingual capsule was given; otherwise the second dose was withheld and the patient reassessed at six hours and again at eight hours if necessary. If at eight hours after the first sublingual capsule the blood pressure and heart rate were still outside these limits the patient was withdrawn from the study but documentation was continued and the patient followed up to 28 days.

After the second sublingual dose six hourly oral treatment with placebo or 10 mg nifedipine capsules was begun a minimum of two hours and a maximum of eight hours later according to the above haemodynamic criteria. Oral treatment was continued until review in the outpatient clinic roughly 28 days after admission to the coronary care unit. During this time patients could be withdrawn at the discretion of the participating physician for the following reasons: systolic blood pressure persistently less than 90 mm Hg; persistent tachycardia >120/min; heart failure needing vasodilator or inotropic drugs; need for calcium channel blocking drugs; presumed "side effects"; refusal by the patient to continue with the trial medication; or another definite non-cardiac cause for the chest pain established.

Patients who had taken a β blocker within 48 hours before admission to the coronary care unit were randomised to placebo or nifedipine capsules separately from the rest. β Blockers could be continued or withdrawn at the discretion of the consultant physician. It was agreed, however, that β blockers given for secondary prophylaxis against further myocardial infarction would not be started in patients included in the trial until their 28 day clinic assessment. It was also agreed to adopt as closely as possible a common therapeutic policy for patients included and excluded during the 28 day study period. Thus no routine anticoagulant or antiarrhythmic drugs were prescribed, digoxin was used only for controlling the ventricular rate in atrial fibrillation, and early mobilisation and discharge from hospital was encouraged.

CLINICAL ASSESSMENT AFTER ADMISSION TO STUDY

Pulse rate and systemic blood pressure (phase V diastolic) were recorded every 15 minutes for the first two hours, every 30 minutes for the next four hours, then two hourly until the second sublingual dose, and thereafter twice daily in all included patients. All patients had continuous electrocardiogram monitoring during their stay in the coronary care unit, and activities of three sets of "cardiac" enzymes (one of which had to be serum aspartate transaminase) were estimated during the first three days together with three 12 lead electrocardiograms. Patients were grouped by the local investigator into one of the following five categories of infarct and non-infarct chest pain.

Patients with definite myocardial infarction had a convincing history accompanied by pathological Q waves in the electrocardiogram and peak enzyme activities exceeding twice the upper limit of normal for that hospital's laboratory.

Patients with probable myocardial infarction had a convincing history plus either pathological Q waves in the electrocardiogram or a rise in cardiac enzyme activities to more than twice the upper limit of normal.

Patients with possible myocardial infarction had a convincing history accompanied by electrocardiographic abnormalities that were not diagnostic of myocardial infarction and by an increase in cardiac enzyme activities that did not exceed twice the upper limit of normal.

Patients with ischaemic heart disease had a history of previous myocardial infarction or angina but without sequential electrocardiographic or enzyme changes during the present admission.

Patients with chest pain of unknown cause did not have a history of previous myocardial infarction or angina or sequential electrocardiographic or enzyme changes, and no alternative *definite* cause for their pain was diagnosed.

All major clinical events which occurred during the 28 day study period were recorded in both included and excluded patients. In addition, we recorded at 28 days any readmissions, current symptoms, and current and subsequent treatment. All patients included in the trial were subsequently followed up for the next 11 months.

The following information was collected about deaths which occurred in the 28 day study period: whether observed or unobserved; whether in or out of hospital; timing of death from onset of original or new main symptoms; and causes of death according to all available evidence, aided by necropsy reports where available.

DATA HANDLING

Demographic and clinical data were recorded in special booklets by the participating consultant physicians and their research assistants. All completed data forms were reviewed in the department of medicine at University Hospital, Nottingham, before being sent for computerisation in the department of mathematics at Nottingham University. From there regular reports were sent to an independent ethical review committee. The committee had the power to recommend that the study should be discontinued at any time for the following reasons: (*a*) if before 100 deaths had been notified there was a benefit to either group and the 99% confidence interval did not embrace zero; (*b*) if at any time thereafter the 95% confidence interval did not embrace a 10% effect (for a beneficial trend) or zero (for an adverse trend); and (*c*) if when the number of entrants to the trial approached the precalculated target it appeared that there was little chance of detecting an unequivocally positive effect.

