JACC Vol. 21, No. 6
May 1993:1365–70

Randomized Placebo-Controlled Trial of Amlodipine in Vasospastic Angina

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Objectives. This study was designed to assess the efficacy and safety of amlodipine, a long-acting calcium channel blocker, in patients with vasospastic angina.

Background. Previous studies have established the value of short-acting calcium channel blockers in the treatment of coronary spasm.

Methods. Fifty-two patients with well documented vasospastic angina were entered into the present study. After a single-blind placebo run-in period, patients were randomized (in a double-blind protocol) to receive either amlodipine (10 mg) or placebo every morning for 4 weeks. Twenty-four patients received amlodipine and 28 received placebo. All patients were given diaries in which to record both the frequency, severity, duration and circumstances of anginal episodes and their intake of sublingual nitroglycerin tablets.

Results. The rate of anginal episodes decreased significantly ($p = 0.009$) with amlodipine treatment compared with placebo and the intake of nitroglycerin tablets showed a similar trend. Peripheral edema was the only adverse event seen more frequently in amlodipine-treated patients. No patient was withdrawn from the double-blind phase of the study because of an adverse event. Patients who completed the double-blind phase as responders to amlodipine or as nonresponders to placebo were offered the option of receiving amlodipine in a long-term, open label extension phase. During the extension, the daily dose of amlodipine was adjusted to 5 or 15 mg if needed and the rate of both anginal episodes and nitroglycerin tablet consumption showed statistically significant decreases between baseline and final assessment.

Conclusion. This study suggests that amlodipine given once daily is efficacious and safe in the treatment of vasospastic angina.

(J Am Coll Cardiol 1993;21:1365–70)

Calcium channel blockers are now considered the agents of choice for the therapy of vasospastic angina (1–14). Over the past 10 to 15 years, the efficacy of these agents has been well documented by numerous studies, including several randomized controlled trials (1–14). The first generation of calcium channel antagonists, nifedipine, verapamil and diltiazem, had comparable effects when appropriate doses were used (6,7). In view of the relatively short half-life of these drugs, all protocols utilized regimens consisting of multiple daily doses. Nicardipine, a second-generation calcium channel blocker, has also been reported (15) to be effective in vasospastic angina when given in multiple doses/day. Newer sustained release or long-acting formulations of the initial three calcium antagonists have now been developed to improve patient compliance (16–18). However, we are not aware of any data regarding the place of these formulations in the treatment of coronary artery spasm. The current study was designed to assess the efficacy and safety of a second-generation calcium channel blocker, amlodipine, which is recommended as a once daily agent (19,20) in view of its long half-life.

Methods

Study patients. Recruitment for this study was performed at 15 participating centers. To be included in the study, the patients had to have a history of rest angina with one or more of the following criteria: 1) at least one or more episodes of chest pain at rest associated with reversible electrocardiographic (ECG) ST segment elevation in the absence of myocardial infarction; 2) spontaneous or ergonovine-induced coronary artery spasm (producing ≥70% narrowing of coronary lumen diameter during angiography) associated with chest pain or ischemic ST segment changes, or both;

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Manuscript received July 25, 1992; revised manuscript received October 23, 1992, accepted October 28, 1992.

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0735-1097/93/$6.00

JACC Vol. 21, No. 6
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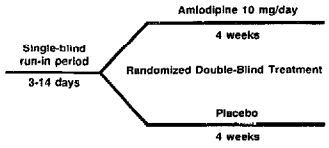


Figure 1. Flow diagram of the study design. During the single-blind run-in period, all patients received placebo. The exact duration of this period was determined by the frequency of anginal episodes. Randomized double-blind treatment consisted of 4-week parallel double-blind treatment in parallel balanced groups.

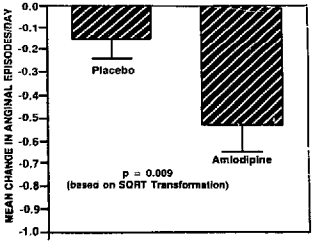


Figure 2. Mean change (final − baseline) in number of anginal episodes/day. ⊥ indicates standard error of the mean. SQRT = square root transformed.

and 3) ergonovine-induced reversible perfusion defect documented by thallium-201 scintigraphy.

Criteria 1) and 3) were used usually in patients with documentation of angiographically normal coronary arteries. Patients were also required to have evidence of disease activity manifested by the occurrence of at least three episodes of angina at rest during a run-in single-blind placebo period of 3 to 14 days.

