Randomized Double-blind Placebo-controlled Comparison of Nicardipine and Nifedipine in Patients with Chronic Stable Angina Pectoris*

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Forty-one patients were studied in a randomized double-blind placebo-controlled crossover trial to compare the antianginal actions of nicardipine 30 mg thrice daily and nifedipine 10 mg thrice daily. Efficacy was assessed using objective criteria from computer-assisted multistage graded exercise testing, performed after a two-week placebo run-in period and at the end of each four-week active treatment period. Thirty-seven patients completed both legs of the crossover trial. The mean (± standard error of the mean) baseline exercise time to development of angina was 6.7 ± 0.4 min and this increased to 9.5 ± 0.6 min on nicardipine (p <0.001) and 9.5 ± 0.5 min on nifedipine (p <0.001 vs baseline; NS vs nifedipine). Both drugs significantly prolonged the time to the development of Imm ST segment depression. The baseline resting heart rate of 83 ± 2 beats/min increased to 87 ± 3 beats/min during nicardipine (p <0.05) and remained unaltered at 83 ± 2 beats/min during nifedipine therapy (p = NS vs baseline and p <0.02 vs nicardipine). Similarly, both drugs increased significantly the maximal heart rate at peak exercise. One patient was lost to follow-up during the placebo run-in period and four patients (two each on nicardipine and nifedipine) were withdrawn due to adverse effects. Our results indicate that nicardipine is comparable in efficacy to nifedipine and has a similar adverse effect profile and can also be considered a useful therapeutic agent for the treatment of chronic stable angina pectoris.

Nicardipine, a new calcium ion antagonist structurally similar to nifedipine (Fig 1) is a dihydropyridine derivative which also possesses phosphodiesterase inhibitory properties. It has been shown to be effective for the treatment of hypertension, stable angina, rest angina and heart failure. It is equipotent to nifedipine as a vasodilator; both drugs increase coronary blood flow and augment oxygen delivery to the myocardium. In a previous study, we evaluated the optimal effective dose and reported the short- and long-term effects of nicardipine in patients with chronic stable angina. The present study compares nicardipine with nifedipine in a large number of patients with chronic stable angina pectoris.

**Material and Methods**

**Patients**

A total of 41 patients (38 men and three women) ages 48-74 years with established grade 2 or 3 chronic stable angina of at least six months’ duration were entered in the trial. All were gradually withdrawn from their current antianginal medication other than sublingual nitrates for a minimum of two weeks prior to entry. Written informed consent was obtained from each patient, and the trial was approved by the Hospital Ethical Committee. All the patients had to fulfill the same inclusion and exclusion criteria which have been reported previously.

**Inclusion Criteria**

The patients were required to have symptomatic stable angina associated with ST segment depression of Imm or more on maximal treadmill exercise testing, and relieved by rest and sublingual glyceryl trinitrate with a minimum incidence of four attacks per

![Molecular structure of nicardipine and nifedipine.](image-url)
week. All the patients developed classic anginal pain on treadmill exercise testing and at least 1 mm ST segment depression with a slope of less than 0.1 mV/mm/sec in two bipolar leads (CM₅ and CC₅) during exercise. Only patients physically capable and mentally motivated for repeated treadmill exercise were entered into the trial.

Exclusion Criteria

Patients above 75 years of age and women of child-bearing age were excluded. Myocardial infarction within the last four months, unstable angina, and patients with severe symptoms who were clinically judged as unsuitable for placebo treatment were also excluded. Cardiac failure, bronchial asthma, peripheral vascular disease, resting blood pressure levels above 160/100 mm Hg, and insulin-dependent diabetes mellitus were other exclusion criteria. Any patient receiving diuretics, digitalis and other cardiovascular medications was also excluded from the study. Any patient showing more than 0.5 mm ST depression on standing, hyperventilation or the Valsalva maneuver, not developing classic angina during the initial ("diagnostic") treadmill exercise test or not showing 1 mm ST segment depression in both bipolar leads was excluded.

Trial Design

All patients entered a two-week placebo run-in phase and were then randomly assigned (double-blind) to either nicardipine 30 mg three times daily or nifedipine 10 mg three times daily for four-weekly treatment periods and then crossed over to the alternative treatment after a blind washout phase of two weeks. Double-dummy techniques were used throughout.