SAMPLE SIZE

Based on our earlier findings we calculated that the overall one month mortality in untreated patients admitted with suspected myocardial infarction to an early entry trial would be 10%. To detect a 30% reduction in mortality in the group given active treatment—that is, a mortality of 7%—the minimum sample size required would be 1820 in each group, assuming that $2\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}1$. After the first few months of the study it became clear that the overall one month mortality was lower than expected and we were thus permitted to redefine our sample size based on an overall death rate of 8%.

DRUG SUPPLIES

Active and placebo capsules were supplied to the pharmacies of the participating hospitals by Bayer UK Ltd as blister packs already randomised in blocks of six. A senior pharmacist at each hospital held a code break in the event of emergency.

TABLE I—*Comparability of study groups at entry*

	Placebo group (n=2251)		Nifedipine group (n=2240)	
	No	%	No	%
Men	1851	82·2	1178	79·4
Women	400	17·8	462	20·6
Age (years):				
<40	148	6·6	116	5·2
41-50	393	17·5	427	19·1
51-60	889	39·5	871	38·9
61-70	816	36·3	815	36·4
Unknown	5	0·2	11	0·5
Previous history:				
Myocardial infarction: Definite	350	15·5	372	16·6
Myocardial infarction: Suggestive	225	10·0	219	9·8
Angina	767	34·0	783	34·9
Hypertension	453	20·1	444	19·8
Diabetes	100	4·4	117	5·2
Smoking:				
Never	475	21·1	503	22·4
Stopped >6 months	533	23·6	538	24·0
1-10/day	178	7·9	184	8·2
10-20/day	482	21·4	449	20·0
>20/day	368	16·3	375	16·7
Pipe or cigars	191	8·5	173	7·7
Unknown	24	1·1	18	0·8
Drugs:				
Diuretics	320	14·2	356	15·9
Digoxin	47	2·1	63	2·8
β Blockers	421	18·7	406	18·1
Other hypotensives	89	3·9	85	3·8
Antiarrhythmics	14	0·6	13	0·6
Others	684	30·3	679	30·3

Results

Recruitment—Participating hospitals comprised four teaching (Bristol Southmead, Bristol Frenchay, Nottingham City, Nottingham University) and five non-teaching (Airedale, Chertsey, Northampton, Norwich, and Swindon). Recruitment began in November 1982 and ended in May 1985; one hospital stopped recruitment in September 1984. During the study period 9292 consecutive patients were considered for the study but 4801 of these were excluded. Reasons for exclusion were age or ability to bear a child (1571 patients; 33%), symptoms for longer than 24 hours (1210; 25%), already taking a calcium blocker (1012; 21%), severe cardiac failure (358; 7%), and refused consent, other disease, haemodynamic reasons, lived away, and protocol violations (1252; 26%); some patients had more than one reason for exclusion. Thus 4491 patients were randomly allocated to receive either placebo (2251 patients) or nifedipine (2240). The two treatment groups were well matched for preadmission characteristics (table I).

Clinical course—The time from onset of major symptoms to the receipt of the first sublingual capsule was similar in the two treatment groups. Of patients in the two groups combined, 1441 (32%) received their first capsule within four hours, 3048 (68%) within eight hours, 3645 (81%) within 12 hours, and most of the remainder within the next four hours. The clinical course and treatment requirements in hospital were also similar (table II), as was the in hospital diagnostic classification, 64% of patients in each group (1442 placebo, 1429 nifedipine) being diagnosed as having had an acute myocardial infarction (table III).

Withdrawals—Of the patients allocated to nifedipine and placebo, 608 (27%) and 572 (25%) respectively were withdrawn from treatment before the 28th day. Table IV lists the reasons. Substantially more patients were withdrawn from the placebo group for elective treatment with a calcium channel blocker, usually for angina persisting despite other treatment. On the other hand, substantially more patients were withdrawn from the nifedipine group because of unwanted effects, particularly headache (49 *v* 20), indigestion (49 *v* 30), and dizziness (24 *v* 17). Most withdrawals occurred in the first few days of treatment and the diagnostic distribution was similar to that of the groups as a whole. Though outcome at 28 days was the main end point of the study, the follow up clinics were, of necessity, sometimes held a few days later. Of the 4200 patients who survived to this time, 2710 (64%) were still taking their trial medication, 377 (9%) had recently run out of capsules, 814 (19%) had been withdrawn by their hospital physician or general practitioner, 229 (5%) had discontinued treatment of their own accord, and in 70 (2%) compliance was not recorded. There were no differences between the nifedipine and placebo treatment groups.

