Alpha-adrenergic Blockade for Variant Angina: A Long-term, Double-blind, Randomized Trial

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SUMMARY Recent reports have shown that β-adrenergic blockade may exacerbate variant angina. On theoretical grounds, α-adrenergic blockade may be beneficial in these patients. To test this hypothesis, we assessed the efficacy of prazosin, an α-adrenergic blocking agent, in six men, mean age 49 years, with variant angina. Prazosin, 14.0 ± 2.4 mg/day (mean ± SD) in three equal doses, was compared with placebo in a double-blind, randomized, double-crossover trial lasting 4½ months: 2 weeks of open-label prazosin followed by four 1-month periods of blinded alternating therapy. No other vasoactive medications were administered during the study.

Prazosin reduced sitting systolic arterial pressure from 145 ± 18 to 127 ± 16 mm Hg (p = 0.02), but exerted no effect on diastolic arterial pressure or heart rate. Prazosin did not change the weekly number of episodes of chest pain (2.5 ± 2.3 with placebo vs 3.1 ± 3.0 with prazosin, NS), nitroglycerin tablets used (3.9 ± 3.7 with placebo vs 4.6 ± 4.2 with prazosin, NS), or transient ST-segment deviations (by calibrated two-channel Holter monitoring for 24 hours/week throughout the study) (6.5 ± 10.1 with placebo vs 11.8 ± 17.4 with prazosin, NS). During prazosin therapy, three patients had orthostatic dizziness and one patient had headache. Thus, in a long-term, randomized, double-blind trial, prazosin exerted no obvious beneficial effect in patients with variant angina.

ALTHOUGH the cause of coronary arterial spasm is unknown, several studies over the past 10 years have suggested that episodes of spasm may be mediated by stimulation of the α-adrenergic receptors of large coronary arteries. Studies in experimental animals have shown that coronary blood flow can be influenced markedly by stimulation or blockade of these α-adrenergic receptors.1–4 Some reports have strongly suggested that in patients with variant angina, α-adrenergic stimulation can induce clinical episodes of spasm, whereas α-adrenergic blockade is effective in alleviating these episodes.7–10 However, these studies were relatively brief and were not randomized or double-blind. Therefore, we designed a long-term, placebo-controlled, randomized, double-blind study to assess the efficacy of prazosin, an α-adrenergic blocking agent, in patients with variant angina.

Methods

Patients

Six male patients, mean age 49 years (range 35–57 years), who had variant angina were enrolled in a 4½-month comparison of placebo and prazosin (packaged appropriately for a double-blind study). All six patients had recurrent episodes of angina at rest in conjunction with transient ST-segment elevation (at least 0.2 mV) on a standard 12-lead ECG, and in five, coronary arterial spasm was demonstrated angiographically. None of the six patients complained of exertional chest pain or had evidence of exercise-induced coronary arterial spasm. They had complained of angina at rest for 1.5 ± 1.1 years (range 1 month to 3 years). Selective coronary arteriography revealed obstructive one-vessel coronary artery disease (at least 70% luminal diameter narrowing) in two patients; the four other patients did not have obstructive coronary artery disease. During the study, no patient received other cardioactive medications, including long-acting nitrate preparations.

Study Design

After the diagnosis of variant angina was established and informed consent was obtained, each patient began taking open-label prazosin for 2 weeks, during which the maximal dose of prazosin that did not cause intolerable adverse effects was determined. Subse-
quently, each patient was randomly assigned to one of two groups for the remaining 4 months of the study. This 4-month period was divided into four 1-month blocks of alternating prazosin and placebo (fig. 1). During these four months, neither the physicians nor the patients knew which agent was being administered.

Variables Assessed

Clinical Response to Therapy

Each patient was seen at least twice monthly by one of the investigators, and the following variables were quantitated: number of episodes of angina per week (recorded daily by the patient in a diary), number of sublingual nitroglycerin tablets consumed per week (recorded daily by the patient in a diary), and number of adverse effects.

Electrocardiographic Response to Therapy

For 24 hours each week, each patient underwent calibrated two-channel ambulatory electrocardiographic monitoring, as previously described.11,12 ST-segment deviations from baseline were considered to have occurred if ST elevation or depression of at least 1 mm (0.1 mV) was present for at least 1 minute. (One minute of ST-segment deviation was required in an attempt to minimize misinterpretation caused by transient motion artifact.) From each tape, the number of episodes of ST-segment deviation was quantitated.

