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Anesthesia for Patients with Congenital Long QT Syndrome

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Long QT syndrome is a malfunction of cardiac ion channels resulting in impaired ventricular repolarization that can lead to a characteristic polymorphic ventricular tachycardia known as torsades de pointes. Stressors, by increasing sympathetic tone, and drugs can provoke torsade de pointes, leading to syncope, seizures, or sudden cardiac death in these patients. Beta blockade, implantation of cardioverter defibrillators, and left cardiac sympathetic denervation are used in the treatment of these patients. However, these treatment modalities do not guarantee the prevention of sudden cardiac death. Certain drugs, including anesthetic agents, are known to contribute to QT prolongation. After reviewing the literature the authors give recommendations for the anesthetic management of these patients in the perioperative period.

LONG QT syndrome (LQTS) is a malfunction of cardiac ion channels resulting from mutations involving genes encoding critical ion channels of the heart (congenital LQTS) or caused by metabolic abnormalities or drugs (acquired LQTS). In both instances the perturbed ion channels impair ventricular repolarization. Patients with LQTS often manifest prolongation of the QT interval and abnormal T wave morphology on 12-lead electrocardiogram secondary to delayed cellular repolarization and heterogeneity in dispersion of repolarization, which, when amplified by sympathetic activity, can lead to early after-depolarization, further dispersion of repolarization, and the formation of reentry circuits.[1] These events can present as syncope, seizures, or sudden cardiac death secondary to a characteristic polymorphic ventricular tachycardia known as torsades de pointes (TdP).[2,3] Symptomatic events may be triggered by physical activity and emotional stress. Several medications, including anesthetic agents, may also interfere with cardiac repolarization, prolong the QT interval, and, sometimes, cause drug-induced TdP and sudden death.

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Congenital LQTS

Congenital LQTS was first described in 1957 by Jervell and Lange-Nielsen[4] as an autosomal recessive cardioauditory syndrome characterized by prolonged QT interval and congenital deafness. Romano *et al.*[5] and Ward[6] later described a similar syndrome involving QT interval prolongation, syncope, and sudden death but without deafness and with an autosomal dominant pattern of inheritance. Since the publication of those articles, five genes encoding cardiac ion channel subunits and ankyrin B have been identified in the pathogenesis of approximately 65–70% of congenital LQTS.[7–11]

Traditionally, LQTS is divided into congenital (c-LQTS) and acquired (a-LQTS) forms. Drug-induced LQTS is one form of a-LQTS. The age at presentation of patients with c-LQTS varies from *in utero* to adulthood. The prevalence of c-LQTS in developed countries is estimated to be approximately 1 in 5,000 persons.[12,13] Patients may present at a young age with a history of abrupt, exertion-triggered or auditory-triggered syncope. In addition, it is not uncommon for a patient with c-LQTS to have been misdiagnosed and treated for epilepsy. A family history of sudden death may be present and approximately 5–10% of the time the sentinel event for c-LQTS involves sudden death or aborted cardiac arrest.[14] The frequency of these attacks varies from once or twice in a lifetime to once to twice per week.[15,16] A family history of sensorineural hearing loss is extremely uncommon for the vast majority of c-LQTS. The general inheritance pattern for c-LQTS is autosomal dominant. Rarely, individuals can have autosomal recessive LQTS, which includes marked QT prolongation and deafness (*i.e.*, Jervell and Lange-Nielsen syndrome). This affects approximately one in 1 million persons. In addition, spontaneous germline mutations also occur.[17–20]

Given the potential for significant morbidity and mortality arising from cardiovascular compromise because of abnormal cardiac repolarization and QT interval prolongation, anesthesiologists should be aware of necessary interventions and treatment modalities for patients with suspected c-LQTS. In this regard, it is important to distinguish between c-LQTS and a-LQTS. Although a-LQTS is of substantial interest, this review focuses on anesthetic recommendations for patients diagnosed with c-LQTS.

