Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes

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Drug-induced long QT syndrome is characterized by a prolonged corrected QT interval (QTc) and increased risk of a polymorphic ventricular tachycardia known as torsade de pointes (TdP). We review mechanisms, predispositions, culprit agents, and management of this potentially fatal phenomenon. Virtually all drugs that prolong QTc block the rapid component of the delayed rectifier current (I_{kr}). Some drugs prolong QTc in a dose-dependent manner, others do so at any dose. Most patients that develop drug-induced TdP have underlying risk factors. Female sex is the most common. Implicated drugs include class 1A and III antiarrhythmics, macrolide antibiotics, pentamidine, antimalarials, antipsychotics, arsenic trioxide, and methadone. Treatment for TdP includes immediate defibrillation for hemodynamic instability and intravenous magnesium sulfate. Potassium levels should be maintained in the high normal range, and all QT prolonging agents must be promptly discontinued. (Am Heart J 2007;153:891-9.)

Drug-induced long QT syndrome (LQTS) is characterized by acquired QT interval prolongation and increased risk of torsade de pointes (TdP). In 1964, Selzer and Wray reported QT prolongation and ventricular fibrillation (VF) in response to quinidine. Two years later, Dessertenne described TdP, a polymorphic ventricular tachycardia where QRS complexes ‘twist’ around an isoelectric line in a sinusoidal fashion (Figure 1). Symptoms of TdP include palpitations, syncope, and seizure-like activity. Torsade de pointes is usually self-limited but may degenerate into VF and cause sudden cardiac death. A variety of medications have been implicated in drug-induced LQTS. QT prolongation and TdP are the most common reasons pharmaceuticals are restricted or removed from the US market. We review mechanisms, predispositions, culprit agents, and management of this potentially fatal phenomenon.

QT measurement

The QT interval is the electrocardiographic (ECG) manifestation of ventricular depolarization and repolarization. It is measured from QRS complex onset to T wave termination (Figure 2). Longest QT intervals are generally measured in precordial leads. V3 or V4 appear most reliable for assessing QT prolongation. QT intervals may vary due to diurnal effects, electrolyte imbalance, autonomic fluctuations, ECG acquisition technique, as well as intra- and interobserver variability. One study suggested that whites have longer QT intervals than African Americans. We were unable to confirm this finding. QT intervals normally shorten with tachycardia and lengthen with bradycardia. Therefore, a rate corrected QT (QTc) interval should be calculated. In 1920, Bazett proposed a formula dividing the longest QT interval by the square root of the RR interval (Figure 2). Although there is no consensus best QTc method, Bazett’s formula remains the gold standard. This formula may overestimate drug-induced QT prolongation. QTc intervals <440 milliseconds are clearly normal. Intervals of 440 to 460 milliseconds in men and 440 to 470 milliseconds in women are considered borderline. Most authorities agree women have longer QTc intervals.

Molnar et al demonstrated circadian QTc variation of 95 ± 20 milliseconds with longest intervals recorded during sleep. Although variability is expected, any QTc prolongation to the abnormal range should alert physicians to a risk of TdP.

The appropriate method for measuring QTc during atrial fibrillation is unclear. QTc may be measured over 10 consecutive beats and averaged. Alternatively, QTc following shortest and longest RR intervals may be averaged. There are no data to guide QTc calculation in the setting of QRS prolongation. Some authors have proposed ignoring the QRS and measuring the JT interval.
interval (as an index of ventricular repolarization). However, evidence suggests the JT interval is dependent on QRS duration, and there are no consensus normal JT values. In an attempt to standardize QT measurement, an expert panel proposed the guidelines noted in Table I.

**Mechanisms of QT prolongation and TdP**

Myocardial repolarization is primarily mediated by efflux of potassium ions. Two subtypes of the delayed rectifier K⁺ current, \( I_{\text{Kr}} \) (rapid) and \( I_{\text{ks}} \) (slow), are predominantly responsible for repolarization. Virtually all drugs that prolong QTc block \( I_{\text{Kr}} \). De Bruin et al demonstrated strong correlation between a drug’s ability to block \( I_{\text{Kr}} \) and its potential to cause ventricular arrhythmias and sudden death. \( I_{\text{Kr}} \) blockade causes a delay in phase 3 rapid repolarization of the action potential (Figure 3). Increased action potential duration is reflected by QT prolongation. Repolarization delays may also distort T waves or produce prominent U waves.

