CALCII-ENTRY blockers, such as verapamil, CALCII-ENTRY blockers, such as verapamil, have proved to be of value in treating vasospastic angina.1 By impeding calcium current through voltage-dependent and receptor-operated sarcolemmal channels, these drugs reduce the amount of intracellular calcium ions available for complexing with calmodulin.2 Calmodulin-Ca++ activation of myosin light-chain kinase is thereby diminished, as are actin-myosin interaction and cardiac and smooth muscle contraction.3 Calcium antagonist drugs, including verapamil, have also been beneficial for treating exertional angina pectoris in several studies in Europe4-8 and in the U.S.9

The present study was undertaken to evaluate the optimal dose of verapamil in the treatment of angina of effort as well as the mechanisms involved in its beneficial effects. A single-blind dose titration drug phase was followed by a randomized double-blind crossover phase to assess maximal drug effect objectively by serial exercise testing and to correlate findings with angina frequency, nitroglycerin consumption, and blood verapamil levels.

Methods

Study Population

The study group consisted of 26 men, mean age 55 years (range 30-72 years), enrolled from August 1979 through March 1981. All patients had chronic stable angina pectoris with at least five episodes of angina per week and an abnormal control treadmill exercise test, defined as at least 1 mm of horizontal or downsloping ST-segment depressions lasting 80 msec after the J point compared with the baseline ST segment. No patient had a history of congestive heart failure, systemic hypertension, sinus bradycardia, left ventricular hypertrophy or left bundle branch block on the resting ECG, renal or hepatic dysfunction, significant valvular or congenital heart lesions, or myocardial infarction within the last 3 months. Each patient signed an informed consent form approved by the Institutional Review Board at Boston University Medical Center.

Study Design

Cardiac medications, including α- and β-adrenergic blocking agents and long-acting vasodilator drugs, were tapered and discontinued at least 48 hours before entering the study. All patients were permitted to use sublingual nitroglycerin tablets freely for angina attacks, but no cardioactive medications were administered, other than the test capsules, which were given four times daily.

The protocol consisted of an open-dose, single-blind, placebo-controlled period followed by a randomized, double-blind, crossover phase (fig. 1). Patients were evaluated weekly throughout the study by the same research assistant and physician. Evaluation included a physical examination, resting ECG, blood tests for a hematologic screen and biochemical profile, urinalysis, and tabulation of angina attacks and nitroglycerin consumption. Study tablets were counted to check patient compliance.

The single-blind phase began with a 2-week placebo period followed by a dose titration phase in which each patient received 1 week of verapamil, 320 mg/day, and then 1 week of verapamil, 480 mg/day, to ascertain the maximally tolerated dose for each patient. All patients tolerated the higher dose of verapamil during the single-blind phase. The patients were then tapered off verapamil over 4 days and received placebo for 10 days. They then entered a 6-week randomized, double-blind, crossover phase during which verapamil, 120 mg four times per day, or placebo was administered for 2 weeks. After each 2-week phase, the study capsules were gradually discontinued over a 1-week period.

Exercise Tests

During the 11-week protocol, eight treadmill exercise tests (fig. 1) were performed using the Bruce pro-
tocol. A 12-lead ECG was recorded at rest and at 1-minute intervals during exercise and recovery, until the heart rate and ST segments resembled the baseline tracing. Blood pressure was recorded at rest, at the end of each stage of exercise or at the onset of ST segment depression or angina, and during recovery. The patients exercised to a symptom-limited end point (moderate angina, dyspnea or exhaustion). Variables analyzed on the exercise test included total exercise duration on the treadmill, the time (in minutes) to the onset of 1 mm of horizontal or downsloping ST-segment depression, the peak ST-segment deviation, and the heart rate, systolic blood pressure and rate-pressure product (heart rate × systolic blood pressure) at rest and during submaximal exercise (defined as the end of stage 1 of exercise) and maximal exercise.

**Blood Verapamil Levels**

Verapamil and norverapamil blood concentrations were sampled in each patient at the end of randomized phases A and B. Samples were drawn within 1–2 hours after the last verapamil or placebo dose. Serum drug concentrations were measured at the Bioscience Laboratories, Chicago, Illinois, using high-pressure liquid chromatography. Verapamil blood levels were obtained as an additional check on patient compliance in taking medication and to assess the completeness of drug washout between the last dose of verapamil and placebo blood sampling, a period of 17 days.

**Statistics**

A one-way analysis of variance was used to determine whether there were significant differences in the group mean values. If the analysis of variance indicated a significant difference, a two-tailed, paired t test was applied. Probabilities were considered significant at the 0.05 level. All values are expressed as mean ± SD.

