Comparison of Acebutolol and Propranolol for Treatment of Chronic Ventricular Arrhythmia: A Placebo-controlled, Double-blind, Randomized Crossover Study

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SUMMARY The effects on ventricular arrhythmia of acebutolol were compared with those of propranolol in 31 patients who averaged more than 30 ventricular premature complexes (VPCs) per hour during 72 hours of ambulatory ECG recording during a placebo-controlled baseline period. The study consisted of an initial 2-week placebo-controlled baseline period followed by two 6-week double-blind treatment periods consisting of incremental dose-titration, maintenance and dose-tapering schedules. The treatment during the double-blind period was randomized to either oral acebutolol or propranolol given three times daily. Twenty-four-hour ambulatory ECGs and maximal (symptom-limited) treadmill exercise tests were performed after 1 and 5 weeks of treatment with either acebutolol (1587 ± 397 mg/day) or propranolol (202 ± 63 mg/day) in each patient. The effects of acebutolol and propranolol on the frequency and grade of ventricular arrhythmia during rest and exercise were compared.

Acebutolol and propranolol produced comparable levels of adrenergic blockade, as reflected by significant reductions in the mean heart rate during 24-hour ambulatory recording (16% and 18%, respectively) and peak exercise (25% and 24%, respectively) compared with placebo (p < 0.01). Acebutolol and propranolol produced comparable and significant reductions in the VPC frequency during ambulatory ECG recordings (52% and 47%, respectively) and exercise testing (51% and 69%, respectively) compared with placebo (p < 0.001). Each agent produced comparable and significant reductions in the mean VPC grade compared with placebo (using a modified Lown classification) during ambulatory ECG recordings; the approximate reduction was one grade (p < 0.001). During exercise testing, acebutolol reduced the VPC grade significantly compared with placebo (p < 0.01); propranolol also reduced the VPC grade, but not significantly. No clinical or laboratory side effects of either agent necessitated drug discontinuance.

Acebutolol is a well-tolerated β-blocking agent that compares favorably to propranolol in reducing the frequency and complexity of VPCs at rest and during maximal exercise. The ventricular antiarrhythmic effects of acebutolol are comparable to those of propranolol. Hence, acebutolol represents an important therapeutic addition to β-adrenergic blocking agents.

MANY β-ADRENERGIC blocking agents with different ancillary properties studied in well-controlled clinical trials have been shown to reduce the frequency of ventricular premature complexes (VPCs), especially those augmented by exercise. However, the comparative efficacy of such agents has not been investigated. The interest in identifying β-blocking agents with minimal adverse effects on bronchial and vascular smooth muscle (so-called cardioselective agents) and limited adverse effects on glucose metabolism further suggests the need for such comparative studies to identify effective and safe antiarrhythmic drugs for chronic treatment of VPCs.

Acebutolol is a new cardioselective β-blocking agent that possesses mild intrinsic sympathomimetic activity, which differs from propranolol, the most widely used and well-studied noncardioselective and nonagonist β-adrenergic blocking agent. In the present study, we compared the effectiveness of acebutolol and propranolol in reducing the frequency and complexity of spontaneous and exercise-related VPCs in a large group of patients with chronic (non-sustained) ventricular arrhythmia using a placebo-controlled, double-blind, randomized crossover study design.

Methods

Subjects The study group consisted of 31 ambulatory patients (26 males and five females), mean age 56 years (range 26–75 years), who were in sinus rhythm and had a history of VPCs without known reversible cause for at least 3 months before entering the study. Each patient gave written informed consent. Fifteen patients (48%) had coronary artery disease, 10 patients...
(32%) lacked evidence of structural heart disease and six had other cardiac diagnoses (table 1).

Exclusion Criteria

Patients who had a recent myocardial infarction or who underwent cardiac surgery within 3 months were excluded. Patients with heart failure, atrioventricular block greater than first degree (or PR interval > 0.30 second), permanent cardiac pacemaker, QRS prolongation > 0.09 second, severe renal insufficiency (serum creatinine > 2 mg%), diabetes mellitus requiring insulin, history of asthma, or signs or symptoms of systemic lupus erythematosus were excluded from study, as were females of childbearing age. Patients who required digitalis, β-blocking agents, sedative hypnotics and sympathomimetics were also excluded from study. All other medications were kept constant throughout the study.

