
Verapamil Versus Placebo in Relieving Stable Angina Pectoris

MICHAEL B. PINE, M.D., P. DENNIS CITRON, M.D., DANIEL J. BAILLY, M.D., SAMUEL BUTMAN, M.D., GILBERT O. PLASENCIA, M.D., DANIEL W. LANDA, M.D., AND RAYMOND K. WONG, M.D.

SUMMARY  Verapamil and placebo were compared in patients with stable, effort-induced angina. Single-blind dose titration (240, 360 and 480 mg/day) preceded a double-blind crossover. Among the 18 patients who completed graded exercise stress tests with reproducible pretreatment effort-limiting angina, exercise duration increased from 348 ± 127 seconds (SD) before treatment to 494 ± 182 seconds after verapamil (p < 0.001), but did not change after placebo. Compared with placebo, verapamil reduced the weekly number of anginal episodes from 4.54 ± 5.03 to 2.44 ± 3.30 (p < 0.05) and reduced nitroglycerin consumption from 3.46 ± 5.30 to 1.55 ± 2.89 tablets per week (p < 0.05). Of 26 patients who completed the single-blind dose titration, 16 were improved (>1 minute) at a dosage of 240 or 360 mg/day. No patient improved (>1 minute) on 480 mg/day who had not already improved on a lower dose, but side effects requiring reduction in dosage occurred in seven patients receiving 480 mg of verapamil per day. Verapamil is an effective antianginal drug that appears most efficacious at a dose of 360 mg/day, but side effects are common at a dose of 480 mg/day.

VERAPAMIL, a derivative of papaverine, blocks slow inward calcium currents in the myocardial conducting system and in smooth muscle cells of systemic and coronary arteries.1 Several studies have shown that verapamil effectively relieves exercise-induced angina if adequate doses are used.2-4 The present study was designed to assess the efficacy of verapamil in treating exercise-induced angina and to evaluate improvement and side effects associated with daily doses of 240, 360 and 480 mg.

Methods and Materials

Thirty male patients with effort-related, stable angina pectoris began the study. The mean age was 57 years (range 45–68 years). The average number of effort-related anginal episodes per week was 7.4 ± 3.8 (SD) by history. Five patients also had occasional pain at rest that recurred without changing significantly in frequency or severity. Seven patients had had angina for less than 1 year, 10 for 1–5 years, and 3 for more than 5 years. Each patient also had at least one of the following: a documented old myocardial infarction (25 patients), coronary artery disease demonstrated by coronary angiography (10 patients), or exercise-induced ST-segment depression of 1.0 mm or greater during the exercise tolerance test given at entry into the study (24 patients). Six patients had residual or recurrent angina after coronary artery bypass grafting. Nine patients received concurrent antihypertensive therapy consisting of diuretics either alone (four patients) or with alpha-methyl dopa (two patients) or prazosin (three patients). None of the patients received digitalis, β-adrenergic blockers, or long-acting nitrates during the study.

After informed consent was obtained, each patient was evaluated with a complete medical history and physical examination, resting ECG, chest x-ray, complete blood count, urinalysis and blood chemistries. Each patient performed a graded exercise stress test on a stationary bicycle with 25-W increases in workload every 3 minutes until angina pectoris occurred. Each patient was given sublingual nitroglycerin for anginal attacks outside of the hospital and a diary in which to record the number of attacks and the number

From the Departments of Anesthesiology and Medicine, Long Beach Veterans Administration Medical Center, Long Beach, and the University of California, Irvine, California.

Address for correspondence: Michael B. Pine, M.D., Veterans Administration Medical Center, 3200 Vine Street, Cincinnati, Ohio 45215.

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of nitroglycerin tablets consumed. During the next 2 weeks (run-in period), each patient received an 80-mg placebo tablet three times a day (single blind). After the run-in period, the resting ECG and exercise stress test were repeated. For the next 3 weeks, a single-blind dose titration was performed; the dose of verapamil (Isoptin, Knoll Pharmaceutical Co.) was increased each week from 80 mg three times daily to 120 mg three times daily to 160 mg three times daily. Exercise stress testing was repeated each week 1–2 hours after the last dose of verapamil. Blood studies and urinalysis were repeated at the end of the single-blind titration. Each patient was then "down-titrated" (single blind) for 1 week, after which a baseline exercise stress test was obtained.

