Effects of Benazepril and Metoprolol OROS Alone and in Combination On Myocardial Ischemia in Patients With Chronic Stable Angina

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The efficacy of benazepril, metoprolol OROS and their combination was evaluated in 29 patients (42 to 74 years of age) with chronic stable angina and documented coronary artery disease in a placebo-controlled, double-blind, crossover trial using serial quantitated exercise testing and ambulatory electrocardiographic (ECG) monitoring. The mean (±SEM) exercise time was 8.5 ± 0.7 min with placebo, 8.3 ± 0.6 min (95% confidence interval [CI] -1.06 to 0.54) with benazepril, 9.4 ± 0.5 min (95% CI -0.32 to 2.14) with metoprolol OROS and 9.6 ± 0.5 min (95% CI -0.25 to 2.47) with the combination of benazepril and metoprolol OROS. The mean exercise time to the development of 1 mm ST segment depression was prolonged from 6.0 ± 0.6 min with placebo to 6.3 ± 0.6 min (95% CI -0.93 to 1.45) with benazepril, 7.9 ± 0.5 min (95% CI 0.83 to 3.0) with metoprolol OROS and 8.1 ± 0.6 min (95% CI 0.88 to 3.29) with the combination of benazepril and metoprolol OROS.

Benazepril did not alter the rest or maximal heart rate, whereas metoprolol OROS alone and in combination significantly lowered the heart rate at rest and during maximal exercise. Systolic blood pressure at rest was nonsignificantly reduced, whereas diastolic blood pressure was lowered significantly by all treatments in comparison with placebo. At maximal exercise, only metoprolol OROS, whether given alone or in combination with benazepril, was able to blunt significantly systolic blood pressure and rate-pressure product.

During ambulatory ECG monitoring, heart rate was lowered throughout the 24 h period with metoprolol OROS but not with benazepril. Total episodes of ST segment depression in 24 h were 221 with placebo, 160 (95% CI -3.72 to 1.28) with benazepril, 136 (95% CI -4.68 to -0.89) with metoprol OROS and 150 (95% CI -5.35 to 0.78) with the combination of benazepril and metoprol OROS. Similarly, total ischemic burden was 1,549 min with placebo, which was reduced to 879 min (95% CI -48.28 to 1.92) with benazepril, 807 min (95% CI -44.87 to -6.63) with metoprol OROS and 828 min (95% CI -49.63 to -0.37) with the combination of these.

In conclusion, metoprolol OROS is an effective anti-ischemic agent. Benazepril did not produce any clinical benefit in terms of exercise test variables. However, a clinically meaningful although statistically nonsignificant reduction in severity and number of ischemic episodes and duration of ST segment depression during ambulatory ST segment monitoring was observed. Because about 97% of ischemic episodes were silent, the findings suggest that benazepril might be beneficial in improving silent myocardial ischemia. Both drugs were well tolerated when administered singly or together. The data also confirm that benazepril did not impair the anti-ischemic effects of metoprol OROS.

Angiotensin-converting enzyme inhibitors are now well established and accepted for the treatment of hypertension and congestive heart failure. However, their usefulness in coronary artery disease is not well explored. A pilot investigation (1,2) of captopril in patients with angina and concomitant essential hypertension suggests that this class of drugs might be beneficial in the management of patients with angina pectoris. Angiotensin II is a potent vasoconstrictor of the systemic and coronary arteries that increases the vascular tone of the large conductive coronary vessels, especially during sodium depletion (3), but it has little effect on the small resistant coronary vessels and possesses positive inotropic effects. Therefore, increased angiotensin II production would further compromise the ischemic myocardium by reducing oxygen supply while increasing myocar-
dial oxygen demand as a result of both the increased inotropic state and increased afterload (3-5).

Angiotensin-converting enzyme inhibitors reduce blood pressure without producing reflex tachycardia and thereby lower the heart rate-blood pressure product, which is a reflection of a decrease in myocardial oxygen consumption (3), and this effect can be beneficial in patients with angina pectoris in whom the primary aim of medical therapy is to improve myocardial oxygen supply and reduce myocardial oxygen consumption. Although the reason for the lack of reflex tachycardia with angiotensin-converting enzyme inhibitors is not fully understood, it has been suggested that it might be due to a sympatholytic or vagomimetic effect during angiotensin-converting enzyme inhibition. It has also been suggested that angiotensin-converting enzyme inhibitors are coronary vasodilators (6,7). In view of the suggested mechanisms, such a study was undertaken in patients with coronary artery disease and established chronic stable angina pectoris to evaluate the safety and antiangiinal and anti-ischemic effects of the new angiotensin-converting enzyme inhibitor benazepril in comparison with the beta-adrenergic blocking agent metoprolol OROS.