Hemodynamic Response to Therapy

During each patient visit, systemic arterial pressure and heart rate were measured in the supine and sitting positions.

Data Analysis

All patient diaries and Holter monitor recordings were analyzed without knowledge of the order in which placebo and prazosin were administered. For each variable, a repeated-measures analysis of variance was performed to determine if some groups were different from others, after which the Newman-Keuls multiple-comparison procedure was performed.13 In addition, for each variable, the two months of placebo therapy were averaged and compared with the average of the two months of prazosin therapy with a paired t test. All values were expressed as mean ± SD. A p value of 0.05 or less was considered significant.

Results

Drug Dosage

The six patients took an average of 14.0 ± 2.4 mg/day of prazosin in three equal doses. Five patients took 15 mg/day and one took 9 mg/day.

Clinical Response to Therapy

The frequency of both chest pain and nitroglycerin usage was similar during therapy with placebo and prazosin (table 1, fig. 2). During placebo administration, there were no adverse effects. During prazosin therapy, one patient complained of headache and three had orthostatic dizziness. In all three, the orthostatic symptoms were mild and intermittent, usually occurring only in the early morning hours. The supine blood pressures during prazosin therapy for these three patients were 115/78, 131/91, and 170/95 mm Hg. The sitting blood pressures were 110/77, 122/87, and 157/90 mm Hg, respectively. There was no discernible relationship between the clinical response to prazosin and the occurrence of orthostatic symptoms.

Electrocardiographic Response to Therapy

The frequency of transient ST-segment deviations was similar during treatment with placebo and prazosin (table 1, fig. 2).

Hemodynamic Response to Therapy

During placebo therapy, the six patients had a mean supine systolic arterial pressure of 145 ± 17 mm Hg and a sitting pressure of 145 ± 18 mm Hg (NS). The average diastolic arterial pressure was 88 ± 11 mm Hg in the supine position and 88 ± 11 mm Hg (NS) in the sitting position. The supine heart rate was 70 ± 10 beats/min and the sitting heart rate was 72 ± 11 beats/min (NS). During prazosin therapy, the systolic arterial pressure averaged 135 ± 19 mm Hg supine and 127 ± 16 mm Hg sitting (p = 0.015). In the sitting position, systolic arterial pressure during prazosin therapy was lower (p = 0.02) than during placebo therapy. The supine diastolic arterial pressure was 85 ± 8 mm Hg; the sitting pressure was 83 ± 8 mm Hg (NS compared with the supine position). In the sitting position, diastolic arterial pressure during prazosin therapy was similar to that during placebo therapy. The supine heart rate during prazosin therapy was 68 ± 7 beats/
min and did not change significantly in the sitting position (70 ± 6 beats/min) (NS compared with both the supine position during prazosin therapy and the sitting position during placebo therapy).

Prazosin’s effects on supine and sitting arterial pressure and heart rate were similar during both months of therapy. During the first month of prazosin treatment, supine systolic pressure averaged 134 ± 17 mm Hg, and sitting systolic pressure 126 ± 17 mm Hg. During the second month, supine pressure was 136 ± 19 mm Hg and sitting pressure was 127 ± 18 mm Hg (NS compared with the values during the first month of prazosin therapy). During the first month of prazosin therapy, supine diastolic arterial pressure was 84 ± 9 mm Hg and sitting pressure was 82 ± 7 mm Hg. During the second month, supine diastolic pressure was 86 ± 8 mm Hg and sitting pressure was 84 ± 9 mm Hg (NS compared with the values during the first month of prazosin treatment). Finally, during the initial month of prazosin therapy, the supine heart rate averaged 69 ± 8 beats/min and the sitting heart rate 71 ± 5 beats/min. During the second month, the supine heart rate was 67 ± 7 beats/min and the sitting heart rate was 69 ± 6 beats/min (NS compared with the values during the first month of prazosin administration). There was no evidence in any of the patients that prazosin’s influence on systemic arterial pressure or heart rate decreased with time.

