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.

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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 antidepressant drugs."(p223)

In a 1992 review of 117 cases of arrhythmias associated with thioridazine administration, Donatini et al.[12] 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.[13] 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.[14] In 1964, Selzer and Wray[15] described 8 patients with 10 reactions (5 documented episodes of ventricular fibrillation/ventricular flutter) among 36 syncopal episodes 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)[16] was the most common underlying mechanism. Syncope may be found in up to 5% to 10% of patients taking quinidine and usually occurs early in treatment.[15] In 1964, the mortality rate from quinidine treatment of atrial fibrillation during conversion attempts was estimated at 3% to 4%.[15]

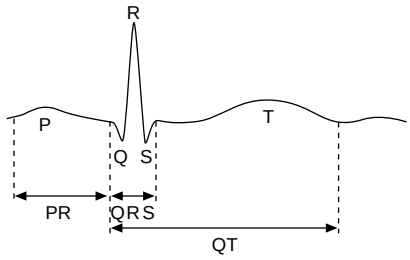
BASIC CARDIAC PHYSIOLOGY

For the interested reader, Grant[17] 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 atrioventricular 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.

Figure 1. Normal Electrocardiogram in Sinus Rhythm[a]



[a]The P wave represents atrial electrical depolarization and leads to right and left atrial contraction. The QRS complex represents ventricular depolarization and leads to left and right ventricular contraction. The ST segment represents isoelectric ventricular repolarization, and the T wave represents directional repolarization. The QT interval includes 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.

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.

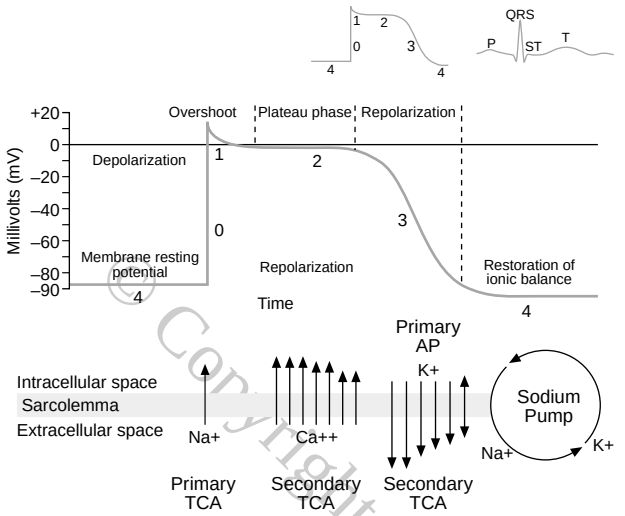
Following ventricular depolarization is the process of electrical recovery–recharging–ventricular repolarization. On the surface electrocardiogram, the process of ventricular repolarization consists of an isoelectric event—the ST segment running from the end of the QRS complex to the beginning of the 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). Normally, ventricular repolarization makes up by far the greater portion of the QT interval.

Cardiac Action Potential

Figure 2 shows the action potential of a single ventricular muscle cell. The surface electrocardiogram depicts the net electrical forces of all the cardiac action potentials at each point in time. The ratio of extracellular potassium to intracellular potassium determines the membrane resting

Figure 2. Ventricular Muscle Cell Action Potential[a]



[a]Abbreviations: AP = antipsychotic, TCA = tricyclic antidepressant. The membrane resting potential is determined largely by the ratio of extracellular potassium to intracellular potassium (phase 4). The sudden surge of sodium into the ventricular muscle cell (phase 0) (sodium "fast" channel) coincides with ventricular depolarization (R wave component of QRS complex). Phase 1 is the initial phase of ventricular repolarization and is mediated by opening of transient outward potassium channels (Ito). Phase 2 (plateau phase) of ventricular repolarization is characterized by high membrane resistance resulting from almost equal flow of outward currents through delayed rectifier potassium channels (IKr, IKs, IKur) and inward flow of current through L-type calcium (calcium "slow" channel) channels. The rate of terminal repolarization (phase 3) is enhanced after the plateau phase because of increasing conductance of rapid delayed rectifier potassium current (IKr) and inward rectifier potassium current (IK1).

potential (phase 4). The sudden movement of sodium ions from outside the cell to inside the cell (phase 0) shifts the membrane resting potential from –90 mV to +20 mV and largely coincides with the QRS complex of the surface electrocardiogram. Repolarization consists of 3 phases (phases 1–3). Phase 1 represents initial rapid repolarization. During phase 2, the outward movement of potassium is balanced by the inward movement of calcium leading to the "plateau" phase. During phase 3, the outward flow of potassium dominates providing restoration of ionic balance and ultimate return to the membrane resting potential (phase 4).

