Drugs and the QTc interval

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SYNOPSIS

Many commonly used drugs can prolong the QTc interval, especially if used in combination with other substances which affect their metabolism. Prolongation of the QTc interval can cause life-threatening polymorphic ventricular tachycardia also known as torsade de pointes. Women and certain susceptible people are more prone to prolongation of the QTc interval. This predisposition could be congenital or due to conditions such as hypokalaemia, hypomagnesaemia, renal failure or cardiac failure. Susceptible patients need an electrocardiogram before and after starting drugs that can prolong the QTc interval. If a drug prolongs the QTc interval beyond normal limits, the benefits of continuing the drug should be weighed against the relatively rare risk of potentially life-threatening arrhythmias.

Index words: torsade de pointes, antiarrhythmic drugs.

Introduction

Many drugs can prolong the QT interval of the electrocardiogram (ECG). This effect is important as it is associated with polymorphic ventricular tachycardia and possible sudden cardiac death. Prescribers need to be aware of the drugs that have been implicated, particularly if the patient is already taking a drug which prolongs the QT interval or has a condition associated with QT prolongation.

QT and QTc interval

The QT interval is the time between the start of the QRS complex and the end of the T wave in the ECG (Fig. 1). It represents the duration between the onset of depolarisation and the completion of repolarisation of the myocardium. There is commonly a variation in the QT interval measured in the various leads of the ECG. This ‘T wave dispersion’ occurs when the terminal portion of the T wave is isoelectric in some leads. When multiple leads are used the longest QT interval is considered to be the true QT interval.

The QT interval is dependent on heart rate, age and gender. A diurnal variation of the QT interval associated with the variations in sympathetic tone has also been described. The observed QT (QTo) interval can be corrected (QTc) for heart rate by using the following formula where RR is the interval in seconds between two successive R waves on the ECG.

\[ QTc = QT_o \cdot (\sqrt{RR}) \]

A QTc interval of 430 milliseconds (ms) is accepted as the upper limit of normal for men and 450 ms as the upper limit of normal for women. In children up to the age of 15, the upper limit of normal is 440 ms.\(^1\)

Long QTc interval and arrhythmia

Prolongation of the QTc interval is either acquired or due to a congenital long QTc syndrome (Table 1). Drugs are by far the commonest cause for an acquired long QTc interval. Grapefruit juice can increase the risk of drug-induced QTc prolongation by inhibiting the metabolism of amiodarone.\(^2\) Women are more

![Fig. 1](image-url)
susceptible than men to drug-induced QTc prolongation. Renal failure, cardiac failure and hepatic failure are also risk factors.

Prolongation of the QTc interval is a sign of prolonged repolarisation of the ventricular myocardium. This leads to the phenomenon of early afterdepolarisation which can trigger polymorphic ventricular tachycardia, also known as torsade de pointes. This abnormal rhythm is characterised by alternating electric polarity, periodic twisting of the points of the QRS complex around the isoelectric line and heart rates of 200–250 (Fig. 2). Each cycle of uniform morphology and axis lasts for 5–20 complexes. The arrhythmia is usually self-terminating, but can degenerate into ventricular fibrillation or rarely sustained ventricular tachycardia. It may result in dizziness, syncope, cardiac arrest and occasionally death.

**Drugs that cause QTc prolongation**

The mechanism of drug-induced QTc prolongation is believed to be usually due to blockade of cardiac potassium channels. A long QT interval is most frequently seen with class I and class III antiarrhythmic drugs. Other classes of drugs that cause QTc prolongation include antihistamines, antidepressants, antibiotics, antifungal drugs and antipsychotics (Table 2). The prolongation of the QTc interval by these drugs is usually seen within several days of starting them. The class Ia antiarrhythmic drugs (quinidine, procainamide) and class III drugs (sotalol, amiodarone) prolong the repolarisation phase of the cardiac action potential.

Sotalol and amiodarone are often used to treat atrial or ventricular tachyarrhythmias. Doses of 160 mg or more of sotalol commonly cause QTc prolongation; this effect has a clear dose-dependent relationship. Amiodarone is unique in that even though it prolongs the QTc interval, it rarely leads to polymorphic ventricular tachycardia. This is believed to be due to its ability to block calcium channels and beta adrenergic receptors.

The combined administration of certain drugs can increase the risk of developing cardiac arrhythmias associated with long QTc syndrome. Any substance that inhibits the metabolism of an implicated drug can enhance its effect on QTc prolongation. Risk of sudden death due to fatal cardiac arrhythmias when erythromycin was taken with terfenadine attracted considerable attention before terfenadine was withdrawn.

