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DRUG INDUCED QT PROLONGATION

Executive Summary

- 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.
- Recent warnings have highlighted the risk of QT prolongation with citalopram, escitalopram, domperidone, ondansetron and hydroxyzine.
- A more comprehensive list of medicines implicated in QT prolongation is provided.
- Extra vigilance is required by healthcare professionals to be alert to the risk of drug induced QT prolongation and drug interactions.

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. Recently there have been warnings relating to drug-induced QT prolongation for four commonly used drugs, citalopram, domperidone, ondansetron and hydroxyzine, all of which have been covered by the *PACE Bulletin*. Extra vigilance is required by healthcare professionals to be alert to the risk of drug induced QT prolongation and drug interactions.

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

- **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 macrolide antibiotics and antifungals which inhibit the CYP3A4 enzyme.
- **Effects on Electrolytes:** Hypokalaemia and hypomagnesaemia can increase the risk of QT prolongation (e.g. diuretics can interact with QT prolonging drugs by causing hypokalaemia).

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.

A normal QTc Interval is <440 ms.

What is considered to be a prolonged QT interval?

The QTc interval is a surrogate marker of pro-arrhythmic risk and literature differs with regard to the QTc interval that would raise concern over development of arrhythmias. As a guide:

Borderline QTc interval >440 ms but <500 ms

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. Please seek expert review if unsure.

Prolonged QTc Interval >500 ms

A QTc interval >500 ms is clinically significant and likely to confer an increased risk of arrhythmia. Any drugs which prolong the QT interval expert advice should be sought.

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:

http://www.fans.scot.nhs.uk/Protocols_new.html

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. Experience in long QT syndrome indicates that for every 10 ms increase in QTc there is a 5% increase in the risk of arrhythmic events. 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 of 7.5 ms; this increases to 16.7 ms with citalopram 60 mg daily. A drug induced increase in QTc interval should be assessed in conjunction with the overall QTc interval.

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:

Medicines

- A list of medicines known to prolong the QT interval can be found at <https://www.crediblemeds.org>

Potentially Modifiable Factors

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

Non-modifiable Factors

- Congenital Long QT Syndrome
- Cardiac Disease (of multiple origins, including congestive heart failure, ventricular hypertrophy, recent conversion from AF)
- Impaired hepatic/renal function (due to effects on drug metabolism)
- Thyroid Disease (more common with hypothyroidism and usually normalises with treatment)
- 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 at <https://www.crediblemeds.org>** . This website 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.

Some of the more commonly encountered drugs that are known to prolong the QT interval are listed below:

Table 1: Drugs that can prolong the QT interval

Antimicrobials

Erythromycin
Clarithromycin
Moxifloxacin
Fluconazole
Ketoconazole

Antipsychotics (all have some risk)

Risperidone
Fluphenazine
Haloperidol
Pimozide
Chlorpromazine
Quetiapine
Clozapine

Antiarrhythmics

Dronedarone
Sotalol
Quinidine
Amiodarone
Flecainide

Antidepressants

Citalopram/escitalopram
Amitriptyline
Clomipramine
Dosulepin
Doxepin
Imipramine
Lofepramine

Others

Hydroxyzine
Methadone
Protein kinase inhibitors (e.g. sunitinib)
Some antimalarials
Some antiretrovirals
Telaprevir
Boceprevir

Antiemetics

Domperidone
Droperidol
Ondansetron/Granisetron

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

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 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. 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.**

When would ECG monitoring be recommended?

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
- Specialist areas that routinely use QT prolonging drugs may consider developing their own protocols for baseline and follow up ECG monitoring
- 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.

Additional Comments

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.

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