BMJ 2016;353:i2732 doi: 10.1136/bmj.i2732 (Published 22 June 2016)

CLINICAL REVIEW

FROM DRUG AND THERAPEUTICS BULLETIN

QT interval and drug therapy

Drug and Therapeutics Bulletin

Drug and Therapeutics Bulletin, Editorial Office, London WC1H 9JR, UK

The QT interval is measured from the beginning of the QRS complex to the end of the T wave on a surface electrocardiogram and represents the period from onset of depolarisation to completion of repolarisation of the ventricular myocardium.[1] The interval varies greatly and is affected by age, sex, sympathetic tone, and diurnal pattern.[2] Because it increases as heart rate falls, measurements of QT interval are usually corrected for heart rate (QTc). Several methods have been used (box 1) but, as the relation between QT interval and heart rate varies between individuals, guidelines recommend use of linear regression functions such as the Framingham rather than the Bazett or Fridericia method.[4]

Measurement of the QT interval is not straightforward and is associated with considerable intraindividual and interindividual variability. There is currently no agreed consensus on how to measure the QT interval in patients with broad complex ventricular conduction abnormalities or paced ventricular rhythm, and measurement in patients with atrial fibrillation requires special consideration. The QT interval also differs between electrocardiograph (ECG) leads, and it is unclear whether normal values—historically derived from single lead measurements—relate directly to those obtained from multi-lead ECG recordings. In addition, details of algorithms used in semi-automated ECG machines are not always readily available. QTc intervals of 450 ms and 460 ms are generally accepted as the upper limits of normal for adult men and women, respectively.[4]

Although QT prolongation is associated with torsades de pointes (TdP) and sudden cardiac death,[5] it is an imperfect predictor. Many patients with prolonged QT never experience TdP, whereas many who experience TdP have a normal QT before the episode. Similarly, some drugs (eg amiodarone) can markedly prolong QT but are rarely associated with TdP.[5] Both the QT interval and increase in QT duration predict the risk of developing TdP. Each 10 ms increase in QTc is associated with a 5-7% increase in the risk of developing TdP[6]; and when the absolute QTc is >500 ms, the risk of TdP is generally regarded as markedly increased and intervention considered necessary.[7]

Conditions that affect the QT interval

A variety of genetic and acquired conditions can cause QT prolongation. Some congenital long QT syndromes (LQTS), such as Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome, have long been recognised to be associated with a high risk of arrhythmia and premature sudden death.[8] These syndromes are caused by mutations predominantly in genes encoding potassium and sodium channels that help regulate the duration of the cardiomyocyte action potential. The mutations contribute to delayed cardiac repolarisation and increased risk of arrhythmia. Variants of at least 13 separate genes have been shown to cause LQTS, but those underlying LQTS types 1-3 (*KCNQ-1*, *KCNH-2*, and *SCN-5A*) account for about 90% of all genotype positive cases.[9] These classic forms of LQTS are typically associated with different abnormal T-wave morphologies on ECG and arrhythmic triggers (eg sleep, exercise, sudden loud noises). A clinical history of presyncopal and syncopal symptoms (eg palpitations, chest pain, dyspnoea) and a family history of sudden cardiac death may be used to support the diagnosis of LQTS. Patients with such symptoms and history, or those with QT prolongation, should be referred for specialist investigation. If a diagnosis of LQTS is confirmed, patients should be offered counselling, risk stratification, screening of family members, drug therapy (eg β blockers) and, where appropriate, be considered for cardiac sympathetic denervation or an implantable cardiac defibrillator. Gene specific management is based on the underlying genetic profile.[10]

Congenital LQTS is rare, with an estimated prevalence of about one in 2000 infants,[9] and drugs are the most common cause of prolonged QT (box 2). Even so, drug induced QT prolongation and TdP are relatively uncommon.[16] Furthermore, TdP is a rarely reported adverse drug reaction, with one study estimating that drug related TdP represented about one in 700 reported adverse drug reactions.[16]

Drugs that can cause QT prolongation[2 3 7 11-15]

Other than a drug itself, various factors increase or amplify the risk of drug induced QT prolongation and TdP (box 3). Most

dtbeditor@bmjgroup.com

Box 1: Formulae used to correct the QT interval for heart rate[3]

Bazett Method: QTc=QT/(√RR)

Fridericia method: QTc=QT/(RR/3)

Framingham method: QTc=QT+0.154(1-RR)

RR, the interval between two successive R waves.

