Verapamil Therapy: A New Approach to the Pharmacologic Treatment of Hypertrophic Cardiomyopathy

II. Effects on Exercise Capacity and Symptomatic Status

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SUMMARY Treadmill exercise capacity and symptomatic status were evaluated in 19 patients with hypertrophic cardiomyopathy while on placebo, low and high dosages of propranolol and low and high dosages of verapamil. Exercise duration on placebo was 6.1 ± 0.8 minutes. Verapamil administration improved exercise duration by 26 ± 8% (1.6 ± 0.5 minutes; p < 0.005); propranolol improved exercise duration by 21 ± 8% (1.3 ± 0.5 minutes; p < 0.025). Twelve patients on verapamil and 11 on propranolol improved their exercise duration by at least 15% compared with placebo. No patient on verapamil but three on propranolol had more than 15% deterioration in exercise capacity. Seven patients considered their symptomatic status “best” while on placebo, nine while on verapamil, and only three while on propranolol. There was no correlation between the exercise or symptomatic response to oral verapamil and the reduction in left ventricular outflow tract obstruction with intravenous verapamil administration. Repeat exercise testing 3.5–6 months after completion of the study in eight patients discharged on chronic verapamil therapy showed exercise capacity improved 45 ± 15% (p < 0.025) compared with placebo and 21 ± 5% (p < 0.005) above values obtained on verapamil in hospital. Eleven of 15 patients discharged on verapamil reported symptomatic benefit, and six improved their functional class by at least one grade. Thus, verapamil can improve exercise capacity and symptomatic status in certain patients with hypertrophic cardiomyopathy, thereby providing physicians with a new therapeutic agent to treat this disorder.

INTRAVENOUS ADMINISTRATION of verapamil to patients with hypertrophic cardiomyopathy reduces both basal and provoked left ventricular outflow obstruction and exerts no clinically significant detrimental effects on left-heart filling pressures or cardiac output. Moreover, Kaltenbach and associates reported that patients with hypertrophic cardiomyopathy experience symptomatic improvement while taking oral verapamil chronically. The present investigation was therefore undertaken to determine objectively, in a randomized double-blind study, whether oral administration of this drug improves exercise capacity and symptomatic status in patients with hypertrophic cardiomyopathy. The answer to this question has important clinical implications, because the primary pharmacologic treatment of this disorder has been limited to propranolol or other β-adrenergic receptor antagonists. Although propranolol has frequently been effective in alleviating symptoms, it has not been uniformly successful, and some patients are unable to take β-adrenergic blocking agents.

METHODS

Subjects

Nineteen patients with hypertrophic cardiomyopathy agreed to participate in this study under a protocol approved by the Human Research Subpanel of the National Heart, Lung, and Blood Institute. The diagnosis of hypertrophic cardiomyopathy was based on echocardiographic demonstration of disproportionate thickening of the ventricular septum with respect to the left ventricular free wall (septal-to-left ventricular free wall thickness ratio ≥ 1.3) in the absence of other acquired or congenital heart diseases. The 19 patients consisted of eight men and 11 women, ages 21–68 years (mean ± sem 46 ± 3 years). Seventeen subjects had obstructive hypertrophic cardiomyopathy (basal or provokable subaortic peak systolic pressure gradient > 30 mm Hg) and two were classified as having nonobstructive hypertrophic cardiomyopathy. The left ventricular outflow tract gradient (when measured), ventricular septal thickness, and septal-to-free wall thickness ratio in these patients while on no cardiac medication other than diuretics are shown in figure 1. Thirteen of these patients had participated in a previous study evaluating the effects of intravenous verapamil on hemodynamics.

Despite what was considered to be optimal medical treatment, 17 patients were classified as functional class III (New York Heart Association criteria) and two patients were in functional class II. Fifteen patients were taking propranolol when admitted to the National Heart, Lung, and Blood Institute. Four patients who had taken propranolol at one time had discontinued it: two because of adverse side effects and two because they did not feel it was helpful. The total daily dose of propranolol treatment in the 15 patients taking the drug before the study was 80–480 mg/day (median dose 320 mg/day). All cardiac medications...
except diuretics were discontinued at least 2 days before the study. All patients were in normal sinus rhythm. One patient had a demand sequential atrioventricular pacemaker in place.

