Effect of Amlodipine, Atenolol and Their Combination on Myocardial Ischemia During Treadmill Exercise and Ambulatory Monitoring

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Objectives. This study compared the effects of amlodipine, atenolol and their combination on ischemia during treadmill testing and 48-h ambulatory monitoring.

Background. It is not known whether anti-ischemic drugs exert similar effects on ischemia during ambulatory monitoring and exercise treadmill testing.

Methods. Patients with stable coronary artery disease and ischemia during treadmill testing and ambulatory monitoring were randomized to receive amlodipine (n = 51) or atenolol (n = 49). Each group underwent a counterbalanced, crossover evaluation of single drug and placebo, followed by evaluation of the combination.

Results. Amlodipine and the combination prolonged exercise time to 0.1mV ST segment depression by 29% and 34%, respectively (p < 0.001) versus 3% for atenolol (p = NS). During ambulatory monitoring, the frequency of ischemic episodes decreased by 28% with amlodipine (p = 0.083 [NS]), by 57% with atenolol (p < 0.001) and by 72% with the combination (p < 0.05 vs. placebo and either single drug). Suppression of ischemia during exercise testing and ambulatory monitoring was similar in patients with and without exercise-induced angina. Exercise time to angina improved by 29% with amlodipine (p < 0.01), by 16% with atenolol (p < 0.05) and by 39% with the combination (p < 0.005 vs. placebo, atenolol and amlodipine). In patients with angina, total exercise time improved by 16% with amlodipine (p < 0.001), by 4% with atenolol (p = NS) and by 19% with the combination (p < 0.05 vs. placebo and either single drug). In those patients without angina, no therapy significantly improved total exercise time.

Conclusions. Ischemia during treadmill testing was more effectively suppressed by amlodipine, whereas ischemia during ambulatory monitoring was more effectively suppressed by atenolol. The combination was more effective than either single drug in both settings.

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was therefore designed to compare the anti-ischemic effects of amloidipine, atenolol and their combination during treadmill testing and ambulatory monitoring.

Methods

Patients. Screening. The study was conducted in the nine Canadian centers listed in the Appendix. Patients with documented coronary artery disease and previous positive treadmill test results were screened. Criteria for documented coronary artery disease were 1) at least one coronary artery stenosis >70% lumen diameter reduction on coronary angiography; 2) a documented previous myocardial infarction; or 3) a previous radionuclide test reported as showing a reversible perfusion defect. The criterion for a positive treadmill test result was >0.1 mV flat or downsloping ST segment depression measured 0.08 s after the J point.

Screening procedure. The study was approved by the research ethics boards of the participating institutions. Potential candidates were identified by direct referral from physicians practicing in participating institutions. All patients screened provided written informed consent. Patients received two tablets every morning resembling amlodipine (10 mg) and atenolol (100 mg). Beta-blockers were tapered and withheld for at least 1 week, and other anti-ischemic medications were stopped for at least 5 half-lives of the individual drug. Patients then underwent treadmill testing using the Bruce protocol and 48-h ambulatory monitoring.

Eligibility criteria. To be eligible, the patient had to have positive findings on the screening treadmill test according to the previous criterion. The presence of angina during treadmill testing was not a criterion for eligibility. In addition, the 48-h ambulatory recording had to include three or more episodes of continuous ST segment depression of at least 0.1 mV lasting for at least 1 min or at least 10 min of total ST segment depression if there were only one or two episodes. These criteria were based on a pilot study that showed that the two each excluded approximately the same number of patients.

Exclusion criteria. Excluded were those patients with unstable symptoms within the previous 3 months, cardiac surgery or stroke within the previous 6 months, congestive heart failure, hemodynamically significant valvular disease, sinus bradycardia <60 beats/min on a 12-lead ECG or any ECG abnormality that would preclude interpretation of the ST segment on ambulatory monitoring. The latter included atrial fibrillation, frequent atrial or ventricular premature beats, Q waves in both inferior and lateral leads, Wolfe-Parkinson-White syndrome, left or right bundle branch block without an interpretable ST segment or rest ST segment elevation or depression of 0.1 mV in the inferior and lateral leads.

