

Q&A 237.1

What issues should be considered regarding drug induced QT prolongation?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

Prolongation of the QT interval can lead to a life threatening ventricular arrhythmia known as torsades de pointes which can result in sudden cardiac death (1). Recently there have been warnings relating to drug-induced QT prolongation for three commonly used drugs – citalopram, domperidone and ondansetron (2-4). There are also a number of other widely used drugs which are known to cause QT prolongation (1) and there are a number of drug interactions which can increase the risk of this adverse effect occurring. This Medicines Q+A discusses the issues to be considered when assessing the risk of drug induced QT prolongation in individual patients.

Answer

What is a normal QT interval?

Normal QT interval: The QT interval varies with heart rate. A number of formulas are used to correct the QT interval for heart rate. Once corrected it is expressed as the QTc interval. Females have a longer QT interval than males. Definitions vary in the literature but as a guide, normal QTc intervals are <440 milliseconds (ms) for men and <460 ms for women (1). A QTc between these values and 500 ms would be considered to be prolonged (5). A QTc >500 ms is considered clinically significant and is likely to confer an increased risk of arrhythmia (5).

Magnitude of drug induced changes in QT interval: The degree by which a drug changes the QTc interval from baseline is also important. An increase in baseline QTc of around 5 ms or less is not considered significant and this is the threshold for regulatory concern (6). For drugs that increase the QTc interval by less than 20 ms the data are inconclusive with regard to arrhythmic risk. A change in baseline QTc of >20 ms should raise concern and a change of >60 ms should raise greater concern regarding the potential for arrhythmias (7). Experience in congenital long QT syndrome indicates that for every 10 ms increase in QTc there is a 5-7% increase in risk of torsades de pointes (8). Drug induced QT prolongation is often dose related and risk is increased with intravenous administration (particularly if given rapidly) (8).

Can drug interactions increase the risk of QT prolongation?

Drug interactions can increase the risk of QT prolongation via three main mechanisms (7,9):

Pharmacodynamic Interaction: The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsades de pointes and ventricular arrhythmia.

Pharmacokinetic Interaction: Some drugs which do not prolong the QT interval themselves can increase the risk of QT prolongation by affecting the metabolism of drugs that do. Commonly used examples of this include drugs such as antifungals which inhibit the CYP3A4 enzyme.

Effects on Electrolytes: Hypokalaemia and hypomagnesaemia can increase the risk of QT prolongation. Therefore drugs that have an effect on electrolytes can interact with QT prolonging drugs e.g. diuretics by causing hypokalaemia.

What patient factors increase the risk of drug induced QT prolongation?

In individual cases of torsades de pointes there are often multiple risk factors present. The main risk factors which should be considered are (7,8,10):

- ◆ Electrolyte disturbances (in particular hypokalaemia, hypomagnesaemia and more rarely hypocalcaemia). Consider the risk of electrolyte disturbance if the patient has gastrointestinal upset.
- ◆ Bradycardia.
- ◆ Concomitant use of more than one drug that prolongs the QT interval.
- ◆ Congenital long QT syndrome.
- ◆ Cardiac disease (of multiple origins, including congestive heart failure, ventricular hypertrophy, recent conversion from atrial fibrillation).
- ◆ Impaired hepatic/renal function (due to effects on drug metabolism/excretion).
- ◆ Thyroid disease (more common with hypothyroidism and usually normalises with treatment).
- ◆ Female sex.
- ◆ Age over 65 years.

Which drugs prolong the QT interval?

It is out with the scope of this document to provide a list of all medicines that prolong the QT interval. The American website <http://www.crediblemeds.org/> has regularly updated lists of medicines which cause prolongation of the QT interval. Information can also be found in the British National Formulary (BNF, available via <http://www.evidence.nhs.uk/>), Summaries of Product Characteristics (SPCs, www.medicines.org.uk) and Stockley's Drug Interactions (subscription required). Medicines information departments and pharmacists can help with determining the risks of individual medicines.

What can be done to minimise the risks of drug induced QT prolongation?

The risk of torsades de pointes depends on patient factors and medication history. A safe drug in one patient may be potentially harmful in another. The risks and benefits must be determined on a case by case basis. Avoid the concurrent use of certain drugs that can cause QT prolongation if they are contra-indicated by the manufacturer. As general guidance (11,12):

- ◆ Consider the risk of QT prolongation when starting a new medicine.
- ◆ Assess the patient's risk factors for QT prolongation.
- ◆ Avoid QT prolonging drugs in patients with congenital long QT syndrome.
- ◆ Correct any modifiable risk factors such as electrolyte disturbance.
- ◆ Where a patient has risk factors and / or is prescribed an interacting medicine, the first line option is to change to an alternative drug that is not known to prolong the QT interval whenever possible.
- ◆ Consider carrying out a baseline ECG prior to starting a QT prolonging drug in patients with risk factors then repeat when the medicine reaches steady state. Interpreting QT intervals from an ECG is not straightforward and should always be carried out by suitably trained personnel.
- ◆ Any patient prescribed a QT prolonging drug who reports symptoms such as palpitations, light-headedness and dizziness should be referred for investigation.

Summary

There are a number of factors to be considered when starting a medicine which can cause QT prolongation. Each patient should be assessed on an individual basis taking into account their past medical history and concurrent medications. In some cases, use of an alternative drug which does not cause QT prolongation may have to be considered.

Limitations

Information on normal QT intervals applies to adults only. Local policies on assessment of QT interval and definitions of prolonged QT intervals may vary; always consult a specialist if unsure.

References

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Search strategy

EMBASE (QT prolongation OR Torsade des pointes OR QT interval AND exp Adverse Drug Reaction, search focused and limit to 2009-current. Separate search limited to review; QT prolongation OR Torsade des pointes OR QT interval AND exp Drug Interaction. Search focused)

MEDLINE (exp Long QT syndrome OR exp Tachycardia, ventricular AND exp Drug Toxicity; exp Long QT syndrome OR exp Tachycardia, ventricular AND exp Drug Interactions, limited to English Language, humans; exp Long QT Syndrome (chemically induced) OR exp tachycardia, ventricular (chemically induced) Limit to review article, English language, humans and 2007-current)