Meta-analysis of the Risk of Torsades de Pointes in Patients Treated with Intravenous Racemic Sotalol

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Abstract. **Objective:** Intravenous (IV) racemic sotalol is useful for the treatment of multiple tachydysrhythmias. The authors hypothesized that the risk of torsades de pointes (TdP) in patients treated with a single IV infusion of sotalol is lower than the 2–4% risk associated with chronic oral sotalol therapy. **Methods:** A MEDLINE search under the subject heading "sotalol" was made of all publications involving humans written in English or German from 1966 to October 1, 2000. A meta-analysis of all original reports including patients who were given a single infusion of at least 1.5 mg/kg or 100 mg of IV sotalol over 30 minutes or less was performed. Potential variables predictive of TdP were assessed. The primary outcome was the observation of TdP associated with IV sotalol infusion. Secondary measurements included hypotension, bradycardia, and worsening of congestive heart failure. All excluded studies and case reports were also examined for evidence of TdP associated with IV sotalol treatment. **Results:** The search included 1,005 publications. There were 37 reports in which 962 patients received IV sotalol and met the inclusion criteria. There was one report of self-terminating TdP lasting 10 seconds among the 962 patients included in the study. There was no report of TdP associated with only IV racemic sotalol administration in any of the excluded studies. If it is assumed that the risk of TdP is homogeneous in the population of patients treated with IV sotalol, then based on the 962 included patients, the rate of TdP is 0.1% (95% CI = 0.003% to 0.6%). **Conclusions:** The overall risk of TdP in patients treated with a single infusion of IV sotalol is low compared with that in patients given chronic oral sotalol therapy. **Key words:** sotalol; torsades de pointes; tachycardia, ventricular; tachycardia, supraventricular; infusions, intravenous; adverse effects. ACADEMIC EMERGENCY MEDICINE 2001; 8:117–124

RACEMIC sotalol is a 1:1 mixture of the enantiomers *d* and *l* sotalol. It has Vaughan-Williams class II and class III antidysrhythmic properties. Both isomers prolong the myocardial action potential and the effective refractory period by blocking the slow potassium rectifier current. The *l*-isomer is also a nonselective beta-adrenergic antagonist with no intrinsic sympathomimetic activity.[1]

A single infusion of intravenous (IV) racemic sotalol has multiple potential uses in the emergency setting. It has been shown to terminate sustained ventricular tachycardia (VT) in 70% of cases, which was significantly better than the results achieved with lidocaine.[2] It may also prove to be useful in the termination and suppression of refractory VT[3] and VT associated with acute myocardial infarction (MI),[3,4] and to facilitate defibrillation of ventricular fibrillation.[5]

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Intravenous racemic sotalol terminates about 70% of cases of atrioventricular nodal reentrant and atrioventricular reciprocating tachycardias[6–9] It is not as effective as adenosine or verapamil,[10] but it may be useful for patients with recurrent or refractory supraventricular tachycardias (SVTs), particularly when calcium-channel blockers are contraindicated. The effective refractory period is usually increased after sotalol administration in all myocardial tissue, including bypass tracts, which are present in patients with Wolff-Parkinson-White (WPW) syndrome.[11–14] It is for this reason that racemic sotalol may be particularly useful in slowing the rapid ventricular response to atrial fibrillation that may occur in patients with WPW syndrome.[15,16]

Clinical enthusiasm for the use of IV sotalol has at least partly been tempered by its potential to act as a prodysrhythmic agent as well as to induce other adverse effects that may be related to its beta-adrenergic antagonist properties such as bradycardia, atrioventricular nodal (AV) block, hypotension, and bronchospasm. Chronic oral administration of sotalol is associated with a 2–4% risk of torsades de pointes (TdP).[17–19] By definition, TdP occurs in association with a prolonged corrected QT (QTc) interval. Other factors that may contribute to its occurrence include an increase in inhomogeneity of repolarization, which may manifest

as increased dispersion of the QTc interval,[20–22] and the presence of early afterdepolarizations (EADs).[23] We hypothesized that the risk of TdP is lower in patients who receive a single IV infusion of sotalol than in those who receive chronic oral therapy. We performed an analysis of all studies in the English and German literature in which patients received at least a 1.5-mg/kg or 100-mg IV infusion of racemic sotalol over 30 minutes or less to determine the risk of occurrence of TdP, and other adverse effects.

