Acebutolol Therapy for Ventricular Arrhythmia
A Randomized, Placebo-controlled, Double-blind Multicenter Study


SUMMARY The safety and efficacy of acebutolol in suppressing ventricular ectopy was evaluated in 60 males (average age 59 years) using 24-hour Holter recordings and a double-blind, randomized, crossover protocol. Acebutolol, 200 mg and 400 mg thrice daily, was compared with placebo. Only patients who had a mean of at least 30 ventricular premature complexes (VPCs) per hour on three 24-hour control Holter recordings were included. Analysis of Holter recordings revealed greater than 70% reduction in VPCs/hour from control levels during acebutolol therapy in over 50% of the 60 patients; dose-related reduction in the mean number of single and paired VPCs and ventricular tachycardia episodes (p < 0.05) by acebutolol; and significant, asymptomatic reduction in resting heart rate and blood pressure. All side effects were transient. Acebutolol was discontinued because of side effects in one patient only.

SINCE propranolol was introduced for the management of angina, hypertension and cardiac arrhythmia, other β-receptor blocking drugs have been introduced or are undergoing evaluation. Acebutolol, which is cardioselective and has membrane-stabilizing as well as weak sympathomimetic properties, is one such drug. Its antiarrhythmic properties have been evaluated and found promising, but previous studies were single-blind and without prolonged observation of baseline ventricular ectopy or evaluation of placebo effects. We undertook a multicenter study using 24-hour ambulatory ECG recordings to evaluate the effects of oral acebutolol in a large number of patients with significant ventricular arrhythmia.

Materials and Methods
Cardiologists from three Veterans Administration Medical Centers (Little Rock, Arkansas; Dallas, Texas; and Long Beach, California) evaluated the antiarrhythmic efficacy and safety of acebutolol using a randomized, double-blind, crossover protocol (fig. 1) between September 1978 and July 1980. Sixty male patients, average age 59 years (range 30–77 years), were recruited and gave informed consent. Thirty-two patients (53%) had stable coronary artery disease; only six (10%) had no organic heart disease. Nine patients (15%) had aortic valve disease; four of these had combined coronary and aortic valve disease. Three patients (5%) had mitral valve prolapse, six (10%) had hypertensive cardiovascular disease and four (7%) had other types of organic heart disease. Three of the 32 coronary artery disease patients (9.4%) had undergone coronary artery bypass grafting and two of the patients with aortic valvular heart disease (25%) had undergone aortic valve replacement at least 6 months before the study. None of the patients were treated for symptomatic ventricular arrhythmia before or during the study. Digoxin, β-blocking agents and other antiarrhythmic preparations were discontinued at least 7 days before the study.

Each patient received six phases of treatment (fig. 1): an initial control phase (C1), two placebo phases (P1, P2), two treatment phases (A200 and A400) and a second control phase (C2) after the treatment sequence. Except during A200 and A400, one placebo capsule was given thrice daily in double-blind fashion. A200 consisted of acebutolol, 200 mg three times daily, and A400 consisted of acebutolol, 400 mg three times daily. Both acebutolol and identical-appearing placebo capsules were given every 8 hours. One-half of the patients started P1 before A200 (group 1) and the other half started A200 before P1 (group 2).

To ensure the reproducibility of the baseline ventricular arrhythmia, all subjects underwent three consecutive 24-hour ambulatory ECG recordings while receiving placebo. To qualify for the study, each patient had to have a mean of at least 30 premature ventricular complexes (PVCs) per hour on each of three control 24-hour Holter recordings. To be sure that the arrhythmia was still reproducible at the end of the protocol, a second control phase during which the patients underwent two 24-hour Holter recordings was included. All Holter recordings were performed using Avionics Model 445A two-channel recorders. All tape recordings from the three study centers were analyzed in a central laboratory (Cardio Data Incorporated). The analysis carried out at this laboratory is periodically subjected to stringent internal quality control using methods that have been reviewed by the Food and Drug Administration: instrumentation testing for performance consistency, individual patient tape quality control, review of all Holter report hard copies by quality control personnel, and blinded insertion of previously characterized tapes in a single- or
double-blind fashion to monitor and provide information on the system. Using these methods of analysis the following data were quantitated for each patient: the mean number of single VPCS/hour, the mean number of paired VPCS/hour, the mean number of ventricular tachycardia beats/hour and the mean total of ventricular ectopic beats per hour (VE total). VE total represented the sum of all forms of ventricular ectopy. The mean heart rate during the 24-hour period was also obtained.

