National Medicines Information Centre

VOLUME 27
NUMBER 2
2021

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DRUG-INDUCED QT PROLONGATION

- **QT prolongation is a recognised risk factor for the development of ventricular arrhythmias including torsades de pointes that may result in sudden cardiac death**
- **Many risk factors are associated with QT prolongation; drugs are the most common risk factor**
- **Before initiating a QT prolonging drug, patients should be assessed for other risk factors and any modifiable risk factors should be corrected**
- **Co-administration of a QT prolonging drug with other QT prolonging drugs and/or hepatic cytochrome P450 isoenzyme inhibitors which interfere with QT prolonging drugs should be avoided**

INTRODUCTION

QT interval prolongation (hereafter referred to as QT prolongation), identified as a prolonged QT interval on an electrocardiogram (ECG), is a recognised risk factor for the development of ventricular arrhythmias which may result in sudden cardiac death (SCD).[1-6] In particular, QT prolongation is a risk factor for torsades de pointes (TdP), a specific form of polymorphic ventricular tachycardia, first described in 1966.[1,2,6-10] TdP is often self-limiting, although frequently recurs and may progress and lead to ventricular fibrillation and SCD.[2]

QT prolongation can occur due to congenital and acquired causes.[2,5,6,11] **Drug-induced QT prolongation is the most common cause of acquired QT prolongation.**[2,5,6,9,12] QT prolongation is one of the most common reasons for withdrawal of a drug from the market (e.g. terfenadine and cisapride).[5,7,8,11,13] Prescribing restrictions have been implemented for other drugs known to be associated with an increased risk of QT prolongation (e.g. citalopram, domperidone, quinine and erythromycin).[3,14-17] The incidence of drug-induced QT prolongation or TdP in the general population is unknown; however **drug-induced QT prolongation and TdP are important to recognise and manage as they can occur as a side effect of many medications and may be fatal.**[8,18] In recent years, there has been an increased understanding of the mechanisms whereby drugs cause QT prolongation.[2,3]

This bulletin, which updates a previous bulletin on drug-induced QT prolongation, provides an overview of the mechanism by which QT prolongation occurs, the risk factors for its occurrence, and the prevention and monitoring of drug-induced QT prolongation.

MECHANISM OF QT PROLONGATION

The QT interval on the ECG represents the period from the onset of depolarisation to completion of repolarisation of the ventricular myocardium.[6,19] The electrical activity of the heart is mediated by ion channels within the myocardial cell membrane, which regulate the flow of ions in and out of cardiac cells.[9] Rapid inflow of positively charged ions (mainly sodium and calcium) results in normal myocardial depolarisation. Outward repolarising currents, mainly through potassium channels (including a specific potassium current (I_{Kr}), which is encoded by the ether-a-go-go related gene [HERG]), result in repolarisation.[2,6,8,9,20] Malfunction of ion channels (mainly potassium but also sodium and calcium channels) may result in an intracellular excess of positively charged ions; this intracellular excess of positively charged ions extends ventricular repolarisation which is represented by QT interval prolongation.[1,9,20] **A delay in ventricular repolarisation creates an electrophysiological environment that may facilitate the development of cardiac arrhythmias, such as TdP.**[2,3,]

Measurement of the QT interval

The QT interval is measured in milliseconds (ms) from the beginning of the QRS complex to the end of the T wave.[1,9,19] The measurement of the QT interval is subject to substantial variability,[3,9] including the method of measurement employed. **Factors which have an impact on the length of the QT interval include age, gender, heart rate, conduction defects and diurnal pattern, of which heart rate is the most important factor.**[1,2,19] The QT interval is usually corrected for heart rate and reported as QTc.[1,2,19] Several formulae are available to correct the QT interval for heart rate including Bazett's, Fridericia and Framingham.[1-3,5,6,20-22] Bazett's formula is most commonly used in clinical practice and is automatically performed by most ECG machines; however limitations of this method include underestimation and overestimation of the QT interval at low and high heart rates respectively.[1,3,6,22,23] Some experts recommend measuring the QT interval manually, although recommendations differ as to the best method.[2,6,22-25]

