Risks of Initiating Therapy With Sotalol for Treatment of Atrial Fibrillation*

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In this issue of the Journal, Chung et al. (1) reviewed complications of sotalol for treatment of atrial arrhythmias in a retrospective analysis of 120 patients in whom sotalol was initiated in the hospital. Because 97.5% of the patients were treated for atrial fibrillation or flutter the study was essentially an evaluation of treatment of this particular arrhythmia. Of these 120 patients, 25 (21%) had 35 complications, including 7 (6%) who developed ventricular arrhythmias, 2 of whom had torsade de pointes. The patient cohort was unique when compared with that of other reported trials of sotalol for torsade de pointes. The patient cohort was unique when compared with that of other reported trials of sotalol for treatment of atrial fibrillation. For example, 24% of patients compared with that of other reported trials of sotalol for torsade de pointes. The patient cohort was unique when compared with that of other reported trials of sotalol for treatment of atrial fibrillation. For example, 24% of patients had permanent pacemakers before the onset of antiarrhythmic therapy. It is therefore not surprising that absence of the pacemaker was the only significant predictor of arrhythmia complications because bradycardia was the most frequent arrhythmia reported. In addition, 12 patients (10%) had a history of sustained ventricular tachycardia or ventricular fibrillation before the start of sotalol therapy. It is well known that patients with sustained ventricular arrhythmias have a higher incidence of proarrhythmia with sotalol. Therefore, it is not unexpected that seven of the patients (6%) developed new onset or increased ventricular arrhythmias. The percentage of arrhythmia complications was enhanced by the inclusion of bradycardia at a rate of <40 beats/min, even during sleep, as “significant arrhythmias.” Of the two patients reported as having torsade de pointes, one had a potassium level of 3.4 mmol/liter from diuretic therapy. Hypokalemia, even in the low “normal range” of 3.5 to 3.9 mmol/liter, is a known risk factor for torsade de pointes. The other patient had an implantable cardioverter-defibrillator and developed polymorphic ventricular tachycardia. It may be difficult to differentiate torsade de pointes from polymorphic ventricular tachycardia unless the classic pattern of the short-long sequence is present, as well as a markedly prolonged QT. It should be mentioned that 24 of the patients had no underlying heart disease. Of these 24, 2 developed bradycardia, and 1 had increased ven-

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tricular ectopic beats that led to discontinuation of sotalol. I would entirely agree with the authors that many, if not the majority, of patients analyzed in this series should have sotalol initiated under telemetric surveillance in the hospital.

Before one accepts the general recommendation of Chung et al. that sotalol treatment for atrial fibrillation should be started in the hospital, the experience of other investigators should be reviewed. Although most of the studies were trials comparing sotalol with other antiarrhythmic drugs, such as propafenone and quinidine, this editorial comment focuses on considerations of safety during the initiation of treatment with sotalol for atrial fibrillation (Table 1).

In the accumulated experience of 384 patients treated with sotalol for persistent or paroxysmal atrial fibrillation only 1 had torsade de pointes during the first few days of treatment, and this patient had a serum potassium level of 3.7 mmol/liter (2–9). Bradycardia was frequent but not life threatening and was often asymptomatic. A few patients required a permanent pacemaker to allow continuation of treatment with sotalol. The bradycardia usually resolved by decreasing the dose or stopping the drug. It should be emphasized that the patients reported in these series had a wide variety of conditions. Most had coronary ischemic heart disease or hypertension, but there were patients with valvular disease. A minority of patients who had no evidence of cardiac disease were also included.

