Medical treatment of patients with severe exertional and rest angina: double blind comparison of β blocker, calcium antagonist, and nitrate

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SUMMARY The role of medical treatment of patients who had resting nocturnal angina as well as exertional angina was investigated. The effects of atenolol 100 mg a day, nifedipine 20 mg three times a day, and isosorbide mononitrate 40 mg twice a day were investigated in a double blind, triple dummy randomised study. Nine patients with coronary artery disease, early positive exercise tests, and transient daytime and nocturnal ambulatory ST segment changes were initially assessed off all antianginal medication. They were then treated with each drug for three five day periods. Angina diaries were reviewed and maximal treadmill exercise tests and 48 hour ambulatory ST segment monitoring were performed at the end of each treatment period. Resting and exercise heart rate and blood pressure were significantly lower on atenolol than on either isosorbide mononitrate or nifedipine. The duration of exercise to 1 mm ST segment depression was significantly greater on atenolol than on isosorbide mononitrate. Only one patient had an improvement in exercise tolerance on nifedipine that was greater than the improvement on atenolol; this patient had single vessel disease. The total number and duration of episodes of ST segment change during ambulatory monitoring were significantly lower with atenolol than on either isosorbide mononitrate or nifedipine. Nocturnal ST segment changes were abolished in six patients on atenolol, in six patients on nifedipine, and in five patients on isosorbide mononitrate. When nocturnal ST segment changes occurred, their frequency was reduced with all three drugs. Pain was abolished in four patients on atenolol and pain relief was significantly better on atenolol than on isosorbide mononitrate. There was no significant difference in pain relief between isosorbide mononitrate and nifedipine.

Thus β receptor blockade with atenolol was the most effective means of reducing myocardial ischaemia both during exercise and at rest at night without causing deterioration in any patient. Nocturnal myocardial ischaemia in patients with severe coronary artery disease can be effectively treated with β receptor antagonists and vasodilators.

Angina and myocardial ischaemia can occur on exertion or at rest in the same individual at different times of the day and night.¹ Different pathophysiological mechanisms have been used to explain ischaemia occurring at rest and on exertion in patients with obstructive coronary artery disease. Exertional angina is believed to be the result of myocardial oxygen demand exceeding supply, but angina at rest and at night is considered to be due to

reduction in coronary blood flow caused by factors such as coronary spasm^{2,3} and platelet aggregation.⁴ Thus if treatment is to be tailored to symptoms β adrenoceptor antagonists should be recommended for ischaemia on exertion, and vasodilators, such as nitrates or calcium antagonists, should be used for rest angina. Recently, there has been evidence that ischaemia at rest and at night tends to occur mainly in patients with severe forms of coronary artery disease and that heart rate often increases before the onset of ischaemia in these patients.⁵ In patients with normal coronary arteries or minor disease who develop ischaemia due to localised coronary spasm,

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however, there are no increases in the indices of myocardial oxygen consumption before the onset of ischaemia.⁶ It is therefore crucial to determine the ideal treatment for patients with coronary artery disease who have evidence of exertional and rest angina.

Several studies with ambulatory ST segment monitoring have demonstrated the occurrence of painless as well as painful ischaemia during daily activities.^{7,8} It is therefore important to perform ambulatory ST segment monitoring during assessment of antianginal agents as this not only provides information on the frequency of ischaemia occurring during normal daily activities, but also demonstrates painless episodes of myocardial ischaemia. In this study we have used ambulatory ST segment monitoring to assess the effects of standard antianginal treatment with a β adrenoceptor antagonist (atenolol), a calcium antagonist (nifedipine), and a nitrate (isosorbide mononitrate) in patients with frequent exertional daytime and nocturnal resting angina pectoris.

Patients and methods

PATIENTS

We studied nine patients, six men and three women, mean (SD) age 62 (7) years, with confirmed coronary artery disease and a history of both exertional and nocturnal angina pectoris and positive exercise tests (table 1). Three patients had had a previous myocardial infarction. One patient (case 2) had single left anterior descending coronary stenosis only, whereas all others had three vessel disease with or without left main stem stenosis. All patients were shown to have reversible ambulatory ST segment changes during the day and at rest at night while off antianginal medication. The patients' symptoms had been stable for at least two months before the study started and none had suffered a recent myocardial infarction.

