

# Angiotensin converting enzyme inhibition in chronic stable angina: effects on myocardial ischaemia and comparison with nifedipine

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## Abstract

**Objectives**—To determine the anti-ischaemic effects of a new angiotensin converting enzyme inhibitor, benazepril, compared with nifedipine, alone and in combination, in chronic stable angina caused by coronary artery disease.

**Design**—Placebo controlled, double blind, latin square design.

**Setting**—Regional cardiology service for a mixed urban and rural population.

**Subjects**—40 patients with stable exertional angina producing at least 1 mm ST segment depression on exercise test with the Bruce protocol. 34 patients completed all four phases of the trial.

**Interventions**—Each patient was treated with placebo, benazepril (10 mg twice daily), nifedipine retard (20 mg twice daily), and a combination of benazepril and nifedipine in the same doses, in random order for periods of two weeks.

**Main outcome measures and results**—Total duration of exercise was not increased by any treatment. Exercise time to the development of 1 mm ST segment depression was not significantly changed with benazepril alone or in combination with nifedipine but was increased with nifedipine from 4.18 (1.8) min to 4.99 (1.6) min (95% confidence interval (95% CI) 0.28 to 1.34;  $p < 0.05$ ). There was a significant relation between increase in duration of exercise and resting renin concentration ( $r = 0.498$ ;  $p < 0.01$ ). Myocardial ischaemia during daily activity, as assessed by ambulatory electrocardiographic monitoring, was reduced by benazepril and by the benazepril and nifedipine combination. This was significant for total ischaemic burden (451(628) min *v* 231(408) min; 95% CI -398 to -41 min;  $p < 0.05$ ) and maximal depth of ST segment depression (-2.47(1.2) mm *v* -2.16 mm; 95% CI 0.04 to 0.57;  $p < 0.05$ ) for the combination and for maximal ST segment depth for benazepril monotherapy (-2.47 (1.2) mm *v* -1.96(1.2) mm; 95% CI 0.18 to 0.91;  $p < 0.05$ ). Benazepril significantly altered the circadian rhythm of cardiac ischaemia, abolishing the peak ischaemic periods at 0700 to 1200 and 1700 to 2300 ( $p < 0.05$ ).

**Conclusions**—Benazepril, an angiotensin converting enzyme inhibitor, had a modest anti-ischaemic effect in effort angina, but this effect was not as pro-

nounced as with nifedipine. The anti-ischaemic action was more noticeable in asymptomatic ischaemia during daily activity, whereas nifedipine had little effect on this aspect of myocardial ischaemia. The combination of benazepril and nifedipine reduced ischaemia of daily activity.

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Myocardial ischaemia is due to an imbalance between myocardial oxygen requirements and supply. Many factors influence this balance, the most important being work and myocardial blood supply. Angiotensin II may also influence this balance by its arterial vasoconstrictor and inotropic actions and through its interactions with the sympathetic nervous system.<sup>1</sup> Blockade of the renin-angiotensin system has been shown to reduce myocardial work and oxygen demands, increase coronary blood flow, and decrease tachycardia. Theoretically, angiotensin converting enzyme (ACE) inhibitors could be effective in the medical management of angina pectoris. Despite considerable experimental evidence to support this theoretical concept,<sup>2-4</sup> clinical experience is controversial.<sup>5-11</sup>

The purpose of this study was first to establish whether a new, non-sulphydryl ACE inhibitor, benazepril, was of therapeutic benefit in chronic stable angina in normotensive patients without heart failure; secondly to assess its efficacy relative to an established anti-anginal drug nifedipine, and thirdly to examine whether a combination of the two agents offered any therapeutic advantages over either one alone in such patients.

## Patients and methods

### PATIENTS

The study population consisted of 40 patients (32 men) aged 39 to 69 (mean 58.5) years with chronic, stable angina. Coronary angiography in 36 cases confirmed more than 70% cross sectional stenosis in at least one major coronary artery. Twenty one patients had had a myocardial infarction but none in the preceding three months. The duration of angina ranged from three to 131 (mean 19.8) months. The study was of a latin square, double blind, double dummy design in which the patients, after a two week drug free period, were randomly assigned in turn to, placebo, benazepril (10 mg twice daily),

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nifedipine sustained action (Adalat Retard, Bayer, Germany, 20 mg twice daily), and a combination of benazepril (10 mg twice daily) and nifedipine sustained action (20 mg twice daily). Each treatment period was of two weeks duration. Evaluations were performed at the end of the second week of each treatment period.