If outpatient treatment with sotalol for treatment of atrial fibrillation is contemplated, the incidence of torsade de pointes, the major life-threatening cardiovascular complication, must be nil. How can this frightening proarrhythmic complication be avoided? There are now a number of risk factors for torsade de pointes from sotalol that have been identified. Of these, one that has been repeatedly implicated is a serum potassium level <4.0 mmol/liter at baseline (10). To avoid hypokalemia, patients receiving sotalol for treatment of atrial fibrillation should not be taking concomitant diuretic therapy. If they are, it should be demonstrated over weeks or months they have stable levels of potassium >4.0 mmol/liter, and serum potassium levels should be checked frequently after treatment with sotalol. Other factors predisposing to torsade de pointes in patients receiving sotalol in decreasing order of importance are female gender, sustained ventricular arrhythmia, history of congestive heart failure and sotalol dose >320 mg daily (11,12). Patients who developed torsade de pointes had longer baseline and maximal corrected QT (QTc) intervals, as well as greater changes in the mean value of these intervals on the electrocardiogram (ECG). Juul-Møller et al. (3) found that lower maintenance doses of sotalol appear to be as effective as higher doses in maintaining normal sinus rhythm. Therefore, dose as a risk factor can be eliminated by restricting the dose to 80 mg twice a day, with an upper limit of 320 mg/day in patients with recurrences. Because sotalol is excreted entirely by renal mechanisms, and because creatinine clearance is often decreased by 50% in patients >65 years old, the dose of sotalol may need to be lower in the elderly (13). Therefore, in elderly patients it is advisable to start with a dose
of 40 mg twice a day for 1 day and observe whether an excessive prolongation of the QT interval or significant bradycardia occurs before proceeding to higher doses.

Most of the early experience with risk factors for torsade de pointes came from experience with quinidine (14). With that drug, torsade de pointes was most commonly observed after cardioversion to normal sinus rhythm with a slow ventricular response. Thus, it may be safer to convert atrial fibrillation to sinus rhythm electrically and reassess suitability for treatment with sotalol 2 h after resumption of sinus rhythm, as was done by Juul-Møller et al. (3), rather than start sotalol before electrical cardioversion. This strategy provides an opportunity to more accurately measure the QT interval and look for sinus bradycardia. The success rate of reversion to sinus rhythm with direct current cardioversion has been reported to be 86% in patients with chronic atrial fibrillation not treated with antiarrhythmic drugs (15). Information (prior to drug administration) that can be obtained from the surface ECG that could predict an increased likelihood of QTc interval prolongation (>500 ms) includes a marked increase in the QT interval after a pause, postextrasystolic T wave abnormality and failure of the QT interval to appropriately shorten during autonomic stimulation maneuvers, such as the Valsalva maneuver, or during exercise (16). Identification of patients receiving anti-

<table>
<thead>
<tr>
<th>Study (ref no.)</th>
<th>Year Published</th>
<th>No. of Pts</th>
<th>Type of A Fib</th>
<th>Dose (mg bid)</th>
<th>Adverse Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman et al. (2)</td>
<td>1990</td>
<td>48</td>
<td>PAF and CAF</td>
<td>80–160</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Juul-Møller et al. (3)</td>
<td>1990</td>
<td>97</td>
<td>CAF</td>
<td>80</td>
<td>—</td>
<td>1*</td>
</tr>
<tr>
<td>Crijns et al. (4)</td>
<td>1991</td>
<td>39</td>
<td>CAF</td>
<td>269 ± 49 (total daily dose)</td>
<td>7.6%</td>
<td>0</td>
</tr>
<tr>
<td>Hohnloser et al. (5)</td>
<td>1995</td>
<td>25</td>
<td>CAF</td>
<td>80 on day 1; 160 on days 2-7</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Singh et al. (6)</td>
<td>1991</td>
<td>24</td>
<td>CAF</td>
<td>40–160</td>
<td>8%‡</td>
<td>0</td>
</tr>
<tr>
<td>Reimold et al. (7)</td>
<td>1993</td>
<td>50</td>
<td>PAF and CAF</td>
<td>80–160</td>
<td>8%§</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al. (8)</td>
<td>1997</td>
<td>38</td>
<td>PAF</td>
<td>80</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Wanless et al. (9)</td>
<td>1997</td>
<td>81</td>
<td>SVT, including 63 with PAF or paroxysmal A flutter</td>
<td>80 or 160 mg</td>
<td>0</td>
<td>6 pts¶</td>
</tr>
</tbody>
</table>