Randomization and study design. Patients were randomized to a crossover, single-drug evaluation of amloidipine versus placebo (n = 51) or atenolol versus placebo (n = 49) (Fig. 1). Each group underwent a counterbalanced crossover evaluation of placebo and active single drug. Patients in both groups were then evaluated with a combination of amloidipine plus atenolol.

Throughout the study, patients received two tablets every morning: amloidipine (5 to 10 mg), or its matching placebo, and atenolol (50 to 100 mg), or its matching placebo.

Dose titration. Single-drug evaluation. Amlodipine was initiated at a dose of 5 mg daily and atenolol at 50 mg daily. After 1 week this was increased to 10 mg of amloidipine and 100 mg of atenolol, unless the patient experienced side effects, unacceptable hypotension (symptomatic or decrease >10% of systolic pressure) or bradycardia (<60 beats/min on a rest ECG). If the higher dose was not tolerated, patients were back-titrated to the lower dose. Patients unable to tolerate the lower dose were dropped from the efficacy evaluation but were included in the safety evaluation. Patients received the final titrated dosage for at least 2 weeks before evaluation with treadmill testing and ambulatory monitoring.

Combination therapy. Combination therapy was initiated at the final dose of active single drug plus the low dose of the alternative agent. If this was well tolerated, the alternative agent was increased after 1 week. If side effects occurred, the alternative agent was back-titrated. Patients received the final titrated dosage of combination therapy for at least 2 weeks before being evaluated with treadmill testing and ambulatory monitoring.

Blinding and compliance. Evaluations of placebo and single-drug therapy were evaluated in double-blinded manner in that the patient and the investigator were unaware of treatment assignment. Combination therapy was evaluated in single-blinded manner in that investigator knew the treatment assignment. Personnel interpreting exercise treadmill tests and ambulatory monitoring remained unaware of treatment assignment until the end of the study. Medications were supplied to clinical centers in prearranged kits covering all possible contingencies. Compliance was evaluated by pill counts.

Evaluation of efficacy. Exercise treadmill testing. Treadmill testing using the Bruce protocol was performed during screening and during each treatment evaluation (placebo, single drug, combination). Tests were performed within 1 h of the same time of day for each patient, at least 2 h after the patient
took the study medications. The l2-lead ECG was monitored continuously. ST segment depression was measured at 0.08 s after the J point in the ECG lead showing maximal ST segment depression during the baseline test. Blood pressure and heart rate were recorded at baseline, at the end of each exercise stage, at the time of 0.1-mV ST segment depression, at peak ST segment depression and at peak exercise. The principal investigator at each clinical center interpreted the exercise tests. The method of interpretation was supervised by the coordinating center (University of Ottawa Heart Institute) to ensure consistency across centers.

Ambulatory monitoring. Ambulatory monitoring was performed during screening and placebo, single-drug and combination treatment. Two consecutive 24-h recordings were performed using a Marquette model 8500 (Marquette Electronics Inc.) or Del Mar Avionics model 459 three-channel recorder. Bipolar electrodes were attached to record leads V6, V2 and aVF. All tapes were calibrated. Patients were instructed to maintain their normal daily routine and to record activities, symptoms and medications in a diary.

Ambulatory ECG analysis. Ambulatory monitoring recordings were analyzed centrally at the Ottawa Heart Institute using a Marquette 8000XP scanner (Marquette Electronics Inc.). Personnel involved in this analysis were unaware of patient identity and treatment assignment. Ischemic episodes were validated by visual inspection of hard copy ECG tracings printed at 25 mm/s. The definition of an ischemic episode was >0.1 mV of flat or downsloping ST segment depression or 0.15 mV of slowly upsloping ST segment depression, lasting at least 1 min. An isoelectric segment of at least 1 min was required between episodes. The duration of ischemia was calculated from onset to offset of 0.1 mV of ST segment depression.

