Mechanisms and Risks of Electrocardiographic QT Interval Prolongation When Using Antipsychotic Drugs

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This article reviews cardiac electrophysiology, with a focus on the assessment of the electrocardiographically determined corrected QT (QTc) interval and its role as a marker for potentially life-threatening cardiac arrhythmias such as torsades de pointes. Presently, using the QTc interval as a surrogate for polymorphic ventricular tachycardia is handicapped, in part, by the limitations of currently available group-derived formulas to estimate the QTc interval. Regulatory agencies have sharpened their interest in this arena. Substantial progress almost certainly awaits the application of individual rather than group-derived formulas to estimate the QTc interval. Until this refinement arrives, clinicians are advised to exercise caution when administering antipsychotic drugs with the potential to significantly prolong the QT interval. Caution is particularly urged in patients with cardiovascular disease or risk factors for cardiovascular disease. (J Clin Psychiatry 2002;63[suppl 9]:18–24)

Certain drugs may cause clinically significant electrocardiographic QT interval prolongation.1–4 This drug effect is more likely to occur in patients with cardiovascular disease than in patients free of cardiovascular disease.5 Rarely, QT interval prolongation may be associated with ventricular tachyarrhythmias, including polymorphic ventricular tachycardia of the torsades de pointes (“twisting of the points”) type. The ever-changing configuration (shape, morphology) of the QRS complex in torsades de pointes derives from the shifting site of ventricular activation during this rhythm disturbance.

When torsades de pointes occurs, patients may experience dizziness, lightheadedness, palpitations, presyncope, and syncope because of an arrhythmia-induced low cardiac output state. Although it may resolve spontaneously, torsades de pointes has been observed to degenerate into ventricular fibrillation with sudden cardiac death if the patient is not provided immediate cardiopulmonary support and subsequent cardioversion.

RELEVANCE OF QT INTERVAL PROLONGATION TO PSYCHIATRY

Antipsychotic drugs may be associated with QT interval prolongation.6–9 The quinidine-like properties of thioridazine have been well known for more than 4 decades. Almost 40 years ago, Kelly et al.10 described 2 fatalities associated with thioridazine administration. The first case involved a 46-year-old woman hospitalized with disruptive behavior. She received thioridazine from December 1959 until her death in February 1960 in doses ranging between 600 and 3600 mg/day. In February 1960, the patient developed “cardiovascular collapse” and “died the following day despite supportive therapy.” According to the authors, “Serial ECGs [electrocardiograms] on the day of death revealed either complete heart block with the ventricular pacemaker located below the bifurcation of the AV [atrioventricular] bundle, runs of ventricular tachycardia, or bizarre combinations of heart block and ectopic beats.”(p547) The authors recommended that clinicians administer thioridazine with care, particularly in high doses, because of the quinidine-like properties of this drug.

In 1976, Fowler et al.11 described electrocardiographic changes and cardiac arrhythmias in patients taking psychotropic drugs. The authors reported episodes of ventricular tachycardia in 5 patients taking thioridazine—1 of whom died. They noted that “major cardiac arrhythmias are a potential hazard in patients without heart disease who are receiving customary therapeutic doses of psychotropic drugs.”(p223) The authors recommended prospective clinical trials “to quantify the risks of cardiac complica-
tions to patients receiving phenothiazines or tricyclic anti-depressant drugs.”

In a 1992 review of 117 cases of arrhythmias associated with thioridazine administration, Donatini et al. found no cases of severe ventricular arrhythmias in children. Among adults receiving therapeutic doses of thioridazine, the authors reported ventricular tachycardia, ventricular fibrillation, or torsades de pointes mainly in patients with concomitant risk factors.

In a survey of medicolegal autopsies performed in Finland over the 3-year period between 1985 and 1988, Mehtonen et al. reported sudden unexpected deaths among 31 women and 18 men associated with either antipsychotic or antidepressant drugs. The authors documented therapeutic use of phenothiazines in all but 3 of the 49 cases, and thioridazine was involved in more than half of the deaths. In 15 of the deaths, thioridazine was the only antipsychotic drug taken. In only 5 of the 49 deaths were drugs other than thioridazine associated with sudden cardiac death.