Patients were eligible for inclusion if they had exertional angina and, on treadmill exercise tests, limiting angina associated with  $\geq 1$  mm ST segment depression in not less than three minutes or more than eight minutes at the end of the two week drug free period.

Assessments of treadmill exercise used the Bruce protocol.<sup>12</sup> The same physician and technician performed all exercise tests in the same room at the same time of the day for a particular patient. Familiarisation tests were performed on two occasions before entry into the trial. At the end of each stage the systolic pressure was recorded by an automatic sphygmomanometer. Electrocardiographic leads CM5 and CC5 and a hybrid lead for analysis of arrhythmia were continuously recorded by means of a Marquette CASE-12 (Marquette Electronics Inc, Milwaukee, Wisconsin) electrocardiographic system. All patients stopped because of angina during the enrolment exercise tests, but breathlessness and fatigue were additional end points while on anti anginal trial treatment. Patients also underwent ambulatory electrocardiographic monitoring for 48 hours at the end of each two week trial sequence. Recordings were carried out on an Oxford Medilog 2 FM recorder. All patients kept a diary of their daily activity, anginal pain, and use of glyceryl trinitrate during the 48 hours of ambulatory monitoring.

During the 48 hour monitoring periods, two electrocardiographic leads CM5 and CC5 were recorded. Only the lead showing the most episodes of ST segment depression during the placebo phase was selected for analysis. Thereafter the same lead was always used for analysis in a patient for comparison between placebo and active phases. The tapes were played on a modified Oxford Medilog analyser. Data from the analyser was acquired by a Hewlett-Packard Vectra microcomputer through an A/D converter. Episodes of ST segment depression of  $\geq 1$  mm were considered significant and their frequency, duration, and maximal depth were recorded.

Summation of symptomatic and silent episodes of ischaemia permitted measurement of the total ischaemic burden to which the ventricle was exposed during the 48 hour monitoring period. Circadian rhythm of ST segment shifts were calculated by fitting the second harmonic regression equation to the data.<sup>13</sup>

Venous blood was taken from each patient for measurement of plasma renin activity. This was done between 0830 and 1000 after 30 minutes supine rest at entry into the randomised portion of the trial.<sup>14</sup>

Left ventricular function was categorised in all subjects who had diagnostic catheterisation by left ventricular cineangiography,<sup>15</sup> and the extent of coronary arterial disease was

assessed by the method of Brandt *et al* in which the amount of myocardium at risk is scored from a total of 15 units.<sup>16</sup>

#### STATISTICAL ANALYSIS

Statistical analyses were performed with the Statistical Analysis System (SAS, SAS Institute) version 5.18. A *p* value of  $<0.05$  from two tailed tests was considered significant. We used analysis of variance for continuous variables and CIs were set at 95% for computing differences between placebo and active treatment. Data are presented as mean (SD).

#### Results

Thirty four patients completed all phases of the protocol and their results are presented. Reasons for withdrawal included myocardial infarction, exacerbation of chronic pancreatitis, rash, headache, and facial flushing.

The mean left ventricular ejection fraction was 58% (12%). The extent of myocardium at risk was 7.8 (2.9) myocardial units<sup>16</sup> and there was no significant relation between left ventricular function or coronary score and response to the trial treatment.

#### EXERCISE TESTS

None of the treatments resulted in significant changes in duration of exercise. Exercise time to the development of 1 mm ST segment depression was significantly increased with nifedipine compared with placebo (4.99 (1.6) min *v* 4.18 (1.8) min; 95% CI 0.28 to 1.34; *p*  $< 0.05$ , fig 1).

Nifedipine retard reduced the maximum ST segment depression from 2.4 mm to 2.0 mm (95% CI 0.01 to 0.77). No other treatment had a statistically significant effect on this index of cardiac ischaemia.

Heart rate at rest and at maximal exercise was significantly increased by nifedipine. The combination of benazepril and nifedipine retard, however, blunted the increase in heart rate at peak exercise. Benazepril did not alter the heart rate at rest or in response to exercise. Mean resting systolic blood pressure was reduced significantly by all treatments (*p*  $< 0.05$ ). Only combined benazepril and nifedipine treatment blunted the blood pressure response at maximal exercise with a reduction of 12 mm Hg (95% CI -4.11 to 19.60).

