Comparison of the Antianginal Efficacy of Acebutolol and Propranolol

A Multicenter, Randomized, Double-blind Placebo-controlled Study

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SUMMARY The effects of oral acebutolol, a cardioselective β-adrenergic blocking agent with partial agonist activity, were compared with those of oral propranolol, a noncardioselective agent devoid of partial agonist activity, on the exercise tolerance and anginal pattern in 46 male patients with chronic stable angina pectoris. A 28-week, multicenter, placebo-controlled, randomized, double-blind, crossover study design was used. Each double-blind treatment phase was followed by a 2-week gradual drug-withdrawal phase and a placebo-controlled drug-free week. Angina frequency, nitroglycerin consumption and symptom-limited exercise tests were assessed throughout the study.

Acebutolol and propranolol produced comparable levels of β blockade at 1650 ± 375 mg/day and 219 ± 50 mg/day (mean ± SD), respectively, as confirmed by a significant reduction in resting and peak exercise heart rates and rate-pressure products. Compared with placebo (acebutolol vs propranolol, NS), acebutolol produced a greater reduction in systolic, mean and diastolic blood pressures and a smaller reduction in resting heart rate than propranolol, presumably reflecting its partial agonist and cardioselective properties during similar dose titration phases. Exercise duration and exercise work improved similarly with each agent.

Acebutolol and propranolol significantly and comparably reduced anginal frequency (56% and 54%, respectively, p < 0.001) and weekly nitroglycerin consumption (57% and 47%, respectively, p < 0.01) compared with placebo. No clinical or laboratory side effects of acebutolol or propranolol necessitated drug withdrawal.

We conclude that acebutolol is a well-tolerated and safe β-adrenergic blocking agent that possesses cardioselective and mild intrinsic sympathomimetic activities and compares favorably with propranolol in antianginal efficacy in patients with chronic stable angina.

THE THERAPEUTIC EFFICACY of propranolol has been well demonstrated for the treatment of ischemic heart disease and angina pectoris.1-4 However, the associated adverse effects on bronchial and vascular smooth muscle and glucose metabolism accompanying this type of β blockade5-11 have stimulated interest in identifying more cardioselective β-blocking agents associated with improved exercise capacity and a lower risk of inducing bronchoconstriction or glucose intolerance.7, 11-13

Acebutolol, a new β-blocking agent, is cardioselective in humans.7, 8, 12, 13 Additionally, it possesses mild intrinsic sympathomimetic activity, which further differentiates it from propranolol. In a previous placebo-controlled, randomized, double-blind comparison, we found that acebutolol significantly increased the exercise capacity and reduced the frequency of spontaneous angina and nitroglycerin consumption in patients with chronic stable angina.14

Propranolol is the most widely used β-blocking agent for the treatment of angina pectoris and is the standard against which new agents must be compared. Thus, we undertook the present study to compare the effects of oral acebutolol and oral propranolol on exercise capacity, frequency of angina and nitroglycerin consumption in a large group of patients with chronic, stable angina pectoris.

Methods

Subjects

The study group consisted of 46 ambulatory male patients, mean age 59 years (range 42-72 years), from the outpatient clinics of the Veterans Administration (VA) Medical Center, Washington, D.C.; Wadsworth VA Medical Center, Los Angeles; and the Baylor College of Medicine, Houston.

Each patient had a primary diagnosis of chronic stable angina pectoris for at least 3 months before entry into the study. Each signed an informed consent.
approved by the respective institutional review committee. At least three episodes of angina during each week, with an overall weekly average of five or more attacks of angina during the first 4 weeks of a single-blind placebo phase, was required to be eligible for entry in the study; each patient also had to demonstrate an abnormal response to a standardized maximal multistage treadmill exercise test with at least 1 mm of flat or downward-sloping ST-segment displacement (0.08 second after the J point) that was associated with angina limitation to continued exercise, and either a prior myocardial infarction or angiographic evidence of at least 60% cross-sectional obstruction of one of the major coronary arteries.

Exclusion Criteria

Patients with the following associated conditions were excluded from the study: recent myocardial infarction or cardiac surgery (within 6 months), severe congestive heart failure, atrioventricular block greater than first degree (or a PR > 0.3 second), QRS prolongation greater than 0.09 second, severe renal insufficiency, diabetes mellitus requiring insulin, systemic asthma or signs or symptoms of systemic lupus erythematosus.

