Suppression of Premature Ventricular Contractions by Acebutolol

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SUMMARY The antiarrhythmic action of the beta-blocking drug acebutolol, was evaluated in patients with frequent premature ventricular contractions (PVCs). In the 12 hours following administration of a single 300 mg oral dose, 8 of 10 patients showed a greater than 50% reduction in PVC frequency, and statistical analysis indicated that PVC reduction persisted for 10 hours after the single dose. Analysis of plasma concentrations of acebutolol and an acetyl metabolite indicated that after single oral doses the plasma concentrations of the metabolite exceed those of unchanged acebutolol.

A POSITIVE CORRELATION between the presence of frequent premature ventricular contractions (PVCs) and the subsequent incidence of sudden cardiac death has been observed, particularly in patients with coronary artery disease. It is a reasonable though unproven hypothesis that suppression of these ectopic impulses would result in a decrease in the incidence of sudden death in these patients. Testing of this hypothesis has been limited to date primarily by the lack of antiarrhythmic drugs suitable for chronic administration. Such drugs should be effective, free of toxicity, and have properties that allow administration on a convenient dosage schedule which permits patient compliance. The development of such agents is currently the goal of extensive laboratory and clinical investigation.

Acebutolol, (M&B 17803A) (±)-1-(2-acetyl-4-n-butyramido-phenoxo)-2-hydroxy-3-isopropylaminopropane (fig. 1) is a new, relatively cardioselective beta-adrenergic antagonist. Acebutolol blocks the myocardial beta-receptors by a competitive inhibition and has a weak sympathomimetic action. In intravenous studies, it has approximately one-seventh the beta-blocking potency of propranolol. In addition, it has the membrane-stabilizing, so-called "quinidine-like" property found in propranolol but not in practolol. In experimental arrhythmia studies, differences from both propranolol and practolol have been noted which have potential clinical utility, and preliminary clinical arrhythmia studies are promising. The drug has less effect on the beta-receptors of bronchial smooth muscle than propranolol and has been administered to asthmatics. Acebutolol has also been used successfully in the treatment of angina pectoris and has been found to reduce left ventricular outflow obstruction in patients with hypertrophic cardiomyopathy.

This report details the effects of short-term administration of acebutolol to a group of ambulatory patients with frequent PVCs.

Methods

Patient Population

Twelve patients, 11 men and one woman, participated in the study after giving written informed consent. The average age of the patients was 56 years (range 46 to 67). Eight patients had coronary artery disease. Of these eight, five had had previous myocardial infarction and four had angina pectoris; two had mild cardiomegaly with compensated congestive heart failure and were taking digitalis glycosides which were continued throughout the study. One patient had a cardiomyopathy without congestive heart failure, and three were middle-aged men with asymptomatic PVCs of unknown etiology. In two patients, symptoms attributable to cardiac arrhythmias were present; one of these had near syncope and another had palpitation associated with increased angina pectoris. Classified symptomatically according to New York Heart Association criteria, five were class 0, two were class I, three were class II, and two were class III.

Patients were selected for study only if control ambulatory electrocardiographic monitoring showed more than one PVC per minute averaged over 24 hours. In nine patients, PVCs were uniform, with relatively fixed coupling intervals in six; in three the coupling interval was variable; in four patients, multiform PVCs were noted. Four patients had at least one consecutive pair seen in a 24-hour electrocardiogram, and one patient had frequent short periods of ventricular tachycardia (three or more consecutive PVCs).

Protocol Design

All antiarrhythmic drugs were discontinued at least five days before entrance into the study. A baseline 12-lead electrocardiogram, chest X-ray, and blood tests evaluating hematologic, hepatic, and renal function were obtained. Patients with renal disease, hepatic disease, uncompensated congestive heart failure, or advanced degrees of heart block, as well as those of childbearing potential, were excluded.