Prolonged repolarization may cause early afterdepolarizations (EADs) due to activation of inward depolarizing currents, most likely L-type calcium channels or sodium-calcium exchange current (\( I_{\text{NCX}} \)). Early afterdepolarizations appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential (Figure 4). Early afterdepolarizations that reach threshold voltage cause ventricular extrasystoles. Purkinje fibers and M cells (midmyocardial) are especially susceptible to drug-induced QT prolongation, EADs, and ventricular extrasystoles. Heterogeneity in ventricular repolarization (dispersion of refractoriness) can create zones of unidirectional block. Repetitive extrasystoles (triggered activity), unidirectional block, and zones of slow conduction can lead to reentry and TdP.

Drug-induced TdP is usually preceded by a short-long-short ECG sequence (Figure 5). This generally starts with one or more premature ventricular complexes followed by a compensatory pause. The subsequent sinus beat may have an especially long QT and deformities of T or U waves. This sinus beat is followed by another premature ventricular complex that precipitates TdP. The period near the T wave peak where premature stimuli may induce ventricular arrhythmias is known as the vulnerable period.

Many patients with marked QT prolongation never develop TdP, although others develop TdP with minimal prolongation. Several other ECG variables have been investigated as predictors of TdP. QT dispersion, the difference between maximum and minimum QT intervals, was postulated to be a more direct measure of spatial heterogeneity of repolarization. However, QT dispersion is mostly dependent on T wave morphology (width, amplitude, and axis) and does not accurately predict drug-induced TdP. Tpeak-Tend measurement, suggested as a measure of transmural dispersion of repolarization, needs prospective validation. Manifest T wave alternans (beat to beat alternation in amplitude or polarity), a harbinger of instability in congenital LQTS, is rare in acquired LQTS and may not have the same implications (Figure 6). Microvolt T wave alternans predicts susceptibility to ventricular arrhythmias. Its use in predicting drug-induced TdP remains unclear. Despite lack of specificity, QT prolongation remains the most useful clinical variable to predict risk of TdP.

**Risk factors**

Most patients treated with QT prolonging medications never develop TdP. Several risk factors predispose patients to drug-induced LQTS and TdP. Zeltser et al reviewed 249 incidents of TdP due to noncardiac medications. Virtually all patients had 1 risk factor, and 71% had multiple risk factors. Female sex, the most common risk, was present in 71%. Other common risk factors included structural heart disease (myocardial infarction, heart failure, valvular disease, or cardiomyopathy), hypokalemia, multiple QT prolonging drugs or agents interfering with their metabolism, higher-than-average drug dosage, prolonged baseline QTc (≥450 milliseconds), family history of congenital LQTS, and prior drug-induced TdP. Hepatic impairment, bradycardia, and atrioventricular block also increase the risk of TdP.

Subclinical mutations in genes causing congenital LQTS have been found in patients with medication-induced QT prolongation and ventricular arrhythmias. Patients with congenital LQTS 6 (mutations in the gene encoding the \( \beta \) subunit of \( I_{\text{Kr}} \)) generally do not have arrhythmias in the absence of provocation. Yang et al found that 10% to 15% of patients with drug-related TdP had mutations or polymorphisms in one of the long QT genes. One mutation, S1103Y, in the cardiac sodium channel gene SCN5A has been primarily identified in African Americans (13.2%). One white family with this mutation has also been reported. The concept of repolarization reserve (variable redundancy of repolarizing currents) may...
explain why some patients with mutant genes do not develop QT prolongation or TdP until additional insults further limit repolarization.34

**QTc prolonging medications**

Some medications prolong QTc and induce TdP in a dose-dependent manner. Others may precipitate TdP at any dose resulting in potassium channel blockade (see below). We will review specific agents that prolong QTc and cause TdP (Table II). Several are metabolized by the Cytochrome P450 3A4 (CYP3A4) system. Familiarity with agents that inhibit this system is critical (Table III).35

**Antiarrhythmics**

Torsade de pointes is most commonly caused by antiarrhythmic medications. Patients taking these commonly have organic heart disease and often take diuretics that cause hypokalemia and hypomagnesemia. Class IA drugs (quinidine, disopyramide, procainamide) block outward K+ currents and inward Na+ currents. Na+ current blockade increases as serum levels increase. K+ current blockade predominates at low serum levels. Therefore, TdP frequently occurs at low or subtherapeutic serum levels.36 The risk of TdP from quinidine is approximately 1.5%.37 Disopyramide has also been implicated.38 Procainamide is less likely to cause TdP. Its metabolite, N-acetylprocainamide, has potent Ikr blocking properties that may result in QT prolongation and TdP.39 This is particularly important in patients with impaired renal function who may develop high N-acetylprocainamide levels.