STUDY PROTOCOL

All regular antianginal medication was withdrawn for 48 hours in hospital before the study began. Sublingual nitroglycerin was given for pain. The ST segment was monitored in ambulant patients for at least 24 hours and up to 48 hours (mean (SD) 35 (12) hours) (table 1). Patients who had reversible ST segment changes during the daytime and also at night (24.00 to 06.00 hours) were recruited into the study after giving informed written consent. The study was approved by the hospital ethics committee.

Three drugs, atenolol, nifedipine, and isosorbide mononitrate were administered for five days each in a double blind, randomised manner according to a latin square design with a triple dummy technique. Atenolol was given in a daily dose of 100 mg, isosorbide mononitrate 40 mg twice a day, and nifedipine was given three times at day at a dose of 10 mg for two days and 20 mg three times a day for three days to overcome the problems that occasionally arise with the higher dose of nifedipine.⁹ Throughout the various treatment periods, patients used sublingual nitroglycerin tablets to relieve pain. Six patients were assessed in hospital throughout the study and the other three patients had drug treatment periods at home. Patients were instructed to be mobile in and around the hospital or at home during the drug treatment periods. During the initial in hospital assessment period when all antianginal medication was discontinued, patients were advised not to undertake full activity in order to avoid frequent pain. The purpose of this part of the study was to identify patients with ST segment changes at night and at rest.

At the end of each treatment period, patients had ambulatory ST segment monitoring for 48 hours and kept angina diaries. Routine treadmill exercise tests were performed at the end of each five day treatment period.

Table 1 Severity of coronary artery disease and the number and duration of painful and painfree episodes of ST segment change during the day and night during 24 hour ambulatory ST segment monitoring in patients who were off all antianginal medication

Patient	Type of coronary artery disease	Total episodes	Nocturnal episodes	Total duration (min)	Number of painful episodes
1	3	7	2	473	2
2	1	11	3	446	0
3	3	11	1.5	316	2
4	3	13	2.5	127	6.5
5	3	11	3	133	4
6	3	2	1	55	2
7	3	12	3	125	4
8	3	8.5	1	264	1
9	3	6	2	150	4
Mean (SD)		9.1 (3.5)	2.1 (0.8)	228 (160)	2.7 (1.9)

AMBULATORY ST SEGMENT MONITORING

ST segment monitoring was performed with the Oxford Medilog II frequency modulated recorders which give good reproduction of low frequency (0.05 – 40 Hz <3 dB down) electrocardiographic signals. The bipolar lead CM5 was recorded continuously for 24–48 hours, initially with the patient off all medication and then at the end of each drug treatment period. The tapes were analysed at 60 times normal speed on the Oxford Instruments MA 20 analyser and the time, duration, and maximum magnitude of ST segment depression or elevation during each episode were noted. The heart rate at the onset of ST segment change was also noted for each episode. Significant ST segment depression was defined as a shift of 1 mm or greater in magnitude 0.08 seconds after the J point that persisted for at least 30 seconds. Significant ST elevation was defined as a shift of the J point of ≥ 1 mm that persisted for more than half a minute. The number, duration, and maximum magnitude of episodes were measured. The number of nocturnal, painful, and painfree episodes were also noted in each treatment period.

EXERCISE TESTING

Symptom limited maximal exercise tests were performed by all patients at the end of each five day treatment period according to the modified Bruce protocol. Patients had had at least two previous exercise tests before the study began. Significant ST segment depression was defined as a planar or down-sloping shift of the ST segment of ≥ 1 mm 0.08 seconds after the J point. Tests were terminated if ST segment depression of ≥ 2 mm occurred with or without pain or if severe chest pain, hypotension, arrhythmias, or exhaustion developed. The heart rate, systolic blood pressure, and rate-pressure product were measured at rest and at the onset of 1 mm ST segment depression during each treatment

period and the duration of exercise to 1 mm ST segment depression was noted.

STATISTICAL ANALYSIS

The different drug treatment periods were compared by analysis of variance. When the *f* value was significant, a paired *t* test was used to compare treatments.