Drug Administration

Verapamil (80 or 120 mg), propranolol (40 or 80 mg), or placebo were administered every 6 hours beginning at 6:00 a.m. on day 1. First a low dose and then a high dose of each drug were prescribed over a 5-day period. Nine low-dose capsules of a drug were administered, and an exercise test was performed at least 2 hours after the last dose. High-dose administration was then carried out for 8 dosages followed by a repeat exercise test. Placebo was always administered at noon, 6:00 p.m. and midnight on days 5 and 10. The sequence of drug prescription was determined by random selection, and the study was carried out in a double-blind manner.

Upright Exercise Testing

All exercise testing was performed on a treadmill, using two protocols: 1) Starting at 2.2 mph and 0% grade, the speed was held constant and the grade increased 2.5% every 2.5 minutes. 2) Starting at 1.9 mph and 10% grade, speed and incline were increased every 2.5 minutes to 2.3 mph and 12%; 2.7 mph and 14%; 3.1 mph and 16%; 3.5 mph and 18%; 3.9 mph and 20%; and 4.7 mph and 20%.

During preliminary testing, protocol selection was determined by the requirement that each patient reach a symptomatic end point of 2.5–12.5 minutes while on no medication except for diuretics. Protocol 2 was used in 17 of the 19 patients.

Symptomatic end points were defined as the onset of chest pain, lightheadedness, or sufficient dyspnea or fatigue that the patient requested that exercise be discontinued.

Before the administration of any study medication, all subjects practiced on the treadmill until they were able to walk comfortably. These practice periods also aided in the selection of the proper exercise protocol. Exercise testing was performed between 9:00 a.m. and 12:00 noon, at least 2 hours after the previous meal.

Symptomatic Status

Subjects were asked to keep a diary to describe their general well-being, cardiac symptoms of dyspnea, chest pain, presyncope and syncope, adverse drug effects and other relevant observations during each of the 15 days. At the end of the study they were asked to consider each 5-day drug period separately and, using their diary, to decide during which period they felt generally “best” and “worst.” These determinations were made while the study was still double-blind.

Statistical Analysis

Duration of exercise while on placebo was defined as the average of the two tests during placebo administration. Because patient response to pharmacologic intervention is highly individualized relative to drug dosage and our aim was to evaluate drug rather than dosage effectiveness, the longest exercise duration, whether on a low or a high dosage of verapamil or propranolol, was used for comparing all findings among placebo, propranolol and verapamil studies. Probability of statistical significance within the group was determined by the t test for paired data; statistical significance between groups was determined by the unpaired t test.

Results

Upright Exercise Testing

Because only two patients fulfilled our definition of nonobstructive hypertrophic cardiomyopathy, and because their results did not differ from those of the group as a whole, the results of exercise testing in the patients with and without obstruction will be reported as a single group (fig. 2). On placebo, the average
duration of exercise was 6.1 ± 0.8 minutes. On verapamil, average exercise capacity increased by 26 ± 8% (1.6 ± 0.5 minutes; \( p < 0.005 \)), and on propranolol, it improved by 21 ± 8% (1.3 ± 0.5 minutes; \( p < 0.025 \)). There was no significant difference between the results of the two drugs.

The mean heart rates at rest and at maximal exercise are compared in table 1. The reduced heart rates at rest and at maximal exercise with propranolol indicate that significant β blockade was present at the time of study. Compared with placebo, verapamil slowed basal heart rate but had less effect than propranolol. The effect of verapamil on the maximal heart rate achieved during exercise was not significantly different from that attained with placebo.

We defined a biologically significant change in exercise capacity as an increase or decrease ≥ 15; by this criterion, 12 patients improved with verapamil and none deteriorated (table 2). Eleven patients improved with propranolol and three deteriorated.

