SADS FOUNDATION
SUDDEN ARRHYTHMIA DEATH SYNDROMES

Acquired, Drug-Induced Long QT Syndrome

A Guide for Patients and Health Care Providers

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Drugs have many potential side effects. One of considerable importance is drug-induced Long QT syndrome, a cardiac abnormality that can lead to loss of consciousness or sudden death.

Why do I need to know about drug-induced Long QT syndrome?

More than 50 commonly prescribed medications can lead to drug-induced Long QT syndrome (LQTS) and serious heart rhythm abnormalities known as cardiac arrhythmias. The problem has become increasingly urgent as more QT prolonging drugs have entered the market.

Physicians, other healthcare providers and patients need to be aware of drug-induced LQTS. Physicians need to know:

- What drugs cause QT prolongation.
- How to identify patients at particular risk.
- How to monitor and protect patients taking a QT prolonging drug.

Patients need to know:

- What LQTS and its symptoms are.
- If they are at particular risk.
- What drugs cause QT prolongation.
- How to protect themselves.

What is LQTS?

LQTS is an inherited or acquired disturbance of the heart's electrical system caused by abnormalities of microscopic pores, or holes, in the heart cells called ion channels. Ions such as potassium, sodium, calcium and chloride pass back and forth across the cell membrane through these channels. As they do, they generate the electrical activity (depolarization and repolarization) that initiates the

heart's mechanical function. These electrical signals are recorded as the electrocardiogram (EKG or ECG).

In LQTS, the abnormal function of one or more ion channels prolongs the repolarization process and the QT interval. This predisposes patients to cardiac arrhythmias.

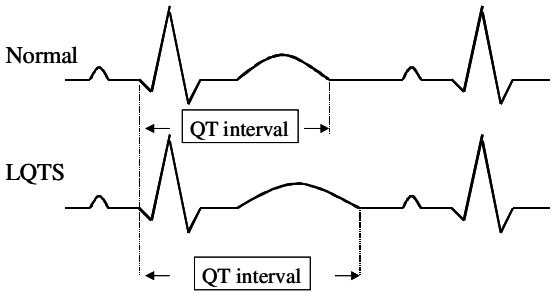
What is the QT interval?

The QT interval represents the time from the electrical stimulation (depolarization) of the heart's pumping chambers (ventricles), to their recharging (repolarization). It is measured in seconds on the EKG and closely approximates the time from the beginning of the ventricles' contraction until the end of relaxation.

The QT interval is variable, like most physiologic parameters such as blood pressure. In particular, the QT varies with the heart rate. It shortens as the rate increases and lengthens as the rate decreases. Therefore, there is no single QT interval that is normal or abnormal.

In order to determine if a given QT is appropriate for a given heart rate, the QT is corrected for the heart rate using a simple mathematical formula, and this quantity is called the QTc. The QTc is the value that doctors generally use when assessing for LQTS.

Normally, the QTc interval varies from 0.35 to 0.46 seconds (350-460 milliseconds). About 95% of people have a value between 0.38 and 0.44 seconds, which is the range doctors generally consider normal. In both inherited and acquired LQTS, repolarization is delayed, resulting in a prolonged QTc interval. The diagram below provides an example of a normal and a prolonged QTc interval.



What are the symptoms of LQTS?

Sudden loss of consciousness (syncope) and sudden death are the common symptoms and usually occur without warning. They are caused by a very fast cardiac arrhythmia known as torsade de pointes.

In patients who experience syncope, the torsade de pointes rhythm spontaneously returns to normal, usually within approximately one minute. 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, the outcome is usually death.

Dizziness, lightheadedness, heart palpitations, and a sustained fast heartbeat that does not cause syncope are uncommon in drug-induced LQTS. Chest pain, persistent shortness of breath, heart valve problems and heart failure are not caused by the condition.

When does a QTc interval indicate a risk of drug-induced LQTS and torsade de pointes?

Torsade de pointes is seen almost exclusively in conditions associated with a prolonged QTc interval. However, the relationship of QTc interval to risk of torsade is complex. Many factors can influence arrhythmia risk, including other drugs, underlying heart disease and low potassium or magnesium. Therefore, there is no single QTc above which torsade is likely to occur.

In addition, the risk depends on what the QTc was before drug administration and how much the QTc increases above the person's baseline. However, a QTc longer than 0.45 seconds (450 milliseconds) may be cause for concern in patients receiving a QT prolonging drug; and a QTc of 0.50 (500 milliseconds) or longer often indicates a high risk of arrhythmia.

What causes drug-induced LQTS?

Drugs are the most common cause of acquired Long QT syndrome. Cardiac disorders are also a frequent cause of acquired LQTS. QT 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 QT interva. Electrolyte imbalance, mainly hypokalemia, hypomagnesemia and hypocalcemia, is also a common cause of prolonged QT interval. Finally many metabolic, nutritional, neurological and endocrine pathological conditions have been reported to prolong the QT interval.

Drug-induced LQTS is usually caused by medications that block a cardiac potassium channel in the heart known as HERG or IKr, which is abnormal in

inherited LQTS. Consequently, there is a clear relationship between inherited and acquired LQTS.