Results

During the initial assessment period all patients had reversible episodes of ST segment change—ST depression in eight and ST elevation in one—both during the day (mean (SD) 9.1 (3.5) episodes) and at rest at night (mean (SD) 2.1 (0.8)) during each 24 hour period (table 1). Only a mean of 30% of episodes were accompanied by pain. One patient (case 2) could not tolerate isosorbide mononitrate because of headaches and nausea and another patient (case 7) could not tolerate nifedipine because headaches occurred even at a lower dose. In these two patients assessment was limited to only two drugs.

HEART RATE

The heart rate throughout the day and night was significantly ($p < 0.01$) lower on atenolol than during the initial assessment period when patients were off all antianginal medication or when they were treated with nifedipine or isosorbide mononitrate. The heart rate on nifedipine and isosorbide mononitrate, however, was not significantly different either during the day or at night from that during the initial assessment period when all antianginal medication was discontinued.

EXERCISE TEST

Table 2 shows the duration of exercise to 1 mm ST segment depression during the different drug treatment periods. The mean duration of exercise to

Table 2 Rest and exercise haemodynamic function and duration of exercise to 1 mm ST segment depression during different drug treatment periods. Values given are mean (1SD)

	Atenolol	Nifedipine	Isosorbide mononitrate	<i>p</i> value		
				Atenolol vs nifedipine	Atenolol vs isosorbide mononitrate	Nifedipine vs isosorbide mononitrate
Rest:						
Heart rate (beats/min)	60 (13)	91 (14)	86 (12)	0.01	0.01	NS
Systolic blood pressure (mm Hg)	130 (28)	142 (26)	149 (34)	NS	NS	NS
Rate-pressure product ($\times 10^3$)	8 (3)	12.9 (3)	12.6 (4)	0.05	0.01	NS
1 mm ST depression:						
Heart rate (beats/min)	81 (11)	118 (28)	109 (17)	0.01	0.01	NS
Systolic blood pressure (mm Hg)	146 (31)	158 (28)	166 (38)	0.01	0.01	NS
Rate-pressure product	11.9 (3)	20.4 (7)	18 (4.8)	0.01	0.01	NS
Duration (min)	3.6 (0.9)	3.2 (2.7)	2.3 (1)	NS	0.01	NS

ischaemia was significantly greater with atenolol than with isosorbide mononitrate ($p < 0.01$). When individual responses were analysed only one patient reached the same level of exercise before ST segment depression developed on both atenolol and isosorbide dinitrate, whereas all other patients achieved a greater workload with atenolol (fig 1). The mean workload achieved on nifedipine was 11% less in the group as a whole than that achieved on atenolol. In two patients similar workloads were achieved before ischaemia developed with the two drugs and one patient (case 2) reached a greater workload on nifedipine than on atenolol (fig 1). In the seven patients in whom treatment with both nifedipine and isosorbide mononitrate can be compared there was no significant difference in exercise duration between these drugs.

The mean resting heart rate was measured after the patient stood for two minutes before the exercise test. It was significantly lower on atenolol than on nifedipine (52%, $p < 0.01$) or on isosorbide mononitrate (43%, $p < 0.01$) (table 2). There was no difference in resting heart rate between nifedipine and isosorbide mononitrate ($p > 0.05$). There was no significant difference between the resting systolic and diastolic blood pressure during the different treatment periods. The heart rate and double product (heart rate $\times$ systolic blood pressure) were both significantly lower at the time of onset of 1 mm ST segment depression during exercise testing on atenolol than on nifedipine ($p < 0.01$) or isosorbide mononitrate ($p < 0.01$) (table 2). During exercise there were no significant differences in these haemodynamic indices between the nifedipine and the isosorbide mononitrate treatment periods.

AMBULATORY ST SEGMENT MONITORING

Eight patients had episodes of ST segment depres-

Fig 1 Duration of exercise to 1 mm ST segment depression during different treatment periods. Individual patient responses and their means (1 SE) are shown.

sion only and one patient had episodes of ST segment elevation and depression. The total number and duration of episodes of ST segment change were significantly lower during treatment with atenolol than during treatment with nifedipine or isosorbide mononitrate (fig 2). Three patients had no episodes of ST segment change during treatment with atenolol. Comparison of individual responses on atenolol and on nifedipine showed that two patients had a similar number of episodes during both treatment periods but that the duration of episodes was reduced on atenolol. In all the other patients the number of episodes was greatly reduced on atenolol. Eight patients had fewer episodes of ST segment depression on atenolol than on isosorbide mononitrate. In the remaining patient the number of episodes of ST segment change on the two drugs was similar but their duration was greatly reduced on atenolol. Nocturnal ST segment changes recurred in only three patients on atenolol, in three patients on nifedipine, and in four patients during treatment with isosorbide mononitrate. The frequency and duration of nocturnal ST segment change were less