On the first ambulatory monitoring day, a control 24-hour ambulatory electrocardiogram was recorded. On another
day, a 24-hour electrocardiographic recording was begun, and a single 300 mg oral dose of acebutolol* was administered between 10 and 30 minutes after the recording was started. Eating was not allowed during the subsequent four hours. Blood samples were obtained after one half hour and then hourly until seven hours after the drug had been given. During this period patients were observed and frequent measurements of pulse rate and blood pressure were made. On the following morning the subjects were instructed to take acebutolol, 300 mg orally every eight hours, for periods ranging from 5 to 10 days, and a final 24-hour electrocardiogram was recorded before the conclusion of that multidose period. Throughout the study, including monitoring days, patients were instructed to go about their normal daily activities, with the exception of the seven-hour blood sampling and observation period after single-dose administration. During that observation period patients were ambulatory but remained in the outpatient center. Patients taking the drug were instructed to report immediately any change in angina pattern, shortness of breath, or other adverse symptoms. All ambulatory electrocardiograms were recorded using a single-channel Avionics recorder with a modified V₁ or V₅ lead system. At the conclusion of the study, the 12-lead electrocardiogram, chest X-ray and biochemical safety tests were repeated.

Data Analysis

The magnetic tapes containing 24 hours of ambulatory electrocardiographic recording were processed using a previously described computer-based system16,17 in which PVCs are quantitated over the entire 24-hour period, and the data are expressed as PVCs per 15-minute segment (PVCs/15'). The accuracy of the quantitation is checked by sampling one representative segment of electrocardiographic signal each half hour over the duration of the recording. The PVC frequency for those minutes, as counted by the computer and the ambulatory monitoring technician, is then compared. A detailed summary of these verification data is contained in the Appendix. In all patients studied, the net percent of error was less than 10%.

Mathematical and statistical analysis of the data was carried out using standard methods. For each individual patient the mean frequency of PVCs/15' over each specified time period was calculated. The antiarrhythmic effect, expressed as percent reduction in PVC frequency, was then evaluated by comparing the mean frequency during the period of drug evaluation with that during the control period. For statistical analysis of PVC data comparing patient groups over time, square root transformation of the data for each patient, expressed as mean PVCs/15' for each hour during the 24-hour recordings, was first performed. A square root transformation is indicated when the variance of the mean is found to be proportional to the mean.18 This was the case with these data. The data for corresponding hours on control and drug days were then compared, using a two-tailed t test for paired data.

Plasma concentrations of acebutolol and its acetyl-homolog-metabolite (see fig. 1) [1-(2-acetyl-4-acetyl-amidophenoxy)-2-hydroxy-3-isopropylaminopropane] were measured by a gas chromatographic method specific for each compound. Briefly, this method involves the selective solvent extraction of the drug and its metabolite, together with an internal standard homolog and their subsequent reaction to form mixed trifluoracetyl- and trimethylsilyl derivatives, which are then separated and quantitated by gas chromatography using electron capture detection. Calibration curves, prepared by adding known amounts of acebutolol and the acetyl metabolite to plasma, were prepared in the range of 50 to 1000 ng, with an average coefficient of variation of 4% for acebutolol and 8% for the metabolite. No peaks which interfered with those of acebutolol, the acetyl metabolite, or the internal standard were observed during the analysis of pre-drug control plasmas from patients in this study. The structure of the acetyl metabolite has been confirmed by comparing extracts of plasma from patients receiving acebutolol, prepared as described for the analysis, with similarly treated authentic synthetic metabolite, using combined gas chromatography-mass spectrometry.19

The maximum, minimum, and average heart rates over 24 hours were determined from the ambulatory electrocardiograms before and during the multiple-dosing period. The PR, QRS, and QT intervals were also measured and the QT intervals corrected for heart rate according to the formula QTc = QT/R-R interval. These electrocardiographic values were compared using a two-tailed t test for paired data.

Results

Single-Patient Example

An example of data generated in this study is illustrated in figure 2. In this figure, control PVC frequency on an hour-by-hour basis is plotted with PVC frequencies for corresponding hours after a single oral dose of acebutolol, and during the multiple-dosing period. After single-dose administration, the frequency falls during the first hour and reaches its nadir five hours after drug administration. This reduction persists until hour 13, after which time the PVC frequency is approximately equal to control. This patient showed a 69% average reduction in total PVCs during the 12-

*Supplied by Ives Laboratories, New York, N.Y.
hour period following a 300 mg dose of acebutolol. The third line in this figure represents PVC frequency late in the multiple-dosing period. The low level of ectopic activity is seen to persist throughout the entire 24-hour monitoring period, and the average PVC reduction was 87%.

