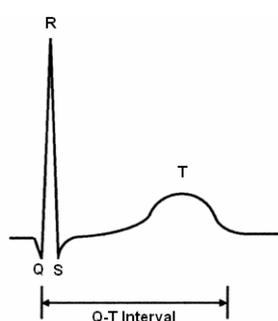


Drug-Induced Q-T Interval Prolongation

In the past few years, much attention has been focused on drugs that prolong the QT interval and may trigger potentially fatal cardiac dysrhythmias such as torsade de pointes ("twisting of the points"). Several drugs have been withdrawn from the market because of their association with this rare form of cardiotoxicity (e.g., terfenadine, astemizole and cisapride).

QT prolongation is generally considered present when the QTc interval (ie. the QT interval corrected for heart rate) is greater than 460msec in men or 480msec in women. The QTc interval is "borderline" prolonged if 440-460msec in men, or 460-480msec in women. Arrhythmias occur most often at intervals of 500msec or more, usually in association with concomitant risk factors.

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).

Prolongation of the QT interval 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.

Torsade de pointes (TdP) is an uncommon variant of ventricular tachycardia. 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. TdP specifically refers to a form of polymorphic ventricular tachycardia (VT) in the presence of a prolonged QT interval. With a normal QT interval, the term "polymorphic VT" is used instead.

Congenital vs Acquired QT Prolongation

Prolongation of the QT interval can be categorized into *congenital* and *acquired* forms. **Congenital** QT prolongation includes underlying gene mutations that result in ion channel malfunction and "congenital long QT syndrome" (LQTS). The **acquired** form of QT prolongation can be attributed to metabolic abnormalities (e.g., acute hypokalemia), medical conditions (e.g., myocarditis, heart failure) and drugs.

Drug Induced QT prolongation

Drug-induced QT prolongation is thought to relate to blockade of cardiac potassium channels. A lengthened QT interval is often seen with Class III antiarrhythmic agents (eg. sotalol, amiodarone). Other classes of drug reported to cause QT prolongation include antihistamines, antidepressants, antibiotics, antifungals and antipsychotics. Risk varies between agents within each drug class. Drug-induced QT interval prolongation usually occurs several days after starting the offending agent.

Drugs associated with causing QT prolongation

amiodarone	clarithromycin	haloperidol	procainamide
amitriptyline	domperidone	methadone	quinidine
chloroquine	droperidol	pentamidine	sotalol
chlorpromazine	erythromycin	pimozide	thioridazine
cisapride	flecainide		

Refer to information, such as at the ArizonaCERT website (www.qtdrugs.org) for a more complete (though not exhaustive) list and other information about risk of QT prolongation with specific drugs.

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)
- Electrolyte disturbances (esp. hypokalemia, hypomagnesemia)
- Female gender
- Heart failure
- Hypoglycemia
- Hypothyroidism
- Myocardial ischemia / infarction
- Renal or hepatic disease (ie. affecting drug clearance)
- Recent cardioversion
- 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. Drugs may interact by the following mechanisms:

- 1) Two drugs may cause QT prolongation independently with an additive effect
- 2) One drug may decrease the clearance of another drug that prolongs the QT interval
- 3) One drug may both decrease the clearance of a QT-prolonging drug while prolonging the QT interval itself.

Prevention of Drug-Induced QT Prolongation

The QT prolonging effects of at risk drugs can be minimised by avoiding use in patients with known risk factors, close attention to appropriate dosing and avoiding relevant drug interactions.

Close monitoring is particularly important when concurrent QT prolonging agents are used in at risk patients. Risk factors that can be treated should be corrected eg. electrolyte disturbances, glycaemic control, thyroid function etc. Patients should be counselled about the potential risks and should be advised to seek medical attention if symptoms such as light-headedness, dizziness, palpitations, shortness of breath, or fainting occur.

Monitor plasma potassium concentrations regularly, particularly if the patient is taking a potassium-losing diuretic. A 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 >500msec.

Final Comment

The use of QT prolonging agents is unlikely to be problematic in patients without other risk factors. In patients with one or more risk factors, consideration should be given to safer alternatives first or carefully monitored. Patients with congenital long QT syndrome pose a significant risk and problematic drugs should be avoided.

Further reading:

NEJM 2004; 350:1013-22 ; JAMA 2003;289:2120-27