All patients underwent routine laboratory studies, including antinuclear antibody (ANA) titer estimation, and detailed ophthalmologic testing before and after the study. Blood pressure was measured in recumbent and erect positions at each visit.

Statistical analysis was conducted in conjunction with the Department of Biometry at the University of Arkansas for Medical Sciences. Because each subject received all levels of treatment (two control phases, two placebo phases and two drug phases) and because the two orders of treatment were randomly assigned, the experimental data were analyzed as a two-factor experiment with repeated measures on one factor.12 In this design, the order of treatment is an intersubject measure and the drug treatments are intrasubject measures.

To further analyze the data, we compared the number of patients who had more than 70% reduction from C1 levels in ventricular ectopy during A100 or A400 with the number of patients who showed a similar reduction during P1 or P2. We also compared the number of patients who showed no reduction from C1 levels in ventricular ectopy during either placebo phase with the number of patients who showed no such reduction during either acebutolol phase. We evaluated the effect of acebutolol on ventricular tachycardia in similar fashion. The chi-square test was used for all of these comparisons.

In a double-blind crossover protocol, a carryover effect from the treatment phase to placebo phases or the final control phase is possible, even though in the present study, a 1-week weaning period always separated one crossover phase from another. To evaluate this carryover effect, the incidence of ventricular ectopy during initial and final control phases was compared according to whether the patient received P1 before A100 (group 1) or A400 before P1 (group 2).

Results
The mean values and standard errors for all measured variables are shown in table 1. The analysis of variance was calculated for each of the measured
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| Table 1. Ventricular Ectopy During Treatment and Control Phases |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Single VPCs/hour| Paired VPCs/hour| VT beats/hour | VE total/hour  |
|                                |                 |                 |                |                |
| C1                              | 374.4 ± 45.3    | 9.7 ± 3.5       | 0.6 ± 0.1      | 413.1 ± 52.6   |
| A200                            | 276.9 ± 42.6    | 2.9 ± 1.3       | 0.2 ± 0.1      | 296.4 ± 49.7   |
| A400                            | 190.2 ± 38.2    | 1.9 ± 1.5       | 0.2 ± 0.1      | 213.1 ± 52.4   |
| Pi                              | 339.4 ± 47.4    | 10.1 ± 3.8      | 0.4 ± 0.1      | 374.8 ± 52.3   |
| P2                              | 299.1 ± 36.7    | 9.1 ± 3.9       | 0.3 ± 0.1      | 311.4 ± 42.3   |
| C2                              | 323.6 ± 44.0    | 6.4 ± 2.4       | 0.5 ± 0.1      | 345.8 ± 52.7   |

Heart rate (beats/min) | Prone diastolic BP (mm Hg)
-----------------------|---------------------------
87.4 ± 1.2             | 78.4 ± 1.1                |
78.3 ± 11.2            | 82.1 ± 1.2                |
65.2 ± 9.0             | 78.4 ± 1.2                |
83.5 ± 10.6            | 82.2 ± 10.4               |
77.2 ± 1.2             | 82.2 ± 10.4               |
81.2 ± 9.2             | 82.2 ± 10.4               |

Values are mean ± SEM.

Abbreviations: C1 = initial control phase; A200 = acebutolol, 200 mg thrice daily; A400 = acebutolol, 400 mg thrice daily; P1 = initial placebo phase; P2 = second placebo phase; C2 = second control phase; BP = blood pressure; VE = ventricular ectopy; VT = ventricular tachycardia; VPCs = ventricular premature complexes.

variables with the following results: the F value for order of treatment (whether patients received placebo or drug first) was not significant for any of the variables; the F value measuring possible interaction between treatment and order of treatment was not significant in any of the analyses; the F value for acebutolol treatment differences was significant (p < 0.025) for all variables.