Single-Dose Study

Of the 12 patients studied, ten participated in the single-dose study. The remaining two patients were unable to remain in the study center for the blood sampling period. During the first 12 hours after the single 300 mg dose of acebutolol, nine patients showed a reduction in total PVCs, and one patient showed an increase (fig. 3). Figure 4 represents an hour-by-hour statistical comparison of the group as a whole, showing a reduction in PVC frequency after single-dose administration. This analysis was done in order to assess the time course of drug action. PVC suppression begins during the first hour after drug administration and persists until hour 10, after which time the frequencies are not statistically different from control frequencies. During hours 1 through 10, the reduction is statistically significant at the $P < 0.05$ level, with the exception of hours 1 and 3, which are of borderline statistical significance.

Figure 5 shows the average plasma concentrations of acebutolol and acetyl metabolite during the period following the single dose. At two hours after the dose the concentration of acebutolol is 389 ng/ml, and that of the metabolite is 402 ng/ml. Thus, at this point the concentration of the metabolite exceeds that of acebutolol. This trend continues throughout the seven hours studied. At seven hours after the dose, the mean concentrations of acebutolol and metabolite were 136 ng/ml and 445 ng/ml. The elimination half-life of acebutolol is approximately 2.5 hours, whereas the metabolite plasma concentration declines more slowly. In some individuals the decrease in plasma concentrations for the acetylated metabolite was very slow. Figure 6 shows the plasma concentrations of acebutolol and the acetylated metabolite in one patient where essentially no decrease in metabolite concentrations occurred between 5 and 7 hours after the dose.

Multiple Dose Study

All 12 patients participated in the multiple-dose study. One patient did not complete the trial period (see below). The 11 patients completing the multiple-dose period demonstrated a reduction in the average PVC frequency over 24 hours, ranging from 37 to 98% of control values (fig. 7). In eight of 11 patients, the percent reduction exceeded 70%. Figure 8 shows the hour-by-hour analysis for all 11 patients studied. A reduction in PVC frequency persists throughout the entire 24-hour monitoring period, and these changes were all statistically significant, with the exception of hour 18, which was of borderline statistical significance. This continuous PVC suppression was seen for each individual patient, as well as for the group as a whole. The phenomenon

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**Figure 2.** PVC frequency, expressed as PVCs/15', is plotted against time after start of 24-hour ambulatory electrocardiogram for control day and both single and multiple-dose drug days. Figure insert shows total reduction in PVCs, expressed as percent control, for the 12 hours following single-dose and the 24 hours during multiple-dose acebutolol therapy.

**Figure 3.** The change in total PVCs, expressed as percent control, is shown for the 12 hours after administration of a 300 mg oral dose of acebutolol.
of nocturnal decrease in PVC frequency, similar to the single-patient example (fig. 2), is observed for the group as a whole and has been noted by other authors.  

Electrocardiographic Effects of Acebutolol

Table 1 summarizes the electrocardiographic effects of acebutolol during dosing with 300 mg every 8 hours. A
reduction in average heart rate over 24 hours from 80.5 to 65.5 was noted, and in 10 of 11 patients the average heart rate decreased by ≥ 10 beats/minute (P < 0.01). Correspondingly, the peak and lowest heart rates observed during the 24-hour monitoring period were also reduced. These changes, all statistically significant, suggest that some degree of continuous beta-blockade was obtained in these patients at the dose levels administered. Asymptomatic sinus bradycardia was frequently observed, but in only one instance was the heart rate less than 50 per minute. This patient's heart rate dropped to 40 per minute while he was asleep, with no apparent ill effects.

A statistically significant lengthening of the mean PR interval from .168 to .179 seconds was noted (P < 0.01). In one instance, this resulted in a PR interval of 0.22 seconds, but no higher degrees of A-V block were seen. The QRS duration and QT interval corrected for heart rate were unchanged by acebutolol administration.

Clinical Toxicity and Laboratory Safety Testing

Toxicity to short-term acebutolol administration was assessed both clinically and by standard hematologic, hepatic and renal laboratory tests. One patient with a history of two previous myocardial infarctions and a chest X-ray showing borderline congestive heart failure complained of shortness of breath and did not complete the multiple-dose period, despite the fact that definite congestive heart failure was not documented. No other clinical toxicity was observed and no laboratory abnormalities were detected after drug administration.

