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REVIEW

Drugs to be avoided in patients with long QT syndrome: Focus on the anaesthesiological management

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Abstract

Long QT syndrome incidence is increasing in general population. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of Torsades de Pointes and malignant arrhythmias. The available data regarding prevention of lethal Torsades de Pointes during anesthesia in patients with long QT syndrome is scant and conflicting: only case reports and small case series with different outcomes have been published. Actually, there are no definitive guidelines on pre-, peri- and post-operative anesthetic management of congenital long QT syndrome. Our review focuses on anesthetic recommendations for patients diagnosed with congenital long QT syndrome furnishing some key points for preoperative optimization, intraoperative anesthetic agents and postoperative care plan, which could be the best for patients with c-long QT syndrome who undergo surgery.

Key words: Long QT Syndrome; Torsades de pointes; Anesthesia; QT-prolongation; Anesthetic drugs

Core tip: Long QT syndrome is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography. This review furnishes important key points for preoperative optimization, intraoperative anesthetic agents and postoperative care in order to fill the lack of definitive guidelines on anesthetic management of c-long QT syndrome.

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INTRODUCTION

Long QT syndrome (LQTS) is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography (ECG). This abnormal repolarization, when amplified by sympathetic activity, can lead to the formation of reentry circuits and may present with syncope, seizures, or torsades de pointes (TdP), ventricular fibrillation and, therefore sudden cardiac death[1]. Moreover, there are other signs of the torsadogenic property of a drug: QT dispersion (difference between the longest and the shortest QT interval) and the transmural dispersion of repolarization (TDR) (time between the peak and the end of the T wave in a precordial lead)[2]. Traditionally, LQTS is divided into congenital (c-LQTS) and acquired

(a-LQTS) forms. Drug-induced LQTS is the most common cause of a-LQTS; as a matter of fact, a survey by Schwartz *et al*[3] of 670 patients in the International LQTS Registry revealed that anesthesia can trigger LQTS.

Ninety-five percent of drug-induced LQTS is due to the obstruction of the rapid component of the late correcting potassium current (I_{k}-r), which physiologically allows the rapid potassium outflow[4]. I_{kr} and the slow component of the same channel (I_{k}-s) are responsible for the repolarization of cardiomyocytes. Some anesthetics and some drugs used in premedication may lead to QT-prolongation. The available data on the prevention of lethal TdP during anesthesia in patients with c-LQTS is scant and conflicting: only case reports and small case series with different outcomes, even when using the same anesthetic agent, have been published[2,5-19]. Although a-LQTS is of significant interest, this review focuses on the anesthetic recommendations for patients diagnosed with c-LQTS. Our aim is to provide some key points which could help both the cardiologists and the anesthetists when approaching a patient with LQTS candidate for anaesthesiological procedures. Firstly, we describe which drugs should be avoided in LQTS and then we move on the specific topic of the review describing the anaesthesiological management of patients with LQTS.

DRUGS TO BE AVOIDED IN LQTS

Certain drugs, including some anesthetics, are known to contribute to QT prolongation. Considering that not all agents that prolong the QT interval increase TDR, drugs can be distinguished into the following groups depending on their simultaneous effects on the QT corrected using the Bazzet's formula (QTc) interval and on TDR[20]: (1) drugs inducing both QTc prolongation and increased TDR, characterized by a high torsadogenic potential; (2) drugs causing QTc prolongation but with a slight effect on TDR and little, if any, ability to induce TdP; and (3) drugs causing both QTc prolongation and increased TDR below a certain concentration, but inducing TdP once a critical value of TDR is exceeded.

Drugs that prolong the QT interval and/or induce Torsades de Pointes in patients with diagnosed or suspected c-LQTS are shown on Table 1[21] and can be found on the web pages www.torsades.org. Some of these drugs are not available in every country (many of them have been withdrawn from the market in several countries). However, this list doesn't include some anesthetic agents which have an influence on cardiac conduction and can lead to intraoperative TdP; hence, they are discussed throughout the text.

ANAESTHETICS IN LQTS

Despite an adequate β-blocking, patients with LQTS candidate to surgical or anesthetic procedure have an increased risk of developing perioperative ventricular arrhythmias. The probability of developing these arrhythmias significantly decreases with a careful pre-, intra- and post-operative management.

Preoperative management

A good anaesthesiological preoperative physical examination should be the cornerstone, mostly in childhood and adolescence. Moreover, an ECG at rest is always needed in order to reveal a QT prolongation. Patients treated with beta-blockers should continue their medication throughout the perioperative period until the operating day. Electrolytes should be normalized. Drugs known to induce TdP (Table 1) should be discontinued or the dose should be decreased if it cannot be discontinued. The presence of a pacemaker or implantable cardioverter defibrillator should be checked.