Each patient who successfully completed the single-blind dose titration was evaluated during a double-blind crossover using the dose of verapamil that gave the best exercise tolerance without side effects. Verapamil or placebo was administered for 4 weeks (crossover A), after which a resting ECG, chest x-ray, blood chemistries, urinalysis and an exercise stress test were performed. The patient was then "down-titrated" for 1 week and a baseline graded exercise test for crossover B was obtained. Each patient received either verapamil or placebo (whichever he had not received during crossover A) for 4 weeks, after which he was evaluated as at the end of crossover A. Each patient was "down-titrated" for 1 week, and a complete physical examination was performed. Fourteen patients who were to begin another study performed a graded exercise test 1–2 weeks after all antianginal medication had been discontinued.

Interim clinical evaluations, pill counts and diary reviews were performed with each exercise test and also 2 weeks after the beginning of each crossover period. Anginal attacks and nitroglycerin consumption were compared using data from the last 2 weeks of each crossover period. The study protocol is outlined in Table 1.

The effect of the order of administration of placebo and verapamil was tested by comparing the means of the two orders (placebo then verapamil vs verapamil then placebo) using a t test for small independent samples. In no case did the order of administration influence the values obtained. Therefore, data from both sequences were combined for subsequent analysis. Each factor was then analyzed separately using analysis of variance (randomized block design). Differences between the two pretreatment exercise durations were analyzed for outlying points using a Z test.

### Results

#### Dropouts and Complications

Of the 30 patients who began the study, 24 completed the 16-week protocol. One patient dropped out for personal reasons after the placebo run-in phase. Another patient was dropped from the study after developing postexercise ventricular tachycardia after his placebo run-in. A third dropped out after single-blind dose titration because of recurrent back pain exacerbated by exercising on the stationary bicycle. A fourth patient was dropped from the study when abnormal liver function test results were obtained after his single-blind dose titration. This fourth patient was later found to be suffering from nutritional cirrhosis (by liver biopsy), which was probably secondary to previously undiagnosed alcoholism. None of these dropouts was attributed to complications of drug therapy.

The final two dropouts were due to complications that occurred while the patients were receiving 480 mg of verapamil per day. One patient suffered a cerebrovascular accident attributed to a left-middle cerebral artery thrombosis. The other patient died in his sleep and was found at autopsy to have severe coronary artery disease, with no other apparent cause of death. Both complications appeared to result from severe vascular disease rather than from verapamil therapy.

While receiving higher doses of verapamil, several patients had new rhythm disturbances or congestive heart failure, which responded to reduction in dosage. Two patients had Wenckebach rhythms, one patient had a sinus bradycardia with a junctional escape and one patient had an accelerated junctional rhythm. These arrhythmias were not accompanied by symptoms, although one patient with a Mobitz I block gained 2 kg, which was lost when his dose of verapamil was reduced. One patient developed pulmonary edema unassociated with an arrhythmia while he was taking 480 mg per day of verapamil, but he was completely free of congestive heart failure and had a 70% increase in exercise tolerance while receiving 360 mg per day of verapamil. Except for the accelerated junctional tachycardia, which occurred in a patient taking 360 mg of verapamil daily, all other cardiac complications occurred in patients taking 480 mg of the drug daily.

### Table 1. Study Protocol

<table>
<thead>
<tr>
<th>Week</th>
<th>Intervention</th>
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<tr>
<td>0</td>
<td>Baseline evaluation off all antianginal medication</td>
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<td></td>
<td>Single-blind placebo run-in</td>
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<td>2</td>
<td>Single-blind 80 mg of verapamil t.i.d.</td>
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<td>3</td>
<td>Single-blind 120 mg of verapamil t.i.d.</td>
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<td>4</td>
<td>Single-blind 160 mg of verapamil t.i.d.</td>
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<td>5</td>
<td>Single-blind &quot;down-titration&quot;</td>
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<td>6</td>
<td>Baseline exercise test for crossover A (verapamil or placebo) using &quot;best&quot; dose</td>
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<tr>
<td>8</td>
<td>Interim evaluation</td>
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<td>10</td>
<td>Evaluation of crossover A (verapamil or placebo) using &quot;best&quot; dose</td>
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<tr>
<td>11</td>
<td>Baseline exercise test for crossover B (verapamil or placebo) using &quot;best&quot; dose</td>
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<tr>
<td>13</td>
<td>Interim evaluation</td>
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<tr>
<td>15</td>
<td>Evaluation of crossover B (verapamil or placebo) using &quot;best&quot; dose</td>
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<tr>
<td>16</td>
<td>Final physical examination</td>
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<td>17</td>
<td>Exercise test in absence of all antianginal medication</td>
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Three patients taking 480 mg of verapamil per day had noncardiac complications that disappeared after the dosage was reduced. One had constipation, another had dizziness, nausea and vomiting, and a third had headaches, paresthesias and palpitations without a documented arrhythmia. Another patient with a history of depressive neurosis had an acute flare-up of this condition while taking verapamil during the double-blind crossover. This acute episode required hospitalization and continued throughout the second part of the double-blind crossover when the patient was taking placebo. A patient with a history of chronic alcoholism and transient elevations of liver function tests had asymptomatic ketonuria and mild elevations in liver function tests after taking verapamil during the double-blind crossover. These abnormalities were absent in three other laboratory evaluations.

