Therapy of Angina Pectoris with Propranolol and Long-Acting Nitrates

By Alberto N. Goldbarg, M.D., John F. Moran, M.D., Thomas K. Butterfield, M.D., Rimgaudas Nemickas, M.D., and Gustavo A. Bermudez, M.D.

SUMMARY
A double-blind study of the effects of isosorbide dinitrate, 10 mg given orally four times a day, propranolol, 40 mg four times a day, and the combination of these two drugs was performed on 21 patients with angina pectoris. Each patient received placebo, isosorbide, propranolol, and the combination of the two drugs for 1 month each in a random sequence over 4 months. The number of anginal pains and nitroglycerin tablets used were recorded, and a multistage treadmill ECG exercise test was performed after each treatment period.

Frequency of anginal pains was reduced significantly with propranolol (7.0 ± 2.5 pains/week) and the combination of propranolol and isosorbide dinitrate (9.9 ± 2.9) as compared with placebo (21.0 ± 6.4). Similarly, the number of nitroglycerin tablets was reduced with propranolol-containing regimens. Isosorbide was not significantly better than the placebo. Symptomatic improvement with propranolol could be related to a reduction in heart rate, and the product of heart rate and systolic blood pressure during exercise (P < 0.001). The capacity of these patients to perform a multistage exercise test, however, was not improved significantly, and the ischemic ST-segment changes were not altered by the treatments. Thus, propranolol appeared to be effective on the symptoms of angina pectoris, but it did not significantly improve exercise performance, and it did not prevent the ischemic patterns in the exercise ECG in this group of patients. Isosorbide dinitrate, alone or in combination with propranolol, was ineffective in this study.

Additional Indexing Words:
Treadmill exercise Heart rate Systolic blood pressure
ST segment Nitroglycerin Placebo
Valsalva maneuver

CORONARY heart disease commonly presents as angina pectoris. The chest pain probably occurs when the myocardial oxygen demands exceed the oxygen that can be supplied by the diseased coronary arteries. Symptoms, thus occur typically during periods of physical or emotional stress. The efficacy of therapeutic interventions in angina pectoris is difficult to evaluate. It is known that 35% of angina patients improve symptomatically on placebo therapy, so that studies which depend only on subjective evaluation by the patient are of questionable reliability. The unpredictability of the natural history and course of coronary heart disease makes evaluation of the effects of therapy on

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morbidity and mortality difficult. Finally, many factors, such as psychologic factors, time lag between control and treatment responses, environmental changes, changes in body weight, and biochemical variables, usually not easily controlled by investigators, may influence the results of clinical studies.

In spite of these difficulties, we have attempted to study the reported beneficial effects of propranolol and long-acting nitrates in patients with angina pectoris. To obtain valid results, careful selection of patients, strict adherence to a protocol, objective exercise data, and proper statistical analysis were necessary.

Methods

Subjects

Patients selected for this therapeutic trial had established angina pectoris for at least 6 months and an abnormal response to a multistage exercise test. Patients with gross cardiomegaly, congestive heart failure, obstructive lung disease, a history of bronchial asthma and those on digitalis therapy were excluded.

From a total of 29 patients selected for this study, 21 were able to complete the study period and will be referred to as the study population. Eight patients were not able to complete the study for the following reasons: Four patients could not tolerate isosorbide dinitrate because of severe headaches. One patient, a 70-year-old male, developed an acute myocardial infarction 2 weeks after starting propranolol but made an uneventful recovery. One patient developed left heart failure 3 days after being placed on propranolol, but responded satisfactorily to withdrawal of propranolol and diuretic therapy. One patient did not take the medication as prescribed and was excluded from the study in the third month. The eighth patient was taken from the study 2 weeks after starting the program at the request of his referring physician.

Personal history and a complete physical examination were obtained by one of the investigators. Table 1 details the personal characteristics of the study population at the beginning of the investigation. Six patients had a clinical history of one myocardial infarction, and one patient had a history of two myocardial infarctions. Five of the patients had adult-onset diabetes, and three other patients had hypertension. Three patients were taking anticoagulants by mouth and continued to take them throughout the project. The patients were asked to continue their other medications, and no other change was instituted during the treatment period. Coronary artery cinearteriograms available for three patients demonstrated diffuse two-vessel disease in two patients and three-vessel disease in the other.