Exercise capacity was 6.4 ± 0.8 minutes on the lower dose of verapamil and 7.1 ± 0.8 minutes on the higher dose; these values did not differ significantly. Six patients did better on the high dose, five on the low dose, and in eight there was no significant difference (± 15%) between the two doses. Exercise capacity was 6.5 ± 0.7 minutes on low-dose propranolol and 6.4 ± 0.7 minutes on high-dose propranolol. Seven patients did better on the high dose, five on the low dose, and in seven there was no significant difference.

The symptomatic complaints at the end of exercise are listed in table 3. It was not necessary to terminate any exercise test because of significant ventricular or supraventricular arrhythmia.

To determine which factors might predict whether verapamil would improve exercise capacity, patients were divided into those whose exercise duration increased by at least 15% on verapamil and those whose did not. The two groups were examined for differences in 1) age and sex, 2) order of administration of drugs, 3) septal thickness, 4) increase in PR interval produced by verapamil, 5) basal and maximal provoking gradient before treatment and 6) decrease in basal and provoked gradients produced by verapamil.1 No significant differences were shown between the two groups (table 4). In addition, the effects of oral verapamil on exercise capacity and of intravenous verapamil on left ventricular outflow obstruction4 were compared (fig. 3). There was no significant correlation between changes in exercise capacity and basal gradient (\( r = 0.27 \)) or exercise capacity and provoked gradient (\( r = 0.50 \)).

Symptomatic Status

Sixteen patients were able to identify a “best” and “worst” period (table 5). Cardiac symptoms for a

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**Table 2. Effect of Verapamil and Propranolol on Exercise Capacity**

<table>
<thead>
<tr>
<th></th>
<th>Both (n)</th>
<th>Verapamil only (n)</th>
<th>Propranolol only (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Deterioration</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Change in exercise duration is defined as an increase or decrease of at least 15% over control levels.

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**Table 3. Symptoms at the End of Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Chest pain (n)</th>
<th>Chest pain and dizziness (n)</th>
<th>Dyspnea and/or fatigue (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Verapamil</td>
<td>7</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>
VERAPAMIL IN HYPERTROPHIC CARDIOMYOPATHY II/Rosing et al.

Table 4. Exercise Testing: Findings in Responders vs Nonresponders

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 4 (12)</td>
<td>47 ± 4 (7)</td>
</tr>
<tr>
<td>Ventricular septal thickness (mm)</td>
<td>23 ± 2 (12)</td>
<td>20 ± 2 (7)</td>
</tr>
<tr>
<td>Basal LVOT gradient (mm Hg)</td>
<td>46 ± 12 (12)</td>
<td>65 ± 23 (6)</td>
</tr>
<tr>
<td>Maximal provokable LVOT gradient (mm Hg)</td>
<td>77 ± 15 (10)</td>
<td>89 ± 29 (2)</td>
</tr>
<tr>
<td>Verapamil effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in basal gradient (mm Hg)</td>
<td>37 ± 14 (5)</td>
<td>36 ± 29 (4)</td>
</tr>
<tr>
<td>Decrease in provokable gradient (mm Hg)</td>
<td>48 ± 9 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Increase in PR interval (msec)</td>
<td>22 ± 4 (11)</td>
<td>17 ± 7 (7)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Numbers in parentheses indicate the number of patients.
*Results are similar if two patients who reported symptomatic improvement, but did not increase exercise capacity on verapamil, are included as "responders" instead of "nonresponders."

Table 5. Subjective Symptomatic Responses in 16 Patients

<table>
<thead>
<tr>
<th></th>
<th>&quot;Best&quot; (n)</th>
<th>&quot;Worst&quot; (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Verapamil</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

*The total number of responses is greater than total number of patients because some patients identified two treatment periods as being equally "best" or "worst."

Given patient tended to follow the pattern observed during exercise testing (Table 3), and no consistent trend was identified for a specific symptom. Generally, patients felt more fatigued and tired on propranolol than on placebo and verapamil; this observation was responsible for the finding that only three patients felt "best" on propranolol. Patient assessment of their symptomatic response to placebo, propranolol and verapamil agreed with the results of exercise testing in nine of 16 patients.