Congenital LQTS: Diagnosis

Children, adolescents, and young adults presenting with a history of abrupt syncope during exertion or auditory stimulation (e.g., from doorbells or alarm clocks), epilepsy, or family history of sudden death should raise suspicion for c-LQTS and should have a preoperative evaluation including an electrocardiogram. Approximately 60% of patients with c-LQTS will manifest diagnostic QT prolongation on the electrocardiogram (QTc >470 ms in males and 480 ms in females).[21] Because the QT interval varies with heart rate (lengthening with bradycardia and shortening with an increase in heart rate), the QT interval is corrected (QTc) for heart rate using Bazett's formula: QTc = measured QT/$\sqrt{}$R to R interval (s). Schwartz *et al.*[21] published a list of diagnostic criteria (the "Schwartz score") for c-LQTS including electrophysiologic findings, family, and clinical history. Although symptomatic c-LQTS is characterized by recurrent syncope, cardiac arrest, and seizures, only 60% of patients are symptomatic at the time of diagnosis.[22] To complicate matters, approximately 25–40% of patients with genetically proven c-LQTS have a nondiagnostic resting QTc ("concealed LQTS").[23–26] Despite these limitations, it seems prudent to obtain an electrocardiogram and carefully assess the QT interval in patients with a history of syncope or seizures without any pathologic correlate or family history of sudden (cardiac) death. Since the discovery of c-LQTS as an ion channel disease of the heart in 1995, genetic testing for c-LQTS is now available as a commercial molecular diagnostic test (Familion test; Genaissance Pharmaceuticals, New Haven, CT).

Congenital LQTS: Clinical Features

As mentioned above, the clinical features of c-LQTS range from a stable rhythm albeit with QT prolongation to the trademark dysrhythmia associated with LQTS, torsades de pointes (TdP). A majority of symptomatic events are triggered by situations of increased sympathetic nervous system output, such as physical activity emotional stress, anxiety, or fear. There are also numerous pharmacological agents that can prolong the QT interval, resulting in drug-induced LQTS or a-LQTS (table 1). It is important to be aware of these medications because their administration to patients with c-LQTS may result in further prolongation of the QT interval, may increase transmural dispersion of repolarization, and may provide the necessary torsadogenic trigger.

Congenital LQTS: Treatment

Beta Blockade

Previously, β-blockers have been described as the most effective medical therapy to reduce mortality in patients with c-LQTS.[27] In 869 patients younger than 41 yr of age, Moss *et al.* found a significant reduction in the mean rate of cardiac events with β-blocker therapy.[28] However, patients who had cardiac symptoms before initiation of β-blocker therapy had a 32% likelihood of experiencing recurrent events. Although β-blockade helps reduce the incidence of cardiac events, it is not entirely effective in preventing TdP and sudden death in c-LQTS.

Implantable Cardioverter Defibrillator Therapy

Some patients continue to have symptomatic cardiac events (defined as syncope or cardiac arrest) despite β-blockade. Implantable cardioverter defibrillators (ICDs) have been used in this patient population and provide an additional therapeutic option to prevent sudden cardiac death.[29]

Left Cardiac Sympathetic Denervation

Although β-blockade is an effective treatment for patients with c-LQTS, ~25% of patients continue to have arrhythmias despite therapy.[28] The insertion of an ICD is indicated for patients who suffer an aborted cardiac arrest.[28] However, in patients who continue to have syncope and an ICD that triggers shocks the management is still controversial. Left cardiac sympathetic denervation reduces the arrhythmogenic potential and has been used in these patients.[30] In a retrospective study by Schwartz *et al.*[31] the yearly number of cardiac events per patient declined by 91% after left cardiac sympathetic denervation and the percentage of patients with greater than five cardiac events decreased from 55% to 8%. In patients with an ICD in place and multiple shocks before the left cardiac sympathetic denervation, the number of shocks after left cardiac sympathetic denervation declined by 95%.