**Exercise Tolerance**

Of the 24 patients who completed the study, one patient had two baseline determinations of exercise tolerance (weeks 6 and 11) that differed by 565 seconds. This degree of inconsistency in baseline exercise tolerance was found to be an "outlying point" when tested by a Z test, and the patient's exercise data were omitted in subsequent analyses. Three other patients who had exercise-induced angina when the study began did not have angina on either baseline exercise test. Because exercise-induced angina was no longer present when therapy was evaluated, these patients' studies were also omitted from subsequent analyses.

In six patients, the exercise tests were limited by angina after one phase of the double-blind crossover, but were limited by fatigue after the other phase of the crossover. In all cases, fatigue limited exercise when verapamil was administered, while angina limited exercise when placebo was administered. In four patients, exercise tolerance increased more than 1 minute when fatigue was the end point. These patients were regarded as therapeutic successes and were included in all subsequent analyses. In the other two cases, exercise tolerance was similar whether fatigue or angina was the limiting symptom. The two patients who no longer had exercise-induced angina while taking verapamil but were unable to improve their exercise tolerance despite the absence of effort-limiting angina, could not be considered either therapeutic failures or successes, because training while receiving verapamil might result in increases in exercise tolerance that would not be apparent using the present study design. Therefore, data from these two patients were omitted from subsequent analyses. Thus, exercise data on 18 patients are presented below except when specifically stated otherwise. Ten of these patients received verapamil during the first phase of the crossover and eight received the drug during the second.

Compared with baseline values, placebo resulted in no significant change in exercise tolerance, whereas verapamil resulted in a 41.9% increase in exercise tolerance ($p < 0.001$, fig. 1). Even when all 24 patients who completed the study were analyzed, a significant increase in exercise tolerance was associated with verapamil (25%, $p < 0.01$), but not with placebo.

In patients at rest, verapamil reduced heart rate 9.0% ($p < 0.05$), diastolic blood pressure 5.7% ($p < 0.05$), and rate-pressure product 13.9% ($p < 0.01$). Verapamil was also associated with a trend toward reduced systolic blood pressure ($-4.7\%$, NS), compared with pretreatment baseline values (table 2, fig. 2). Placebo treatment was associated with similar resting heart rates, systolic and diastolic blood pressures, and rate-pressure products before and after therapy.

At maximal exercise, neither verapamil nor placebo altered heart rates, systolic or diastolic blood pressures, or rate-pressure products compared with pretreatment baseline values (table 3, fig. 3).

Maximal exercise-induced ST-segment depression was reduced from a baseline value of 1.50 ± 0.91 mm to 0.97 ± 0.52 mm (SD) after verapamil administration ($p < 0.02$). A trend toward reduction of maximal exercise-induced ST depression from a baseline value of 1.53 ± 1.10 mm to 1.19 ± 1.10 mm after placebo was not statistically significant.

![Figure 1. Exercise tolerance during therapy with verapamil and with placebo. Exercise duration was significantly greater than pretreatment baseline values after verapamil ($p < 0.001$), but not after placebo.](image-url)
Anginal Episodes and Nitroglycerin Consumption

During the last 2 weeks of placebo therapy, 23 patients had 4.54 ± 5.03 episodes (SD) of angina each week, compared with 2.44 ± 3.30 episodes during the corresponding period of verapamil therapy (p < 0.05). Similarly, consumption of nitroglycerin was reduced from 3.4 ± 5.3 tablets per week during placebo therapy to 1.55 ± 2.89 tablets per week during verapamil therapy (p < 0.05). One patient who completed the study lost his diary.