Adverse Drug Effects

It was necessary to discontinue drug administration in two patients, who were excluded from the study. A 77-year-old woman developed sinus arrest and systemic hypotension after one 80-mg verapamil capsule. Intravenous atropine and calcium administration did not restore sinus rhythm or increase blood pressure, and it was necessary to maintain the patient on a phenylephrine infusion for 6 hours until the drug effect had dissipated. This patient had manifested no findings that would have suggested the presence of sick sinus syndrome. The second patient had several brief episodes of type II second-degree atrioventricular block on telemetry during the first day of the study. He had received two 40-mg capsules of propranolol at the time. No other clinically significant adverse drug effects were identified in other patients during the study.

Two patients complained of minor noncardiac symptoms that may have been related to drug effect. While on propranolol, one patient had diarrhea, which improved with Lomotil administration. While on verapamil, another patient had recurrent upper abdominal discomfort, which was relieved by antacids.

Two serious clinical events occurred when intravenous and/or oral verapamil was administered to 53 patients either before or after this study. A 52-year-old man developed severe chest pain with no recordable blood pressure after receiving four 80-mg doses of verapamil given orally every 6 hours. Cardiopulmonary resuscitation was successful, but the patient died 1 week later, having received no additional verapamil. He had been on chronic disopyramide phosphate treatment, which had been terminated with the institution of verapamil. His disopyramide blood level (performed by Searle Lab-
oratory, Chicago, Illinois) was 0.7 μg/ml at the time of this event (therapeutic level 2–4 μg/ml). Post-mor tem examination revealed severe hypertrophic cardiomyopathy.

The second event occurred in a 64-year-old man who first complained of lightheadedness when standing and within minutes developed pulmonary edema. He had been receiving 120 mg of oral verapamil every 6 hours for 13 doses. He quickly responded to oxygen administration and intravenous furosemide and returned to his previous status. The patient was also taking quinidine sulfate at the time of this event. His quinidine blood level of 4.8 μg/ml was in the therapeutic range. He received no further verapamil, but died 3 weeks later while undergoing ventricular septal myotomy-myectomy. Postmortem examination revealed severe hypertrophic cardiomyopathy. Although events similar to these occur in patients with hypertrophic cardiomyopathy who are not receiving verapamil, the initiation of verapamil treatment in these two patients may have been causally related to their clinical decompensation.

Long-term Follow-up

Fifteen patients were discharged from the hospital on verapamil therapy. The usual dose was 120 mg four times a day. Eight patients have had repeat exercise tests 3.5–6 months after discharge, and the results of the serial exercise testing are shown in figure 4. The average long-term improvement in exercise capacity compared with performance on placebo in hospital was 45 ± 15% (11.6 ± 1.5 minutes vs. 8.0 ± 1.4 minutes; p < 0.025) and compared with the best performance while on verapamil in hospital was 21 ± 5% (11.6 ± 1.5 minutes vs. 9.6 ± 1.1 minutes; p < 0.005). All eight patients had at least an 8% improvement in exercise capacity at late study compared with in-hospital exercise capacity while on placebo; seven of eight manifested an increase in exercise capacity at late study compared with their best performance while on verapamil in-hospital. When questioned 4–9 months after hospital discharge, nine of 12 patients who were in functional class III before initiation of chronic verapamil treatment reported an improvement in symptoms. Four of the nine patients described marked improvement and were reclassified as functional class II; the other five remained in class III. The two patients who were in functional class II before study both stated that they were free of symptoms, except for infrequent "skipped heart beats," 7 and 9 months after beginning verapamil. The remaining patient had to discontinue verapamil 1 month after discharge because she developed upper abdominal discomfort apparently due to drug administration. She has subsequently undergone successful septal myotomy-myectomy.

Discussion

The short-term oral administration of verapamil to symptomatic patients with hypertrophic cardiomyopathy increased exercise capacity by at least 15%, improved symptomatic status, or improved both exercise capacity and symptomatic status compared with placebo in 14 of 19 subjects. Although there was no significant difference between average exercise capacity while on verapamil compared with that while on propranolol (fig. 2), exercise capacity deteriorated compared with placebo in three patients on propranolol therapy, but in none on verapamil treatment (table 2). Furthermore, nine patients felt "best" in verapamil, while only three patients felt "best" on propranolol (table 5).