Management of TdP

TdP may occur at any time during the perioperative period and may be short-lived and self-terminating. However, prolonged episodes can cause severe hemodynamic compromise and can degenerate into ventricular fibrillation. Such episodes should be treated immediately with emergent asynchronous defibrillation and cardiac massage following the basic life support and advanced cardiovascular life support guidelines by the American Heart Association.[32] Short TdP episodes, which may occur in association with bradycardia, can be treated effectively with overdrive pacing and magnesium sulfate therapy. Magnesium sulfate is the treatment of choice for prevention of recurrence in patients with drug-induced TdP even with normal magnesium concentrations. Furthermore, there appears to be no contraindication to its use in patients with c-LQTS. According to the advanced cardiovascular life support guidelines magnesium sulfate

Table 1. Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes

Well Documented Association	Moderate Association/ Case Reports	Increased Potential Risk in Congenital QTS Patients*	Unclear Association† (at therapeutic doses)
CARDIAC			
Amiodarone	Flecainide	Dobutamine	Mexiletine
Bepridil	Moexipril/HCTZ	Dopamine	
Disopyramide	Nicardipine	Ephedrine	
Dofetilide	Isradipine	Epinephrine	
Ibutilide		Isoproterenol	
Procainamide		Midodrine	
Quinidine		Norepinephrine	
Sotalol		Phenylephrine	
ANTIMICROBIALS			
Clarithromycin	Azithromycin		Ampicillin
Erythromycin	Foscarnet		Ciprofloxacin
Grepafloxacin‡	Gatifloxacin		Fluconazole
Pentamidine	Levofloxacin		Itraconazole
Sparfloxacin‡	Moxifloxacin		Ketoconazole
	Telithromycin‡		TPM/SMX
PSYCHOTROPICS			
Chlorpromazine	Lithium		Amitriptyline**
Haloperidol	Quetiapine		Amoxapine
Mesoridazine	Risperidone		Clomipramine
Pimozide	Venlafaxine		Desipramine
Thioridazine	Ziprasidone		Doxepin
			Fluoxetine
			Galanthamine
			Imipramine
			Nortriptyline
			Paroxetine
			Protriptyline
			Sertraline
MISCELLANEOUS			
Arsenic trioxide	Amantadine	Albuterol	
Chlorpromazine	Astemizole‡	Cocaine	
Cisapride‡	Chloral Hydrate	Fenfluramine	
Domperidone‡	Dolasetron	Levalbuterol#	
Droperidol‖	Felbamate	Metoproterenol	
Halofantrine	Fosphenytoin	Phentermine	
Haloperidol	Granisetron	Phenylpropanolamine‡	
Levomethadyl	Indapamide	Probucol‡	
Mesoridazine	Octreotide	Pseudoephedrine	
Methadone	Ondansetron	Ritodrine	
Organophosphates§	Salmeterol	Terbutaline	
Pimozide	Tacrolimus		
Thioridazine	Terfenadine‡		
	Tamoxifen		
	Tizanidine		
	Voriconazole		

* These agents are in addition to those in the well documented and moderate risk associations lists, to be avoided in patients with congenital QTS. † Limited case reports available. ‡ Products which have been withdrawn from and/or not available on the United States market. § Onset may be delayed. ‖ FDA black box warning. # Proposed risk, marketed with an advantage of decreased cardiac side effects. ** Prolongation seen in overdose.

A continuously updated list of drugs is available at www.torsades.org (accessed July 6, 2004).

can be used in the treatment of stable polymorphic ventricular tachycardia when there is evidence of a QT prolongation. Patients should receive an initial bolus of 30 mg/kg magnesium sulfate intravenously, followed by an infusion of 2–4 mg/min. The bolus may be repeated after 15 min.

