MedicinesUpdateExtra

NHS Greater Glasgow and Clyde

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DRUG INDUCED QT PROLONGATION

NB. This bulletin supersedes Medicines Update Extra No. 2*

- Prolongation of the QT interval can lead to a life threatening arrhythmia known as torsades de pointes.
- Over the last few years a number of warnings have highlighted the risk of QT prolongation with citalopram, domperidone, ondansetron, hydroxyzine and quinine.
- Extra vigilance is required by healthcare professionals to be alert to the risk of drug induced QT prolongation and drug interactions.
- Refer to flowchart and patient scenarios for further detail.

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. There are a number of widely used drugs which are known to cause QT prolongation. The Medicines and Healthcare products Regulatory Agency (MHRA) has issued a number of warnings relating to drug-induced QT prolongation for some commonly used drugs – citalopram, domperidone, ondansetron, hydroxyzine and quinine.[1-5] Extra vigilance is required by healthcare professionals to be alert to the risk of drug induced QT prolongation and drug interactions.

Interactions

There are three mechanisms by which drugs can interact and increase the risk of QT prolongation:[6]

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 antifungals which inhibit the CYP3A4 enzyme.*

*Lists of drugs known to inhibit or induce liver enzymes can be found in Stockley's Drug Interactions here

Effects on Electrolytes: Hypokalaemia and hypomagnesaemia can increase the risk of QT prolongation e.g. diuretics causing hypokalaemia can increase the risk of QT prolongation especially when given with QT prolonging drugs.

What is a 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. The QTc interval is reported on the ECG printout. The QTc is commonly normalised to a heart rate of 60bpm and may be inaccurate in patient with faster or slower heart rates.

Normal QTc Interval

<450 ms in males and <460 ms in females[7]

What is considered to be a prolonged QT interval?

The QTc interval is a surrogate marker of proarrhythmic risk and literature differs with regard to the QTc interval that would raise concern over development of arrhythmias.

As a guide:

Borderline prolonged QTc interval

>450 ms but <500 ms in males
>460 ms but <500 ms in females[7]

Although literature differs, a QTc interval within these values is considered borderline prolonged. Consideration should be given to dose reduction of QT prolonging drugs or changing to an alternative non QT prolonging drug.

Prolonged QTc Interval >500 ms in males and females

A QTc interval >500 ms is clinically significant and likely to confer an increased risk of arrhythmia. Any drugs which prolong the QT interval should be reviewed immediately.[6,8,9,10]

Interpretation of the QT interval on an ECG is not always straightforward and the value noted on the computerised printout may not always be accurate. The following website gives some guidance on interpretation of the QT interval: FANS website

What is considered a significant drug induced change in QTc interval?

The degree by which a drug changes the QTc interval from baseline is also important. An increase in baseline QTc of less than 5 ms is not considered significant and this is the threshold for regulatory concern. For drugs that increase the QTc interval by less than 20 ms the data is 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.[6] Experience in long QT syndrome indicates that for every 10 ms increase in QTc interval there is a 5-7% increase in the risk of arrhythmic events.[10,11] Drug induced QT prolongation is often dose related. For example, citalopram 20 mg daily has been shown to cause a mean change in baseline QTc interval of 7.5 ms; this increases to 16.7 ms with citalopram 60 mg daily (unlicensed dose).[1]

A drug induced increase in QTc interval should be assessed in conjunction with the overall QTc interval.

A list of medicines known to prolong the QT interval can be found at https://www.crediblemeds.org/ (Registration is required)

What are the risk factors for 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:[10-13]

Potentially Modifiable

- Electrolyte disturbances (in particular hypokalaemia, hypomagnesaemia and more rarely hypocalcaemia). Consider the risk of electrolyte disturbance if the patient has diarrhoea/vomiting
- Bradycardia
- Concomitant use of more than one drug that prolongs the QT interval

Non-modifiable

- Congenital long QT syndrome
- Cardiac disease (of multiple origins, including congestive heart failure, ventricular hypertrophy, recent conversion from AF, myocardial infarction)
- Impaired hepatic/renal function (due to effects on drug metabolism)
- Thyroid disease (more common with hypothyroidism and usually normalises with treatment[13])
- Female sex
- Age over 65 years

What medications can cause QT prolongation?

