Drug-induced QT prolongation: consequences and current dilemma

Introduction

The QT interval usually represents a period of time of approximately 400 msec on a resting electrocardiogram (ECG). Prolongation of this interval of time is now the commonest cause for drugs failing to be developed (Roden, 2004). The concern is an association with ventricular rhythm disturbance and particularly torsade de pointes (TDP), with its propensity to decay into ventricular fibrillation and death. This article describes a case of extreme QT interval prolongation in association with drug therapy and the measures required to treat it. An overview of the current situation is also presented.

Discussion

The period of time between depolarization of the ventricles (start of the Q wave) and the end of repolarization (termination of the T wave), termed the QT interval, is now 'under the spotlight'. Any tendency for a drug to prolong the QT interval will severely jeopardize its chances of development or restrict its current use. The drug in question may have a benefit that outweighs the determined risk as with several of the cardiac antiarrhythmics. Additional factors, including female gender, hypokalaemia and hypomagnesaemia can exacerbate risk.

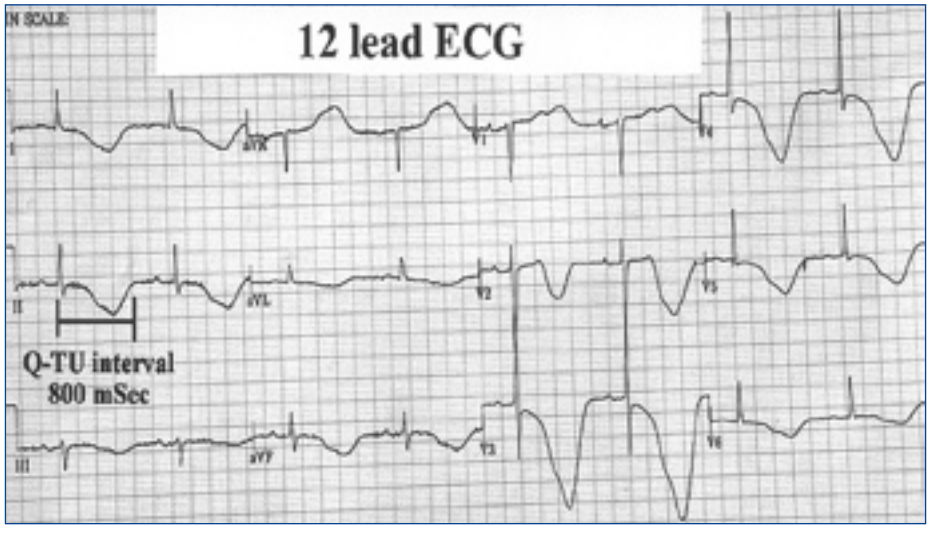
The drug contributing in the case described was sotalol, but the antiarrhythmics dofetilide, disopyramide and quinidine all cause significant QT prolongation. Interestingly, amiodarone, which is widely used in the UK and frequently associated with a QT interval of greater than 500 msec, rarely causes TDP. Usually known as a drug that shortens the QT interval, a facilitatory role in TDP has been shown with digoxin toxicity (Makkar et al, 1993), and in combination with amiodarone (Bajaj et al, 1991).

Common drugs confering risk by their combination with the above antiarrhythmics are the antibiotics erythromycin or clarithromycin and major neuroleptics, including haloperidol and chlorpromazine. Medicines which compete with the excretion of such drugs can also exacerbate the pro-arrhythmic risk.

It is suspected that 5–10% of people in whom QT interval drugs have caused TDP may possess a mutation associated with the long QT syndrome (Napolitano et al, 2000). In some of these cases the baseline QT interval will appear normal.

An absolute QT interval of 500 msec is considered a risk for TDP and extension to beyond 500 msec with a drug-inducing therapy should merit consideration of alternative therapy. At the other end of the spectrum are drugs associated with TDP, that increase the QT interval minimally. Terfenadine, a widely used antihistamine, was withdrawn because of an association with TDP. In normal individuals, it increased the QT interval on average by only 6 msec. Currently, the heart rate corrected QT interval, the QTc, is used as a surrogate for TDP. Most authorities would accept a normal QTc in males as <430 msec and <450 msec in females with prolonged as >450 msec in males and >470 msec in

Figure 1. 12-lead electrocardiogram showing deep T and U wave inversion with extreme QT or Q-TU prolongation of up to 800 msec.