Deaths—Altogether 150 (6·7%) of the patients allocated to nifedipine died in the first 28 days compared with 141 (6·3%) of those allocated to placebo. There was a higher proportion of deaths among patients withdrawn from their allocated treatments than among those who continued but there were no differences between the nifedipine and placebo groups in this respect (figure). The excess deaths among the patients who were withdrawn occurred particularly in those whose reason for withdrawal was persistent hypotension or tachycardia or severe heart failure. By intention to treat analysis there was thus an increase in overall mortality of 7% in the nifedipine group (approximate 95% confidence interval +30% to −16%). Of all 291 deaths that occurred during the study, 280 (96·2%—146 in the nifedipine group, 134 in the placebo group) were in patients who had an in

TABLE II—*Treatment and complications in hospital and treatment on discharge from hospital*

	Placebo group				Nifedipine group			
	In hospital (n=2251)		On discharge (n=2148)		In hospital (n=2240)		On discharge (n=2135)	
	No	%	No	%	No	%	No	%
Treatment:								
Diuretics	738	34·7	565	26·3	817	36·4	566	26·5
β Blockers	475	21·1	385	17·9	439	19·5	350	16·4
Antiarrhythmics	242	10·7	73	3·4	220	9·8	60	2·8
Digoxin	121	5·4	82	3·8	136	6·1	100	4·7
DC shock	144	6·4	—	—	120	5·3	—	—
Pacemaker	49	2·2	17	0·8	54	2·4	10	0·5
Complications:								
Recurrent myocardial infarction	33	1·5	—	—	49	2·2	—	—
Ventricular fibrillation	133	5·9	—	—	114	5·1	—	—
Asystole	28	1·2	—	—	36	1·6	—	—
Pulmonary embolism	10	0·4	—	—	16	0·7	—	—
Other*	377	16·7	—	—	384	17·1	—	—

*Heart failure, other embolism, other serious arrhythmia, ventricular septal rupture, mitral regurgitation, etc.

TABLE III—*Diagnostic categorisation of patients in study groups. Figures are numbers (percentages) of patients*

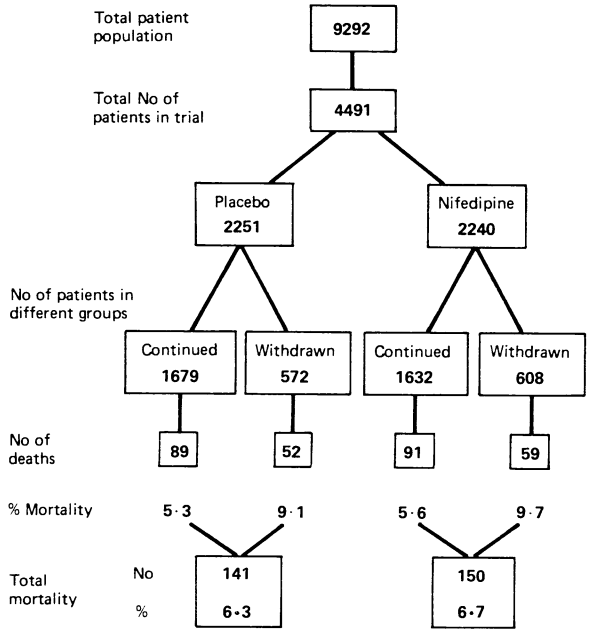
	Placebo group (n=2251)		Nifedipine group (n=2240)	
Myocardial infarction	1442 (64·1)		1429 (63·8)	
Definite	1080 (48·0)		1087 (48·5)	
Probable	205 (9·1)		180 (8·0)	
Possible	157 (7·0)		162 (7·2)	
Anterior	669		662	
Inferior	628		603	
Unsited	138		156	
Not recorded	7		8	
Ischaemic heart disease	389 (17·3)		370 (16·5)	
Chest pain of unknown cause	326 (14·5)		342 (15·3)	
Other diagnosis	94 (4·2)		99 (4·4)	

hospital diagnosis of acute myocardial infarction. The 28 day fatality rate of patients with myocardial infarction was thus 10·2% (146/1429) for the nifedipine group and 9·3% (134/1442) for the placebo group. Of the remaining 11 deaths (3·8%) during the study, seven occurred in patients with an in hospital diagnosis of ischaemic heart disease, three in patients with other diagnoses, and one in a patient with chest pain of unknown cause. Five of the patients with ischaemic heart disease died suddenly, four of them at home and one in hospital (proved ruptured aortic aneurysm). One died during coronary artery bypass grafting and one was readmitted in congestive cardiac failure and died of intractable ventricular fibrillation. All three deaths in patients with other diagnoses occurred in hospital (two ruptured aortic aneurysms, one pulmonary embolus, all proved at necropsy). The single death among patients categorised as chest pain of unknown cause occurred out of hospital in a patient with recurrent pleural effusions of some three years' duration. For the first two years of recruitment patients who entered the study were followed up for one year. There was no significant difference in survival between the two groups at the 12 month follow up.

