Hemodynamic Effects of Intravenous Sematilide in Patients With Congestive Heart Failure: A Class III Antiarrhythmic Agent Without Cardiodepressant Effects

BRUCE S. STAMBLER, MD, FACC,* STEPHEN S. GOTTLIEB, MD, FACC†
BRAMAH N. SINGH, MD, PhD, FACC‡ KODANGUDI B. RAMANATHAN, MD, FACC§
J. DAVID OGILBY, MD,∥ KENNETH A. ELLENBOGEN, MD, FACC

Richmond, Virginia; Baltimore, Maryland; Los Angeles, California; Memphis, Tennessee; and Philadelphia, Pennsylvania

Objectives. This study sought to evaluate the hemodynamic effects of intravenous sematilide hydrochloride, a selective class III antiarrhythmic agent, in patients with heart failure and left ventricular systolic dysfunction.

Background. Class I antiarrhythmic agents, which primarily slow conduction, can depress ventricular function, particularly in patients with heart failure. In contrast, pure class III agents, which selectively prolong repolarization, do not adversely affect hemodynamic variables in animal models, but there are no data evaluating their hemodynamic effects in humans.

Methods. In 39 patients with congestive heart failure and a left ventricular ejection fraction <40%, hemodynamic and electrocardiographic measurements were obtained at baseline, after a loading dose and during a maintenance infusion of intravenous sematilide using either a low (0.75 then 0.3 mg/min) or high dose (1.5 then 0.6 mg/min) regimen. The study had an 80% power to detect clinically meaningful differences in hemodynamic variables.

Results. Both low (n = 20) and high (n = 19) dose sematilide infusions produced dose-dependent increases in QT interval (5 ± 8% [mean ± SD] and 18 ± 10%, respectively) and corrected QT interval (4 ± 8% and 14 ± 10%), and high dose sematilide decreased heart rate by 7 ± 10% (all p < 0.025 vs. baseline). Neither dose regimen had a statistically significant effect on any other hemodynamic variable, including mean arterial, right atrial, pulmonary artery and pulmonary capillary wedge pressures; cardiac index, stroke volume, systemic and pulmonary vascular resistances; and left ventricular stroke work index. Sematilide showed no adverse hemodynamic effects in patients with left ventricular ejection fraction ≤25% or >25% and in patients with cardiac index <2 or ≥2 liters/min per m². Sustained polymorphic ventricular tachycardia (n = 1) and excessive QT prolongation (n = 4) were seen during the high dose.

Conclusions. Sematilide, in the doses administered, prolonged repolarization but did not alter hemodynamic variables in patients with heart failure. These data suggest that class III antiarrhythmic agents, which selectively prolong repolarization, are not cardiodepressant but may be proarrhythmic in humans, especially at high doses.

(J Am Coll Cardiol 1995;26:1679–84)
safety of two dosage regimens of intravenous sematilide hydrochloride in patients with congestive heart failure and left ventricular systolic dysfunction.

Methods

Patients. Patients were considered for entry into this study if they had congestive heart failure of at least 2 months in duration (New York Heart Association functional classes II to IV) and a left ventricular ejection fraction <40%. Left ventricular ejection fraction was determined by radionuclide angiography or two-dimensional echocardiography. The exclusion criteria were unstable angina, myocardial infarction within 4 weeks, severe aortic stenosis, acute pulmonary edema or cardiogenic shock, constrictive pericarditis, restrictive cardiomyopathy, amyloid heart disease, long QT syndrome or baseline corrected QT interval (QTc) >450 ms, complete heart block, symptomatic bradycardia (heart rate <45 beats/min), symptomatic hypotension (systolic blood pressure <80 mm Hg), serum creatinine >2.4 mg/dl, amiodarone therapy within the previous 3 months and known allergic response to procainamide or N-acetylprocainamide.