It is not possible to include a full list of all medicines known to increase the QT interval in this bulletin. A list of medications known to prolong the QT interval can be found in the Credible Meds website here.[14] This is an American website which categorises drugs based on their risk. It is recommended that you check the lists for drugs commonly used in your area of practice to familiarise yourself with the risks. This site requires registration in order to gain access to the lists (registration is free). It is advised that you set up registration and become familiar with the site. Alternatively, you can access a table from Stockley's Drug Interactions here.[6] Print versions of the BNF contain a table with a list of drugs that prolong the QT interval within Appendix 1, Interactions.[15] In addition to familiarising yourself with these sources, the BNF and Summary of Product Characteristics should be checked for individual drug contra-indications, cautions and interactions.

Some of the more commonly encountered medicines known to prolong the QT interval are listed in table 1. These medicines are listed by CredibleMeds® as known to have a risk of torsades de pointes or are described as high risk in Stockley's Drug interactions.

This list is not exhaustive but is designed to give examples of medicines which have the greatest risk of arrhythmia due to prolongation of the QT interval.

Prescribers are advised to be aware of the QT prolonging potential of the medicines that they prescribe, particularly when prescribing to high risk patients.

Antimicrobials	**Antipsychotics**
Azithromycin	Most antipsychotics have a risk of QT prolongation, and should be used with caution in patients with other risk factors. The following are listed as high risk in the sources described above
Ciprofloxacin	Chlorpromazine
Clarithromycin	Haloperidol
Erythromycin	Pimozide
Fluconazole	Sulpride
Levofloxacin	
Moxifloxacin	**Antidepressants**
	Many antidepressants have been associated with QT prolongation in overdose. For this reason they should be used with caution. The following are listed as high risk at therapeutic doses in the sources described above
Antiarrhythmics	Citalopram
Amiodarone	Escitalopram
Disopyramide	
Dronedarone	**Antiemetics**
Flecainide	Domperidone
Sotalol	Droperidol
	Ondansetron
Others	
Anagrelide	
Hydroxyzine*	
Methadone	
Quinine*	
Tolterodine**	
Lithium**	
Some antimalarials	
Some antiretrovirals	
Protein kinase inhibitors and some other oncology drugs – seek specialist advice if unsure	

Table 1: Common drugs that can prolong the QT interval [6,14,15]

This list is not exhaustive but is designed to give examples of more commonly used drug classes

* Hydroxyzine and quinine are not listed as high risk in the sources above but recent MHRA alerts have highlighted the risks of QT prolongation with these medicines. Refer to MHRA alerts for further advice.[4,5]

**Tolterodine and lithium are not listed as high risk in the sources above but are commonly prescribed medicines included in the BNF table

Consider the risk of QT prolongation when starting any new medicine

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

The risk of torsades de pointes depends on patient factors and current medication. 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.

As general guidance:

- Consider the risk of QT prolongation when starting a new medicine (if unsure of medicine related risk contact pharmacy for advice).
- Assess 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.**
- If the decision is made to concurrently prescribe two drugs that are known to prolong the QT interval this should be clearly documented in the medical notes. If the combination is contra-indicated specialist advice must be sought.

When would ECG monitoring be recommended?

The following advice is aimed at the non-specialist. Specialist areas using medicines known to prolong the QT interval may have local guidelines to follow.

It is not practical to recommend an ECG every time a QT prolonging medicine is prescribed, particularly in primary care. The decision should be made on a case by case basis taking into account any additional risk factors the patient has. The following could be considered as a guide:

- 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. Inform the patient of potential adverse effects to be aware of.
- If there is no alternative to using two drugs in combination that are known to prolong the QT interval, especially in patients with additional risk factors, carry out an ECG at baseline and then repeat when the new medicine is likely to reach steady state.
- If long term use of two medicines that can prolong the QT interval is deemed necessary the patient should be followed up and monitored via specialist clinic.
- Any patient on a QT prolonging drug who reports symptoms such as palpitations, light-headedness and dizziness should be referred for investigation and have their medication reviewed.
- If a prolonged QT interval is detected on an ECG during hospital admission, ensure communication with the GP on discharge including any medication changes.

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