Twenty-five patients in this study (54%) had coronary arterial narrowing confirmed by coronary arteriography; 19 of these patients (76%) had multivessel disease with narrowing of more than 60% cross-sectional area in each involved artery, and six (24%) had one-vessel disease. Twenty-one patients (46%) had clinically documented myocardial infarctions more than 6 months before the study.

Study Design (fig. 1)

During the study, patients were permitted sublingual nitroglycerin tablets (0.6 mg, Eli Lilly) as the only antianginal medication other than the test capsules, which were administered three times daily. Nitroglycerin tablets were used when necessary to abort anginal episodes but not prophylactically. Daily patient diaries of anginal attacks and investigator-confirmed counts of the returned capsules and nitroglycerin tablets were kept throughout the study. All concomitant medications were maintained throughout the study, except for digitalis, other β-blocking agents, long-acting nitrates and sedative-hypnotics, which were withdrawn at least two weeks before entry.

The protocol consisted of an initial 4-week single-blind, placebo-controlled baseline period followed by two 9-week double-blind treatment periods, each terminated by 1- (n = 17) or 2-week (n = 29) weaning schedules, followed by a placebo-controlled drug-free week. Each double-blind treatment stage consisted of an initial 3-week dose-titration phase, during which successive weekly increases in the dose of the β-blocking agent were made, and a 6-week maintenance phase. Patients received either acebutolol (200, 400 or 600 mg) or propranolol (30, 60 or 80 mg) as capsules three times daily, provided there were no side effects. The aim during the dose-titration phase was to achieve a resting heart rate of 55 beats/min in the absence of side effects.

The weaning schedule consisted of twice-daily administration of study capsules for 2–8 days and once-daily administration for the next 4–5 days. This was followed by 1 week of placebo treatment (placebo II or drug-free period); patients were then crossed over to the alternative medication. The patients who were crossed over to the other medication underwent a 3-week dose-titration and a 6-week maintenance phase as before. Patients were seen on at least 15 visits over the 28-week protocol; daily diaries, nitroglycerin tablet and study capsule consumption, supine and stand-
ing vital signs and an ECG were recorded at each visit. Randomization of crossover during the double-blind phase was accomplished through the coding and pre-packing of the drugs.

A laboratory profile, including a complete blood count, erythrocyte sedimentation rate, platelet count, blood sugar, BUN, creatinine, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, uric acid, serum sodium, potassium, calcium, fluorescent antinuclear antibody (FANA) titer and urinalysis, was obtained before entry and at the end of each treatment period. Blood samples were drawn (preexercise) on the last day of each study phase and later analyzed for levels of acebutolol, N-acetyl acebutolol and propranolol for patients at the VA Medical Center in Washington, D.C. For the estimation of acebutolol and its metabolite, the method of Guentert et al. was used.

Exercise Protocol

Exercise tests were conducted before entry into the study and on the final day of each phase of the study. Each exercise test, done approximately 2–4 hours after drug administration, consisted of identical sequential 3-minute stages of increasing work load, speed and elevation on a calibrated motor-driven treadmill according to an adaptation of the Bruce protocol, complying with recommendations for the slow application of work load, to further encourage reproducibility as described.14

Statistics

The data, expressed as mean ± sd, were analyzed using the paired t test (two-tailed). During the double-blind phase, the lack of carryover, sequence and period effects allowed application of an analysis of variance to the data (paired t test) with the exception of subjective criteria, including the number of spontaneous anginal attacks or nitroglycerin tablets consumed. These are reported separately for this study.14 A large sample size also justified the use of this statistical method. Changes in the ST segment were evaluated using a uniformly most powerful unbiased test for the trinomial distribution.16 Probabilities were taken from standard distribution tables and considered statistically significant at the 0.05 level; levels of significance were not expressed beyond the 0.001 level.

Results

Results are exclusively based on paired comparisons for the variables tested and reflect the incomplete data of six patients who failed to complete the crossover period and three patients who were confirmed to be noncompliant.