METHODS

Study Design. This study was a meta-analysis of the risk of TdP associated with infusion of therapeutic doses of IV racemic sotalol. All available original human research and case reports in the English and German literature over a 34-year period were eligible for inclusion. Included individual studies were approved by respective local institutional review processes.

Study Protocol. A National Library of Medicine MEDLINE search under the subject heading "sotalol" was performed for all studies involving humans occurring from 1966 to October 1, 2000. The search was performed separately for English and German language articles. All available abstracts of the articles were reviewed. The articles whose abstracts or titles described patients who might meet the enrollment criteria of our study were obtained and reviewed. Other studies in the bibliography sections of these articles that were considered relevant were also obtained and read.

All original studies or case reports that described the IV administration of a bolus of at least 1.5 mg/kg or 100 mg of racemic sotalol over 30 minutes or less to one or more patients were included in the meta-analysis. Any patients in the included studies who received less than 1.5 mg/kg or 100 mg, or in whom the medicine was infused over more than 30 minutes, were excluded. Whether a subject's single initial dose was followed by a prolonged IV infusion or "drip" of longer duration or recurrent infusions had no bearing on inclusion in this study. No study was excluded based on study design. Review articles that summarized previously reported data were not included. Authors who had published multiple studies were contacted to confirm that the treatment of an individual patient had not been described multiple times, and that the same patient had not been treated on multiple occasions. If either of these conditions was confirmed, then the study with the largest number of patients was included, and the other study or studies were excluded. However, if a precise description of the patients who were represented twice could be obtained, then both studies were included but the duplicate patients were excluded from the second study.

Measurements. For the articles under study, available data were collected with regard to patient characteristics potentially associated with the occurrence of TdP or other adverse events. Characteristics such as female gender, history of ventricular dysrhythmias and left ventricular dysfunction, greater magnitude of QT-interval prolongation, and hypokalemia increase the risk of TdP in patients given oral sotalol.[1,17–19] If subgroups of included patients were described in sufficient detail, the characteristics of each subgroup were described.

The descriptions of TdP or any other adverse effects thought to be related to treatment with IV sotalol were analyzed. If the adverse effects of IV sotalol were inadequately or not specifically described, the primary authors were contacted and asked: "Were there are any adverse effects including proarrhythmia such as torsades de pointes, hypotension, or bradycardia after administration of IV sotalol?" All historical and diagnostic assessments were determined by the primary authors and treating physicians according to their own criteria.

For each study included in the analysis, the number of different patients who met the inclusion criteria and the dosages and durations of the sotalol infusions were documented. The sex, mean age, and past cardiac history of the patients were recorded. This data set included any history of coronary artery disease (CAD) or MI, which were classified separately, left ventricular aneurysm, congestive heart failure (CHF) or congestive cardiomyopathy, hypertension, valvular heart disease, or an explicit statement of the absence of known cardiac disease. Frequently, the age and sex of the patients included in the analysis were presented in addition to the data of excluded patients. For these studies the demographic data of the entire group of patients are described. Any previous knowledge of the presence or absence of dysrhythmias was recorded. Whether therapy with all other antidysrhythmic medicines excluding digoxin was stopped for at least four half-lives prior to sotalol administration was noted. A stated history of the presence of asthma was documented.

The cardiac rhythms at the time of sotalol infusion were noted. If it was implied but not explicitly stated by the authors that the patients had a sinus rhythm, the rhythm was classified as "presumed sinus." If, after review, the cardiac rhythm could not be determined it was defined as uncertain. It was noted whether a patient was experiencing an MI at the time of sotalol infusion.

The patients' average weight, heart rate, and systolic, diastolic, and mean blood pressures were recorded, if available. The average QT and QTc intervals of conducted supraventricular beats on the electrocardiogram (ECG), the left ventricular ejection fraction, which may have been measured by a variety of modalities, and the serum potassium and magnesium were recorded.

Adverse effects attributed to sotalol infusion, including the occurrence of TdP, CHF or dyspnea, presyncope, hypotension, either asymptomatic or symptomatic, heart block or bradycardia, which may or may not have occurred after cardioversion, and other dysrhythmias such as premature ventricular contractions (PVCs) or nonsustained VT, were recorded. The occurrence of TdP in patients who received IV racemic sotalol but were excluded from the study was also noted. If there was any uncertainty with regard to the interpretation of an adverse effect or another aspect of an individual study, the primary study authors were contacted and questioned.