*The one patient who developed torsade de points had a serum potassium level of 3.7 mmol/liter; in addition the QT interval prolonged to 0.67 s, and she developed bradycardia of 47 beats/min, which occurred on day 2 of treatment with sotalol (80 mg twice daily). †Adverse effects within 1 week of therapy; no further details given. ‡Paroxysmal atrial fibrillation (PAF) and chronic atrial fibrillation (CAF). §Not stated if this occurred during initiation of sotalol or during follow-up. ¶Not stated when they occurred; no ventricular proarrhythmia or congestive heart failure; “typical beta-blocking side effects, including bradycardia, dyspnea and fatigue.” A Fib = atrial fibrillation; A flutter = atrial flutter; AV = atrioventricular; bid = twice daily; CHF = congestive heart failure; DC = direct current; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; Pts = patients; QTc = corrected QT interval; ref = reference; SBP = systolic blood pressure. |
arrhythmic drug therapy at risk for torsade de pointes is aided not only by measurement of the QT interval but also by observing the appearance of prominent U waves, which can be equal to or greater in amplitude than the T wave (17,18), or abnormal QTU prolongation and distortion after pauses (19,20). A paradoxical increase in the QTc interval was observed during exercise in 11 patients taking class 1A antiarrhythmic drugs who developed polymorphic ventricular tachycardia compared with patients taking these drugs who did not develop this arrhythmia (21). Technology has now been developed to measure the QT interval from a 24-h Holter recording. This technology could permit outpatient assessment of the QT interval during treatment with low dose sotalol (22,23). It has been reported (24) that excessive prolongation of the QTc interval during treatment with sotalol may be predictive of a predisposition to torsade de pointes.

There is limited experience with initiating antiarrhythmic drug therapy for treatment of atrial fibrillation on an outpatient basis. Prystowsky (25) reviewed the published reports on complications associated with starting antiarrhythmic drug therapy for atrial fibrillation using a variety of antiarrhythmic drugs. He concluded that patients without structural heart disease, sinus node dysfunction or atrioventricular conduction abnormalities who have a normal baseline QT interval do not need to be admitted to the hospital for initiation of drug therapy. However, patients with heart disease should be observed in the hospital when quinidine, disopyramide, procainamide, amiodarone or sotalol are prescribed. The recently published American Heart Association Guidelines (26) for management of patients with atrial fibrillation states that proarrhythmia is relatively rare in patients without heart disease and that initiation of antiarrhythmic treatment is reasonable in this select patient population. This document also states that patients with ventricular hypertrophy may be at increased risk for developing torsade de pointes, although this statement was not based on clinical data.

Maisel et al. (27) performed a retrospective chart review of 597 drug trials for treatment of atrial fibrillation. Antiarrhythmic drugs included procainamide, quinidine, disopyramide, propafenone and sotalol. Structural heart disease was present in 90% of patients. Of the 72 patients treated with sotalol, the usual dose was 80 mg twice a day. Eight of these patients had bradyarrhythmias. It is not stated whether these required immediate therapy other than decreasing the dose or stopping the drug. Two patients treated with sotalol had nonsustained ventricular tachycardia. One patient had QT interval prolongation. Recently a trial of outpatient initiation of antiarrhythmic drug therapy for patients with atrial fibrillation was reported (28). There were 113 patients who were in sinus rhythm after having undergone cardioversion or had reverted spontaneously. Patients with ventricular arrhythmias, the long QT syndrome or an implanted pacemaker were excluded. Transtelephonic monitoring of ECGs was performed daily. Patients were followed up for 10 days. Sotalol was used in 12 patients. Of these 12 patients, 1 developed QT prolongation >0.50 ms, leading to discontinuation of the drug, and 1 developed symptomatic bradycardia with subsequent permanent pacemaker implantation. Torsade de pointes was not observed. All these adverse effects with sotalol occurred beyond the usual 72 h period for inpatient antiarrhythmic drug monitoring. Chung et al. (1) concluded that outpatient initiation of antiarrhythmic drug therapy using transtelephonic monitoring after cardioversion of atrial fibrillation or flutter is safe.

By selecting patients who have a low risk for torsade de pointes, utilizing low doses and by careful outpatient ECG monitoring, there is evidence that sotalol can be initiated safely on an outpatient basis for the treatment of atrial fibrillation or flutter. It would seem that the risk of torsade de pointes or severe bradycardia may be minimized if the drug is started after cardioversion. It is likely that this strategy can be applied safely to patients with underlying heart disease, such as those with a history of hypertension, coronary ischemic heart disease or valvular heart disease.

To hospitalize or not to hospitalize for initiating treatment with sotalol—that is the question. Whether ‘tis safer to do so or risk the unlikely event of torsade de pointes and bring on the wrath of the malpractice lawyers is yet unknown. This is the question that must be answered by prospective clinical trials.

References
11. MacNeil DJ. The side effect profile of class III antiarrhythmic drugs; focus on d,l-sotalol. Am J Cardiol 1997;80:90G–8G.