Dose Effectiveness

Exercise tolerance on the same dose of verapamil was similar during the single-blind run-in (513.28 ± 166.94 seconds) and double-blind crossover (494.11 ± 180.93 seconds) for the 18 patients considered in the final analysis. Therefore, data obtained during the initial dose titrations appear to be a valid index of drug effectiveness and can be used to analyze the effectiveness of different doses of verapamil.

Of the 26 patients who completed titration and a baseline exercise test on week 6 (just before crossover A), 16 (62%) demonstrated at least a 1-minute improvement in exercise tolerance during verapamil therapy, compared with baseline exercise tolerance after being weaned from verapamil. Of these 16 patients, 10 (63%) had improved exercise tolerance (>1 minute) on 240 mg/day, and all had improved exercise tolerance on 240 or 360 mg/day. Of the 10 patients who improved on 240 mg/day, four (40%) improved further (>1 minute additional increase in exercise tolerance) on 360 mg/day. Five patients who improved on 240 or 360 mg/day had a further increase in exercise tolerance (>1 minute) on 480 mg/day, but two of these patients had complications requiring a reduction in dosage to 360 mg/day.

The dose associated with the best exercise tolerance was used in the double-blind crossover regardless of the magnitude of the difference between the longest exercise duration and other exercise durations. Therefore, the dose administered in the double-blind crossover did not reflect the analysis presented above. Of the 18 patients considered in the final analysis of exercise data, five received 240 mg/day, six received 360 mg/day and seven received 480 mg/day.

Effect of Placebo

The 14 patients who exercised while receiving no placebo or antianginal medication after the double-blind crossover study was completed exercised for 348.71 ± 143.88 seconds (SD). All were limited by angina pectoris. Four weeks of placebo therapy resulted in a 12.3% greater exercise tolerance (391.50 ± 152.39, p < 0.05), although angina also limited exercise duration in all these patients during placebo therapy. Heart rate, systolic and diastolic blood pressures and rate-pressure product, both at rest and at maximal exercise, were not affected by placebo treatment, compared with values while receiving no medication. Maximal exercise-induced ST-segment depression was similar after placebo and after no medication.

In these patients, baseline exercise tolerance for crossover A was similar to baseline exercise tolerance for crossover B, indicating that the effect of training was not a confounding variable in this analysis of the placebo effect.

Discussion

By all standards of efficacy used in the present study, verapamil was effective in relieving symptoms in patients with stable effort-related angina. The frequency of anginal attacks and the number of nitroglycerin tablets consumed were both reduced by about half from values during placebo treatment. In patients with satisfactory exercise evaluations, there was a 42% increase in exercise duration and a 35% reduc-
tion in maximal exercise-induced ST-segment depression, compared with pretreatment baseline values. These results clearly indicate the effectiveness of verapamil in relieving effort-related angina pectoris, and are in agreement with the results of other double-blind clinical trials.2

Like propranolol and other β-adrenergic blocking agents, verapamil lowers resting blood pressure and heart rate. However, verapamil is not a β-adrenergic blocker; it appears to lower resting blood pressure by blocking slow calcium channels in vascular smooth muscle, thereby reducing peripheral vascular resistance.1 When a single i.v. dose of verapamil is given to healthy subjects, the decrease in peripheral vascular resistance results in a decrease in blood pressure and a reflex tachycardia.6 The present data indicate that during chronic oral therapy in patients with coronary artery disease, a direct negative chronotropic effect on the sinus node6 outweighs reflexes favoring increases in heart rate. Reductions in heart rate and blood pressure at rest result in a reduction in the rate-pressure product, which is an accurate reflection of myocardial oxygen consumption.10

At maximal exercise, the rate-pressure product was similar before and after treatment with verapamil. This finding suggests that oxygen demand associated with the development of myocardial ischemia was similar in the presence and absence of the drug. The increased exercise capacity that resulted from treatment appeared to be due to verapamil’s peripheral vasodilatory properties and its negative chronotropic action rather than to improvement in myocardial oxygen supply to previously ischemic areas. The similarity of maximal exercise-related rate-pressure products before and after verapamil treatment contrasts sharply with the clear reduction in rate-pressure product associated with maximal exercise in angina patients treated with propranolol.11 This observation suggests that verapamil may have a different, and possibly more favorable, effect on cardiac perfusion and function in exercising patients being treated for stable angina.