The rate-pressure product at maximal exercise was reduced by all treatments but only combination treatment had a significant effect (*p*  $< 0.05$ ).

#### AMBULATORY ELECTROCARDIOGRAM

The number of episodes of  $\geq 1$  mm ST segment depression on placebo during 48 hours was not significantly different from that before treatment. All active treatments reduced the number of these episodes but none achieved a significant result. The total ischaemic burden in 48 hours was similar before treatment and in the placebo phases. It fell with all treatments but only the combination treatment resulted in a significant result

Figure 1 Time to 1 mm ST segment depression on various treatments (\* $p < 0.05$ ). Ba, baseline; P, placebo; B, benazepril; N, nifedipine.

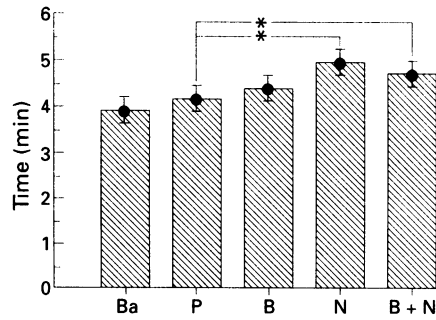
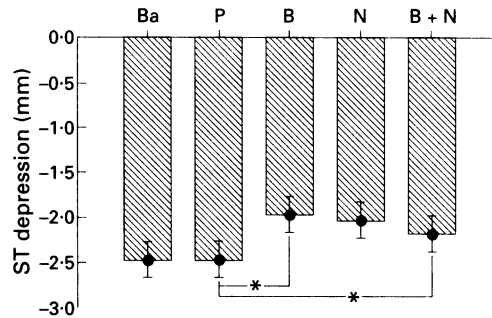


Figure 2 Maximal depth of ST segment depression during 48 hours of ambulatory monitoring in various trial phases (\* $p < 0.05$ ). Abbreviations as for fig 1.



(451(628) min *v* 231(408) min; 95% CI -398 to -41;  $p < 0.05$ ). Benazepril and the combination of benazepril and nifedipine retard produced significant reductions in the severity of ischaemia as measured by maximal depth of ST segment depression (fig 2).

There was a trend towards reduction in number of episodes of silent ischaemia with all treatments but none of these were significant. On placebo 98.3% of ischaemic episodes were silent; 97.5% with benazepril, 97.4% with nifedipine, and 98.2% with the combination. There was no difference between groups for symptomatic episodes of ischaemia.

The depth of ST segment depression showed the circadian pattern of myocardial ischaemia reported by Mulcahy *et al.*<sup>13</sup> On placebo there was a peak between 0700 and 1100 and a second one from 1700 to 2100. Circadian rhythm plots of ST segment shift showed a reduction in ST segment depression with benazepril throughout the 24 hours, and this was significant between 0600 and 1200 and between 1900 and 2300 (fig 3).

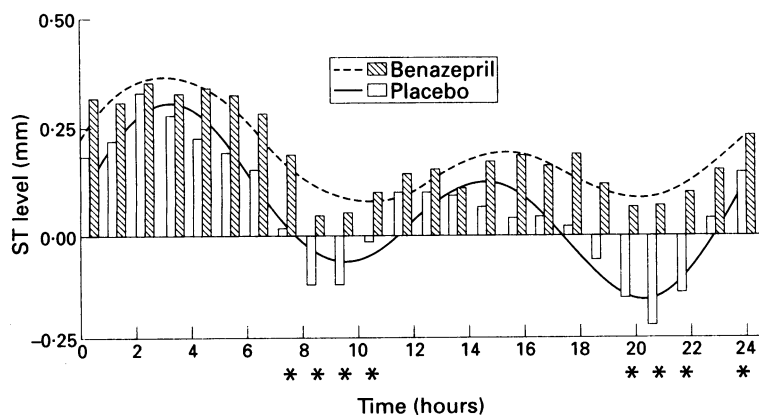


Figure 3 Plot of ST segment levels (bars) and the second harmonic regression equation (lines) *v* time over 24 hours (\* $p < 0.05$ ).