Statistical analysis. Data were analyzed at the Ottawa Heart Institute using Systat for DOS and Windows (Systat Inc.), version 5.02. Baseline characteristics were compared using the chi square or Fisher exact test for categoric data and the Student t statistic for continuous data. The crossover design allowed intrasubject comparisons among each single drug therapy, placebo and combination therapy, thereby increasing the statistical power of these comparisons. To control for carryover effects, order of treatment was entered as a factor into repeated measures analysis of variance models. A two-tailed significance level of 5% was used, with the Bonferroni correction applied for multiple related comparisons. The distributions of episode frequency, total ischemia duration and ST segment time integral on ambulatory monitoring were skewed. To adjust for this, parametric statistical tests were performed on square root–transformed data, and ischemia suppression was determined using the adjusted means calculated as (mean of square root–transformed data)2. Treadmill testing data were normally distributed and were not transformed.

Time to angina was analyzed as a secondary end point for the subset of patients reporting angina during treadmill testing during either placebo or active single-drug therapy. To avoid biasing the result in favor of the less effective treatment, total exercise time was substituted for time to angina if angina did not occur during the other treatments. This assumes that angina would have occurred at peak exercise had the patient not stopped for other reasons and provides a conservative estimate of improvement.

Results

Study patients. Of 194 patients screened, 100 met ambulatory monitoring criteria and were randomized. Clinical and demographic features of randomized patients are shown in Table 1. Coronary artery disease was documented by angiography in 57 patients, positive radionuclide test results in 28 and a previous myocardial infarction in 29. Some patients met more than one criterion. During baseline treadmill testing, angina was present in 28 of 51 patients in the amlodipine group and 22 of 49 in the atenolol group. Total exercise time averaged 399 ± 145 s (mean ± SD), time to onset of angina averaged 278 ± 123 s, and time to onset of 0.1-mV ST segment depression averaged 226 ± 128 s. Maximal ST segment depression averaged 0.253 ± 0.09 mV. During baseline ambulatory monitoring, the median number of ischemic episodes was 7 (range 2 to 38), and the median total duration of ischemia was 45.5 min (range 4 to 519).

Eighty-two patients completed the study: 44 of 51 in the amlodipine group and 38 of 49 in the atenolol group. In the amlodipine group, one patient was withdrawn for administrative reasons and six because of side effects (two during placebo, one during active single-drug therapy and three during combination therapy). In the atenolol group, three patients were withdrawn for administrative reasons and eight because of side effects (one during placebo, eight during active single-drug therapy and none during combination therapy). Of the 44 patients in the amlodipine group, 40 received 10 mg daily, and 4 received 5 mg daily. Of the 38 patients completing the protocol in the atenolol group, 35 received 100 mg daily, and 3 received 50 mg daily.

Suppression of ischemia. Exercise treadmill testing. During placebo, exercise times to 1.0- and 1.5-mm ST segment depression averaged 258 and 331 s, respectively, with no significant

<p>| Table 1. Clinical and Demographic Features of Randomized Study Patients |
|------------------|------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Amlodipine Group</th>
<th>Atenolol Group</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>60.8 (8.0)</td>
<td>60.9 (8.1)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>43 (84)</td>
<td>39 (80)</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>8 (16)</td>
<td>10 (20)</td>
</tr>
<tr>
<td><strong>History of angina</strong></td>
<td>36 (71)</td>
<td>31 (65)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>8 (16)</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>17 (33)</td>
<td>17 (35)</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>9 (18)</td>
<td>12 (25)</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>11 (22)</td>
<td>18 (37)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>35 (70)</td>
<td>39 (81)</td>
</tr>
</tbody>
</table>

Data presented are mean value (SD) or number (%) of patients. MI = myocardial infarction.
difference between the amlodipine and atenolol groups (Table 2). The time to 0.1-mV ST segment depression was prolonged by 29% with amlodipine (p < 0.001), by 3% with atenolol (p = NS) and by 34% with the combination (p < 0.001 vs. placebo and atenolol; p < 0.05 vs. amlodipine). Exercise time to 0.15-mV ST segment depression was increased by 29% with amlodipine (p < 0.01), by 16% with atenolol (p = NS) and by 17% with the combination (p < 0.001 vs. placebo and atenolol; p = NS vs. amlodipine).