**QUINIDINE SYNCOPE**

Quinidine was introduced into clinical practice around 1920 to facilitate restoration of normal sinus rhythm in patients with atrial fibrillation most commonly due to rheumatic heart disease. In 1964, Selzer and Wray described 8 patients with 10 reactions (5 documented episodes of ventricular fibrillation/ventricular flutter) among 36 syncope patents thought to be related to quinidine administration. All patients developed syncope within 1 to 6.5 hours of drug administration. These 8 patients were seen over 4 years in a cardiopulmonary clinic. The authors estimated that 200 to 300 patients received quinidine during this time as a part of drug administration to convert them from atrial fibrillation to normal sinus rhythm. Patient complaints were nonspecific and included “nausea,” “faintness,” and “ill feeling.” Although not recognized at the time, torsades de pointes (first described in 1966) was the most common underlying mechanism. Syncpe may be found in up to 5% to 10% of patients taking quinidine and usually occurs early in treatment. In 1964, the mortality rate from quinidine treatment of atrial fibrillation during conversion attempts was estimated at 3% to 4%.

**BASIC CARDIAC PHYSIOLOGY**

For the interested reader, Grant provides an excellent review of basic cardiac electrophysiology.

**Surface Electrocardiogram**

Figure 1 represents electrocardiographic events seen typically in lead II of a surface electrocardiogram. The P wave represents electrical depolarization of the left and right atria. The “pacemaker” of the heart is located in the sinoatrial node (SAN) found in the superior portion of the right atrium. Electrical signals from the SAN travel via 3 intra-atrial pathways to the atioventricular node (AVN) activating right atrial tissue in the process. A fourth pathway, Bachmann’s bundle, passes from the SAN to the left atrium, activating left atrial tissue in the process.

The QRS complex represents electrical depolarization of the left and right ventricles. Because the left ventricle is so much larger than the right ventricle, the electrical forces making up the QRS complex largely arise in the left ventricle.

The purpose of the electrical circuitry of the heart is to activate the left and right atria in such a fashion that these chambers eject blood into their respective left and right ventricles just before ventricular contraction. Optimum filling of the left and right ventricles just before ventricular contraction maximizes ventricular ejection of blood, employing principles described in Starling’s law of the heart. Following ventricular depolarization is the process of electrical recovery—recharging ventricular repolarization. On the surface electrocardiogram, the process of ventricular repolarization consists of an isoelectric event—the ST segment running from the end of the QRS complex to the beginning of the T wave and the T wave itself representing directional electrical recovery.

The QT interval then consists of both ventricular depolarization (QRS complex) and ventricular repolarization (ST segment + T wave; sometimes called the JT interval). The great majority of the QT interval represents ventricular repolarization.
Figure 2. Ventricular Muscle Cell Action Potential

Membrane Currents and Potential Sites of Drug Action

 Space does not allow a detailed description of the contribution of individual membrane currents to phases of the action potential. The initial repolarization (phase 1) is mediated by the opening of transient outward potassium channels. The plateau phase (phase 2) is characterized by high membrane resistance resulting from almost equal flow of outward currents through delayed rectifier potassium channels and inward flow through calcium channels. The rate of terminal repolarization (phase 3) is enhanced after the plateau phase because of increasing conductance of rapid delayed rectifier potassium and inward rectifier potassium current.

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Figure 2 shows actions sites for both tricyclic antidepressants (TCAs) and some antipsychotic drugs. The principal quinidine-like properties of TCAs are mediated by the sodium channel. However, secondary properties of TCAs act during the end of phase 2 and during phase 3 to delay repolarization. Antipsychotic drugs, such as thioridazine, act principally during the end of phase 2 and during phase 3 to block the rapid component of the delayed rectifier potassium channel (IKr), leaving ventricular tissue vulnerable to early after depolarizations (EADs) and QT interval prolongation. This increase in the duration of the action potential contributes to T wave abnormalities and QT interval prolongation. EADs plus the inhomogeneity of ventricular recovery lead to polymorphic ventricular tachycardia of the torsades de pointes type.

Reilly et al. found that corrected QT (QTc) interval prolongation was present in 8% of psychiatric patients taking only antipsychotic drugs (particularly thioridazine and droperidol). The QTc interval was prolonged in 11% of patients taking TCAs alone and in 15% of patients taking both TCAs and antipsychotic drugs.