In the heart magnesium sulfate acts as a calcium channel blocker. In addition, it activates sodium-potassium adenosine triphosphatase in the cell membrane, which promotes resting repolarization (phase 4) and reduction of arrhythmias. However, it does not shorten the QT interval. While receiving magnesium sulfate therapy, magnesium concentrations should be checked regularly to avoid toxicity. In c-LQTS patients that do not respond to magnesium sulfate therapy, temporary pacing may be effective. In contrast to drug-induced or a-LQTS, sympathomimetic agents such as isoproterenol or dobutamine should be considered contraindicated in c-LQTS because the increase in adrenergic tone caused by these agents may exacerbate arrhythmias.[33]

Congenital LQTS: Anesthetic Implications

The available data regarding prevention of lethal TdP during the course of anesthesia for patients with c-LQTS is scant and inconclusive. Studies examining the effects of different anesthetic agents on the QT interval have involved young healthy patients. Reports on patients with c-LQTS undergoing anesthesia have been published as case reports and small case series with a variety of outcomes even when using the same anesthetic agents.[27,34–38] Although it is apparent that further research is necessary to delineate the differences among anesthetic agents, patient populations, and cardiac events in developing evidence-based standard of care recommendations, the authors still think that it is important to provide the reader with basic information regarding patients with c-LQTS and their anesthetic management. In this regard, we will attempt to distill the available literature into a logical approach to anesthesia for patients with recognized congenital LQTS and provide a source for the given recommendations whether case reports, case series in patients with c-LQTS, or studies in healthy patients.

General Considerations

Patients with c-LQTS may be at increased risk of developing malignant TdP in the perioperative period. Successful management of these patients depends on proper recognition of the syndrome and appropriate management. Sympathetic stimulation including abrupt and loud noises can trigger TdP. Accordingly, attention should be paid to keeping these patients in a quiet environment especially during induction. Premedication should be provided to blunt the sympathetic system response. The patient temperature should remain at approximately 37°C because hypothermia could theoretically prolong the QT interval through prolonged recovery of inactivated sodium channels.[39] No matter what anesthetic technique is used, light or insufficient anesthesia, hypertension, bradycardia, tachycardia, hypoxemia, and hypocapnia or hypercapnia must be avoided because they all potentially affect repolarization of the cardiac myocyte and augment sympathetic tone. Patients should have adequate pain relief to avoid any stress response. Patients should be monitored throughout the perioperative period in a calm and quiet environment, and special attention should be paid to monitoring the QT interval.

Beta Blockade

If a patient is being actively treated with β-blockers for LQTS, they should continue to be β-blocked perioperatively and should be given their usual dose the morning of surgery.

Implantable Devices

Preoperative interrogation of cardiac pacemakers or implantable cardiac defibrillators is always advisable. Concomitant electrocardiographic and pulse monitoring is necessary to evaluate conducted paced beats. If a patient is unable to provide information about the pacing or defibrillating device, radiographic evaluation to determine the product code is indicated. Because monopolar devices such as electrocautery interfere with pacemaker and ICD function, preoperatively reprogramming these devices to an asynchronous pacing mode is helpful. The defibrillating function of any ICD should always be turned off before any surgical procedure. Accidental shock delivery may put both patient and operating room personnel at risk. External defibrillation is possible in patients with ICDs. If there is concern regarding the patient's safety with regard to their underlying cardiac rhythm problems, pacemaker/defibrillator patches may be applied before induction of anesthesia. The external pacemaker/defibrillator should be checked preoperatively and be made available for immediate use in the operating room. Postoperatively the ICD should be turned back on while the patient is being monitored in the recovery room.

Electrolytes

Hypokalemia, hypomagnesemia, and hypocalcemia predispose the myocardium to delayed repolarization. Therefore, serum electrolytes should be measured and replaced as appropriate before surgery.[40] It has been suggested that pretreatment with magnesium (30 mg/kg) may be beneficial, even in patients with normal serum magnesium concentration. Magnesium is very unlikely to cause toxicity, and may block the inward sodium and potassium currents implicated in generating early after-depolarizations.[41]

Triggering Medications

Medications known to prolong the QT interval or precipitate TdP (table 1) should be evaluated before surgery with regard to the indication for the medication. If it can be discontinued without problems, it might be prudent to do so but if the patient has taken it before without any problems it is probably safe to be continued as well, particularly as the patient will be closely monitored.

