Effect of bepridil in patients with chronic stable angina: results of a multicenter trial

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ABSTRACT The effects of bepridil, a calcium antagonist with a half-life of approximately 42 hr, were assessed in a double-blind, randomized, placebo-controlled crossover trial. Forty-four patients (39 men, five women) with exercise-induced angina pectoris and ST segment depression with exercise testing (modified Bruce protocol) were studied. Compared with placebo bepridil (400 mg daily) increased total exercise time, time to onset of angina, time to 1 mm of ST segment depression, time to 2 mm of ST segment depression, and total work achieved (all p = .001). Both frequency of angina and nitroglycerin consumption decreased during the bepridil compared with the placebo period (p = .02 and .03, respectively). Minor side effects were noted during both the bepridil and placebo phases. Four patients experienced side effects that limited therapy (dizziness in three and abnormal results of liver function tests in one) and one patient died during the bepridil phase. This study suggests that bepridil, 400 mg daily, is effective for the treatment of exercise-induced myocardial ischemia and angina pectoris.


BEPRIDIL HYDROCHLORIDE, β-[(2-methylpropoxy)methyl]-N-phenyl-N-(phenylmethyl)-pyrrolidineethanamine monohydrchloride monohydrate, is a calcium antagonist currently in use in Europe for the treatment of angina pectoris. Recent single-blind studies have reported its use in patients with ischemic heart disease and arrhythmias. The long half-life of bepridil (≈42 hr) allows for once-a-day dosing. This limits fluctuation in drug level and provides a prolonged effect. This report details results of a multicenter double-blind randomized crossover trial in which effects of bepridil compared with placebo were investigated in patients with exertional angina.

Methods

Patient population. Forty-four patients (39 men and five women) participated in this investigation. The average age was 59.7 years. All patients had a history of classic angina pectoris provoked by exertion and relieved by rest and/or nitroglycerin. Patients who had experienced a myocardial infarction within 3 months were excluded from the study. All patients had a positive exercise treadmill test result, as defined by the presence of angina associated with downsloping or horizontal ST segments shifts of at least 1 mm measured 80 msec from the J point in 3 consecutive beats. No patients were taking cardiovascular drugs other than sublingual nitroglycerin, for relief from angina, or antihypertensive drugs, the dosages of which remained constant throughout the study. Specifically, use of β-blocking or calcium-blocking drugs or long-acting nitrates was not permitted during the study. Patients with congestive heart failure, significant valvular heart disease, serious hepatic or renal disease, inadequately controlled hypertension, atrioventricular or intraventricular block, ventricular arrhythmias, or electrocardiographic patterns that did not allow interpretation of exercise tests were not included. Informed consent was obtained from all patients and the study was approved by respective institutional review committees.

Study design. Before the study all patients underwent a thorough clinical examination, serum chemistry and hematologic testing, electrocardiography, and exercise testing. The study consisted of four phases. Phase I was a 2 week period during which the patient received placebo in a single-blind fashion. At the end of this phase, repeat exercise testing was performed. Patients advanced to phase II if they had five or more episodes of angina per week during phase I or if the exercise test was positive within 6 min. Phase II consisted of a 4 week period during which the patient received either 400 mg bepridil once daily or placebo in a randomized double-blind fashion. During phase III patients crossed over to alternate therapy for another 4 week period. Phase IV consisted of a 3 week single-blind placebo period. Total study duration was 13 weeks and clinical evaluation was carried out at the end of each phase. Early crossover or termination was allowed at the investigator’s discretion if patients experienced intolerable side effects or change in symptoms.

Participating centers include University of Florida and Gainesville VAMC, Gainesville; University of Massachusetts, Worcester; Massachusetts General Hospital, Boston; Medical College of Virginia, Richmond; and The New York Hospital–Cornell Medical Center, New York.

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Investigational medications were prepackaged and supplied as identically appearing capsules containing 400 mg bepridil or placebo. Bottles of fresh nitroglycerin tablets (0.04 mg) for sublingual use were also provided.

**Exercise tests.** Treadmill exercise tests were performed according to a modified Bruce protocol. The preentry test was performed within 3 months of study entry while the patient was not taking cardioactive medications. This test, by the same protocol, was repeated at the end of each of the four phases. Exercise tests were performed at least 24 hr after the last dose of bepridil had been given and every effort was made to ensure the test was performed at the same time of day and in the same laboratory.