A least significant difference (LSD) test was applied to the treatment means to determine which treatment differences contributed to the significant treatment F-value. A significance level of 0.05 was chosen; the results are summarized in table 2. The treatments are listed in increasing order of their mean values. A line connecting any two treatments indicates no significant difference between the means for those treatments; any treatment means not connected by a continuous line can be considered significantly different at the 0.05 level. For example, for single PVCs, A400 significantly reduced ventricular ectopy compared with all other treatments. A200 was significantly different from A400 and C1. The treatment means for C2, P1, and C1 were not different from each other. The means for A400 and A900 rank lowest and next to lowest, respectively, for all variables except for diastolic blood pressure; C1 is the highest or second highest mean value in all cases (table 2). Both A200 and A400 produced significant, but asymptomatic, reductions in mean heart rate and diastolic blood pressure compared with all other treatment periods (table 2).

Six patients failed to achieve the initial inclusion criterion of 30 PVCs/hour during the C1, in which each patient underwent two 24-hour Holter recordings. The analysis of variance for VE total without these six patients showed no significant difference from the results of the entire group. The F-value was still highly significant (p < 0.01), and the LSD test was the same except for the lack of a significant difference between A200 and A400.

For all arrhythmia variables, the ventricular ectopy documented during the C1 was higher than that during C1 (table 1). To determine whether this was caused by a carryover effect due to patients receiving A400 as the last of the crossover phases, the ventricular ectopy total data during C1 and C2 were compared in group 1 and group 2 patients. A larger number of patients who received the A400 phase last (group 1) had decreasing ventricular ectopy from C1 to C2 (20 patients) than in the group of patients that received the P2 phase last (group 2, 17 patients). However, nine patients in group 1 and 11 patients in group 2 had a higher ventricular ectopic total during C2 than during C1. These differences were not statistically significant. Thus, there was no evidence of a significant carryover effect from drug to placebo in the present study.

Significantly more patients had more than 70% reduction in ventricular ectopy from initial control levels during acebutolol therapy than had a similar reduction during the placebo phases of the study (fig. 2). Acebutolol therapy also produced significantly fewer patients who had no reduction in ventricular ectopy compared with C1 than did placebo (fig. 2). Ven-

Table 2. Least Significant Difference Test Results

<table>
<thead>
<tr>
<th>Mean single VPCs/hour</th>
<th>Mean paired VPCs/hr</th>
<th>Mean VT beats/hour</th>
<th>Mean VE total/hour</th>
<th>Mean heart rate (beats/min)</th>
<th>Mean prone diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A400</td>
<td>190.2</td>
<td>A400</td>
<td>1.9</td>
<td>0.2</td>
<td>A400</td>
</tr>
<tr>
<td>A200</td>
<td>276.9</td>
<td>A200</td>
<td>2.9</td>
<td>0.2</td>
<td>A200</td>
</tr>
<tr>
<td>P1</td>
<td>299.1</td>
<td>C2</td>
<td>6.4</td>
<td>0.3</td>
<td>P2</td>
</tr>
<tr>
<td>C2</td>
<td>323.6</td>
<td>P2</td>
<td>9.1</td>
<td>0.4</td>
<td>C2</td>
</tr>
<tr>
<td>P1</td>
<td>339.4</td>
<td>C1</td>
<td>9.7</td>
<td>0.5</td>
<td>P1</td>
</tr>
<tr>
<td>C1</td>
<td>374.4</td>
<td>P1</td>
<td>10.1</td>
<td>0.6</td>
<td>C1</td>
</tr>
<tr>
<td>LSD</td>
<td>66.5</td>
<td>5.9</td>
<td>0.1</td>
<td>0.2</td>
<td>70.7</td>
</tr>
</tbody>
</table>

See text for explanation of vertical lines.

Abbreviations: LSD = least significant difference at p < 0.05. See table 1 for other abbreviations.
tachycardia was abolished in a significantly larger number of subjects during acebutolol therapy than during placebo.