Protocol. This was an open-label study of two dosage regimens of intravenous sematilide hydrochloride administered by loading and maintenance infusions and was conducted at five centers. The two dose levels selected have been used previously (unpublished data) to measure the electrophysiologic response to sematilide in patients with sustained ventricular tachycardia. The protocol was prospectively designed to study two groups of patients. Twenty patients in functional class II or III with a left ventricular ejection fraction between 21% and 39% were classified as group A, and 19 patients in functional class III or IV with a left ventricular ejection fraction <30% were classified as group B. In group A, the initial 10 patients received low dose, then the subsequent 10 patients received high dose, sematilide; in group B, 10 patients received low dose, then 9 patients received high dose, sematilide. All patients received constant doses of digoxin, diuretic drugs and vasodilator agents, except that patients in functional class II or III had their cardiovascular medications withheld on the morning of the study until the hemodynamic evaluations were completed. Patients in functional class IV were allowed to continue their cardiovascular medications. Antiarrhythmic drugs (class I and III) were discontinued at least 5 half-lives before the study. No cardioactive medications other than sematilide were administered during the hemodynamic study protocol. The protocol was approved by the institutional review boards at the five centers, and all patients gave written informed consent before participating in the study.

After completion of the clinically indicated cardiac catheterization or electrophysiologic study, a right heart catheterization was performed. One patient had hemodynamic variables measured and sematilide administered after angiographic dye used during coronary angiography and left ventriculography. All other patients were studied without preceding exposure to angiographic dyes. The following baseline measurements were made before administration of intravenous sematilide hydrochloride in the fasting state and at least 15 min after placement of the right heart catheter: mean right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, mean arterial pressure, heart rate, surface ECG intervals (PR, QRS, QT, QTc) and cardiac output. Mean arterial pressure (MAP) was derived from the systolic (SBP) and diastolic (DBP) blood pressures (MAP = DBP + (SBP - DBP)/3). The QTc interval was derived using the Bazett formula. Cardiac output was determined by the thermodilution technique using the average of three consecutive measurements that did not vary by ±10% from one another. The following hemodynamic variables were calculated at baseline: cardiac index, stroke volume, stroke index, systemic vascular resistance index, pulmonary vascular resistance index and left ventricular stroke work index. After completion of baseline hemodynamic evaluations, the loading infusion (low dose 0.75 mg/min; high dose 1.5 mg/min) of intravenous sematilide was administered over a 15-min period and was immediately followed by the maintenance infusion (low dose 0.3 mg/min; high dose 0.6 mg/min). The maintenance infusion of intravenous sematilide continued until completion of the hemodynamic evaluations and did not exceed 75 min in duration. Hemodynamic and ECG evaluations, obtained in the same manner as the initial baseline measurements, were undertaken at the end of loading infusion and 30 min after the start of the maintenance infusion. Blood pressure and heart rate were determined at the end of the loading infusion and at 15-min intervals during the maintenance infusion. Blood samples for plasma sematilide concentrations were obtained before the administration of sematilide, at the end of the loading infusion and once every 15 min during the maintenance infusion.

Statistical analysis. Comparisons of baseline demographics for low and high dose groups were made using the Student two-tailed t test at the alpha 0.05 level of significance. Hemodynamic and ECG measurements were analyzed using a repeated-measures analysis of variance model, including the effects of dose group (low, high), time (baseline, loading, maintenance) and the dose group-by-time interaction effect (p < 0.15) for a variable; then comparisons with baseline values were made separately for each dose group, using the within-patient estimate of variability to compare the mean change from baseline to zero at the alpha 0.025 level. The minimal detectable difference for comparisons with baseline values, within a dose group, was calculated using the within-patient estimate of variability for power 0.80 (alpha 0.025). Subgroup analyses were performed separately on the basis of baseline cardiac index (<2 vs. ≥2 liters/min per m2) and left ventricular ejection fraction (≤25% vs. >25%). Univariate linear regression analysis was used to investigate possible correlations between the plasma sematilide concentrations and the changes in QTc and RR intervals. A two-tailed t test was used to test the null hypothesis that the slope was equal to zero (i.e., no relation). Mean values ± SD are reported.
Table 1. Effects of Low Dose Sematilide Infusion on Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Loading</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>84 ± 18</td>
<td>83 ± 17</td>
<td>81 ± 18</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>96 ± 15</td>
<td>96 ± 14</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>10 ± 6</td>
<td>9 ± 6</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>31 ± 12</td>
<td>31 ± 11</td>
<td>31 ± 12</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>20 ± 10</td>
<td>21 ± 10</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.6</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>29 ± 10</td>
<td>29 ± 10</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>SVRI (dynes.s.cm⁻⁵/m²)</td>
<td>3,155 ± 966</td>
<td>3,242 ± 902</td>
<td>3,401 ± 1,182</td>
</tr>
<tr>
<td>PVRI (dynes.s.cm⁻⁵/m²)</td>
<td>416 ± 221</td>
<td>373 ± 160</td>
<td>355 ± 160</td>
</tr>
<tr>
<td>LVSWI (g/m²/m²)</td>
<td>32 ± 15</td>
<td>32 ± 15</td>
<td>35 ± 14</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. CI = cardiac index; HR = heart rate; Loading = 15 min after start of loading infusion; LVSWI = left ventricular stroke work index; Maintenance = 30 min after start of maintenance infusion; MAP = mean arterial pressure; MRAP = mean right atrial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SI = stroke index; SVRI = systemic vascular resistance index.