Study Design

The protocol consisted of an initial 2-week single-blind, placebo-controlled baseline period followed by two randomly determined 6-week double-blind drug treatment periods (fig. 1). Study capsules were ad-
ministered orally three times daily throughout the study and consisted of placebo, acebutolol and propranolol; each was identical in appearance. Each double-blind drug treatment period began with 1 week of incremental dose titration (acebutolol 200 mg, 400 mg or 600 mg three times daily; propranolol 30 mg, 60 mg or 80 mg three times daily) with either β blocker, provided that patients experienced no side effects and did not have bradycardia of less than 55 beats/min or a standing systolic blood pressure less than 105 mm Hg. The dose-titration phase was followed by 4-week maintenance and 1-week dose-tapering phases. Patients who could not tolerate the lowest dose of the first β blocker could be withdrawn and crossed over to the second β blocker; patients who could not tolerate the lowest dose of either β blocker were dropped from the study. A 1-week placebo-controlled drug-free period was interposed before cross over to the next double-blind treatment period.

Randomization of initial drug treatment and the alternate crossover treatment was accomplished by coded and prepackaged medications. Patient compliance was confirmed by capsule counts at each visit.

A laboratory profile, including a complete blood count, erythrocyte sedimentation rate, platelet count, urinalysis, blood sugar, BUN, creatinine, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, uric acid, serum sodium, potassium, calcium and fluorescent antinuclear antibody titer, was obtained before entry and at the end of each double-blind treatment period.

Twenty-four-hour ambulatory ECGs were performed on three sequential days (72 hours) during the initial single-blind placebo period and on the final day of each dose-titration and maintenance phase and drug-free week (fig. 1). Each ambulatory recording was analyzed by Cardio Data System (Haddonfield) as reported previously.17 The hourly VPC frequency was analyzed and classified.

VPCs were classified according to a modification of the grading system of Lown and Wolf:1 1 = fewer than 30 VPCs/hour; 2 = 30 or more VPCs/hour; 3 = multiform VPCs; 4 = couplets; and 5 = ventricular tachycardia (three or more repetitive VPCs). Early-cycle VPCs (R-on-T) were not included in this analysis because the significance of this criterion in ambulatory patients is controversial.19

Treadmill exercise tests were done at the end of the placebo period and on the final day of the maintenance phases to evaluate occurrence of exercise-induced arrhythmia.20 Each exercise test consisted of identical, sequential 3-minute stages of increasing work load (speed and percent elevation) on a calibrated, motor-driven treadmill according to a modification of the Bruce protocol.21 The patients performed maximally symptom-limited exercise in the presence of one of the investigators. Exercise tests were analyzed for the heart rate, systolic and diastolic blood pressure, calculated rate-pressure product at peak exercise, total exercise time and the reason for exercise limitation.

VPC frequency and complexity (highest grade) during exercise were evaluated by visual inspection and quantitation of all beats from a compressed single-channel ECG recording that included the upright exercise time and 10 minutes of supine rest after exercise. The VPC frequency and classification recorded during each exercise test were verified independently by at least two of the investigators.

**Statistical Analysis**

Statistical methods used included the paired t test and the Wilcoxon rank-sum test as used by Winkle et al.22 Intraindividual-hour and 24-hour VPC counts, log (total VPCs + 1.01), and highly hourly VPC classification were compared for the initial placebo, second placebo, acebutolol and propranolol treatments. Group mean data were similarly analyzed.
Results

Ambulatory ECGs During Placebo Treatment

During the initial 24 hours of placebo treatment, the heart rate averaged 81 ± 10 beats/min (± SD), the average frequency of VPCs from the 24-hour ambulatory recording was 477 ± 418 VPCs/hour (range 35-1807 VPCs/hour), and ventricular tachycardia (nonsustained) was recorded in 15 patients. The second and third sequential 24-hour ECG recordings during placebo treatment revealed similar mean heart rates, VPC frequencies and grades for this group and only modest intraindividual spontaneous fluctuations (tables 1 and 2). Individual fluctuations in VPC frequency were modest for the group as estimated by the comparison of the standard deviation of the mean hourly VPC rate with the magnitude of the mean hourly VPC rate during each day of the 3 days of placebo treatment. The ratio of the standard deviation of the mean to the mean hourly VPC frequency was less than 30% (fig. 2).

Similarly, comparison of the VPC rate for each patient during the second and third day of placebo treatment with the first day showed that most patients had

### Table 2. Mean Hourly Grade of Ventricular Premature Complexes for Each Patient During Comparable Study Periods

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Mean values for propranolol and acebutolol were not significantly different.
Abbreviations: See table 1.
fluctuations of less than 35% (71% of patients on day 2 and 82% of patients on day 3 showed less than 35% variability compared with day 1) (fig. 3).

There was little fluctuation in the mean VPC rate for the group (table 1). The individual and group mean fluctuations in hourly VPC grade between the 3 days of placebo treatment were small. Similar numbers of patients displayed ventricular tachycardia, paired VPCs and multiform VPCs on days 2 and 3 of placebo treatment (table 3), but a patient seldom had identical complex VPC forms recorded during each 24-hour period.