The only serious side effects during the acebutolol phases were a skin rash that necessitated discontinuation of therapy in one patient and transient congestive heart failure during the \( A_{200} \) phase in another. The latter patient's cardiac failure responded well to diuretic therapy alone and he subsequently tolerated the \( A_{400} \) phase without further difficulty. The four patients who were easily fatigued during acebutolol therapy only showed no other evidence of congestive heart failure. One patient experienced fatigue during the placebo phase only and two other patients experienced fatigue during both placebo and acebutolol phases. Three patients with a negative ANA titer at study entry had positive ANA titers at the end of the study (titer of 1:20 in all three patients). Three other patients with weakly positive tests (ANA titer 1:20) at study entry had ANA titers of 1:160 at the end of the study. However, these six patients remained asymptomatic. Transient gastrointestinal distress occurred in one patient during acebutolol therapy and in another during the placebo phase. One patient suffered a fatal myocardial infarction during \( P_1 \), after being weaned from \( A_{200} \). No patient reported symptoms compatible with unstable angina during the study or required additional antihypertensive therapy; no patient had symptomatic postural hypotension, symptomatic bradycardia or atrioventricular block greater than first degree.

**Discussion**

Acebutolol, when rigorously tested by a placebo-controlled, double-blind, randomized protocol, significantly reduced the mean frequency of ventricular arrhythmia in the 60 patients in this study. Few antiarrhythmic agents in clinical use today have been so tested. We attempted to exclude patients whose PVCs were likely to disappear spontaneously. Only patients who, on three 24-hour control Holter monitor recordings (done in the absence of cardioactive medication over a 2-week period), had a mean of at least 30 PVCs/hour were included. This feature was incorporated into the protocol because spontaneous variations in PVC frequency may be great enough to mimic therapeutic effect.\(^{14-16}\) Failure to establish consistency in PVC frequency has been a weakness in studies of PVC suppression by antiarrhythmic agents.\(^{14,16}\)

The results of this study show a clear and significant reduction of ventricular ectopy during acebutolol therapy compared with all other treatment periods (table 2, fig. 2). Of the two doses studied, \( A_{400} \) appeared more effective than \( A_{200} \) in reducing ventricular ectopy (table 2). For five of the six variables tested, \( A_{400} \) had the lowest mean and the \( A_{200} \) the second lowest mean. The exception was prone diastolic blood pressure. The order of therapy did not significantly affect the results.

Our findings in the present study corroborated findings of previous studies that oral or i.v. acebutolol on a short- or long-term basis significantly reduced ventricular ectopy in patients with organic heart disease.\(^{3,9}\) This protocol adhered closely to the predictions of Morganroth et al.\(^{14}\) and Sami et al.\(^{17}\) for suitable studies of PVC suppression in terms of the number of patients required, the number of control observations and the number of observations during therapy.

After the randomized portion of the study, the two control 24-hour Holter recordings showed that all but six of the 60 patients again had a mean of at least 30 PVCs/hour. When these six patients were excluded from the analysis, the F value remained significant (\( p < 0.01 \)), with acebutolol showing a significant reduction of ventricular ectopy compared with placebo and the two control periods.

To determine any carryover effect from drug to placebo phases of the present study, the changes from \( C_1 \) to \( C_2 \) for the ventricular ectopy total were compared for the two orders of treatment (group 1 and group 2). The number of patients in whom the ventricular ectopy total decreased was not significantly different within or between groups. However, for the group, the ventricular ectopy values tended to decrease from \( C_1 \) to \( C_2 \). Another factor that may influence this decrease may be the feeling of security experienced by patients being followed closely by cardiology personnel. Ventricular ectopy related to anxiety is more likely to be affected in this manner. This factor cannot be documented and is hypothetical.

The side effects were all transient and not life-threatening. The three patients with ANA conversions and the two patients with increasing ANA titers remained asymptomatic. The patient who developed congestive heart failure during the study continued therapy without dosage reduction after the addition of a diuretic to his drug regimen. The patient with a generalized skin rash had to discontinue acebutolol, but had no permanent sequelae from his skin rash.
which responded promptly to steroid therapy. Even though the mean heart rate was significantly reduced during both acebutolol periods compared with other treatment periods, symptomatic bradyarrhythmias or atrioventricular block greater than first degree was not encountered. No ophthalmologic side effects were observed.

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