Perioperative management

Some anesthetics and some drugs used for premedication may lead to QT-prolongation. The torsadogenic effect is related both to the drug and to the anaesthesiological and surgical manoeuvres.

Drugs used for premedication and sedation

Since anxiety and pain can trigger arrhythmias in patients with LQTS, pre-anesthetic medication is recommended. Anesthetic premedication is usually performed using vagolytic and sedative/analgesic drugs. Among these drugs, atropine causes a lengthening of the QT interval and should not be used[22]. On the other hand many studies demonstrated that midazolam does not modify either QT_c or TDR[23,24]; hence, it should be used for premedication in patients with c-LQTS. Midazolam reduces sympathetic activity in unstimulated patients but it does not blunt the hemodynamic response to oral or nasal intubation[23]. Few authors verified the utility of different drugs to prevent lengthening of QTc interval associated to intubation: Owczuk *et al*[25] demonstrated that the use of intravenous lidocaine (1.5 mg/kg) before laryngoscopy and intubation prevented prolongation of the QTc interval induced by the maneuver. Therefore, it seems useful the association of midazolam in premedication and lidocaine before intubation.

Droperidol, used for neuroleptanalgesia in intensive-care treatment since 1970, extends the QTc interval by the IKr current blockade through the HERG channel; because of this effect on QTc this drug was withdrawn from the market in 2001[26,27]. This decision was focus of debate;hence, the drug was licensed again in 2008 and it is used in premedication both for sedation and antiemetic treatment[28-31]. However, Staikou *et al*[32] advise against the use of droperidol in patients with LQTS in a recent review.

Lastly, an adequate sedoanalgesia reduces catecholamine release; the most used drugs are morphine, meperidin and fentanyl. Though the effects of fentanyl on QTc interval are conflicting, fentanyl and morphine have been used in patients with c-LQTS without any adverse effect[17,33-36]. On the other hand, Song *et al*[37] recently re-

Table 1 Drugs that prolong the QT interval and/or induce torsades de pointes

Drugs to be avoided in patients with c-long QT syndrome	
Class	**Generic name**
Anesthetic	Sevoflurane
Anti-anginal	Ranolazine, Bepridil
Anti-arrhythmic	Sotalol, Quinidine, Amiodarone, Ibutilide, Disopyramide, Procainamide, Flecainide, Dofetilide, Dronedarone
Antibiotic	Moxifloxacin, Clarithromycin, Ciprofloxacin, Gemifloxacin, Ofloxacin Telithromycin, Levofloxacin, Roxithromycin, Trimethoprim-Sulfa, Gatifloxacin, Sparfloxacin, Azithromycin Erythromycin
Anti-cancer	Tamoxifen, Lapatinib, Nilotinib, Arsenic trioxide, Eribulin, Sunitinib Vandetanib
Anti-convulsivant	Fosphenytoin, Felbamate
Anti-depressant	Mirtazapine, Citalopram, Venlafaxine, Paroxetine, Fluoxetine, Sertraline, Trazodone, Escitalopram, Clomipramine, Amitriptyline, Imipramine, Nortriptyline, Desipramine, Doxepin, Trimipramine, Protriptyline
Anti-fungal	Voriconazole, Fluconazole, Ketoconazole, Itraconazole
Antihistamine	Astemizole, Terfenadine, Diphenhydramine, Diphenhydramine
Anti-hypertensive	Nicardipine, Isradipine, Moexipril/HCTZ
Anti-infective	Pentamidine
Antilipemic	Probucol
Anti-malarial	Artenimol + piperaquine, Chloroquine, Halofantrine
Anti-mania	Lithium
Anti-nausea/antiemetic	Granisetron, Dolasetron, Ondansetron
Anti-psychotic	Clozapine, Ziprasidone, Thioridazine, Risperidone, Mesoridazine, Quetiapine, Haloperidol, Pimozide, Amisulpride, Sertindole, Sertindole, Iloperidone, Paliperidone, Chlorpromazine
Anti-viral	Foscarnet, Ritonavir, Atazanavir
Appetite suppressant	Phentermine, Fenfluramine, Sibutramine
Bladder Antispasmodic	Tolterodine
α1-blocker	Alfuzosin
Bronchodilator/decongestant	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Metaproterenol, Levalbuterol, Ephedrine, Phenylpropanolamine, Pseudoephedrine
Cholinesterase inhibitor	Galantamine
CNS stimulant	Amphetamine
	Methylphenidate
	Amphetamine
	Dexmethylphenidate
	Methylphenidate
	Lisdexamfetamine
Diuretic	Indapamide
Dopaminergic/anti-viral/anti-infective/	Amantadine
Endocrine	Ocreotide
GI stimulant	Cisapride
H2-receptor antagonist	Famotidine
Imaging contrast agent	Perflutren lipid microspheres
Immunosuppressant	Tacrolimus, Fingolimod
Inotropic agent/vasconstrictor	Dopamine, Isoproterenol, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine
Local anesthetic	Cocaine
Muscarinic receptor anatagonist	Solifenacin
Muscle relaxant	Tizanidine
norepinephrine reuptake inhibitor	Atomoxetine
Opiate agonist	Methadone, Levomethadyl
Oxytocic	Oxytocin
phosphodiesterase inhibitor/vasodilator	Vardenafil
Sedative	Chloral hydrate
Sedative; Anti-nausea/anesthesia adjunct	Droperidol
Uterine relaxant	Ritodrine
Vasconstrictor	Midodrine

