Propranolol in Angina Pectoris

Comparison of Long-acting and Standard-formulation Propranolol

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SUMMARY In a double-blind, crossover study in 20 patients with stable angina pectoris, the effects of long-acting propranolol, 160 mg administered once daily for 4 weeks, were compared with those of standard propranolol, 40 mg given four times daily for 4 weeks.

The patients suffered no adverse effects when they were switched between treatment schedules. The average number of episodes of angina during the 4 weeks on long-acting propranolol was 7.3 and on standard propranolol, 6.3. Average nitroglycerin consumption was 5.8 and 4.9 tablets during therapy with these two drug programs. The resting values for heart rate, systolic blood pressure and rate-pressure product were similar when determined 25.4 hours after a dose of long-acting propranolol and 10.7 hours after standard propranolol. When the patients exercised at these times, patients on long-acting propranolol and standard propranolol had similar walking times to the onset of angina and to the development of moderate angina. The values for heart rate, systolic blood pressure and rate-pressure product were similar at rest and during exercise during these two treatment programs.

We conclude that long-acting propranolol administered in a dose of 160 mg daily is as effective as 40 mg of standard propranolol four times daily.

PROPRANOLOL is an effective antianginal agent that is usually prescribed in four daily divided doses. However, in recent studies, single oral doses of propranolol, 80 and 160 mg, prolonged exercise tolerance for 12 hours in patients with stable angina pectoris. In a double-blind, crossover study, Thadani and Parker compared the efficacy of equal daily doses of propranolol given twice and four times daily. The frequency of angina pectoris recorded by diary and exercise tolerance as determined by treadmill testing was similar during the two treatment programs, and they concluded that twice-daily therapy with propranolol was effective in the management of patients with stable angina pectoris.

A long-acting formulation of propranolol has been developed. Preliminary data suggest that this preparation modifies the heart rate and systolic blood pressure response to exercise for as long as 24 hours and improves exercise tolerance in patients with angina pectoris for as long as 24 hours.

This investigation was designed to compare the effects of a single 160-mg daily dose of long-acting propranolol with standard-formulation propranolol, 40 mg administered four times daily, on exercise tolerance and the electrocardiographic and circulatory patterns at rest and during exercise in patients with chronic stable angina pectoris.

Methods

Patients

Twenty male patients, ages 47-62 years (average 56 years) with stable exertional angina were studied. The history of angina pectoris ranged from 6-192 months (average 52 months). Eight patients had electrocardiographic evidence of a previous myocardial infarction, but none had occurred in the year before the investigation. Eighteen patients had undergone selective coronary angiography and left ventriculography, which demonstrated significant two- or three-vessel disease in all patients. The two patients who had not undergone coronary angiography had electrocardiographic evidence of a previous myocardial infarction.

These subjects were selected from a population of patients with stable, exercise-induced angina pectoris who felt that they had been improved during propranolol therapy. All patients had been taking propranolol for at least 3 months (range 3-48 months). The total daily dose of propranolol in each patient was 160 mg. It was given four times daily in 17 patients and twice daily in three. While on propranolol therapy, they felt that the frequency of exertional angina pectoris had been reduced and that they could participate in more physical activity. Nine of the 20 patients had treadmill exercise tests before and after the institution of propranolol therapy. In each instance, the exercise time to angina pectoris had been increased by 60 seconds or more during propranolol therapy. The average value (+ SD) for the exercise time to moderate angina pectoris before therapy in these nine patients was 329 ± 88 seconds and increased to 440 ± 50 seconds during propranolol therapy (p < 0.001). Although propranolol had subjectively improved all patients, angina was readily induced by activity, and patients were classified as New York Heart Association functional class II or III. Angina pectoris could also be induced during treadmill exercise testing in all patients.

