Electropharmacology of sotalol in patients with Wolff-Parkinson-White syndrome

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ABSTRACT The β-adrenoceptor–blocking and class III effects of sotalol were assessed in 11 patients with inducible orthodromic reciprocating tachycardia. Serum sotalol concentration, maximum exercise heart rate, and electrophysiologic study data were obtained at control, at the β-adrenoceptor–blocking dosage (407 ± 149 mg/day, 1.4 ± 0.5 μg/ml), and at the maximum well-tolerated dosage (924 ± 337 mg/day, 3.2 ± 1.3 μg/ml). Class III effects (increases in anterograde and retrograde accessory connection effective refractory periods, ventricular effective refractory period, and the QT interval during fixed-rate atrial pacing) were evident at the β-adrenoceptor–blocking dosage of sotalol and became more marked at the maximum well-tolerated dosage. For example, the mean anterograde accessory connection effective refractory period was significantly increased over control (272 ± 41 msec) by the β-adrenoceptor blocker (324 ± 52 msec) and was further significantly increased by the maximum well-tolerated dose (364 ± 37 msec). Similarly, the minimum preexcited RR interval during atrial fibrillation was increased in all patients at each dosage tested. Antiarrhythmic efficacy, defined by the absence of inducible, sustained, orthodromic reciprocating tachycardia and a minimum preexcited RR interval during atrial fibrillation of 300 msec or greater, was achieved in four patients at the β-adrenoceptor–blocking dosage and in another four patients at the maximum well-tolerated dosage. These eight patients received long-term sotalol therapy and none has had recurrent, sustained reciprocating tachycardia during 15 ± 12 months of follow-up. Therefore, although class III effects of sotalol occur at β-adrenoceptor–blocking dosages, higher dosages increase class III effects and antiarrhythmic efficacy in the setting of the Wolff-Parkinson-White syndrome.


SOTALOL is a newer antiarrhythmic agent with both β-adrenoceptor–blocking and class III electrophysiologic activity.1–6 Although its antiarrhythmic efficacy had been documented for ventricular arrhythmias,7–11 the efficacy and safety of oral sotalol therapy for the supraventricular tachyarrhythmias complicating Wolff-Parkinson-White (WPW) syndrome have not been assessed systematically. The β-adrenoceptor–blocking effects of sotalol should be advantageous in the treatment of the reciprocating tachycardias of WPW syndrome primarily by slowing conduction and prolonging refractoriness of the atrioventricular (AV) node. However, in these patients with accessory AV connections, isolated β-adrenoceptor blockade may fail to control and may even accelerate the ventricular response rate to atrial fibrillation.12–15 In distinction to other β-adrenoceptor–blocking agents, the additional class III effects of sotalol should contribute to efficacy in the treatment of the reciprocating tachycardias of WPW syndrome primarily by prolonging refractoriness of the accessory connection. Furthermore, class III activity can also reduce the ventricular response rate to atrial fibrillation.16 Therefore, a major determinant of the balance between efficacy and safety of sotalol therapy in patients with the WPW syndrome will be the dose ranges over which these two classes of electrophysiologic effects are manifest.

The purpose of this study was to determine the dosage range over which the β-adrenoceptor–blocking and class III electrophysiologic effects of sotalol become manifest and to determine the relative contributions of these effects to the safety and antiarrhythmic efficacy of sotalol in patients with WPW syndrome.
Methods

Protocol. Eleven adult patients with WPW syndrome and drug-resistant, supraventricular tachyarrhythmias consented to participate in this study. The study protocol (figure 1) was approved by our Institutional Ethics Review Board. All medications were discontinued for five half-lives and a baseline exercise test and catheter electrophysiologic study were performed. Oral sotalol therapy was then introduced at a dosage of 80 mg twice daily. The dosage was doubled every 3 days until antiarrhythmic efficacy was documented, side effects occurred, or a maximum dosage of 640 mg twice daily was reached. Measurement of trough serum sotalol levels and exercise testing were repeated on the third day of each dosage. The electrophysiologic study was repeated at the 160 mg twice daily and subsequent dosage levels.