Results

Patient characteristics. Thirty-nine patients were enrolled in the study (38 men, 1 woman; mean [±SD] age 56 ± 11 years, range 37-74; mean left ventricular ejection fraction 24 ± 9%, range 8% to 38%; mean cardiac index 2.2 ± 0.5 liters/min per m², range 1.2 to 3.5). Sixteen patients were in functional class II, 18 in class III and 5 in class IV. Twenty patients received a low dose and 19 patients received a high dose of intravenous sematilide. There were no statistically significant differences in baseline demographic characteristics or hemodynamic indexes between the low and high dose sematilide groups with respect to age, weight, creatinine clearance, left ventricular ejection fraction or cardiac index. Twelve patients in the low and 11 in the high dosage group had a left ventricular ejection fraction ≤25%; 8 patients in each dosage group had a left ventricular ejection fraction >25%.

Hemodynamic evaluations. The effects of intravenous sematilide on hemodynamic variables were evaluated separately for patients receiving the low and high dose regimens at the end of the loading infusion and 30 min after the start of the maintenance infusion. The minimal detectable differences with 80% power for each of the hemodynamic variables in the study were as follows: heart rate 4 beats/min, mean arterial, right atrial, pulmonary artery and pulmonary capillary wedge pressures 3, 1, 3 and 2 mm Hg, respectively, cardiac index 0.2 liters/min per m², stroke index 2 ml/m², systemic and pulmonary vascular resistance indexes 326 and 105 dynes·s·cm⁻⁵·m², respectively, and left ventricular stroke work index 2 g·m/m². Thus, the study had sufficient power to detect clinically meaningful differences in hemodynamic variables. Low dose sematilide (20 patients) did not change heart rate significantly (Table 1), whereas high dose sematilide (19 patients) produced a small but statistically significant decrease in heart rate (Table 2). Heart rate decreased by 7 ± 10% (p < 0.025 vs. baseline) during the maintenance infusion of high dose sematilide.

Neither the low nor the high dosage regimen of intravenous sematilide had a statistically significant effect on any other hemodynamic variable (Tables 1 and 2). The hemodynamic effects of intravenous sematilide were also evaluated in patients with a left ventricular ejection fraction ≤25% (Fig. 1) versus >25% and in patients with a cardiac index <2 versus ≥2 liters/min per m². In each of these categories, sematilide showed no adverse hemodynamic effects at the low or high dose regimen.

Electrophysiologic effects. The PR and QRS intervals were not significantly altered during either the loading or maintenance infusions in patients receiving either the low or high dose regimen of intravenous sematilide (Table 3). The QT and QTc intervals increased significantly after the low dosage infusion of intravenous sematilide at 30 min after the start of the maintenance infusion. In patients receiving the high dosage infusion, QT and QTc intervals increased significantly at the end of the loading infusion and at all time points during the maintenance infusion. The QT interval increased by 5 ± 8% and 18 ± 10%, and the QTc interval increased by 4 ± 8% and 14 ± 10% (all p < 0.025 vs. baseline) during low and high dose infusion, respectively, at 30 min after the start of the maintenance infusion.

