MedicinesUpdateExtra

NHS Greater Glasgow and Clyde

No. 2, May 2015 ◆ Produced by NHS Greater Glasgow and Clyde Medicines Information Service

DRUG INDUCED QT PROLONGATION

**** This bulletin supersedes PostScript Extra No. 21, Dec 2012 *****

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

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 and hydroxyzine.[1,2,3,4] 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 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, which is reported on the ECG printout. The QTc is commonly normalised to a heart rate of 60bpm and may be inaccurate in patients with faster or slower heart rates.

Normal QTc Interval
<450 ms in males and <460 ms in females

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 QTc interval
>450 ms but <500 ms in males
>460 ms but <500 ms in females
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.[5,6,7,8]

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

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.[9] 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.[8] 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.[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[9,10,11,12]

Potentially Modifiable

- 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

- 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[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 at https://www.crediblemeds.org/**[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. It is advised that you set up registration and become familiar with the site. Alternatively, users with an Athens password can access a table from Stockley's Drug Interactions at https://www.medicinescomplete.com/mc/stockley/current/Table9.2.htm[9] Ensure that you have logged in to your Athens account before following this link.

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.

Antimicrobials	**Antipsychotics**
Azithromycin	*Many 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*	
Clarithromycin	
Erythromycin	
Fluconazole*	
Levofloxacin	
Moxifloxacin	Chlorpromazine
Antiarrhythmics	Haloperidol
Amiodarone	Pimozide
Disopyramide	Sulpride
Dronedarone	
Flecainide	**Antidepressants**
Sotalol	*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*
Others	
Anagrelide	
Hydroxyzine**	
Methadone	
Protein kinase inhibitors	
Some antimalarials	
Some antiretrovirals	
Antiemetics	Citalopram
Domperidone	Escitalopram
Droperidol	
Ondansetron	

Table 1: Drugs that can prolong the QT interval[9,14]

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

*Ciprofloxacin and fluconazole are not listed as high risk medicines in the sources described above. These medicines have been included as they are relatively commonly prescribed medicines known to prolong the QT interval. Fluconazole also interacts to increase the bioavailability of a number of medicines known to prolong the QT interval.

**Hydroxyzine is not listed as a high risk medicine in the sources described above, however, a recent European review concluded that hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes. Refer to MHRA alert for further advice.[4]

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.

Produced by NHS Greater Glasgow and Clyde Medicines Information Service

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?

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
- 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, lightheadedness 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.
- If a prolonged QT interval is detected on an ECG during hospital admission, ensure communication with the GP on discharge including any medication changes.
- See flowchart and patient scenarios for further information.

References

1. Medicines and Healthcare products Regulatory Agency. Citalopram and escitalopram: QT interval prolongation – new maximum daily dose restrictions (including in elderly patients), contraindications and warnings. Drug Safety Update Dec 2011, Vol 5, issue 5:A1
2. Medicines and Healthcare products Regulatory Agency. Domperidone: risks of cardiac side effects - indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use. Drug Safety Update May 2014, vol 7, issue 10:A1
3. Medicines and Healthcare products Regulatory Agency. Ondansetron (Zofran): risk of QTc prolongation – important new intravenous dose restriction. Drug Safety Update Aug 2012, vol 6 issue 1:A2
4. Medicines and Healthcare products Regulatory Agency. Hydroxyzine: risk of QT interval prolongation and Torsades de Pointes. Drug Safety Update Apr 2015. Accessed via https://www.gov.uk/drug-safety-update on 06/05/15.
5. Yap YG, Camm AJ. Drug Induced QT Prolongation and Torsades de Pointes. Heart 2003;89:1363-1372
6. Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289:2120-2127
7. Zareba W. Drug induced QT prolongation. Cardiology Journal 2007;14(6):523-533
8. Taylor D, Paton C, Kapur S. The South London and Maudsley NHS Foundation Trust Oxleas NHS Foundation Trust. Prescribing Guidelines in Psychiatry. 11th Edition 2012. Wiley Blackwell
9. Baxter K (ed), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press www.medicinescomplete.com (accessed December 2014).
10. Roden DM. Drug Therapy: Drug induced prolongation of the QT interval. NEJM 2004;350(10):1013-1022
11. Heist EK, Ruskin JN. Drug-induced arrhythmia. Circulation 2010;122:1426-1435
12. Drew BJ, Ackerman MJ, Funk M, Gibler B, Kligfield P, Menon V et al. Prevention of Torsades de Pointes in hospital settings. A scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010;121:1047-1060
13. Epstein FH, Klein I, Ojamaa K. Thyroid Hormone and the Cardiovascular System. The New England Journal of Medicine 2001;344(7):501-509
14. AZCERT, Inc. (2014). QTDrugs Lists. Available at: https://www.crediblemeds.org/new-drug-list/. Accessed December 2014.

Produced by NHS Greater Glasgow and Clyde Medicines Information Service
Tel: 0141 211 4407
Email: medinfo@ggc.scot.nhs.uk

Approved by the Medicines Utilisation Subcommittee of the ADTC