Figure 2 offers the hypothesis that the primary effects of antipsychotic drugs and the secondary effects of TCAs on delayed rectifier potassium channels may explain the additive risks observed by Reilly et al. However, Idle, in a letter to the editor, argued that TCAs probably blocked the cytochrome P450 (CYP) isoenzyme 2D6 and that this blockade increased drug levels of antipsychotic drugs because these drug were principally metabolized by this isoenzyme. Therefore, it may be an indirect effect rather than a direct effect of TCAs on delayed rectifier potassium channels that best explains the additive risks reported by Reilly et al.

ASSESSING THE QTc INTERVAL

Why do clinicians concerned about the symptoms and signs of drug-induced torsades de pointes focus on QT interval prolongation when QT interval prolongation in and of itself poses no cardiac hemodynamic problem? Torsades de pointes is exceedingly rare and highly unpredictable. However, for many drugs that prolong the QT interval, there is a relationship between QT interval prolongation and this potentially life-threatening polymorphic ventricular tachycardia. Thus, the best we can do for the moment is to use QT interval prolongation as a surrogate for torsades de pointes, however imperfect this surrogate may be.

QTc Interval

In 1920, Bazett noted that as the heart rate slowed, the QT interval lengthened. From personal and reported observations of fewer than 80 subjects (both men and
women), he derived the Bazett formula that corrects (or normalizes) the QT interval for a heart rate of 60 beats/min. The QTc interval is the measured QT interval divided by the square root of the RR interval measured in seconds.

The Bazett formula is the most widely used formula to estimate the QTc interval and is the formula used in most automated interpretations of the electrocardiogram. However, at least 20 formulas have been developed to estimate the QTc interval in response to perceived inadequacy of the Bazett formula. A. J. Camm, M.D., stated (e-mail communication) that the Fridericia formula employing the cube root instead of the square root (Bazett) to estimate the QTc interval actually provides a better fit for Bazett’s original data than the Bazett formula itself.

“Regression to the Mean” and Assessing Drug Effect On QTc Interval

The principle of “regression to the mean” may be defined as the tendency for random increases or decreases to be followed by observations closer to the average. The problem of regression to the mean quickly surfaces when plotting baseline QTc interval measurement versus QTc interval measurements inevitably will vary at different times. Both drug effect and autonomic conditioning effect may alter heart rate independent of possible drug effect on the QT interval. In the study by Malik, the influence of heart rate was not removed by employing any one of 20 previously published formulas to “correct” the QT interval. That is, using group-derived formulas to apply to individual drug-induced changes of the QT interval gives unsatisfactory results.

Malik recommends individual regression analysis to ensure that no QTc interval undercorrection or overcorrection is present in any study subject because heart rate

Figure 3. Baseline Corrected QT (QTc) Interval Measurements (before drug administration) and QTc Interval Change From Baseline Following Sertindole Administration in Phase 2/3 Drug Trials

Figure 4. Baseline Corrected QT (QTc) Interval Measurements (before drug administration) and QTc Interval Change From Baseline Following Ziprasidone Administration in Phase 2/3 Drug Trials

*Data from Vieweg et al. Findings are explained, in part, from the concept of regression to the mean (the tendency for random increases or decreases to be followed by observations closer to the mean). That is, when baseline QTc interval measurements are shorter (< 394 and 394–408 ms), the next QTc interval measurement (following sertindole administration) tends to be greater (closer to the mean) as reflected by prominent QTc interval increase from baseline. When baseline QTc interval measurement is longer (> 424 ms), the next QTc interval measurement (following sertindole administration) tends to be lower (closer to the mean) as reflected by diminished QTc interval change from baseline. Thus, the “signal” of drug effect is partially lost in the “noise” of QTc interval measurement as estimated by the group-derived Bazett formula.

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QT Prolongation With Antipsychotics

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correction varies from subject to subject. His technique involves multiple QT measurements to determine baseline values and then multiple QT measurements during drug administration to determine the effect of the drug on the QTc interval. Importantly, using this approach reduces or eliminates problems related to regression to the mean.