**Results**

**Blood Verapamil Levels**

Mean verapamil levels were 298.1 ± 161.5 ng/ml (range 80–701 ng/ml) in blood samples measured after 14 days of drug therapy. Corresponding norverapamil levels were 263.1 ± 96.9 ng/ml (range 143–422 ng/ml). Verapamil/norverapamil serum concentration ratios also varied widely (0.52–1.60). Blood samples drawn after 2 weeks of placebo therapy showed no measurable verapamil or norverapamil levels in 13 of the 26 patients. Eleven of the other 13 patients had minimal blood levels of verapamil (13–18 ng/ml) and two had higher levels (88 and 112 ng/ml).

**Effect on Angina Frequency and Nitroglycerin Consumption (table 1)**

During the initial single-blind, dose-titration phase, the mean frequency of anginal attacks decreased from 11.7 ± 8.7 attacks per week during placebo therapy to 3.7 ± 6.0 attacks per week during verapamil therapy with 320 mg/day and 3.7 ± 5.8 attacks per week during verapamil therapy with 480 mg/day (both p < 0.05). During the double-blind phase, angina frequency was reduced from a mean of 5.6 ± 7.3 attacks per week with placebo to 2.2 ± 3.9 attacks per week with verapamil, 480 mg per day (p < 0.001). Nitroglycerin consumption was significantly reduced in both the single- and double-blind phases during verapamil therapy compared with placebo.

**Effects on Resting Hemodynamics**

The resting heart rate was 69 ± 9 beats/min during the placebo period. Verapamil, 320 mg/day, reduced the resting heart rate to 65 ± 8 beats/min, and verapamil, 480 mg/day, further decreased the resting heart rate, to 61 ± 5 beats/min (both p < 0.05). The resting systolic blood pressure was not significantly altered by verapamil in either phase of the study (table 1, fig. 2). The rate-pressure product at rest was reduced by 10% (p < 0.05) when patients were taking verapamil in the double-blind phase (fig. 2).

**Effects on Exercise Hemodynamics**

At submaximal exercise during both the single- and double-blind phases, the study group had significant decreases in heart rate, systolic blood pressure, and rate-pressure product when taking verapamil, 480 mg/day (table 1, fig. 2). No significant changes were found in these variables at maximal exercise.

**Exercise Tolerance**

Verapamil therapy significantly increased the treadmill time during the single-blind phase, from a mean of 5.1 ± 1.6 minutes during placebo to 6.9 ± 2.3 minutes with 320 mg/day and to 8.0 ± 1.7 minutes with 480 mg/day (table 1). Data from the double-blind phase also showed that the majority of patients receiving verapamil exercised longer than they did during the placebo period (fig. 3).
Table 1. Results of the Single-blind and Double-blind Crossover Comparison

<table>
<thead>
<tr>
<th></th>
<th>Single blind</th>
<th>Double blind</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (320 mg/day)</td>
<td>Verapamil (480 mg/day)</td>
</tr>
<tr>
<td>Anginal episodes per week</td>
<td>11.7 ± 8.7</td>
<td>3.7 ± 6.0*</td>
</tr>
<tr>
<td>Nitroglycerin tablets per week</td>
<td>4.5 ± 5.7</td>
<td>1.9 ± 3.1*</td>
</tr>
<tr>
<td>Treadmill time (min)</td>
<td>5.1 ± 1.6</td>
<td>6.9 ± 2.3†</td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset (min)</td>
<td>3.2 ± 1.5</td>
<td>4.9 ± 2.1†</td>
</tr>
<tr>
<td>Peak (mm)</td>
<td>2.2 ± 0.9</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>69 ± 9</td>
<td>65 ± 8*</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>112 ± 15</td>
<td>100 ± 12†</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>128 ± 17</td>
<td>129 ± 17</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>125 ± 12</td>
<td>128 ± 16</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>145 ± 15</td>
<td>140 ± 15</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>161 ± 21</td>
<td>160 ± 22</td>
</tr>
<tr>
<td>Rate-pressure product (beats/min * mm Hg * 10^-2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>87 ± 17</td>
<td>83 ± 13</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>163 ± 28</td>
<td>140 ± 23†</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>206 ± 39</td>
<td>207 ± 37</td>
</tr>
</tbody>
</table>

*p < 0.05 vs placebo,
†p < 0.001 vs placebo,
$\ddagger$ p < 0.05 vs verapamil, 320 mg/day.

During the double-blind phase of the study, nine patients had less than 10% improvement in treadmill time while taking verapamil as compared with placebo. Three other patients actually had a slight decline in treadmill time while taking verapamil. These 12 patients (group A) who had minimal or no response in treadmill endurance were compared with the 14 patients (group B) who had more than 10% improvement in treadmill capacity. There was no difference between the two groups in angina functional class (Canadian Heart Association), nitroglycerin consumption, or cardiac size by x-ray before entry into the study. Group B patients did have a significantly shorter control treadmill exercise test time (4.4 ± 1.4 vs 5.7 ± 1.3 minutes, p < 0.02) and initial placebo exercise time (4.5 ± 1.0 vs 5.9 ± 2.0 minutes, p < 0.01) than did group A patients. No significant difference in blood verapamil levels was found between group A (330 ± 151 ng/ml) and group B (262 ± 172 ng/ml) patients. Although they had minimal or no improvement in treadmill time, six of the 12 patients in group A had more than 30% reduction in angina frequency while taking verapamil compared with placebo during the double-blind phase.