**Ambulatory monitoring.** Atenolol produced a 57% suppression in episode frequency during ambulatory monitoring (p < 0.001). A 28% reduction with amlodipine did not reach statistical significance (p = 0.083). The combination of amlodipine and atenolol produced a 72% reduction in episode frequency, which was significantly greater than placebo and either single drug (p < 0.05 vs. both single drugs; p < 0.001 vs. placebo). Amlodipine caused a mild increase in average heart rate during ambulatory monitoring, whereas atenolol and the combination caused a substantial decrease. Figure 2 compares the drugs' effectiveness in suppressing ischemia during ambulatory monitoring with that observed during exercise treadmill testing.

**Effect on exercise treadmill testing times.** *Time to angina.* Angina during treadmill testing was present in 28 of 44 patients completing the study in the amlodipine group and 19 of 38 in the atenolol group. Exercise time to angina averaged 279 ± 124 s, with no significant difference between the two groups. It was increased by 29% with amlodipine (p < 0.01), by 16% with atenolol (p < 0.05) and by 39% with the combination (p < 0.005 vs. placebo, amlodipine and atenolol).

**Total exercise time.** During placebo, total exercise time averaged 424 ± 162 s, with no significant difference between the amlodipine and atenolol groups. It averaged 356 ± 136 s in patients with angina during treadmill testing versus 515 ± 149 s in those without angina (p < 0.0001). Amlodipine improved exercise time by 9% (p < 0.001 vs. placebo) overall, 16% in those with (p < 0.001) versus 3% in those without (p = NS) angina. Atenolol improved exercise time by 3% overall, 4% in those with and 2% in those without (all p = NS) angina. The combination improved exercise time by 13% (p < 0.01 vs. placebo and atenolol; p < 0.05 vs. amlodipine), 19% in subjects with angina (p < 0.01 vs. placebo and atenolol; p < 0.05 vs. amlodipine) and 6% in those without angina (p < 0.05 vs. placebo; p = NS vs. either single drug). Therefore, amlodipine and combination therapy significantly improved treadmill exercise time only in patients with angina during treadmill testing.

To clarify this result, we compared ischemia suppression in patients with and without angina. Amlodipine delayed ischemia onset during exercise testing by 26% (p < 0.01) and 29% (p < 0.01) in patients with and without angina, respectively (p = NS). Combination therapy delayed ischemia onset by 33% (p < 0.01) and 34% (p < 0.01), respectively, in patients with and without angina (p = NS), whereas atenolol did not significantly delay ischemia in either subgroup. During ambulatory monitoring, amlodipine reduced ischemia by 53% (p < 0.01) in those with and by 63% (p < 0.01) in those without (p = NS) angina, whereas combination therapy suppressed ischemia by 69% (p < 0.01) and 79% (p < 0.01), respectively, in patients with and without angina (p = NS). The majority of ischemic episodes during ambulatory monitoring were silent regardless of therapy (95% during placebo, 93% during amlodipine, 97% during atenolol and 98% during combination therapy, p = NS). These data suggest that the drug treatments were equally effective in suppressing silent and symptomatic ischemia but that only the suppression of symptomatic ischemia improved exercise tolerance.
Table 3. Hemodynamic Variables at 0.1-mV ST Segment Depression During Ambulatory Monitoring and Exercise Treadmill Testing

