QT interval and drug therapy

The QT interval varies greatly and is affected by age, sex, sympathetic tone, and diurnal pattern. Because it increases as heart rate falls, measurements of QT interval are usually corrected for heart rate (QTc).

Measurement of the QT interval is not straightforward and is associated with considerable intraindividual and interindividual variability.

QTc intervals of 450 ms and 460 ms are generally accepted as the upper limits of normal for adult men and women, respectively.

Although QT prolongation is associated with torsades de pointes and sudden cardiac death, it is an imperfect predictor. Many patients with prolonged QT never experience torsades de pointes, whereas many who experience torsades de pointes have a normal QT before the episode. Similarly, some drugs (eg amiodarone) can markedly prolong QT but are rarely associated with torsades de pointes.

Drugs that can cause QT prolongation

Anti-arrhythmic drugs
- Amiodarone, disopyramide, dronedarone, flecainide, sotalol

Other cardiac drugs
- Ranolazine

Antibiotics
- 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)

Minimising the risks of drug induced QT prolongation 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 torsades de pointes with individual drugs are not readily available.

Adapted from BMJ 2016;353:i2732

QT prolonging drugs should not be used in patients with congenital long QT syndromes. When they are used in patients without inherited long QT syndrome 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

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 long QT syndrome (see box below) and concomitant drugs that might interact and increase the risk of QT prolongation.

Risk factors for torsades de pointes with drug induced QT prolongation

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

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. Therefore, while it is 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.

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Date approved by FWG: 16.3.17
To be reviewed by: 16.3.20

Adapted from BMJ 2016;353:i2732