**Electrocardiographic Effects**

During the single-blind phase, the time to the onset of ST-segment depression increased significantly with verapamil, 480 mg/day, compared with placebo. Verapamil delayed the onset of ST depression by 1.7 minutes while patients were taking 320 mg/day and by 2.7 minutes while taking 480 mg/day (table 1). The maximal ST-segment depression during exercise was reduced from 2.2 ± 0.9 mm to 1.5 ± 0.7 mm while the patients were taking verapamil, 480 mg/day (p < 0.05). Similar changes in these variables were also documented during the double-blind phase of the study (table 1).

**Placebo Effects**

There was no significant difference between the initial control exercise test just before entry into the pro-
Adverse Reactions

Six patients (22%) became constipated within 7–10 days after beginning verapamil, but only three required treatment with stool softeners. One patient had abnormal liver function tests at the end of the double-blind phase while taking verapamil. No patient reported ankle swelling, acroparesthesia, facial flushing, or headaches while receiving verapamil.

Discussion

Verapamil has been used extensively in Europe to treat ischemic heart disease. Recent double-blind studies have confirmed the efficacy of verapamil in the treatment of vasospastic angina pectoris. One single-blind study in the U.S. suggested that verapamil can be used to treat stable angina of effort and may be more effective than propranolol. The present double-blind placebo-controlled study establishes the benefits of verapamil in patients with exertional angina.

Subjective patient improvement was manifested by the reduced frequency of angina attacks and the decreased number of nitroglycerin tablets consumed during verapamil therapy. Objective improvement during verapamil therapy was documented by the increased exercise tolerance compared with that during placebo therapy. Enhancement of exercise capacity was dose related, as many patients benefited more from a verapamil dose of 480 mg/day than from a dose of 320 mg/day. Patients with more than 10% improvement in treadmill time while taking verapamil during double-blind testing (group B) had a more restricted initial exercise capacity. Verapamil therapy, therefore, may be of greatest benefit to patients whose exercise capability is moderately curtailed by stable angina. Although group A patients had less than 10% enhancement in treadmill time, 50% of them still reported a substantial reduction in angina frequency. Side effects from verapamil were mild, usually consisting of constipation, remedied by dietary adjustment or stool softeners. Only one patient had to discontinue the drug after the study because of deterioration of liver function tests while taking verapamil. None of the side effects associated with β-antagonist drugs (asthma, nightmares, fatigue, or impotence) were seen with verapamil. In fact, many patients who had been taking propranolol reported feeling much less fatigued while taking verapamil.

The hemodynamic response to exercise with verapamil gives insight into the mechanism involved in its antianginal effect. Heart rate and blood pressure, which are major determinants of myocardial oxygen consumption, were reduced at submaximal exertion. The rate-pressure product at peak exercise, however, was unchanged during verapamil therapy compared with placebo. While taking verapamil, patients exercised longer because the rate-pressure product increased more slowly. This hemodynamic effect of verapamil was most marked on the heart rate response to exercise, although the submaximal blood pressure was also significantly reduced.

A direct inhibiting action of verapamil on sinus node automaticity has been documented. In addition, verapamil noncompetitively inhibits the chronotropic effects of catecholamines on the sinus node. Thus, verapamil would retard heart rate at rest and during submaximal exercise. Naylor et al. showed that verapamil exerts a direct peripheral vasodilating effect on the arteriolar smooth muscle. This action could explain the beneficial effect of the drug in lowering the blood pressure at rest and during submaximal exercise.

Verapamil also exerts a negative inotropic effect, which could also decrease myocardial oxygen...
demand at rest and during submaximal exercise. Although this effect could benefit patients with ischemic heart disease by lowering myocardial oxygen consumption, this salutary action might be offset by myocardial depression, which could provoke congestive heart failure. However, 10 patients with variant angina treated with a mean verapamil dose of 400 mg/day had no adverse hemodynamic response during exercise radionuclide ventriculography. And, in patients with stable exertional angina, verapamil partially reversed the decrease in left ventricular ejection fraction that accompanied myocardial ischemia during exercise and pacing.

Our results also demonstrated a significantly lower maximal ST-segment deviation in patients taking verapamil despite the similar rate-pressure product at peak exercise. Verapamil, through its vasodilatory action, might have increased ischemic zone coronary blood flow in these patients. Previous studies of the effects of verapamil on coronary blood flow yielded conflicting results, however. Weintraub et al. suggested that the change in coronary blood flow during calcium blocking therapy may depend upon the severity of the underlying coronary constriction.