Data Analysis. The SPSS software package (SPSS, Version 9.0, SPSS Inc., Chicago, IL) was used to tabulate data and Statxact software (Statxact 3, Version 3.0.2, Cytel Software Corporation, Cambridge, MA) was used to calculate exact 95% confidence intervals (95% CIs). The estimated rate and 95% CI of occurrence of TdP and other adverse effects were calculated by pooling data from the studies included in the analysis.[24] The Freeman-Halton extension of Fisher's exact test was used to determine whether there was an association between the occurrence of hypotension and the cardiac rhythm at the time of sotalol administration.

RESULTS

The English- and German-language MEDLINE searches yielded 932 and 73 articles, respectively. One hundred sixteen full articles were obtained and evaluated for inclusion. Both investigators initially reviewed abstracts and collected data on included studies, although ultimately one investigator (KAM) reviewed all abstracts, titles, and collected data. There were 35 English- and two German-language articles in which one or more patients were treated with IV racemic sotalol with a protocol that met the inclusion criteria. A total of 962 unique patients described in the 37 articles were included in the analysis.[2–4,6–9,11,15,16,25–52] A subgroup of 25 patients in one article[33] and all of the patients in another article[52] were excluded because some of them had also been enrolled in a larger included study performed by the same research group.[34] Two patients were excluded from an included study[43] because the individuals had been enrolled and described in another included study.[2] One study[45] was excluded because the results had been previously described.[44] The mean and median number of patients included per article were 26.7 and 17.0, respectively, and the minimum and maximum numbers of patients included from an individual article were 2 and 109.

TABLE 1. History of Cardiac Disease in the Study Population

Cardiac Disease	Number of Patients
Coronary artery disease	239
Myocardial infarction	57
Left ventricular aneurysm	12
Congestive heart failure or dilated cardiomyopathy	11
Hypertension	24
Valvular heart disease	21
None	184

Total N = 536 patients where a history of cardiac disease was described. Multiple diseases were described in some patients.

Age and sex were described precisely for 572 patients of interest. There were 423 men and 149 women, with a male:female ratio of 2.84:1, and the average age was 56.1 years. There were 292 patients included in the study who were described, in addition to 106 patients who were excluded. For this group of 398 patients, the male:female ratio was 2.06:1, and the average age was 52.1 years. There were 98 included patients whose age and sex were not stated.

The presence or absence of a history of cardiac disease was defined for 536 patients, and is described in Table 1. The history of dysrhythmias was stated for 843 patients and the primary dysrhythmia of interest for each patient is presented in Table 2. In 832 patients all antidysrhythmic agents excluding digoxin were stopped for at least four half-lives or 24 hours prior to administering sotalol. Fifteen patients were noted to have a history of asthma.

The cardiac rhythms of all the patients at the time of sotalol administration are shown in Table 3. Ten patients in two studies were experiencing an acute MI at the time of sotalol infusion.[2,4] The average heart rate before sotalol administration was stated for 287 patients. Average heart rate as a function of heart rhythm was as follows for the larger patient groups: presumed sinus rhythm (n = 128) was 79 beats/min, atrial fibrillation (n = 120) was 137 beats/min, SVT (n = 10) was 173 beats/min, and VT (n = 18) was 176 beats/min. Average blood pressure prior to treatment was stated for 105 patients. The systolic and diastolic values were 133 and 82 mm Hg. The average weight, corrected QT interval, and ejection fraction were stated for 188, 130, and 184 patients, respectively.

TABLE 2. History of Dysrhythmias in the Study Population

Dysrhythmia	Number of Patients
SVT (type unspecified)	124
AV nodal SVT	14
AV SVT with nonconcealed bypass tract (WPW)	48
AV SVT with concealed bypass tract	11
WPW, dysrhythmia unspecified	6
Atrial fibrillation	208
Atrial flutter	38
Atrial fibrillation or flutter	17
Wide QRS complex tachycardia or tachycardia of uncertain etiology	14
Premature ventricular contractions	21
Nonsustained VT	2
Sustained VT	97
VT (duration unspecified)	10
Sustained VT or ventricular fibrillation	217
Ventricular fibrillation	6
None	10

Total N = 843 patients where a history of dysrhythmia was described, and each patient is represented only once by the dysrhythmia of primary interest. SVT = supraventricular tachycardia; AV = atrioventricular; WPW = Wolff-Parkinson-White syndrome; VT = ventricular tachycardia.