The QT interval is used during drug development and in clinical practice, as a surrogate marker for the prediction of serious adverse drug effects such as syncope or death due to TdP.[10] There are varying definitions as to what is considered an abnormal QT.[3,21,24-27] **QTc intervals of 450ms (in adult men) and 460ms (in adult women) are**

generally accepted as the upper limits of normal.[6,19] The 2015 European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, recommends diagnosing long QT syndrome (LQTS) in patients with a QTc ≥480 ms in repeated 12-lead ECGs or an LQTS score >3;[27,28] LQTS should also be considered in patients with a QTc ≥460ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.[27]

AETIOLOGY OF QT PROLONGATION

QT prolongation can occur as a result of congenital LQTS or because of acquired conditions.[2,5,6,20,29] Acquired causes of QT prolongation are much more common than congenital causes.[29] **It is important to appreciate that there is frequently more than one cause or risk factor for QT prolongation present in an individual patient.**[7]

Congenital long QT syndrome

Congenital LQTS has a prevalence of 1 in 2,000-2,500 live births.[6,20] The number of patients with congenital LQTS in Ireland is estimated to be between 400 and 1000 patients.[30] Most patients with congenital LQTS are asymptomatic and a diagnosis is made either incidentally on an ECG, by a family history of SCD, or after surviving an episode of syncope or ventricular arrhythmia.[6,20,23] These patients require specialist assessment. There are more than 13 recognised different types of congenital LQTS.[1,19] The most prevalent congenital disorders are LQT1 (>50%) and LQT2 (up to 40%) that are due to mutations in the potassium channels and LQT3 (up to 15%) that is caused by mutations in the sodium channels.[20] LQT1 events may be triggered by exercise or stress, LQT2 by emotional stress and LQT3 events occur usually during sleep or at rest.[1,9,23] **Patients with congenital LQTS should avoid known QT prolonging drugs and be aware of the need to avoid and correct potential causes of hypokalaemia** (e.g. gastrointestinal disturbance).[6,23]

There is a growing understanding of the genetics associated with cardiac arrhythmias.[19] In addition to the recognised congenital LQTS, there is increasing evidence that the QT interval is a heritable trait and that subclinical mutations or polymorphisms may explain why some patients appear to be at higher risk from drugs that cause QT prolongation.[5,8,10,13,31] However patients with polymorphisms are likely to have normal or near normal QT at baseline; QT prolongation may only become apparent on exposure to certain drugs or other factors such as hypokalaemia or heart failure.[1,8,10,13] It is known that 5 to 20% of patients with drug-induced TdP have gene mutations which cause QT prolongation.[1,3,10,20] Furthermore, polymorphism of genes coding for cytochrome P450(CYP)2D6 can lead to poor metabolism of CYP2D6 dependent drugs and patients with these polymorphisms are at risk of QT prolongation and TdP if the parent drug has a tendency to cause QT prolongation (e.g. risperidone and haloperidol).[1,5,20,32]

Acquired QT prolongation

QT prolongation can result from multiple factors including drug and patient factors.[13] Factors that **predispose to acquired QT prolongation include female sex, older age, bradycardia, electrolyte abnormalities, low left ventricular ejection fraction, left ventricular hypertrophy, and myocardial ischaemia**.[3,6,22]

After puberty women have a longer baseline QT interval than males and they are more susceptible to drug-induced QT prolongation.[1,9] The mechanism for the gender difference is incompletely understood although it appears that sex hormones affect repolarisation.[1,9] The susceptibility of women to prolonged QT diminishes with increasing age.[6]

Bradycardia decreases potassium outflow during repolarisation and thereby increases the QT interval.[1] **The most common pathological conditions associated with QT prolongation are electrolyte disturbances including hypokalaemia, hypocalcaemia and hypomagnesaemia.**[13] Low extracellular potassium is thought to modify the function of potassium channels and have an effect on sodium channels.[1,26] There is a down-regulation of potassium channels and up-regulation of calcium channels in patients with heart failure and left ventricular hypertrophy, which increases the risk for QT prolongation and TdP.[1] Differences in individual susceptibility to QT prolongation may relate to specific genetic factors.[19]