A second placebo period was interposed between crossover treatments at least 7 days after completion of a gradual 6-day withdrawal schedule, to eliminate any residual effect of the previous β blocker. The mean heart rate during this period was 82 ± 10 beats/min and compared favorably with mean heart rates during the first placebo period. The mean frequency and grade of the VPCs during this period were comparable to the values during the initial placebo period (NS) (fig. 3). The number of patients who had ventricular tachycardia, paired VPCs and multiform VPCs was similar to that in the preceding placebo period (table 3). As in the initial placebo period, the same subject seldom had identical complex VPC forms on serial recordings despite identical treatments.

Ambulatory ECGs During Acebutolol and Propranolol

The mean dose of acebutolol, 1587 ± 397 mg/day, was associated with a heart rate of 69 ± 7 beats/min
ACEBUTOLOL VS PROPRANOLOL FOR VENTRICULAR ARRHYTHMIA/Singh et al.

Table 3. Ventricular Ectopic Activity During Placebo, Acebutolol and Propranolol Treatments Recorded on Ambulatory Electrocardiographic Recordings

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Abbreviations: VPC = ventricular premature complex; DT = dose titration; maint. = maintenance.

(16% reduction). Acebutolol significantly reduced the mean VPC frequency and grade for the group recorded on the final day of the dose-titration and maintenance periods compared with the initial placebo period (table 1, fig. 4). Similarly, the number of patients with ventricular tachycardia, paired VPCs and multiform VPCs was reduced during acebutolol treatment (table 3). No significant differences in the dose-titration and maintenance periods were observed for mean VPC frequency or grade or the number of patients with specific complex VPC forms during acebutolol treatment.

Propranolol, mean dose 202 ± 63 mg/day, produced a heart rate of 67 ± 7 beats/min (18% reduction compared with the initial placebo period). Propranolol significantly reduced the mean VPC frequency and grade for the group recorded on the final day of the dose-titration and maintenance periods compared with the initial placebo period (table 1, fig. 4). Similarly, the number of patients with ventricular tachycardia, paired VPCs and multiform VPCs was reduced during propranolol treatment compared with placebo treatment (table 3). No significant differences in the dose-titration and maintenance periods were observed for VPC frequency or grade or the number of patients with specific complex VPC forms during propranolol treatment (tables 1, 2 and 3).

Acebutolol and propranolol treatments were not statistically different with respect to the mean heart rate, mean VPC frequency or grade and number of patients with complex VPC forms during exercise testing averaged 160 ± 202 (range 0–880 VPCs) and was reduced significantly by both acebutolol and propranolol compared with the initial placebo-controlled baseline period (table 4), thereby confirming comparable β-adrenergic blocking activity for both drugs. The total exercise time during placebo was 438 ± 174 seconds and changed insignificantly after acebutolol (486 ± 162 seconds) and propranolol (444 ± 192 seconds) treatments (table 3). Statistical analyses showed no significant differences in heart rate, systolic blood pressure, rate-pressure product, total exercise time or work between acebutolol and propranolol.

With placebo treatment the number of VPCs during exercise testing averaged 160 ± 202 (range 0–880 VPCs) and was reduced significantly by both acebutolol and propranolol (table 5). Acebutolol reduced the VPC number during exercise by more than 70% in 10 of 16 patients (63%), each of whom had more than 1.2 VPCs/min (range 4–110 VPCs/min) on their initial placebo exercise test. Propranolol reduced the number of VPCs during exercise by more than 70% in 12 of 16 patients (75%) who had more than 1.2 VPCs/min on their initial placebo-period exercise test. The mean VPC grade with exercise during placebo treatment was 2.65 ± 1.5 and was significantly reduced by acebutolol treatment (table 5). Propranolol did not reduce the mean VPC grade significantly, but the VPC grade with exercise was not significantly different from that during acebutolol treatment.

During placebo treatment, three patients (15%) had
ventricular ectopy of grade 1 or less during exercise testing; during acebutolol treatment 10 patients (50%) and during propranolol treatment eight patients (40%) had this level of VPC activity. Acebutolol and propranolol did not differ significantly in reducing VPC activity to grade 1 or less during exercise testing.

During placebo, the highest VPC grade with exercise was ventricular tachycardia in three patients, paired VPCs in three patients, multiform VPCs in three patients and more than 30 VPCs/hour in eight patients; the remaining three patients had grade 1 or less VPC activity as their highest grade during exercise. Acebutolol and propranolol each reduced the number of patients with these specific and highest complex forms during exercise (table 6).