**Safe prescription of drugs which prolong the QTc interval**

Drug-induced QTc prolongation is not a universal phenomenon. Why some individuals are susceptible to this condition and others are not, is still unclear. They may possibly have a subclinical genetic mutation that is only revealed when they are exposed to certain drugs. Before prescribing a drug that is known to cause QTc prolongation, it is important to enquire about any past history of syncope or cardiac arrest. Also obtain a detailed family history of syncope, sudden death at a younger age or congenital deafness (a feature of Jervell and Lange-Nielsen syndrome). Any suspicion of a congenital long QTc syndrome should be confirmed with a 12 lead ECG. If the ECG shows prolongation of the QTc interval, drugs which could make it worse should be avoided.

Co-administration of two or more implicated drugs or an offending drug with a substance capable of inhibiting its hepatic metabolism should be avoided. It is important to question the patient about the consumption of non-prescription medications (such as terfenadine and astemizole) before prescribing a drug which can prolong the QTc interval. An association with a medication that prolongs the QTc interval should be sought in patients who present with syncope or cardiac arrest. Such a relationship should particularly be looked for in patients with no cardiac history or relevant family history.

When an implicated drug is prescribed to a high-risk patient (Table 1), it is advisable to perform a 12 lead ECG within the first few days of treatment to look for QTc prolongation beyond normal limits. If QTc prolongation is observed, it is advisable to stop the offending drug or switch to an alternative drug that has no such effect.
Management of torsade de pointes due to long QT syndrome

Brief episodes of self-terminating polymorphic ventricular tachycardia do not require any specific treatment apart from withdrawal of the suspect drug and correction of metabolic abnormalities. If torsade de pointes has haemodynamic consequences it requires prompt termination. Electrical defibrillation is usually effective. Infusion of magnesium or acceleration of the heart rate with rapid pacing or isoprenaline infusion can be useful as stabilisation therapy in the acute setting. To prevent a recurrence the offending drug is withdrawn and any electrolyte abnormality is corrected. Patients with proven congenital or idiopathic long QT syndrome who have a history of cardiac arrest, syncope, documented torsade de pointes or a family history of sudden death at a young age are usually treated with an implantable cardiac defibrillator.

Conclusion

Accurate identification of the patients at risk of QTc prolongation and torsade de pointes is a difficult task. It is important to assess each patient before prescribing an implicated drug and then closely monitor them afterwards. Clinicians should be alert to the increasing list of drugs causing QTc prolongation and to the presence of predisposing conditions.

Book review

Dartnell, J. Understanding, influencing and evaluating drug use.
Price: $33, students $25.30, plus postage.*

Peter McManus, former secretary, Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee

It is appropriate that a review of Jonathan Dartnell’s book appears in the pages of Australian Prescriber, as the subject matter encompasses a common heartland – that of working towards the more rational use of medicines in society.

There are essentially three core sections in the book, beginning with the complex environment in which prescribing decisions are made, involving such influences as attitudes, time pressures, patient expectations and commercial incentives. It also outlines the current regulatory and funding processes, although mention in Figure 1 of the technical advice from the Pharmaceutical Evaluation Section going to the Pricing Authority should more correctly be from the Economics Sub-Committee to the Pharmaceutical Benefits Advisory Committee.

The following chapter moves on to the specific strategies that can be used to improve drug use. It considers the range of interventions that have proved effective and the settings in which they have been applied. It rightly highlights the importance of skilled personnel and adequate and sustained resources.

Chapter 4 on the methods for monitoring and evaluating these strategies is particularly well researched and written. It highlights the iterative quality assurance cycle that is at the centre of drug use evaluation. The two main phases in the cycle are: firstly investigative (defining drug use, identifying problems and measuring the impact of interventions), while the second is interventional (problem solving, consensus building and activity implementation towards improving drug use).

This is not a ‘how-to-do’ manual but rather a detailed review of developments in the discipline of drug usage evaluation over time. It also sets the likely directions and challenges for the future in an area, given the inexorable pressure of rising drug expenditure within the health budget, whose importance will only grow.

Although this review is set in an international context, it is obvious that Australia has had a proud history of activity in this field, and this book adds to the recognition that drug use evaluation is an essential service for assuring and improving the way medicines are used.

It is a valuable resource for health professionals and students interested in drug usage evaluation. But it will also be of interest to wider groups such as epidemiologists, social scientists, health economists and administrators, whose disciplines either make significant contributions towards or could gain valuable insights from, a field that is working towards ensuring the best possible health outcomes from the medicines we use.

Conflict of interest: none declared

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REFERENCES


Self-test questions

The following statements are either true or false (answers on page 75)

5. Grapefruit juice prolongs the QT interval.
6. Women are more susceptible than men to drug-induced prolongation of the QT interval.

* For more information contact Therapeutic Guidelines Limited 1800 061 260.