A continuously updated list of these drugs is available at www.torsades.org (accessed December 16, 2012). CNS: Central Nervous System.

ported that the intravenous injection of meperidine led to QTc prolongation, polymorphic ventricular tachycardia and ventricular fibrillation, in a 16-year-old boy without neither underlying cardiac disease nor mutation in *LQTS* genes, but with a single nucleotide polymorphism, including H558R in *SCNA5A* and K897T in *KCNH2*. Alfentanil does not extend repolarization time[2]. On the contrary, sufentanil prolongs QTc interval[38].

General anesthesia

Induction and maintenance: Induction of anesthesia can be done using halogenated volatile anesthetics or using intravenous agents, which are distinguished in barbiturates (sodium thiopental) and non barbiturates

Table 2 Normal QT corrected using the Bazzet's formula duration by age and gender

QT corrected using the Bazzet's formula			
QTc value (s)	Children (1-15 yr)	Male (> 15 yr)	Female (> 15 yr)
Normal	< 0.44	< 0.43	< 0.45
Borderline	0.44-0.46	0.43-0.45	0.45-0.46
Prolonged	> 0.46	> 0.45	> 0.46

QTc: QT corrected using the Bazzet's formula.

(Propofol or Ketamine). Maintenance of anesthesia is usually achieved by allowing the patient to breath a carefully controlled mixture of oxygen, nitrous oxide, and a volatile anaesthetic agent or by having a total intravenous anesthesia (TIVA) using intravenous agents in infusion together with analgesia.

Halogenated volatile anesthetics (Halothane, Enfluorane, Isoflurane, Desflurane and Sevoflurane) prolong the QTc interval, even if data is controversial for some of them[39-43]. Isoflurane has been used safely in patients with LQTS[13,44]. Sevoflurane produced significant arrhythmias in a pediatric patient with c-LQTS[10]; moreover, it causes lengthening of QTc interval both in young and adults[5,45-49]. The clinical significance of these findings in patients with LQTS is unclear[50], but it is recommended to avoid these agents.

Thiopental (sodium thiopental) has been used safely in patients with c-LQTS even if it causes QTc prolongation in humans[13,51-53]. Thiopental may reduce TDR through a longer prolongation of the action potential duration in endocardial and epicardial cells compared to M-cell and theoretically it could prevent the spontaneous onset of TdP[51,54].

Data about the effect of Propofol on QTc is conflicting, while we certainly know that this drug does not modify TDR[55-58]. Moreover, Propofol rapidly reverses Sevoflurane-induced QTc prolongation in healthy patients and therefore may be beneficial[59]. Although Ketamine was used in premedication in children with undiagnosed c-LQTS, it is not recommended in patients with LQTS because its sympathomimetic properties can favor incidents of TdP[51]. Etomidate does not affect the duration of ventricular repolarization[25,60]. However, Erdil *et al*[61] compared the effect of Propofol and Etomidate during electroconvulsive therapy, which may cause an acute rise in QT dispersion, and they found out that Etomidate increased QT more than Propofol.

Anesthesiologic maneuvers

Intubation and extubation: Usually the prophylactic administration of muscle relaxants eases intubation. Succinylcholine has been used in some patients with c-LQTS but it may either prolongs the QT interval in patients with c-LQTS, especially during tracheal intubation, or determine a vagal stimulation or result in asystole after pacemaker inhibition by fasciculations; for these reasons it should be avoided[19,22,62-64]. The effects of succinylcholine on QTc can be reversed by alfentanil; the same is not possible with fentanyl[65]. Moreover, alfentanil was better than esmolol in preventing the increase in QTi induced by succinylcholine during tracheal intubation[66]. Rocuronium, vecuronium, atracurium, and cisatracurium do not extend the QTc interval and can be used in c-LQTS, while pancuronium should be avoided because of its vagolytic properties and because it caused ventricular fibrillation in a case report[14,23,35,51,52].

