Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias

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ABSTRACT  Sotalol is a unique β-blocker that lengthens cardiac repolarization and effective refractory period (ERP). Its efficacy after intravenous (1.5 mg/kg) and oral (160 to 480 mg bid) administration was therefore evaluated in 37 patients with refractory recurrent ventricular tachycardia/fibrillation (VT/VF). Thirty-five patients, 33 with inducible VT/VF, underwent electrophysiologic testing. Intravenous sotalol lengthened the ERP in the atrium (+24.6%, p < .01), atrioventricular node (+24.9%, p < .01), and ventricle (+14.9%, p < .01). It also significantly lengthened sinus node recovery time, corrected QT interval (QTc), and the AH interval, but not the HV interval. Sotalol prevented reinduction of VT/VF in 15 patients (45.5%). Twenty-five of the 33 patients (15 with positive results of electrophysiologic tests; 10 with negative results) were given oral sotalol. The drug was ineffective in seven (26.9%) and aggravated arrhythmia in one (3.8%). In four patients sotalol was withdrawn because of side effects; arrhythmias recurred late in two (7.7%). Eleven patients (42.3%) have continued on oral sotalol over a mean follow-up period of 9.2 ± 8.6 months. Sotalol reduced (n = 21) total premature ventricular complex (PVC) count on the Holter electrocardiogram by 73% (p < .01), paired PVCs by 89% (p < .01), and beats of ventricular tachycardia by 95% (p < .01). In 52% (n = 11), total reduction in PVCs was at least 85%, and incidence of paired and tachycardic beats was reduced at least 90% (group A). In the remainder (n = 10), PVC suppression was not significant (group B). Group A included nine patients with nonreinducible VT/VF and two in whom it was inducible; in group B, eight of 10 patients had inducible VT/VF. The difference between the two groups (Fisher exact test) was significant (p < .01). The prevention of reinduction of VT/VF by intravenous sotalol and suppression of spontaneously occurring arrhythmias by the oral drug were both predictive of long-term drug efficacy. Sotalol is a significant advance in the short- and long-term management of life-threatening ventricular tachyarrhythmias.


ALTHOUGH SOTALOL was introduced as a specific β-blocking drug 24 years ago,¹ interest in it as a broad-spectrum antiarrhythmic compound has been relatively recent.²–⁴ In 1970 Singh and Vaughan Williams,⁵ and subsequently Strauss et al.,⁶ showed that in concentrations somewhat greater than those required to produce significant β-blocking activity in isolated cardiac muscle, sotalol consistently lengthened the action potential duration without effect on the upstroke velocity of phase 0 of the action potential. The drug, administered intravenously, was found to prolong the corrected QT interval (QTc) of the surface electrocardiogram in anesthetized guinea pigs in which the compound prevented the onset of ventricular fibrillation due to ouabain toxicity.⁷ Since these overall electrophysiologic and antiarrhythmic actions differed from those of either the quinidine-like drugs or other β-antagonists, sotalol was thought to act by homogeneously lengthening cardiac repolarization and refractoriness.⁸

Subsequent studies in patients have confirmed that sotalol administered over the both the short and long term lengthens repolarization and refractoriness in the heart.⁹–¹¹ Its so-called class III⁴ antiarrhythmic actions have also been confirmed from the direct recordings of monophasic action potentials via suction electrodes in
However, there remains a paucity of data dealing with the effect of sotalol on cardiac arrhythmias. The purpose of the present study was to evaluate the efficacy and safety of sotalol in patients with symptomatic, sustained, life-threatening ventricular tachyarrhythmias. The study was conducted in two parts. In the first, the effects of the intravenously administered drug on the inducibility of ventricular tachycardia by programmed electrical stimulation of the heart relative to the electrophysiologic actions of the compound were determined. In the second, the effects of the orally administered drug on spontaneously occurring tachyarrhythmias documented on 24 hr ambulatory electrocardiographic recordings relative to the dose and plasma concentrations of the drug were evaluated.