Treatment Procedures

This prospective, double-blind study was carried out in a crossover fashion. The treatment periods were divided into four monthly periods of treatment in which the subjects took: (I) placebo and placebo (PLAC); (II) isosorbide dinitrate by mouth, 10 mg four times daily, and placebo (ISO); (III) propranolol 40 mg by mouth four times daily and placebo (PROPRA); and (IV) the combination of propranolol and isosorbide dinitrate (COMB). The tablets were given to the patients in numbered bottles coded by a research

<table>
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<th>Table 1</th>
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<td>Characteristics of 21 Patients with Angina Pectoris Who Completed the Study</td>
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<td>Range</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Sex</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>Weight (kg)</td>
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<tr>
<td>Duration of angina (yr)</td>
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<tr>
<td>Serum cholesterol (mg%)</td>
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<tr>
<td>2 hr p.c. glucose (mg%)</td>
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<tr>
<td>Blood urea nitrogen (mg%)</td>
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<td>Hemoglobin (mg%)</td>
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<tr>
<td>Chest x-rays</td>
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<td>12-lead resting ECG</td>
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pharmacist. The treatments were given in a random time sequence. The dose of isosorbide dinitrate of 10 mg four times a day was selected because that was the dose used by previous investigators who reported beneficial results.

Each patient was asked to keep a log of the number of anginal pains experienced and the number of nitroglycerin tablets consumed. At the end of each monthly period the patient was examined by one of the investigators, and his log of chest pains and nitroglycerin tablets was recorded. A 12-lead resting ECG was obtained prior to each exercise test.

Exercise Studies

A multistage treadmill test was used in the objective evaluation of the efficacy of each treatment. Each patient performed the treadmill test at least two times on different days before being included in the study, and therefore, the patients were thoroughly familiar with the testing procedure. Exercise on the treadmill was continuous and consisted of 3-min stages of gradually increasing speed and grade. The patients exercised to the level of established anginal pain and were asked to perform to the same level of pain in each subsequent exercise study. Endurance time was defined as the duration of exercise on the treadmill. Electrocardiographic monitoring and recording were performed with a minor modification of the precordial electrocardiogram described by Abarquez and associates. From the two previous exercise tests the leads which showed the maximal ST-segment depression was selected and used throughout the study. Resting heart rate was determined just before the exercise from the electrocardiogram after 5 min in the standing position. Blood pressures at rest, during each stage of exercise, and in the recovery period were obtained with a mercury sphygmomanometer by the cuff method. As a rough index of the myocardial oxygen demands, the product of maximal heart rate and systolic blood pressure during exercise was determined in each subject.

The heart rate response to a 6-min Valsalva maneuver (blowing against a closed sphygmomanometer to maintain 40 mm Hg pressure for 15 sec) was determined in each visit before the treadmill test. The Valsalva ratio (the longest R-R cycle divided by the shortest R-R cycle after the strain) was calculated to estimate the effects of the treatments on the heart rate response (mediated by the autonomic nervous system) to the Valsalva maneuver.

Exercise studies were interpreted independently by two of us (A.N.G. and J.F.M.). In our laboratory, interobserver variation was found to be small; in a previous study, disagreements occurred in six of 91 cases. The maximal ST-segment depression during or after exercise was recorded to the nearest 0.5 mv. The presence of arrhythmias was noted.

Statistical Analysis

Means, standard deviations, and standard errors of the mean (SEM) were obtained. Analysis of variance was performed to determine the statistical significance of the effects of the treatments upon the variables studied. When the F ratio reached the 5% level of significance, multiple comparisons among individual treatments were made by the Scheffé method of contrast. To investigate the possibility of interaction, the Tukey test statistic for non-additivity (interaction) was computed. Significant interaction was found for the number of anginal pains, nitroglycerin consumption, maximal blood pressure, and ST-segment depression. Through logarithmic transformation of these variables (log10 [x + 1], where x is an observed value), significant interaction was eliminated and, in addition, the transformation appeared to have stabilized the variances. Therefore, the transformed data were used in analyzing the above-mentioned variables.

Time Sequence

To investigate the possibility that the order in which the treatments were given had any effect on the results observed, the data were placed in chronologic order rather than by treatments, and analyses of variance were performed. No F ratios were significant; thus these tests failed to reveal any indication that the results were related to the time sequence in which the treatments were given.

Results

Anginal Pains and Nitroglycerin Consumption (Table 2)

The frequency of anginal pain was significantly reduced by PROPRA (7.0 ± 2.5 anginal pains/week) and by COMB (9.9 ± 2.9) when compared either with PLAC (21.0 ± 6.4) or ISO (16.8 ± 4.3 anginal pains/week). There was no difference between PLAC and ISO. The number of nitroglycerin tablets consumed was also reduced significantly by the propranolol-containing regimens.