Drug-induced QT prolongation

Drug-induced QT prolongation is the most common cause of acquired QT prolongation.[2,5,12] Both cardiovascular and non-cardiovascular drugs have been associated with drug-induced QT prolongation.[2,20] Table 1 provides some examples of the many classes of drugs which have been associated with QT prolongation; please note that this list is not exhaustive.

Table 1: Examples of some drugs that can cause QT prolongation* [1,5,7,19,33-36]

Antiarrhythmic drugs • Class I** e.g. quinidine, flecainide • Class III** e.g. amiodarone, sotalol, dronedarone **Antibiotics** • Macrolides e.g. erythromycin, clarithromycin, azithromycin • Quinolones e.g. levofloxacin, moxifloxacin **Anticancer agents** • e.g. tamoxifen, ceritinib, crizotinib, sorafenib, sunitinib **Antifungals** • e.g. fluconazole, ketoconazole	**Antimotility and antiemetic agents** • e.g. domperidone, granisetron, ondansetron **Antimalarials** • e.g. quinine, chloroquine, hydroxychloroquine **Antipsychotics** • e.g. chlorpromazine, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone **Antidepressants** • e.g. amitriptyline, citalopram, escitalopram, dosulepin, lofepramine. **Opioids** • e.g. methadone

*note that this list only gives some example and is not exhaustive; **Vaughan Williams classification

Most drugs that cause acquired QT prolongation primarily target potassium channels;[3,6,13,22,26] however drugs may also target other channels including sodium and calcium channels.[1,3,22] In general **the risk of drug-induced QT-**

prolongation is directly related to the dose and plasma concentration of the drug;[8,19] the risk of QT prolongation is often greater with intravenous administration of drugs, possibly as a result of higher plasma concentrations.[3,13] The use of drugs such as loop or thiazide diuretics may cause electrolyte imbalances such as hypokalaemia. Hypokalaemia can lead to an increased risk of QT prolongation in patients using drugs associated with QT prolongation.[6,8]

QT prolongation may occur due to pharmacodynamic and pharmacokinetic drug-drug interactions, for example the co-prescribing of 2 drugs that are associated with QT prolongation (pharmacodynamic e.g. escitalopram and clarithromycin), and/or when one drug inhibits the metabolism or clearance of another drug associated with QT prolongation (pharmacokinetic e.g. erythromycin and domperidone).[1,19] **A large proportion of QT prolonging drugs are metabolised by CYP1A2 (e.g. clozapine), CYP2D6 (e.g. amitriptyline, flecainide) and CYP3A4/5 (e.g. erythromycin, domperidone, methadone);**[5,22] therefore it is important to be aware that concomitant use of drugs that inhibit the relevant isoenzyme may result in an increased plasma concentration of the QT prolonging drug, with a subsequent increased risk of QT prolongation. Similarly the use of two drugs that share the same isoenzyme pathway for clearance may result in increased plasma concentrations of both.[1] The NMIC bulletins on drug interactions (NMIC 2020;Vol 26:Numbers 3 and 4) provide further information on this topic; they are available at www.nmic.ie.