Box 2: Drugs that can cause QT prolongation[2 3 7-15]

Anti-arrhythmic drugs

Amiodarone, disopyramide, dronedarone, flecainide, sotalol

Other cardiac drugs

Ranolazine, macrolides (eg erythromycin, clarithromycin, azithromycin), quinolones (eg levofloxacin, moxifloxacin)

Antifungals

Fluconazole, ketoconazole

Antimotility and antiemetic agents

Domperidone, granisetron, ondansetron

Antimalarials

Quinine, chloroquine

Antihistamines

Hydroxyzine

Antipsychotics

Chlorpromazine, clozapine droperidol, fluphenazine, haloperidol, olanzapine, pimozide, paliperidone, quetiapine, risperidone

Antidepressants

Amitriptyline, citalopram, escitalopram, dosulepin doxepin, fluoxetine, imipramine, lofepramine

Miscellaneous

Methadone, antiretrovirals (eg foscarnet), protein kinase inhibitors (eg sorafenib, sunitinib)

clinical cases of drug induced QT prolongation occur in the presence of at least one of these risk factors, with over 70% occurring in the presence of two or more risk factors.[17]

How do drugs affect QT?

Most drugs that prolong QT do so through inhibition of the rapid component of the delayed rectifier potassium (IKR) channel, encoded by the human ether-a-go-go related gene (*hERG*), which is affected in LQTS type 2.[18] However, drug induced QT prolongation is not specific to inhibition of the IKR current, as not all drugs that block this current cause TdP.

In general, the risk of drug induced QT prolongation is directly related to the dose and plasma concentration of the drug. Pharmacokinetic and pharmacodynamic interactions can also cause QT prolongation.[8] Drug-drug interactions that inhibit drug metabolism may increase the plasma concentration of the affected drug and precipitate QT prolongation. Similarly, QT prolongation may occur when two drugs have an additive effect. Differences in individual susceptibility to QT prolongation may relate to specific genetic factors.[19]

Minimising the risks of drug induced QT prolongation

Screening during drug development

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which includes drug regulatory authorities and drug companies in Europe, Japan, and the United States, has published guidance for monitoring the effect on QT through preclinical and clinical phases of drug development.[20 21] Potential new drugs are routinely screened in preclinical development for interaction with the *hERG* encoded potassium channel with in vitro and in vivo studies.[20] In the early clinical phase of drug development, a "thorough QT/QTc test" is undertaken to determine a drug's effect on QT and the dose-response association of any effect detected.[21] This often involves testing the drug at therapeutic and supratherapeutic doses, with comparisons made against placebo as well as active controls with known QT prolonging properties. A positive result is recorded when the upper limit of the 95% one sided confidence interval for the largest time matched placebo corrected mean effect of the drug on the QTc exceeds 10 ms. Generally, a positive QT/QTc test will almost always lead to a requirement by regulatory authorities for expanded ECG monitoring and safety evaluation during later stages of development.

Regulation and postmarketing surveillance

At a regulatory level, judgments have to be made about the degree of QT prolongation, risk of life threatening arrhythmia, and clinical benefits associated with a drug. The risk-benefit assessment is influenced by the size of the prolongation in the QT/QTc interval, whether the effect occurs in most patients or only in certain defined outliers, and the utility and feasibility of risk management options.[20] Generally, a mean prolongation in QTc of 5 ms is considered the threshold of concern, with a prolongation >20 ms considered to be associated with a substantial likelihood of the drug being proarrhythmic. Irrespective of the degree to which a drug prolongs the QT/QTc interval, decisions to grant marketing authorisation for a drug depend on several factors: morbidity and mortality associated

Box 3: Risk factors for torsades de pointes with drug induced QT prolongation[3 6 7 12]

Demographic

Female sex, advanced age

Biochemical

Electrolyte disturbances (eg hypokalaemia)

Genetic

Genetic predisposition, ion channel abnormalities

Systemic conditions

Hepatic impairment, renal impairment

Cardiac

Occult long QT syndrome, bradycardia, baseline QT prolongation, recent cardioversion with QT prolonging drug, underlying heart disease (heart failure, left ventricular hypertrophy, myocardial infarction)

Drug therapy

Concurrent use of more than one QT prolonging drug, concurrent diuretic therapy, digoxin, rapid rate of intravenous infusion of QT prolonging drug, high concentration of QT prolonging drug

with the untreated disease; the demonstrated benefits of the drug—especially when compared with other therapeutic options; the overall benefit of the drug; whether the drug has clear advantages over existing drugs; and whether available therapeutic options meet the needs of most patients. Where drugs with the potential to prolong QT offer sufficient benefit, appropriate warnings and monitoring requirements are specified in the summary of product characteristics.