### Discussion

Several studies have suggested that α-adrenergic stimulation may induce variant angina and that α-adrenergic blockade may alleviate these episodes.⁷⁻¹⁰ At the same time, β-adrenergic blockade, usually accomplished with propranolol, may exacerbate variant angina, presumably by allowing α-adrenergic stimulation of the large coronary arteries to occur unopposed.¹⁴ In patients with variant angina, Yasue et al.⁷ showed that α-adrenergic stimulation (produced by epinephrine or methacholine, a parasympathomimetic agent that reflexly stimulates sympathetic activity) as well as β-adrenergic blockade (with propranolol) induced episodes of variant angina. Yasue et al.⁸ consistently provoked coronary arterial spasm with subcutaneous epinephrine in patients already receiving propranolol. Subsequently, some unblinded and relatively short-term studies have demonstrated that episodes of variant angina can be abolished with i.v. phentolamine or oral phenoxycyanazine, both α-adrenergic blocking agents,⁹,¹⁰ whereas others have failed to demonstrate this effect.¹⁵ Thus, these preliminary reports suggested that α-adrenergic blockade may be effective in at least some patients with variant angina. The success of α blockade may offer insight into the pathophysiology of coronary arterial spasm.

The present study was performed to assess the efficacy of prazosin in patients with variant angina. Because many patients with variant angina have marked variability in disease activity,¹⁶,¹⁷ we assessed prazosin’s efficacy in a 4½-month, placebo-controlled, randomized, double-blind study. Prazosin was administered in doses similar to those used in patients with systemic arterial hypertension¹⁸,¹⁹ and those with severe congestive heart failure.²⁰⁻²² Although prazosin induced a significant fall in systemic arterial pressure, it exerted no effect on the frequency of chest pain, nitroglycerin usage or transient ST-segment deviations.

### Table 1. Clinical and Electrocardiographic Responses to Placebo and Prazosin Therapy

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Prazosin</th>
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<th>Placebo</th>
<th>Prazosin</th>
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</thead>
<tbody>
<tr>
<td>Chest pains/week</td>
<td>2.2 ± 2.1</td>
<td>2.4 ± 2.8</td>
<td>2.8 ± 2.6</td>
<td>3.8 ± 3.9</td>
<td>2.5 ± 2.3</td>
<td>3.1 ± 3.0</td>
</tr>
<tr>
<td>Nitroglycerin</td>
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<tr>
<td>tablets/week</td>
<td>3.3 ± 3.1</td>
<td>3.6 ± 3.9</td>
<td>4.4 ± 4.4</td>
<td>5.6 ± 5.7</td>
<td>3.9 ± 3.7</td>
<td>4.6 ± 4.2</td>
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<td>ST-segment</td>
<td></td>
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<tr>
<td>deviations/week</td>
<td>8.3 ± 13.0</td>
<td>10.3 ± 12.1</td>
<td>4.6 ± 7.2</td>
<td>13.2 ± 22.9</td>
<td>6.5 ± 10.1</td>
<td>11.8 ± 17.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

### Figure 2. The number of chest pains per week (left), nitroglycerin tablets consumed per week (middle), and transient ST-segment deviations per week by two-channel Holter monitoring (right) during 2 months of placebo and 2 months of prazosin therapy. Each line represents the data from one patient; the mean ± s.d. are shown on either side of each set of lines. Compared with placebo, prazosin exerted no significant effect on any of the variables.
There are two basic subtypes of α-adrenergic receptors. Postsynaptic α₁ receptors mediate the contraction of vascular smooth muscle and presynaptic α₂ receptors inhibit norepinephrine release at nerve terminals. Although the regulation of vascular tone in vivo appears to be mediated primarily by postsynaptic α₁ receptors, it may also be influenced by postsynaptic α₂ receptors, which have been identified in a number of vascular tissues in experimental animals. Because these postsynaptic α₂ receptors may help to control vascular tone in human coronary arteries, their stimulation may induce coronary arterial spasm and their blockade may prevent it. Prazosin has marked selectivity for postsynaptic α₁ receptors. In this respect, it differs from phentolamine and phenoxybenzamine, which block both α₁ and α₂ receptors. Therefore, although the present study demonstrates that postsynaptic α₁-receptor blockade with prazosin is not effective in patients with variant angina, it does not exclude the possibility that coronary arterial spasm is mediated by postsynaptic α₂ receptor stimulation.

Acknowledgment

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References

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