AEJ ANESTHESIA EJOURNAL
Volume 12- No. 1 2024

Congenital Long QT Syndrome: A Cardiac Ion Channelopathy with Important Anesthetic Considerations

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Grant/Financial Support:
None

KEYWORDS: Long QT syndrome, cardiac ion channel, Channelopathy

Abstract

Congenital long QT syndrome (cLQTS) is the most common genetic cardiac ion channelopathy in the US. Patients with cLQTS are at risk for ventricular tachycardia (VT) in the "torsades de pointes" (TdP) pattern from physical and emotional stress, including during the perioperative period. This narrative review outlines the history and pathophysiology of the most common types of cLQTS, describes treatments for cLQTS, discusses the experience of anesthesia providers with cLQTS, and reports recommendations for safe administration of anesthesia to these patients. No definitive guidelines exist for the anesthetic management of patients with cLQTS, therefore the anesthesia provider must rely on existing evidence to choose a safe anesthetic for this challenging patient population.

Introduction

Congenital cardiac ion channelopathies are familial syndromes caused by mutations in the genes coding for cardiac ion channel proteins.[1] Congenital long QT syndrome (cLQTS) is the most common congenital cardiac ion channelopathy in the US.[2] It is present in apparently healthy patients with structurally normal hearts and can cause premature ventricular contractions (PVCs), initiating ventricular tachycardia (VT) in the "torsades de pointes" (TdP) pattern in which the QRS complex "twists" around the isoelectric line of the ECG. TdP can lead to ventricular fibrillation (VF) and sudden arrhythmic cardiac death (SCD).[3] The ventricular ectopy of cLQTS can be triggered by adrenergic stimulation, including from physical and emotional stress[1], or during the perioperative period.[4]

The likelihood of an anesthesia provider encountering a patient with LQTS may be increased due to: 1) some patients (including young children) with cLQTS benefit from implantable cardioverter defibrillators (ICDs)[5] or cardiac sympathetic denervation[6,7] and will need anesthesia for the device insertion or surgery[8,9], and 2) people with one subtype of cLQTS (LQT1) are often born with congenital sensorineural deafness[10] and may present for cochlear implants.[11]

This paper is a narrative literature review of cLQTS focusing on the anesthesia implications of the most common types (LQT1 through 3). cLQTS is of interest to anesthesia providers because patients with cLQTS may require anesthesia for any reason and for issues related to cLQTS, and because cLQTS can produce sudden cardiac death in the perioperative period. The goals of paper of this paper are to:

- Review the history and pathophysiology of cLQTS,
- Describe common treatments for cLQTS,
- Discuss the experience of anesthesia providers with patients with cLQTS, and
- Report recommendations for safe administration of anesthesia to these patients.

Methods

Searches of MEDLINE (PubMed) and Google Scholar were conducted using the terms "congenital long QT syndrome", "LQTS", and "cardiac ion channelopathy" combined with "surgery" and "anesthesia". Further relevant articles were identified from the bibliographies of these sources. A total of 215 articles were reviewed and 49 selected for inclusion based on relevance, scope, and unique information.

Results

History of cLQTS: cLQTS was first described in 1957 when Jervell and Lange-Neilsen reported a family in which 4 of 6 children had congenital deafness and "fainting spells". Two of the children with fainting spells had prolonged QT intervals and three died suddenly but had no structural cardiac defects on autopsy.[12] In 1964, ECG and genogram analysis of children in "schools for the deaf" showed that the syndrome of congenital deafness, prolonged QT interval, and high risk of sudden cardiac death was inherited in an autosomal recessive pattern.[13] Another family with a history of sudden cardiac death across multiple generations and 3 siblings who had syncopal attacks, prolonged QT intervals, but normal hearing was described by Romano in 1965. The normal hearing and multi-generational presentation in this family suggested a distinct autosomal dominant form of cLQTS.[14]

