Long QT syndrome: what the pharmacist should know

Lynn Lambert, BPharm
Amayeza Info Centre

Correspondence to: Lynn Lambert, e-mail: lynn@amayeza-info.co.za

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Abstract

Long QT syndrome is a cardiac conduction disorder in which cardiac repolarisation is delayed following a heartbeat. This condition creates an electrophysiological environment that favours the development of serious ventricular dysrhythmias which can quickly deteriorate, leading to cardiac arrest and sudden cardiac death. The pharmacist is in a pivotal role as awareness of this condition and the impact of drugs can play a major role in exacerbating underlying long QT syndrome or causing long QT syndrome.

Introduction

It is estimated that the heart beats approximately 100 000 times a day in order to ensure blood circulation through the body by contracting and relaxing the heart muscle. These actions are controlled by electrical impulses created by cells in the upper right chamber of the heart, called the sinus node. After each heartbeat, the electrical system of the heart recharges itself in preparation for the next heartbeat. This process is known as repolarisation.¹

When cardiac cells are at rest, they are considered to be polarised, which means that no electrical activity takes place. Electrical impulses in the heart are generated by the automaticity of specialised cardiac cells, which cause the ions, such as sodium, potassium, and calcium, to cross the cell membrane and cause depolarisation. The movement of ions across the cardiac cell membrane through sodium, potassium and calcium channels is the cause of the cardiac muscle contracting. Repolarisation is the return of the ions to their previous resting state, which corresponds with relaxation of the cardiac muscle. Depolarisation and repolarisation are electrical activities which cause cardiac muscular activity and are detected on an electrocardiogram (ECG).²

An ECG is a test that measures the electrical signals that control the rhythm of the heart. The test measures how electrical impulses move through the heart muscle as it contracts and relaxes. The ECG translates the electrical activity of the heart into line tracings on paper, represented as spikes and dips, which are called waves. There are four components to an ECG report, namely:³

- **The P wave**: The P wave is a record of the electrical activity through the atria (upper heart chambers).
- **The QRS complex**: The QRS complex is a record of the movement of electrical impulses through the ventricles (lower heart chambers).
- **The ST segment**: The ST segment shows when the ventricle is contracting, but that no electricity is flowing through it. The ST segment usually appears as a straight, level line between the QRS complex and the T wave.
- **The T wave**: The T wave shows when the ventricles reset electrically and prepare for their next muscle contraction.

The Q-T interval on the ECG is measured from the beginning of the QRS complex to the end of the T wave.⁴ It is the measurement used to assess the duration of ventricular depolarisation and repolarisation of the electrical system of the heart, i.e. the duration of the heartbeat.⁵ ⁶ The Q-T interval is longer when the heart rate is slower, and shorter when heart rate is faster.² The heart muscle takes longer than normal to recharge between beats in long QT syndrome. This electrical disturbance, which often can be seen on an ECG, is referred to as a prolonged Q-T interval or long QT syndrome¹ (Figure 1).

Long QT syndrome

Long QT syndrome is a cardiac conduction disorder of disturbance of the electrical system of the heart, caused by abnormalities of the ion channels in the heart. The abnormal function of one or more ion channels prolongs the repolarisation process in long QT syndrome, and in turn, the Q-T interval.⁶ A long Q-T interval creates an electrophysiological environment that favours the development of life-threatening, prolonged ventricular dysrhythmias.⁸ Long QT syndrome can either be an inherited or acquired condition.¹⁰
Congenital long QT syndrome

Congenital long QT syndrome is a genetic mutation of the ion channels in the cardiac cells, which affects the flow of potassium and sodium into and out of these cells. A diagnosis of congenital long QT syndrome relies on ECG findings, and a careful clinical and family history. Genetic testing may potentially enhance future diagnostic reliability. Congenital long QT syndrome is frequently found to be the cause of sudden death in young people. Symptoms usually manifest in childhood or adolescence, and include syncope, palpitations or pseudoseizures. These are often triggered by conditions that increase sympathetic tone, such as exercise, sudden loud noises and emotional stress.

Acquired long QT syndrome

Acquired long QT syndrome is caused by drugs that prolong the QT-interval through their mode of action or adverse reaction profile, electrolyte imbalances (such as those caused by anorexia), bradycardia or neurological injury. Symptoms usually manifest in childhood or adolescence, and include syncope, palpitations or pseudoseizures. These are often triggered by conditions that increase sympathetic tone, such as exercise, sudden loud noises and emotional stress.