FACTORS AFFECTING THE QTc INTERVAL

Risk factors contributing to QTc interval prolongation are shown in Table 1. Whatever the limitations may be for group-derived formulas such as the Bazett formula to estimate the QTc interval, Malik’s method employing individual regression analysis is labor intensive, time consuming, and expensive. For the foreseeable future, clinicians must work within the limitations of such formulas as the Bazett formula to estimate the QTc interval when making clinical decisions.

Circadian Variation

QTc interval measurements vary throughout the 24-hour day, in part driven by changes in autonomic (sympathetic and parasympathetic) tone. Differences between sleeping and waking QTc interval determinations vary by about 20 ms, with nocturnal values greater than daytime values. In 20 normal subjects, circadian variability was 76 ± 19 ms (range, 35–108 ms) from day to night. Circadian variations in QTc interval may be accentuated by cardiovascular disease.

Time of Day and Sudden Cardiac Death

Acute cardiac events occur most commonly between 6 a.m. and noon and least commonly at night. Thus, the extent to which nocturnal QTc interval lengthening may place patients at increased risk for acute cardiac events remains unclear. Lavery et al. argue that sleep state–dependent changes in autonomic nervous system tone may trigger acute cardiac events. Schwartz asserts that sympathetic imbalance further compromises patients with QTc interval prolongation.

Sex Differences in QTc Interval

At birth, QTc interval measurements are the same for male and female infants. At puberty, the male QTc interval shortens and remains shorter than its female counterpart by about 20 ms until ages 50 to 55 years, coincident with a decline in male testosterone levels. This sex difference appears to be androgen driven. Based on the usual cardiac risk factors, we would expect about 45% of cases of torsades de pointes to occur in women; however, about 70% of cases of this rhythm disturbance occur in women.

QTc Interval and Phases of the Menstrual Cycle

Rodriguez et al. studied 58 healthy subjects (38 men and 20 women) between ages 21 and 40 years. Subjects received intravenous low-dose ibutilide (an antiarrhythmic agent known to prolong the QT interval). Men were studied once, and women were studied 3 times during the month coincident with the 3 phases of the menstrual cycle (follicular phase, ovulation, and luteal phase). The greatest increase in QTc interval measurements occurred during the first half of the menstrual cycle. Absent administration of QTc interval–prolonging drugs, QTc interval measurements are stable throughout the menstrual cycle.

Age, Cardiovascular Disease, and the QTc Interval

Elderly patients have longer QTc interval measurements than nonelderly patients even without cardiovascular disease. Also, age-matched patients with cardiovascular disease tend to have longer QTc interval measurements than those free of cardiovascular disease.

Electrolytes and the QTc Interval

Electrolyte disturbances, particularly hypokalemia and hypomagnesemia, may contribute to or even cause QT interval prolongation. Various factors may contribute to
hypoventilation, including diuretics and excessive vomiting and diarrhea. Even postprandial states may be associated with hypokalemia.

Hatta et al.36 found that intensive exercise and anxiety may be associated with hypokalemia. These authors also reported that serum potassium was lower in severely agitated patients (3.59 mmol/L) than in mildly agitated patients (3.79 mmol/L).

Hatta and associates4 later reported that the mean QTc interval of psychiatric emergency patients was prolonged (453 ± 40 ms). They also noted that QTc intervals of psychiatric inpatients were longer than those of psychiatric outpatients. Hypokalemia was thought to contribute to these observations.

Pharmacodynamic/Pharmacokinetic Factors

Drugs may affect delayed rectifier potassium channel flow (pharmacodynamic factor), thereby disrupting the synchrony of action of individual cardiac cells during repolarization. The rapidly activating component of IK plays a central role in generating arrhythmias.37

Five percent to 10% of European Americans on a genetic basis (pharmacokinetic factor) are “poor metabolizers.” This genetic disturbance principally involves CYP2D6. The potential for metabolic inhibitors to raise antipsychotic drug levels was assessed in the Pfizer 054 study.23

Congenital Long QT Syndrome

A detailed review of the congenital long QT syndrome is beyond the scope of this article. Severe forms of this syndrome are associated with a high incidence of sudden death. The interested reader is referred to reviews by Vincent38 and others.37,39,40 There are 2 main congenital long QT syndromes. The Jervell and Lange-Nielsen syndrome is marked by autosomal recessive inheritance and severe congenital deafness. The Romano-Ward syndrome has autosomal dominant inheritance and normal hearing.