Effects on Resting Hemodynamics (table 1)

Heart Rate

Resting heart rate, which averaged 74 ± 14 beats/min (mean ± sd) during the initial placebo period, showed significant reductions during treatment with both acebutolol and propranolol in the dose titration (figs. 2-4) and the maintenance phases. The average resting heart rates on acebutolol during the final week of the dose-titration and maintenance phases (mean dose 1650 ± 375 mg) were similar (NS). The average resting heart rates on propranolol (mean dose 219 ± 50 mg) during these same times were comparable (NS), indicating that both acebutolol and propranolol individually produced the same effects on the heart rate during the dose-titration phases as maintenance (extended treatment duration with either agent did not produce any further effect). The resting heart rate during propranolol treatment was slightly but significantly lower than that observed on acebutolol during both dose-titration (p < 0.001) and maintenance (p < 0.02) phases. The resting heart rate during the second introduction of placebo treatment (i.e., the first drug-free week, placebo II) was slightly lower (NS) than that during the initial placebo period. The final drug-free week (placebo III) showed a resting heart rate that was also comparable to these values. Postural effects of standing produced a minor increase in heart rate of 4.1 ± 9.9 beats/min during placebo treatment, slightly less on acebutolol (3.3 ± 3.8 beats/min) than on propranolol (5.8 ± 4.9 beats/min); however, neither of these alterations was significant.

Rate-Pressure Product

The resting rate-pressure product averaged 10.8 ± 3.7 during the initial placebo period and showed significant reductions after treatment with both acebutolol and propranolol during the dose-titration and the maintenance phases. The average rate-pressure products during the peak dose titration and maintenance phases were comparable for each agent and between agents (NS). The average rate-pressure products during the initial, second and final placebo periods were comparable.
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and comparable reductions in blood pressure were produced by both drugs. Throughout the study, diastolic and mean blood pressure changes were reflected by the systolic blood pressure, and hence will not be discussed. Postural effects (of standing) produced an unimportant change in systolic blood pressure (< 5 mm Hg) regardless of placebo or β-blocking treatment forms (NS).

Effect at Maximal Exercise (table 1)
Heart Rate
During the initial placebo period, the heart rate at peak exercise averaged 124 ± 20 beats/min; this value was reduced significantly after acebutolol and propranolol in both the dose-titration and the maintenance phases. The peak exercise heart rate during the final week of dose titration on acebutolol was slightly but significantly lower than this value on propranolol; this did not occur during the maintenance phases. Thus, both acebutolol and propranolol produced a significant and comparable β-blocking effect. Mean exercise heart rates for both acebutolol and propranolol at matched work loads were significantly and similarly reduced compared with placebo treatment (fig. 2).

Rate-Pressure Product
During the initial placebo period, the rate-pressure product at maximal exercise averaged 21.4 ± 5.5 and was significantly decreased by acebutolol and propranolol treatments during both the dose-titration and maintenance phases. The rate-pressure products at maximal exercise for either drug were similar during dose-titration and maintenance phases. Acebutolol reduced the rate-pressure product at maximal exercise more than propranolol during dose titration and during the maintenance phases.

The rate-pressure products at maximal exercise during the initial placebo period and the drug-free weeks were comparable. In the dose-titration phase, the systolic blood pressure at peak exercise decreased significantly after both acebutolol and propranolol treatments compared to placebo; however, acebutolol produced a slightly but significantly (p < 0.02) larger reduction in this value.

Exercise-induced ST Changes
The maximal ST-segment depression during multi-stage treadmill exercise testing with acebutolol and propranolol was less than that during the initial placebo period; however, only for acebutolol was this reduction statistically significant. The maximal ST-segment depression during the final week of dose titration was similar (NS) to that observed during the maintenance phase for each drug individually. The maximal ST-segment depression during treatment with acebutolol was significantly less than that with propranolol during both the dose-titration and maintenance phases. The maximal ST-segment depression during both of the drug-free weeks was not significantly different from that during the initial placebo
TABLE 1. Effect of Acebutolol and Propranolol on Hemodynamics and Exercise Variables