Study population. Seven men and four women with supraventricular tachyarrhythmias secondary to WPW syndrome participated. Their mean age was 33 ± 11 years (range 19 to 50). Ten patients had no other structural heart disease. One had coexistent arrhythmogenic right ventricular dysplasia. These patients had had unsuccessful therapy with 3.3 ± 1.7 antiarrhythmic drugs (range 1 to 5). All patients had inducible, sustained, orthodromic reciprocating tachycardia.

Exercise testing. Symptom-limited, treadmill exercise tests were performed according to a Bruce protocol.17 Maximum exercise heart rates were determined from the average of 10 consecutive beats. The sotalol dosage resulting in physiologic β-adrenergic blockade was defined as that which caused minimal further reduction in the maximum exercise heart rate. Specifically, the dosage in use when the maximum heart rate was reduced by less than 10% from the previous exercise test was termed the β-adrenergic-blocking dosage.

Electrophysiologic studies. Surface electrocardiographic leads I, aVF, and V1 were recorded simultaneously with intracardiac electrograms from the high lateral right atrium, proximal and distal coronary sinus, His bundle recording site, and the right ventricular apex on an Electronics for Medicine VR-16 recorder at paper speeds of 100 mm/sec. Standard pacing and extrastimulus techniques were applied with a Bloom Associates programmable stimulator (pulse width 2 msec, stimulus intensity twice late diastolic threshold). A two- or three-catheter electrophysiologic study was repeated on the third day of the 160 mg twice daily dosage and subsequent sotalol dosages.

Class III effects were assessed by changes in the QT interval and in the effective refractory periods of the accessory AV connection, the right atrium and the right ventricle. The QT interval was determined during atrial pacing at a cycle length of 600 msec. Refractory periods were determined by the extrasinus technique after 8 beat trains of cycle length 600 msec. S1 and S2 represent stimulus artifacts of the last beat of the pacing train and of the extrasinus, respectively. A1 and A2 represent the resulting atrial electrograms during atrial extrastimulation and V1 and V2 represent the corresponding ventricular electrograms during ventricular extrastimulation. The atrial (ventricular) effective refractory period was the longest A1A2 (V1V2) interval at which A2 (V2) failed to produce a propagated response. The atrial (ventricular) functional refractory period was the shortest A1A2 (V1V2) interval created during determination of the atrial (ventricular) refractory curve. The accessory AV connection anterograde effective refractory period was the longest A1A2 interval that did not result in ventricular preexcitation, as manifest by loss of the surface QRS delta wave. The accessory connection retrograde effective refractory period was defined as the longest V1V2 interval that did not result in atrial preexcitation as manifest by normalization of the retrograde atrial activation sequence. Accessory connection refractory periods were determined by pacing and recording close to the location of the accessory connection.

AV nodal effects were assessed by changes in the AH interval during atrial pacing at a cycle length of 600 msec and by changes in the AV nodal functional and effective refractory periods. The latter were determined by the extrastimulus technique after 8 beat trains of atrial pacing at a cycle length of 600 msec. The AV nodal effective refractory period was the longest A1A2 interval at which A2 was not conducted to the ventricles via the normal conduction system. The AV nodal functional refractory period was the shortest H1H2 obtainable by atrial extrastimulation. AV nodal refractory periods could be determined only in patients with conduction via the normal system at extrastimulus coupling intervals less than the accessory connection effective refractory period.

Each study also included attempted induction of both orthodromic reciprocating tachycardia and atrial fibrillation. The tachyarrhythmias were noninducible if no more than four ventricular cycles could be produced, were sustained if their duration exceeded 30 sec, and were nonsustained if five or more cycles of less than 30 sec duration were produced.

