

Drug-Induced QT Interval Prolongation: Mechanisms, Risk Factors, Genetics and Clinical Management

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ABSTRACT

Long QT syndrome (LQTS) characterized by prolongation of the QT interval, may occur as congenital or drug-induced forms. Drug-induced QT interval prolongation (DI-QTP) is closely associated with severe ventricular arrhythmias [especially torsade de pointes (TdP)] and sudden cardiac death. In particular, development of DI-QTP is generally associated with multiple risk factors. Cardiac and non-cardiac drugs may cause QT interval prolongation (QTP) and TdP. Most of the QT-prolonging drugs act by blocking the rapid component of the delayed rectifier potassium channel whereas a smaller number of drugs act by modifying Ca²⁺ and Na⁺ currents. In addition, pharmacokinetic drug interactions are among the reasons of DI-QTP. The corrected QT interval (QTc) according to heart rate by Bazett's formula is the most commonly used. Genetic susceptibility is another important issue in predicting DI-QTP and TdP risk. Silent mutations and/or polymorphisms associated with cardiac ion channels may cause a risk for DI-QTP. Firstly, for treatment, drugs that cause QTP should be stopped rapidly, electrolyte abnormalities and other pathologies should be rapidly corrected. Intravenous magnesium sulphate, overdrive pacing, isoproterenol and plasma alkalinisation via sodium bicarbonate are the main useful treatments for DI-QTP and related TdP therapy. Class 1B antiarrhythmic drugs and intravenous potassium are thought to may be effective in TdP.

The purpose of this article is to review the underlying mechanisms of QTP, risk factors and genetics of DI-QTP, how to measurement of QT interval and treatment of acquired LQTS.

Key-words: Drugs, QT interval, QT prolongation and torsade de pointes.

INTRODUCTION

Sudden cardiac death which is caused by mostly (% 80–85) acute ventricular arrhythmias, is a common cause of mortality. Prolongation of ventricular repolarization is an important cause of ventricular arrhythmias (1). Long QT syndrome (LQTS) characterized by QT interval prolongation (QTP) which represents ventricular depolarization and repolarization, may occur as congenital form or acquired form which induced by drugs. Many drugs have QT-prolonging effects and they may cause severe ventricular arrhythmias. Drug-induced QT interval prolongation (DI-QTP) is more common than congenital QT prolongation and particularly important in people with multiple risk factors (1–4).

The purpose of this article is to review the underlying mechanisms of QTP, risk factors and genetics of DI-QTP, how to measurement of QT interval and treatment of acquired LQTS.

Drugs that have QT-prolonging effects

Cardiovascular and non-cardiovascular many agents may cause QTP and severe ventricular arrhythmias [especially torsade

de pointes (TdP) which is defined as ventricular polymorphic tachycardia] (4). Drugs that have been associated with QTP and TdP, are shown in Table 1 (1, 5–11). TdP is important in routine clinical practice because it may degenerate into ventricular fibrillation and drug-induced TdP incidence is not sufficiently known (10, 12). In a observational study, 3.1% of patients treated with non-cardiac drugs have been reported to develop TdP (13).

Most antiarrhythmic drugs, such as quinidine and sotalol, usually have a higher risk of TdP than non-cardiovascular drugs (7). Amiodarone, an antiarrhythmic drug, is one of the exceptions. Although amiodarone can significantly prolong QT interval, it rarely causes TdP (14). Antimicrobials and psychotropic drugs, which are non-cardiovascular drugs, are also one of the most common cause of DI-QTP (10). Macrolides and fluoroquinolones are antimicrobial drug groups that frequently prescribed and known to associated with QTP (4).