Premedication

It is known that anxiety (*e.g.*, emotional stress before surgery) and loud noise can trigger c-LQTS. Therefore, sufficient anxiolysis before induction of anesthesia seems prudent. In a study in young and healthy adults without cardiovascular problems, Michaloudis *et al.*[42] used intramuscular midazolam (0.8 mg/kg) for premedication followed by intravenous midazolam (0.4 mg/kg) during induction of anesthesia. Midazolam decreased sympathetic activity in unstimulated patients but did not

blunt the hemodynamic response to intubation, causing a prolongation in QT interval thereafter.[42] Further support for the use of midazolam as an anxiolytic is provided by a study examining electrocardiogram rhythm changes during the induction of anesthesia in patients with coronary artery disease.[43] There were no apparent dysrhythmias and no change in the QTc when midazolam was used in combination with fentanyl. Although ketamine has been used as premedication in children with undiagnosed c-LQTS,[44] it is probably best avoided in patients with LQTS because it stimulates sympathetic nervous system activity.

Induction Agents

Thiopental prolongs the QT interval in healthy patients.[45] Despite this effect, thiopental has been used safely in patients with c-LQTS.[27,34] Because of its prolongation of the action potential duration, thiopental may in fact reduce the heterogeneity of action potential dispersion through the ventricular wall (*i.e.*, reduce transmural dispersion of repolarization). This effect would theoretically prevent the spontaneous onset of TdP.[46]

Propofol has been found to have little or no effect on the QT interval in healthy patients undergoing minor surgery.[35,40] Propofol has been shown to rapidly reverse sevoflurane-induced QTc prolongation in healthy patients[36] and therefore may be beneficial.

With regard to benzodiazepines, midazolam has been studied the most; it does not seem to adversely affect the QT interval when used as an anxiolytic[43] or induction agent.[42] However, previous studies were done in patients without a history of c-LQTS. Whether there is exacerbation of prolonged QT in patients with c-LQTS receiving benzodiazepines is not known.

Volatile Anesthetics

Volatile anesthetics (halothane, enflurane, isoflurane, and sevoflurane) have been studied in healthy children and reported as agents used in patients with c-LQTS. Although all of these agents prolong the QT interval to some extent, they have been successfully used in patients with c-LQTS receiving beta blocker therapy.[37,38,47,48] In contrast, there is one report in which isoflurane shortened the QT interval in a patient with c-LQTS.[27] In general, isoflurane has been reported as the agent of choice because of its apparent safety.[27,37,49] Nitrous oxide has been used in conjunction with some of these reports without any adverse effects. Because halothane sensitizes the heart to catecholamines, it seems to be prudent to avoid it in patients with LQTS.

Muscle Relaxants

The ideal muscle relaxant should avoid bradycardia, vagal stimulation, and potassium shifts. It should have little or no histamine release and be short acting to avoid the use of reversal agents. Accordingly, succinylcholine, because of its autonomic effects and potassium release, is far from ideal. It prolongs the QT interval in patients with c-LQTS unless pretreatment with a priming dose of tubocurarine is used.[48,49]

Vecuronium and atracurium have been studied in a group of healthy patients, and have been found to have no effect on the QT interval.[42] Pancuronium was associated with ventricular fibrillation in one case report.[50] Because of its vagolytic properties, avoiding pancuronium in these patients seems prudent, especially as there is an alternative drug that can be used.

Neuromuscular Reversal Agents

Anticholinergic medications, such as atropine, can precipitate TdP in c-LQTS patients.[51] Glycopyrrolate has also been shown to lengthen the QT interval in healthy subjects.[52]

The use of combined anticholinergic medications (glycopyrrolate or atropine) plus anticholinesterases (neostigmine or edrophonium) has been shown to prolong the QT interval in healthy subjects.[52] Because neostigmine or edrophonium cause bradycardia *via* blocking the break down of acetylcholine, which may lead to QT prolongation or pauses, their use and the combination of an anticholinergic plus anticholinesterase should be done with caution to avoid any profound changes in heart rate. In contrast, it has been shown in patients with c-LQTS that bradycardia induced by β-blockade does not affect the QT interval and decreases baseline QTc dispersion.[53]