Long-term therapy. Antiarrhythmic efficacy was defined as prevention of induction of sustained orthodromic reciprocating tachycardia along with a minimum preexcited RR interval during atrial fibrillation of 300 msec or greater. Patients with an antiarrhythmic response were discharged on sotalol. Follow-up consisted of a clinical evaluation, 12-lead ECG, 24 hr ambulatory ECG recording, and determination of trough serum sotalol levels at 3 month intervals.

Biochemical analyses. Serum samples were assayed for sotalol by high-performance liquid chromatography. An internal standard (soteronol: 0.1 ml of solution containing 0.01 mg/ml) was added to serum. Briefly, 1 ml of serum was extracted with the solution containing 7 mg of ethyl acetate and 0.1 ml of 2M Bicine (Calbiochem, La Jolla, CA) at pH 9.3. The organic phase was decanted and the serum reextracted. The organic phases were pooled and evaporated to dryness. Sotalol and soteronol were separated by a C-18 Microbondapak (Waters) reverse-phase column with a mobile phase consisting of 35% methanol/0.0015M (NH4)2 HPO4. The day-to-day variation on a 1 μg/ml sample was 5% (mean 0.95 ± 0.05 μg/ml).

Statistical analysis. Continuous data are presented as mean

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Dose-response data were compared at baseline, at the dosage producing physiologic β-adrenoceptor blockade, and at the maximum well-tolerated dosage. These comparisons included only patients assessed at all three dosage levels. Significance was determined by two-way analysis of variance and Duncan’s multiple range test. The null hypothesis was rejected at p < .05. Concentration-response relationships were examined by fitting individual data points to five mathematical models (linear, exponential, power series, Emax, and sigmoid Emax) with the NONLIN curve fitting program. When the best fit was obtained with an Emax model, the maximum effect (Emax) and the concentration producing 50% maximum effect (EC50) were calculated.

Results

β-Adrenoceptor blockade. The dosages producing physiologic β-adrenoceptor blockade were 160 mg twice daily for eight patients and 320 mg twice daily for three patients (407 ± 149 mg/day). The mean trough serum sotalol concentration on this dosage was 1.4 ± 0.5 μg/ml. Dosages exceeding those required for β-adrenoceptor blockade were assessed in the nine patients without antiarrhythmic efficacy at the β-adrenoceptor–blocking dosage. The maximum well-tolerated dosage was 320 mg twice daily for five of these nine patients and the maximum dosage of 640 mg twice daily was reached in the other four (924 ± 337 mg/day). The mean trough serum sotalol concentration on this dosage was 3.2 ± 1.3 μg/ml.

Dosage-response relationships. The effects of sotalol dosage on sinus and AV nodal electrophysiologic variables are shown in figure 2. The maximum exercise heart rate was significantly decreased from control (167 ± 14 beats/min) by the β-adrenoceptor–blocking dosage (125 ± 15 beats/min) and was decreased significantly further by the maximum well-tolerated dosage (108 ± 14 beats/min). The mean resting heart rate was significantly decreased from control (76 ± 17 beats/min) by the β-adrenoceptor–blocking dosage (58 ± 10 beats/min). However, it was not reduced significantly further by the maximum well-tolerated dosage (53 ± 10 beats/min). The mean AH interval was significantly increased over control (100 ± 26 msec) by the β-adrenoceptor–blocking dosage (137 ± 35 msec). No further change was produced by the maximum well-tolerated dosage (138 ± 37 msec). AV nodal effective and functional refractory periods could be determined in four patients. These refractory periods were significantly increased by the β-adrenoceptor–blocking dosage but were not further increased by the maximum well-tolerated dosage (figure 2).

The effects of sotalol dosage on measurements of class III activity are illustrated in figure 3. The mean anterograde accessory connection effective refractory period was significantly increased over control (272 ± 1 SD.}

FIGURE 2. Effects of treatment with sotalol on sinus and AV nodal electrophysiologic variables. Each panel shows mean (± 1 SD) data relating an electrophysiologic measurement and sotalol dosage. An asterisk indicates a statistically significant difference in response from the previous sotalol dosage. β-BLOCK = β-adrenoceptor–blocking dosage; ERP = effective refractory period; exercise = maximum exercise sinus heart rate; FRP = functional refractory period; MAX = maximum well-tolerated sotalol dosage; rest = resting sinus heart rate.