**Materials and methods**

**Patients.** The study population consisted of 37 patients who had clinically manifest sustained symptomatic recurrent ventricular tachycardia and/or ventricular fibrillation (VT/VF). There were 36 male and one female patient with a mean age of 58 (range 25 to 72) years. None had an identifiable reversible cause of the ventricular arrhythmia or recent myocardial infarction (i.e., in the 4 weeks immediately before the study). Except for one patient who had sarcoidosis, all others had coronary artery disease. The mean ejection fraction measured either by contrast or radionuclide ventriculography for 23 patients was 33.0 ± 14.0%. Patients in whom there was a contraindication to β-blockade or who had evidence of decompensated cardiac failure were excluded from the study. Data from two patients in whom ventricular tachycardia could not be induced during the control study were excluded from analysis (see below). All patients except one had failed on or had not tolerated one or more (mean number, 2.76 ± 1.3) conventional antiarrhythmic drugs. In two patients with recurrent and frequent VT/VF that had not responded to intravenous lidocaine, procainamide, and bretylium tosylate, intravenous sotalol was given but electrophysiologic studies were not done either before or after the drug was given because of clinical exigencies. These patients were both men, and were 55 and 67 years old.

**Protocol.** All patients were admitted to the coronary care unit for continuous electrocardiographic monitoring. Previously prescribed antiarrhythmic drugs were discontinued for at least five elimination half-lives of these agents. Whenever possible a 24 hr ambulatory electrocardiographic recording was obtained at a time the patients were not taking any other antiarrhythmic drugs. This recording served as a baseline with respect to the spontaneously occurring tachyarrhythmias and was subsequently used for gauging the efficacy of drug therapy. Thirty-five patients underwent electrophysiologic studies for the evaluation of the effects of 1.5 mg/kg iv sotalol hydrochloride (Bristol-Myers, Evansville, IN), administered over a period of 5 to 10 min, on the inducibility of ventricular tachycardia relative to the electrophysiologic effects and plasma concentrations of the drug. Oral sotalol was started if the intravenous drug prevented the inducible VT/VF. However, a patient was started on the oral regimen even if the intravenous drug failed to prevent the inducible tachycardia, provided the baseline 24 hr Holter recording demonstrated significant ventricular ectopy so that the changes in the severity of the spontaneously occurring arrhythmias could be used as an index for judging the effects of the oral drug. Oral sotalol was not given to any patient in whom ventricular tachycardia was induced while he was on the intravenous drug and who did not exhibit frequent ventricular arrhythmias on 24 hr Holter recordings.

The initial oral dosage was 160 mg bid. In some patients the dose was increased in a stepwise fashion to 320 or 480 mg bid, respectively, if ventricular tachycardia was not controlled at the lower dose or if the goal of therapy was not met according to the Holter recordings. This goal was 85% suppression of the mean premature ventricular complexes (PVCs) and 90% suppression of paired PVCs and beats of ventricular tachycardia (three or more PVCs in a row exceeding a rate of 100 beats/min). The criterion for drug failure was the occurrence of VT/VF or cardiac arrest on oral sotalol. Oral sotalol was discontinued when clinical VT/VF occurred or side effects precluded the continuation of the drug therapy. The patients in whom sotalol was not effective were subsequently treated with amiodarone empirically, beginning with a loading dose followed by a maintenance regimen.

After the in-hospital stabilization period and control of the ventricular arrhythmias, the patients were discharged on sotalol and their clinical progress was followed at 3 month intervals in the arrhythmia clinic. The protocol was reviewed and approved by the Wadsworth Hospital Research Committee for the Protection of Human Subjects.