Clinical trial programs are not usually large enough to determine most unwanted adverse effects, including the proarrhythmic potential of a drug with modest QT prolonging effects. Postmarketing surveillance is therefore crucial to an ongoing assessment of risk of TdP and cardiac arrhythmia with drugs that have the potential to prolong QT. In fact, QT prolongation is one of the main reasons for withdrawal of drugs from markets across the world (eg astemizole, cisapride, grepafloxacin, terfenadine, and thioridazine).

Minimising risks in clinical practice

Few recommendations exist for managing the risk of drug induced QT prolongation. Precise estimates of relative and absolute risks of QT prolongation and TdP with individual drugs are not readily available. Although some information is available in the *BNF* and summaries of product characteristics, we are not aware of any regularly updated UK based list of drugs associated with QT prolongation. In the US, lists of drugs that have a risk of QT prolongation and cardiac arrhythmia are maintained on the CredibleMeds website, under a contract with the Food and Drug Administration (https://crediblemeds.org/healthcare-providers/; registration on the CredibleMeds site is required so that users can be notified when the lists have been revised).

QT prolonging drugs should not be used in patients with congenital LQTS. When they are used in patients without inherited LQTS but who are at risk of QT prolongation, patients should be educated on the common symptoms of cardiac arrhythmias, such as dizziness, palpitations, and syncope, and advised on when to seek medical attention.[7]

Before starting a QT prolonging drug, patients should be assessed for risk factors for QT prolongation and their overall risk of drug induced QT prolongation. The evaluation should include risk factors for inherited LQTS (see box 3) and concomitant drugs that might interact and increase the risk of QT prolongation. An assessment of the risk-benefit balance of initiating the QT prolonging drug should be carefully made. If possible, modifiable risk factors for QT prolongation (eg electrolyte abnormalities) should be corrected. Where a patient has a high risk of drug induced QT prolongation or is already taking a drug that can enhance QT prolongation, an alternative drug not known to prolong QT should be prescribed instead.

There is no agreed consensus on when to undertake ECG monitoring and follow-up for patients started on drugs with the potential to prolong QT. It has been estimated that about 16 000 screening ECGs are needed to identify a single case of asymptomatic long QT syndrome.[22] Therefore, while it is probably impractical to perform an ECG before prescribing a drug that may prolong QT (particularly in primary care), it is prudent to consider baseline ECGs on a patient by patient basis. For instance, where the risk of drug induced QT prolongation is deemed high (eg where use of an alternative non-QT prolonging drug is not possible in a patient at risk of drug induced QTc prolongation), an ECG should be performed both at baseline and when the added drug reaches steady state. Where a QT prolonging drug is associated with a QTc of 470-500 ms in men, 480-500 ms in women, or an increase in QTc ≥60 ms, dose reduction or discontinuation is advised. If the QTc reaches or exceeds 500 ms, the drug should be discontinued, the ECG repeated, and specialist advice sought.[7]

Conclusion

The QT interval is a key part of the surface ECG, and when prolonged it is associated with a potentially fatal cardiac arrhythmia—TdP. Several rare inherited LQTS can cause prolongation of QT, but it is more often caused by drugs, typically in the presence of additional risk factors for QT prolongation. Although measurement of the QT interval can be problematic, it is required by regulatory agencies when determining and managing the risk of drug induced cardiac arrhythmias during drug development, and in subsequent clinical practice. However, it is of concern that there is no readily accessible and regularly updated UK based list of drugs that prolong the QT interval.

