Simplifying QT prolongation for busy clinicians

Kelly A. Grindrod PharmD MSc Jeff Nagge PharmD

Case description

Mary is a 67-year-old woman with a history of bipolar disorder that is well managed with 300 mg of quetiapine daily. She visits her family physician complaining of a wet cough, chest pain, and fever. Chest radiographs confirm that she has pneumonia. The physician prescribes 1000 mg of amoxicillin 3 times daily and 500 mg of clarithromycin 2 times daily for 7 days. Later that day, the community pharmacist faxes the physician a note that says, "Risk of QT prolongation with quetiapine and clarithromycin, please advise."

Background

QT prolongation is a risk factor for torsades de pointes (TdP), a potentially fatal arrhythmia that can result in sudden death. While the incidence of TdP is rare, the severity of the reaction makes QT prolongation a serious concern when prescribing medications.

For family physicians and pharmacists, warnings about QT prolongation are common, but recommendations for management are often vague. It can be difficult to weigh the risk of TdP against the potential benefit of a QT-prolonging drug and even more challenging to determine a care plan when the drug is needed. We developed a 1-page infographic (**Figure 1**), also available at **CFPlus**,* to support clinicians and simplify the process.

Stepwise approach to assessing drug interactions affecting the QT interval

QT prolongation refers to the lengthening of the QT interval, which is measured on an electrocardiogram (ECG). The QT interval is the distance between the start of the Q wave and the end of the T wave, and is measured in milliseconds (ms). The ECG will typically include 2 readings: the QT interval and the corrected QT (QTc) interval, the latter of which is adjusted for heart rate. In clinical practice, the QTc interval is used to assess the risk of QT-prolonging drugs.

If one of your patients is prescribed a medication that can prolong the QT interval, consider using a systematic approach to assess and manage the risk of TdP.

Step 1: Assess the patient. The main risk factors for drug-induced TdP include congenital long QT syndrome and previous TdP.[1] If the patient has either of these high-risk features, QT-prolonging drugs should be avoided where possible. If the QT-prolonging drug is required, the patient should be monitored with ECG testing.

Minor risk factors for drug-induced TdP include bradycardia and electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia).[1] Women and older adults are also more likely to experience drug-induced TdP.[1] Caution should be used when prescribing QT-prolonging drugs for patients with multiple minor risk factors.

Step 2: Assess the drug. Not all drugs that prolong the QT interval are associated with TdP. Amiodarone, for example, prolongs the QT interval but is not associated with TdP, likely owing to its inherent antiarrhythmic properties.[2] Other drugs such as domperidone, citalopram or escitalopram, and macrolides, quinolones, and various antipsychotics have a clear association with TdP, including several published case reports of sudden death.[1]

While a complete list of drugs that are associated with TdP is beyond the scope of this article, the CredibleMeds website (**www.crediblemeds.org**) and mobile application provide a freely available database of QT-prolonging drugs, including a drug's association with TdP. At the CredibleMeds website, a drug's TdP risk is designated to a risk category: having a known risk of causing TdP; having a possible risk of causing TdP; being known to cause TdP under certain conditions (eg, overdose); and needing to be avoided in patients with congenital long QT syndrome.[3] The website also links to the case reports associated with the drug and TdP. While a drug monograph is also a useful way to identify if the drug is associated with QT prolongation, it provides less useful information about the actual association with TdP.

For drugs that cause TdP, the risk is often dose related; for example, the commonly prescribed dose for domperidone is 10 mg 4 times per day, but the risk of TdP is highest with a dose greater than 30 mg per day.[4] For patients who require domperidone, a lower dose can be tried. A similar dose-related effect is seen with a methadone dose greater than 100 mg per day.[5] There are similar warnings for citalopram doses greater than 40 mg per day and escitalopram doses greater than 10 mg per day; however, recent research suggests QT prolongation can occur at lower doses in higher-risk patients.[6] Be wary of drugs that inhibit the metabolism of a QT-prolonging drug, as the increased serum concentrations can also increase the risk of TdP, even if the dose of the QT-prolonging drug is low.