Table 1. Drugs associated with QT interval prolongation and torsade de pointes	
Drugs	
Antiarrhythmics	
Class IA	Quinidine, Disopyramide, Procainamide
Class IC	Flecainide, Propafenone
Class III	Amiodarone, Sotalol, Ibutilide, Dofetilide
Antimicrobials, antifungals, antimalarials	
Macrolides:	Erythromycin, Clarithromycin, Azithromycin, Roxithromycin
Antifungals:	Ketoconazole, Fluconazole, Voriconazole
Antiprotozoal:	Pentamidine
Antimalarials:	Quinine sulfate, Chloroquine, Halofantrine
Quinolones:	Levofloxacin, Moxifloxacin, Sparfloxacin, Grepafloxacin, Ciprofloxacin
Antidepressants	
Amitriptyline, Citalopram, Escitalopram, Fluoxetine, Desipramine, Imipramine, Clomipramine, Maprotiline, Doxepin, Fluvoxamine, Venlafaxine	
Antipsychotics	
Haloperidol, Droperidol, Mesoridazine, Thioridazine, Chlorpromazine, Amisulpride, Ziprasidone, Pimozide, Risperidone, Sertindole	
Antiemetics	
Ondansetron, Dolasetron, Granisetron	
Antihistamines	
Terfenadine, Astemizole, Hydroxyzine, Diphenhydramine	
Opiates	
Methadone, Levomethadyl	
Antineoplastic	
Arsenic trioxide	
Gastrointestinal drugs	
Cisapride, Domperidone, Metoclopramide	
Others	
Tamoxifen, Anagrelide, Probucof, Cocaine, Bepridil, Tacrolimus	

In the last decade, there are many marketed drugs [antibiotics (sparfloxacin, grepafloxacin), atypical antipsychotic (sertindol), antihistaminics (terfenadine, astemizol) and prokinetic agent (cisapride)] which are withdrawal because of the risk of the TdP (13, 15). Therefore, clinicians should be careful about possible risks before prescribing QT prolonging medications (9).

Measurement of the QT interval

The QT interval on a surface electrocardiogram (ECG) is the period from the beginning of the QRS complex to the end of the T wave (15). There is insufficient data about which lead should be used to measure the QT interval (16). Lead II is one of the most widely used leads because of the possibility of having the longest QT interval. Determining the T wave end point is an important issue in the measurement of the QT interval (17). In this regard the tangent method is one of the methods of determining the end of the T wave. This method determine the T wave end point by using

Table 2. Corrected QT interval formulas

Formula	QTc calculation
Bazett	$QT/(RR)^{1/2}$
Fredericia	$QTc=QT/(RR)^{1/3}$
Framingham	$QTc=QT+0.154 \times (1-RR)$
Hodges	$QTc=QT+1.75 \times (HR-60)$

the intersection of a tangent to the steepest slope of T wave and the baseline (13).

Heart rate changes influence the duration of QT interval, therefore usually the corrected QT interval (QTc) according to heart rate is used. For the rate correction, the RR interval prior to the QT interval should be measured (3). There are several methods for calculating the QTc value and it is not defined which is the most effective method. In clinical practice, Bazett's formula is the most

frequently used formula (especially at the heart rate 60–100 per minute) (13). QTc formulas are shown in Table 2 (18).

In generally, the QT interval is longer in women. In men, QTc values above 450 millisecond (ms) are considered prolonged and values between 430–450 ms are considered borderline. In women, values above 470 ms are considered prolonged and values between 450–470 ms are considered as borderline (13). Additionally, QTc interval >500 ms is associated with severe arrhythmias, mainly TdP (15).

Moreover, it is stated that every 10 ms increase in QTc, raises the risk of TdP occurrence by 5–7% and every 20 ms increase in QTc also raises the risk of TdP significantly (9).

In addition to QTc interval, there are several useful ECG variables to predict TdP. QT dispersion (QTd) (difference between maximum and minimum QT intervals) is the one of the variables used to predict TdP. It also has important role in the direct measurement of the spatial heterogeneity of repolarization. QTd values above 100 ms are considered abnormal. Apart from the QTd, interval from the peak to the end of the electrocardiographic T wave (TpTe), TpTe/QT ratio, slow QRS upstroke, giant T-U waves and short-term variability of QT intervals are principal predictors of drug-induced TdP. Yamaguchi et al also concluded that in acquired LQTS, the TpTe/QT ratio is a better predictor of TdP as compared to QTc and QTd (10, 12).