Methods

Study patients. Thirty-one patients (28 men and 3 women, 42 to 74 years of age) with established grade II or III stable effort-induced angina pectoris (8) were recruited for the study. Twenty-five patients were nonsmokers, five were smokers and one patient’s smoking status could not be established. The duration of angina ranged from 4 to 120 months (mean 29.8). Coronary artery disease was confirmed in all 31 patients with selective coronary arteriography, which demonstrated >75% occlusion of one or more major coronary arteries. The left ventricular function as assessed by ejection fraction was normal in all patients (mean 65%, range 53% to 80%). Ten patients had previous myocardial infarction.

The previous antianginal treatment was nifedipine (n = 1 patient), verapamil (n = 3), diltiazem (n = 7), gallopamil (n = 2), sotalol (n = 1), atenolol (n = 2), metoprolol (n = 7) and isosorbidemononitrate (n = 15). All patients were gradually and completely withdrawn from their current antiangiinal treatment other than sublingual nitroglycerin to control anginal pain for at least 1 week before the start of the study. The study was approved by the Hospital Ethical Committee and all patients gave informed consent after the nature and purpose of the study were explained. All patients were required to fulfill the following inclusion and exclusion criteria, which have been described previously (9-11).

Inclusion criteria. Patients were required to develop angina on treadmill exercise testing accompanied by ≥1 mm horizontal or downsloping ST segment depression at the J point in one of the monitored bipolar electrocardiographic (ECG) leads CM₁ and CC₂. If the ST segment slope was ≤0.1 mV/s, they were required to have ≥1 mm ST segment depression. If the ST slope was >1 mV/s, the patients were excluded, whereas for those whose ST slope was between 0.1 mV and 1 mV/s, ≥2 mm ST segment depression was required. The patients were required to have had for ≥4 months symptomatic stable angina that was relieved by rest and sublingual nitroglycerin with an average incidence of four anginal attacks per week. Patients also had to have unequivocal evidence of coronary artery disease by selective coronary arteriography (that is, ≥75% narrowing of one or more coronary arteries) or previous myocardial infarction. All patients were required to be physically capable of undertaking regular exercise tests.

Exclusion criteria. Patients were excluded from the study if they were receiving any drug likely to influence heart rate or ST segment level, such as digitalis or diuretic drugs, or if they had a rest blood pressure >170/105 mm Hg, left ventricular hypertrophy or bundle branch block. Patients with a history of recent myocardial infarction within the preceding 4 months, unstable angina, clinical congestive heart failure, bronchial asthma, peripheral vascular disease, insulin-dependent diabetes mellitus or the labile ST-T syndrome were also excluded, as were patients >75 years of age and women of childbearing age. Any patient not developing classic anginal pain and ≥1 mm ST segment depression during the initial control test or who had an exercise time during the placebo run-in test >8 min or exercise time variability on two control tests ≥20%, or both, was excluded.

Trial design. All patients were withdrawn from their current antianginal treatment gradually and completely and were maintained on sublingual nitroglycerin alone to control anginal pain for ≥1 week before performing a baseline control exercise test. Thereafter, all patients were entered in a single-blind placebo run-in period of 1 week. Subsequently, they were randomly allocated in equal numbers to a randomized treatment sequence (Fig. 1) (using a Latin square design) of the following four trial treatments using a double-dummy technique: 1) Benazepril, 20 mg twice daily; one 20 mg benazepril tablet and one metoprolol OROS placebo tablet in the morning and in the evening. 2) Metoprolol OROS, 14/190 mg (release rate/total dose) once daily; one active tablet of metoprolol OROS and one placebo tablet of benazepril in the morning and one placebo tablet of benazepril in the morning and one placebo tablet of metoprolol OROS in the evening. 3) Benazepril, 10 mg twice daily, plus metoprolol OROS, 14/190 mg once daily: one active tablet of each in the morning and one active tablet of benazepril and one placebo tablet of metoprolol OROS in the evening. 4) Placebo: one placebo tablet of benazepril and one placebo tablet of metoprolol OROS in the morning and in the evening.