There are 17 known subtypes of cLQTS (LQT1 – LQT17).[3,15] The genes responsible for the most common types of cLQTS (LQT1 – LQT3) were identified in the 1990s. In 1995 a gene (KCNH2) coding for the cardiac voltage-gated potassium channel which produces the rapid potassium repolarization current (IKr) was found responsible for LQT2[16] and a gene (SCN5A) coding for cardiac voltage-gated sodium channel responsible for the depolarization current (INA) was found responsible for LQT3.[17] A gene (KCNQ1) for the voltage-gated potassium channel producing the slow potassium repolarization current (IKs) was determined responsible for LQT1 in 1997.[18] Subsequently, the genes responsible for rarer types of cLQTS have been identified.[3,15,19,20,21,22]

cLQTS in the general population: The prevalence of cLQTS is 1/2000 live births.[23] Patients with cLQTS are often identified via genetic testing when a family member is diagnosed. They are also diagnosed after episodes of syncope, palpitations, or even after surviving sudden cardiac arrest.[2] If symptomatic, people with cLQTS are usually diagnosed as children, but they may be asymptomatic and undiagnosed well into adulthood.[24] Thus, patients with both diagnosed and undiagnosed cLQTS present for anesthesia.

The triggers for TdP differ by cLQTS subtype. For patients with LQT1, adolescent and preadolescent males are at greatest risk for TdP, which is often triggered by exercise, including swimming. In LQT2, adult female patients are most at risk for TdP, particularly in the postpartum period and when exposed to sudden alarming auditory stimuli. For LQT3, adult males are at greatest risk and TdP commonly occurs during rest or sleep.[3,25] As many as one in five untreated patients with symptomatic cLQTS die within a year but the mortality rate falls to 1% over 15 years with appropriate therapy.[2]

Electrophysiology of cLQTS: The action potential in ventricular cardiac muscle is divided into phases. Beginning at a resting membrane potential of ~ -96 mv, phase 0 is a rapid depolarization to ~ +20 mv caused by the opening of voltage-gated Na+ channels. During phase 1 there is a slight repolarization as Na+ channels close. This repolarization is interrupted by the opening of slow, long acting, voltage-gated (L-type) Ca++ channels. This produces phase 2, a prolonged plateau at ~ +10 mv during which the depolarizing calcium current is balanced by the repolarizing rapid and slow potassium currents (Ikr and IKs). Next the L-type Ca++ channels close and current flow through K+ channels increases. This causes a rapid repolarization (phase 3) that reestablishes the resting membrane potential (phase 4).[1,25,26] On the ECG, the QT interval is measured from the beginning of the QRS complex (ventricular depolarization) to the end of the T wave (ventricular reoperation).[26] However, because depolarization and repolarization are brief events, most of the QT interval reflects the plateau of phase 2.[1] Any channelopathy that prolongs the plateau will lengthen the QT interval.

LQT1, 2, and 3 account for 75 to 85% of cLQTS cases.[2,27] The remaining variants (LQT4 – LQT17) are each responsible for ≤1% of cases.[28] LQT1 and LQT2 are caused by loss of function

mutations to genes (KCNQ1 and KCNH2) coding for the K+ channels responsible for the IKs and IKr currents that cause cardiac repolarization. These mutations delay repolarization. LQT3 is caused a gain of function mutation in the gene (SCN5A) coding for the Na+ channel responsible for the depolarizing INA current. This mutation delays inactivation of the channel. All three prolong phase 2 of the cardiac action potential and the QT interval.[15,27]

Voltage gated ion channels, including the L-type Ca++ channel, generally enter a refractory period after closing. Normally, by the time the L-type Ca++ channel leaves its refractory state the cardiac myocyte membrane has repolarized and the channel is not reactivated. However, in patients with cLQTS, the L-type Ca++ channels of some cardiac myocytes leave their refractory period before the end of the prolonged plateau phase when the membrane is still depolarized. The L-type Ca++ channels are reactivated in a process known as an "early afterdepolarization" and cause a premature ventricular contraction (PVC).[1,2,27]

Because different areas of the ventricular myocardium repolarize at different rates, a single PVC can give rise to VT via a reentry mechanism. This VT takes the form of TdP as the depolarization pathway circling the ventricle changes.[2,28]

Sympathetic stimulation, with its tachycardia, put patients with cLQTS, particularly those with LQT1 and 2, at risk for TdP. In the normal heart, sympathetic stimulation activates potassium channels responsible for the IKs current and repolarization so that the duration of the cardiac action potential, and the QT interval, shorten as the heart rate increases and the RR interval decreases. (The RR interval is the time, in seconds, between consecutive R waves.) This allows the myocardium to repolarize fully before the next normal depolarization occurs. However, in LQT1 the channel responsible for IKs does not respond to sympathetic stimulation, the QT interval is not shortened as heart rate increases, parts of the myocardium remain depolarized, and L-type calcium channels can cause early afterdepolarizations giving rise to TdP. The normal inverse relationship between the QT interval and the heart rate also explains why the raw QT interval length must be corrected for heart rate to assess if the QT interval is prolonged.[1,25]

