Precordial QT Interval Dispersion as a Marker of Torsade de Pointes
Disparate Effects of Class Ia Antiarrhythmic Drugs and Amiodarone

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Background. Patients with a history of class Ia drug–induced torsade de pointes have been treated with chronic amiodarone without recurrence of torsade de pointes despite comparable prolongation of the QT interval. We hypothesized that in such patients, class Ia drugs cause nonhomogeneous prolongation of cardiac repolarization times, whereas amiodarone causes homogeneous prolongation of cardiac repolarization times.

Methods and Results. Thirty-eight consecutive patients who received both class Ia drug therapy and chronic amiodarone therapy were evaluated. Standard 12-lead ECGs at baseline and during each therapy were used to calculate precardial QT interval dispersion (maximum QT in leads V₁ through V₄ minus minimum QT leads V₁ through V₄) as a measure of regional variabilities in ventricular repolarization times. Nine of these patients had torsade de pointes during class Ia drug therapy. In these nine patients, class Ia drug therapy and amiodarone significantly prolonged the maximum QT interval to comparable extents. However, class Ia drug therapy but not amiodarone therapy significantly increased precardial QT interval dispersion (101±37 versus 49±26 msec; baseline, 44±12 msec; p=0.002). In the 29 patients without class Ia drug–induced torsade de pointes, neither class Ia drug therapy nor amiodarone therapy significantly increased QT interval dispersion (50±6 versus 69±7 msec; baseline, 54±5 msec). None of the patients with class Ia drug–induced torsade de pointes had recurrent torsade de pointes during chronic amiodarone therapy.

Conclusions. An increase in regional QT interval dispersion during class Ia antiarrhythmic drug therapy is associated with torsade de pointes. Chronic amiodarone therapy in patients with a history of class Ia drug–induced torsade de pointes produces comparable maximum QT interval prolongation but does not increase QT interval dispersion. This characteristic may explain its apparent safe use in patients with a history of class Ia drug–induced torsade de pointes. (Circulation 1992;86:1376–1382)

KEY WORDS • antiarrhythmics • torsade de pointes • QT interval • proarrhythmia

The ECG QT interval reflects the process of ventricular repolarization. Changes in ventricular repolarization times often produce corresponding changes in the ECG QT interval. Accordingly, the QT interval is used clinically to monitor the effects of antiarrhythmic drugs on ventricular repolarization times. All antiarrhythmic drugs that prolong ventricular repolarization times and, therefore, the QT interval may cause torsade de pointes ventricular tachycardia in susceptible individuals, particularly in the presence of hypokalemia and/or bradycardia. This proarrhythmic potential is well documented with class Ia antiarrhythmic drugs such as quinidine, procainamide, and disopyramide.

As a class III agent, amiodarone also prolongs ventricular repolarization times and the QT interval, but torsade de pointes is rare during amiodarone therapy. Furthermore, chronic amiodarone therapy has been reported to be safe in patients who previously had developed torsade de pointes due to class Ia antiarrhythmic drugs.

We hypothesized that the difference between class Ia antiarrhythmic drug therapy and chronic amiodarone therapy in terms of their potential to induce torsade de pointes is that prolongation of ventricular repolarization times with class Ia drug therapy is nonhomogeneous and prolongation of ventricular repolarization times with amiodarone therapy is homogeneous. Nonhomogeneous prolongation of ventricular repolarization times is manifested by nonhomogeneous regional QT interval prolongation, whereas homogeneous prolongation of ventricular repolarization times is paralleled by homogeneous regional QT interval prolongation. The purpose of this study was to compare the relative effects
of class Ia antiarrhythmic drug therapy and amiodarone therapy on regional QT interval dispersion in both patients with and without antiarrhythmic drug-induced torsade de pointes. Regional QT interval dispersion was measured from standard 12-lead ECGs in a manner similar to that described and validated by Campbell and colleagues.8-10

Methods

Patient Population

From our arrhythmia service data base, we identified and included a consecutive series of patients who developed class Ia drug-induced torsade de pointes and subsequently received chronic amiodarone therapy. A second consecutive series of patients who were exposed to a class Ia antiarrhythmic drug without developing torsade de pointes and subsequently received chronic amiodarone therapy served as a comparison group.