The congenital long QT syndrome occurs in about 1 in 5000 births. It accounts for about 3000 to 4000 deaths/year in the United States—mostly in children and young adults. Sudden cardiac death is the presentation in 9% of pediatric long QT syndrome subjects. More than 71% of patients will die within 15 years if not treated.38

The electrocardiographic features derive, in part, from adrenergic stimulation or increased sympathetic nervous system tone. Both exercise and emotions may leave the patient vulnerable to torsades de pointes. β-Blockers are the most widely used agents in treating patients with this congenital syndrome.

Initial indicators of this syndrome may be syncopal episodes secondary to torsades de pointes. Often, this polymorphic ventricular tachycardia will spontaneously revert to normal sinus rhythm after a short run of ventricular beats. Occasionally, it will degenerate into ventricular fibrillation with resultant death if not immediately treated.

<p>| Table 2. Compilation of QT Interval and Corrected QT (QTc) Interval Measurements in Cases From the Literature Associated With Torsades de Pointes* |
|--------------------------------------------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Interval, ms</th>
<th>No. of Cases</th>
</tr>
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<tbody>
<tr>
<td>QTc &lt; 500</td>
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<tr>
<td>500–549</td>
<td>9</td>
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<tr>
<td>550–599</td>
<td>16</td>
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<tr>
<td>600–649</td>
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</tr>
<tr>
<td>650–699</td>
<td>6</td>
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<td>≥ 700</td>
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<tr>
<td>QTc &lt; 500 ms</td>
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<tr>
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<tr>
<td>500–549</td>
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<td>Total cases</td>
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</tr>
<tr>
<td>Cases &lt; 500 ms</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

*Data from Bednar et al.8

QTc INTERVAL MEASUREMENTS

AND THRESHOLDS FOR INTERVENTION

Unless otherwise stated, QTc interval measurements are derived using the group-derived Bazett formula. Garson27 describes in some detail how to measure the QT interval. Moss41 reviewed a number of studies reporting normal values of QTc interval. For purposes of this article, I will define the normal range for women between 350 and 450 ms and the normal range for men between 350 and 430 ms.

Table 2 relates QT and QTc interval measurements and torsades de pointes.8 Bednar et al.8 collected data from 86 cases of torsades de pointes for which QT interval values were reported and 116 cases of this arrhythmia for which QTc interval measurements were reported. Most cases of torsades de pointes occurred when either QT or QTc intervals were greater than 500 ms. Physicians should become clinically concerned when the QTc interval is between 450 and 500 ms and alarmed when the QTc interval exceeds 500 ms.

Do levels of alarm increase as QTc interval prolongation moves from 500 ms to 700 ms? While it is true that the greater the QTc interval prolongation the greater the risk of torsades de pointes, limitations in QT interval measurements and of the group-derived formulas used to estimate QTc interval confound this point to some extent.

The following steps are recommended when a report of suspected QTc interval prolongation reaches mental health professionals. The initial step is to obtain another electrocardiogram. Clinicians should also assess serum potassium, magnesium, calcium, and thyroid hormone levels. Patient assessment should include a careful cardiac history including family history of syncope or sudden death. In
patients with confirmed QTc interval prolongation, complaints of palpitations, presyncope, or syncope are grounds for urgent referral to a cardiologist.

**CONCLUSIONS**

The magnitude and extent of QTc interval prolongation as a predictor of life-threatening cardiac arrhythmias such as torsades de pointes remain areas of intense interest and investigation. In particular, regulatory agencies have sharpened their focus in this arena. Refinement of our current understanding of this relationship almost certainly awaits the application of individual- rather than group-derived formulas to estimate the QTc interval. Until these refinements arrive, clinicians are advised to exercise caution when administering antipsychotic drugs with the potential to significantly prolong the QT interval. This principle is particularly urged in patients with cardiovascular disease or risk factors for cardiovascular disease.

**Drug names:** ibutilide (Corvert), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

**REFERENCES**

36. Hatta K, Takahashi T, Nakamura H, et al. Hypokalemia and agitation in patients with confirmed QTc interval prolongation, complaints of palpitations, presyncope, or syncope are grounds for urgent referral to a cardiologist.