For the most realistic assessment of DI-QTP, ECG readings should be performed when the daily blood level of the drug, which affecting the QT interval, is maximum or close to the maximum. It is also emphasized that if the QT interval is estimated automatically, it should also be confirmed with manual measurements (19). Beside these, QT values can be different from up to 75–100 ms, depending on ECG recording technique, electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), sympathovagal activity, diurnal variation, drugs, genetic abnormalities, and cardiac or metabolic diseases (10, 12).

Mechanisms of drug-induced long QT syndrome

Simultaneous and equilibrated several ionic currents regulate action potential in cardiac muscle cell. Ventricular depolarization result from inward depolarizing currents, mainly through Na⁺ and Ca²⁺ channels, ventricular repolarization result from outward repolarizing currents, mainly through K⁺ channels (1, 6). Results from a decrease in repolarizing current, prolong the ventricular action potential duration (APD) and QT interval. IKr (rapid) and IKs (slow) are two important subtypes of the delayed rectifier potassium current (12, 20).

Production of IKr is regulated by the human ether-a-go-go-related gene (hERG or KCNH2 in the new nomenclature), therefore hERG expression is a significant factor in QTP (19). Most QT-prolonging drugs act by inhibition the IKr (8). Prolonged repolarization can cause early afterdepolarizations (EADs) which occurring in phase 2 or 3 of the cardiac action potential due to decrease in outward current (potassium) or increase in inward currents (sodium or calcium) (6, 12). If EADs arrives threshold and take place in

Table 3. Major risk factors for drug-induced QT interval prolongation

Risk factors
Female sex
Advanced age
Electrolyte abnormalities
Hypokalemia
Hypocalcemia
Hypomagnesemia
Cardiac abnormalities
Bradycardia
Myocardial infarction
Heart failure
Left ventricular hypertrophy
Genetic predisposition
Diuretic or digoxin therapy
Some medical conditions
Renal-hepatic dysfunction
Hypertension
Diabetes mellitus
Hypothyroidism
Obesity
Anorexia nervosa
Prolongation of the baseline QT interval
Polypharmacy

broad area of the heart, ventricular ectopic beats may occur before a long QT interval (21, 22). Furthermore, heterogeneity in ventricular repolarization, can cause unidirectional block, recurrent extrasystoles, reentry and TdP (20, 23).

Some drugs prolong the QTc interval by modifying calcium and sodium currents. For example antimony which antiprotozoal agent, can lead to prolonged QT interval via increase calcium currents.

Sodium channel blocking drugs such as antihistamines, beta blockers, tricyclic antidepressants and phenothiazine can cause slowed intraventricular conduction with the development of a re-entrant circuit. As a result of that, ventricular tachycardia may be develop (1, 11, 15, 24).

There are at a minimum three types of cells in a myocardium, including epicardial, endocardial, and midmyocardial, and the action potentials in these cell types differ from each other (20). Beside this, midmyocardial cells show much more marked action potential prolongation in reaction to IKr blockade compared to subendocardial and subepicardial cells. This feature may cause increase in dispersion of repolarisation (16).

Another mechanism of DI-QTP is pharmacokinetic interactions. Many drugs such as macrolide antibiotics, ketoconazole, cimetidine, fluoxetine, protease inhibitors, and amiodaron inhibit cytochrome P450 isoenzymes (especially CYP3A4). Therefore concurrent administration of these drugs may enhance the torsadogenic potential of other drugs which are substrate for CYP3A4 (3, 15).

Risk factors for drug-induced QT interval prolongation and torsades de pointes

DI-QTP and TdP arrhythmia may not be seen in every patient taking QT-prolonging drug. Several risk factors have been defined,

Table 4. Major genes related to congenital long QT syndrome

	Genetic Subtype of Congenital Long QT		
	LQT1	LQT2	LQT3
Associated gen	KVLQT1 (called KCNQ1)	hERG (known as KCNH2)	SCN5A
Affected ion current	IKs	IKr	INa
Affected ion channel subunit	alpha subunit	alpha subunit	alpha subunit
Pathophysiological effect	Decreased K ⁺ outward currents	Decreased K ⁺ outward currents	Increased Na ⁺ inward current
Detection rate	40–55%	35–45%	8–10%

including both genetic causes and extrinsic causes, which are also associated with the mechanism of DI-QTP. People with drug-induced QT interval prolongation are stated to have at least one risk factor in addition to drug exposure in general (9, 25). The major risk factors are presented in Table 3 (1, 3, 4, 7, 13, 15, 17). It is important to consider these risk factors for the evaluation of QTP and TdP.