Drugs from almost every therapeutic class are known to prolong the QTc interval. Recently, several prescription medications have been pulled from the market, restricted from use or given serious warnings due to their QTc prolonging effect. These drugs include:

- Antihistamines–Seldane® (terfenadine) and Hismanal® (astemizole)
- Antibiotics–Raxar® (grepafloxacin)
- Antipsychotics–Mellaril® (thioridazine), Serentil® (mesoridazine)
- The gastrointestinal prokinetic agent Propulsid® (cisapride)

For a complete list of drugs in every class that prolong the QTc interval and/or induce torsade de pointes, visit www.sads.org or www.torsade.org.

Who is at risk for drug-induced LQTS?

Almost anyone who takes a QT prolonging drug has some risk. Usually, the risk is very low. However, certain patients have a higher risk due to other existing factors. Risk factors for drug-induced LQTS include:

- Taking a drug known to prolong the QT.
- Simultaneous treatment with more than one QT prolonging drug.
- Taking multiple medications (drug-drug interactions) that may cause high blood levels of the QT prolonging drug and increase the risk of arrhythmia.
- Overdose of medication, which also increases the blood level. Overdoses can relate to an individual's size, ethnicity and mental/emotional state.
- Female gender.
- Baseline QTc prolongation.
- Excessive QTc prolongation (for example, >500 milliseconds on a drug).
- Electrolyte imbalance (for example, diuretics can lower potassium levels).
- History of cardiovascular disease, particularly heart hypertrophy, heart failure or coronary artery disease.
- Liver or kidney disease (e.g., hepatitis), which may reduce the metabolism of the drug.

People who have more risk factors for QTc prolongation than the general population are particularly vulnerable to drug-induced LQTS. They include:

- Individuals with major psychiatric disorders.
- Individuals with cardiovascular disease.
- The elderly.
- Women.

For example, the elderly commonly suffer from cardiovascular disease or take multiple medications. Individuals with major psychiatric disorders tend to have a

higher likelihood of receiving QT prolonging medication, often have comorbidities, including heart disease and hepatitis, and may not comply with the prescribed medication dose, which can lead to an overdose. Women typically have longer baseline QT intervals than men and may be at twice the risk for LQTS.

How can doctors protect their patients from drug-induced LQTS?

Physicians can take the following steps to identify high-risk patients, assess their cardiac safety profiles, and diminish the risk of drug-induced LQTS. When prescribing drugs:

- Review the label. Is the drug associated with QTc prolongation? If so, obtain an EKG. If the baseline QT interval is on the high side of the normal range or is prolonged, consider a non-QT prolonging drug.
- Consider what impact a higher than prescribed dose may have on the risk for QTc prolongation.
- Question whether the drug's benefits outweigh its potential risks.
- Determine if another drug, without the risk for QTc prolongation, can be substituted.
- Consider whether the patient will be compliant. Is there a possibility that the patient will take a higher dose than prescribed?
- Verify whether the patient is taking multiple medications that may interact and induce cardiac arrhythmias.
- Determine if the patient possesses any other risk factors for drug-induced LQTS.
- Counsel the patient about the risks for LQTS.
- Recommend that the patient obtain medication from only one pharmacy so the pharmacist is aware of all medications the patient takes and can advise accordingly.

When physicians and other providers prescribe QT-prolonging medication, they should consider baseline and periodic screening of the patient, including QT interval and serum potassium and magnesium levels. This is especially important for high-risk patients or those whose cardiac or prescription history is unknown, as is often the case in the emergency room.

How can patients protect themselves from drug-induced LQTS?

- Write a list of all your medications and provide that list to any doctor/other provider/pharmacist you see.
- Ask the doctor/other provider/pharmacist if any prescribed medications can affect the QT interval. If so, what is the risk versus benefit of taking these drugs?
- Go to only one pharmacist, who can keep a record of all your prescribed medications and search for potential drug interactions using electronic databases.

- Do not take unnecessary drugs. Never take someone else's medication.
- Avoid excessive alcohol use.
- Be very cautious about using herbal or alternative medications. Little is known about these agents, but some can interfere with the metabolism of prescribed medications or directly affect the possibility of QTc prolongation.
- If you experience palpitations or loss of consciousness, stop any new drug immediately and contact your doctor.

The SADS Foundation is a non-profit organization committed to saving the lives and supporting the families of children and young adults who are genetically predisposed to sudden death due to heart rhythm abnormalities through education, research and advocacy.

SADS Programs:

Patient & Family Support
- Physician Referral
- Networking
- Education & notification of new research
- Support Groups

Medical Education
- Diagnostic Guidelines
- Seminars

Awareness
- National & local publicity
- Materials for distribution
- Speakers bureau

Advocacy
- Policies to advocate for patient protection
- AED program support

SADS staff & local Affiliate Groups organize and support volunteers in conducting these programs around the world.

For further information about the long QT syndrome, SADS programs or to add your name to our mailing contact us at:
www.sads.org
email: sads@sads.org
800-STOP SAD (800-786-1123)

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