**Electrophysiologic studies.** Studies were performed in the electrophysiologic laboratory in patients in the preabsorptive state who had not received premedication. Electrode catheters were inserted percutaneously and positioned at multiple cardiac sites under fluoroscopic control. The recording sites included the high right atrium, His bundle, and right ventricular apex. Standard quadrupolar electrode catheters with 1 cm interelectrode distance (USCI, Billerica, MA) were used for stimulation and recording from specific sites. Surface electrocardiographic leads I, aVF, and V₁ were displayed simultaneously with the intracardiac signals and were recorded on a VR-12 (Electronics for Medicine) recorder at a paper speed of 100 mm/sec. Cardiac stimulation was performed with a programmable constant-current stimulator (Medtronic 5325) that delivered rectangular pulses of 2 msec duration at twice the diastolic threshold. Intracardiac electrograms were filtered at 30 to 500 Hz. The right atrial, right ventricular, and atrioventricular nodal (when possible) refractory periods were obtained with the extrastimulus method. Sinus node recovery time was determined by pacing the right atrium at incrementally higher fixed pacing rates at 1 min intervals to a maximum of 170 beats/min or until atrioventricular nodal Wenckebach block developed.

**Ventricular tachycardia induction protocol.** VT/VF was induced by programmed electrical stimulation (PES) with the following protocol: (1) Premature right ventricular stimulation with single (S₀) or double (S₀S₁) extrastimuli was used during ventricular pacing or sinus rhythm. The S₀S₁ technique was used when S₀ during scanning from late diastole to ventricular refractoriness did not induce tachycardia. S₀S₁ extrastimuli were introduced at an S₀S₁ interval 50 msec longer than the ventricular refractory period, with the S₀S₁ interval being equal to the S₀S₁ interval. The S₀S₁ interval was progressively shortened, and when S₀ failed to elicit a V₁, the S₀S₁ interval was decreased until S₁ did elicit a response or until tachycardia developed. This technique was used until both S₀ and S₁ reached ventricular refractoriness. At least three cycle lengths (sinus and 600, 500, and 400 msec) were used sequentially in every patient. (2) If ventricular tachycardia could not be elicited this way, brief bursts of rapid ventricular pacing at the cycle length close to the ventricular refractory period were undertaken for 10 beats. If no inducible tachycardia resulted from use of either technique, the right ventricular outflow tract was stimulated by
a technique identical to that used for the stimulation of the right ventricular apex. (3) Repeat electrophysiologic studies after 10 min of sotalol infusion were performed in the same manner as those during the baseline period. The protocol for ventricular stimulation was identical to that described above and we went through at least three cycle lengths sequentially before considering that ventricular tachycardia was not inducible (see below for the definition of inducible ventricular tachycardia). We stimulated only the right ventricular site at which tachycardia was produced before sotalol was tested. (4) During ventricular tachycardia, programmed single or double extrastimuli and rapid ventricular pacing were used to terminate the arrhythmia: cardioversion was used in refractory cases or for hemodynamic deterioration.

Definition of sustained vs nonsustained ventricular tachycardia. A sustained tachycardia was defined as one that persisted for at least 30 sec and required pacing or external defibrillation for termination. Nonsustained tachycardia was defined as that which persisted for at least 6 beats and reverted to sinus rhythm spontaneously within 30 sec.

Analysis of Holter electrocardiographic intervals. The electrocardiogram was analyzed for alterations in PR, QRS, and QT intervals before and after the drug was given. The QTc interval was obtained from the formula: QTc = QT/VRR. The 24 hr Holter tapes were analyzed commercially (Cardio-Data, Haddonfield, NJ) for mean heart rates, total number of PVCs per 24 hr, and paired and total beats of ventricular tachycardia per 24 hr.

Measurement of sotalol plasma levels. Plasma levels were determined by high-performance liquid chromatography by the method described by Karkkainen and Neuovonen. The blood samples were obtained shortly after intravenous injection of sotalol and during long-term administration of drug.

Data and statistical analysis. The data are presented as mean ± SD. Student’s t test for paired data (two-tailed) was used to evaluate the significance of the changes in various parameters at baseline and during sotalol therapy. The Fisher exact test was used when appropriate. A probability less than .05 was accepted as the limit of statistical significance.