Computer-assisted exercise testing was performed at the end of the placebo run-in period and after each active treatment period. All patients were instructed in keeping an accurate diary for recording adverse effects, angina attacks and quantity of sublingual trinitrate tablets consumed.

Exercise testing

All exercise tests were performed in the morning at least two hours after a light breakfast and 120-180 minutes after the administration of the last dose of tablets. The patients arrived at the exercise laboratory at least 30 minutes before the test and rested comfortably. They were instructed not to smoke or take glyceryl trinitrate tablets on the morning of the test.

The laboratory temperature was controlled and the exercise test was performed with a microcomputer-based system (Computer Assisted System for Exercise, N. Electronics) linked to a motor-driven treadmill (Quinton Electronics). The treadmill protocol used for each test is shown in Table 1. The speed and gradient were automatically controlled by the computer and the test was timed with a built-in digital clock. All tests were continued until the patients developed symptoms. The criteria for cessation were angina (grade 2), dyspnea, fatigue, three consecutive ventricular ectopic beats, or a fall in systolic blood pressure of 20 mm Hg or more. Standard safety procedures and legal requirements as recommended for adult exercise testing laboratories by the American Heart Association were strictly observed. Two bipolar electrocardiographic leads were continuously monitored at rest, during exercise, and for a minimum of five min after exercise. Systolic blood pressure was monitored at rest and every three min during exercise using a mercury sphygmomanometer.

The monitored leads were CM₅ (manubrium sterni negative and LV₅, exploring electrode) and CC₅ (RV₅, negative and LV₅, exploring electrode) and a lead showing large P waves to monitor arrhythmias. The resting electrocardiogram was passed to the computer to form the resting template. The computer calculated ST segment depression at the J point in reference to the most horizontal part of the PR segment and expressed the results in multiples of 0.1 mm. The averaged ST segment depression, heart rate and ectopic beat count were printed automatically for both leads at every minute during and after exercise. The electrocardiogram during the entire test was recorded continuously as 25 beat averages at a paper speed of 1 mm/sec with ectopic complexes being recorded in real-time. At the end of the test the computer printed out the exercise time, maximal ST-segment depression, heart rate and ectopic count. A continuous trend plot of heart rate and ST-segment depression in all three leads was also obtained. The measurement circuits of the computer were calibrated every day before each test. The digital values of ST segment change, heart rate, systolic blood pressure and exercise time were stored on a tape cassette and later played back into a PDP 11/23 minicomputer (MINC: Digital Electronics Corporation). A program calculated and stored all the objective variables listed below automatically at minute intervals during and after exercise.

1. Exercise time.
2. Resting heart rate.
3. Maximal heart rate.
4. Heart rate gain = maximal heart rate minus heart rate at rest.
5. Heart rate recovery during five minutes post exercise.
6. Time interval = time taken for developing 1 mm ST segment depression relative to the resting level.
7. Maximal ST-segment depression in lead CM₅ and CC₅ = ST segment depression immediately at the point of termination of exercise minus value at rest.
8. Maximal ST-segment depression divided by exercise time.
9. ST-segment recovery in five minutes post exercise.
10. Rate/pressure product = systolic blood pressure at peak of exercise multiplied by maximal heart rate and divided by 100.

During each visit the patients were interrogated in detail, using standard questionnaire, and examined for pedal edema, raised jugular venous pressure and basal crepitations. Blood was withdrawn for routine biochemical and hematologic investigations at each visit. Statistical analysis was performed using Student's paired t test (two-tailed).

RESULTS

Forty-one patients entered the trial and 37 completed both legs of the crossover. One was lost to follow-up during the initial placebo run-in period; one refused to continue the study medication after the first active treatment period because of lack of efficacy (nifedipine); one was withdrawn due to severe headaches, palpitations and pedal edema during the first active treatment (nifedipine); one withdrew one week early because of dizziness while taking nicardipine but completed the final assessment; and one withdrew after ten days of the first active treatment period (nicardipine) because of drug-induced angina.