Female sex is the most common risk factor and the QT interval in women is approximately 20 ms longer than men. The probable cause of this condition is the effects of sex hormones on QT interval (13, 17, 20). Estrogen prolongs QT interval by decreasing the IKr current, whereas testosterone shortens QT interval by increasing the IKs and IKr currents (6, 13).

It has been reported that increasing age is associated with QTP. The drug-induced TdP risk is higher in patients over 65 years of age (18, 26). It is thought that this could be associated with a decrease in testosterone levels in men and a decrease in progesterone levels in women (5).

Electrolyte abnormalities such as hypokalemia, hypomagnesemia and hypocalcemia have been associated with QTP (27). Low extracellular potassium may cause QTP by inhibiting IKr current and sodium pumping while hypomagnesemia may prolong the QT interval by inhibiting the Na-K-ATPase pump and modulating the L-type calcium channel function (9, 22, 28). Hypomagnesemia is usually not proarrhythmic alone, it usually found combination with other abnormalities of electrolytes. In addition, hypocalcemia is also associated with QTP, but it is reported that TdP associated with hypocalcemia is quite rare (6). Some conditions such as therapy with diuretics, renal dysfunction, anorexia nervosa partly causes QTP by electrolyte imbalance (19).

In heart failure, QT interval may be prolonged due to decreased ejection fraction (5). It is reported that repolarization reserve is diminished in chronic heart failure, there is a downregulation of potassium channels (6, 29). In left ventricular hypertrophy and heart failure, upregulation of calcium channels and downregulation of potassium channels may occur (13).

Bradycardia is related with longer action potential and QT interval, especially in M and Purkinje cells. It reduces the outflow of potassium current, therefore it prolongs the APD and QT interval duration (13, 28).

In addition to all these, polypharmacy is also important risk factor because it may increase the risk of DI-QTP (15).

Genetic susceptibility and drug-induced long QT syndrome

There is a significant variability among individuals in susceptibility to DI-QTP. Silent mutations and/or polymorphisms in cardiac ion channels related genes may reduce cardiac repolarization reserve and they may cause a risk for DI-QTP (15). Numerous gene mutations and genetic polymorphisms related to QTP and congenital LQTS have been described (30). Detection of these genes in patients with DI-QTP, as well as patients with congenital LQTS, has raised the issues of "genetic predisposition and the subclinical form of congenital LQTS" (18).

Approximately 15 genes have been identified as associated with LQTS (6). Among these genes, KCNQ1, KCNH2, SCN5A are the major LQTS genes. (Table 4) (13, 26, 31).

Shimizu et al. reported that these 3 genes were present in more than 80% of genotyped patients with LQTS in Japan (32). Yang et al. found that 10% to 15% of patients who developed drug-induced TdP had mutation or polymorphism in one of the LQTS genes (33).

Besides, KCNQ2, KCNE1, KCNE2 and KCNE3 are some of the other genes that are being investigated related to DI-QTP (30). For example, polymorphism in KCNE1 and KCNE2 genes has been associated with LQTS caused by quinidine and erythromycin (34, 35).

Although many mutations in LQTS genes have been reported, two clinical phenotypes have been identified that differ according to the presence or absence of hearing loss. Romano-Ward is an autosomal dominant syndrome and it courses with cardiac events (including QTP).

Jervell and Lange-Nielsen syndrome (JLNS) is a more malignant syndrome, is related with congenital sensorineural deafness and QTP and it has an autosomal recessive pattern of inheritance. In patients with JLNS, mutations in the KCNQ1 (LQT1) and KCNE1 (LQT5) genes have been reported. These genes encode the alpha and beta subunit of IKs in the heart and the inner ear (31, 36, 37). Beside, mutations in these genes may cause deafness by disrupting endolymph production in the stria vascularis in the cochlea (38). Timothy and Andersen-Tawil syndromes are other syndromic diseases, course with QTP (39).

