Anti-Ischemic Effects of Amlodipine in Patients With Stable Angina Pectoris and Myocardial Ischemia During Daily Life

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Numerous studies have focused on the impact of anti-ischemic therapy directed toward reducing total ischemia during routine daily life as identified by ambulatory electrocardiographic (ECG) monitoring. Studies have shown that active treatment significantly reduces the frequency and duration of myocardial ischemia. In the Asymptomatic Cardiac Ischemia Pilot study, treatment eliminated ischemia in 39% to 55% of patients. A number of unique pharmacokinetic properties make amlodipine a good candidate for anti-ischemic therapy, including its high bioavailability and long elimination half-life, which permit once-daily administration with minimal variation between peak and trough blood levels. Because the incidence of ischemia is known to be highest in the morning, the long duration of action may translate directly to clinical benefit. Additionally, amlodipine is well tolerated, with a low potential for interaction with other drugs, including highly protein-bound drugs such as digoxin, warfarin, phenytoin, and indomethacin. The current study evaluates the anti-ischemic effects of amlodipine during routine daily life in patients with stable angina using 48-hour ambulatory ECG monitoring.

The study was a 14-week, randomized, placebo-controlled withdrawal trial of amlodipine in patients with stable exertional angina pectoris. The details of the study design were reported previously. Of the 226 patients enrolled in the trial, 56 participated in this substudy and underwent 48-hour ambulatory ECG monitoring (Figure 1). After a 2-week, single-blind, placebo run-in period during which all antianginal drugs except sublingual nitroglycerin were withdrawn, patients were given amlodipine (starting at 5 mg/day and titrated to 10 mg/day, based on clinical response) in a single-blind fashion for 8 weeks (Figure 1). Responders (patients with ≥7% improvement in symptom-limited exercise time from baseline) then entered a 4-week, double-blind withdrawal phase, randomly receiving either amlodipine or placebo. Ambulatory ECG monitoring was performed at weeks 0, 8, and 12. Evidence of ischemia was apparent in 40 of the 56 patients participating in the substudy; 20 received amlodipine and 20 received placebo in the double-blind phase.

Study subjects included men and women between 18 and 80 years of age who had a history of stable exertional angina pectoris due to ischemic heart disease and reproducible exercise-induced angina with diagnostic ischemic ST-segment depression on at least 2 consecutive exercise tests during the placebo lead-in phase. Patients were excluded from study participation if they had evidence of unstable angina or an acute myocardial infarction within the past 3 months, clinically evident congestive heart failure, hemodynamically significant cardiac valvular disease, moderate or severe anemia, hypoxic states (e.g., chronic obstructive pulmonary disease), atrial fibrillation or other significant tachyarrhythmias, second- or third-degree atrioventricular block, left bundle branch block, pregnancy or lactation, active hepatic or renal disease, or any other major concurrent illness. The incidence of daily-life ischemia was recorded using ST-segment analysis from 2-channel, continuous, 48-hour ambulatory ECG monitoring using amplitude-modulated recorders (Cardiodata, Cambridge, Massachusetts). The 48-hour recordings were analyzed by a central laboratory (Cardio Data Services, Haddonfield, New Jersey) for frequency and duration of episodes of myocardial ischemia (symptomatic and asymptomatic). All ECG monitoring was completed by week 0 (before patients were switched from placebo to amlodipine), at week 8 (before patients were switched from single-blind amlodipine therapy to double-blind therapy with placebo or amlodipine), and at week 12, at the end of double-blind therapy. Two ECG leads were recorded: (1) modified V5 in all cases, and (2) the lead showing maximum ischemia in the initial study treadmill exercise test (if different from V5 or aVF if maximum change is shown in V5). The leads identified at baseline were used throughout the study.

Transient ischemic events (TIEs) were defined using the 1 × 1 × 1 rule: ≥1-mm ST-segment depression, ≥1-minute duration, and ≥1-minute separation between 2 TIEs. Events were analyzed for time of onset, maximum ST-segment depression (mm), offset time for ST-segment depression, and heart rate at onset 5 minutes before ST-segment depression and at peak ST depression.

Primary analysis was based on the differences between baseline, week 8 (values at the end of the single-blind amlodipine phase), and at the end of the double-blind period at week 12, using 2-way analysis
of variance (ANOVA). Statistical significance was defined as p < 0.05.