Diagnosis of cLQTS: The possibility of cLQTS should be investigated in patients with QT intervals corrected for heart rate (QTc) calculated using the Bazett formula (QTc=QT/ √RR interval) > 440 ms for males and > 460 ms for females (normal values). A definitive diagnosis is based on the extent of QTc prolongation and also requires consideration of other ECG issues (abnormal T waves or a history of TdP), clinical history of episodes suggesting cLQTS (syncope or palpitations), and family history of cLQTS or sudden cardiac death. The "Schwartz Criteria" delivers a diagnostic score based on these criteria and the anesthesia provider should consult the following references for a full understanding of how this score is determined.[2,24,25,26]

However 20-25% of patients with cLQTS confirmed by genetic testing have normal QT intervals.23 A QTc>500 ms strongly predicts cLQTS in asymptomatic patients with no significant family history.[25]

Variation in T wave morphology, variability in the QT interval, and prolongation of the T wave all reflect abnormal and varying cardiac repolarization rates among different regions of the myocardium and are associated with TdP risk.[25,29] One measure of abnormal and prolonged repolarization, increased transmural dispersion of repolarization (TDR), is quantified as the time from the peak of the T wave to its end (TPE). A prolonged TPE may actually reflect TdP risk more accurately than QTc alone in patients with cLQTS.[26] Values indicating elevated TPE are disease dependent but TPE>113 ms indicates arrhythmia risk in the general population.[25]

Management of cLQTS: Management includes avoiding triggers specific for the patient's cLQTS type and medications that prolong the QT interval.[3,23] QT prolonging antiarrhythmic medications include the class IA antiarrhythmics that slow conduction through the depolarized myocardium and block the IKr current (e.g. quinidine and procainamide) and the class III antiarrhythmics that also block the IKr (including ibutilide and the nonselective beta blocking medication sotalol).[25.26] Amiodarone, a class III antiarrhythmic medication, and verapamil, a calcium channel blocking medication, prolong the QTc and should be avoided in patients with cLQTS[25] but produce a lower risk of TdP, probably because they do not increase TDR.[11,26]

For a full list of medications that prolong the QT interval see www.crediblemeds.org. A discussion of the impact of common perianesthetic agents on the QT interval is included in the section on "Induction & maintenance of anesthesia" below.

Long-acting ß receptor antagonists are the mainstay of cLQTS medical treatment.[3,23] However, they may be more effective for patients with LQT1, where they almost completely eliminate TdP episodes, than in LQT2 and 3.[2] Sodium channel blocking medications (e.g. mexiletine) can be added to beta blocking therapy for some patients with LQT[3.23] Their efficacy may depend on the patient's specific mutation.[2]

Implantable cardioverter defibrillators (ICDs) are recommended for patients with cLQTS who have survived an episode of SCD or who continue to experience syncope despite ß receptor antagonists. But they are not without complications, including inappropriate shocks and the necessity of periodic additional procedures.[3,5,23,30]

First evaluated in 1991, left cardiac sympathetic denervation (LCSD) also shortens the QTc and can prevent episodes of TdP in 50% or more of symptomatic patients with cLQTS.[6,30] LCSD is used for patients with cLQTS who remain symptomatic on optimized beta blocking therapy and for young children who are at higher risk for complications of ICD insertion.[23]

The procedure is generally performed with the patient in the right lateral decubitus position. It can be accomplished either with thoracotomy or via minimally invasive video-assisted thoracoscopic surgery (VATS) but one-lung ventilation is usually required.[30,31]

The mechanism by which LCSD reduces arrhythmias in patients with cLQTS is multifaceted. LCSD prevents efferent adrenergic outflow to the heart from the left sympathetic ganglia, reducing tachycardia and increasing the electrical stability of the myocardium. It also may increase parasympathetic cardiac efferent activity both by removing the sympathetic cardiac afferent pathways that usually inhibit it and by preventing release of the long-acting cardiac sympathetic co-transmitter neuropeptide Y (NPY), an inhibitor of postganglionic parasympathetic cardiac acetylcholine release.[7]

Discussion

While there are no definitive guidelines for the anesthetic management of patients with cLQTS, much can be learned from case studies and the recommendations of authoritative review articles.