The trial medication was administered twice daily. The double-blind treatment periods were of 3 weeks’ duration.
At the end of each double-blind treatment period, a symptom-limited treadmill exercise test was performed in the morning without the administration of the trial medication to allow evaluation of the effect 12 h after administration of benazepril and 24 h after administration of metoprolol OROS. Ambulatory ECG monitoring was performed for 24 h at the end of each treatment period.

**Assessment.** The patients maintained a detailed diary of adverse effects, anginal attacks and sublingual nitroglycerin consumption. They were asked not to use sublingual nitroglycerin prophylactically. Objective evaluation was achieved by performing serial maximal symptom-limited treadmill exercise tests (9,10) as already described. All exercise tests were performed in the morning ≥2 h after a light breakfast and without administration of the morning dose of active or inactive study medication. The patients rested comfortably in the exercise laboratory for ≥30 min before each test and were asked not to smoke or take sublingual nitroglycerin tablets on the morning of the test.

**Exercise testing.** Exercise tests were performed on an electrically braked treadmill (Trottoir Roland, Enraf Nonius) in a temperature-controlled laboratory (20° to 24°C) by the same investigator at the same time of the day. During the pretrial screening period, one to two familiarizing tests were performed for technical training and physiologic adaptation of the patient in case he or she was not familiar with the nature of the test situation. A multistage symptom-limited exercise test employing increasing work loads with each stage of 3 min duration was performed according to the Bruce protocol (12) (Table 1). The speed and gradient for each stage were fixed by the protocol. At the end of each stage, systolic blood pressure was recorded with a mercury sphygmomanometer. The six lead ECG was continuously monitored and the ST segment level and heart rate were recorded at rest, every minute during exercise and for 5 min thereafter. The end points considered for possible termination of the exercise test were anginal pain, breathlessness, fatigue, the appearance of a life-threatening arrhythmia, a decrease in systolic blood pressure ≥20 mm Hg with increasing work load or excessive increase in blood pressure (for example, systolic blood pressure 220 mm Hg and diastolic blood pressure ≥125 mm Hg). However, in this study, all exercise tests except one were terminated because of moderate to severe chest pain of a magnitude that would have limited the patient's daily activities. The standard safety precautions as outlined by the American Heart Association (13) for exercise testing laboratories were followed.

**Ambulatory ECG monitoring.** Patients underwent 24 h Holter monitoring after exercise testing. After appropriate preparation of the skin, pregelled disposable electrodes were applied using a bipolar lead system. Two bipolar ECG leads (CM5 and CC5) were recorded utilizing a two channel 24 h tape recorder (Reynolds Tracker TRIB) (10,11,14). The ST segment changes induced by position (prone, supine, left side, right side, sitting and standing) or hyperventilation were investigated. Patients were instructed to perform their usual daily activities during the 24 h monitoring period. They were asked to keep a detailed diary of all activities and symptoms. Ambulatory ECG tapes were analyzed (14) by a dynamic electrocardioscanner (Reynolds Pathfinder III).

**ST segment analysis.** Calibrated tapes were replayed at 60 times normal speed under the control of the operator. A reference point within the PQ segment, an ST-1 point at the J point and an ST-2 point 0.06 to 0.08 s thereafter were preselected by the operator at the beginning of the playback. The difference between the ST-1 and ST-2 point and the reference point and heart rate were averaged over a period of 8 to 64 cycles and simultaneously plotted on a strip chart recorder together with the changes in slope and area. ST segment elevations resulted in positive deflections and ST segment depressions in negative deflections of the ST trend. ST-1 and ST-2 deflections were considered significant when they were >100 µV, slope changes when <1 µV/s and area changes when >10 µV/s. A paper speed of 0.7 to 6 cm/h was selected for the trend recordings. Ventricular ectopic beats...
were automatically excluded from ST segment analysis. During each episode with ST segment deviation of >1 mm, the ECG was printed out at a paper speed of 25 mm/s. By visual analysis, ST segment elevations and horizontal or downsloping ST segment depressions of >1 mm, persisting for ≥60 s, were regarded as ischemic episodes. After automatic analysis, all ECG strips showing episodes of ST segment deviation were printed out and their duration and maximal magnitude were measured.