The average values were a weight of 77.6 kg, a corrected QT interval of 411 milliseconds, and an ejection fraction of 40%. An average plasma potassium of 4.0 mmol/L and magnesium of 0.88 mmol/L were noted in 92 and 52 patients, respectively.[35,51]

Fifty-seven patients received a fixed dose of sotalol and 905 patients received a weight-based dose. Among the patients who received a fixed dose, 46 received 100 mg, ten received 120 mg, and one received 150 mg. Among the patients who received a weight-based dose, 887 received 1.5 mg/kg and 18 received 2.0 mg/kg. The minimum duration of infusion of sotalol was 1 minute and the maximum, defined as a study exclusion criterion, was 30 minutes. The mean and median durations of infusion were 13.6 and 10 minutes, respectively.

There were 12 trials involving 219 included patients in which the description of adverse effects due to IV sotalol was limited or absent.[9,26–28,36–38,42,43,47,49,50] One of the primary authors of each of these studies was contacted for clarification. Close clinical monitoring was described in association with IV sotalol infusion in all of these studies, and in 11 studies the infusion was performed in the electrophysiology lab.

Of the 962 patients included in the study, one patient was known to develop TdP after receiving IV sotalol[35]; a 62-year-old woman with a prior anterior MI presented with atrial fibrillation and a mean ventricular rate of 100 beats/min. The patient had normal renal function with normal plasma potassium and magnesium, and the QT interval was 360 msec. The patient was given 1.5 mg/kg (120 mg) sotalol over 15 minutes for chemical cardioversion of atrial fibrillation. Sixteen minutes after the infusion was begun, the patient had a 10-second episode of TdP, which was associated with mild dizziness. The TdP terminated spontaneously, after which magnesium infusion was administered to prevent recurrence. The QT interval was 500 msec, with a mean heart rate of 85 beats/min before this event. The patient subsequently converted from atrial fibrillation to sinus rhythm 41 minutes after the start of the sotalol infusion with no further TdP noted. There was no other instance of TdP in the population under study, and there was no report of TdP associated with only IV racemic sotalol administration in any of the excluded studies. If it is assumed that the rate of TdP is homogeneous in the sample of 962 patients included in the study, then the rate of TdP is 0.1% (95% CI = 0.003% to 0.6%).

Of the patients included in the analysis, asymptomatic hypotension was reported in five,[35] and 13 had hypotension with uncertain symptomatology.[7,32,43] Five patients experienced symptomatic hypotension or presyncope that did not necessitate specific treatment.[6,7] Two patients had hypotension that responded to fluid replacement,[41] two required discontinuation of therapy,[7] and two required both fluid replacement and discontinuation of therapy.[51] In one study, 30 patients were given sotalol while in VT.[2] One of 16 who received sotalol as a first drug became hypotensive, lost consciousness, and required electrical cardioversion. Two of 14 patients who received sotalol after lidocaine lost consciousness and required cardioversion. One patient, a 90-year-old man with CHF, renal failure, and a serum potassium level of 6.3 mEq/L, became hypotensive, developed asystole, and died after receiving lidocaine and sotalol. The rate of all forms of hypotension or presyncope as a function of the cardiac rhythm at the time of sotalol administration in the meta-analysis was as follows: sinus or presumed sinus 3 of 545 (0.5%), SVT or atrial fibrillation or flutter 26 of 379 (6.9%), and VT 4 of 31 (13.3%), $p < 0.0001$.

Ten patients developed bradycardia and four patients were thought most likely to have nonsustained monomorphic VT as opposed to SVT with aberrancy.[32,35] Five patients developed transient asymptomatic bradycardia[2] or new dysrhythmias[6] after cardioversion with sotalol. One patient received atropine and adrenaline for sinus bradycardia associated with hypotension (Joseph AP, personal communication, 2000).[51] None of the other dysrhythmias were noted to require specific intervention.