Case Report

An 86-year-old woman was admitted with falls. She was taking no medication and had no family history of long QT syndrome. An electrocardiogram (ECG) revealed atrial fibrillation at 160 beats per minute.

Rate control was commenced with digoxin and metoprolol, to a total dosage of 625 μg and 137.5 mg respectively. On day 8, the therapy was changed to attempt chemical cardioversion with sotalol at a dosage of 40 mg daily. After a cumulative sotalol dosage of only 120 mg, given over 3 days, the ECG showed extreme QT interval prolongation (800 msec) and bizarre T, or TU wave inversion (*Figure 1*). Blood tests were normal (K+ 5.3 mmol/litre, Mg++ 0.97 mmol/litre, Ca++ 2.45 mmol/litre) and troponin T was negative. An echocardiogram showed normal dimensions and function.

The patient experienced numerous runs of polymorphic ventricular tachycardia (torsade de pointes) precipitated by repeated 'R on T' events (*Figure 2*). Intravenous magnesium had no effect. Temporary pacing was used to overdrive pace the patient. The patient was commenced on a low dose of bisoprolol and made a complete recovery to sinus rhythm and a normal QT interval.

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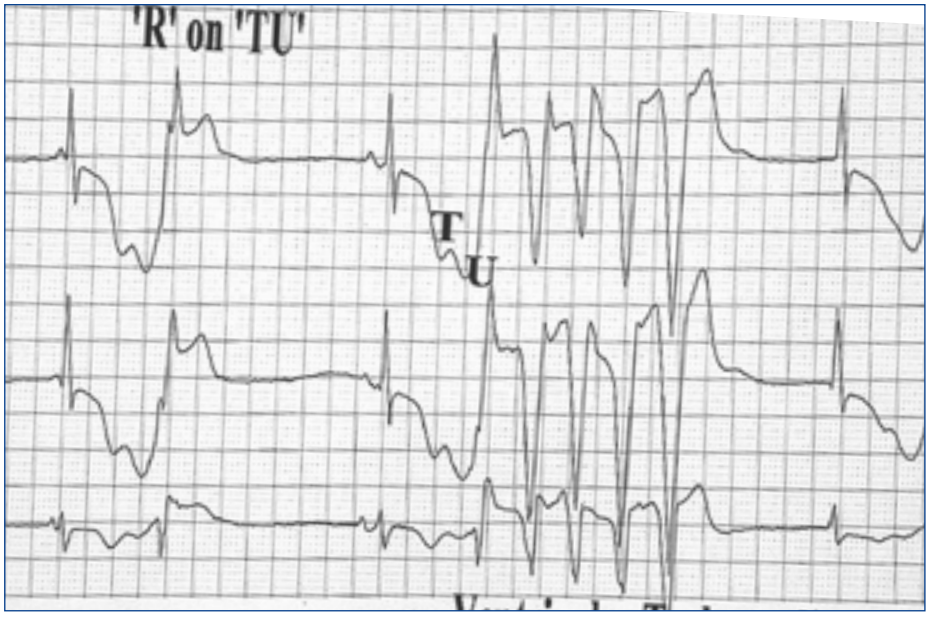
females. The Food and Drug Administration have expressed concern over products that extend the QT or QTc by a mean of 10–20 msec and that those causing extension to beyond 20 msec are likely to be pro-arrhythmic.

Conclusions

Eighty years have elapsed since it was found that some patients developed syncope with quinidine therapy, later shown to be caused by polymorphic ventricular tachycardia. The evaluation of a drug's propensity to cause QT prolongation and more importantly whether this transmutes into TDP is complex. For the pharmaceutical industry, the thorny issue of QT prolongation is here to stay. For the clinician, as with most pharmacological therapies, the benefits must be measured against the risks.

The Drug-induced arrhythmia risk evaluation study (DARE study) was launched in 2003 and will recruit from throughout England. It is an epidemiological and genetic study to examine the hypothesis that there is a significant association of genotype and drug-induced arrythmia (www.dsru.org). BJHM

Figure 2. An electrocardiogram rhythm strip showing R on TU wave phenomena with precipitated ventricular tachycardia. Of note, the underlying rhythm is one of sinus bradycardia.



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