**Measurements.** Time to onset of angina, 1 mm of ST segment depression, and 2 mm of ST segment depression, as well as total exercise time and total work were recorded. Total work was defined as: kilopond-meters (kpm) = sin × exercise time (sec) × body weight (kg) × treadmill speed (m/sec)/1000, where × = angle of the treadmill grade. The end point of the exercise test was the appearance of moderately severe anginal pain or segment depression of 1 mm or more. The end point used was consistent from one test to another in the same patient. After this end point was reached, the final electrocardiogram was recorded, blood pressure was taken, and the treadmill was stopped. This was defined as the total exercise time. Blood pressure measurements were made, using a standard arm blood pressure cuff, immediately before exercise testing in patients in the supine position. During exercise blood pressure measurements were made with the same cuff on the same arm while the patient was in the standing position. Heart rate was measured from the supine electrocardiogram taken immediately before exercise testing. During exercise heart rate was measured from the electrocardiogram.

Determination of serum chemistries, hematologic characterization, and urinalysis were performed periodically throughout the study. Patients were questioned regarding specific side effects and were also asked general questions regarding any adverse effects they experienced. Pill counts were performed to determine compliance.

To assess individual patient variability during the study, the three placebo periods were compared. This was done to assess possible changes in the patients’ clinical status and to determine if an exercise training effect was apparent.

Resting electrocardiograms were recorded by standard clinical techniques and the PR, QRS, QT, and R-R intervals were measured. The QT interval corrected for rate (QTc) was defined as

\[
\text{QTc} = \frac{\text{QT}}{\sqrt{R-R\text{ interval}}}
\]

**Statistical analysis.** Statistical analysis of exercise test results was performed with a special analysis of variance for the two-treatment crossover design incorporating a washout period. Comparison of the exercise test parameters from the three placebo phases was performed by a two-way (patient by phase) analysis of variance. Comparison of order of treatment at baseline was performed by a two-way (investigator by order group) analysis of variance. Statistical analysis of changes in frequency of angina, nitroglycerin consumption, and exercise test parameters from the bepridil to the double-blind placebo phase was also performed. Changes from values obtained in the double-blind placebo phase were evaluated for statistical significance by paired t test. Analysis of changes in heart rate and blood pressure was done by comparing measurements obtained in patients on bepridil to the baseline placebo measurements. Within-investigator differences were analyzed by a one-way analysis of variance to assess the interaction between investigator and differences between treatments. When differences between effects of bepridil and placebo in a group of patients exhibiting the same characteristics (such as an adverse reaction) were being analyzed, McNemar’s test for matched proportions was used. Statistical significance was defined as p < .05. All values are means ± SD.

**Results**

Fifty patients were initially entered into the trial and 44 completed all four phases according to the protocol. Of the six patients who failed to complete the trial, three did not continue to phase II because of insufficient angina or lack of positive ST segment response on exercise testing, two other patients withdrew before completion (no reason given), and another patient died. Only data from the 44 patients who completed the trial were analyzed. Five patients crossed over to the bepridil phase early during the double-blind placebo phase; in all there was a lack of drug effectiveness and one also had side effects. Four patients crossed over early during the double-blind bepridil phase: two because of nonorthostatic dizziness, one because of elevated levels of liver enzymes, and one because of shakiness, heartburn, and lightheadedness. Pill counts confirmed excellent compliance (>95%).

**Order of therapy.** During phase II, the first double-blind period, 21 patients received bepridil and 23 received placebo. There were no differences with regard to age, sex, race, any exercise parameter measured, frequency of angina, or nitroglycerin consumption between these two groups (p = NS). No difference in therapeutic response could be attributed to order of therapy alone.

**Effect of drug on resting heart rate and blood pressure.** In the group as a whole, mean resting heart rate during the first placebo period (phase I) and the double-blind placebo and the third placebo (phase IV) periods was 75.1 ± 12.1, 72.6 ± 10.4, and 73.5 ± 11.7 beats/min, respectively. When these placebo phases were compared no statistically significant differences were found. During bepridil therapy resting heart rate was 66.3 ± 9.6 beats/min. The mean change from the baseline placebo value was 7.8 ± 10.8 (p < .001).