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Placebo I</th>
<th>Acebutolol (A)</th>
<th>Propranolol (P)</th>
<th>p A vs P</th>
<th>Placebo II (drug-free)</th>
<th>p placebo III vs placebo II</th>
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</thead>
<tbody>
<tr>
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<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 14</td>
<td>63 ± 10‡</td>
<td>58 ± 10‡</td>
<td>0.001</td>
<td>67 ± 11</td>
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<td>Rate-pressure product</td>
<td>10.8 ± 3.7</td>
<td>8.1 ± 1.9‡</td>
<td>8.0 ± 1.7‡</td>
<td>NS</td>
<td>9.9 ± 2.5</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>139 ± 17</td>
<td>129 ± 1.9‡</td>
<td>137 ± 17</td>
<td>0.05</td>
<td>143 ± 24</td>
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<td>Exercise</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>124 ± 20</td>
<td>93 ± 13‡</td>
<td>99 ± 19‡</td>
<td>0.05</td>
<td>125 ± 23</td>
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<tr>
<td>Rate-pressure product</td>
<td>21.4 ± 5.5</td>
<td>13.9 ± 3.7‡</td>
<td>15.9 ± 4.4‡</td>
<td>0.005</td>
<td>24.5 ± 6.6</td>
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<td>Systolic BP (mm Hg)</td>
<td>176 ± 27</td>
<td>150 ± 26‡</td>
<td>161 ± 23‡</td>
<td>0.02</td>
<td>194 ± 22</td>
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<td>ST displacement</td>
<td>−1.5 ± 1.0</td>
<td>−0.6 ± 0.7†</td>
<td>−1.1 ± 0.9</td>
<td>0.05</td>
<td>−1.1 ± 0.6</td>
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<tr>
<td>Exercise duration (seconds)</td>
<td>355 ± 120</td>
<td>410 ± 107*</td>
<td>419 ± 113‡</td>
<td>NS</td>
<td>413 ± 143</td>
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<tr>
<td>Exercise work (kpm)</td>
<td>888 ± 303</td>
<td>1001 ± 319*</td>
<td>1034 ± 336‡</td>
<td>NS</td>
<td>961 ± 328</td>
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<td>Angina frequency/week</td>
<td>8.4 ± 8.7</td>
<td>3.7 ± 7.4‡</td>
<td>3.8 ± 6.5‡</td>
<td>NS</td>
<td>7.8 ± 11.2</td>
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<td>Nitroglycerin tablets/week</td>
<td>9.5 ± 12.1</td>
<td>4.1 ± 11.3‡</td>
<td>5.0 ± 12.3†</td>
<td>NS</td>
<td>6.9 ± 12</td>
<td></td>
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</tbody>
</table>

*p compared with the initial placebo-controlled baseline period:

*†p < 0.05.
†p < 0.01.
‡p < 0.001.

Abbreviation: BP = blood pressure.

Table 1A. Effect of Acebutolol and Propranolol on Hemodynamics and Exercise Variables

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Maintenance</th>
<th>Acebutolol (A)</th>
<th>Propranolol (P)</th>
<th>p A vs P</th>
<th>Placebo III (drug-free)</th>
<th>p placebo III vs placebo II</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 ± 9‡</td>
<td>59 ± 8‡</td>
<td>0.02</td>
<td>75 ± 13</td>
<td>0.02</td>
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<tr>
<td>Rate-pressure product</td>
<td>8.4 ± 1.7†</td>
<td>7.9 ± 1.5‡</td>
<td>NS</td>
<td>9.9 ± 1.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>132 ± 19*</td>
<td>133 ± 20*</td>
<td>NS</td>
<td>136 ± 18</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>94 ± 13‡</td>
<td>97 ± 12‡</td>
<td>NS</td>
<td>122 ± 20</td>
<td>NS</td>
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<tr>
<td>Rate-pressure product</td>
<td>14.5 ± 3.5‡</td>
<td>15.3 ± 3.4‡</td>
<td>NS</td>
<td>22.9 ± 5.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>150 ± 24‡</td>
<td>156 ± 24‡</td>
<td>NS</td>
<td>184 ± 23</td>
<td>0.02</td>
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<tr>
<td>ST displacement</td>
<td>−0.7 ± 0.7‡</td>
<td>−0.9 ± 0.8</td>
<td>0.05</td>
<td>−1.0 ± 0.7</td>
<td>NS</td>
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<tr>
<td>Exercise duration (seconds)</td>
<td>412 ± 122‡</td>
<td>424 ± 112†</td>
<td>NS</td>
<td>402 ± 162</td>
<td>NS</td>
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<tr>
<td>Exercise work (kpm)</td>
<td>1017 ± 340‡</td>
<td>1022 ± 315‡</td>
<td>NS</td>
<td>948 ± 382</td>
<td>NS</td>
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<td>Angina frequency/week</td>
<td>4.3 ± 9.4†</td>
<td>4.2 ± 8.1†</td>
<td>NS</td>
<td>5.7 ± 6.6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin tablets/week</td>
<td>3.8 ± 8.3‡</td>
<td>4.3 ± 8.6†</td>
<td>NS</td>
<td>4.3 ± 5.0</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*p compared to the initial placebo-controlled baseline period:

*†p < 0.05.
†p < 0.01.
‡p < 0.001.