Symptoms and causes

Fainting, which is the sudden loss of consciousness (syncope), and sudden death are common symptoms of long QT syndrome. These symptoms usually occur without warning. They are caused by a fast cardiac arrhythmia, known as torsades de pointes (torsades). The torsade rhythm spontaneously returns to normal in patients who experience syncope. When this occurs, the patient quickly regains consciousness, usually without disorientation or residual symptoms, although some fatigue may be present. However, if the torsade rhythm persists, it degenerates into a condition known as ventricular fibrillation, which rarely reverts back to a normal rhythm without medical intervention. If ventricular fibrillation is not electrically converted, usually the outcome is death. Signs and symptoms that may be experienced before fainting include lightheadedness, heart palpitations, an irregular heartbeat, weakness and blurred vision. However, such warning signs before fainting are unusual in long QT syndrome. Chest pain, persistent shortness of breath, heart valve problems and heart failure are not caused by long QT syndrome.

Drugs are the most common cause of acquired long QT syndrome. Cardiac disorders are also a frequent cause of acquired long QT syndrome. Q-T interval prolongation has been reported in chronic heart failure, acute and chronic heart disease and cardiomyopathies. Bradycardia, due to sinus dysfunction, as well as conduction block, has also been shown to prolong the Q-T interval. An electrolyte imbalance, mainly hypokalaemia, hypomagnesaemia and hypocalcaemia, is also a common cause of a prolonged Q-T interval. Many metabolic, nutritional, neurological and endocrine pathological conditions have been reported to prolong the Q-T interval.

Drugs that prolong the QT-interval

Drug-induced Q-T interval prolongation commonly occurs through alterations to the intracellular ion channels. Prolonged depolarisation is associated with increased function of the inward sodium channels. Drugs may reduce repolarisation by inhibiting the outward potassium channels. Potassium and magnesium electrolyte abnormalities alter the function of potassium ions, increasing the risk of arrhythmias or of Q-T interval prolongation and torsades.

The liver and kidneys eliminate many drugs associated with Q-T interval prolongation. When either of these elimination pathways is impaired, patients may accumulate the drug, thus increasing their risk of Q-T interval prolongation and torsades. Administration factors must also be taken into account with Q-T interval-prolonging medications.

Antiarrhythmics

Quinidine

Quinidine is known to reduce the depolarisation rate and prolong the refractory period by blocking potassium channels at low concentrations, and blocking sodium channels at higher concentrations. This causes torsades to occur in approximately 4–8% of patients treated with quinidine.

Procainamide

Procainamide is converted to its active metabolite, N-acetylprocainamide. Toxic levels of this metabolite can increase the risk of Q-T interval prolongation and torsades.

Amiodarone

Amiodarone works by blocking beta adrenergic receptors, as well as sodium, potassium and calcium channels. Amiodarone has a low incidence of proarrrhythmia (new arrhythmia or worsening of existing arrhythmia) and torsades, compared with other antiarrhythmic agents because it uses different mechanisms of action.
action. The incidence of torsades may increase with long-term therapy, electrolyte disturbances, and in combination with other medications that may prolong the Q-T interval.12

**Sotalol**

Sotalol blocks beta adrenergic receptors and inhibits potassium repolarisation. Sotalol is eliminated by the kidneys. Therefore, dosage adjustments based on creatinine clearance help to prevent toxicity and Q-T interval prolongation. Treatment with sotalol should be initiated while the patient is hospitalised to ensure monitoring because Q-T interval prolongation may be experienced at therapeutic dosages.12

**Q-T interval prolongation in drugs as a result of an adverse reaction**

**Antipsychotics**

**Haloperidol**

Haloperidol is used to treat schizophrenia and severe agitation. Both the oral and the intravenous formulations of haloperidol block the potassium channels and are associated with torsades. Haloperidol prolongs the Q-T interval, which may be amplified when the drug is combined with other medications that also do this.12

**Chlorpromazine**

Chlorpromazine is an antipsychotic with antiemetic properties. It also suppresses potassium channels, creating the potential for Q-T interval prolongation.12

**Ziprasidone**

Ziprasidone works by blocking dopamine and serotonin, but it can increase repolarisation time by suppressing potassium ion exchange.12

**Antidepressants**

**Tricyclic antidepressants**

Tricyclic antidepressants (TCAs) cause prolonged depolarisation through the sodium channels. This class of drugs constitutes the major mechanism of Q-T interval prolongation. The combination of TCAs and drugs with increased effects on potassium channels may confer a greater risk of torsades and Q-T interval prolongation. Amitriptyline, doxepin, desipramine and clomipramine are TCAs that are noted for their ability to prolong the QT-interval.12

**Antibiotics**

**Fluoroquinolones**

Fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, have been shown to cause the most pronounced Q-T interval prolongation through interaction with the potassium channels.12

**Macrolides**

Macrolides, such as clarithromycin, roxithromycin, and erythromycin, are believed to have the greatest ability to reduce repolarisation through the potassium channels, which means that theoretically, they have the largest effect on the QT-interval. Macrolide antibiotics have a varied ability to inhibit cytochrome enzyme activity, increasing the risk of Q-T interval prolongation associated with concomitantly administered drugs that are also metabolised by the same pathways as the macrolides.12