Fifty-six patients underwent 48-hour ambulatory ECG monitoring. They were mostly men (80%) and white (89%), with a mean age of 67 years (range 44 to 83). A small percentage (11%) were active smokers. Forty of the 56 patients (71%) had evidence of myocardial ischemia during the 48-hour ambulatory ECG monitoring; of these, 20 patients were randomized to receive amlodipine during the double-blind study period and 20 received placebo. The average number of TIEs was 4.4 (range 1 to 23), and the average duration of ischemia per 48 hours was 127 ± 23 minutes. Exercise testing at baseline revealed that there were no significant differences in heart rate, systolic or diastolic blood pressure, or exercise time to onset of ischemia between the 2 groups.

During single-blind therapy, amlodipine (average dose 8.2 mg) was associated with a significant decrease in the overall number of TIEs. The average number of episodes was reduced from 4.4 at baseline to 2.5 after single-blind therapy (p < 0.005) (Figure 2).

The benefit of amlodipine in suppressing ischemia was maintained during the double-blind portion of the study (Figure 3). In the 20 patients with ischemia who received amlodipine for the 2 active phases of the study, the mean number of TIEs was 4.2 during the placebo lead-in phase, 2.9 during the amlodipine single-blind phase, and 2.1 during the double-blind phase. A marked difference was apparent in patients with ischemia who were randomized to placebo for the double-blind phase. As shown, the mean number of TIEs was 4.6 in this group at baseline, 2.2 after single-blind amlodipine therapy, and 3.8 during double-blind placebo treatment (p = 0.01 by ANOVA).

This study shows that amlodipine provides a significant antimyocardial ischemic benefit during routine daily-life activities. During the initial phase, when all patients received amlodipine, there was a substantial reduction in the number of TIEs experienced. After randomization, patients who received amlodipine continued to have fewer TIEs. In contrast, there was an upward trend in the number of TIEs among those who received placebo—almost reaching baseline levels. This difference was statistically significant (p = 0.01 by ANOVA).

These findings are consistent with previous reports showing that the clinical antianginal efficacy of amlodipine is accompanied by significant reductions in ECG evidence of myocardial ischemia.1-4 Notably, the effects of amlodipine on angina attack rate, nitroglycerin consumption, and ST-segment depression were shown to be sustained during long-term therapy.10,11

Data comparing different management strategies are sparse but indicate that long-acting calcium antagonists such as amlodipine may have an important role in the management of cardiac ischemia. In the large-scale international Circadian Anti-Ischemia Program in Europe trial, once-daily amlodipine was shown to significantly reduce transient myocardial ischemia in patients with chronic stable angina.1 At baseline, evaluable patients (n = 250) had at least 3 attacks of angina per week, with at least 4 ischemic episodes and/or ≥20 minutes of ST-segment depression during 48-hour ambulatory ECG monitoring. They continued to receive their usual antianginal therapy (if any) during the study. The effect of amlodipine was demonstrated by objective measurement of ST-segment changes during ambulatory ECG monitoring, improvement in anginal symptoms, and reduction in nitroglycerin consumption.1 Compared with placebo, amlodipine (5 to 10 mg/day) significantly reduced the frequency of ischemic episodes (60% for amlodipine vs 44% for placebo; p = 0.025) and reduced the total integrated ST ischemic area (p = 0.042), which is a
Anginal symptoms were reduced by 70% in amlodipine-treated patients compared with 44% in placebo-treated patients (p = 0.0001). Similarly, nitroglycerin consumption was reduced by 67% in the amlodipine group versus just 22% in the placebo group (p = 0.0006). In addition, ambulatory ECG monitoring showed that amlodipine was not associated with reflex tachycardia. There was no significant increase in heart rate at any time during 24-hour monitoring, and the investigators speculated that this may be an important factor contributing to the efficacy noted over the 24-hour period and the low incidence of adverse effects with amlodipine.1 The unique aspect of the present study is the double-blind withdrawal phase at the end of the study, which showed that patients switched to placebo returned to baseline, whereas those taking amlodipine continued to show beneficial effects in ischemic indexes.

Evaluation by ambulatory ECG monitoring demonstrated that amlodipine (5 to 10 mg/day) is significantly effective in suppressing myocardial ischemia during daily life. These results show that amlodipine can provide around-the-clock protection against ischemic events in patients with stable angina.

APPENDIX

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