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.[17] 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.

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.[9] 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.[9] However, Idle,[18] 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.[9]

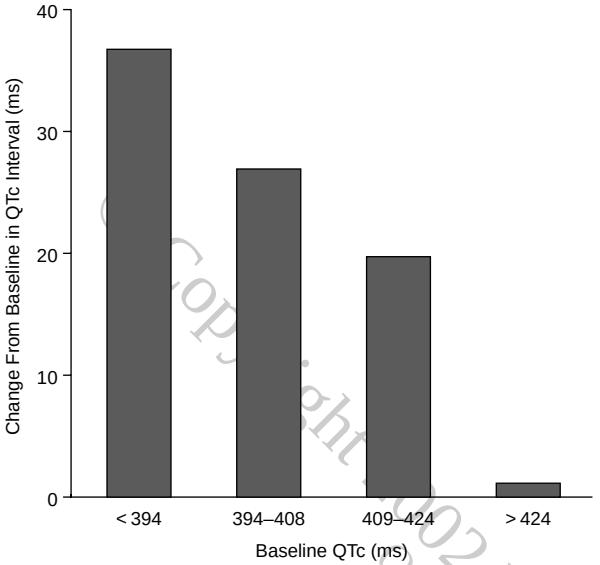
ASSESSING THE QTc INTERVAL

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

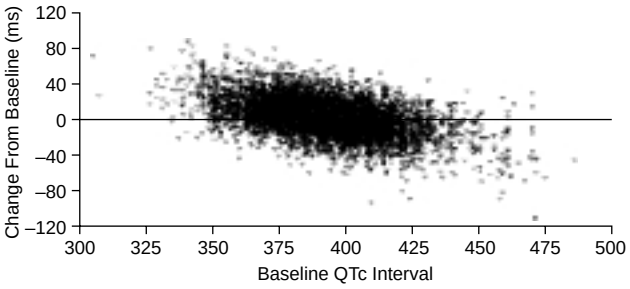
In 1920, Bazett[19] noted that as the heart rate slowed, the QT interval lengthened. From personal and reported observations of fewer than 80 subjects (both men and

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[a]



[a]Data from Vieweg et al.[22] 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 (409–424 and > 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.

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[a]



[a]Data from the U.S. Food and Drug Administration Advisory Committee.[23] 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 (< 400 ms), the next QTc interval measurement (following ziprasidone administration) tends to be greater (closer to the mean) as reflected by QTc interval increase from baseline. When baseline QTc interval measurement is longer (> 400 ms), the next QTc interval measurement (following ziprasidone 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.

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.[4,20,21] 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 measurement after drug administration. Data may be difficult to interpret because the "signal" of drug effect may be lost amid the "noise" of inherent QTc interval variability using group-derived formulas such as the Bazett formula.

Figures 3 and 4 depict examples of regression to the mean in drug trials of sertindole[22] and ziprasidone.[23] In each of these figures, QTc interval measurements following drug administration showed similar patterns. When baseline QTc intervals were shorter, the subsequent QTc interval measurement tended to be great. In contrast when baseline QTc intervals were longer, the subsequent QTc interval tended to be modest. That is, the inherent variability of QTc interval measurements as assessed in these drug trials contributed more to the subsequent QTc interval measurement than the drug effect itself.