Supine systolic blood pressure during the three placebo phases was 135.5 ± 16.8, 135.4 ± 18.1, and 135.8 ± 19.3 mm Hg, respectively, and during bepridil therapy it was 132.8 ± 17.0 mm Hg, not signifi-
Significantly different from the value at baseline \((p = \text{NS})\). Supine diastolic blood pressure during the three placebo phases was 82.9 \(\pm\) 10.9, 83.0 \(\pm\) 8.6, and 84.4 \(\pm\) 9.4 mm Hg, respectively, and during bepridil therapy it was significantly lower (79.4 \(\pm\) 7.1 mm Hg, \(p = .02\)) than that during the baseline placebo phase.

Twenty patients were on antihypertensive therapy throughout the study without change in dosage. Sixteen of these 20 were on diuretics alone. The other four were on a diuretic plus prazosin or methyldopa or one of these drugs alone.

**Exercise test parameters.** A list of values recorded for treadmill exercise test parameters is presented in table 1.

**Total exercise time.** In the group as a whole, the mean total exercise time during the three placebo phases was 7.5 \(\pm\) 2.2 min. In contrast, total exercise time during bepridil therapy was 8.7 \(\pm\) 2.2 min. Compared with the double-blind placebo phase there was a mean increase in exercise time during bepridil therapy of 1.3 \(\pm\) 1.9 min \((p < .001)\). Thirty-one of the 44 (70%) patients increased their exercise time on bepridil compared with that during the blinded placebo period. Of the other 13 patients, 12 decreased their total exercise time and in one it remained the same.

**Time to onset of angina.** In the group as a whole the mean time to onset of angina during the three placebo phases was 6.3 \(\pm\) 2.0 min. Time to angina onset during the bepridil period was 7.9 \(\pm\) 2.6 min. When the bepridil and double-blind placebo phases were compared it was found that angina onset was delayed 1.5 \(\pm\) 2.4 min by bepridil \((p < .001)\). Compared with the double-blind placebo period, 31 of 44 (70%) patients increased their time to onset of angina while taking bepridil. Of the 13 other patients, 10 had a shortened time to angina onset and in three there was no change.

**Time to 1 mm of ST segment depression.** In the group as a whole, the mean time to 1 mm of ST segment depression during the three placebo phases was 5.9 \(\pm\) 2.5 min. Time to 1 mm of ST segment depression during bepridil therapy was 7.0 \(\pm\) 2.5 min, with a mean increase of 1.2 \(\pm\) 2.0 min \((p < .001)\) compared with that during the double-blind placebo phase. Twenty-seven of the 44 (61%) patients increased their time to 1 mm of ST segment depression while on bepridil compared with during the double-blind placebo period. Of the 17 other patients, 12 had shortened times to 1 mm of ST segment depression and in five there was no change.

**Time to 2 mm of ST segment depression.** Twenty (45%) patients developed 2 mm of ST segment depression during the initial placebo period and 14 of these developed 2 mm depression during both double-blind periods. Of these 14 patients, 12 (86%) increased their time to 2 mm depression while on bepridil compared with during the double-blind placebo period. One of the remaining two patients had shortened time to 2 mm depression and in the other there was no change. In the group that developed 2 mm of ST segment depression as a whole, the mean time to depression during the three placebo phases was 6.5 \(\pm\) 2.2 min; time to 2 mm depression during bepridil therapy increased to 7.4 \(\pm\) 2.5 min. The mean increase of 1.7 \(\pm\) 1.5 min was a significant one when compared with the value during the double-blind placebo phase \((p < .001)\).

**Total work.** In the group as a whole the mean total work achieved during the three placebo phases was 3.0 \(\pm\) 1.5 kpm. Total work achieved during bepridil therapy increased to 3.8 \(\pm\) 1.7 kpm. The mean increase of 0.9 \(\pm\) 1.4 kpm over that during the double-blind placebo phase was a significant one \((p < .001)\). Thirty-one of the 44 (70%) patients increased total work achieved while on bepridil compared with that during the double-blind placebo period. Of the other 13 patients, total work achieved decreased in 12 and in one it remained the same.