Abbreviation: BP = blood pressure.

period. Compared with the initial placebo period, the change in maximal ST-segment depression during treatment with either acebutolol or propranolol correlated poorly with the respective absolute or percentage change in peak rate-pressure product (r < 0.32) or the change in total exercise time (r = 0.27 and 0.43, respectively). During the dose-titration phase, 10 patients had at least 0.5 mm of ST-segment depression on propranolol compared with acebutolol, whereas four patients demonstrated at least 0.5 mm more ST-segment depression on acebutolol compared with propranolol (NS). The remaining patients had less than 0.5 mm of ST-segment change between drugs.

Exercise Capacity

Exercise capacity as assessed by the duration of exercise and total exercise work on standardized treadmill exercise testing improved significantly during acebutolol and propranolol treatments (table 1). The improvement in exercise capacity during dose titration did not differ from that during the maintenance phase for each drug. The differences between acebutolol and propranolol treatments were not sig-
significant. The exercise capacity at the end of the inter-
vening and final placebo-controlled drug-free weeks
was not significantly different from that during the ini-
tial placebo period. During the dose-titration phase,
12 of 35 patients (34%) demonstrated at least a 30-
second increase in exercise time during propranolol
compared with acebutolol treatment; 10 patients
(29%) demonstrated at least a 30-second increase in
exercise time during acebutolol compared with pro-
pranolol treatment. Thirteen patients (38%) showed
changes of less than 30 seconds in exercise time
between acebutolol and propranolol. Comparisons
were precluded by failure to complete both double-
blind treatment periods in eight patients and by in-
complete data in three patients.

Anginal Attack Frequency and
Nitroglycerin Tablet Consumption (table 1)

During the initial 4-week placebo period, the aver-
age weekly frequency of angina attacks was 8.4 ± 8.7;
this was reduced significantly, to 3.7 ± 7.4 attacks per
week (p < 0.001), at the maximal dose of acebutolol
(1650 ± 375 mg/day) and to 3.8 ± 6.5 attacks per
week (p < 0.001) at the maximal dose of propranolol
(219 ± 50 mg/day) during the dose-titration phase for
each drug. The average number of nitroglycerin
tablets consumed for the same period decreased
similarly with either drug compared with placebo. The
3-week dose-titration phase permitted an evaluation
of the effects of incremental dosages of acebutolol and
propranolol on the anginal frequency and number of
nitroglycerin tablets consumed. The results (figs. 3 and
4) demonstrate a progressive and statistically signifi-
cant decline in the angina frequency and nitroglycerin
tablet consumption after acebutolol in doses of
600–1800 mg/day and after propranolol in doses of
90–240 mg/day. During the 6-week maintenance
phase, the average frequency of anginal attacks and
number of nitroglycerin tablets consumed with each
treatment were comparable.

The anginal frequency and nitroglycerin consump-
tion during the second introduction of placebo treat-
ment (i.e., the first drug-free week) were both slightly
but significantly lower than those during the initial
placebo-controlled baseline period. These variables
were further reduced upon the reintroduction of pla-
cebo treatment for a third time in the final drug-free
week. The prompt reduction in anginal frequency and
nitroglycerin consumption after treatment with either
drug in the dose-titration (figs. 3 and 4) and mainte-
nance phases compared with the preceding placebo
treatment contrasted with the gradual decline in these
variables during the extended course of this 6-month
study.14

A contrast between acebutolol and propranolol was
noted when the maximal improvement in angina fre-
quency and nitroglycerin consumption, as a percent-
age change from baseline, was compared with the rest-
ing heart rate during treatment with each agent. On
acebutolol, the largest percent reduction in angina
frequency and nitroglycerin tablet consumption oc-
curred in patients with resting heart rates of more than
66 beats/min. Patients with resting heart rates of
55–65 beats/min and below 55 beats/min during ace-
butolol treatment showed less improvement. Patients
who took propranolol experienced the largest reduc-
tion in angina frequency and nitroglycerin consump-
tion when the resting heart rate was less than 55
beats/min and improvements of lesser magnitude
were observed at resting heart rates of 55–65
beats/min and greater. The significance of this find-
ing remains unclear.