**Table I. Guidelines for QT measurement**

1. Measurements should be:
   (a) Made manually from a 12-lead ECG
   (b) Done from beginning of QRS complex to end of the T wave
   (c) Averaged over 3 to 5 beats in a single lead
2. Prominent U waves should be included in the measurement if they merge into the T wave
3. QT should be assessed during peak plasma concentration of QT prolonging substance
4. QT should be corrected for heart rate

Unlike class IA agents, class III antiarrhythmics (potent Ikr blockers) prolong QTc in a dose-dependent manner. Dofetilide, ibutilide, and sotalol, which are class III drugs that pose the highest risk, progressively prolong QTc as serum levels increase.22,38 These drugs block Ikr most effectively at low heart rates, a phenomenon known as reverse use dependence. Therefore, risk of TdP increases with bradycardia. For sotalol, TdP risk ranges from 0.8% to 3.8%.50 Similar rates (0.9% to 3.3%) have been reported with dofetilide.40,41 Intravenous ibutilide has caused TdP in 3.6% to 8.3% of patients when administered for conversion of atrial fibrillation or atrial flutter.32,43 Amiodarone is unlikely to cause TdP despite significant QT prolongation. The incidence of TdP at currently used doses is <1%.44,45 In addition to blocking Ikr without reverse use dependence, amiodarone prolongs action potential duration in a homogenous manner, reducing heterogeneity of refractoriness and making the myocardium less susceptible to reentry.46 Additional electrophysiologic
effects that help explain its safety include noncompetitive β antagonism and inward L-calcium channel blockade (which may reduce EADs). Unlike other calcium channel blockers, Bepridil prolongs QTc and has been associated with TdP. It can block INCX and possesses class 1A properties. Bepridil was removed from the US market in 2003.

Promotility medications

Cisapride, used to treat esophageal reflux, causes high affinity \( I_{Kr} \) blockade and has been among the most common agents implicated in TdP. Between 1993 and 1999, the Food and Drug Administration received 341 reports of QT prolongation, ventricular arrhythmia, or cardiac arrest related to cisapride. Cisapride marketing, in the United States, was stopped in July 2000.

Antimicrobials

The macrolide antibiotics erythromycin and clarithromycin have been implicated in sudden death due to TdP. Proarrhythmia may be precipitated by \( I_{Kr} \) blockade. In addition, these drugs are metabolized by and inhibit CYP3A4. They are especially dangerous for patients receiving another CYP3A4 inhibitor or a QT prolonging medication metabolized by CYP3A4 (Table III). Although TdP with azithromycin has been reported, its arrhythmogenic potential is well below erythromycin or clarithromycin.

Sporadic incidents of TdP have been reported with fluoroquinolone antibiotics. The overall incidence of fluoroquinolone-induced TdP is very low. Sparfloxacin, resulting in the greatest action potential prolongation, has been removed from the US market. There is no evidence that currently available fluoroquinolones cause TdP without underlying risk factors.

QT prolongation and TdP have been noted with pentamidine, an antiprotozoal, antifungal drug used to treat parasitic infections and \( Pneumocystis carinii \) pneumonia. Pentamidine-induced QT prolongation is related to reduction in available \( I_{Kr} \) channels. Although case reports describe TdP in patients receiving other systemic antifungals (fluconazole, itraconazole, ketoconazole, and voriconazole), these are unlikely to cause TdP without preexisting risk factors.

Antimalarials have been associated with QT prolongation and TdP. Halofantrine and chloroquine are the most potent \( I_{Kr} \) inhibitors. Torsade de pointes risk is highest with halofantrine. These drugs are frequently used around the world, and TdP incidence is likely underreported.

Psychiatric drugs

Dose-dependent QT prolongation has been observed with antipsychotic medications. Phenothiazine (thioridazine, chlorpromazine, and mesoridazine), butyrophenone (droperidol and haloperidol), and diphenylpiperidine (pimozide) neuroleptics have all been associated with TdP. In 495 patients receiving psychiatric medications, 8% had QT prolongation. Thioridazine and droperidol posed the highest risk. Both have been shown to block \( I_{Kr} \) in animal models.

### Figures

**Figure 3**

Representation of a myocardial action potential. Phase 0 rapid depolarization is mediated by sodium entry into cells. Phase 1 and 3 repolarization results from potassium efflux from cells. Balanced slow calcium entry and potassium exit cause the plateau in phase 2. Potassium reenters and sodium exits cells during phase 4 recovery. Adapted with permission from Arnsdorf, M, Lee, P. Myocardial action potential and action of antiarrhythmic drugs. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA 2006. For more information visit www.uptodate.com.

