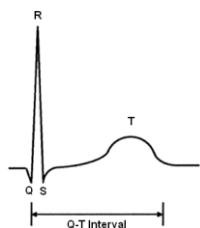


## Drug-Induced QT Interval Prolongation

In the past few years, much attention has been focused on drugs that prolong the QT interval and may trigger potentially fatal cardiac arrhythmias such as Torsade de Pointes ("twisting of the points"). Several drugs (e.g. cisapride and terfenadine) have been withdrawn from the world market because of their association with this rare form of cardiotoxicity. Recently the US Food and Drug Administration (FDA) advised health professionals that the macrolide antibiotic **azithromycin** can cause potentially fatal irregular heart rhythms, especially in those patients with existing QT prolongation.

### Understanding QT interval Prolongation



The QT interval represents the duration of the ventricular action potential and is measured from the beginning of depolarisation (Q wave) until the end of repolarisation (T wave).

QT prolongation is a sign of prolonged repolarisation of the ventricular myocardium, which is largely controlled by potassium channels.

With repeated prolonged repolarisation of sufficient extent, ventricular arrhythmias may develop.

QT prolongation is generally considered present when the QTc interval (i.e. the QT interval corrected for heart rate) is greater than 450 msec in men or 470 msec in women. Arrhythmias occur most often at intervals of 500 msec or more, usually in association with concomitant risk factors.

Torsade de pointes (TdP) is an uncommon variant of ventricular tachycardia and refers to a form of polymorphic ventricular tachycardia (VT) in the presence of a prolonged QT interval. It is usually self-limiting, but can degenerate into ventricular fibrillation, or rarely, sustained ventricular tachycardia. It may result in dizziness, syncope, cardiac arrest and occasionally death. There is no straightforward relationship between QT prolongation and TdP and/or ventricular fibrillation. If VT occurs with a normal QT interval, the term "polymorphic VT" is used.

### Congenital versus Acquired QT Prolongation

QT prolongation may be congenital or acquired. Congenital QT prolongation includes underlying gene mutations that result in ion channel malfunction and "congenital long QT syndrome". The acquired form of QT prolongation can be attributed to metabolic abnormalities (e.g., acute hypokalaemia), medical conditions (e.g. myocarditis, heart failure) and drugs (see next section).

### Drug-Induced QT Prolongation

Drug-induced QT prolongation is thought to relate to blockade of cardiac potassium channels. A lengthened QT is often seen with Class III antiarrhythmic agents (eg. sotalol, amiodarone) but may also be caused by other drugs. Drug-induced QT prolongation usually occurs within several days of starting the offending agent. Below are some drugs with reasonable evidence associating them with TdP (list not exhaustive). Several drugs prolong QT but at this time, lack substantial evidence for causing TdP. It is important to be aware of the strength of evidence associating the drug with TdP when assessing patient risk.

Table 1: Drugs generally accepted to have a risk of TdP\*

amiodarone	citalopram	flecainide	pimozide
azithromycin	clarithromycin	haloperidol	quinidine
chloroquine	domperidone	methadone	sotalol
chlorpromazine	erythromycin		

\* reference: www.qtdrugs.org

### Predisposing Factors

The risk of developing arrhythmias at any given QT interval varies widely between patients. The risk for developing TdP when starting a QT prolonging agent is influenced by the specific drug and by the following predisposing factors:

- |   |   |
|---|---|
| • Bradycardia (<50 beats/min)                                   | • Hypothyroidism  |
| • Electrolyte disturbances (esp. hypokalaemia, hypomagnesaemia) | • Myocardial ischemia / infarction                        |
| • Female gender   | • Renal or hepatic disease (ie. affecting drug clearance) |
| • Heart failure   | • Recent cardioversion                                    |
| • Hypoglycaemia   | • Congenital long QT syndrome                             |
|   | • High drug concentrations                                |

### Drug Interactions

Drug interactions play a major role in QT prolongation and may also increase the risk of TdP by the following mechanisms:

- 1) Two drugs may cause QT prolongation independently with an additive effect
- 2) One drug may decrease the clearance (and therefore increase the plasma concentrations) of another drug that prolongs the QT interval
- 3) One or more drugs may cause electrolyte disturbance, bradycardia or other effects that predispose the individual to the QT prolonging effects of another drug

### Prevention of Drug-Induced QT Prolongation

The QT prolonging effect of drugs can be minimised:

- by avoiding their use in patients with known risk factors
- addressing modifiable risk factors (electrolyte disturbances, glycaemic control, thyroid function, etc)
- close attention to appropriate dosing (dose-dependent)
- avoiding relevant drug interactions, particularly multiple drugs associated with QT prolongation
- ECG monitoring (baseline ECG should be considered and routinely monitored after initiation or dose increase of drugs that may prolong the QT interval. Dose reduction or discontinuation should be considered when the QTc is > 500 msec or if it increases > 60msec compared with baseline)

Patients should be counselled about the risk of QT prolongation and should be advised to seek medical attention if symptoms such as light-headedness, dizziness, palpitations, shortness of breath, or fainting occur.

### Macrolide antibiotics

As noted above the macrolide antibiotic azithromycin has recently been the subject of a QT prolongation FDA warning. This is a class effect. The literature suggests that the incidence and severity of the prolongation is highest with erythromycin. Clarithromycin is the next highest followed by azithromycin and roxithromycin. In addition inhibition of CYP3A4/5/7 is strongest with erythromycin and clarithromycin. This has implications when macrolides are co-prescribed with CYP3A4/5/7 substrates that themselves prolong the QT interval.