Preoperative period: Patients with diagnosed cLQTS requiring anesthesia will usually, but not always, be receiving ß receptor antagonists preoperatively.[32,33] These medications must be continued on the day of surgery[25], a precaution that has been called the most important preoperative intervention to reduce perioperative TdP risk in cLQTS, although adherence is not absolute.[33]

During the immediate preoperative period, patients with cLQTS should be maintained in quiet, warm surroundings and should receive adequate preoperative medication to reduce the sympathetic activity that accompanies anxiety.[11,25] For pediatric patients with cLQTS, anxiolysis has been accomplished with midazolam.[34,35,36] Additional preoperative precautions for patients with cLQTS include cardiology consultation and scrutiny of the 12-lead ECG (including measurement of a baseline QTc), correction of electrolyte imbalances that can lengthen the QT interval (e,g, hypokalemia, hypomagnesemia, and hypocalcemia) and the placement of external defibrillator pads.[11,25]

Patients with cLQTS who have ICDs should have the device's function checked by a cardiologist.[25,35,37] The importance of this precaution is illustrated by the case of a 7-year-old child with LQT2 and an ICD who presented for myringotomy. After general anesthesia was induced with sevoflurane the patient developed TdP but the ICD failed to function. The child was successfully defibrillated with an external defibrillator and the surgical procedure was cancelled. A postoperative chest x-ray revealed a fractured ICD wire.[36]

Intraoperatively, electromagnetic interference in the function of an ICD, particularly the use of monopolar electrosurgery superior to the umbilicus, is a concern.[38] ICDs can be left on if the surgery allows[35] but turning off the antitachyarrhythmia functions of an ICD can prevent unnecessary shocks.[38] In some centers, ICDs are turned off for patients with cLQTS who are not pacemaker dependent once defibrillator pads and cardiac monitoring are instituted before induction.[34]

Induction & maintenance of anesthesia: General anesthesia may prolong the QT interval even in patients without cLQTS[39] possibly because hypothermia and positive pressure ventilation both prolong the QTc.[11] Neuraxial anesthesia has been used successfully in patients with cLQTS, including LQT2[40], although it also may prolong the QTc.[39] During neuraxial anesthesia, the QTc prolonging effects of local anesthetic agents mostly occur if the drugs enter the systemic circulation at high levels.[41] Epidural anesthesia, which allows the gradual establishment of the desired level of sympathetic block to avoid hypotension, may be safer than "one shot" spinal blocks[4,37] and epidural catheter insertion for intra and postoperative analgesia has also been successful.[35]

Among intravenous (IV) anesthetic agents, ketamine increases the QTc and TdP risk via its sympathomimetic properties and should be avoided in patients with LTQS. Propofol, midazolam, and fentanyl (and fentanyl analogues) do not increase QTc significantly and have all been used effectively. Halogenated volatile anesthetics generally increase the QTc by blocking the IKr and IKs currents responsible for repolarization.[25,42,43,44] Sevoflurane has seen extensive use in patients with cLQTS. However, even sevoflurane is listed among medications that prolong the QTc increasing TdP risk[25,29], and expert consensus on the management of patients with cLQTS recommends avoiding all QTc prolonging medications.[23]

Two centers that regularly perform cochlear implant surgery report the use of total IV anesthesia (TIVA) with propofol, fentanyl (or an analogue), and a nondepolarizing muscle relaxant either exclusively[45] or preferentially[11] for patients with cLQTS (presumably mostly LQT1 and all patients ≤ 8 years of age) undergoing these procedures. Potentially life-threatening perioperative arrhythmias occurred in 5 of the 45 (11%) cases in these two series, all of which were treated successfully with cardiac pacing. Practitioners in these (and other) centers also administer magnesium IV prophylactically in this patient population to block calcium currents and reduce TdP risk.[4,11,35,45] Suxamethonium should not be used because it induces potassium shifts and causes sympathetic stimulation. Pancuronium is also a poor choice for a muscle relaxant for patients with cLQTS because of its parasympathetic blocking properties.[11]