Statistical analysis. All statistical analyses were performed using the statistical analysis system (SAS, SAS Institute), version 5.18. For statistical significance testing (two-tailed tests), the significance level was set at 5%. The confidence level was set at 95% for computing of confidence limits or intervals for the differences between active treatment and placebo: benzazepril dosage is 20 mg twice daily; metoprolol OROS dosage is 14/190 mg once daily; benzazepril + metoprolol OROS dosage is benzazepril 10 mg twice daily + metoprolol OROS 14/190 mg once daily.

Results
A total of 31 patients (28 men and 3 women, 42 to 74 years of age) were recruited for the study. One patient (Case 31) withdrew his consent during the first treatment period and one patient died suddenly at home during the first double-blind treatment period. This latter patient was receiving placebo; the exact cause of death could not be established because the cardiologist in charge was not informed. It was thought that the patient, who had triple vessel disease, died of massive myocardial infarction. Therefore, only 29 patients successfully completed the study.

Protocol violators. Four patients were considered protocol violators because their exercise time during the initial two control tests was either >8 min or the variability of exercise time in two tests was >20%. Two patients took sublingual nitroglycerin tablets before the exercise test and their data could not be used for efficacy analysis. Therefore, only 23 patients were analyzed for exercise test data. However, all 29 patients were analyzed for ambulatory ST segment and heart rate data as well as tolerability and safety.

Exercise Test Results (Table 2)

Exercise time. All patients developed moderate to severe anginal pain at maximal exercise during all exercise tests, except one patient who discontinued the test because of shortness of breath while receiving the combination of benzazepril and metoprolol OROS. The exercise time (mean ± SEM) was 8.5 ± 0.7 min with placebo and 8.3 ± 0.6 min (95% confidence interval [CI] −1.06 to 0.54) with benzazepril. This increased to 9.4 ± 0.5 min (95% CI =0.32 to 2.14) with
metoprolol OROS and 9.6 ± 0.5 min (95% CI -0.25 to 2.47) with the combination of benazepril and metoprolol OROS. Using analysis of variance, there was a statistically significant treatment effect (p < 0.038), which was most probably due to metoprolol OROS. However, this effect became nonsignificant in comparison with placebo (p < 0.054), most probably because of an unbalanced trial design.

**ST segment changes.** The mean exercise time to 1 mm ST segment depression in lead CM₁ was 6.0 ± 0.6 min with placebo, which increased to 6.3 ± 0.6 min (95% CI -0.93 to 1.45) with benazepril, 7.9 ± 0.5 min (95% CI 0.83 to 3.0) with metoprolol OROS and 8.1 ± 0.6 min (95% CI 0.88 to 3.29) with the combination of benazepril and metoprolol OROS. Maximal ST segment depression in lead CM₁ at peak exercise remained unaltered during the active treatment, probably because of increased exercise time.

**Blood pressure, heart rate and rate-pressure product.** None of the treatments significantly altered systolic blood pressure at rest as compared with placebo. However, diastolic blood pressure was significantly reduced by 5.8 mm Hg with benazepril (95% CI -9.8 to -1.5), 4.4 mm Hg with metoprolol OROS (95% CI -8.4 to -0.6) and 4.7 mm Hg (95% CI -8.7 to -0.6) with the combination of benazepril and metoprolol OROS. The systolic blood pressure at maximal exercise was only blunted significantly by metoprolol OROS and the combination of benazepril and metoprolol OROS, but not by benazepril alone. Heart rate at rest and maximal exercise was significantly blunted by metoprolol OROS and the combination of benazepril and metoprolol OROS but not by benazepril alone. The rate-pressure product of 224.2 ± 8.8 units on placebo was reduced to 207.9 ± 8.2 units (95% CI -37.15 to 4.62) on benazepril, 172.5 ± 5.9 units (95% CI -69.20 to -34.26) with metoprolol OROS and 173.7 ± 6.1 units (95% CI -67.03 to -34.04) with the combination of benazepril and metoprolol OROS.

**Anginal Attacks and Sublingual Nitroglycerin Consumption**

During the 3 week treatment period, 342 anginal attacks were recorded with placebo; the number of attacks was reduced to 326 with benazepril, 318 with metoprolol OROS and 268 with the combination of benazepril and metoprolol OROS. Similarly, the consumption of nitroglycerin tablets was 174 with placebo and was reduced to 171 with benazepril, 128 with metoprolol OROS and 129 with the combination of benazepril and metoprolol OROS. These data were evaluated only descriptively and no statistical tests were performed because some patients failed to return or fill in the diary cards completely. However, it appears that the changes observed during active treatment are neither clinically relevant nor statistically significant.