#### PLASMA RENIN

Plasma renin concentrations were within the normal range (0.15—1.55 nmol/l/hr) for this laboratory in all cases. There was a significant relation between percentage change in duration of exercise with benazepril monotherapy and resting renin concentrations at the start of the trials ( $r = 0.498$ ;  $n = 32$ ,  $p < 0.01$ ).

#### Discussion

Angiotensin II is a potent constrictor of systemic and coronary arteries.<sup>17</sup> It increases the vascular tone of large conductance coronary arteries, but has little effect on the small resistance coronary arteries.<sup>18</sup> Also, it has a positive inotropic action.<sup>19</sup> Hence an increase in angiotensin concentrations could increase myocardial oxygen demands, due both to increased contractility and afterload, while at the same time reducing coronary supply to the area by coronary vasoconstriction. Increase in myocardial oxygen demands due to angiotensin II may be made worse by the increase in tone of the sympathetic nervous system.<sup>20</sup>

Under the conditions of a graded incremental treadmill exercise test this study failed to show an overall significant beneficial effect of benazepril monotherapy compared either with placebo or nifedipine. This is in keeping with other negative studies of ACE inhibitors in angina of effort.<sup>2,7,21,22</sup> Although the overall effect is small and statistically not significant, a proportion of patients (half in this study and about two thirds in the study by Gibbs *et al.*<sup>9</sup>) do show a benefit as defined by an increase in the time to ischaemia—that is, 1 mm ST depression. Patients with high renin concentrations, indicating greater activation of the renin angiotensin system, showed a trend towards benefit whereas those with lower concentrations did not. This was consistent with findings in animals<sup>23</sup> and human,<sup>24</sup> where coronary vasodilatation with ACE inhibitors was only seen if the renin angiotensin system was activated. These findings confirm that in some patients, ACE inhibitors reduce exercise induced ischaemia.

Benazepril monotherapy had a favourable effect on silent ischaemia. There was a trend towards reduction in total ischaemic burden and a significant reduction in the intensity of ischaemia as judged by the maximal ST depression over 48 hours. Despite a lack of statistical significance, the 22% reduction in ischaemic episodes by benazepril compared with placebo was an encouraging trend and consistent with the 27% reduction reported by Klein *et al.*<sup>22</sup> and 28% by Tzivoni *et al.*<sup>25</sup> in similar studies to this.

Nifedipine monotherapy did not seem to have an anti-ischaemic action on ambulatory monitoring. This dichotomous action of nifedipine on exercise and silent ischaemia has been reported by Shell and Dobson.<sup>26</sup> Earlier studies with nifedipine reported benefits on ambulatory ischaemia,<sup>26,27</sup> but more recent studies have been unable to confirm this.<sup>13,28</sup>

The explanation as to why benazepril

monotherapy had an insignificant effect on exercise induced angina while possibly benefiting silent ischaemia might lie in the data of Remme *et al* on neuroendocrine effects of angina induced by atrial pacing.<sup>29</sup> They postulated that the massive neurohumoral response to maximal exercise would overwhelm the competitive blockade of the renin angiotensin system making it difficult to show any benefit. On the other hand the favourable anti-ischaemic action could be shown in resting ischaemia or by atrial pacing where the neuroendocrine effects are not as great.

This study and others have shown that patients with chronic stable angina, both symptomatic and silent as well as pure vasospastic angina, exhibit a circadian variation in severity of ischaemia with the greatest ischaemia and highest incidence of acute myocardial infarction and sudden cardiac death in the early wakeful hours of morning.<sup>13 30-33</sup>

We recognised two limitations of this study—namely, the use of multiple end points for electrocardiographic monitoring and the lack of a clearly consistent effect of treatment on ischaemia related end points. The use of multiple end points may have led to the observation of false positive results that can be statistically corrected. The choice of correction method to be applied is arbitrary and was not undertaken in this study.

Although we were unable to show consistent effects of treatment on ischaemia related electrocardiographic end points, the trends found with benazepril were consistent with reports from similar studies.<sup>21 22 25</sup>

The place of benazepril in chronic stable angina seems to be as adjunctive treatment in combination with other antianginal agents—for example,  $\beta$  adrenoceptor antagonists.<sup>22</sup> Another indication for the use of ACE inhibitors as adjunctive treatment in chronic stable angina may be in their usefulness in potentiating the action of long acting nitrate preparations.<sup>34</sup> This has recently been reported for benazepril and transdermal nitrate patches.<sup>35</sup>

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