Malik[21] and Boyle and Weiss[24] noted that a standardized methodology for investigation of drug-induced QT interval prolongation does not exist. In studying drugs, heart rate 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,[21] 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[21] recommends individual regression analysis to ensure that no QTc interval undercorrection or overcorrection is present in any study subject because heart rate

Table 1. Risk Factors Contributing to Corrected QT (QTc) Interval Prolongation

Risk Factors	Causes/Implications
Female sex	QT intervals longer than in men QT interval longer during first half of menstrual cycle
Elderly age	Increased risk for coronary artery disease Multiple medications Pharmacokinetic/pharmacodynamic differences
Electrolyte imbalance (eg, hypokalemia, hypomagnesemia)	Diuretic use, excessive vomiting/diarrhea, postprandial hypokalemia
Congenital long QT syndrome	Associated with torsades de pointes and sudden death
Cardiac disease, with history of acute or chronic myocardial ischemia, cardiac arrhythmias, or congestive heart failure	Predisposed to cardiac arrhythmias
Drugs known to prolong QTc interval	May potentiate QTc prolongation
Medication overdose with drugs prolonging QTc	QTc prolongation generally dose dependent
Concomitant medications	Adverse events with cytochrome P450 enzyme system inhibited, leading to increased drug levels that increase QT interval
Endocrine/metabolic (eg, diabetes, obesity, hypothyroidism, pituitary insufficiency)	Via electrolytes or cardiovascular disease
Central nervous system (eg, stroke, infection, trauma)	Via autonomic nervous system

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[19] to estimate the QTc interval, Malik's method[21] 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.[25–27] 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.[26] 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.[28,29] Thus, the extent to which nocturnal QTc interval lengthening may place patients at increased risk for acute cardiac events remains unclear. Lavery et al.[30] argue that sleep state–dependent changes in autonomic nervous system tone may trigger acute cardiac events. Schwartz[31] 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.[32,33] 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.[33]

QTc Interval and Phases of the Menstrual Cycle

Rodriguez et al.[34] 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.[5] 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.[35] Various factors may contribute to

hypokalemia, 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 associates[8] 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 Vincent[38] 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.

Table 2. Compilation of QT Interval and Corrected QT (QTc) Interval Measurements in Cases From the Literature Associated With Torsades de Pointes[a]

Interval, ms	No. of Cases
QT	
< 500	17
500–549	9
550–599	16
600–649	33
650–699	6
≥ 700	5
Total cases	86
Cases < 500 ms	19.8%
QTc	
< 500	9
500–549	13
550–599	24
600–649	36
650–699	21
≥ 700	13
Total cases	116
Cases < 500 ms	7.8%

[a]Data from Bednar et al.[4]

QTc INTERVAL MEASUREMENTS AND THRESHOLDS FOR INTERVENTION

Unless otherwise stated, QTc interval measurements are derived using the group-derived Bazett formula. Garson[27] describes in some detail how to measure the QT interval. Moss[41] 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.[4] Bednar et al.[4] 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