**Ambulatory ECG Monitoring (Table 3)**

During 24 h ambulatory ECG monitoring, two leads (CM₁ and CC₂) were recorded. However, for analysis only one lead (either CM₁ or CC₂) that showed the greater number of episodes of ST segment depression on placebo was chosen. Thereafter, the same lead was kept constant for comparison throughout the study in the same patient.

**Mean hourly heart rate over 24 h.** The average heart rate over 24 h was significantly lower with metoprolol OROS and the combination of benazepril and metoprolol OROS, but not with benazepril alone as compared with placebo, respectively. The mean hourly heart rate also remained lowered throughout the 24 h period on metoprolol OROS treatment (Fig. 2).

**Total number of episodes of ST segment depression.** The total number of episodes (seen in either lead CM₁ or CC₂) (Fig. 3) with placebo treatment was 221 (range 2 to 25 per patient). These decreased nonsignificantly with benazepril to 160 (95% CI -3.72 to 1.28), significantly with metoprolol OROS to 136 (95% CI -4.68 to -0.89) and nonsignificantly with the combination of benazepril and metoprolol OROS to 150 (95% CI -5.35 to 0.78). During placebo treatment, 2.7% of the episodes were symptomatic and 97.3% were asymptomatic. With benazepril, 9.4% were symptomatic and 90.6% were asymptomatic. With metoprolol OROS, 6.6% were symptomatic and 93.4% were asymptomatic. With the combination of benazepril plus metoprolol OROS, 4.7% were symptomatic and 95.3% were asymptomatic.

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**Table 3. Variables of Ambulatory Electrocardiographic Monitoring for 24 h in 29 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Benazepril (95% CI)</th>
<th>Metoprolol OROS (95% CI)</th>
<th>Benazepril + Metoprolol OROS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total episodes of ST segment depression &gt;1 mm in 24 h</td>
<td>221</td>
<td>160 (-3.72 to 1.28)</td>
<td>136 (-4.88 to -0.89)</td>
<td>150 (-5.35 to 0.78)</td>
</tr>
<tr>
<td>Total duration of ST segment depression in 24 h (min)</td>
<td>1.549</td>
<td>0.879 (-4.82 to 1.92)</td>
<td>0.87 (-4.48 to -6.63)</td>
<td>0.82 (-49.63 to -0.37)</td>
</tr>
<tr>
<td>Mean maximal depth of ST segment depression (mm)</td>
<td>2.48</td>
<td>1.81 (-1.45 to 0.10)</td>
<td>1.81 (-1.08 to 0.31)</td>
<td>1.41 (-1.01 to -0.11)</td>
</tr>
<tr>
<td>Average heart rate during 24 h (beats/min)</td>
<td>75 ± ± 2</td>
<td>75 ± 2 (-4.5 to 3.9)</td>
<td>62 ± 2 (-16.6 to -8.7)</td>
<td>61 ± 2 (-18.5 to -10.5)</td>
</tr>
</tbody>
</table>

Abbreviations and drug dosage as in Table 2.
Total duration of ST segment depression in 24 h (Fig. 3). As seen on either lead CM₅ or CC₃, the total duration (ischemic burden) was 1.549 min (range 3 to 264 min/patient) on placebo treatment. It was reduced nonsignificantly to 879 min (95% CI -48.28 to 1.92) with benazepril, significantly to 807 min (95% CI -44.87 to -6.63) with metoprolol OROS and significantly to 828 min (95% CI -49.63 to -10.7) with the benazepril and metoprolol OROS combination.

Severity of episodes of ST segment depression. The severity averaged 2.48 mm on placebo treatment, which was reduced to 1.81 mm (95% CI -1.45 to 0.10) with benazepril, 1.81 mm (95% CI -1.08 to 0.31) with metoprolol OROS and 1.41 mm (95% CI -1.01 to -0.11) with the combination of benazepril and metoprolol OROS.

Tolerance and Adverse Effects

Subjective tolerance was good to very good with all treatments in all patients except one who reported poor tolerance during placebo treatment. The mean body weight was 77 kg with placebo and with benazepril, 77.3 kg with metoprolol OROS and 77.1 kg with the combination of benazepril and metoprolol OROS. During the placebo run-in period one patient (Case 5) reported a transient skin rash that was not attributed to the trial medication. No other side effects were reported or observed in this study.