Resting Heart Rate and Blood Pressure (Table 3)

Heart rate at rest was slower on propranolol-containing regimens as compared with placebo or isosorbide or both regimens. The treatments did not affect systolic blood pressure.
Table 2

Effect of Treatments on Anginal Pains and Nitroglycerine Tablets Taken per Week (Means ± SEM)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Anginal pains/week</th>
<th>Nitroglycerine tablets/week</th>
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<tbody>
<tr>
<td>PLAC (I)</td>
<td>21.0 ± 6.4</td>
<td>16.0 ± 5.7</td>
</tr>
<tr>
<td>ISO (II)</td>
<td>16.8 ± 4.3</td>
<td>9.2 ± 1.9</td>
</tr>
<tr>
<td>PROPRA (III)</td>
<td>7.0 ± 2.5</td>
<td>4.4 ± 1.4</td>
</tr>
<tr>
<td>COMB (IV)</td>
<td>9.9 ± 2.9</td>
<td>6.3 ± 2.1</td>
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Analysis of variance*:
F = 4.29, P < 0.01

Significant differences (P < 0.05) among individual treatments*:
I vs. III and IV
II vs. III and IV

* This was performed on the log-transformed data (see text).

Table 3

Effect of Treatments on Resting Heart Rate and Blood Pressure (Means ± SEM)

<table>
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<th>Heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
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<td></td>
<td></td>
<td>Systolic</td>
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<tr>
<td>PLAC (I)</td>
<td>81.4 ± 2.6</td>
<td>137.8 ± 4.5</td>
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<tr>
<td>ISO (II)</td>
<td>77.7 ± 2.8</td>
<td>138.2 ± 4.8</td>
</tr>
<tr>
<td>PROPRA (III)</td>
<td>65.3 ± 2.5</td>
<td>135.0 ± 4.8</td>
</tr>
<tr>
<td>COMB (IV)</td>
<td>67.3 ± 2.8</td>
<td>128.1 ± 5.3</td>
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</table>

Analysis of variance:
F = 13.2, P < 0.001

Significant differences (P < 0.05) among individual treatments:
I vs. III and IV
II vs. III and IV

pressure (F 2.0, P not significant), but affected the level of diastolic blood pressure at rest (F 4.0, P < 0.05). The resting diastolic blood pressure was reduced by COMB versus PLAC or ISO.

Valsalva Ratio

The treatments did not affect the Valsalva ratio (F 2.3, P not significant).

Exercise Studies

Figure 1 shows the effect of the various treatments on the capacity of patients to perform the multistage exercise test. Regardless of the treatment given, these patients were severely limited by their angina. As a group they were able to exercise only into the second stage of the treadmill test which is considerably less exercise than can be performed by age-matched normals.7 Although the treatments were found to affect the endurance time (F 3.5, P < 0.05), the individual differences were very small. The only significant difference among the treatments was found between COMB (5 min, 19 ± 26 sec) and ISO (4 min, 19 ± 30 sec). The therapeutic importance of this difference appears doubtful, however, because a small decrease in endurance time occurred with ISO when it was compared with PLAC (4 min, 29 ± 26 sec) or PROPRA (4 min, 47 ± 26 sec).

Ten patients performed better on PROPRA and 11 did worse as compared with their performance on PLAC. Fourteen patients

Figure 1

Effect of the various treatments upon the capacity to perform the exercise test in the study population (mean ± standard error of the mean, see text).
were able to do better on COMB while seven did worse. The proportion of patients with either a history of, or ECG evidence of, myocardial infarction was similar in the group that improved on propranolol-containing regimens and in the group that showed deterioration in exercise capacity.

Maximal Heart Rate and Blood Pressure

As can be seen in table 4, the treatments affected both maximal heart rate (F 24.2, P < 0.001) and maximal systolic pressure (F 3.2, P < 0.05) with no effect on maximal diastolic blood pressure (F 2.4, P not significant). However, no individual differences between treatments could be found for maximal systolic blood pressure. Significant slowing of the maximal heart rate was obtained with propranolol-containing regimens when compared with either PLAC or ISO. The product of maximal heart rate and maximal systolic blood pressure was also significantly reduced by PROPRA and by COMB. It decreased from 22.1 ± 1.2 × 10⁶ on PLAC to 17.3 ± 0.7 × 10⁶ on PROPRA and 17.0 ± 0.6 × 10⁶ on COMB of drugs (F 17.2, P < 0.001).