Pharmacokinetics. The plasma sematilide concentrations suggested linear disposition kinetics comparing the low and high dosage regimens during the loading (0.653 ± 0.496 and 1.447 ± 1.667 μg/ml, respectively) and maintenance (0.612 ± 0.501 and 1.111 ± 0.879 μg/ml, respectively) infusions. There were weak but statistically significant (p < 0.05) linear correlations between the plasma concentrations of sematilide and the changes in QTc intervals at the end of the loading infusion and at 15 (r = 0.38) and 30 min of the maintenance infusion. There were no statistically significant correlations between the plasma concentrations of sematilide and the changes in RR interval at any time point studied.

Adverse effects. The two dosage regimens of sematilide were generally well tolerated. Adverse effects occurred in four patients who received high dose sematilide and were in functional class III. Four patients had excessive QT prolongation outside the limits defined in the protocol (QT > 515 ms or
Hemodynamic effects of sematilide in 11 patients with left ventricular ejection fraction <25%. Other than the decreases in heart rate (HR), there were no adverse hemodynamic effects. CI = cardiac index; MAP = mean arterial pressure; MRAP = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index. Open columns = baseline; hatched columns = loading dose; solid columns = maintenance dose. Results shown are mean value (columns) ± SD (vertical lines). *p < 0.05 versus baseline.

Discussion

Present study. The present study used invasive monitoring to evaluate the hemodynamic effects of an intravenous class III antiarrhythmic drug in patients with chronic congestive heart failure (functional classes II to IV) and left ventricular systolic dysfunction (left ventricular ejection fraction <40%). Antiarrhythmic drugs can depress myocardial contractility, reduce cardiac output and produce a marked deterioration in function when given to patients with congestive heart failure (2–6). Sematilide did not cause any acute adverse hemodynamic effects, even in the subset of patients with markedly depressed ventricular function (left ventricular ejection fraction <25% or cardiac index <2 liters/min per m²). The doses administered produced clear electrophysiologic effects on ventricular repolarization as evidenced by QTc interval prolongation. There was also a modest but significant decrease in heart rate at the higher dose. The findings of the present study may have important clinical implications. All currently available intravenous antiarrhythmic drugs (lidocaine, procainamide and bretylium) used for the acute termination or prevention of cardiac arrhythmias either markedly depress cardiac function or produce hypotension. To our knowledge, the present study is the first to evaluate the hemodynamic effects of a pure class III antiarrhythmic agent in humans, particularly those with congestive heart failure. It confirms previous suggestions that the cardiodepressant effects of antiarrhythmic drugs in humans are related to sodium channel, calcium channel or beta-adrenergic blockade and are unrelated to selective effects on repolarization.

Previous studies. The results of a number of recent clinical investigations (1–3,20) have emphasized that class I antiarrhythmic agents, which slow conduction, can depress cardiac function and are potentially proarrhythmic. The combination of cardiodepression and proarrhythmia may explain the failure of antiarrhythmic drugs to prevent sudden cardiac death and

Table 3. Effects of Sematilide Infusion on Electrocardiographic Intervals

<table>
<thead>
<tr>
<th></th>
<th>Low Dose</th>
<th></th>
<th>High Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Loading</td>
<td>Maintenance</td>
<td>Baseline</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>189 ± 35</td>
<td>184 ± 40</td>
<td>184 ± 44</td>
<td>174 ± 24</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>113 ± 37</td>
<td>114 ± 41</td>
<td>117 ± 41</td>
<td>100 ± 29</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>381 ± 56</td>
<td>383 ± 53</td>
<td>398 ± 56*</td>
<td>356 ± 44</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>443 ± 47</td>
<td>444 ± 49</td>
<td>459 ± 50*</td>
<td>424 ± 29</td>
</tr>
</tbody>
</table>