Narcotics

Although the effects of fentanyl on the QT interval are conflicting,[27,43] fentanyl and morphine have been used without adverse effects in patients with c-LQTS.[27,37,38] The authors chose either fentanyl or morphine as part of a balanced anesthesia technique to avoid sympathetic stimulation during laryngoscopy and tracheal intubation. Sufentanil has been shown to prolong the QT interval in a patient undergoing coronary artery bypass surgery.[54] In patients enrolled in a methadone maintenance program, methadone was associated with TdP when given in very high doses.[55]

Antiemetics

It is well known that some patients and some procedures are more likely than others to cause postoperative nausea and vomiting. Droperidol, a butyrophenone, has been commonly used as a potent antiemetic in these situations.[56] Previously, droperidol carried a warning to avoid use in doses >25 mg because of its ability to prolong the QT interval.[57] However, the United States Food and Drug Administration issued a "black box warning" in 2001 after several cases of cardiac arrest allegedly caused by low-dose droperidol administration.[57,58] The warning suggests the use of droperidol in low doses only

if alternative drugs have failed. Although the data that led to the 2001 black box warning resulted from case reports and surveillance data rather than scientific publications in medical journals, it seems prudent to avoid using droperidol in the perioperative setting in patients with c-LQTS. Antiemetics like ondansetron are as effective as droperidol in preventing postoperative nausea and vomiting and have a favorable side effect profile.[59] However, there are *in vitro* studies showing an interaction between 5-hydroxytryptamine 3 receptor antagonist and different human cardiac ion channels, thereby prolonging the QT interval.[60] In addition, ondansetron is listed as a medication with "possible" risk for TdP.# For patients with c-LQTS, an antiemetic regimen including ondansetron seems preferable to droperidol based on current data.

Regional Anesthesia

The same basic principles apply for the management of the LQTS patient undergoing regional anesthesia. A quiet and calm environment with a relaxed patient help in the prevention of any dysrhythmias caused by stress and anxiety. There are very few reports on regional anesthesia in patients with c-LQTS. Spinal anesthesia has been successfully used.[34,61] Epidural anesthesia (lidocaine or chloroprocaine) with or without epidural morphine has been used in c-LQTS patients undergoing cesarean section.[62,63]

Epidural bupivacaine for vaginal delivery has also been used without adverse effects in a patient with Romano Ward syndrome.[64] All authors avoided the use of epinephrine as an adjunct to the local anesthetic to avoid dysrhythmias because epinephrine can paradoxically prolong the QT interval in individuals with some forms of c-LQTS.[25]

Conclusions

Congenital long QT syndrome (c-LQTS) is being recognized with increasing frequency among the general population. It requires special attention and careful management in the perioperative period. The existing literature provides some insight into management of these patients. However, there are no definitive guidelines for anesthetic management of c-LQTS. After reviewing the literature, we provide some recommendations for preoperative optimization and intraoperative anesthetic agents that may be used for patients with c-LQTS. A synopsis of these recommendations is as follows:

Preoperative:
- Monitor baseline QT interval.
- Adequate β-blockade.
- Quiet and calm environment.
- Defibrillator should be available for immediate use during the perioperative period.
- Premedication, if applicable.

Intraoperative:
- Monitor QT interval.
- Quiet and calm environment.
- avoid hypothermia.
- General anesthesia:
  i) propofol (for induction or as continuous infusion throughout),
  ii) isoflurane as volatile agent of choice,
  iii) vecuronium for muscle relaxation (dose appropriately to avoid pharmacologic reversal), intravenous) fentanyl for analgesia.
- Ensure patient is adequately anesthetized before laryngoscopy and tracheal intubation to avoid sympathetic stimulation.
- Consider topical anesthesia before intubation.
- Regional anesthesia: local anesthetics (lidocaine and chloroprocaine) can be safely used; avoid addition of epinephrine.

Postoperative:
- Monitor until patient has recovered from anesthesia and the monitored QT interval has returned to baseline.
- Maintain calm and quiet environment.
- Ensure adequate pain control.

Available at www.torsades.org. Accessed July 6, 2004.

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