Exclusion criteria included: 1) women of childbearing potential; 2) myocardial infarction within 3 months of screening; 3) history of life-threatening events associated with previous episodes of coronary artery spasm, such as ventricular tachycardia, ventricular fibrillation or syncopal episodes; 4) decompensated congestive heart failure; 5) significant valvular heart disease; 6) systolic blood pressure <100 mm Hg or diastolic blood pressure >100 mm Hg; 7) life-threatening arrhythmias; 8) ECG abnormalities precluding interpretation of ST changes; 9) concomitant use of another investigational drug or cardiac glycoside; 10) coronary artery bypass surgery or percutaneous transluminal coronary angioplasty within 3 months of screening; 11) active hepatic or renal disease; and 12) other major concomitant disease.

All patients provided written informed consent. The protocol was approved by the Institutional Review Boards of all participating centers.

Study Protocol

Double-blind trial. The study design (Fig. 1) included a period of a single-blind placebo run-in (3 to 14 days) after withdrawal of coronary vasodilators (calcium channel blockers or long-acting nitrates). Patients were allowed only sublingual nitroglycerin as needed for episodes of chest pain. Patients were entered into the double-blind phase of the study after developing a minimum of three episodes of angina at rest. The single-blind placebo run-in period was designed to last 2 weeks but could be shortened as needed to a minimum of 3 days if patients had such a severe flare-up of their anginal syndrome that they were unlikely to tolerate it for the full 2 weeks.

Once a patient qualified for the study with documentation of the coronary spasm and at least three anginal attacks during the single-blind placebo run-in period, they were randomized according to a parallel design to receive either amlodipine (10 mg) or placebo every morning. The double-blind parallel period lasted 4 weeks, with patients coming for follow-up visits at weekly intervals. An angina diary for detailing the frequency, severity, duration and circumstances of anginal episodes and intake of sublingual nitroglycerin was given to the patient at the initiation of the run-in period. Contents of the diaries were reviewed and tabulated at weekly intervals. Safety was monitored by clinical evaluation, with assessment for any side effects at each visit and laboratory tests at baseline and at the end of the double-blind period. Premature termination of the study was considered if the patient had a major adverse experience or evidence of therapeutic failure, defined as significant worsening of the anginal syndrome resulting in intolerable symptoms or admission to the hospital to rule out myocardial infarction.

Open label extension. Patients who completed the double-blind phase as responders to amlodipine were offered the option to continue treatment in an open label long-term protocol. Also, patients who completed the short-term placebo phase with unchanged or worsened symptoms were offered the option of undergoing an open label trial of amlodipine. Placebo responders were not entered into the long-term study. All patients in the open label long-term protocol were followed up for efficacy and safety with visits at 4-week intervals for the 1st 2 months and every 3 months thereafter for up to 3 years. Adjustment of amlodipine dosage to 5 or 15 mg daily, depending on clinical status, was allowed as needed during this phase of the study.

Statistics. The diary-derived variables (rate of angina attacks and nitroglycerin consumption) were analyzed by the Wilcoxon rank-sum test using the final baseline difference in median values (the data were not normally distributed).

In addition, the data on rate of anginal episodes (Fig. 2) were analyzed by analysis of variance, using the change

Table 1. Demographic Data for the 52 Study Patients

	Amlodipine Group	Placebo Group
Patients	24	28
Age (yr)		
Mean	55.3	55.4
Range	41–71	35–67
Male/female	11/13	15/13
Anginal episodes/day (no.)	1.96	1.57
Previous MI	5	4

Unless otherwise indicated, data are reported as number of patients. MI = myocardial infarction.

from baseline (square root transformed). This adjustment for baseline values was made because the baseline rate of anginal episodes and nitroglycerin use was higher in the amlodipine-treated patients than in the placebo-treated group. However, the difference between the two groups was not statistically significant at baseline.

The therapeutic failure rate (discontinuation of treatment because of lack of efficacy) was subjected to logistic regression analysis with the baseline rate of anginal episodes as covariate.

Results

Fifty-two patients with well documented vasospastic angina entered the study. Twenty-four patients were randomized to receive amlodipine and 28 to receive placebo. The two treatment groups were comparable with regard to age, gender, severity of angina at baseline and history of previous myocardial infarction (Table 1). Coronary angiography data near the time of randomization were available for 44 patients and showed comparable findings in both groups (Table 2). The qualifying spasm occurred during these studies in 38 patients, and in 14 patients (7 receiving amlodipine and 7 receiving placebo), coronary spasm was documented by indirect (ECG or thallium-201 scintigraphy) criteria. Efficacy (anginal attack rate) was analyzed from data for 50 patients (23 receiving amlodipine and 27 receiving placebo). Two

Table 2. Coronary Angiographic Data in 44 Study Patients

	Amlodipine Group	Placebo Group
Data available	20	24
Angiographically normal coronary arteries or minimal disease	15	18
Critical coronary artery disease	5	6
Spasm documented during study	17	21
In left anterior descending artery	9	6
In right coronary artery	4	12
In left circumflex artery	1	0
In two vessels	2	2
In three vessels	1	0

All data are reported as number of patients.