<table>
<thead>
<tr>
<th></th>
<th>Ambulatory Monitoring</th>
<th>Treadmill Testing</th>
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<tbody>
<tr>
<td></td>
<td>Heart Rate (beats/min)</td>
<td>Heart Rate (beats/min)</td>
</tr>
<tr>
<td>Amlodipine group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>92</td>
<td>116</td>
</tr>
<tr>
<td>Single drug</td>
<td>96</td>
<td>120</td>
</tr>
<tr>
<td>Combination</td>
<td>75*</td>
<td>106§</td>
</tr>
<tr>
<td>Atenolol group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>98</td>
<td>121</td>
</tr>
<tr>
<td>Single drug</td>
<td>79*</td>
<td>103§</td>
</tr>
<tr>
<td>Combination</td>
<td>79*</td>
<td>106§</td>
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</table>

*p = 0.05, tp = 0.001 versus placebo. *p = 0.05, §p = 0.001 versus single drug.

Hemodynamic variables at onset of ischemia. During treadmill testing, amlodipine produced no significant difference in the double product at 0.1-mV ST segment depression despite a 29% increase in the exercise time to this end point. Atenolol significantly reduced the heart rate, systolic pressure and double product at onset of ischemia, whereas amlodipine and the combination caused a significant decrease (Table 3). Combination therapy produced results similar to amlodipine alone. During ambulatory monitoring, amlodipine caused a significant elevation in heart rate at onset of ischemia.

Adverse events. Fourteen patients withdrew because of adverse events (placebo [n = 3], amlodipine [n = 1], atenolol [n = 7], combination [n = 3]) (Table 4). Although the rates of adverse effects during atenolol and combination therapy were equivalent and approximately double those observed during amlodipine and placebo therapy, the low frequency of side effects precluded statistical comparisons.

Discussion

The present study found the relative anti-ischemic efficacy of amlodipine and atenolol to differ during treadmill testing and ambulatory monitoring. During treadmill testing, amlodipine but not atenolol significantly delayed onset of ischemia. During ambulatory monitoring, atenolol caused a statistically significant reduction in the frequency of ischemia, whereas a smaller reduction with amlodipine was not significant. During both treadmill testing and ambulatory monitoring, the combination was more effective than either drug given alone. These results support the idea that the pathophysiology of ischemia differs in these two settings and suggest that the actions of amlodipine and atenolol are complementary.

Mechanism of action of amlodipine. Dihydropyridine calcium channel blockers reduce coronary tone, decrease coronary vasoreactivity and lower cardiac demand by reducing afterload (25,26). Consistent with studies of other dihydropyridines (27–30), amlodipine delayed angina during treadmill testing and improved total exercise time in patients with angina. However, amlodipine increased treadmill testing time to onset of ischemia without altering the double product at this end point, suggesting that reduction of ischemia is mediated predominantly by a decrease in cardiac work load at a given level of exercise rather than by improved blood supply to ischemic areas. Similar findings have been reported in previous studies of other dihydropyridines (27,28,31).

Mechanism of action of atenolol. Beta-blockers have been shown to improve survival (32,33) and are the most effective class of drugs for suppressing ischemia during ambulatory monitoring (9–13). Despite this, atenolol reduced both the double product at onset of ischemia during treadmill testing and heart rate at onset of ischemia during ambulatory monitoring. These observations suggest that beta-blockade may cause a reduction in absolute myocardial blood supply that partially offsets the beneficial effect of lowered cardiac demand. This possibility is consistent with the known coronary vasoconstrictor effects of beta-blockers (34,35).

Differences between treadmill testing and ambulatory monitoring ischemia. The relative efficacies of amlodipine and atenolol differed for treadmill testing and ambulatory monitoring. This suggests that there are important differences in the pathophysiology of ischemia in these two settings. Similar to earlier studies (36), we found that onset of ischemia during ambulatory monitoring occurred at lower heart rates than