**Diary results.** Diary results are summarized in table 2.

**Frequency of angina.** As expected, there was considerable variability in frequency of angina. In the group as a whole a mean frequency during the three placebo phases was 6.4 \(\pm\) 7.5 attacks per week. Angina frequency during bepridil therapy was 3.1 \(\pm\) 4.9 attacks per week, a significant decrease of 2.9 \(\pm\) 8.7 attacks per week.

### Table 1: Exercise test parameters

<table>
<thead>
<tr>
<th></th>
<th>Bepridil(^a)</th>
<th>Placebo I</th>
<th>Placebo II</th>
<th>Placebo III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total exercise time (min)</td>
<td>8.7 (\pm) 2.2</td>
<td>7.2 (\pm) 2.5</td>
<td>7.4 (\pm) 2.2</td>
<td>7.9 (\pm) 2.5</td>
</tr>
<tr>
<td>Time to onset of angina (min)</td>
<td>7.9 (\pm) 2.6</td>
<td>5.5 (\pm) 2.4</td>
<td>6.4 (\pm) 2.4</td>
<td>7.1 (\pm) 2.4</td>
</tr>
<tr>
<td>Time to 1 mm ST depression (min)</td>
<td>7.0 (\pm) 2.5</td>
<td>5.4 (\pm) 2.6</td>
<td>5.8 (\pm) 2.7</td>
<td>6.5 (\pm) 3.0</td>
</tr>
<tr>
<td>Time to 2 mm ST depression (min)</td>
<td>7.4 (\pm) 2.5</td>
<td>5.7 (\pm) 2.2</td>
<td>6.3 (\pm) 2.5</td>
<td>6.4 (\pm) 2.0</td>
</tr>
<tr>
<td>Total work (kpm)</td>
<td>3.8 (\pm) 1.7</td>
<td>2.8 (\pm) 1.7</td>
<td>2.9 (\pm) 1.6</td>
<td>3.3 (\pm) 1.8</td>
</tr>
</tbody>
</table>

\(^a\)Bepridil compared with double-blind placebo, all \(p \leq .001\).
per week \((p = .02)\) from the number of attacks per week during the double-blind placebo phase.

**Nitroglycerin consumption.** As did frequency of angina, nitroglycerin consumption showed large variability. In the group as a whole mean nitroglycerin consumption during the three placebo phases was 5.0 ± 6.9 tablets per week. During bepridil therapy nitroglycerin consumption was 2.2 ± 4.2 tablets per week, a significant decrease of 2.2 ± 7.3 tablets per week \((p = .03)\) from the rate of consumption during the double-blind placebo phase.

**Comparison of placebo periods.** Comparison of the three placebo periods failed to reveal any differences among the three in total exercise time, time to 1 mm of ST segment depression, time to 2 mm of ST segment depression, and total work achieved in the group as a whole. There was no significant increase in time to onset of angina when the double-blind placebo and the first placebo (phase I) phases were compared \((p = \text{NS})\), but comparison of the third placebo (phase IV) and the first placebo (phase I) phases did reveal a difference \((p = .001)\). There were also no significant differences found among the placebo periods with regard to frequency of angina or nitroglycerin consumption.

**Electrocardiographic changes.** There were no significant changes noted in PR or QRS intervals during bepridil therapy. There was a significant difference in QT and QTc interval during bepridil therapy, however. During the three placebo periods the QT interval was 0.38 ± 0.03, 0.38 ± 0.04, and 0.38 ± 0.04 sec, respectively \((p = \text{NS})\). During bepridil this increased to 0.43 ± 0.06 sec, which was a significant increase \((p < .001)\) over that in the preceding placebo phase. During the three placebo periods the QTc was 0.42 ± 0.04, 0.42 ± 0.04, and 0.42 ± 0.04 sec, respectively \((p = \text{NS})\). During bepridil therapy this increased to 0.45 ± 0.05 sec, a significant increase \((p < .001)\) over that in the preceding placebo phase.