No patient had been in heart failure and none was taking digitalis. Eight patients were taking oral isosorbide dinitrate in doses of 40-120 mg/day. This therapy was continued during the trial, but was not administered on the mornings of exercise testing.
The resting ECG was normal in 12 patients, showed anterior wall myocardial infarction in two and inferior wall myocardial infarction in six. All 20 patients experienced angina pectoris during preliminary multistage treadmill testing and 18 patients exhibited ischemic ST-segment depression characterized by 1 mm of horizontal or downsloping segments at least 0.08 second in duration in modified lead V₅. One patient who had a previous myocardial infarction and angiographic documentation of three-vessel disease had 0.5 mm of ST-segment depression during exercise of angina. The remaining patient had isoelectric ST segments during repeated exercise tests despite angina pectoris and angiographic documentation of severe three-vessel disease.

### Study Design

After giving informed, written consent, the patients underwent a treadmill exercise test using the Bruce protocol to document the exercise level required to induce angina and to study the hemodynamic and electrocardiographic response to exercise. The control exercise test was carried out while the patients were on standard-formulation propranolol before initiation of the double-blind study. The test was done in the fasting state before the morning medications, 10–12 hours after the evening dose of propranolol. None of the patients took nitroglycerin in the 2 hours before this or subsequent exercise tests.

The definitive study was double-blind, placebo-controlled, and crossover in design. Patients were allocated randomly to one of two treatment groups. One was initially given long-acting propranolol and the other, standard-formulation propranolol for 4 weeks. Then, the patients were placed on the other treatment program for 4 weeks. Standard propranolol was given in regular tablet form (40 mg) and long-acting propranolol was supplied as a capsule containing spheroids of propranolol with a sustained release coating (160 mg, Inderal LA, Ayrst Canada Ltd.).

The 10 patients in group 1 initially received long-acting propranolol in a single dose of 160 mg at 8:00 a.m. and a placebo tablet of propranolol at 8:00 a.m., 12:00 noon, 6:00 p.m. and 10:00 p.m. (treatment A). At the end of 4 weeks the patients were given a long-acting propranolol placebo at 8:00 a.m. and standard propranolol, 40 mg, at 8:00 a.m. and 12:00 noon, 6:00 p.m. and 10:00 p.m. (treatment B). The 10 patients in group 2 received the medications in the reverse order. Both groups of patients were provided with diaries and instructed to keep a daily record of the frequency of angina pectoris and nitroglycerin consumption. Patients were evaluated after each 2-week period. Patients taking oral nitrates were instructed not to take them after the previous evening dose. No patient required nitroglycerin before exercise testing. Patients were fasting and did not smoke before assessment and exercise testing. The exercise tests were done between 8:00 and 9:00 a.m., which represented an interval of approximately 10 hours after the last dose of standard-formulation propranolol and 24 hours after long-acting propranolol.

During exercise, the patients were asked to indicate the time of onset of angina pectoris (P₁) and were encouraged to continue exercise until angina became of moderate severity (P₂). This was the end point for exercise, but in patients who did not progress to moderate angina, the time to fatigue or undue breathlessness was substituted for P₂.

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### Table 1. Summary of Clinical, Hemodynamic and Electrocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise P₁</th>
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<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>Control</td>
<td>61 ± 9</td>
<td>128 ± 20</td>
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<tr>
<td>A</td>
<td>64 ± 7</td>
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<tr>
<td>B₂</td>
<td>63 ± 10</td>
<td>136 ± 19</td>
</tr>
<tr>
<td>B₄</td>
<td>64 ± 9</td>
<td>131 ± 19</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p < 0.01 TWT at P₁ during B₄ vs control. There were no other significant differences among other hemodynamic measurements.

Abbreviations: HR = heart rate; SBP = systolic blood pressure; RPP = rate-pressure product; ST = ST-segment depression; TWT = treadmill walking time; A = average of data for A₂ and A₄; A₂ = results at end of 2 weeks of long-acting propranolol; A₄ = results at end of 4 weeks of long-acting propranolol; B = average of data for B₂ and B₄; B₂ = results at end of 2 weeks of standard-formulation propranolol; B₄ = results at end of 4 weeks of standard-formulation propranolol; P₁ = onset of angina pectoris; P₂ = onset of moderate angina pectoris.
Measurement and Recordings

Modified lead V6 of the ECG was monitored on an oscilloscope throughout the study and records were taken on a standard electrocardiograph at a paper speed of 25 mm/sec at 1-minute intervals during exercise. Further records were taken at P1 and P2 or just before the termination of exercise when fatigue or undue breathlessness was the end point. The average values for heart rate and ST-segment depression during 10 consecutive beats were measured from the ECG. The blood pressure was recorded by sphygmomanometry at rest, at 3-minute intervals during exercise, and at the time of P1 and P2. The ECG and blood pressure were also recorded at 1-minute intervals during a 5-minute recovery period.