41 msec) by the β-adrenoceptor–blocking dosage (324 ± 52 msec) and was increased significantly further by the maximum well-tolerated dosage (364 ± 37 msec). These changes were paralleled by increases in atrial and ventricular effective refractory periods, retrograde accessory connection refractory period, and QT interval (figure 3).

Concentration-response relationships. Figure 4 relates serum sotalol concentration to percent reduction in maximum exercise heart rate (left panel) and percent increase in anterograde accessory connection effective refractory period (right panel). These data were fit to the five mathematical models. The maximum exercise heart rate concentration-response relationship was best described by the Emax model illustrated (r = .63). The Emax was a 41% reduction in exercise heart rate, and the sotalol EC50 was 0.7 μg/ml. The anterograde accessory connection effective refractory period concentration-response relationship was best described by a linear model over the concentration range tested (r = .70). Linear relationships were also observed between sotalol concentration and the increase in atrial and ventricular effective refractory periods, retrograde
accesory connection effective refractory period, and QT interval. Data relating sotalol concentration and increase in AH interval showed marked interindividual variability and were not well described by any of the mathematical models tested. AV nodal refractory periods could not be determined in enough patients (n = 4) to allow assessment of their concentration-response relationships.

Antiarrhythmic efficacy. The minimum preexcited RR interval during induced atrial fibrillation was significantly increased from control (236 ± 48 msec) by the β-adrenoceptor–blocking dosage of sotalol (326 ± 81 msec) and was increased significantly further by the maximum well-tolerated dosage (426 ± 99 msec) (figure 5). The relationship between this increase in RR interval and serum sotalol concentration was linear. A reduction in the minimum RR interval was not observed at any sotalol concentration in any patient.

The effects of sotalol on inducibility of orthodromic reciprocating tachycardia are summarized in figure 6. At control, each patient had inducible, sustained ortho-
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FIGURE 4. Sotalol concentration-response relationships. Left, Individual data relating percent reduction in maximum exercise heart rate and serum sotalol concentration (thin lines). These data best fit the Emax model represented by the thick line ($r = .63$). Right, Individual data relating percent increase in anterograde accessory AV connection effective refractory period (ACERP) and serum sotalol concentration (thin lines). These data best fit the linear model represented by the thick line ($r = .70$). Above each panel the left arrow indicates the mean $\beta$-adrenoceptor-blocking sotalol concentration and the right arrow indicates the mean maximum well-tolerated sotalol concentration.

agent, the additional property of prolonging action potential duration without effect on upstroke velocity was demonstrated in isolated mammalian cardiac tissue. This class III effect is secondary to inhibition of the $i_k$ and $i_{k1}$ currents, is independent of $\beta$-adrenoceptor blockade, and in some preparations was apparent only with concentrations greater than those required for $\beta$-adrenoceptor blockade. In humans, evidence for a class III effect of sotalol includes an increase in the QT interval, an increase in mono-

FIGURE 5. Effect of therapy with sotalol on the minimum preexcited RR interval during atrial fibrillation. Left, Individual data relating percent increase in the minimum preexcited RR interval during atrial fibrillation (A.fib) and serum sotalol concentration (thin lines). These data best fit the linear model represented by the thick line ($r = .64$). Right, Mean ($\pm$ 1 SD) data relating the minimum preexcited RR interval during atrial fibrillation and sotalol dosage. An asterisk indicates a statistically significant difference in response from the previous sotalol dosage.
phasic action potential duration,\textsuperscript{24, 25} and an increase in effective refractory periods.\textsuperscript{10, 11, 21–28} Although some other $\beta$-adrenoceptor–blocking agents have minor class III effects,\textsuperscript{29–32} sotalol has substantial and diffuse class III activity.