1. Vieweg WVR, Nicholson CS. Torsade de pointes ventricular tachycardia, QT interval, and psychotropic drugs. Med Update Psychiatrists 1997;2:48–54
2. Stratmann HG, Kennedy HL. Torsade de pointes associated with drugs and toxins: recognition and management. Am Heart J 1987;113:1470–1482
3. DePonti F, Poluzzi E, Montanaro N. Organizing evidence on QT prolongation and occurrence of torsade de pointes with non-antiarrhythmic drugs: a call for consensus. Eur J Clin Pharmacol 2001;57:185–209
4. Bednar MM, Harrigan EP, Anziano RJ, et al. The QT interval. Prog Cardiovas Dis 2001;43:1–45
5. Khan SP, Dahlvani S, Vieweg WVR, et al. Electrocardiographic QT interval in a geropsychiatric inpatient population: a preliminary study. Med Psychiatr 1998;1:71–74
6. Welch R. Antipsychotic agents and QT changes. J Psych Neurosci 2000;25: 154–160
7. Fayek M, Kingsbury SJ, Zada J, et al. Cardiac effects of antipsychotic medications. Psychiatr Serv 2001;52:607–609
8. Hatta K, Takahashi T, Nakamura H, et al. Prolonged QT interval in acute psychotic patients. Psychiatry Res 2000;94:279–285
9. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000;355:1048–1052
10. Kelly HG, Fay JE, Laverty SG. Thioridazine hydrochloride (Mellaril): its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. Can Med Assoc J 1963;89:546–554
11. Fowler NO, McCall D, Chou T, et al. Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. Am J Cardiol 1976;37:223–230
12. Donatini B, Blaye I, Krupp P. Transient cardiac pacing is insufficiently used to treat arrhythmia associated with thioridazine. Cardiology 1992;81: 340–341
13. Mehtonen O-P, Aranko K, Malkonen L, et al. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta Psychiatr Scand 1991;84:58–64
14. Clark-Kennedy AE. Quinidine in the treatment of auricular fibrillation. Q J Med 1922;16:204–235
15. Selzer A, Wray W. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 1964;30:17–26
16. Dessertenne F. Tachycardie ventriculaire a deux foyers opposes variables. Arch Mal Coeur 1966;59:263–272
17. Grant AO. Basic cardiac electrophysiology. In: Naccarelli GV, Curtis AB, Goldschlager NF, eds. Electrophysiology Self-Assessment Program. Bethesda, Md: American College of Cardiology; 2000:1.1–1.26
18. Idle JR. The heart of psychotropic drug therapy [letter]. Lancet 2000;355: 1824–1825
19. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–370
20. Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. Am J Cardiol 1993;72(suppl):17B–22B
21. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol 2001;12:411–420
22. Vieweg V, Driscoll R, Silber C. Long-term cardiovascular safety of sertindole. Presented at the 49th annual meeting of the Institute on Psychiatric Services; Oct 24–28, 1997; Washington, DC
23. US Food and Drug Administration Advisory Committee. Zeldox Capsules (ziprasidone): Summary of Efficacy and Safety and Overall Benefit Risk Relationship. Bethesda, Md: US Food and Drug Administration; July 19, 2000
24. Boyle NG, Weiss JN. Making QT correction simple is complicated. J Cardiovasc Electrophysiol 2001;12:421–423
25. Browne K, Prystowsky E, Heger JJ, et al. Prolongation of the QT interval in man during sleep. Am J Cardiol 1983;52:55–59
26. Morganroth J, Brozovich FV, McDonald JT, et al. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. Am J Cardiol 1991;67:774–776
27. Garson A. How to measure the QT interval: what is normal? Am J Cardiol 1993;72:14B–16B
28. Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–1322
29. Cohen MC, Rohtla KM, Lavery CE, et al. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997;79:1512–1516
30. Lavery CE, Murray A, Mittleman MA, et al. Nonuniform nighttime distribution of acute cardiac events: a possible effect of sleep states. Circulation 1997;96:3321–3327
31. Schwartz PJ. QT prolongation, sudden death, and sympathetic imbalance: the pendulum swings. J Cardiovasc Electrophysiol 2001;12:1074–1077
32. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8: 690–695
33. Woosley R, Sketch MH. Gender and Drug-Induced Torsade de Pointes. ACCEL 30, No. 2. Bethesda, Md: American College of Cardiology; 1998
34. Rodriguez I, Kilborn MJ, Liu XK, et al. Drug-induced QT prolongation in women during the menstrual cycle. JAMA 2001;285:1322–1326
35. Compton SJ, Lux RL, Ramsey MR, et al. Genetically defined therapy of inherited long-QT syndrome: correction of abnormal repolarization by potassium. Circulation 1996;94:1018–1022
36. Hatta K, Takahashi T, Nakamura H, et al. Hypokalemia and agitation in acute psychotic patients. Psychiatry Res 1999;86:85–88
37. Tan HL, Hou CJ, Lauer MR, et al. Electrophysiologic mechanisms of the long QT interval syndromes and torsade de pointes. Ann Intern Med 1995;122:701–714
38. Vincent GM. Long QT syndrome. Cardiology Clin 1999;18:309–325
39. Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovas Dis 1988;31:115–172
40. el-Sherif N, Turitto G. The long QT syndrome and torsade de pointes. Pacing Clin Electrophysiol 1999;22:91–110
41. Moss A. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol 1993;72:23B–25B