Table 4. Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 96)</th>
<th>Amlodipine (n = 50)</th>
<th>Atenolol (n = 48)</th>
<th>Combination (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts with any adverse event</td>
<td>42 (43.8%)</td>
<td>19 (38%)</td>
<td>28 (58.3%)</td>
<td>47 (55.3%)</td>
</tr>
<tr>
<td>No. of events with possible or unknown relation to drug</td>
<td>96</td>
<td>60</td>
<td>100</td>
<td>172</td>
</tr>
<tr>
<td>Event rate/pt evaluated</td>
<td>1.0</td>
<td>1.2</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>No. of events requiring discontinuation of study drug</td>
<td>3 (3.1%)</td>
<td>1 (2%)</td>
<td>7 (14.6%)</td>
<td>3 (3.6%)</td>
</tr>
<tr>
<td>Details of events requiring discontinuation of study drug</td>
<td>MI, angina, ruptured AAA</td>
<td>Pressure at base of throat</td>
<td>Headache, angina, dry mouth and fatigue, dizziness and fatigue, bronchospasm, nausea and dizziness, hypotension</td>
<td>Edema and headache, bradycardia (n = 2)</td>
</tr>
</tbody>
</table>

AAA = abdominal aortic aneurysm; MI = myocardial infarction; pt(s) = patient(s).
during treadmill testing, which may be because this study used the Bruce protocol. Others (37) have shown that heart rate at onset of ischemia is lower with more gradual exercise protocols.

More recent studies (4,38-41) have emphasized the importance of increased cardiac demand in causing ambulatory monitoring ischemia. In agreement with this concept, we found that the majority of ischemic episodes were associated with an immediately preceding heart rate increase. Differences between treadmill testing and ambulatory monitoring ischemia may relate to the dissimilarities in the provoking stimuli. Episodes of ambulatory monitoring ischemia usually occur during sedentary activity and can be provoked by mental stress (42,43), cold exposure (44) and tobacco smoke (45). Psychologic stressors, especially situations that trigger emotional distress, cause increases in heart rate and blood pressure and may trigger coronary vasoconstriction. Beta-blockers, possibly through their effects on the central nervous system, may be particularly effective at inhibiting these responses. A better understanding of the nature of response patterns during psychologic stress may therefore help to explain the advantage of beta-blockers during ambulatory monitoring.

**Potential biases.** There are a number of factors affecting recruitment in studies such as this that may influence the results. First, the requirement for ischemia during ambulatory monitoring as well as treadmill exercise testing restricted the study patients to those with relatively severe ischemia. This is evidenced by a baseline maximal ST segment depression averaging >2.5 mm and mean time to onset of ischemia of only 4 min 13 s. Second, the fact that the patients' usual physician approved participation in a placebo-controlled study restricted the study to those with relatively mild symptoms, as evidenced by the fact that ~50% did not report angina during treadmill exercise. Finally, the exclusion of patients with recent unstable angina or myocardial infarction may influence the relative importance of supply and demand in provoking ischemia during ambulatory monitoring. Although the majority of episodes in this study were associated with increased cardiac demand, other studies (46-48) have shown that ischemia in unstable coronary syndromes has little or no associated change in heart rate. These results apply to patients with relatively severe ischemia and mild symptoms, and different results might be obtained in other patients.

**Clinical implications.** Although amlodipine appeared to be more effective during treadmill testing, and atenolol appeared to be more effective during ambulatory monitoring, the combination was significantly better than either single drug in both testing situations. This suggests that the real advantage of these drugs may be their complementary modes of action. Our results agree with previous studies (11,16-20) in suggesting that the combination of a beta-blocker with a long-acting dihydropyridine such as amlodipine is an effective pharmacologic strategy for suppressing both silent and symptomatic ischemia.

**Conclusions.** The present results underscore the need for further research into the utility of treating silent ischemia. Although pharmacologic therapy suppressed treadmill testing and ambulatory monitoring ischemia in patients with and without exercise-induced angina, exercise times improved only in those with overt angina. It is not known whether treating asymptomatic ischemia during treadmill testing or ambulatory monitoring improves prognosis, and a trial that will test this hypothesis is in the planning stage (49).

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### Appendix

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### References