Results

Electrophysiologic effects of intravenously administered sotalol. Of the 37 patients enrolled in the study, 35 patients underwent electrophysiologic studies. The effects of 1.5 mg/kg iv sotalol could be evaluated in 33. The time course of change in the mean plasma levels of sotalol measured in 14 patients is shown in figure 1. The range of plasma levels of sotalol at 10 min after administration of the drug was 982 to 12,096 ng/ml (the latter high value was recorded in only one patient, the remainder having levels lower than 4000 ng/ml), 1208 to 3123 ng/ml after 20 min, and 917 to 1685 ng/ml after 30 min.

The mean data on the effects of sotalol on various electrophysiologic parameters are summarized in table 1. The effects of the drug were characterized essentially by a prolongation in the effective refractory (ERP) period in all tissues, with an increase in the intranodal conduction time. Intravenous sotalol reduced the heart rate by 29.4% (p < .01) and lengthened the intranodal conduction time.

FIGURE 1. The time course of plasma sotalol levels after intravenous injection of 1.5 mg/kg of the drug in patients undergoing electrophysiologic studies. The data points represent means ± SD for 14 patients.

(AH) conduction time by 17.8% (p < .01), but it had no significant effect on intranodal conduction (HV interval). Sotalol did, however, increase the QTc interval (+10.8%, p < .01), as well as the ERP in the atrium (+24.6%, p < .01), atrioventricular node (+24.9%, p < .01), and ventricle (+14.9%, p < .01). In the case of the ventricle, the ratio QTc/ERP was 1.65 before sotalol was given and 1.59 after the drug. The difference was not statistically significant.

Effects of intravenous sotalol on inducibility of ventricular arrhythmias (tables 2 and 3). Electrophysiologic studies were not undertaken in two of the 37 patients. These patients (Nos. 25 and 26) had incessant VT/VF in the coronary care unit; they were given intravenous sotalol intermittently for control of arrhythmias (figure 2). While the control of VT/VF was achieved, one of the patients died of anoxic brain damage because of recurrent cardiac arrests suffered before institution of sotalol therapy, and the other died from acute myocardial infarction. Of the remaining 35 patients, ventricular tachycardias could not be induced in two patients and their data were excluded from the final analysis. Therefore the effect of sotalol on the clinical outcome could be assessed in a homogeneous group of 33 patients in whom VT/VF could be provoked by PES. Of these 33 patients, 24 had inducible sustained ventricular tachycardia, eight had nonsustained tachycardia, and one had ventricular fibrillation. Intravenous sotalol prevented the induction of VT/VF in 15 patients (45.5%), but did not prevent it in 18 (in nine induced ventricular tachycardia was sustained and in nine it was nonsustained). Sotalol converted a sustained tachycardic response to a nonsustained one in three patients (9.1%; see table 2). However, the latter was not
considered to be a "protective" response. In those patients in whom the drug did not suppress ventricular tachycardia, the cycle length of the inducible tachycardia increased from 256 ± 65 to 306 ± 77 msec (± 19.5%, p < .05). No systemic relationship was found between the lengthening of the ERP by sotalol and its effect on the inducibility of ventricular tachycardia by PES of the heart. However, the possibility of such a relationship is not excluded by the data because of the limited number of patients studied in this series.

The clinical outcome in patients with inducible vs noninducible VT/VF after intravenous sotalol relative to the subsequent administration of oral sotalol was as follows. Of the patients in whom intravenous sotalol prevented inducible VT/VF (n = 15), the arrhythmia could be controlled in 13 (86.7%) by oral sotalol; the drug failed early (within the first month) in one and appeared to aggravate the condition of another. During long-term therapy (longer than 1 month), arrhythmia recurred in two patients (at 8 and 8.4 months), and side effects precluded the continued use of the drug in an additional two patients. Eight patients remain free of arrhythmias and without side effects during a mean follow-up period of 14.5 ± 7.5 (range 2 to 23) months. Of 18 patients in whom sotalol failed to suppress VT/VF, oral sotalol was given to 10; in the other eight it was not given because they did not have significant PVCs on baseline ambulatory electrocardiographic recordings. Of the 10 patients who were given oral sotalol even though they had inducible ventricular tachycardia after intravenous sotalol, six had recurrent VT/VF and one had a limiting side effect. The remaining three patients have been free of arrhythmias (mean follow-up 8.6 months, range 8 to 9). In the patients treated with 160 mg bid oral sotalol the mean plasma levels were 2.3 ± 0.8 μg/ml (n = 6) and levels of 3.1 ± 0.4 μg/ml (n = 3) were found in those treated with 320 mg bid.