**Adverse effects.** Of the 46 patients who received bepridil, 35 (76%) experienced adverse effects while receiving the drug and of the 44 patients who completed the double-blind placebo period, 20 (45%) experienced adverse effects during this phase. There was a significant difference between the two at \(p = .001\). Evaluated more specifically, headache (17%), dizziness (17%), and dyspepsia (11%) were the most common adverse effects with bepridil. The incidence of adverse effects on the gastrointestinal system was significantly higher in those on bepridil than in those on placebo \((p = 0.01)\) and the difference in incidence of effects on the central nervous system was only marginally insignificant \((p = .06)\), but there were no differences with respect to other systems evaluated. As reported earlier, adverse effects limited therapy in only five patients. A summary of the adverse effects by body system is provided in table 3.

**Comparison between centers.** The 44 patients in the study were entered from five centers, with the largest number enrolled from one center being 13 and the smallest number five. There were no differences found between centers with respect to any parameter measured except time to 2 mm of ST segment depression. For this parameter there was a significant lack of consistent bepridil vs placebo difference across investigators \((p = .01)\).

**Discussion**

This multicenter study of effects of a single daily dose of bepridil shows that this new calcium antagonist is effective for prevention of exercise-induced myocardial ischemia and angina. Patients studied showed improvement in all exercise parameters measured: 70% had improved total exercise time, time to onset of angina, and total work, 61% had increased time to 1 mm of ST segment depression, and 86% had increased time to 2 mm of ST segment depression while on the drug. The group as a whole also showed improvement in these parameters and frequency of angina and nitroglycerin consumption were also decreased.

Several limitations of this study deserve mention. First, objective parameters of daily activity level such as miles walked were not measured. It is conceivable that patients did not report subtle changes in activity when questioned. Because angina was always related to exertion, quantitation is difficult. Obviously, the
same limitation holds true for nitroglycerin consumption. Second, the Bruce protocol may not be the most sensitive for assessing subtle differences in exercise parameters. Despite this, we were able to show improvement in the parameters evaluated. Third, with repeated exercise testing there is the possibility of a training effect. Comparison of the three placebo periods failed to reveal any significant changes except in time to onset of angina, indicating clinical stability over time and probable lack of a significant training effect. Comparison of bepridil and the double-blind placebo periods showed significant improvement in all parameters. Additionally, analysis for effect of order of therapy failed to reveal any difference. The final limitation is that in this study we used only one dose of bepridil. Other studies have shown that 400 mg per day is more effective than lower doses for prolonging exercise duration. However, the adverse effect profile at other doses has not been comparatively evaluated and the optimal dose cannot be determined from our study results.

There are several points worthy of emphasis. First, the study was of a randomized, blinded, and crossover design so that all patients received both therapies, placebo and bepridil. Second, there were multiple placebo periods that allowed for the assessment of patient stability over time and the possibility of a training effect. Finally, the multicenter nature of the study resulted in a larger and more varied group of patients and investigators.

The relatively high incidence of side effects deserves comment. There appear to be two reasons for this. First, as with other calcium antagonists, the incidence of side effects with bepridil appears to be dose related. In this study a relatively high dose was used and there was a correspondingly higher incidence of side effects than in other studies. Second, the analysis of side effects is influenced by the interpretation of complaints that are often subjective. The 45% incidence of side effects during the double-blind placebo period indicates very thorough reporting and some of the side effects reported as secondary to bepridil may not have been drug related. The relatively small number of patients in this study and the short duration of treatment make a definite appraisal of safety impossible, however.

Bepridil is a relatively long-acting compound with antianginal and electrophysiologic effects. It has been shown to have systemic and coronary vasodilatory properties and seems to alter myocardial metabolic properties. As was found in this study and in others, there is a sinus bradycardic effect of bepridil and data collected in vitro suggest that bepridil increases atrioventricular conduction time. Patients in the present study did not demonstrate any atrioventricular conduction problems. The prolongation of QT interval noted has been reported previously, but its clinical significance is unknown. No patient in this study experienced ventricular arrhythmias brought on by bepridil therapy but this was not looked for aggressively. The patient who died did not appear to have arrhythmia related to a prolonged QT interval and probably had a myocardial infarction.

This study suggests that bepridil is an effective drug for prevention of exercise-induced transient myocardial ischemia. Its long half-life allows for more stable drug levels and thus provides an advantage over other currently available calcium antagonists. The electrophysiologic effects warrant continued investigation with relation to its safety and efficacy. An effective antianginal drug with a long half-life and beneficial electrophysiologic properties would be potentially very useful.

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References
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