The present investigation assessed the relationship between $\beta$-adrenoceptor–blocking and class III effects of oral sotalol with a dose-ranging protocol in patients with WPW syndrome. The percentage reduction in maximum exercise heart rate was used as a prospective measure of the extent of $\beta$-adrenoceptor blockade. Physiologically relevant $\beta$-adrenoceptor blockade was observed with a mean sotalol dosage of 407 ± 149 mg/day and a mean trough serum concentration of 1.4 ± 0.5 $\mu$g/ml. The relationship between $\beta$-adrenoceptor–blocking activity and serum sotalol concentration was best described by an Emax model. In contrast, class III effects were linearly related to concentration up to the maximum well-tolerated dosage (924 ± 337 mg/day, 3.2 ± 1.3 $\mu$g/ml). Using invasive measures of class III activity and paired statistical analysis, we have demonstrated that class III activity is evident at the sotalol dosage producing physiologically relevant $\beta$-adrenoceptor blockade. Wang et al.\textsuperscript{20} using the noninvasive rate-corrected QTc interval and a mathematical extrapolation technique, concluded that there was no significant class III effect at sotalol concentrations less than 2.5 $\mu$g/ml. The basis for this difference may relate to the measurements of class III activity and analysis techniques used.

The changes in measures of class III activity noted in this study at the $\beta$-adrenoceptor–blocking dosage of sotalol (atrial paced QT interval increased 14%, atrial effective refractory period increased 10%, ventricular effective refractory period increased 12%) were within the range reported with intravenous sotalol (0.3 to 1.5 mg/kg).\textsuperscript{10, 21–26} Changes at the maximum well-tolerated dose (atrial paced QT interval increased 29%, atrial effective refractory period increased 43%, ventricular effective refractory period increased 23%) exceeded the changes observed with intravenous sotalol.\textsuperscript{10, 21–26} However, the serum concentrations achieved in the intravenous studies were lower than those of the present investigation.\textsuperscript{10, 24, 25} In another study of this wide dosage range patients with ventricular tachyarrhythmias, we noted similar electrophysiologic changes.\textsuperscript{33}

**Electrophysiologic effects of sotalol in WPW syndrome.** The electrophysiologic characteristics of accessory AV connections are similar to those of atrial or ventricular muscle.\textsuperscript{15, 34} Accordingly, isolated $\beta$-adrenoceptor–blocking therapy has no direct effect on clinical measures of accessory connection electrophysiology.\textsuperscript{12–14} In contrast, class III antiarrhythmic agents prolong the effective refractory period of the accessory connection in both anterograde and retrograde directions.\textsuperscript{16, 35} The changes in these measures noted in this study at the $\beta$-adrenoceptor–blocking dosage (anterograde accessory connection effective refractory period increased 19%, retrograde accessory connection effective refractory period increased 27%) were within range reported with intravenous sotalol (0.4 to 1.5 mg/kg).\textsuperscript{21, 23, 26, 27} The changes at the maximum well-tolerated dosage (anterograde accessory connection effective refractory
period increased 34%, retrograde accessory connection effective refractory period increased 42%) were comparable to those of oral amiodarone.  

Antiarrhythmic effects of sotalol. The antiarrhythmic efficacy of sotalol has been reported in animals and for human tachyarrhythmias. Some early reports implied the antiarrhythmic profile of sotalol was similar to that of other β-adrenoceptor–blocking agents. Recent comparative studies, however, suggest that sotalol is more effective than other β-adrenoceptor–blocking agents for supraventricular tachycardia and is as effective as procainamide or amiodarone for premature ventricular beats.

Patients with WPW syndrome are at risk for a number of tachyarrhythmias, reciprocating tachycardias and atrial fibrillation being the most common. The initiation and maintenance of reciprocating tachycardias are dependent on conduction velocities and refractory periods of both the AV node and the accessory AV connection. Since one or more of these factors are depressed by nearly all antiarrhythmic drugs, the list of potentially effective agents is long.