ECG Interval Measurements

Standard 12-lead ECGs (Hewlett-Packard digital recorder model 4745A) were performed daily at a paper speed of 25 mm/sec in all patients during the initiation of class Ia antiarrhythmic drug therapy. The ECGs used for interval measurements were those performed 1) at baseline, after discontinuation of antiarrhythmic drugs for at least five half-lives; 2) during therapy with class Ia antiarrhythmic drugs at steady-state therapeutic drug levels, except as noted below; and 3) after 10 weeks of amiodarone therapy. This duration of amiodarone therapy was chosen because the class III effects of amiodarone are maximal at this time.11 For patients who developed torsade de pointes early after the initiation of class Ia antiarrhythmic drug therapy, before reaching steady state, the ECG representing the effects of class Ia therapy was that performed closest to the episode of torsade de pointes.

ECG interval measurements were performed by an observer blinded to the treatment in use and the subsequent occurrence or nonoccurrence of torsade de pointes. The RR, QT, and JT intervals were measured during sinus rhythm in each of the standard V1 through V6 precordial leads. For the latter two measurements, the point of T wave offset was defined by return of the terminal T wave to the TP baseline. When a U wave was present and interrupted the T wave, the terminal portion of the visible T wave was extrapolated to the TP baseline to identify the point of T wave offset. Each interval measurement recorded was the average of those intervals available on the patient’s 12-lead ECG. The difference between the maximum and minimum precardial QT intervals on each ECG was used as a measure of regional QT interval dispersion.8-10 Similarly, the difference between maximum and minimum precardial JT intervals was used as a measure of regional JT interval dispersion. Each QT interval, JT interval, QT interval dispersion, and JT interval dispersion were corrected for the patient’s heart rate using Bazett’s formula \[QT_c = QT/\sqrt{RR(\text{sec})}\] where QTc is corrected QT interval.12

Torsade de Pointes

Torsade de pointes was considered to have complicated antiarrhythmic drug therapy when ECG monitoring revealed the spontaneous occurrence of a polymorphic ventricular tachycardia of at least seven consecutive beats with a long–short initiation sequence in the presence of excessive QT interval prolongation (QTc >500 msec) immediately before tachycardia. A typical example of torsade de pointes complicating class Ia drug therapy is shown in Figure 1.

Statistical Analysis

Continuous data are presented as mean±1 SD. One-way ANOVA and the Bonferroni correction for multiple comparisons were used to test the significance of differences in ECG interval measurements at baseline, during class Ia antiarrhythmic drug therapy, and during chronic amiodarone therapy in each group of patients. Unpaired Student’s t tests were used to test the significance of differences between patients who did and those who did not develop torsade de pointes. Differences in proportional data were tested using \(x^2\) analysis or Fisher’s exact test as appropriate. A two-tailed value of \(p<0.05\) was considered statistically significant.

Results

Study Population

The clinical and demographic characteristics of the study population are presented in Table 1. The majority of the patients in this study had received antiarrhythmic drug therapy for the treatment of ventricular tachyarrhythmias occurring in the setting of chronic atherosclerotic heart disease. Accordingly, most were middle-age men with significantly depressed left ventricular function. Torsade de pointes complicated therapy with class Ia antiarrhythmic drugs in nine patients, whereas 29 patients did not develop this complication. The demo-
graphic characteristics of patients with and without torsade de pointes are summarized in Table 1. Patients who responded to class Ia antiarrhythmic drug therapy by developing torsade de pointes were more likely to be female and had lower left ventricular ejection fractions, but these differences were not statistically significant.

Individual characteristics of patients who developed class Ia drug–induced torsade de pointes are presented in Table 2. Quinidine was responsible for torsade de pointes in the majority of these patients. The median time to torsade de pointes was 4 days after class Ia drug therapy initiation. In three patients, torsade de pointes occurred within 2 days of initiating antiarrhythmic drug therapy. In these three patients, the ECG representing the effects of class Ia therapy was recorded after two, three, and three drug dosages (2, 7, and 12 hours before torsade de pointes, respectively). Trough antiarrhythmic drug serum concentrations and serum potassium concentrations (when available within 48 hours of torsade de pointes in the absence of dosage change or therapeutic intervention) also are presented in Table 2.

 Patients With Torsade de Pointes

Population QT interval, QTc, interval, JT interval, and JTc, interval data at baseline, during class Ia drug therapy, and during chronic amiodarone therapy in patients who developed class Ia drug–induced torsade de pointes are given in Figure 2. Both class Ia drug therapy and amiodarone therapy increased the maximum QT, QTc, JT, and JTc intervals to comparable extents in this patient population. In contrast, class Ia drug therapy but not amiodarone therapy significantly increased regional QT dispersion, QTc dispersion, JT dispersion, and JTc dispersion in these patients (Figure 3).