Step 3: Act. Symptoms that can precede TdP include heart palpitations and syncope. Patients can be educated when they receive a new prescription and asked about symptoms on follow-up.

An ECG can be done when the clinician is concerned that the patient is at risk of TdP, such as when a patient

*The **infographic** (**Figure 1**) is available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Figure 1

QT PROLONGATION

QT prolongation can cause a serious arrhythmia called Torsades de Pointes (TdP). Here are 3 steps for preventing TdP.

1

assess the patient:

Ask about history. Previous TdP and congenital long QT are major risk factors for TdP.

Other risk factors include bradycardia, electrolyte abnormalities, female gender, and older age.

Ask about symptoms. Symptoms of TdP include heart palpitations and fainting.

If you're concerned, enquire about these symptoms at every refill.

2

assess the drug:

Check the treatment. Macrolides and quinolones can cause TdP in higher risk patients.

Safer options include beta lactams, cephalosporins and tetracyclins. Other drugs to watch are methadone, e/citalopram, ondansetron and antipsychotics. See crediblemeds.org for a full list.

Check the dose. The risk of TdP tends to increase as higher doses are used (e.g., domperidone ≥30 mg/day).

Make sure the patient doesn't have any factors that can cause higher than expected serum concentrations, such as a drug-drug interaction or renal impairment.

Check the ECG. An ECG is appropriate if the patient has multiple risk factors for TdP and is prescribed a drug that prolongs the QT interval.

Order an ECG at baseline and after 5 half-lives when the drug has reached steady state.

3

take action:

Make a decision. Patients are at higher risk for TdP if the drug prolongs their QTc interval to >450 for males and >460 for females, or if it prolongs their QT interval by >60 msec.

If this happens, stop the drug if possible. If not, decrease the dose.

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

Content: Kelly Grindrod, BScPharm, PharmD MSc; Jeff Nagge, BScPhm, PharmD
Design: Adrian Poon, BA

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is taking multiple QT-prolonging drugs or has several minor risk factors. Ideally, an ECG should be done at baseline and repeated after the drug has been taken for 5 half-lives, when the drug has reached steady state in the body; for example, if the half-life of the QT-prolonging drug is 8 hours, the ECG can be repeated in 2 days. A guideline written for clinicians practising in hospital settings suggests avoiding or stopping the drug if the QTc is greater than 500 ms.[1] However, there is less opportunity for close follow-up in primary care than in hospital. A more conservative approach is to stop the drug or reduce the dose if the QTc interval is prolonged by more than 450 ms in men and 460 ms in women, or if it increases by more than 60 ms.[7]

Case resolution

In the case of Mary, a quick search on the CredibleMeds website identifies that clarithromycin has a known risk of TdP and that quetiapine's risk of TdP is conditional on the presence of other serious risk factors such as the concomitant use of another QT-prolonging drug. Mary does not have any other serious risk factor features; however, her sex (female) and age (older than 65) mean that she is more likely to experience TdP. In this case, the treatment of choice for community-acquired pneumonia is doxycycline, which CredibleMeds does not classify as a QT-prolonging drug. Treatment could be switched from amoxicillin or clarithromycin to doxycycline. If Mary had an allergy to doxycycline, an ECG should be done when starting the clarithromycin and repeated after 5 half-lives. Clarithromycin's half-life is around 3 to 7 hours, so the ECG can be repeated between 15 and 35 hours later. If the QTc interval is prolonged beyond 460 ms or by more than 60 ms, serious consideration should be given to stopping clarithromycin.

Conclusion

Most clinicians will routinely encounter QT prolongation warnings. A stepwise approach can be helpful for sorting between nuisance warnings and high-risk adverse events. It helps to consider the patient and drug risks separately, and to identify when an ECG is needed. Sources such as CredibleMeds are an invaluable resource for the busy clinician.

Dr Grindrod is Associate Professor in the School of Pharmacy at the University of Waterloo in Ontario, and a clinical pharmacist at the Kitchener Downtown Community Health Centre. **Dr Nagge** is Clinical Associate Professor in the School of Pharmacy at the University of Waterloo.

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Competing interests

None declared

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