Two case series of pediatric patients with cLQTS undergoing general anesthesia for a range of procedures, some of which were LQTS-related (eg, ICD insertion), may provide more generalizable results. A total of 179 patients underwent 272 procedures and 194 of these encounters (71%) involved exposure to inhalation anesthetics. Adverse events including TdP occurred during 8/272 (3%) of these procedures. Five of these adverse events occurred in patients undergoing LQTS-related procedures, including 3 TdP episodes in neonates in the first day of life.[32,33]

In a case series of 22 patients ages 1 month to 17 years undergoing LCSD with general anesthesia (20 of whom had cLQTS) sevoflurane was employed as the induction agent for 11 (50%) while 10 (45%) received propofol. Anesthesia was maintained with inhalation agents (predominantly isoflurane) in 19/22 = 86% of cases. No anesthetic complications occurred.[35] The apparent low risk of sevoflurane for patients with cLQTS may be explained by the results of a randomized controlled study that assigned healthy children (age 1-16 years) scheduled for elective surgery to receive either TIVA with propofol or inhalation anesthesia with sevoflurane. Propofol increased neither the QTc nor the TDR as measured by TPE. Sevoflurane increased the QTC but not the TPE.[33]

Sevoflurane was also employed for anesthetic induction for a 17-month-old patient with cLQTS (presumably LQT1) undergoing cochlear implants[47] and an 11-year-old patient with epilepsy and LQT2 undergoing an MRI.[47] In both cases, the airway was secured following the administration of propofol IV and general anesthesia was maintained with sevoflurane and propofol. No anesthetic complications occurred. Similarly, a 5-year-old undergoing LCSD had anesthesia induced and underwent tracheal intubation following administration of fentanyl, propofol, and a nondepolarizing muscle relaxant. Anesthesia was maintained with sevoflurane, fentanyl, and an epidural block without incident. (These cases also highlight the importance of suppressing the sympathetic response to laryngoscopy with adequate IV medications including propofol and fentanyl or an analogue.[11,43])

Sevoflurane anesthesia has been associated with TdP in patients with cLQTS, however. The 7-year-old patient with LQT2 who developed TdP after sevoflurane induction was described above.[37] Similarly, an adult with LQT2 experienced TdP during anesthesia with sevoflurane. As in the pediatric case, TdP for this adult was terminated with external defibrillation. Then magnesium sulfate was administered IV, and an isoproterenol infusion (shortens the QTc) begun. The patient's QTc was 497 ms preoperatively, 534 ms on the morning of postoperative day 1, and 495 ms later that day. The patient subsequently revealed that they had not taken prescribed ß receptor antagonists for 2 days before surgery.[44] There is also a report of 4-year-old patient with undiagnosed cLQTs undergoing surgical correction of velopharyngeal dysfunction. While the patient was under sevoflurane anesthesia, the surgeon injected 1 ml of 1% lidocaine with 1:100,000 epinephrine into the surgical field, the patient's heart rate increased from 113 bpm to 175 bpm, and TdP developed – which resolved spontaneously in 60 seconds.[48] This case illustrates why some authors suggest that local anesthetics with epinephrine are contraindicated in patients with cLQTS.[25]

Treatment of intraoperative TdP: If TdP does develop in patients with cLQTS under anesthesia the provider should discontinue the use of QT-prolonging medications (e.g. switch from inhalation anesthesia to TIVA) and treat with IV magnesium sulfate, ß receptor antagonists (e.g. esmolol), and lidocaine, as well as cardiac pacing if needed.[4,11,25,37,43] (The equipment to establish transvenous cardiac pacing/ defibrillation should be available in the OR prior to induction.[11]) If TdP deteriorates into VF, standard resuscitation including external defibrillation has been used successfully.[37,45]

Emergence from anesthesia: Three patients, ages 11 to 15 years, with cLQTS developed arrhythmias (2 including VT) during emergence from general anesthesia with inhalation agents and directly after receiving anticholinesterase/ anticholinergic medications to reverse nondepolarizing neuromuscular blockage as well as ondansetron as prophylaxis against postoperative nausea and vomiting (PONV). All were treated successfully with ß receptor antagonists and/or lidocaine.[32] Anticholinesterase/ anticholinergic drug combinations as well as the antiemetics ondansetron and droperidol carry TdP risk for patients with cLQTS.[25,29] Dexamethasone has been used safely as an antiemetic.[11,35,47] Sugammadex does not substantially prolong the QTc – at least among healthy patients.[25]