 Patients Without Torsade de Pointes

The ECG interval measurements at baseline, during class Ia drug therapy, and during chronic amiodarone therapy in patients who did not develop class Ia drug–induced torsade de pointes are shown in Figures 4 and 5. Again, both class Ia drug therapy and amiodarone therapy prolonged maximum QT, QTc, JT, and JTc intervals. However, in this patient population, the increase in these intervals during amiodarone therapy was significantly greater than that during class Ia drug therapy (Figure 4). The increases in uncorrected QT and JT intervals with class Ia drug therapy in patients without torsade de pointes did not reach statistical significance. Furthermore, in this patient population, neither class Ia drug therapy nor amiodarone therapy significantly increased QT dispersion over their respective baseline values (Figure 5).

### Table 1. Characteristics of Patients With and Without Class Ia Drug-Induced Torsade de Pointes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Patients with torsade de pointes</th>
<th>Patients without torsade de pointes</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>38</td>
<td>9</td>
<td>29</td>
<td>. .</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64±10</td>
<td>65±11</td>
<td>64±9</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>30 (79)</td>
<td>6 (67)</td>
<td>24 (83)</td>
<td>0.36</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.39±0.16</td>
<td>0.31±0.13</td>
<td>0.41±0.16</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASHD</td>
<td>37 (97)</td>
<td>8 (89)</td>
<td>29 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Rhythm treated (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>37 (97)</td>
<td>8 (89)</td>
<td>29 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>AF</td>
<td>1 (3)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVEF, radionuclide left ventricular ejection fraction; ASHD, atherosclerotic heart disease; Other, nonatherosclerotic heart disease; VT, ventricular tachycardia; VF, ventricular fibrillation; AF, atrial fibrillation; NS, not statistically significant.

### Table 2. Characteristics of Patients With Class Ia Drug-Induced Torsade de Pointes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/sex</th>
<th>Drug</th>
<th>Exposure time (days)</th>
<th>Drug level (μM)</th>
<th>K⁺ (mM)</th>
<th>QTc (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66/female</td>
<td>Quinidine</td>
<td>1</td>
<td>10.3</td>
<td>4.3</td>
<td>45 98</td>
</tr>
<tr>
<td>2</td>
<td>66/male</td>
<td>Quinidine</td>
<td>2</td>
<td>10.8</td>
<td>ND</td>
<td>43 604</td>
</tr>
<tr>
<td>3</td>
<td>54/male</td>
<td>Quinidine</td>
<td>2</td>
<td>5.4</td>
<td>4.6</td>
<td>47 535</td>
</tr>
<tr>
<td>4</td>
<td>71/male</td>
<td>Quinidine</td>
<td>4</td>
<td>15.8</td>
<td>4.2</td>
<td>51 558</td>
</tr>
<tr>
<td>5</td>
<td>71/male</td>
<td>Quinidine</td>
<td>4</td>
<td>13.6</td>
<td>5.6</td>
<td>48 711</td>
</tr>
<tr>
<td>6</td>
<td>77/male</td>
<td>Quinidine</td>
<td>10</td>
<td>9.5</td>
<td>5.0</td>
<td>40 512</td>
</tr>
<tr>
<td>7</td>
<td>61/male</td>
<td>Quinidine</td>
<td>60</td>
<td>11.8</td>
<td>4.4</td>
<td>45 493</td>
</tr>
<tr>
<td>8</td>
<td>43/female</td>
<td>Procainamide</td>
<td>9</td>
<td>40</td>
<td>4.7</td>
<td>47 514</td>
</tr>
<tr>
<td>9</td>
<td>78/female</td>
<td>Disopyramide</td>
<td>17</td>
<td>10.3</td>
<td>ND</td>
<td>353 643</td>
</tr>
</tbody>
</table>

Drug level, trough antiarrhythmic drug serum concentrations (μM); K⁺, serum potassium concentration (mM); NAPA, N-acetyl-procainamide; ND, not done.
Comparison of Patients With and Without Torsade de Pointes