Results

All 20 patients completed the 8-week investigation. Medication counts and patient attitudes suggested a high degree of compliance during the study. None of the patients experienced side effects during either treatment program and none admitted to being aware of any difference in symptoms or sense of well-being when changed from one treatment program to the other.

The two patient groups showed no significant differences with respect to age, body weight, blood pressure, serum cholesterol, smoking habits, duration of angina, functional class or duration of propranolol therapy.

Episodes of Angina Pectoris

Two patients did not keep adequate records of the frequency of angina pectoris. In the remaining 18, the average number of episodes of angina pectoris during the 4 weeks while on long-acting propranolol was 7.3 and while on standard propranolol was 6.3. Nitroglycerin consumption was 5.8 and 4.9 tablets during therapy with long-acting propranolol and standard propranolol, respectively. Five patients had an increase of four more episodes of angina pectoris during the 4 weeks they were on long-acting propranolol and four patients had a similar increase in frequency while on standard propranolol.

Treadmill Exercise Tolerance (Table 1)

All patients developed angina pectoris during exercise testing in the control study and while taking long-acting and standard propranolol. The data obtained at rest, at P1 and at P2 are shown in Table 1.

The interval between the last medication and the morning treadmill exercise test was determined for each patient for each phase of the investigation. The interval during the control study was 10.3 hours, during long-acting propranolol 25.4 hours, and during standard propranolol 10.7 hours.

Control Period

All 20 patients developed angina during the control exercise period. The time to P1 was 262 ± 79.1 seconds. Nineteen patients stopped exercise because of moderate angina and one patient stopped because of fatigue. The duration of exercise to fatigue was substituted for the time to moderate angina in this circumstance and the time to P2 was 388 ± 90 seconds.

Long-acting Propranolol Period

All patients developed angina during treadmill exercise. The average time of P1 for the two studies was 266 ± 70 seconds, with values at weeks 2 and 4 of 251 ± 73 and 279 ± 97 seconds, respectively. Exercise was stopped because of moderate angina in 17 patients and fatigue in three. The average time to P2 for the two studies was 410 ± 87 seconds, with values at weeks 2 and 4 of 401 ± 76 and 418 ± 106 seconds, respectively.

Standard Propranolol Period

All patients had angina during exercise. The average time to P1 for the two studies was 284 ± 76 seconds, with values at weeks 2 and 4 of 277 ± 80 and 292 ± 79 seconds, respectively. Exercise was stopped because of moderate angina in 18 patients and fatigue in two. The average time to P2 for the two studies was 417 ± 89 seconds, with values at weeks 2 and 4 of 413 ± 103 and 422 ± 84 seconds, respectively.

Treadmill walking times to P1 and P2 during therapy with long-acting propranolol and standard propranolol were not significantly different. When similar analyses were performed comparing treadmill walking time during the control period and the two study periods, treadmill walking time was slightly longer for both treatment programs than for the control period. These changes probably represent familiarization with treadmill exercise and a training effect, and only reached statistical significance when the time to P1 during the control period was compared to the time at the end of the treatment program with standard propranolol (p < 0.01).

The exercise data from the first 4 weeks of therapy in the 10 patients of group 1 showed no significant difference in treadmill walking time to P1 or P2 com-

<table>
<thead>
<tr>
<th>HR (beats/mm)</th>
<th>SBP (mm Hg)</th>
<th>RPP (mm Hg/min × 10⁻²)</th>
<th>TWT (sec)</th>
<th>ST (mm)</th>
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<tr>
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<td>156</td>
<td>179</td>
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<td>± 48</td>
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<td>112</td>
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<td>179</td>
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<td>± 13</td>
<td>± 20</td>
<td>± 38</td>
<td>± 84</td>
<td>± 1.0</td>
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pared with the control exercise values. Likewise, the 10 patients of group 2 who received standard propranolol during the initial 4 weeks showed no significant differences in walking time to P₁ or P₂ from the control period.