The mean number of angina attacks per week during the placebo run-in period was 6.8 and this was reduced to 4.2 during nicardipine and 4.7 during nifedipine.
therapy. The mean weekly sublingual glyceryl trinitrate consumption fell from 6.4 tablets during the placebo run-in period to 4.4 during nicardipine and 4.6 during nifedipine therapy.

**Placebo Run-In Period (Table 2, Fig 2, 3 and 4)**

All patients developed classic angina during treadmill testing and the mean (± SEM) exercise time was 6.7 ± 0.4 min. The time to development of 1mm ST-segment depression was 4.6 ± 0.3 min and the maximal ST-segment depression was 2.0 ± 0.1mm in lead CM₄. The resting heart rate of 83 ± 2 beats/min increased to 123 ± 2 beats/min at peak exercise. The resting systolic blood pressure increased from 131 ± 2 mm Hg to 142 ± 3 mm Hg during exercise and the rate/pressure product at peak exercise was 181 ± 6 units.

**Nicardipine (Table 2, Fig 2, 3 and 4)**

Nicardipine treatment increased the mean exercise time to 9.5 ± 0.6 min (p <0.001 with respect to placebo run-in period) and rendered two patients angina-free during treadmill testing. The time to development of 1mm ST-segment depression was prolonged to 6.0 ± 0.5 min (p <0.001) and the maximal ST-segment depression remained unaltered at 2.0 ± 0.1mm. The heart rates at rest and peak exercise were increased to 87 ± 3 beats/min (p <0.05) and 131 ± 2 beats/min (p <0.001) respectively. The systolic blood pressure at rest and peak of exercise was 125 ± 2 mm Hg and 141 ± 2 mm Hg (p = NS) respectively. The rate/pressure product at peak exercise was 183 ± 6 units, which was not significantly different from that during the placebo run-in period.

**Nifedipine (Table 2, Fig 2, 3 and 4)**

During nifedipine treatment, five patients became free of angina during treadmill testing and the mean exercise time increased to 9.5 ± 0.5 min (p <0.001 vs placebo run-in period; NS vs nicardipine). The time to development of 1mm ST-segment depression was prolonged to 6.2 ± 0.5 min (p <0.001 vs placebo run-in; NS vs nicardipine) and the maximal ST-segment depression was 2.1 ± 0.1mm. The heart rate at rest was 83 ± 2 beats/min, but the heart rate at peak of exercise was increased to 130 ± 2 beats/min (p <0.01 vs placebo run-in; NS vs nicardipine). There was no significant alteration in the resting and peak systolic blood pressure.

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**Table 2—Exercise Test Values during Placebo, Nicardipine and Nifedipine Therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Nicardipine</th>
<th>Nifedipine</th>
<th>Placebo vs nicardipine</th>
<th>p values Placebo vs nifedipine</th>
<th>Nicardipine vs nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time (min)</td>
<td>6.7±0.4</td>
<td>9.5±0.6</td>
<td>9.5±0.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>1mm time CM₄ (min)</td>
<td>4.6±0.3</td>
<td>6.0±0.5</td>
<td>6.2±0.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>1mm time CC₄ (min)</td>
<td>4.0±0.4</td>
<td>5.0±0.5</td>
<td>5.7±0.5</td>
<td>&lt;0.02</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal ST-segment depression CM₄ (mm)</td>
<td>2.0±0.1</td>
<td>2.0±0.1</td>
<td>2.1±0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal ST-segment depression CC₄ (mm)</td>
<td>1.7±0.1</td>
<td>1.8±0.1</td>
<td>1.7±0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Max ST dep/Ex ST</td>
<td>0.3±0.03</td>
<td>0.2±0.02</td>
<td>0.2±0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>ST recovery CM₄ in 5' post exercise (mm)</td>
<td>1.6±0.1</td>
<td>1.7±0.2</td>
<td>1.6±0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ST recovery CC₄ in 5' post exercise (mm)</td>
<td>1.4±0.1</td>
<td>1.4±0.1</td>
<td>1.3±0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>83±2</td>
<td>87±3</td>
<td>83±2</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>133±2</td>
<td>131±2</td>
<td>130±2</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate gain</td>
<td>41±2</td>
<td>43±3</td>
<td>46±2</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate recovery in 5' post exercise</td>
<td>44±2</td>
<td>45±2</td>
<td>46±2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>131±2</td>
<td>125±2</td>
<td>128±2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
<td>142±3</td>
<td>141±2</td>
<td>142±2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rate pressure product (peak units)</td>
<td>181±6</td>
<td>183±6</td>
<td>186±6</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Max = maximal; Ex = exercise; Data expressed as mean ± standard error of the mean. 1mm time = time for development of 1mm ST segment depression relative to the resting value. NS = not significant; p = probability.
sure or rate/pressure product at peak of exercise when compared to the placebo run-in or nifedipine.