Many patients may take drugs that cause QT prolongation without any problems, while others receiving the same drug and dose but with additional risk factors develop fatal arrhythmias such as TdP.[3,18-20] For example terfenadine (now withdrawn), a potent blocker of potassium channels was almost completely biotransformed by CYP3A4 before entering the systemic circulation and its major metabolite was non-cardioactive. It caused minimal QT prolongation in most patients at normal concentrations.[10] However, when CYP3A4 metabolism was inhibited (e.g. by erythromycin) or overwhelmed as in terfenadine overdose, the concentration of unmetabolised terfenadine markedly increased resulting in a greater QT prolongation and risk of TdP.[2,10]

It is considered that up to 30% of patients who develop drug-induced QT prolongation carry mutations for one of the LQTS genes or have polymorphisms, whereby QT prolongation becomes apparent when these patients receive a QT prolonging drug.[7,31]

TORSADES DE POINTES

The incidence of TdP, which is represented on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline,[21] is unknown.[7] **TdP can occur in many settings**; however it is most commonly seen in congenital LQTS or in association with drug therapy.[8,10] It is important to note, that by itself, QT prolongation does not always result in TdP.[3,8,18] For some individuals TdP may occur with modest QT prolongation, while others may experience no effects even with markedly prolonged QT.[6]

Some patients who experience drug-induced TdP may have a genetic predisposition.[7] QT prolongation is therefore an imperfect biomarker for predicting TdP.[2,6,8,19] However, in general there is a qualitative relationship between QT prolongation and risk of TdP, especially for drugs that cause substantial prolongation of the QT interval and **particularly if the patient has other risk factors.**[1,8,10,21] **Prolongation of the QT interval beyond 500ms is commonly regarded as conferring an increased risk of TdP**, which should prompt an urgent evaluation of the risks and benefits of the drugs prescribed in that patient.[3,6,8,18,26] Evidence suggests that a QTc of >500ms is associated with a 2 to 3-fold higher risk of TdP.[31] The magnitude of the increase in QT interval from baseline is also useful in evaluating the risk. In particular, there is an increased risk for TdP whenever a drug increases QTc by >60ms, especially when the increase occurs rapidly.[8] **It is estimated that each 10ms increase in QT contributes to a 5 to 7% increase in risk of TdP.**[6,19,26]

Drug-induced TdP is relatively rare and usually occurs as a result of multiple risk factors (see table 2 below).[7,8,18,19,22,27] Evidence suggests that **most clinical cases of drug-induced TdP occur in the presence of at least one risk factor, with over 70% occurring in the presence of two or more risk factors.**[37]

Table 2: Risk factors for torsades de pointes with drug-induced QT prolongation[6,19]

Risk factors	Risk factors
Demographic • Female gender • Age >65 years • Hospital inpatients Genetic • Congenital long QT syndrome* • Genetic predisposition • Ion channel abnormalities Cardiac • Occult long QT syndrome • Bradycardia • Baseline QT prolongation • Underlying heart disease (heart failure, left ventricular hypertrophy, myocardial infarction) Thyroid disease (untreated); more common with hypothyroidism	Biochemical • Uncorrected electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia) Systemic conditions • Hepatic impairment • Renal impairment Drug therapy • Concurrent use of more than one QT-prolonging drug • Rapid rate of intravenous infusion of QT-prolonging drug • High drug concentration of QT-prolonging drug • Concurrent diuretic therapy • Recent cardioversion with QT-prolonging drug (Vaughan Williams Class I and Class III antiarrhythmics)

* QT prolonging drugs should not be used in these patients

The overall incidence of drug-induced TdP depends on the relative risk of the drug prescribed and the frequency of its use in a specific population. **Hospitalised patients are thought to be more at risk of QT prolongation and TdP** as they are more likely to have a larger number of risk factors, such as electrolyte abnormalities, renal disease and

cardiovascular disease.[3] For example, antiarrhythmic-induced TdP is often precipitated in the presence of hypokalaemia or hypomagnesaemia.[6]

Current information on QT prolongation is found in the Summary of Product Characteristics (SmPC) for each medicinal product, in particular in the contraindications, special precautions, drug interaction and adverse effects sections.

There are some information resources (e.g. specialist psychiatric sources such as the Maudsley Prescribing Guidelines in Psychiatry) that provide comparison tables/relative risks of classes of drugs and their association with QT prolongation.[38]

An extensive but not exhaustive list of drugs (>90), associated with QT prolongation and TdP is available on the CredibleMeds® website: **www.crediblemeds.org**.[18] CredibleMeds® is a US website which categorises drugs as those with a 1) Known risk of TdP, 2) Possible risk of TdP, 3) Conditional risk of TdP and 4) Drugs to avoid in congenital LQTS. The list is updated every 30 to 60 days and is divided into categories according to the **perceived** degree of risk.