Effects of orally administered sotalol on spontaneously occurring ventricular tachyarrhythmias. This could be evaluated in 21 of 25 patients on oral sotalol in whom baseline 24 hr ambulatory electrocardiographic recordings (obtained while they were off all antiarrhythmic drugs and showing high-density PVCs exceeding 30 beats/hr) were obtained under control conditions and when a steady-state level of sotalol was reached during oral administration. The overall data relative to the inducibility of VT/VF and clinical outcome are presented in table 2.

The mean data showed that sotalol reduced the total PVC count by 73% (p < .01), paired PVCs by 89% (p < .01), and beats of ventricular tachycardia by 95% (p < .01). In 11 of the 21 patients, sotalol reduced total PVCs by at least 85%, and paired PVCs and tachycardic beats by at least 90% (group A). In the other 10 patients, sotalol did not significantly suppress spontaneously occurring arrhythmias (group B). There was no systematic relationship between changes in heart rate and the degree of PVC suppression by sotalol.

As is evident in table 2 and figure 3, A, group A (11 patients) included nine patients in whom ventricular tachycardia could not be reinduced and two in whom it remained inducible. By contrast, ventricular tachycardia remained inducible in eight of 10 patients in group B. Analysis by Fisher exact test showed that group A included a significantly greater number of patients

### Table 1: Electrophysiologic effects of intravenously administered sotalol in patients with life-threatening ventricular tachycardia

<table>
<thead>
<tr>
<th>Electrophysiologic parameters (msec)</th>
<th>Baseline</th>
<th>After sotalol</th>
<th>Percentage change from control</th>
<th>Significance of change from control</th>
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<tbody>
<tr>
<td>RR interval</td>
<td>738.2 ± 163</td>
<td>955 ± 182</td>
<td>+ 29.4</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>AH</td>
<td>85.7 ± 20.0</td>
<td>101 ± 24.36</td>
<td>+17.8</td>
<td>p &lt; .01</td>
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<td>HV</td>
<td>59.6 ± 18.2</td>
<td>60.9 ± 19.8</td>
<td>+2.2</td>
<td>NS</td>
</tr>
<tr>
<td>QTc</td>
<td>397 ± 50</td>
<td>440 ± 40</td>
<td>+10.8</td>
<td>p &lt; .05</td>
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<tr>
<td>Atrial ERP</td>
<td>248.4 ± 39.0</td>
<td>309.4 ± 52.3</td>
<td>+24.6</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>AVN ERP (anterograde)</td>
<td>345.5 ± 59.0</td>
<td>431.4 ± 61.4</td>
<td>+24.9</td>
<td>p &lt; .01</td>
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<tr>
<td>AVN Wenckebach cycle length</td>
<td>371.1 ± 65.4</td>
<td>466.1 ± 84.1</td>
<td>+25.6</td>
<td>p &lt; .01</td>
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<tr>
<td>Ventricular ERP</td>
<td>240.6 ± 29.1</td>
<td>276.6 ± 27.5</td>
<td>+14.9</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>SNRT</td>
<td>870.4 ± 275.4</td>
<td>1149.5 ± 405.2</td>
<td>+32.0</td>
<td>p &lt; .01</td>
</tr>
</tbody>
</table>

The data represent mean ± SD data from 33 patients to whom sotalol (1.5 mg/kg iv) was given during electrophysiologic study. The significance of the difference between the control value of a particular parameter and that after sotalol was tested by Student’s paired (two-tailed) t test.