*p < 0.025 versus baseline. QTc = corrected QT interval; other abbreviations as in Table 1.
the finding that these agents may actually increase mortality in certain patient groups (21–26). Thus, class III antiarrhythmic agents have received increased interest and investigation, even though these agents have clearly been demonstrated to produce proarrhythmic effects, in particular torsade de pointes (27). Amiodarone and sotalol appear to have high efficacy in suppressing ventricular tachyarrhythmias and potentially in decreasing mortality, but several studies (5–7) indicate that these agents can worsen congestive heart failure. However, neither of these agents is a pure class III agent because they exert a number of other clinically significant actions, including beta-adrenergic blockade. A recent study (18) demonstrated that sematilide, a selective class III agent, was effective in suppressing the induction of sustained ventricular tachycardia in 41% of patients treated with this agent.

It has been suggested that a pure class III agent might have a positive inotropic effect that could be beneficial in the treatment of arrhythmias in patients with congestive heart failure. The mechanism of this effect is hypothesized to be secondary to prolongation of phase 3 of the action potential, which theoretically can increase intracellular calcium (28) without directly influencing peak calcium currents. In animal studies (9,29) the prolongation in action potential duration produced by class III antiarrhythmic agents is associated with increases in contractile force. The hemodynamic effects of sematilide have been examined in conscious and anesthetized dogs with normal hearts or ischemia-induced heart failure (10). No significant deleterious effects on blood pressure, cardiac output, maximal rate of increase of left ventricular pressure (dP/dt) or coronary blood flow were demonstrated with intravenous doses up to 100 mg/kg. Dofetilide, another class III antiarrhythmic agent, has also been used in investigations in both conscious and anesthetized dogs with normal or ischemic hearts or cardiac failure (14,15). In doses over a wide range, dofetilide produced either no significant change in cardiac function or small increases in left ventricular contractility. Studies with at least two other investigational class III agents have demonstrated similar findings in animal models (16,17). The results of the present study extend these observations to humans with congestive heart failure.

Electrophysiologic effects. The electrocardiographic effects of sematilide, which included decreases in heart rate and QTc prolongation without effect on PR or QRS intervals, are consistent with selective class III actions. The decrease in heart rate has been observed previously with sematilide and with other selective class III agents, such as d-sotalol (30), and is most likely a result of prolongation of action potential duration in the sinus node (31). In contrast to a previous study with sematilide (20), there were no statistically significant correlations between the plasma concentrations of sematilide and changes in RR intervals. As has been demonstrated with other agents that have the potential to produce torsade de pointes (32–34), the increases in QT and QTc intervals produced by sematilide were dose dependent and were linearly correlated with plasma sematilide concentrations. The combination of decreasing heart rate and prolonging repolarization may be particularly hazardous and raises concern regarding the potential proarrhythmic effect of sematilide. Four (21%) of 19 patients who received the high dose of sematilide had excessive QT prolongation. One of these patients developed spontaneous, sustained, polymorphic ventricular tachycardia. This finding may limit the drug's usefulness at higher doses and is consistent with other reports of class III antiarrhythmic agents.

Study limitations. 1) The present study was not designed as a blinded, placebo-controlled trial. However, the findings that sematilide did not alter hemodynamic variables and prolonged QT and QTc intervals in a dose-dependent manner make the need for a placebo control less important. 2) The hemodynamic effects of antiarrhythmic drugs should be assessed after both short- and long-term oral therapy. A previous investigation (18) that evaluated the electrophysiologic actions of sematilide and included patients with depressed ventricular function found that no patient developed worsening or new symptoms of congestive heart failure during long-term oral sematilide therapy. 3) The decreases in heart rate may have offset any potentially positive inotropic effect of sematilide, and changes in autonomic tone may have obscured the direct effects of this agent on cardiac function.

Conclusions. Intravenous sematilide, in the doses administered, produced consistent class III antiarrhythmic effects on repolarization but exerted no adverse hemodynamic or cardio depressant effects in patients with moderate to severe congestive heart failure. These results suggest that selective class III antiarrhythmic drugs that block outward potassium channels and are devoid of sodium channel and autonomic effects may be used safely and will not adversely affect hemodynamic variables in patients with congestive heart failure. Concerns regarding the proarrhythmic potential of these agents secondary to excessive QT prolongation continue and may limit their clinical utility at higher doses. Larger studies with other intravenous and oral class III antiarrhythmic drugs designed to determine their long-term safety profile are warranted.