Blood Levels of Acebutolol,
N-acetyl Acebutolol and Propranolol

In 30 patients, blood samples, taken before exercise
testing, were obtained at various intervals during the
study.

Twenty-eight patients showed good medication
compliance while taking acebutolol, confirmed by
blood levels of acebutolol and its metabolite. Two pa-
tients did not receive acebutolol treatment. Twenty-
nine of 30 patients (97%) demonstrated good medica-
tion compliance while taking propranolol, confirmed
by blood levels of propranolol. The mean blood level
of acebutolol for patients taking 1800 mg/day (n =
26) was 1177 ± 775 ng/ml (mean N-acetyl acebutolol
level 2405 ± 1142 ng/ml) during the last week of dose
titration and this value was not significantly different
during the maintenance phase (acebutolol, 1269 ± 773
ng/ml and N-acetyl acebutolol 2305 ± 950 ng/ml).
The N-acetyl metabolite of acebutolol generally main-
tained a blood concentration of one to three times that
of the parent compound; this has been noted by Miffin
et al.17 The mean blood level of propranolol for 24 pa-
tients who took 240 mg/day was 96 ± 64 ng/ml dur-
ing the last week of dose titration and was similar dur-
ing the maintenance phase (121 ± 89 ng/ml).

The mean blood level of acebutolol (including N-
acetyl metabolite) and propranolol were nondetect-
able, by the methods used, in 24 of 25 patients during
the placebo-controlled treatment in the drug-free week
interposed between crossover maintenance periods;
the only exception was one patient who had a reduced
propranolol level of 26 ng/ml.

The mean blood levels of acebutolol, N-acetyl ace-
butolol and propranolol correlated poorly with the
change (or percentage change) in heart rate, rate-
pressure product or systolic blood pressure at rest or
maximal exercise (all r values < 0.48).

The most striking contrast between the correlation
of blood levels of acebutolol and propranolol oc-
curred with the absolute and percentage change in rest-
ing heart rate. The acebutolol blood level correlated
positively with the absolute and percentage change in
resting heart rate (r = 0.39 and 0.17), whereas the pro-
pranolol level did not correlate or correlated nega-
tively with these measurements (r = 0.01 and −0.39,
respectively). At maximal exercise, the correlations
of blood level with the absolute and percentage change
in heart rate were similar.
Initial Placebo-controlled Baseline Period
vs the Midstudy and Final Drug-free Periods

The resting and maximal exercise values for heart rate, rate-pressure product and systolic blood pressure and the maximal ST-segment displacement, exercise duration and exercise work were comparable after withdrawal from both acebutolol and propranolol. A progressive increase in exercise duration was observed during both the midstudy and final drug-free weeks compared with the initial placebo-controlled baseline period (table 1); this trend did not attain statistical significance, however, which largely reflected the wider range of values (with an increased standard deviation) rather than the magnitude of change for the mean. The exercise duration during the midstudy and final drug-free weeks was similar regardless of whether the preceding treatment was with acebutolol or propranolol.

Adverse Reactions (table 2)

During the 5 months after randomization, nine of the 46 patients in this study were dropped from further analysis, including three who died suddenly (one during the placebo period after propranolol and two during the maintenance phase at the maximum dose of propranolol), three patients who developed unstable angina that necessitated additional treatment (one patient during the placebo period after propranolol and one each during the maintenance phase at maximum dose of acebutolol and propranolol), and three

<table>
<thead>
<tr>
<th>Table 2. Side Effects of Treatment with Placebo,* Acebutolol and Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Lightheadedness, dizziness, headache</td>
</tr>
<tr>
<td>Impotence</td>
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<tr>
<td>Claudication</td>
</tr>
<tr>
<td>Cold extremities</td>
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<tr>
<td>Loose teeth</td>
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<tr>
<td>Abdominal distention</td>
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<tr>
<td>Shortness of breath</td>
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<tr>
<td>Blurred vision</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Laboratory</td>
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<tr>
<td>ANA conversions titer ≤ 1:40</td>
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<tr>
<td>ANA conversions titer &gt; 1:40</td>
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</table>