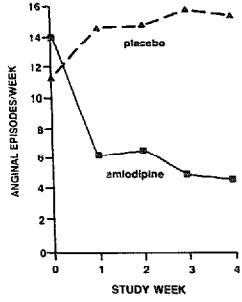


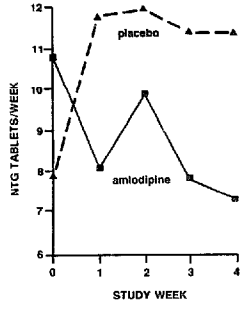
Figure 3. Course of weekly anginal episodes in the two groups. Each point represents a group mean value. Week 0 is baseline; weeks 1, 2, 3 and 4 are during double-blind therapy.

patients (one from each treatment group) did not have valid analyzable data. Efficacy data for nitroglycerin consumption were available for analysis from 48 patients (22 receiving amlodipine and 26 receiving placebo).

Anginal episode rate. The rate of anginal episodes decreased significantly ($p = 0.009$) during amlodipine therapy compared with the rate during placebo treatment (Fig. 2) and the improvement with amlodipine was consistent throughout the 4-week study period (Fig. 3). Nitroglycerin intake showed a similar trend, but the difference failed to attain statistical significance (Fig. 4).

Therapeutic failure. Two of 24 patients receiving amlodipine were withdrawn from the study because of therapeu-

Figure 4. The course of nitroglycerin (NTG) tablet consumption in the two groups. Each point represents a group mean value. Week 0 is baseline; weeks 1, 2, 3 and 4 are during double-blind therapy.



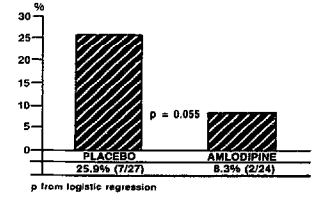


Figure 5. The percent of patients in the two groups **(bottom row)** who discontinued therapy because of therapeutic failure (lack of efficacy). The number of patients who discontinued and the number of patients in each group are shown in parentheses. Logistic regression analysis resulted in p = 0.055 for between-group difference.

tic failure (1 patient because of admission to the hospital to rule out myocardial infarction and 1 as a result of persistent intolerable angina). Seven of 28 patients receiving placebo were withdrawn for the same reason (lack of efficacy). Regression analysis of these data showed that the probability of discontinuations for lack of efficacy was higher with placebo than with amlodipine therapy, regardless of baseline severity of angina. However, the difference was only marginally significant (p = 0.055, Fig. 5).

Hemodynamic effects. The administration of amlodipine had no significant effect on supine or standing heart rate or supine or standing systolic and diastolic blood pressure. The results of administration of amlodipine and placebo are shown in Table 3.

Adverse reactions. Adverse reactions (side effects) are presented in Table 4. The only side effect clearly more common with amlodipine than with placebo was peripheral edema. No patient was withdrawn from the double-blind phase of the protocol because of an adverse reaction.

Long-term open label protocol. Twenty-nine patients entered the long-term open label protocol and 20 were continuing in this protocol at 1 year. Data on anginal episodes and nitroglycerin consumption were obtained from 17 and 19 patients, respectively (Fig. 6, A and B).

The mean frequency of angina was 1.6 episodes/day at baseline and decreased significantly to 0.1 episodes/day at 1 year (p = 0.0094, Fig. 6A). The mean baseline nitroglycerin intake was 1.3 tablets/week and significantly decreased to 0.2 tablet/week at 1 year (Fig. 6B).

The adverse reaction profile with one exception was similar to the short-term pattern, consisting of infrequent and mild side effects. The exception was peripheral edema, which was noted more frequently (12 of 29 patients), with the increase usually attributable to increased dosage. The edema was mostly mild and well tolerated and improved in most cases with or without reduction in the maintenance dose. Only one patient was withdrawn from the long-term trial because of a side effect (pruritus). Eight other patients were withdrawn for various administrative reasons related mostly to impracticality of follow-up.

Table 4. Side Effects in 51 Study Patients

	Amlodipine Group	Placebo Group
Patients	24	27
With side effects	9	10
Peripheral edema	5	3
Headache/dizziness	4	7
GI symptoms	2	4
CNS symptoms	2	0
Respiratory symptoms	1	1
Pruritus	1	0
Visual disturbance	1	0

CNS = central nervous system; GI = gastrointestinal. All data are reported as number of patients.