Direct comparisons of the ECG interval measurements in patients with and without class Ia drug-induced torsade de pointes are presented in Figures 6 and 7. At baseline and during chronic amiodarone therapy, there were no significant differences in maximum QT, QTc, JT, or JTc intervals between patients with and those without class Ia drug–induced torsade de pointes. However, during class Ia drug therapy, patients who developed torsade de pointes had significantly greater increases in QT intervals (but not QTc, JT, or JTc intervals) than did patients who did not develop torsade de pointes (Figure 6). In patients with and those without class Ia drug–induced torsade de pointes, QT, QTc, JT, and JTc dispersions were similar and unchanged from baseline values during amiodarone therapy (Figure 7). However, during class Ia drug therapy, patients who developed torsade de pointes had significantly greater increases in QT, QTc, JT, and JTc dispersion measurements (Figure 7).

Figure 2. Bar graphs of comparisons of mean (+1 SD) QT, QTc, JT, and JTc interval data in the antiarrhythmic drug–free state (DF), during class Ia drug therapy (Ia), and during chronic amiodarone therapy (AMIO) in the nine patients who developed class Ia drug–induced torsade de pointes. *p<0.05; NS, not statistically significant.

Figure 3. Bar graphs of comparisons of mean (+1 SD) regional QT, QTc, JT, and JTc dispersion data in the antiarrhythmic drug–free state (DF), during class Ia drug therapy (Ia), and during chronic amiodarone therapy (AMIO) in the nine patients who developed class Ia drug–induced torsade de pointes. *p<0.05; NS, not statistically significant.

Figure 4. Bar graphs of comparisons of mean (+1 SD) QT, QTc, JT, and JTc interval data in the antiarrhythmic drug–free state (DF), during class Ia drug therapy (Ia), and during chronic amiodarone therapy (AMIO) in the 29 patients who did not develop class Ia drug–induced torsade de pointes. *p<0.05; NS, not statistically significant.

Figure 5. Bar graphs of comparisons of mean (+1 SD) regional QT, QTc, JT, and JTc dispersion data in the antiarrhythmic drug–free state (DF), during class Ia drug therapy (Ia), and during chronic amiodarone therapy (AMIO) in the 29 patients who did not develop class Ia drug–induced torsade de pointes. *p<0.05; NS, not statistically significant.
In the present study, we assessed the effects of class Ia antiarrhythmic drugs and amiodarone on precordial QT interval dispersion in patients with and without class Ia drug–induced torsade de pointes. The results demonstrate a unique response of precordial ECG measures of ventricular repolarization times in patients who develop class Ia drug–induced torsade de pointes. Such patients demonstrate prolongation of both single-lead measures of ventricular repolarization time and precordial-lead measures of dispersion of regional ventricular repolarization times. However, patients who do not develop class Ia drug–induced torsade de pointes and patients receiving amiodarone therapy (regardless of their response to class Ia drug therapy) demonstrate prolongation of only single-lead measures of ventricular repolarization time. Specifically, chronic amiodarone therapy is not associated with increases in measures of dispersion of regional ventricular repolarization times, even in patients exhibiting this response and torsade de pointes on class Ia drug therapy. This disparate effect of class Ia drug therapy and amiodarone therapy on measures of dispersion of regional ventricular repolarization times occurs despite comparable prolongation of single-lead measures of ventricular repolarization times.

**Previous Studies of Dispersion of Ventricular Repolarization Times**

Lead-dependent variabilities in measured QT intervals have been recognized for many years,14–16 The choice of lead is the single most important factor contributing to QT interval measurement variability.17 Lead dependence of QT interval measurements was originally ascribed to technical rather than to biological phenomena. That lead-dependent QT interval differences reflect regional differences in ventricular repolarization times was originally postulated by Wilson et al.18 The ample contemporary demonstrations of these differences include demonstration of regional differences in monophasic action potential durations over both endocardial and epicardial surfaces of the in situ human heart.19–21 Furthermore, arrhythmogenic conditions known to be associated with torsade de pointes, such as congenital long QT interval syndromes, drug-induced long QT interval syndromes, and acute myocardial ischemia or infarction, have been demonstrated to increase the dispersion of both endocardial monophasic action potential durations22,23 and surface ECG QT intervals.5,10,15,24

In normal individuals, the difference between maximum and minimum QT intervals measured on the standard 12-lead ECG has been reported to be 54±27 msec15 and 48±18 msec.17 This difference is slightly greater (60–90 msec) when measured using multiple-lead (120–150) body surface potential map recordings.15,16 At baseline, precordial QT interval dispersions in the present study of patients with chronic atherosclerotic heart disease were comparable to the normal values cited above and did not differ between patients who later did or did not develop torsade de pointes in response to class Ia antiarrhythmic drug therapy (44±12 versus 53±29 msec, respectively). In contrast, torsade de pointes patients with congenital long QT interval syndromes have been reported to have greater regional dispersion of ventricular repolarization times as measured by mean ECG QT interval dispersions of 128–185
In the present study, patients with class Ia drug-induced torsade de pointes had increased ECG QT interval dispersion (101±37 msec) to a degree more comparable to that of patients with congenital long QT syndrome.