Discussion

Antianginal drugs and their evaluation. Angina pectoris typically results from myocardial ischemia due to an imbalance between the myocardial oxygen demand and supply (15-18) and in most patients is caused by obstructive coronary artery disease. The objective of drug therapy, therefore, is either to decrease those factors that increase myocardial oxygen demand or decrease myocardial blood supply (19-21). Three classes of drugs are now used for the treatment and secondary prevention of chronic stable angina: nitrates, beta-adrenergic blocking agents and calcium-channel blocking drugs (19-26). It is vital that the pharmacology, comparative efficacy and unwanted effects profile of the available antianginal drugs is fully understood to prescribe effectively the appropriate medical therapy for patients with stable angina pectoris (19-21). Beta-blockers act by reducing the myocardial oxygen demand by slowing the heart rate at rest and during exercise (22-26). They also lower systemic arterial pressure, particularly during exercise (25). This class of drugs has negative inotropic effects and may increase left ventricular size and filling pressure (24-26). Beta-blockers also inhibit coronary vasodilation and cause an increase in coronary vasomotor tone (24,27). Objective methods to evaluate antianginal drugs are essential if the results are to be meaningful (9-11) because reduction of the anginal attack rate and sublingual nitroglycerin consumption as a sole criterion for antianginal efficacy is not sufficient because these indexes are influenced by the marked variability of the symptoms due to varying levels of activity and changing emotional and environmental influences.

During the evaluation of any new drug, it is imperative that 1) the drug be compared with placebo under double-blind conditions; 2) it be compared with the standard drugs used for the same indication; and 3) its safety and efficacy when given in combination with the standard drugs be established. This study was undertaken to explore all three possibilities. A multicrossover design with 3 week treatment periods was used: 1) benazepril was compared with placebo;
2) benazepril was compared with a standard beta-blocker, metoprolol OROS; and 3) the safety and efficacy of combined treatment of benazepril and metoprolol OROS were evaluated.

**Benazepril hydrochloride, a new angiotensin-converting enzyme inhibitor.** This agent is a non-sulphhydryl, orally active, selective inhibitor of angiotensin-converting enzyme and is a prodrug, being deesterified to the free acid metabolite benazeprilate. Like other angiotensin-converting enzyme inhibitors, it is a potent antihypertensive agent (28) and its beneficial effects have been shown in patients with heart failure (29). The usefulness of this class of angiotensin-converting enzyme inhibitors in angina pectoris has not been studied systematically. A few clinical studies (1,2,30–32) using enalapril or captopril in a small number of patients with angina pectoris have been performed with variable results. However, their usefulness in ischemic heart disease has been advocated at least theoretically (33,34) because angiotensin II is a potent vasoconstrictor that possesses positive inotropic effects that could compromise the ischemic myocardium by reducing oxygen supply while increasing myocardial oxygen demand (3–5).

Angiotensin-converting enzyme inhibitors reduce left ventricular diastolic pressure, aortic systolic pressure and sympathetic drive (30), effects that should reduce myocardial work and oxygen consumption, and therefore that should be useful in the treatment of angina. Other possible mechanisms of angiotensin-converting enzyme inhibitors include coronary vasodilation (6,7), which improves myocardial blood supply and reduces blood pressure without inducing reflex tachycardia, thereby reducing rate-pressure product, an index of myocardial oxygen demand (15–18,30). To test the hypothesis that benazepril is useful in patients with chronic stable angina, the higher dosage of benazepril (20 mg twice daily) rather than the usual dosage (10 to 20 mg once daily) in essential hypertension was chosen (28).

**Metoprolol OROS, a new sustained-release formulation of metoprolol fumarate.** This new drug formulation (administered once daily) was chosen as the comparative agent. In clinical studies (35), metoprolol OROS has been shown to possess similar antihypertensive (Research report June 1989: unpublished observations, Ciba-Geigy) and antianginal effects as standard metoprolol. Metoprolol OROS consists of a core of metoprolol fumarate surrounded by a semipermeable membrane in which a minute orifice has been created with a laser beam. This membrane allows water to enter, but does not permit the larger molecules of metoprolol to escape. As soon as water from the digestive tract penetrates through the membrane into the interior of the system, metoprolol begins to dissolve. The result is a saturated solution, the osmotic pressure of which causes more water to diffuse into the core, propelling an equal volume of metoprolol solution out through the orifice. The osmotic and hence hydrostatic pressure within the system is great enough to ensure that the orifice is always flushed clear and cannot become blocked (for example, by food particles). The process continues as long as there is still some undissolved active substance in the core of the system. Throughout this period (zero-order release), constant delivery of metoprolol is maintained. Afterwards, metoprolol is released in the form of a solution that becomes more and more diluted until the osmotic pressure within the system equals that outside it. During this second phase, the release rate gradually diminishes. The semipermeable membrane surrounding the core consists of an inert cellulose derivative that is insoluble in water, gastric juice and the alkaline intestinal milieu. After its transit through the gut, it is excreted unchanged in the feces.