Fig 2 Daily frequency of daytime and nocturnal (shaded columns) episodes of ST depression, their duration and magnitude, and the frequency of painful episodes during the initial off treatment period and during various treatment periods. Results are expressed as means (1 SE).

during each treatment period than during the initial assessment period when patients were off all anti-anginal medication.

Pain was much less frequent on atenolol; four patients experienced no pain at all during the 48 hour monitoring period (fig 2). Two patients became pain free on nifedipine and five had less pain on atenolol than on nifedipine. Two patients experienced more pain on atenolol than on nifedipine, although the number of painfree episodes of ST segment change and their duration were greater on nifedipine. In all patients the frequency of pain on atenolol was significantly less than that experienced on isosorbide mononitrate (65%, $p < 0.01$). There was no overall significant difference in pain frequency between isosorbide and nifedipine treatment periods ($p > 0.05$).

ADVERSE EFFECTS

None of the patients had more episodes of angina during any of the three treatment periods than during the initial assessment period when they were off all antianginal medication. One patient was intolerant of nifedipine and one of isosorbide mononitrate and they were assessed on two drugs only.

Discussion

ST segment changes have been shown to be reliable indicators of underlying myocardial ischaemia^{10 11} with the magnitude of change signifying either the size of myocardium affected or the severity of the ischaemia.¹¹ With the recent advent of frequency modulated recording systems it is possible faithfully to record and reproduce ST segment changes occurring during normal daily activities.¹² This technique provides an increased insight into the frequency of daily ischaemia experienced by a patient with angina. It not only detects painless episodes of myocardial ischaemia, but also demonstrates the duration and magnitude of each episode of ischaemia. Some patients develop ischaemia that is entirely painfree^{1 13} and it is thus unreliable to depend totally on a patient's history of chest pain as an indicator of the frequency of myocardial ischaemia. Furthermore, the history does not always indicate the severity and duration of the ischaemic episode.¹ Ambulatory ST segment monitoring also allows the detection of ischaemia not only on exertion during the daytime but also at rest and at night.

There has been controversy about the pathophysiology of ischaemia that occurs at night and at rest. Several studies have demonstrated that ischaemia occurring at rest is secondary to factors which primarily reduce coronary blood flow, such as coronary spasm or platelet aggregation.^{2-4 14} If this mechanism is important vasodilators such as nifedipine or isosorbide mononitrate would be expected

to improve rest angina and ischaemia. Furthermore, β adrenoceptor antagonists theoretically may be contraindicated in these patients because they can increase coronary vascular resistance by direct β_1 receptor blockade and unopposed α receptor stimulation.¹⁵ It is important to establish which form of medical treatment is most suitable for the considerable numbers of patients with severe coronary artery disease and frequent rest and exertional angina.

We compared the efficacy of three established antianginal agents, which are currently widely used and have diverse modes of action, in the treatment of patients with exertional and nocturnal angina. We also assessed whether any agent was likely to cause deterioration of myocardial ischaemia experienced during normal daily activities or at night. Atenolol is a β_1 selective receptor antagonist with no intrinsic sympathomimetic activity.¹⁶ It has been shown to be an effective antianginal agent in placebo trials and as effective as other β receptor antagonists.¹⁷ At a dose of 100 mg daily atenolol has significant negative chronotropic effects. In this study it reduced the heart rate and rate-pressure product not only at rest during the day and night but also on exercise. Thus, atenolol must have reduced myocardial oxygen consumption at rest and on exercise.

