Drug-Induced Long QT Interval

—Prepared from research by the editorial staff for subscribers of Pharmacist's Letter and Prescriber's Letter—
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Background

The term Long QT Syndrome (LQTS) refers to an abnormal condition of the heart's electrical system. The QT interval is a measure of how long it takes the heart to repolarize (recharge) after each beat. In patients with LQTS the QT interval is abnormally prolonged, leaving the patient vulnerable to an arrhythmia known as torsade de pointes. Symptoms of torsade de pointes can range from syncope (when torsade de pointes stops spontaneously) to cardiac arrest (when torsade de pointes degenerates to ventricular fibrillation).[1] LQTS may be an inherited or acquired condition. It is estimated that inherited LQTS is present in one of every 5,000 people and causes approximately 3,000 deaths in the U.S. each year.[2] Acquired LQTS is more common than the inherited form and is frequently caused by medications.[3]

Myocardial depolarization and repolarization involves the inflow and outflow of positively charged sodium, calcium, and potassium ions.[1] Repolarization occurs when the outflow of potassium ions exceeds the inflow of the sodium and calcium ions. In the case of LQTS, there is a malfunction of ion channels on the myocardial cell membrane which leads to an excess of intracellular positive charges. This malfunction can affect either the outflow of potassium or the inflow of sodium or calcium. Some antiarrhythmics are specifically designed to prolong repolarization by blocking the potassium channel (I_{kr}), which prevents potassium outflow and may help suppress certain arrhythmias.[4] Antiarrhythmic medications are not the only agents to produce this effect on the I_{Kr} channel. Many noncardiac medications also block the I_{kr} channel and can cause LQTS, which can lead to subsequent torsade de pointes.

Medications and Prolonged QT Interval

There are over 50 prescription drugs that have been implicated as causing LQTS.[5] Several of these drugs have recently been removed from the market including astemizole (*Hismanal*), grepafloxacin (*Raxar*), and terfenadine (*Seldane*), or their use has been severely restricted, as with cisapride (*Propulsid*).[6] Medications from many drug classes have been linked to LQTS including Classes Ia and III antiarrhythmics, several antibiotics, tricyclic antidepressants, certain nonsedating antihistamines, and several typical and atypical antipsychotics.[3]

Before starting therapy with a drug that prolongs the QT interval, several risk factors for torsade de pointes should be assessed. Women have a higher risk of drug-induced torsade de pointes because they have longer QT intervals than men.[1,4] Other groups also at risk include the elderly, psychiatric patients, and patients with anorexia nervosa.[1,5] Hypokalemia and hypomagnesemia should be corrected, with periodic monitoring of potassium and magnesium levels, especially before initiating therapy with a QT-prolonging antiarrhythmic.[4] Certain cardiac conditions such as bradycardia and heart failure will increase the risk of torsades as well.[1] Patients with congenital LQTS, even those who are symptom-free, will also be at higher risk of life-threatening drug-induced arrhythmias.[1]

High blood levels of drugs that prolong the QT interval is a major risk factor for torsade de pointes, except with quinidine.[4] Excessive blood levels can be due to administration of large doses, impaired metabolism or elimination, and drug interactions. As an example, the problem associated with terfenadine (*Seldane*) occurred when it was used with erythromycin. Both drugs block the I_{kr} channel, and erythromycin also inhibits the metabolism of terfenadine.

As a result of the growing concern about drug-induced LQTS, the FDA has intensified their screening of new drugs prior to approval.[5,7] For example, the recent approval of the antipsychotic ziprasidone (*Geodon*) was held up due to concerns about its QT-prolonging effect.[8] For the fluoroquinolones levofloxacin, gatifloxacin, and moxifloxacin, the FDA required post-marketing testing to further

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assess their ability to prolong the QT interval.[3] The following chart lists some of the drugs reported to cause QT prolongation and/or torsade de pointes.