**Comparative effects of benazepril and metoprolol OROS during exercise.** In this study, both benazepril and metoprol OROS were well tolerated, whether given alone or in combination. No clinically relevant biochemical abnormalities were detected. During exercise testing, benazepril did not produce any significant effects on exercise tolerance, blood pressure, ST segment changes and heart rate. Only diastolic blood pressure at rest was significantly lowered with benazepril as compared with placebo. Similar findings have been reported (30,32) with other angiotensin-converting enzyme inhibitors. Metoprol OROS significantly increased the time to the development of 1 mm ST segment depression and blunted the heart rate both at rest and during maximal exercise. Although significant treatment effect on maximal exercise time, which is most probably due to metoprol OROS, was observed with analysis of variance, it failed to achieve statistical significance when contrasted with placebo, most probably because of an unbalanced study design. Systolic blood pressure was also blunted at maximal exercise, resulting in a lower rate-pressure product as compared with placebo. Diastolic blood pressure at rest was significantly lower on metoprol OROS as compared with placebo. Similar findings have been observed (22,36–38) with other beta-blockers. Subjective variables, such as number of anginal attacks and sublingual nitroglycerin consumption, were reduced by metoprol OROS alone.

**Effects of benazepril and metoprol OROS on ambulatory ECG monitoring.** Only metoprol OROS was able to blunt the heart rate significantly throughout the 24 h ambulatory ECG monitoring period. Similar findings have been reported (38,39) with propranolol. The number of episodes of ST segment depression and total ischemic burden (duration of ST depression) were reduced significantly by metoprol OROS. Similar findings have been reported (38–43) with other beta-blockers, including the standard formulation of metoprolol and calcium antagonists. Benazepril was also able to reduce the number of episodes and duration of ST segment depression as compared with placebo. However, the change in ischemic burden in patients treated with benazepril was not statistically significantly different from those treated with placebo, but the size of the mean differ-
ence does appear to be clinically significant and relevant. If a few more patients had been studied, statistical significance would have been achieved. Moreover, if one examines the effect of double-blind placebo on ischemic burden or episodes of ST segment depression as compared with single-blind placebo (Fig. 3), there are no relevant differences (209 episodes during the single-blind placebo run-in and 221 during double-blind placebo randomized). Similarly, duration of ischemia was 1,464 min during the single-blind placebo run-in and 1,549 min during double-blind placebo randomized. Therefore, one can confidently say that the changes observed are real treatment effects and not placebo or variability effects. We performed ambulatory monitoring for only 24 h for practical reasons instead of 48 h, which could have been more informative.

In this study, 97% of the ischemic episodes were silent and our findings with benazepril indicate that this class of drugs might be beneficial in silent myocardial ischemia. It is difficult to speculate on the exact mechanisms of action. However, the alterations in vasomotor tone due to suppression of angiotensin II, as well as a sympathtolytic action of benazepril, might well play a role in reducing ambulatory as opposed to exercise-induced ischemia. Second, benazepril failed to alter the systolic blood pressure and rate-pressure product at maximal exercise, thereby suggesting that myocardial oxygen demand, which is one of the predictors for improving exercise-induced ischemia, was not reduced.

When both benazepril and metoprolol OROS were combined, no further benefit was observed, although a tendency to improve further was noticed in some of the measured variables. It was also noteworthy that when two classes of drugs were combined, the efficacy of metoprolol OROS was maintained and did not impair any of the measured variables of exercise testing and ambulatory ECG monitoring. Conclusions. The results of this study suggest that benazepril is well tolerated by patients with chronic stable angina. Benazepril did not produce any clinical benefit in exercise-induced ischemia and other angiotensin-converting enzyme inhibitors have also been ineffective in studies in angina. Benazepril did not produce any clinical benefit in OROS, which are similar to those reported with other groups of patients.

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References