We gratefully acknowledge the assistance of the clinical cardiovascular research division of Berlex Laboratories in data collection and statistical analysis.

References
5. Winters SL, Kakin M, Pf E, Stewart D, Deitchman D, Gomes IA. Effect of oral sotalol on systemic hemodynamics and programmed electrical stimula-
HEMODYNAMIC EFFECTS OF SEMATILIDE

10. Wiggins J, Sullivan ME, Doroshuk CM, Reiser HJ. Antiarrhythmic and
13. Argentieri TM, Carroll MS, Sullivan ME. Cellular electrophysiologic effects
15. Mortensen E, Yang T, Refsum H. Class III antiarrhythmic action and
14. Dalrymple HW, Butler P, Dodd MG, et al. Electrocardiographic and
19. Wong W, Pavlou HN, Birgersdotter UM, Hilleman DE, Mohiuddin SM.
17. Spinelli W, Moubarak IF, Parsons RW, Colatsky TJ. Electrophysiological
14. Dailymple HW, Butler P, Dodd MG, et al. Electrocardiographic and
hemodynamic effects in conscious dogs of UK-68,798, a new class III
and hemodynamic profile of sematilide HCl in canine cardiac tissues
15. Mortensen E, Yang T, Refsum H. Class III antiarrhythmic action and
inotropy: effects of dofenitide in acute ischemic heart failure in dogs.
selective prolongation of refractoriness. Electrophysiologic actions of se-
19. Wong W, Pavlou HN, Birgersdotter UM, Hilleman DE, Mohiuddin SM.
Rodent DM. Pharmacology of the class III antiarrhythmic agent sematilide
20. Stambler BS, Wood MA, Ellenbogen KA. Sudden death in patients with
21. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators Prelimi-
inary Report. Effect of encainide and flecainide on mortality in a randomized
22. Cardiac Arrhythmia Suppression Trial II Investigators. Ethmozine exerts
an adverse effect on mortality in survivors of acute myocardial infarction.
23. Mason JW, for the Electrophysiologic Study Versus Electrocardiographic
Monitoring Investigators. A comparison of the electrophysiologic testing
with Holter monitoring to predict antiarrhythmic efficacy for ventricular
24. Mason JW, for the Electrophysiologic Study Versus Electrocardiographic
Monitoring Investigators. A comparison of seven antiarrhythmic drugs in
25. Furberg CD. Effects of antiarrhythmic drugs on mortality after myocardial
infarction. Am J Cardiol 1993;52:22C-6C.
safety of quinidine therapy for the maintenance of sinus rhythm after
cardioversion. A meta-analysis of randomized control trials. Circulation
1990;82:1106-16.
27. Singh BN, Sarma JS, Zhang ZH, Takanaka C. Controlling cardiac arrhyth-
rias by lengthening repolarization: rationale from experimental findings and
28. Cingolani HE, Wiedman RT, Lynch JJ, Sanguinetti M. Negative lusitropic
effects of DPI 201-106 and E4031: possible role of prolonging action
29. Morad M, Trautwein W. The effect of the duration of the action potential on
contraction in the mammalian heart muscle. Pflugers Arch 1968;299:66-82.
30. Funk-Bretano C, Silverstein DJ, Wood AJJ, Roden DM, Woosley RL. A
mechanism of d-(-)-sotalol effects on heart rate not related to beta-
31. Campbell TJ. Cellular electrophysiological effects of o- and n-sotalol in
guinea pig sinoatrial node, atrium and ventricle and human atrium: differ-
32. Ncuvonen PJ, Elonen E, Vuorenmaa T, Lankso M. Prolonged QT interval
and severe tachyarrhythmia, common features of sotalol intoxication. Eur J
33. Chow MJ, Pierson AA, Bowler DJ, et al. Torsades de pointes induced by
34. McKibbin JK, Pockoo WA, Barlow JB, Millar RNS, Obel IWP, Sotalol,