Patients should be assessed for the risk of QT prolongation before being started on a QT prolonging drug. Risk factors such as electrolyte disturbances should be corrected and potential drug interactions that might enhance the risk of QT prolongation avoided. Where there is a serious risk of QT prolongation from a particular drug, an alternative drug that has not been show to

prolong QT should be prescribed instead. QT prolonging drugs should be avoided in patients with inherited LQTS. Patients at risk of drug induced QT who need to be started on a drug with potential to prolong QT should have a baseline and follow-up ECG, be provided with information on the common symptoms of cardiac arrhythmias, and be advised when to seek medical attention if they experience such problems.

Competing interests: Competing interests are in line with *DTB*'s policy on conflicts of interests.

1 Moss AJ. The QT interval and torsade de pointes. *Drug Saf* 1999;21(Suppl 1):5-10, discussion 81-7. doi:10.2165/00002018-199921001-00002 pmid:10597863.
2 Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *Br J Clin Pharmacol* 2013;76:48-57. doi:10.1111/bcp.12040 pmid:23167578.
3 Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf* 2012;3:241-53. doi:10.1177/2042098612454283 pmid:25083239.
4 Surawicz B, Gettes LS, et al. American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology American College of Cardiology Foundation Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. *J Am Coll Cardiol* 2009;53:982-91. doi:10.1016/j.jacc.2008.12.014 pmid:19281931.
5 Yang T, Snyders D, Roden DM. Drug block of I(kr): model systems and relevance to human arrhythmias. *J Cardiovasc Pharmacol* 2001;38:737-44. doi:10.1097/00005344-200111000-00010 pmid:11602820.
6 Drew BJ, Ackerman MJ, Funk M, et al. American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 2010;121:1047-60. doi:10.1161/CIRCULATIONAHA.109.192704 pmid:20142454.
7 Trinkley KE, Page RL IInd, , Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin* 2013;29:1719-26. doi:10.1185/03007995.2013.840568 pmid:24020938.
8 Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991;84:1136-44. doi:10.1161/01.CIR.84.3.1136 pmid:1884444.
9 Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. *Circ Arrhythm Electrophysiol* 2012;5:868-77. doi:10.1161/CIRCEP.111.962019 pmid:22895603.
10 Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* 2013;34:3109-16. doi:10.1093/eurheartj/eht089 pmid:23509228.
11 Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013-22. doi:10.1056/NEJMra032426 pmid:14999113.
12 Medicines and Healthcare products Regulatory Agency. Citalopram and escitalopram: QT interval prolongation. *Drug Safety Update* 2011;5:A1. https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation.
13 Joint Formulary Committee. *British National Formulary* . 70th ed. BMJ Group and Pharmaceutical Press, 2015.
14 Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. *J Antimicrob Chemother* 2002;49:593-6. doi:10.1093/jac/49.4.593 pmid:11909831.
15 Shah AA, Aftab A, Coverdale J. QTc prolongation with antipsychotics: is routine ECG monitoring recommended?*J Psychiatr Pract* 2014;20:196-206. doi:10.1097/01.pra.0000450319.21859.6d pmid:24847993.
16 Aström-Lilja C, Odeberg JM, Ekman E, Hägg S. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. *Pharmacoepidemiol Drug Saf* 2008;17:587-92. doi:10.1002/pds.1607 pmid:18449951.
17 Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. *Medicine (Baltimore)* 2003;82:282-90. doi:10.1097/01.md.0000085057.63483.9b pmid:12861106.
18 Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res* 2003;58:32-45. doi:10.1016/S0008-6363(02)00846-5 pmid:12667944.
19 Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med (Berl)* 2004;82:182-8. doi:10.1007/s00109-003-0522-z pmid:14760488.
20 European Medicines Agency. 2005. ICH S7B: the nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf.
21 European Medicines Agency. 2005. ICH E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002879.pdf.
22 Rodday AM, Triedman JK, Alexander ME, et al. Electrocardiogram screening for disorders that cause sudden cardiac death in asymptomatic children: a meta-analysis. *Pediatrics* 2012;129:e999-1010. doi:10.1542/peds.2011-0643 pmid:22392183.

- This article was originally published in *Drug and Therapeutics Bulletin* (*DTB* 2016;54:33-36 doi:10.1136/dtb.2016.3.0390).
- *DTB* is a highly regarded source of unbiased, evidence based information and practical advice for healthcare professionals. It is independent of the pharmaceutical industry, government, and regulatory authorities, and is free of advertising.
- *DTB* is available online at http://dtb.bmj.com.