### Adverse Effects

Acebutolol and propranolol were well tolerated in all patients, except for one patient who became drowsy during peak dose titration with acebutolol (con-
TABLE 6. Ventricular Ectopic Activity with Exercise During Placebo, Acebutolol and Propranolol Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acebutolol</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ectopy</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Single VPCs</td>
<td>18</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Multiform VPCs</td>
<td>8</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Paired VPCs</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: VPC = ventricular premature complex.

comitantly taking α methyldopa, 1.5 g/day). No drug-associated laboratory abnormalities were identified. All but 12 patients (39%) tolerated the maximal daily dosages of both β-blocking agents. Maximal dosages of acebutolol (three patients), propranolol (four patients) or both (five patients) were not tolerated because of asymptomatic hypotension and bradycardia. No significant differences in adverse effects occurred with β-blocking agents.

Discussion

This study showed that both oral acebutolol and propranolol comparably and significantly reduced the frequency and grade of VPCs during ambulatory ECG recordings and during treadmill exercise. The reduction in spontaneous VPC frequency was more than 65% — the expected maximal individual variability based on the monitoring duration of 72 control hours and 48 treatment hours in 15 patients (48%) taking acebutolol and 11 patients (35%) taking propranolol (NS).

Our results are in agreement with previous short- and long-term observations that support the individual pharmacologic activity of acebutolol and propranolol in reducing the frequency of ventricular arrhythmia. This study provides new information on the comparable antiarrhythmic effectiveness of these two β-blocking agents with different grades of cardiodepressant, intrinsic sympathomimetic and membrane-stabilizing activities.

The search for new, safer and more effective long-term treatments of ventricular arrhythmia continues, despite admonitions that the benefits of therapy are largely unproved.29, 30 Because β-blocking agents are among the best-tolerated antiarrhythmic agents, can be used at convenient dosing schedules, encouraging compliance, and have been shown in at least two studies in the convalescent phase of acute myocardial infarction to reduce sudden deaths (albeit possibly secondary to their antianginal properties), each agent should prompt a thorough evaluation.31-38

Beta-adrenergic blockade is the preferred treatment for ventricular arrhythmias related to catecholamine excess;29, 34, 36 which may explain their success in the treatment of postoperative or anesthetic-induced ventricular arrhythmia and that precipitated by exercise.29, 34-36 These agents are also valuable in treating ventricular arrhythmia associated with a variety of cardiac disorders, including digitalis toxicity and mitral valve prolapse.2-7, 22, 26-28

Shand44 and Vaughn-Williams49 suggested that the antiarrhythmic effects of β blockers (especially propranolol) are closely related to the production of β blockade because at the doses used in man, direct effects (variously referred to as nonspecific, local anesthetic, quinidine-like or membrane-stabilizing effects) are not seen.44-47 However, this concept is controversial. Woosley et al.1 suggested that antiarrhythmic effects are dissociated from the β-adrenergic effects of propranolol.

Beta blockers can vary with respect to factors that alter their clinical value.12, 15, 51 Pharmacologic properties, including cardiodepressant, partial agonist activity and other differences, make comparative studies of different agents a necessity.10, 12, 15, 51

Acebutolol has clinical electrophysiologic properties similar to those of propranolol.55, 89 Acute high-dose acebutolol in man has produced His-Purkinje delays, as measured by the HV interval, when plasma levels exceeded 100 ng/ml.49 This effect has not been observed for propranolol, which has been suggested as safe for patients with abnormalities of the specialized conduction system.90 This pharmacologic activity may play an important role in suppressing ventricular arrhythmias. Each of the type I antiarrhythmic agents prolongs His-Purkinje conduction, a property that may be valuable in treating reentrant ventricular arrhythmia.

The lack of a progressive dose-dependent bradycardia with agents possessing partial agonist activity has been reported in patients with angina pectoris.31, 40 and suggests that differential properties among β-adrenergic blockers are relevant clinically.

Exercise-related Ventricular Arrhythmia

Quantitation of exercise-related ventricular arrhythmia during treadmill exercise is a new and unstandardized tool for evaluating the efficacy of different antiarrhythmic treatments.20, 24, 36, 41 It also lacks the sensitivity of ambulatory ECG recordings for detecting important ventricular arrhythmia.3, 24, 42 However, the exercise method of provoking arrhythmia may reveal unique information with regard to electrophysiologic mechanisms.20, 24, 55, 56 examines an activity that is common for most patients, augments potentially dangerous increases in adrenergic activity, and is widely available. Therefore, we assessed the effects of acebutolol and propranolol, compared with placebo, on the frequency and complexity of exercise-related as well as spontaneous ventricular arrhythmia. Both β-blocking agents were equally effective in reducing the frequency and grade of exercise-related VPCs.

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