TABLE IV—*Reasons for withdrawal before 28 day follow up. Figures are numbers (percentages) of patients**

	Hypotension	Tachycardia	Heart failure	Treatment with calcium channel blockers	Side effects	Others†
Placebo group (n=572)	127 (22·2)	46 (8·0)	34 (5·9)	113 (19·7)	96 (16·7)	176 (30·8)
Nifedipine group (n=608)	151 (24·8)	53 (8·7)	45 (7·4)	76 (12·5)	148 (24·3)	171 (28·1)

*Some patients had more than one reason for withdrawal.
†Errors, protocol non-compliance, etc.



Outcome at 28 days in patients entered for study.

SUBGROUP ANALYSIS

Patients who had taken β blocking drugs before admission formed the only predetermined subgroup studied. Nevertheless, because of the large size of the trial it was possible to look at subgroups defined retrospectively provided that their initial comparability could be ensured and caution was used in interpreting any differences found.

Treatment with β blockers—On admission to hospital 406 patients (18·1%) subsequently allocated to nifedipine and 421 (18·7%) allocated to placebo were taking β blocking drugs. They differed from those not taking β blockers with regard to the prevalence of previous myocardial infarction (259 patients (31%) *v* 463 (13%)), suspected myocardial infarction (138 (16%) *v* 306 (8%)), angina pectoris (522 (63%) *v* 1028 (28%)), and hypertension (458 (55%) *v* 439 (12%)). Though the proportion of patients diagnosed as having a myocardial infarction in hospital was lower in the β blocker groups irrespective of trial randomisation, the infarct fatality rate was higher (table V). There were no definite adverse interactions, however, between nifedipine and previous treatment with β blockers.

Time to treatment and outcome—There was no difference in the delay between the onset of symptoms and the initiation of trial medication between the placebo and nifedipine groups. Post hoc stratification by time, however, suggested that patients receiving nifedipine after eight hours did slightly worse than those given placebo (table VI).

Others—The expected increase in mortality with age was seen in both treatment groups. Overall, smokers fared little worse than non-smokers, though smokers taking β blockers had a higher mortality than smokers not taking β blockers. Women did better than men, and patients taking diuretics on admission did worse than those not taking diuretics, irrespective of trial allocation.

TABLE V—*Total and infarct mortality at 28 days among patients taking and not taking β blocker on admission*

	Placebo group (n=2251)	Nifedipine group (n=2240)
Not taking β blocker on admission		
No of patients	1830	1834
No (%) dead	103 (5·6)	112 (6·1)
No (%) with myocardial infarction	1198 (65·4)	1178 (64·2)
No (%) dead	98 (8·2)	109 (9·2)
Taking β blocker on admission		
No of patients	421	406
No (%) dead	38 (9·0)	38 (9·3)
No (%) with myocardial infarction	244 (57·9)	251 (61·8)
No (%) dead	36 (14·7)	37 (14·7)

TABLE VI—*Mortality at 28 days by time to treatment*

	Time to treatment (hours)				
	≤4	5-8	9-12	13-24	≤24*
Placebo group (n=2251)					
No studied	732	838	290	356	35
No (%) dead	55 (7·5)	49 (5·8)	19 (6·5)	16 (4·5)	2 (3·5)
Nifedipine group (n=2240)					
No studied	709	769	307	419	36
No (%) dead	52 (7·3)	43 (5·6)	23 (7·5)	28 (6·7)	4 (11·1)

*Known ≤24 hours but time not specified.

DRUG EFFECTS

By 30 minutes after beginning treatment the average systolic blood pressure was roughly 5 mm Hg lower in the nifedipine group and the average diastolic pressure roughly 4 mm Hg lower. Heart rate was higher in the nifedipine group by an average of 3 beats/min. These small differences were still discernible at the 28 day assessment.

EXCLUDED PATIENTS

In hospital diagnostic coding was available for 4798 of the 4801 excluded patients. Of these, 2926 (61%) were diagnosed as having an acute myocardial

infarction, 1039 (22%) ischaemic heart disease, 374 (8%) chest pain of unknown cause, and 322 (7%) other diagnoses.