Nifedipine is a calcium channel blocking agent with no appreciable negative chronotropic effects.¹⁸ Calcium antagonists are effective smooth muscle relaxants, causing not only peripheral arteriolar vasodilation but also coronary arterial dilatation.¹⁹ Nifedipine is an effective antianginal agent not only in patients with exertional angina²⁰ but also in patients with variant angina and unstable angina.^{21 22} Some studies, however, have demonstrated a variable response to nifedipine. Although patients improved at a lower dose of 30 mg a day they became worse at higher doses.⁹ To overcome this we started all patients on 10 mg of nifedipine three times daily for the first two days and increased the dose to 20 mg three times daily thereafter. If no deterioration in symptoms occurred this dose was continued. Isosorbide mononitrate is more reliably and effectively absorbed from the gastrointestinal tract than isosorbide dinitrate.²³ Isosorbide mononitrate reduces ventricular end diastolic pressure and probably also has direct coronary arterial dilating action.^{24 25} At a dose of 40 mg twice daily it was effective in improving the exercise haemodynamics and pain frequency in patients with angina pectoris.²⁶

The results of ambulatory ST segment monitoring demonstrate that overall the patients improved most on atenolol in terms of the number, duration, and

magnitude of episodes of myocardial ischaemia experienced. The effects of nifedipine and isosorbide mononitrate were not significantly different. The improvement on atenolol was not only striking with the daytime exertion related episodes but persisted during the episodes at rest at night. None of the patients experienced worsening of angina, either daytime or nocturnal, on atenolol.

Nocturnal ischaemia was improved on all three drugs; most patients did not experience nocturnal pain or ischaemia during any of the treatment periods. When it did recur, the frequency and duration of nocturnal ischaemia were less than during the initial assessment off all antianginal medication. This result indicates, firstly, that atenolol was effective not only in exertion related ischaemia but it also improved or abolished nocturnal resting angina without causing deterioration in any patient studied. Secondly, nocturnal resting ischaemia can also be treated effectively by the vasodilators nifedipine and isosorbide mononitrate which are, however, considerably less effective than atenolol for treating daytime exertion related angina. Finally, the mechanism of precipitation of nocturnal ischaemia in patients with severe coronary artery disease is likely to be multifactorial and a reduction of myocardial oxygen demand by β receptor antagonists is probably the most effective way of preventing ischaemia in this group of patients.

Most patients in this study had three vessel coronary artery disease, frequent angina, and greatly reduced exercise tolerance. In order to characterise the patients adequately, they were taken off all antianginal medication so that ambulatory monitoring could be performed. All patients had exertional angina and the purpose of this phase of the study was primarily to identify those patients who also had demonstrable nocturnal ischaemia. Patients were all admitted to hospital for this phase and advised not to undertake normal activity. This advice was likely to reduce exertion related ischaemia but would not be expected to influence resting or nocturnal ischaemia. For this reason, we have limited comparisons to the three double blinded treatment periods in this study because all these were performed in similar circumstances.

The only patient whose exercise response was most markedly improved with nifedipine had single vessel disease. This may be because this patient differed from the others in that an increase in vasomotor tone was an important mechanism in precipitating myocardial ischaemia—hence the good response to nifedipine and the relatively poor response to atenolol. Further investigations in this patient seemed to confirm this hypothesis as intravenous ergometrine produced pronounced localised

coronary vasoconstriction.

Atenolol also increased the duration of exercise to ischaemia during conventional exercise testing more than isosorbide mononitrate did. Also only one patient reached a greater workload on nifedipine than on atenolol. As expected, the heart rate, blood pressure, and the rate-pressure product at rest were significantly lower on atenolol than on the two vasodilators. At the onset of 1 mm ST depression the heart rate and double product were lower on atenolol and remained significantly lower despite the duration of exercise being significantly longer on atenolol than on nifedipine or isosorbide mononitrate. This paradoxical reduction of the double product at peak exercise despite an improvement in exercise tolerance by β receptor antagonists has been reported before.^{27,28} The apparently detrimental effects of raising end diastolic filling pressure and coronary vascular resistance produced by β blockers may explain why the same rate-pressure product is not reached before ischaemia develops.^{29,30} Because all three drugs were beneficial in reducing the frequency of nocturnal angina and because their mechanisms of action are different, combination treatment of such patients may be appropriate.²⁰ None the less, the overall effect of atenolol in this study was an improvement in exercise tolerance and a considerable reduction in myocardial ischaemia during the day and night. Thus β receptor blockade, far from being contraindicated, is in fact of benefit in patients who have severe exertional and nocturnal angina caused by severe coronary artery disease.

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