PRACTICAL ASPECTS OF DRUG-INDUCED QT PROLONGATION

It is important to consider the risk of QT prolongation when prescribing a medicine and to be aware of those that can cause QT prolongation. The balance of benefit versus harm for the individual patient must always be assessed if a QT prolonging drug is being considered.[19,22] **Aspects to consider before starting a medicine that may prolong QT interval include: 1) patient risk factors, 2) the risk posed by the individual drug, 3) the potential impact of drug interactions on the QT interval and 4) the correction of modifiable risk factors.**[6]

QT prolonging drugs should not be used in patients with congenital LQTS and should be avoided whenever possible in patients with additional risk factors for QT prolongation.[3,6,19] The use of an alternative drug not known to prolong QT, should be considered when a drug has a significant risk of QT prolongation. **The potential for drug-induced TdP may be reduced by correcting modifiable risk factors, such as the correction of electrolyte deficiencies (e.g. hypokalaemia, hypomagnesaemia), the avoidance of drugs that inhibit the metabolism of QT prolonging drugs and appropriate dose adjustment for QT prolonging drugs in patients with renal and hepatic impairment.**[3,6,7,19] In certain circumstances it may be necessary to use a QT prolonging drug when the benefits outweigh the risks.[22,26] **If a QT prolonging drug is required, the lowest effective dose of the drug should be used, ensuring appropriate adjustment for renal or hepatic disease as well as for drug interactions.**[3,22] For patients with an elevated risk of TdP, the decision to start a QT prolonging drug should be made collaboratively with the patient,[6] who should be educated on the common symptoms of cardiac arrhythmias and warned to promptly report any symptoms such as syncope, dizziness and palpitations.[6,19]

Many sources recommend that patients should have an ECG to assess their QT interval, either prior to initiating, or prior to a dose increase of a drug that is reported to be associated with QT prolongation,[2,3,6,19] especially in patients commenced on a drug with a high risk of QT prolongation, or with other patient risk factors for QT prolongation.[6] The ECG needs to be repeated once the drug reaches steady state.[6]

Table 3 summarises steps to reduce the risks of drug-induced TdP.

Table 3: Steps to reduce the risks of drug-induced torsades de pointes[3,27]

Assess risk factors for QT prolongation	See table 2
Minimise risk factors	• Where possible use alternative agents that do not prolong QT interval • If QT interval prolonging drugs are required, use lowest effective dose • Correct underlying causes of electrolyte abnormalities or drug-induced bradycardia
Monitoring parameters	Consider ECG • At baseline prior to initiation or dose increase of QT interval prolonging drug • Once QT interval prolonging drug reaches steady state (5 half-lives) • Monitor regularly
Educate patient	Instruct patient to get medical advice if they experience: • Palpitations • Light-headedness • Dizziness • Syncope
When and how to modify therapy	If baseline ECG shows QTc of 480ms • Consider alternative drug that does not cause QT prolongation • Correct electrolyte imbalances If follow-up ECG shows QTc ≥500ms and/or absolute increase in QTc ≥60 ms • Discontinue QT prolonging drug • Correct electrolyte imbalances

FURTHER SOURCES OF INFORMATION

- The Summary of Product Characteristics of the individual medicine available on **www.hpra.ie** and **www.medicines.ie**
- CredibleMeds® regularly updates lists of medicines that cause QT prolongation **www.crediblemeds.org**
- British National Formulary **www.bnf.org**
- Cardiac Risk in the Young (CRY) website **www.cry.ie**
- The NMIC clinical enquiry answering service is available to prescribers and can deal with specific drug-induced QT prolongation enquiries: nmic@stjames.ie

List of references available on ePublication on www.nmic.ie. Date of publication: April 2021