AVN = atrioventricular node; SNRT = sinus node recovery time.
with noninducible ventricular tachycardia than did group B (p < .01). Moreover, in group A (figure 3, B) there were only two patients (18%) who had recurrent VT/VF whereas there were seven patients in group B with recurrent VT/VF (70%, p < .06). Two patients in group A and one patient in group B had significant side effects necessitating discontinuation of drug therapy.

### TABLE 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PVC/hr Control</th>
<th>Paired PVC's/24 hr Control</th>
<th>VT/24 hr Control</th>
<th>Dose (mg bid)</th>
<th>VT induction Control</th>
<th>Sotalol</th>
<th>Clinical outcome</th>
<th>Duration of therapy (months)</th>
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<tr>
<td>1</td>
<td>49</td>
<td>83</td>
<td>20</td>
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<td>yes</td>
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<td>2</td>
<td>311</td>
<td>402</td>
<td>76</td>
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<td>6</td>
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<td>7</td>
<td>201</td>
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<td>226</td>
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<td>53</td>
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<td>3548</td>
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<td>2995</td>
<td>yes</td>
<td>no</td>
<td>VT recurrence; given Am</td>
<td>1.4</td>
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</table>

**Mean** 484 179 1893 202 2947 430  
**± SD** 446 323 1291 417 1242 118 
**p value** < .01 < .001 < .001

*VT = ventricular tachycardia; Am = amiodarone; CHF = congestive heart failure.*

*Conversion of sustained VT to nonsustained VT.*

*The level of significance refers to the difference between control and sotalol periods.*

**Adverse reactions.** During the intravenous administration of sotalol there were no significant hemodynamic disturbances in the patients. In four patients, distal atrioventricular block developed transiently: the details on this effect will be reported elsewhere. 

During oral administration, lethargy, weakness, and fatigue developed in four patients and were depres-
ven tricular fibrillation; all other abbreviations are as in table 2.

3 Patient had coronary artery disease and previous myocardial infarction with a left ventricular ejection fraction of 26%. He had over 100 episodes of fibrillation in the cardiac care unit before he was given sotalol. The possibility that the recurrence of fibrillation was caused by antiarrhythmic drugs was ruled out.

**Summary of overall clinical outcome.** Thirty-three patients who had inducible ventricular tachycardia during the control period were followed to determine clinical outcome. Of the 33 patients, 25 (15 with positive results of electrophysiologic tests; 10 with negative results) were given oral sotalol. Arrhythmia was aggravated early in one (3.8%) and in seven (26.9%) the drug was not effective during the dose adjustment period (over the first month). In four patients the drug was withdrawn because of side effects (three early and one late); late occurrence of the arrhythmia supervened in two (7.7%). Eleven patients (42.3%) currently continue on oral sotalol without significant side effects or recurrence of arrhythmia over a mean follow-up period of 9.2 ± 8.6 months.

Of the 22 patients who were either not initially given oral sotalol (n = 8) or did not respond to or tolerate sotalol (n = 14), one was subsequently treated with flecainide and 21 were given amiodarone in the manner previously described.18 The patient given flecainide developed incessant VT/VF in-hospital and could not be resuscitated. In the remaining patients, during a minimum follow-up period of 6 months, there have been two cases of sudden death. Another patient failed to respond to amiodarone and underwent successful surgical treatment for his ventricular tachycardia. Eighteen patients continue to be treated with amiodarone and remain free of arrhythmias and limiting side effects.