**Adverse Effects**

Four patients developed pedal edema during nicardipine therapy and one patient also complained of dizziness and was withdrawn for this reason. One patient reported severe angina one hour after ingestion of nicardipine and was withdrawn. During nifedipine treatment, one patient developed pedal edema and another patient complained of severe headache, palpitations and pedal edema and was withdrawn. No other adverse effects were reported. No hematologic or biochemical abnormalities were observed during either treatment period.

**DISCUSSION**

The number of available calcium ion antagonist drugs has rapidly increased since these drugs have been shown to be effective therapy for the treatment of
chronic stable,13,14,16-17 unstable and rest angina,18,19 hypertension20,21 and heart failure.5 Recent research has sought to identify new drugs with improved efficacy, longer duration of action and fewer adverse effects; molecular manipulation and slow release formulations have been used to reduce the known adverse effects.13,19 New members of this group of drugs must be compared with established ones and, in this regard, nifedipine is one of the longest established drugs in this group22,23 which has been extensively investigated for use in chronic stable angina. However, the effect of nifedipine in patients with severely impaired left ventricular function is controversial; although preliminary data showed improvement in cardiac performance,24,27 other studies have demonstrated the reverse.28 As left ventricular dysfunction is common in patients with angina, it is preferable to avoid drugs with inherent negative inotropic properties and this was the rationale for the development of another calcium ion antagonist drug closely related to nifedipine. Another recently identified problem of nifedipine is the risk of precipitating angina because of reflex tachycardia.29,30 The use of combinations of nifedipine and beta-adrenoreceptor blocking drugs29 has circumvented the tachycardia but carries an increased risk of depressing left ventricular function. Nicardipine has been developed as an analog of nifedipine (Fig 1) and found to have similar potent vasodilating properties and also diuretic and antiarrhythmic actions but no negative inotropic effects in animal studies.30,31

In our previous communication, the maximum overall improvement in exercise tolerance occurred with 120 mg nicardipine, and this effect was sustained over a period of six months, but there was no significant difference in any of the measured parameters at the 120 mg dose when compared with the 90 mg dose.3 The variable effects attributable to the cerebral and peripheral vasodilating properties of the drug were more prominent with the 120 mg dose. The 90 mg dose was therefore selected as the optimal dose for comparison with nifedipine. We chose a 30 mg dose of nifedipine as we have previously found the 60 mg dose to produce excessive adverse effects and tachycardias.30

In this study, both drugs produced comparable improvements in exercise tolerance and delayed the onset of ischemia. Nicardipine in a dose of 30 mg three times daily consistently produced an increase in resting heart rate which was not seen with nifedipine. Both drugs elevated the maximum exercise heart rates, and this was probably due to the overall increase in exercise workload on treatment rather than to direct central or peripheral effects of the drugs on heart rate mechanisms.

The mechanism of action of nicardipine appears to be similar to nifedipine. Of particular note is that neither drug produced a reduction in the rate/pressure product, suggesting that their mode of action is direct coronary vasodilation or an oxygen-sparing effect at the cellular level. One patient was withdrawn from nicardipine treatment because of accelerated angina which appeared consistently related to the time of dosing; although it is not possible to prove a causal relationship between the angina and reflex tachycardia, the history is similar to other reports with nifedipine.29,30

In conclusion, nicardipine is a promising new calcium ion antagonist drug with significant antianginal efficacy comparable to that of nifedipine which may be a useful therapeutic agent for the prevention of chronic stable angina pectoris.

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