The agents that appear to be most potent in this setting are those that combine AV nodal and accessory connection effects. Such effects have been shown with intravenous sotalol and with low, fixed dosages of oral sotalol. The present investigation examines the contributions of β-adrenoceptor blockade and class III effects to the antiarrhythmic efficacy of oral sotalol in WPW syndrome. Induction of sustained reciprocating tachycardia was prevented at β-adrenoceptor–blocking dosages in 55% of patients. Larger dosages, with increased class III effects, prevented induction in 73% of patients. The contribution of class III activity to antiarrhythmic efficacy is supported by the significant difference between EC50 for β-adrenoceptor blockade and that for antiarrhythmic efficacy.

Antiarrhythmic treatment of patients with WPW syndrome requires more than just suppression of reciprocating tachycardia. Atrial fibrillation is common in these patients and rapid ventricular rates can precipitate ventricular fibrillation. The effects of treatment on the ventricular response rate to atrial fibrillation in patients with WPW syndrome are related to at least three factors. An increase in accessory connection anterograde refractory period will decrease the response rate. However, isolated β-adrenoceptor–blocking therapy does not prolong refractoriness of the accessory connection. A catecholamine surge associated with atrial fibrillation and a fall in arterial pressure will shorten accessory connection refractoriness and increase the response rate. Isolated β-adrenoceptor blockade could decrease the response rate by inhibition of this effect. Finally, concealed penetration of the retrograde accessory connection by impulses conducted through the AV node will reduce the response rate. Isolated β-adrenoceptor blockade could increase the response rate by the effect of AV nodal blockade on such concealed penetration. When this last effect predominates, isolated β-adrenoceptor blockade could be a hazard. Therapy with sotalol would share this risk if, as suggested by some investigators, isolated β-adrenoceptor blockade occurred at low dosages. However, the present results demonstrate that class III effects are present at β-adrenoceptor–blocking dosages. Furthermore, no patient’s ventricular response rate to atrial fibrillation increased after sotalol.

The eight patients with an antiarrhythmic response to oral sotalol received long-term therapy. Long-term absence of recurrent, sustained reciprocating tachycardia was well predicted by electrophysiologic study. Significant side effects occurred in 25% of these patients but were usually the typical benign adverse effects of β-adrenoceptor blockade that have been previously reported. An association between sotalol therapy and torsade de pointes ventricular tachycardia has been reported and was also noted in this study. This association is not unexpected considering the potent class III activity of sotalol.

Limitations. The purpose of this investigation was to determine the dosage ranges over which the β-adrenoceptor–blocking and class III effects of sotalol become manifest and to determine the relative contributions of these effects to the safety and antiarrhythmic efficacy of sotalol in patients with WPW syndrome. Both classes of electrophysiologic effect may be manifest in all cardiac tissues. Nevertheless, regional differences in expression of effects should permit assessment in vivo of the relative β-adrenoceptor–blocking and class III activities of sotalol. The refractory periods of the atrium, ventricle, and accessory connection and the QT interval during atrial pacing provide measures of class III activity minimally influenced by β-adrenoceptor–blocking effects. Similarly, the sinus heart rate response to exercise and the AH interval during atrial pacing provide measures of β-adrenoceptor–blocking activity minimally influenced by class III effects. These in vivo measures are frequently used for this purpose. However, β-adrenoceptor blockade can affect refractoriness of the atrium, ventricle, and accessory connection and the QT interval.

*Refs. 7–11, 21, 23, 24, 26–28, 40–42.*
under conditions of sympathetic stimulation, and class III activity may affect sinus nodal automaticity. Therefore, in a clinical research study, absolute separation of the two classes of electrophysiologic activity may not be achieved.

**Conclusions.** Sotalol is frequently effective antiarhythmic therapy for patients with WPW syndrome by virtue of both prevention of reciprocating tachycardia and slowing of the ventricular response rate to atrial fibrillation. Although class III effects of sotalol occur at dosages associated with physiologically relevant degrees of β-adrenoceptor blockade, higher dosages increase the class III effects and antiarrhythmic efficacy of sotalol.

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