Discussion

Verapamil, the first clinically useful calcium channel blocker, and nifedipine, the first dihydropyridine derivative, were synthesized in Germany in the early 1960s. However, it was 10 to 15 years later before they received any significant

Table 3. Effects on Blood Pressure and Heart Rate

	Amlodipine Group		Placebo Group	
	Baseline	Final	Baseline	Final
Heart rate (beats/min)				
Supine	71.0 ± 2.1	71.5 ± 2.4	75.3 ± 3.2	74.2 ± 2.2
Standing	75.0 ± 2.2	79.2 ± 2.4	80.5 ± 2.9	79.1 ± 2.3
Blood pressure (mm Hg)				
Supine				
Systolic	126.8 ± 4.3	122.3 ± 4.6	131.2 ± 3.6	131.8 ± 4.6
Diastolic	76.9 ± 2.5	74.6 ± 1.9	80.6 ± 1.8	81.0 ± 2.6
Standing				
Systolic	125.4 ± 3.5	122.7 ± 3.1	128.9 ± 3.5	128.5 ± 4.2
Diastolic	75.9 ± 2.4	78.1 ± 1.9	82.9 ± 2.2	81.5 ± 2.9

Data are reported as mean value ± SE.

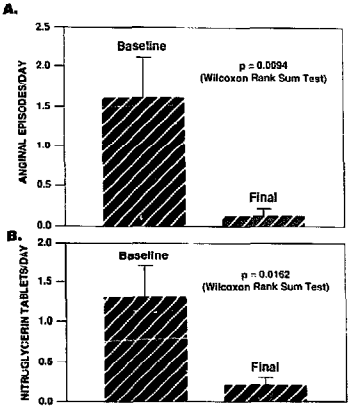


Figure 6. Results of the long-term open label study. **A**, Mean rate ± SEM of daily anginal episodes at baseline and final assessment (n = 17). **B**, Mean ± SEM daily consumption of nitroglycerin tablets at baseline and final assessment (n = 19).

attention in the United States. The first real notice of these agents was probably the result of their potential value in the treatment of coronary artery spasm (21). Nevertheless, only a few studies (15,22) evaluated newer calcium channel blockers in patients with vasospastic angina, perhaps in part because of the difficulty in recruiting patients for such studies. It is well recognized that patients with vasospastic angina today may receive effective therapy by a primary care physician without any documentation of the vasospasm. A good number of these patients may never report to a cardiologist, let alone to a research cardiology group in a major medical center. Thus, an investigator studying spasm may have access to fewer potential candidates and many of these may be patients who 1) have shown resistance to the commercially available calcium channel blockers, or 2) present diagnostic difficulties because of atypical features and may have a less predictable course than that of more typical patients. The frequency of spontaneous remission (23), which complicates therapeutic assessment, particularly when placebo-controlled trials are attempted, presents another impediment to such studies.

In the current trial, we successfully recruited patients at 15 centers. Fifty-two patients with well documented vasospastic angina were entered, with 50 patients fully satisfying the rigid protocol and producing analyzable data that showed statistically significant differences in end points.

Although this study was not designed to survey or confirm the frequency of spontaneous remissions, the parallel design clearly afforded an opportunity to confirm the relative frequency of such episodes. Nevertheless, the decrease in frequency of angina was significantly greater with amlodipine than with placebo and the response was consistent throughout the double-blind period (Fig. 3). Furthermore, the rate of withdrawal from treatment was lower in patients receiving amlodipine (Fig. 5). In addition, the two patients receiving amlodipine who were withdrawn from the study had been previously treated unsuccessfully with several commercially available calcium channel blockers. The long-term study provided further support for the efficacy of amlodipine, with a marked decrease in frequency of angina and nitroglycerin intake from baseline (Fig. 6).

The hemodynamic effects of amlodipine were minimal and insignificant (Table 2). Although amlodipine is an effective antihypertensive agent (24), there were no significant effects on blood pressure in our normotensive patients. Also, the lack of significant tachycardiac response to amlodipine constitutes an advantage of this agent over older dihydropyridine derivatives (25–27). The apparent absence of a tachycardiac response in healthy volunteers and hypertensive patients is attributed to the gradual onset of action of amlodipine (27).

This study also demonstrates that amlodipine is a safe product with infrequent and mild side effects. The only significant side effect clearly more frequent than with placebo was pedal edema. This symptom seemed to be related to the dose of amlodipine used and tended to lessen with dose adjustments and sometimes with time while the same dose was continued. No patient had to be withdrawn from the study because of edema. The only withdrawal was the result of pruritus, which was relieved promptly after discontinuation of amlodipine.

Conclusions. This study suggests that amlodipine is efficacious and safe in the treatment of vasospastic angina. Its convenient once a day dosage and hemodynamic and safety profile may contribute to making it a potential agent of choice in vasospastic angina.

We are grateful to John Hackman for performing the statistical analyses. We also appreciate the secretarial assistance of Shirley Delgado in the preparation of the manuscript.

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