**Discussion**

Although the β-blocking properties of sotalol have been recognized for about two decades, interest in its clinical antiarrhythmic actions resulting from its non-β-blocking activity has been relatively re-
It has followed in the wake of reports that have demonstrated the unusually potent actions of amiodarone, a drug that is thought to act, at least in part, by lengthening cardiac repolarization. This prolongation of the action potential duration and the corresponding increase in refractoriness is also produced by sotalol.5-9 Thus, there has always been a sound theoretical basis for significant electrophysiologic and antiarrhythmic actions of sotalol in man. In recent years, there have been experimental10 and clinical reports that have indicated that such effects of sotalol differ from those of conventional β-blocking drugs.14,19 Our data clearly establish the broad-spectrum electrophysiologic effects produced by the drug after intravenous administration in man. They also provide further confirmatory evidence of the efficacy of the drug in the control of life-threatening ventricular tachyarrhythmias, both in terms of preventing the inducibility of VT/VF and in suppressing spontaneously occurring arrhythmias documented on baseline Holter recordings.

**Electrophysiologic effects.** It is now well established that sotalol, unlike other β-adrenergic–blocking drugs,21 lengthens the duration of the cardiac action potential,2,4-9 and hence the QTc interval, of the surface electrocardiogram.5,22 The electrophysiologic effects noted in our study in man are consistent with these observations. Our data confirm and extend the earlier clinical reports that the drug significantly lengthens the effective refractory period of all cardiac tissues2-4 and, as in patients on long-term amiodarone treatment,18 it prolongs the monophasic cardiac action potentials as recorded by suction electrodes placed in intracardiac chambers.7-9 In our studies, the intravenously administered drug increased the ERP more in the atria than in the ventricle. There was also a significant increase in this parameter corresponding to an increase in the QTc interval and the slowing of the ventricular tachycardia cycle length in patients in whom the drug did not prevent the induction of the arrhythmia. The drug had no effect on the HV interval, its depressant effect on conduction being confined to intranodal conduction. Such an aggregate of electrophysiologic effects is not the result of calcium antagonism, inhibition of the myocardial sodium channel, or β-blockade alone. Instead, these effects suggest that

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**FIGURE 2.** Effects of intravenous sotalol in a patient with recurrent VT/VF resistant to lidocaine, procainamide and bretylium.  
*Top,* The characteristic patterns of incessant ventricular tachyarrhythmias uncontrolled by conventional antiarrhythmic therapy.  
*Bottom,* The changes in the total PVC count and number of episodes of ventricular tachycardia before and after the intravenous injection of sotalol. Note that after sotalol was given, there were no further recurrences of VT/VF.
the somewhat unique electrophysiologic properties of the drug are due to the combined effects of β-blockade and the lengthening of the cardiac action potential.

Antiarhythmic efficacy. In our study, intravenous sotalol prevented the reinduction of VT/VF in 45.5% of the patients, a figure that is generally higher than those reported for the so-called membrane-active or class I compounds. There is little data on this issue for other class III agents, with the exception of amiodarone, which has been reported to prevent reinduction of VT/VF after long-term therapy in 8% to 50% of patients. However, Senges et al., recently showed that in their hands, intravenous sotalol prevented reinduction of VT/VF in 12 of 18 patients (67%), which is a somewhat higher success rate than that in our own series in which VT/VF became noninducible in 15 of 33 patients after intravenous sotalol. The VT/VF of nine of 12 patients in the previous study, who were subsequently treated with oral sotalol over the long term, was completely or partially controlled over a mean follow-up period of 16 months. Our own data on long-term oral therapy is in line with their observations. For example, in 13 of the 15 patients (85.7%) in whom intravenous sotalol had prevented reinduction of VT/VF, early control of arrhythmia was achieved with oral sotalol; in one of the remaining two the arrhythmia was aggravated and in the other there was no effect. Late arrhythmias occurred in only two of the 13 patients, and side effects necessitating drug withdrawal developed in three at a time when their arrhythmias were controlled. Over a mean follow-up of 14.5 (range 6 to 24) months, eight patients have continued to be treated without recurrence of arrhythmias or the development of side effects. Thus, in 11 of 15 patients (73.3%), sotalol was effective over both the short and long term, although only eight could tolerate long-term therapy. In contrast, oral sotalol was effective in the long-term control of arrhythmias in only three of 10 (30%) of those in whom the intravenous drug had failed to prevent induction of VT/VF. Although the number of patients in our series has been limited, there appears to be a trend indicating the clinical utility of electrophysiologic testing in predicting long-term effectiveness of oral sotalol in controlling VT/VF. Our data, as well as those of Senges et al., have dealt with the predictive value of the response to intravenous sotalol and do not exclude the possibility that a greater predictive accuracy with respect to the inducibility of VT/VF might be attained by the use of oral drug testing.