Both intubation and extubation may trigger a TdP in patients with c-LQTS: hence, additional care should be taken during these maneuvers and analgesic or beta-blockers should be administered before them. As aforementioned, the use of lidocaine before intubation proved to be safe to prevent arrhythmias[25]. Finally, during ventilation with positive pressure, anesthesiologists should avoid high inspiratory pressure peaks and wide inspiratory/expiratory ratios, since the Valsalva maneuver also prolongs the QTc interval[65].

Postoperative management

Postoperative management of patients with c-LQTS should include the permanence in a postsurgical intensive care unit for at least 24 h, avoiding stimuli that could trigger TdP. An adequate postoperative analgesia and beta-blocking must be guaranteed. Postoperative nausea and vomiting (PONV) prevention can not be performed with setrones (ondansetron, granisetron and dolasetron) in patients with c-LQTS because these drugs block not only the $5HT_3$ receptors but also the HERG channel, determining a prolongation of repolarization. A study by Charbit *et al*[67] demonstrated that 4 mg of ondansetron induced prolongation of the QTc, similar to the effect of 0.75 mg of droperidol, therefore questioning the greater safety of ondansetron when compared to droperidol in the treatment of PONV; Accordingly Staikou *et al*[32] advise against its use in patients with c-LQTS.

CONCLUSION

The prevalence of Long QT syndrome is close to 1/3000-1/5000[68,69]. The QT interval duration is physiologically variable : the QTc is calculated using the Bazett's formula [(QTc = QT/√RR), Table 2][70,71]. Genetic testing can help to recognize specific subtypes of c-LQTS. The most common phenotypes are LQT1, LQT2 and LQT3. People with LQT1, the most common variant of LQTS, are more likely to have a cardiac event during exercise than patients with LQT2 or LQT3. LQT1 is associated with a mutation in the *KvLQT1* gene (also known as KCNQ1), which codes for a protein that co-assembles with another protein (minK) to form the I_{k}-s[72]. In patients with LQT2 arrhythmic events are usually triggered by auditory stimuli or sudden startle[73]. LQT2 is caused by the loss of Ikr[72]. Patients with LQT3 are prone to syncope or cardiac arrest at rest or during sleep; as a matter of fact, their electrocardiographic abnormalities become less marked at increased heart rate[72,74]. Table

Table 3 Electrocardiograph pattern in long QT syndrome

ECG in LQTS	
LQT1	Prolonged QT, T wave normal or with increased amplitude with a wide base
LQT2	Prolonged QT, T wave with low amplitude and often bifid
LQT3	Late onset of the T wave, prolonged isoelectric segment

ECG: Electrocardiography; LQTS : Long QT syndrome.

3 shows the electrocardiographic patterns of the most common phenotypes of LQTS. Both in the a-LQTS and in the c-LQTS, the blockade of ionic channels, the lengthening of the QT interval and the intensification of QTD can provoke the induction of TdP[75]. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of TdP and malignant arrhythmias. We speculate that genetic subtyping of patients with LQTS could help tailor anesthetic therapy for these high-risk patients.

Actually, there are no definitive guidelines for pre-, peri- and post-operative anesthetic management of c-LQTS. After reviewing the literature, we furnish some key points for preoperative optimization, intraoperative anesthetic agents and postoperative care plan that may be the best for patients with c-LQTS who undergo surgery. In the preoperative period it is necessary to calculate QTc, perform a 12-lead ECG at rest, discontinue or decrease the dose of drugs which could increase QTc interval and trigger a TdP in these patients (Table 1), continue beta-blocking therapy until the operating day and maintain calm and quiet environment. Defibrillator must be available for immediate use during the perioperative period.

In the perioperative period, it would be better to do premedication with midazolam, sedoanalgesia with morphine or fentanyl, induction and maintenance of anesthesia with thiopental or propofol TIVA avoiding halogenated volatile anesthetics and ketamine. Before intubation and extubation, the use of a topic anesthetic, an analgesic or a beta-blocker could be recommended. Among muscle relaxant drugs, we should prefer vecuronium and atracurium. It is important to monitor not only heart rate, blood pressure, oximetry, capnometry but also ECG in at least two leads, as short episodes of TdP are hardly distinguished from monomorphic VT, when traced in one lead. In the postoperative the patient must be monitored and ECG should last until patient emerges from anesthesia and QTc turns into preoperative values. Any kind of stimulus should be avoided since they could trigger TdP and pain must be adequately controlled.

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