ST-Segment Changes

Although the treatments affected the maximal ST-segment depression during and after exercise (F 4.0, P < 0.05), no significant differences were found among individual treatments. The ST-segment changes on propranolol-containing regimens tended to be smaller, but these were attained when the maximal heart rate showed a mean reduction of 21 beats/min, or 16% decrease in maximal heart rate.

Discussion

Propranolol has pharmacologic actions that may be either beneficial or harmful to patients with angina pectoris. Beneficial effects could result from a reduction in myocardial oxygen requirements brought about by a decrease in heart rate,¹⁰ a decrease in the velocity of myocardial fiber shortening,¹¹ and a reduction in arterial pressure.¹² Harmful effects of propranolol might occur, however, as an effect of depression of myocardial contractility, possibly leading to heart failure in those patients with impaired myocardial function. An increase in cardiac dimensions,¹³ by Laplace's Law, would increase ventricular wall tension at any given pressure. Furthermore, prolongation of the systolic ejection period would extend the time that the ventricles must maintain tension and thereby increase myocardial oxygen demands.¹⁰ In addition, propranolol has been shown to reduce coronary blood flow by a passive increase in coronary vascular resistance.¹⁴ For these reasons, it is difficult in any individual patient to predict the therapeutic efficacy of propranolol.

Detailed physiologic studies¹⁵,¹⁶ are available on the effects of sublingual nitroglycerin in anginal patients. However, no such information is available for long-acting nitrates.

Table 4

<table>
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<tr>
<th>Effect of Treatments on Maximal Heart Rate, Maximal Blood Pressure and ST-Segment Changes During Treadmill Exercise (Means ± SEM)</th>
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<tr>
<td>PLAC  (I)</td>
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* This was performed on the log-transformed data.
Still, it has been suggested that isosorbide dinitrate lowers peripheral resistance and venous return and may improve circulation to a hypoxic myocardium.\textsuperscript{17}

Some earlier clinical trials have demonstrated symptomatic improvement in angina patients with the use of propranolol,\textsuperscript{18, 19} whereas others have shown objective improvement with exercise tests in these patients.\textsuperscript{20, 21} Recently Russek\textsuperscript{17} suggested a synergistic effect between propranolol and sublingual isosorbide dinitrate, but this synergism could not be demonstrated by Battock and associates\textsuperscript{2} and Aronow and Kaplan.\textsuperscript{22} Furthermore, these latter authors were unable to confirm the beneficial effects of propranolol when compared to placebo. The present study confirms the symptomatic improvement in angina patients on propranolol, while isosorbide dinitrate was found to be of no value when compared to placebo and no synergism could be demonstrated between propranolol and isosorbide dinitrate. In contrast to the paper by Battock and associates, who studied 10 patients, no objective improvement in exercise performance was observed in our study population.

In agreement with Gianelly and co-workers,\textsuperscript{23} ischemic ST-segment depression was not prevented by propranolol and developed at lower heart rates. These authors suggested that significant myocardial ischemia still occurred at comparable levels of exercise, but that chest pain was delayed by propranolol. They were unable to use urinary catecholamines as an indicator of those patients who would improve on propranolol. In this study, the presence or absence of healed myocardial infarction also appeared to be of no value in predicting favorable responses to propranolol.

In long-term follow-up studies, Amsterdam and associates\textsuperscript{24} suggested that propranolol decreased mortality in angina patients, but Zeft and co-workers\textsuperscript{25} found no apparent reduction in mortality and suggested that propranolol did not affect the natural course of symptomatic coronary artery disease. Since our study was initiated, four of our patients experienced significant progression of their coronary artery disease while receiving propranolol. Two sustained myocardial infarctions, and one of these died suddenly at home after an apparently uneventful recovery. Two other patients needed other measures for symptomatic control of their angina: one underwent a myocardial revascularization operation, and the other had a carotid sinus stimulator implanted.

The ideal agent for the treatment of patients with angina pectoris should reduce symptoms, improve exercise performance, eliminate ischemic changes in the exercise electrocardiogram, and improve longevity. Our data and a critical review of the literature suggest that propranolol is not that agent and that isosorbide dinitrate appears to be not much better than a placebo. However, in carefully selected patients propranolol can be used in the symptomatic treatment of angina pectoris.

Acknowledgment

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