Two patients developed "mild CHF"[44] and two

developed "dyspnea."[7] There was no report of bronchospasm. Three patients experienced AV block necessitating discontinuation of sotalol infusion.[32] There was one death directly associated with sotalol administration as noted above.

DISCUSSION

The primary interest of this meta-analysis was to determine the rate of TdP associated with the IV administration of racemic sotalol. All studies with therapeutic sotalol regimens of less than 1.5 mg/kg or 100 mg were excluded because these doses have proven effective in the termination of VT and SVT.[2,6–9] Studies where the stated infusion duration was more than 30 minutes were also excluded. Although it is uncertain whether longer infusions would be as effective and associated with the same risk of TdP, their application would be less desirable in an emergency setting. The inclusion of studies with lower total doses and longer infusion durations might have lowered the perceived risk of TdP while not representing the regimen necessary for effective treatment.

This analysis used the pooling method for combining data from divergent studies. In the homogeneous case, where the same value appears to be measured in each study, it is most common to calculate a weighted mean statistic where the weights are the inverse of the variance of each individual value.[53,54] In all but one study in this analysis there were 0 cases of TdP. Consequently, the variances in these studies would be zero and the inverse would be infinity. In this situation the statistic may be approximated by pooling the data.[24] Other more complex models and techniques that approximate the variance within and between studies can be used.[55] Ultimately, given the variety of designs and sizes of studies and the incomplete predictor data set in this meta-analysis that could confound any model, the simplest and most transparent appropriate combining methodology was chosen.

There was only one case of TdP after treatment with IV racemic sotalol and the rate of TdP, 0.1% (95% CI = 0.003% to 0.6%), was significantly lower than the 2–4% risk associated with oral sotalol treatment. Why is this so? Certainly the duration of exposure is longer with chronic oral therapy. MacNeil et al., however, found that the majority of known TdP occurred within the first three days of starting or adjusting the dose of oral sotalol treatment.[17] Average plasma sotalol levels of 1.7 to 4.0 mg/L were comparable after IV infusion[7,25,26,30,31,40,44,46,48] and during oral therapy with commonly used doses.[26,31,44,47] However, plasma levels may not directly reflect cardiac electrophysiologic activity. Peak plasma levels of 5.4 and 4.0 mg/L were measured 5 minutes after rapid sotalol infusions of 1 and 5 minutes, respectively, in one study, but there was no corresponding peak in the duration of the right ventricular effective refractory period (RVERP).[41] When plasma concentrations are comparable, there is conflicting evidence of differential prolongation of the QT interval and RVERP between oral and IV treatments.[26,47,49] There may also be differential beta-adrenergic antagonist effects, although the magnitudes of induced bradycardia are similar.[26,31,47,49] If there are differential effects at similar plasma levels, it is postulated this could be due to tissue accumulation of the drug with chronic oral treatment or the presence of active metabolites. To date, no active metabolites have been identified.[1]

TABLE 3. Cardiac Rhythm at the Time of Initiation of Sotalol Infusion

Rhythm	Number of Patients
Sinus rhythm	62
Presumed sinus rhythm	475
Sinus with demand right ventricular pacemaker	8
Atrial fibrillation	247
Atrial flutter	28
Atrial fibrillation or flutter	17
Supraventricular tachycardia	87
Ventricular tachycardia	31
Uncertain	7

Total N = 962 patients.

Patients who received IV sotalol for termination of tachydysrhythmias may have been protected from developing TdP for multiple reasons. First, tachycardic patients have a shortened QT interval irrespective of medical therapy. Second, there is conflicting evidence that sotalol has the property of reverse use-dependence.[7,28,42] The phenomenon of reverse use-dependence refers to a relative decrease in the prolongation of the action potential and refractory period as a function of increasing heart rate. If sotalol does manifest reverse use-dependence, then TdP may be relatively less likely to occur after sotalol administration to tachycardic patients. Studies in which sotalol was administered IV often included invasive electrophysiologic procedures. The increased adrenergic tone and secondary tachycardia that may be associated with these investigations[56] may have been protective, regardless of the cardiac rhythm.

It is difficult to compare the rates of TdP associated with the IV infusion of different class III antidysrhythmics. The patient populations, infusion protocols, and study designs are highly variable. Despite these limitations, it is interesting to note that prolonged IV infusions of amiodarone for the treatment of refractory or recurrent VT have been described in multiple trials. In this popula-

tion of severely ill patients, the rate of TdP was about 1%.[57,58] The rate of TdP was 1–3% in trials involving patients with a variety of dysrhythmias treated with various doses of IV ibutilide.[32,59–61] Torsades de pointes has not been associated with infusion of bretylium[62–64] or lidocaine,[2,65,66] a class IB antidysrhythmic.