**Figure 4**

Action potential recordings showing early EADs. The panel on the left depicts single EADs, whereas the one on the right depicts multiple EADs from progressively more negative transmembrane potential. Reprinted with permission from El-Sherif et al.
QT prolongation has also been noted with tricyclic antidepressants. Torsade de pointes is primarily limited to patients with additional risk factors.73

Miscellaneous medications
Arsenic trioxide, which is used to treat promyelocytic leukemia, has been associated with a very high rate of QT prolongation.74,75 In 99 patients treated with arsenic trioxide, 38% developed significant QT prolongation; however, only 1 patient developed TdP.75 The high incidence of QT prolongation but low risk of TdP may be explained by its unique electrophysiologic properties.76,77 In addition to blocking $I_{kr}$, $I_{ks}$, and reducing surface expression of $I_{kr}$ channels, arsenic appears to activate a current ($I_{kATP}$) that promotes repolarization and decreases the arrhythmic milieu.

Methadone, a long-acting synthetic opiate, is widely used and considered safe, effective treatment for heroin addiction and chronic pain. However, methadone blocks $I_{kr}$ and prolongs QTc in a dose-dependant fashion.78,79 Fifty-nine cases of methadone-induced LQTS or TdP

Figure 5
Characteristic short-long-short sequence preceding a short run of TdP in a patient on high-dose procainamide and amiodarone. Adapted with permission from Trohman and Sahu.21

Figure 6
Twelve-lead ECG depicting manifest T wave alternans in a patient who had drug-induced TdP. The T wave alternans occurred “paradoxically” after the ventricular arrhythmias had stabilized. Adapted with permission from Trohman and Sahu.21
were reported to the Food and Drug Administration between 1969 and 2002. An additional risk factor was found in 75% of these cases.

**Vitamins, supplements, and herbals**

Torsade de pointes has been described in patients taking nutritional or herbal supplements. Cesium, which is used to treat or prevent cancer, induces EADs and prolongs QTc. It has been used experimentally to mimic LQTS. Torsade de pointes has been reported in patients taking cesium. Licorice and zhigancao (a Chinese herbal prepared from licorice), which is used to treat dyspepsia and peptic ulcer disease, cause hypokalemia and have been associated with TdP. Extracts from licorice, grapefruit juice, olive leaves, and red grape skins inhibit CYP3A4 and may interfere with metabolism of QT-prolonging medications (Table III). Corn silk, dandelion, juniper, and uva-ursi have diuretic properties and may potentiate arrhythmias if hypokalemia occurs.

**Recommendations**

It is impractical (perhaps impossible) for patients and clinicians to memorize all medications implicated in QT prolongation. The University of Arizona (Arizona-CERT) maintains a database of QT-prolonging drugs. This list, stratified by relative risk, can be accessed via the internet (www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org).

Our discussion of electrophysiologic mechanisms has been intentionally brief. Readers should refer to the consensus statement from Fenichel et al and a review by Yap and Camm for greater detail.
Despite limitations, treatment with QT prolonging medications is frequently necessary. Risks of therapy must be weighed against benefits. Alternative treatments should be considered. Underlying risk factors should be assessed, and reversible conditions must be corrected before drug initiation. Polypharmacy (multiple QT prolonging medications or agents that interfere with their metabolism) should be avoided. Patients should be counseled about proarrhythmic risk.

Great caution is necessary when initiating class III antiarrhythmics. Patients are routinely hospitalized for at least 72 hours during dofetilide initiation. Ibutilide should be administered while the patient is hospitalized in a telemetry unit. A monitoring period of at least 4 hours post ibutilide is recommended. Hospitalization for sotalol initiation is controversial. Patients with underlying risk factors should be hospitalized and monitored.90,91

Conclusions

Drug-induced LQTS remains an important, potentially preventable source of morbidity and mortality. Many unrelated drugs may lengthen QTc and cause TdP, usually via \( I_{Kr} \) blockade. The list of these agents is constantly evolving. Clinicians and patients must be familiar with resources providing comprehensive information. Predisposing risk factors and drug-drug interactions should be considered. If drug-induced TdP develops, prompt treatment is critical and may be life saving.

References


47. Prystowsky EN. Effects of bepridil on cardiac electrophysiologic properties. Am J Cardiol 1992;69:63D-7D.