Drugs That Prolong the QT Interval and/or Induce Torsade de Pointes[6]

Antiarrhythmics	
Amiodarone (*Cordarone*)*#+	Disopyramide (*Norpace*)*#
Dofetilide (*Tikosyn*)*#	Flecainide (*Tambocor*)*#
Ibutilide (*Corvert*)*#	Procainamide (*Procan*)(*Pronestyl*)*#
Quinidine*#	Sotalol (*Betapace*)*#
Antidepressants	
Amitriptyline (*Elavil, Endep*)+	Desipramine (*Norpramin*)*+
Doxepin (*Sinequan*)+	Fluoxetine (*Prozac*)*
Imipramine (*Tofranil*)+	Venlafaxine (*Effexor*)*
Sertraline (*Zoloft*)*#	
Antihistamines	
Astemizole (*Hismanal*)-off market	Terfenadine (*Seldane*)-off market
Anticancer	
Arsenic trioxide (*Trisenox*)*#+	Tamoxifen (*Nolvadex*)*
Misc. Cardiac	
Bepridil (*Vascor*)*#	Isradipine (*Dynacirc*)*
Moexipril/HCTZ (*Uniretic*)*	Nicardipine (*Cardene*)*
Antipsychotics	
Chlorpromazine (*Thorazine*)+	Haloperidol (*Haldol*)*#
Mesoridazine (*Serentil*)*	Pimozide (*Orap*)*+
Quetiapine (*Seroquel*)*	Risperidone (*Risperdal*)*
Thioridazine (*Mellaril*)*#	Ziprasidone (*Geodon*)*#
GI Stimulant	
Cisapride (*Propulsid*)*# - restricted use	
Antibiotics	
Clarithromycin (*Biaxin*)+	Erythromycin*#
Gatifloxacin (*Tequin*)*	Grepafloxacin (*Raxar*)* - off market
Levofloxacin (*Levaquin*)#	Moxifloxacin (*Avelox*)*
Sparfloxacin (*Zagam*)*#	Trimethoprim-Sulfa (*Bactrim/Septra*): questionable case report.
Antimigraine	
Naratriptan (*Amerge*)*	Sumatriptan (*Imitrex*)*
Zolmitriptan (*Zomig*)*	
Miscellaneous	
Droperidol (*Inapsine*)*#+	Felbamate (*Felbatrol*)#
Foscarnet (*Foscavir*)*	Fosphenytoin (*Cerebyx*)*
Halofantrine (*Halfan*)*#	Indapamide (*Lozol*)*+
Levomethadyl (*Orlaam*)*	Octreotide (*Sandostatin*)*
Pentamidine*#	Probucol (*Lorelco*)*#
Salmeterol (*Serevent*)*	Tacrolimus (*Prograf*)+
Tizanidine (*Zanaflex*)*	

* QT prolongation is mentioned in the FDA-approved labeling.
# The FDA-approved labeling includes mention of cases or a risk of torsade de pointes.
+ There are case reports of torsade de pointes in the medical literature.

Commentary

Future research is being aimed at methods to identify those patients most at risk for drug-induced

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arrhythmias. The National Institutes of Health has developed a registry to track patients who are suspected of having had a drug-induced arrhythmia.[7] By genetically analyzing these patients it is hoped that a marker will be found to enable quick identification of patients at risk for drug-induced arrhythmias. Methods to identify drugs prone to QT interval prolongation early in clinical development are also being studied.[7] Researchers hope to develop a computer screening test to predict which drugs will likely cause LQTS.

Until these screening tests are available, healthcare providers will have to rely on an increased awareness of the problem. Clinicians need to pay particular attention towards adherence to warning labels, drug interactions, and identification of patients at risk for drug-induced LQTS. More information on LQTS is available by contacting The Sudden Arrhythmia Death Syndromes (SADS) Foundation at 800-786-7723 or www.sads.org. Updated information about drugs that cause QT prolongation can be found at www.QTdrugs.org.

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