Electrocardiographic Changes

The degree of ST-segment depression at P₁ and P₂ was similar during the control study and during the 4-week periods the patients were on long-acting propranolol and standard propranolol.

Circulatory Changes

At rest, the average values for heart rate, systolic blood pressure and rate-pressure product were similar during the control period and during therapy with either form of propranolol. At P₁, during these three phases of the study, the heart rate, systolic blood pressure and rate-pressure product were also similar. At P₂, the heart rate was similar during these three phases of the investigation. Systolic blood pressure and the rate-pressure product were higher during therapy with long-acting propranolol and standard propranolol than during the control study (p < 0.05). However, the values for systolic blood pressure and rate-pressure product at P₂ were similar during the two treatment periods with either long-acting or standard propranolol.

Discussion

In this study in patients with stable angina pectoris, a single daily dose of long-acting propranolol, 160 mg, was as effective as standard propranolol, 40 mg given four times daily, for the prevention of angina. This conclusion is supported by the similar frequency of angina pectoris and nitroglycerin use during therapy with each agent. Treadmill exercise carried out 25.4 hours after long-acting propranolol showed exercise tolerance similar to that recorded 10.7 hours after standard propranolol. Heart rate, systolic blood pressure, and rate-pressure product were similar at rest, at P₁, and at P₂.

This investigation was designed to assess exercise tolerance by treadmill exercise testing when plasma levels from both the long-acting propranolol and standard propranolol would be at their trough. Treadmill exercise testing showed no difference in exercise tolerance at these times, between patients taking long-acting propranolol or standard propranolol. Similarly, heart rate, systolic blood pressure and rate-pressure product at rest and during exercise at the times of testing were similar, suggesting an equivalent degree of β blockade at these times.

Earlier studies have shown that long-acting propranolol modifies the heart rate and systolic blood pressure response during exercise for as long as 24 hours, and some data suggest that long-acting propranolol in angina pectoris may be effective for 24 hours.

We did not assess the comparative effects of long-acting propranolol and standard propranolol throughout a 24-hour period. After a single daily dose of long-acting propranolol, 160 mg, plasma levels are relatively stable between 5 and 30 hours, suggesting that continued daily dosage with long-acting propranolol would produce a relatively constant plasma concentration. We also have shown that with standard propranolol in doses of 80 and 160 mg twice daily, exercise tolerance is improved for 12 hours and there is little difference in treadmill exercise tolerance between 2 and 12 hours. Thus, the effects of long-acting propranolol and standard propranolol at the time of exercise testing chosen in this study may be representative of the effect of the two regimens over the 24-hour period.

The patients in this investigation all had chronic stable angina pectoris with reproducible symptoms during exercise. Each patient was considered to be a propranolol responder; in nine of the 20 patients, this was confirmed by exercise testing before and after initiation of propranolol therapy. Eight of the patients were taking isosorbide dinitrate, but this was not administered for at least 10 hours before exercise testing. At this interval, there would be no significant residual effects of isosorbide dinitrate on exercise tolerance.

In a recent investigation the effect of a single daily dose of slow-release oxprenolol was compared with standard propranolol administered four times daily. The design of the investigation was such that the effect of slow-release oxprenolol on the circulatory dynamics at rest and exercise and exercise tolerance were tested at 7.5 and 24 hours after a dose of oxprenolol and compared with the findings 4 and 12 hours after standard propranolol. When assessed in this fashion, slow-release oxprenolol, given once daily, was not as effective as propranolol given four times daily. The results of the present investigation, however, indicate that long-acting propranolol is as effective as standard-formulation propranolol four times daily.

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Circulation. 1982;65:1351-1355
doi: 10.1161/01.CIR.65.7.1351
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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