Hypotension was the most common adverse effect reported in the meta-analysis. It was most common and severe in patients who received sotalol alone or after lidocaine for termination of VT. Considering only the initial treatment of VT, the rates of hypotension were similar in the patients randomized to sotalol (1 of 16, 6.3%) and lidocaine (1 of 17, 5.9%).[2] In the only other prospective trial of medical treatment of spontaneous stable VT, hypotension was observed in two of 27 (7.4%) cases treated with lidocaine and one of 28 (3.6%) treated with procainamide.[65] Despite the descriptive term "stable," patients with this condition often have profound underlying cardiac illness. In a retrospective study of spontaneous sustained stable VT, the mortality associated with current treatment regimens was two of 40 (5%).[67]

Because the *l*-isomer of sotalol is a nonspecific beta-adrenergic antagonist, adverse effects associated with this class of drugs might be expected. Two patients developed dyspnea, but there was no case of bronchospasm despite the administration of sotalol to some patients with known reactive airways disease.[41] Nevertheless, exacerbation of bronchospasm has been described in association with oral racemic sotalol ingestion.[68] Sinus bradycardia and AV block necessitating discontinuation of therapy were also rarely observed. These adverse events may be related to both class II and class III effects.[69]

Limitations and Future Questions

This meta-analysis had multiple limitations. The literature search was limited to two languages in the MEDLINE database, and associated bibliographies. There may be unincluded studies that were referenced in other indexes but not in MEDLINE, or were written in other languages. However, it is unlikely exclusion of such studies would have biased the results.

When analyzing the rate of TdP associated with IV sotalol administration, it was assumed that the rate is homogeneous. While there currently are insufficient data to determine whether this assumption is valid, consideration of the data regarding oral sotalol therapy suggests that the rate is not homogeneous. Risk factors for TdP in association with oral sotalol treatment include female sex, history of VT or ventricular fibrillation, history of CHF, and higher daily dose.[17,19] Thus, the value that was derived may be an approximation reflecting the characteristics of the sample populations that have been investigated.

The reporting of adverse events, including TdP, may have suffered from multiple biases. There may have been bias toward disproportionate reporting of adverse events because it allows the publication of case reports. Conversely, the majority of included studies were designed to test efficacy and electrophysiologic effects, not toxicity. Twelve reports inadequately addressed the adverse effects of IV sotalol. Furthermore, authors may have been less likely to monitor closely for or to report adverse events that would diminish the perceived utility of a novel therapeutic approach. Post-infusion monitoring was not standardized in the included studies. Some self-limited cases of TdP may simply not have been observed. However, most infusions were performed in the electrophysiology lab. It is likely that patient monitoring after IV infusion was more intense than that experienced by patients receiving oral sotalol on a chronic basis, and if TdP were to have occurred after sotalol infusion, it would likely have occurred early during this intense monitoring period. Thus, if this was a source of bias, it is unlikely to have caused a qualitative change in the primary result.

The majority of patients in this meta-analysis were treated with IV sotalol only after other antidysrhythmics had been stopped for four half-lives or 24 hours. The presence of other agents could affect both the efficacy and, in particular, the toxicity of IV sotalol. This may limit the generalizability of our findings to ED patients who present while taking chronic oral antidysrhythmic therapy.

The database regarding the efficacy and adverse effects of IV sotalol is encouraging but limited. Future prospective studies should be performed to confirm sotalol's utility in the management of a variety of tachydysrhythmias and to clarify further its adverse effect profile.

Conclusions

Intravenous racemic sotalol is an effective medication for the termination or control of multiple dysrhythmias. Torsades de pointes is an important but rare complication of IV therapy. Torsades de pointes occurred in association with the administration of therapeutically proven doses in one of 962 (0.1%, 95% CI = 0.003% to 0.6%) cases, which is substantially lower than the rate associated with chronic oral sotalol therapy. Other reported complications include hypotension, AV block, and bradycardia. Further study of the utility of this medicine in the emergency setting is warranted.

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