Our data also demonstrate that orally administered sotalol is moderately effective in suppressing PVCs, particularly complex and repetitive forms. In over 50% of patients, the drug was found to suppress at least 85% of total PVC counts and nearly abolish complex forms (paired PVCs and tachycardia beats), a feature that was concordant with drug-induced prevention of induction of VT/VF by PES of the heart when evaluated in the same patients (table 2 and figure 3). Furthermore, 70% of the patients in whom sotalol was found to be effective in suppressing spontaneously occurring ventricular arrhythmias on Holter recordings have continued to do well clinically and to remain free of their arrhythmias. In contrast, only 20% of the patients in whom sotalol did not suppress PVCs on Holter recordings remained free of arrhythmias; the remaining 70% had recurrence of arrhythmias or side effects. It was note-
worthy that no systematic relationship could be established between the magnitude of heart rate reduction and the degree of PVC suppression induced by sotalol. However, the reduction in resting heart rate is a crude index of β-blockade and the contribution of β-antagonism to the observed suppression of PVCs by sotalol cannot be excluded as a possibility. A comparison of the effects of sotalol demonstrated here with those of conventional β-blockers21 nevertheless suggests that the major antiarrhythmic effects of the drug in patients with life-threatening VT/VF refractory to conventional antiarrhythmic drugs. Our preliminary data suggest that sotalol has a lower order of potency than amiodarone, another class III antiarrhythmic drug, but that it has a more predictable side effect profile. Sotalol appears to have low arrhythmogenic potential and since it has a rapid onset of action with a predictable long-term outcome, as determined by electrophysiologic testing after intravenous administration, it appears to represent a significant advance in the short-term and prophylactic management of ventricular tachyarrhythmias.

Arrhythmogenicity and other adverse reactions. Previous reports have suggested that torsade de pointes in association with QTc prolongation may complicate the course of sotalol therapy.24-28 However, most such cases have occurred in the context of drug overdose or of significant hypokalemia. Neither in our series nor in that of Senges et al.14 was torsade de pointes encountered. In one of our patients, there was a marked increase in the frequency of all categories of PVCs and nonsustained runs of ventricular tachycardia. Fibrillation in another patient who had previously experienced this arrhythmia while on sotalol was documented.

The remainder of the side effects noted in our study, as in those of Senges et al.,14 could be attributed to β-blockade, but it is noteworthy that heart failure was exacerbated in only one patient despite the mean low ventricular ejection fraction in the group given oral sotalol. This is in line with the report by Brooks et al.,29 who showed that the intravenous drug, unlike other β-blockers, had little or no depressant effect on systemic hemodynamics in patients with heart failure. It would therefore appear that lengthening of the action potential duration induced by the drug augments contractility, a phenomenon that has been demonstrated in isolated cardiac muscle.5,30 Such an effect may, in part, offset the depressant effect of β-blockade in the patient with cardiac decompensation, a feature that distinguishes sotalol from conventional β-blocking drugs.

In summary, our data show that sotalol is an effective antiarrhythmic compound for a significant number of patients with life-threatening VT/VF refractory to conventional antiarrhythmic drugs. Our preliminary data suggest that sotalol has a lower order of potency than amiodarone, another class III antiarrhythmic drug, but that it has a more predictable side effect profile. Sotalol appears to have low arrhythmogenic potential and since it has a rapid onset of action with a predictable long-term outcome, as determined by electrophysiologic testing after intravenous administration, it appears to represent a significant advance in the short-term and prophylactic management of ventricular tachyarrhythmias.

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