In contrast to the alterations in heart rate, blood pressure and rate-pressure product associated with verapamil administration, placebo therapy did not alter any of these measurements compared with control values. A significant increase of 12% in exercise duration was found to be associated with placebo therapy. This increased exercise tolerance was not related to training, for the exercise test in the absence of all medication was performed after the evaluation on placebo. The mechanism for the increase in exercise tolerance during placebo therapy is unclear.

The use of a single-blind dose titration in this study not only permitted more accurate assessment of therapeutic efficacy during the double-blind crossover, but also allowed evaluation of the effectiveness and side effects of different doses of the drug. The fact that exercise duration on similar doses of verapamil was similar during single-blind and double-blind evaluations is evidence that observer bias did not affect the single-blind evaluation of exercise tolerance. When verapamil was taken three times daily, there were few side effects or complications associated with doses of 240 and 360 mg, and all patients who responded to the drug clearly improved their exercise tolerance at these dosages. No improvement at doses above 240 mg/day was observed in six of the 16 patients who responded to verapamil during the dose titration. The 10 other patients either improved further or had the same response at 360 mg/day. Therefore, 360 mg/day appears to be the most efficacious dose of verapamil, although patients who fail to tolerate this dose may still benefit from treatment with 240 mg/day. Treatment with 480 mg/day of verapamil resulted in little additional improvement, and relatively frequent side effects were associated with this dosage. From these
data, it appears that if verapamil is administered three times daily, increasing the dose of verapamil to more than 360 mg/day is rarely indicated.

Thus, verapamil is highly effective in the treatment of stable effort-related angina, and is well tolerated when the daily dose is 360 mg/day or less.

Acknowledgment
We are indebted to Clifford Rousseve for his technical assistance and Debra Meza for her secretarial assistance. We are also grateful for the statistical consultation of Dr. Perri Stinson.

References

The 24-hour Ambulatory Blood Pressure Profile with Verapamil

BRIAN A. GOULD, M.B., STEWART MANN, M.A., HASSAN KIESO, M.B., V. BALA SUBRAMANIAN, M.D., AND EDWARD B. RAFTERY, B.SC., M.D.

SUMMARY The blood pressure response in hypertensive subjects to chronic treatment with verapamil, a calcium antagonist (or, more precisely, a slow-channel inhibitor), was studied using the Oxford system for continuous monitoring of intraarterial blood pressure. Sixteen patients underwent continuous monitoring over a 48-hour period before and after at least 6 weeks of therapy (dose range 120–160 mg three times daily). Each monitoring period included physiologic tests designed to show the effects of different types of exercise. Verapamil produces a consistent reduction of blood pressure over 24 hours, but particularly during the day. Heart rate was similarly reduced. There was no evidence of postural hypotension, and the absolute responses to dynamic and isometric exercise were reduced. The degree of reduction of the blood pressure was consistent, suggesting that slow-channel inhibitors may be appropriate for antihypertensive therapy.

THE ONLY CONSISTENT hemodynamic difference between hypertensive and normotensive persons is an increase in the peripheral resistance. This presumably arises because of arteriolar vasoconstriction, and although the mechanism of this effect is not known, it would seem logical to counteract the vasoconstriction by using drugs that produce direct vasodilatation.

Verapamil is a slow calcium-channel blocking drug1, derived from papaverine. It has been widely used to treat arrhythmias4, and has an antianginal effect in high dosages.5,6 It is a potent peripheral vasodilator,7,8 acting directly on arteriolar smooth muscle, and reduces arterial blood pressure after i.v. injection.8,10 There have been a number of reports suggesting that it is also effective given orally.14-18 We performed a controlled study to monitor the reduction of the blood pressure over 24 hours achieved with verapamil in patients with essential hypertension using the Oxford system for continuous recording of intraarterial blood pressure. Recent studies in our department demonstrated that the administration of placebo alone has no demonstrable effect on the intraarterial blood pressure.15 As a result of these data and the invasive nature of the technique, a double-blind placebo crossover trial was not considered justified.
Verapamil versus placebo in relieving stable angina pectoris.
M B Pine, P D Citron, D J Bailly, S Butman, G O Plasencia, D W Landa and R K Wong

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