Discussion

Present uncertainty concerning the most desirable therapeutic approach to stable patients with frequent PVCs and coronary artery disease reflects in part our inability to accurately identify patients at high risk for sudden death. Though frequent PVCs are a risk factor, they are a low order
Clinical sudden death prevention trials thus have been, of necessity, directed at large numbers of patients at only moderate risk of developing fatal ventricular arrhythmias. It is therefore essential that the drugs used on a prophylactic basis in these asymptomatic patients be relatively nontoxic, in addition to being effective in suppressing ventricular ectopic activity.

Most observers agree that the currently available antiarrhythmic agents are deficient in many respects. A recent study evaluating quinidine and procainamide showed these drugs to be effective in controlling PVCs to the satisfaction of the authors in less than half of treated patients. Other studies have documented drug toxicity necessitating discontinuance of these drugs in a significant percentage of patients on long-term therapy. These two agents, furthermore, have rather short half-lives, making patient compliance with effective therapeutic regimens difficult. Propranolol, though generally better tolerated than procainamide and quinidine, also controlled ventricular ectopic beats in less than half of the patients studied by ambulatory electrocardiographic monitoring. However, comparisons of efficacy between different antiarrhythmic drugs are difficult to make because of differences in the patient populations studied and the dosage regimens used.

The present report details the results of short-term administration of the relatively cardioselective beta-blocking drug, acebutolol, to ambulatory outpatients with frequent PVCs. In eight of ten patients studied, a single 300 mg oral dose of acebutolol resulted in a reduction of greater than 50% in total PVCs in the 12 hours following its administration. Analysis indicated that a statistically significant arrhythmia reduction persisted for 10 hours after single-dose administration.

During dosing with 300 mg of acebutolol every 8 hours, all patients studied showed a decrease in total PVCs during the 24-hour monitoring period compared with control. In eight of 11 patients, this reduction was greater than 70% of control. Analysis of PVC frequencies over time indicated that this arrhythmia suppression was present throughout the 24-hour monitoring period. These latter data show the continued suppression of PVCs by acebutolol when it is administered on an 8-hourly basis. This represents an advantage of acebutolol over antiarrhythmic drugs currently in use, all of which are usually given at shorter than 8-hour dosing intervals in order to control arrhythmias. Such regimens necessitate the patient's awakening at night to take medication, often resulting in poor compliance.

It is noteworthy that these results were obtained with a paucity of deleterious side effects. Clinical toxicity was minimal and resulted in withdrawal of the drug in only one patient. Laboratory and electrocardiographic evidence of toxicity were not encountered. Thus, in this preliminary short-term study, we found acebutolol to be well tolerated in our patients.

The antiarrhythmic potency of the acetyl metabolite is unknown at this time. It is probable, because of its general chemical structure, that the high plasma concentrations of the acetyl metabolite noted in this study contribute significantly to the antiarrhythmic effect seen following the oral administration of acebutolol.

Recently, three controlled studies two with alpenrolol and one with practolol, demonstrated that long-term prophylactic administration of beta-blocking agents to survivors of myocardial infarction resulted in a decreased incidence of sudden death. Whether this was due to prevention of lethal arrhythmias or was affected by other mechanisms is unclear from these studies. Future drug intervention studies using ambulatory electrocardiographic recordings will be required to determine whether reduction in the incidence of sudden death is seen in that subgroup of patients who demonstrate a reduction in asymptomatic arrhythmias. Acebutolol, if found to be free of long-term toxicity, may be a drug suitable for such an intervention study.

In summary, acebutolol was found to be effective in suppressing PVCs, was well tolerated, and was possessed of a sufficiently long duration of action to permit convenient dosage scheduling. Extrapolation of these results, obtained in a small group of patients, to larger populations awaits further studies.

Acknowledgment

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References


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APPENDIX 1

Summary of PVC Verification Data

<table>
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<td>340</td>
<td>4.1</td>
<td>2.0</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Abbreviations: No. = number; PVCs = premature ventricular contractions.
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A H Gradman, R A Winkle, J W Fitzgerald, P J Meffin, J Stoner, 3rd, P A Bell and D C Harrison

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