The 28 day outcome was unknown for 127 (2·6%) of the total excluded group. Among the 4674 patients for whom complete data were available the overall fatality rate was 18·2% (855 deaths) as compared with the 6·5% among patients entered into the nifedipine versus placebo trial. This difference was largely due to a much higher mortality in patients with diagnosed infarcts (786/2926; 26·8%) as compared with the trial placebo group (134/1442; 9·3%) and trial nifedipine group (146/1429; 10·2%), reflecting their older age and poorer cardiovascular state on admission to the coronary care units.

Discussion

During this trial several other clinical studies were reported suggesting that the optimism engendered by animal studies for using calcium channel blocking drugs in myocardial ischaemia was not supported by clinical experience. In a large Danish multicentre study of acute infarction verapamil was given firstly intravenously, then by mouth in a daily dose of 120 mg for six months. Of 3498 patients randomised to verapamil or placebo there was no difference either in the number who progressed to proved myocardial infarction or in the fatality rates at six months.[17]

Sirnes *et al* entered 227 patients with suspected acute myocardial infarction within 12 hours from onset of symptoms to treatment with nifedipine or placebo in a manner comparable to our study.[18] They found no evidence that nifedipine reduced infarct size as determined by enzyme kinetics. They considered nifedipine to be safe in this setting, however, and its use was associated with a reduction in frusemide requirements during the first four days. This may reflect a beneficial effect of nifedipine on left ventricular function and is in keeping with invasive studies which showed that nifedipine reduced myocardial oxygen requirements and enhanced cardiac and peripheral haemodynamics with subsequent improvement in cardiac output.[19,20] In our study, however, we saw no difference in the incidence of or treatment for heart failure between the nifedipine and placebo treated patients.

Muller *et al* screened almost 10 000 patients admitted to four coronary care units and ultimately randomised 243 patients with symptoms suggestive of myocardial ischaemia of less than six hours' duration to either placebo or nifedipine 20 mg every four hours for 14 days.[21] They found no evidence of a reduced progression from "threatened" to acute myocardial infarction, no difference in cardiac enzyme kinetics in those with proved myocardial infarction, and no difference in mortality at six months. They attributed this neutral effect of nifedipine to the delay between the onset of symptoms and the beginning of treatment (mean 4·6 hours). We did not randomise patients separately according to time from symptoms but in our much larger study retrospective stratification by time did not disclose a potential advantage in those patients treated early. As with other "cardioprotective" strategies, however, the time interval between symptoms and treatment may be crucial.[22-24]

The optimal dose of nifedipine is uncertain. We used a dose schedule and rate of administration which had been shown to result in "therapeutic" plasma concentrations of nifedipine and to be clinically safe, avoiding any large falls in blood pressure. We were, perhaps, unduly worried by the possibility of an unfavourable fall in systolic blood pressure or increase in heart rate that a larger dose might have caused. In a recent study Gottlieb *et al* gave placebo or oral nifedipine 120 mg daily for 10 days to 30 patients with acute myocardial infarction.[25] Using two dimensional echocardiography they found a significant reduction in what they termed early infarct expansion. They attributed this ostensibly advantageous effect of nifedipine to the modest reduction in systolic blood pressure (mean 9 mm Hg). In our study using a much smaller daily dose we found a mean fall in systolic blood pressure of 5 mm Hg.

At the inception of the study we were also concerned about a potentially deleterious interaction between nifedipine and β blockers.[26,27] Hence we randomised patients separately according to whether or not they were already taking β blocking drugs on admission to the coronary care units. In the event we saw no cause for concern, though we cannot say whether the same would have occurred had we used a larger dose of nifedipine. Furthermore, our patients were acutely withdrawn from nifedipine, either for specified reasons of protocol or at the end of the 28 day treatment period, and we saw no evidence of an acute withdrawal syndrome as described for verapamil and diltiazem.[28]

Though the withdrawal rates in our study were comparable for the two treatment groups, we saw two interesting patterns. The first was an increase in unwanted effects among the patients withdrawn from nifedipine, though most of these were non-specific and not worrying, and the second was the substantial difference in numbers of patients withdrawn from trial medication in order to be treated electively with a calcium channel blocking drug because of persistent angina. This accords with the known antianginal effect of nifedipine and, because of its relative safety with regard to left ventricular function, may commend it for this purpose in patients in the early postinfarction phase.

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