Propranolol had a more beneficial effect on exercise testing than on symptomatic status, perhaps because it delayed the appearance of chest pain, lightheadedness, and dyspnea during exertion, but created a general feeling of fatigue and tiredness in many patients. This adverse effect of propranolol, which was not observed with verapamil, probably influenced the patients' sense of well-being more than it did their performance during a short bout of exercise.

Because the response to verapamil was not uniform, we tried to determine whether there were any factors that might identify patients who benefited from the drug by improving either exercise capacity or symptomatic status (table 4). There was no difference in the degree of septal thickness or the septal-to-left ventricular free wall thickness ratio between patients who increased exercise capacity or improved symptomatic
status compared with placebo and those who did not. Similarly, drug effect, as measured by PR prolongation, was the same in responders and nonresponders.

The hemodynamic effects of intravenous verapamil were determined at cardiac catheterization in 13 subjects in this study. In each patient, catheterization was performed within 4 weeks of the exercise studies. Verapamil led to a decrease of at least 30 mm Hg (50%) in either basal or provoked left ventricular outflow tract gradient in 10 of the 13 patients. Two of the three patients who failed to benefit hemodynamically from the drug improved their exercise tolerance, and one of the two described an improvement in symptomatic status on verapamil compared with placebo. In addition, one patient whose gradient decreased by 96 mm Hg in response to the drug failed to improve exercise tolerance or symptomatic status (fig. 3). Thus, from the hemodynamic response to acute intravenous administration of verapamil, we could not reliably predict which patients with hypertrophic cardiomyopathy would improve symptomatically on oral verapamil therapy.

Additional long-term symptomatic evaluation was undertaken to determine whether the short-term beneficial effects of verapamil on exercise capacity and symptomatic status were sustained with chronic administration of the drug. Eleven of the 15 patients discharged on verapamil after a 4-9-month follow-up have described symptomatic benefit, and six improved their functional status by at least one class. In the eight patients who have undergone repeat exercise testing (fig. 4), the improved in-hospital exercise capacity shown by four patients was maintained (one patient) or improved further (three patients). Four of the eight patients did not respond favorably to verapamil in hospital. Three of these patients at late study had at least a 12% improvement in exercise capacity compared with their best in-hospital performance on verapamil or on placebo.

The mechanisms by which verapamil produces these beneficial symptomatic effects are unknown. The primary cardiac pharmacologic effect of the drug is to block the transport of calcium into myocardial cells through the so-called slow channel. This effect may be associated with depressed myocardial contractility and depressed left ventricular outflow tract gradient in patients with hypertrophic cardiomyopathy and obstruction. Hypothetically, patients with hypertrophic cardiomyopathy might have a basic abnormality of calcium metabolism in which increased levels of myocardial cellular calcium lead to the characteristic hyperdynamic state of the left ventricle in such patients. If such an abnormality in calcium metabolism is part of the underlying disease process, the beneficial effects of verapamil, a potent inhibitor of calcium transport across cell membranes, might be due to a primary influence on one of the basic biochemical aberrations in hypertrophic cardiomyopathy.

The findings of this study and of our study on the hemodynamic effects of verapamil, as well as the clinical observations of Kaltenbach and associates — that 120 mg of oral verapamil administered four times daily for an average of 12 months provided an impressive improvement in symptoms in patients with hypertrophic cardiomyopathy compared with β-adrenergic blocking agents — indicate that verapamil will provide a much needed new approach for the medical treatment of patients with hypertrophic cardiomyopathy. This eventuality is especially important for severely symptomatic patients with obstruction to left ventricular outflow who do not respond adequately to or cannot take propranolol or other β-adrenergic blocking agents, and whose only other therapeutic alternative at present is operation. Verapamil might also provide a therapeutic alternative for patients with nonobstructive hypertrophic cardiomyopathy who, if medical therapy has failed, are not candidates for surgical intervention.

Acknowledgment

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References

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