The wide scatter in blood verapamil and norverapamil levels despite a fixed daily verapamil dose can be explained by the large first-pass hepatic catabolism of this drug. The interpatient variability in such catabolism is marked.

Questions concerning reproducibility and training effects must be considered in exercise protocols designed to evaluate drug effects. In this study, control and the first placebo treadmill tests revealed comparable hemodynamic and ST segment changes. Comparison of the exercise tests performed at the end of the single-blind placebo with subsequent double-blind placebo tests showed that exercise tolerance, as measured by treadmill time, increased and submaximal heart rate and rate-pressure product decreased after the patients had performed a minimum of five treadmill tests. Lingering verapamil effects 3 weeks after discontinuation of the drug do not explain this trend, as 13 patients had no measurable verapamil in their blood and only two patients had blood verapamil levels exceeding 50 ng/ml. Enhanced treadmill performance during double-blind, contrasted with earlier, single-blind, placebo testing is best explained by training effects, as during multiple exercise testing procedures. Additional improvement in treadmill performance with verapamil was demonstrated in the double-blind phase between 7 and 10 weeks, by which time training effects, if present, would probably already have occurred.

We conclude that verapamil is an effective drug for treating patients with stable exertional angina. Adverse drug effects appear to be mild and infrequent if patients are carefully screened for evidence of severe congestive heart failure, sinoatrial and atrioventricular conduction disease and liver dysfunction and if dose schedules are individualized. The beneficial effect of verapamil appears to be related mostly to its ability to lower heart rate and blood pressure during submaximal exercise. Verapamil may be especially useful in patients whose exercise capacity is moderately or severely limited by angina.

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A Double-blind Randomized Trial of Propranolol and Verapamil in the Treatment of Effort Angina


SUMMARY In 18 patients with stable effort angina, verapamil, 80 mg four times daily, was compared with propranolol, 80 mg four times daily, in a double-blind, placebo-controlled trial to assess the effects on anginal threshold, exercise capacity and left ventricular function measured by gated equilibrium blood pool scanning. Both propranolol and verapamil improved exercise capacity (placebo 424 ± 135 W-min; propranolol 513 ± 165 W-min, p < 0.01; verapamil 545 ± 215 W-min, p < 0.005) and prolonged the time to 1 mm of ST depression (placebo 4.5 ± 1.3 minutes; propranolol 7.4 ± 1.4 minutes; verapamil 6.6 ± 1.9 minutes, p < 0.005). At rest, the mean left ventricular ejection fraction did not change significantly during drug therapy (placebo 57 ± 13%, propranolol 55 ± 12%, verapamil 55 ± 13%). While taking placebo, all 18 patients had a decrease in exercise ejection fraction. In contrast, 12 patients taking propranolol and 14 patients taking verapamil had a 5% or greater increase in ejection fraction during exercise. Verapamil is an effective primary therapy and a satisfactory alternative to propranolol in patients with stable effort angina.

BETA-blockade therapy is effective in patients with effort angina.1,2 The mode of action is mainly due to a decrease in myocardial oxygen consumption,3,4 but side effects are common. Verapamil also relieves effort angina.5 The mode of action of verapamil is not fully understood, but side effects even at high dosage are uncommon. Objective studies comparing the effects of B blockers with those of verapamil in the treatment of stable effort angina are few.6-8

We performed a double-blind, placebo-controlled study, using intrapatient comparisons, of the antianginal effects of oral propranolol (320 mg/day) and oral verapamil (320 mg/day) to measure the effects of these drugs on left ventricular function at rest and during exercise, and to determine whether the plasma drug concentrations were related to the physiologic changes produced.

Methods

Patient Population

Eighteen patients (17 males and one female), mean age 53 years (range 40–66 years), participated in the study. The entry criteria included a typical history of effort angina with no change in anginal pattern during the 3 months before entry into the study, two or more episodes of typical exertional angina per week, and a positive exercise test (defined as 1 mm of flat or downsloping ST depression for 0.08 second in three consecutive beats accompanying exercise-induced angina). Patients with clinical features of coronary artery spasm, recent episodes of nocturnal or prolonged chest pain at rest, hypertension, congestive cardiac failure, asthma, diabetes or abnormalities in resting ECG that made interpretation of ST-segment changes difficult (e.g., left ventricular hypertrophy or left bundle branch block) were excluded. Fourteen patients had New York Heart Association class II angina and four

From the Hallstrom Institute of Cardiology and the Department of Nuclear Medicine, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia.
Supported by the National Heart Foundation of Australia and the Postgraduate University of Sydney.
Address for correspondence: Professor David T. Kelly, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050, Australia.
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