*Placebo treatment was limited to the initial 4-week and each of the two drug-free weeks (total 6 weeks), whereas each drug treatment totalled 9 weeks.
effects); this is particularly true in diseases with an acute course toward progression or recovery, or when the actual performance of the study may be associated with either an improvement in function (e.g., the training effect) or a deterioration (e.g., deconditioning). In addition, a crossover design should not be used when there is an expected carryover of effect of one treatment into the next treatment period, especially with the use of agents having prolonged biologic half-lives or when study conditions themselves may alter the individual participants for an extended period. The chronic nature of stable angina pectoris, which is characterized by stability for long periods of time, provides an optimum entity for the application of the crossover design, provided safeguards relating to sample size, duration of treatments, investigator-confirmed pill counts, drug levels, double blinding and randomization are observed.25, 26

A small but definite percentage of angina acceleration, deceleration and new coronary events occurs annually and was observed in this study. A large enough group of patients in each treatment group at any one time, as in this study, counterbalances the temporal effects on each specific treatment and provides for parallel group analysis of treatment effects during the first or the second treatment phase. Because half the group received one drug initially and was then switched to the alternate treatment (after a withdrawal schedule and drug-free interval) while the other half of the group concurrently did the opposite, the effects of training or other effects stemming from the actual performance of the study occurred equally among the two treatments and groups with respect to time of introduction.

Comparison of exercise capacity at the end of the initial placebo period, the midstudy drug-free week (between the two maintenance periods) and the final drug-free week (all placebo-controlled) suggests that a training effect, defined as an increase in exercise duration and work, occurred during the course of this 6-month study. This phenomenon, previously called a placebo effect, is unexplained, but may reflect the consequences of repeated treadmill testing, a more active lifestyle possibly promoted by effective drug treatment, or other unidentified effects of performing the study.28 We reported a similar phenomenon previously.14

Unrecognized carryover effects that are quite unexpected may contribute to this observed improvement. In this trial, an interval of more than 25 half-lives of either acebutolol or propranolol was interpolated between prior drug weaning and a subsequent alternate drug treatment; this provided a maximal opportunity for drug washout and therefore separation of individual drug effects. The fact that during the drug-free week, the objective measurements (resting and exercise heart rates, rate-pressure products, exercise capacity and maximum ST-segment depressions) returned to the levels observed during the initial placebo period indicated that there was no carryover of drug effect into the second half of the study. Carryover effects do not explain the improvement in the exercise capacity for this group. The advantages of a crossover study design include the opportunity to maximize the information obtained from a minimum number of patients. Additionally, matching for age, sex, disease severity and other characteristics, which is at times quite difficult, is avoided because each patient becomes his own control with this study design.

The time required for the complete assessment of individual drug effects in studies of \(\beta\)-adrenergic blockade is controversial; hence, exposure times to these agents and accompanying observation periods have been variable. In this study, statistically significant differences for resting and exercise hemodynamics between the two drugs were almost exclusively noted during the initial 3 weeks of drug exposure, i.e., during dose titration, whereas during the final day of maintenance treatments (6 weeks later for a total of 9 weeks on treatment), statistical significance was lost for all but the resting heart rate, though definite trends persisted. This feature confirms our observation14 that the effects of a \(\beta\) blocker occur during dose titration and do not require additional maintenance treatment for evaluation. Whether the similarity of these two agents at 9 weeks on treatment represents an adjustment to a common response to \(\beta\) blockade on chronic treatment, or is an outgrowth of some characteristic of this type of study, is not known.

Because \(\beta\) blockade consistently produces a reduction in both the resting and peak exercise heart rate in volunteers28 and patients with coronary heart disease, we14 have used a reduction in resting heart rate as the end point against which to titrate the dose of acebutolol and propranolol. Gorlin and Swartz29 also suggested using the heart rate to determine the dose during the titration of a \(\beta\) blocker, thus reducing the requirements for serial exercise tests and avoiding the training effect of repeated exercise during dose titration. The results from the current study support this procedure in that both \(\beta\) blockers significantly lowered the resting heart rate; however, acebutolol was not associated with as substantial or as proportionate a reduction in this value as propranolol, probably a reflection of its partial agonist (intrinsic sympathomimetic) activity, though an indirect peripheral vascular effect with indirect (reflex) adjustments cannot be excluded. For acebutolol and other \(\beta\)-blocking agents with intrinsic sympathomimetic activity (for example, pindolol), titration against the resting heart rate appears to be inappropriate, because antianginal efficacy does not appear to be correlated with this variable.29 This contrasts with the antianginal efficacy for nonagonist blockers such as propranolol, with which additional improvements are found as resting heart rate is lowered, as shown in our study and previously.29