In recent years, common variants in LQTS-associated candidate genes also have been identified (*NOSTAP*, *PLN*, *RNF207*, *LITAF*, *NDRG4* and *GINS3*, *LIG3* and *RFFL*). In the QTGEN meta-analysis of three genome-wide association studies, the fourteen genetic variants in ten loci have been detected. According to this study, these variants explained 5.4–6.5% of QT interval variability in the population (1, 40, 41).

Similarly, genetic variants that affect the metabolism of QT prolonging drugs may increase the risk of DI-QTP. For example, CYP2D6 enzyme that metabolizes thioridazine is non-functional due to the loss of function of the genetic variants in 7–10% of the population. These people are also called poor metabolizers therefore they have higher risk for thioridazine-induced TdP than other people (20).

The elucidation of gene-specific and mutation-specific variants is important issue in predicting the risk of arrhythmia in patients taking QT-prolonging drugs.

Standard and novel treatment options for drug-induced QT interval prolongation and torsades de pointes

In acquired long QT syndrome, generally short-term treatments are recommended and administered. Because, QT values usually return to normal limits after the correction of conditions that cause long QT (42).

In the case of QTP, QT prolonging medications should be rapidly discontinued, electrolyte abnormalities and conditions that predispose to electrolyte abnormalities should be corrected (43).

Intravenous magnesium sulphate, overdrive pacing, isoproterenol and plasma alkalinization via sodium bicarbonate are the short-term therapies with useful in LQTS and related TdP. Class 1B antiarrhythmic drugs (lidocaine, phenytoin etc.) and intravenous potassium are thought to may be effective in TdP (7, 18, 43).

K channel openers (nicorandil, pinacidil, cromakalim), atropine, calcium channel blockers and alpha adrenergic receptor blockers are also the novel treatment options (44). The long-term treatment of QTP is rarely required. A permanent pacemaker may be required in patients with chronic bradyarrhythmia due to AV block or sick sinus syndrome (7).

Magnesium sulphate is a first-line agent in the treatment of TdP arrhythmias or ectopic beats associated with congenital and acquired long QT syndromes. Magnesium has been reported to prevent both short-term recurrences of TdP and to be an effective option in the treatment of TdP (7, 13, 42, 43). The mechanism underlying its beneficial effects are uncertain. But, it is thought to decrease EAD amplitude associated with ectopic beats by inhibiting calcium and sodium inward currents (26, 28). Magnesium does not affect the QTc interval significantly. Regardless of serum magnesium level, intravenous bolus magnesium sulphate (1 to 2 g) followed by intravenous infusion of magnesium can be administered in TdP episodes in adults (42, 43).

Overdrive transvenous pacing is a treatment option after magnesium sulphate administration. It is effective in preventing both acquired and congenital long QT-related TdP recurrences. Especially, it reported to be useful if TdP is caused by pause or bradycardia. Evidence suggests that pacing rates of approximately 90–110 beats/min, increases IK current, thus it shortens QTc interval, decreases EAD and QTd (13, 43).

Isoproterenol is a treatment options that may prevent short-term recurrences of acquired LQTS related-TdP in patients not responding to magnesium treatment. It should use especially in TdP cases where recurrence is due to bradycardia or pause (7, 43).

It is also contraindicated in patients with congenital QTP and ischemic heart disease. Because of its adrenergic effects, it can increase the heart rate and shorten the QT interval and can be used as a temporary measure prior to pacing (7, 13). Isoproterenol can be administered by titrating to achieve a heart rate of 100 beats/min in adults (43).

It has been reported that alkalinization of plasma with sodium bicarbonate may be useful in patients who develop TdP due to quinidine (18).

CONCLUSION

All physicians should take precautions to prevent DI-QTP, TdP and/or sudden cardiac death. Patients treated with QT-prolonging drugs should be monitored and the QT interval measured correctly. Drugs that have QT prolongation effects should not be used exceeding the recommended dose in clinical practice. In patients with risk factors the use of these drugs should be avoided. Drugs that inhibit the cytochrome P450, prolong the QT interval and cause electrolyte imbalance should be avoided concomitant use. In individuals with genetic susceptibility drug selection should be done carefully.

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