**Tyrosine-kinase inhibitors**

Tyrosine-kinase inhibitors, used in the treatment of various cancers, have been noted to cause significant Q-T interval prolongation. Sunitinib, nilotinib and dasatinib have been associated with varied amounts of Q-T interval prolongation. Depending on the indication, dasatinib may be a favourable alternative owing to the lesser likelihood of Q-T interval prolongation.12

**Diuretics**

Diuretics may indirectly increase the risk of torsades by causing the excretion of potassium and magnesium. If untreated, these electrolyte disturbances can increase the patient risk of Q-T interval prolongation. The effects of other drugs that prolong the Q-T interval are exacerbated by hypokalaemia and hypomagnesaemia.12

**Ondansetron**

Ondansetron is a serotonin antagonist used to prevent nausea and vomiting associated with cancer treatment and postoperative procedures. A study of postoperative nausea and vomiting found that there were longer Q-T intervals in post-anaesthesia patients. Therefore, it is recommended that these agents are used with caution post-surgery, owing to the risk of torsades.12

Table I lists drugs that affect the Q-T interval, and which should be avoided in patients with long QT syndrome.

**Treatment**

The prophylactic use of beta blockers, even if patients are symptom free, is the mainstay of treatment in long QT syndrome. Left cardiac sympathetic denervation has been shown to reduce the risk of malignant arrhythmias associated with long QT syndrome in those who are intolerant of beta blockers. Cardiac pacing, by increasing the heart rate and shortening the QT-interval, has also been shown to be effective in high-risk subjects. An implantable cardioverter defibrillator should be strongly considered in those with difficult-to-control symptoms or in survivors of cardiac arrest.9

**The role of the pharmacist**

Pharmacists are in a position to help to reduce the occurrence of torsades through clinical intervention by identifying potential drug interactions that may increase the patient’s risk of Q-T interval prolongation, and potentially, torsades. Pharmacists must also take note of the clearance of Q-T interval-prolonging
medications. Decreased hepatic and renal function may increase the patient’s exposure to Q-T interval-prolonging medications, thereby increasing risk. The use of drugs which alter renal and hepatic function, such as enzyme inducers or inhibitors, may alter serum concentrations and decrease therapeutic benefit, or place patients at risk of prolonged drug exposure.

## Conclusion

Long QT syndrome is a disorder of the electrical system of the heart, and is a life-threatening condition. Pharmacists are placed in a challenging situation when assessing or explaining the risks and associated warnings for drugs that may prolong the Q-T interval. Pharmacists should be cautious and abide by maximum-dose recommendations, avoid potential drug interactions, and help to guide therapy to include alternatives to Q-T interval-prolonging agents by referring the patient to an appropriate healthcare practitioner if there is any suspicion of drug-induced ventricular arrhythmias.

## References


### Table 1: Drugs that prolong the Q-T interval and/or induce torsades

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Sotalol, quinidine and amiodarone</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Moxifloxacin, clarithromycin, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, erythromycin and co-trimoxazole</td>
</tr>
<tr>
<td>Anticancer</td>
<td>Tamoxifen, lapatinib, eribulin and sunitinib</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Mirtazapine, citalopram, venlafaxine, paroxetine, fluoxetine, sertraline, trazodone, escitalopram, amitriptyline, imipramine and desipramine</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Voriconazole, fluconazole, ketoconazole and itraconazole</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Terfenadine and diphenhydramine</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>Nicardipine and isradipine</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>Artenninol plus piperaquene, chloroquine and halofantrine</td>
</tr>
<tr>
<td>Antinausea or antientemic</td>
<td>Granisetron and ondansetron</td>
</tr>
<tr>
<td>Antimania</td>
<td>Lithium</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Clozapine, ziprasidone, thioridazine, risperidone, quetiapine, haloperidol and chlorpromazine</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Ritonavir and atazanavir</td>
</tr>
<tr>
<td>Appetite suppressant</td>
<td>Phentermine and sibutramine</td>
</tr>
<tr>
<td>Bronchodilator or decongestant</td>
<td>Salmeterol, terbutaline, ephedrine, phenylpropanolamine and pseudoephedrine</td>
</tr>
<tr>
<td>Central nervous system stimulant</td>
<td>Amphetamine and methylphenidate</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Indapamide</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Octreotide</td>
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<tr>
<td>Immunosuppressant</td>
<td>Tacrolimus</td>
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<tr>
<td>Inotropic agent or vasconstrictor</td>
<td>Dopamine, isoproterenol, dobutamine, adrenalin, noradrenalin and phenylephrine</td>
</tr>
</tbody>
</table>