A larger relative dose is not the explanation for the greater reduction in resting heart rate by propranolol compared with acebutolol. This is shown by the hemodynamic measurements of heart rate, systolic blood pressure and rate-pressure product at maximal exer-
exercise, which were certainly comparable, if not of greater magnitude, during acebutolol treatment. During the dose-titration phase, acebutolol appeared to be more effective in reducing the exercise-induced changes in heart rate; during maintenance, blockade produced by either agent was comparable. The value of the exercise heart rate for estimating the degree of \( \beta \) blockade is thus clear.\(^9\) The relative dosages of acebutolol and propranolol used in this study (7:1 ratio) are in close agreement with the evaluations of relative \( \beta \)-blocking potency determined by Decalmer et al.\(^7\), Collett et al.\(^8\) and Thadani et al.\(^4\). The results from this study further support the comparability of these relative oral dosages in improving exercise capacities and similar levels of \( \beta \) blockade as assessed by hemodynamics at maximal exercise. Furthermore, the three-times-daily administration of both drugs agrees with other effective regimes.\(^4\) Knowledge of relative dosages is important in the clinical use of \( \beta \) blockers with intrinsic sympathomimetic activity, because the reduction in resting heart rate produced by the \( \beta \) blocker does not seem to correlate with the level of \( \beta \)-blockade or efficacy. The lack of excessive bradycardia at rest may be a valuable property of acebutolol in patients with coronary artery disease who require \( \beta \) blockade treatment, but who are troubled by symptomatic slow resting heart rates.

Acebutolol produced a greater reduction in systolic pressure than propranolol at rest and maximal exercise during the dose-titration phase. At rest, the reduced systolic pressure offset the significantly higher resting heart rate of acebutolol treatment compared with propranolol, with the result that the rate-pressure products were comparable for each agent. This favorable reduction in systolic pressure, which parallels the alterations in mean and diastolic blood pressure produced by acebutolol, probably reflects the less marked peripheral vascular smooth muscle constriction of cardioselective \( \beta \) blockade and is consistent with the findings of others.\(^9\) At equivalent work loads (peak exercise) and expected equal cardiac outputs, the reduction in blood pressure would suggest a reduced systemic vascular resistance. That the reduction in blood pressure is secondary to reduced left ventricular performance is unlikely in view of the significantly improved exercise duration and increased total exercise work associated with acebutolol treatment. At effective \( \beta \)-blocking doses, slightly lower than those used in this study, Katz et al.\(^2\) demonstrated that myocardial performance determined by radionuclide cineangiography was not altered by acebutolol treatment in patients with chronic angina.

Consistent with the findings of Collett et al.,\(^9\) there was not a strong correlation between the blood levels of acebutolol or propranolol and any individual resting or peak exercise variable; however, that the blood level of acebutolol correlated positively with heart rate at rest (unlike propranolol) may reflect the presence of intrinsic sympathomimetic activity. The previously demonstrated elimination of acebutolol by renal (40%) and nonrenal (60%) mechanisms would be expected to produce a plateau effect with incremental dosing that is observed at plasma levels greater than 100 ng/ml, which is well established for propranolol.\(^9\), \(^9\) These relationships with blood levels were not studied.

Adverse effects of \( \beta \)-adrenergic blockade consisted of common clinical complaints\(^6\), \(^10\), \(^11\) that accompany \( \beta \)-blocking treatment (table 2); both drugs showed good patient acceptance and compliance. Despite an observation period of only 6 weeks on placebo (compared with 9 weeks for each \( \beta \) blocker), fatigue (three patients), central nervous system side effects (two patients) and shortness of breath (three patients) were noted frequently on placebo treatment, somewhat limiting the specificity of subjective complaints. This suggested to us that investigational drug protocols engender complaints necessitating double-blind and placebo-control safeguards.

Asymptomatic laboratory findings, including elevated fasting and 2-hour postprandial blood glucose levels\(^8\) and elevated antinuclear antibody titers, were found; both accompany treatment with these and other agents (especially antihypertensives).\(^11\), \(^8\), \(^8\) Three patients developed elevation of FANA titers on placebo; this raises questions of the significance of such low-level elevations. In no instance was treatment associated with either clinical or laboratory side effects that necessitated drug discontinuation. Many of these patients have continued successfully on long-term acebutolol therapy without any adverse effects.

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