The effects of antiarrhythmic drug therapy on measures of dispersion of ventricular repolarization times have received little attention. In animal models or in humans without torsade de pointes, class Ia antiarrhythmic drug therapy is not associated with increases in the regional disparities of right ventricular refractory periods.25,26 We are unaware of any previous reports evaluating the effects of class Ia antiarrhythmic drug therapy on QT interval dispersion. The present study indicates that class Ia drug therapy increases QT interval dispersion only when that therapy is associated with torsade de pointes.

In a canine model, therapy with the class III agent bretylium was associated with a decrease in regional disparities of right ventricular effective refractory periods.27 Furthermore, in patients convalescing from acute myocardial infarction, therapy with the class III agent sotalol was associated with a decrease in QT interval dispersion.9 In the present study, therapy with the class III agent amiodarone had no significant effect on QT interval dispersion.

Pathophysiology of Class Ia Drug–Induced Torsade de Pointes

An evaluation of the potential mechanisms of torsade de pointes was the subject of a recent editorial by Surawicz.28 Although the two major theories of torsade de pointes pathogenesis (early afterdepolarizations and regional dispersion of ventricular repolarization times) are not mutually exclusive, each has its proponents. The results of the present study could be interpreted as support of the regional dispersion of ventricular repolarization time hypothesis. Nevertheless, to the extent that regional differences in ventricular afterdepolarizations may be manifest as regional QT interval variabilities, the results of the present study are not inconsistent with the early afterdepolarization hypothesis.

In the present study, baseline QT interval dispersions in patients who subsequently developed class Ia drug–induced torsade de pointes were not abnormally large and were comparable to baseline QT interval dispersions in patients who subsequently did not develop class Ia drug–induced torsade de pointes. Thus, the abnormality that predisposes an individual to develop class Ia drug–induced torsade de pointes cannot be detected by baseline, resting QT interval dispersion.

Clinical Implications

Patients who develop class Ia drug–induced torsade de pointes generally are considered to be at risk of developing the same complication when exposed to other class Ia or III antiarrhythmic drugs.29 Nevertheless, chronic amiodarone therapy in such patients has been reported to be safe.5,7 The results of the present study are consistent with these latter reports in that none of the patients with class Ia drug–induced torsade de pointes developed torsade de pointes while receiving chronic amiodarone therapy. One possible explanation for this observation is that the propensity for the class III actions of amiodarone to cause torsade de pointes is counterbalanced by the protective effects of the calcium antagonist and β-adrenoceptor–blocking actions of amiodarone. The data of the present study indicate that another possible explanation for this observation is regional homogeneity of the class III actions of amiodarone.

The data of the present study also suggest that routine determination of precordial dispersion of repolarization times during the initiation of class Ia antiarrhythmic drug therapy may have value in assessing the risk of a patient developing torsade de pointes. The potential use of QT interval dispersion as a screening test in this setting can only be evaluated in a large, consecutive series of patients exposed to class Ia drug therapy. Nevertheless, such a predictor of torsade de pointes would have value given that no relation between torsade de pointes and a critical QT, interval or critical increase in QTc interval has been established.

Conclusions

Class Ia antiarrhythmic drug therapy prolongs global measures of ventricular repolarization time. In patients who do not develop class Ia drug–induced torsade de pointes, this effect is regionally homogeneous as reflected in the absence of an increase in QT interval dispersion. However, in patients who develop torsade de pointes, ventricular repolarization times are prolonged in a nonhomogeneous fashion accompanied by an increase in QT interval dispersion. Chronic amiodarone therapy prolongs ventricular repolarization times in a homogeneous fashion, even in patients with a history of class Ia drug–induced torsade de pointes. This characteristic could, in part, explain the safe use of amiodarone in patients with a history of class Ia drug–induced torsade de pointes.

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