The importance of preventing PONV in patients with cLQTS is illustrated by the case of an adult patient with syncope but no known cLQTS. This patient suffered from chronic diarrhea and was scheduled for esophagogastroduodenoscopy under monitored anesthesia care. After an uneventful procedure, the patient experienced PONV in the post anesthesia care unit (PACU) and received ondansetron and promethazine. About 1 hour later they developed a tachycardia (later identified as TdP) and then pulseless ventricular fibrillation, successfully treated with chest compressions and defibrillation. After resuscitation, the cQT was >600 ms and the serum potassium = 2.4 mmol/L. The patient received magnesium and potassium replacement IV.[49] The initial symptom of diarrhea, the pre-procedure bowel prep, and the PONV may all have contributed to the hypokalemia that sparked this episode.

Summary and conclusions

Patients with cLQTS are a high-risk population and require special anesthetic precautions. The findings of this narrative review can be summarized as follows:

- The most common types of cLQTS (LQT1-3) are caused by defects in genes coding for myocardial potassium or sodium channels. They cause delayed repolarization, a prolonged QTc, a prolonged TPE, and an elevated risk of sudden cardiac death.
- cLQTS is diagnosed with the Schwartz Criteria and treated with ß receptor antagonists, ICDs, and LCSD.
- Pre-anesthetic precautions include the following:
    - Consider cardiology consultation,
    - Have function of the ICD (if present) checked,
    - Determine baseline QTc,
    - Correct any electrolyte imbalances,
    - Premedicate to prevent anxiety,
    - Use of a warm, quiet preoperative waiting area, and
    - Continue ß receptor antagonists on the day of surgery.
- Intraoperative, the anesthesia provider should:
    - Apply external defibrillator pads and all standard monitors prior to induction,
    - Turn off ICD or adjust its settings to avoid electromagnetic interference,
    - Monitor the QT interval,
    - Have magnesium salts ready for administration if TdP develops and consider prophylactic administration for high-risk patients,
    - Consider TIVA and consider the use of sevoflurane if an inhalation agent is needed,
    - Use propofol and/or fentanyl (or an analogue) to blunt the sympathetic response of airway manipulation,
    - Avoid ketamine, suxamethonium, and pancuronium, and
    - Maintain normothermia and avoid high inspiratory pressures.
- If TdP does develop, the anesthesia provider should be prepared to:
    - Give magnesium salts IV,
    - Consider administration of ß receptor antagonists and lidocaine,
    - Initiate cardiac pacing if pharmacologic treatment unsuccessful, and
    - Initiate standard resuscitation including defibrillation if needed.
- During emergence for anesthesia and in the PACU, the provider should:
    - Consider alternatives to anticholinesterase/ anticholinergic drug combinations,
    - Avoid droperidol or ondansetron but consider the use of dexamethasone as prophylaxis against PONV,
    - Maintain the patient in a warm, quiet environment,
    - Be aware that TdP may occur in the PACU.

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SUMMARY OF KEY POINTS

- The most common types of cLQTS (LQT1-3) are caused by defects in genes coding for myocardial potassium or sodium channels. Patients with cLQTS are at risk for VT in the TdP pattern from adrenergic stimulation, including that which occurs during the perioperative period.
- cLQTS is diagnosed using the Schwartz Criteria and treated with ß receptor antagonists, ICDs, and LCSD.
- Pre-anesthetic precautions include cardiology consult, determining a baseline QTc, correcting electrolyte imbalances, premedicating to prevent anxiety, using a warm quite preoperative waiting area, and continuing beta blocking medications on the day of surgery.
- Intraoperative precautions include applying external defibrillation pads and all monitors prior to induction, ensuring that no electromagnetic interference occurs to the ICD, monitoring the QT interval, avoiding medications that prolong the QT interval, blunting the adrenergic response to laryngoscopy with adequate medication, considering TIVA but favoring the use of sevoflurane if an inhalation agent is required, maintaining normothermia, avoiding high inspiratory pressures, and being prepared to administer magnesium salts IV if TdP develops.
- During emergence from anesthesia the provider should consider alternatives to anticholinesterase/ anticholinergic drug combinations, consider the use of dexamethasone as prophylaxis against PONV, maintain the patient in a warm, quiet environment, and be aware that TdP may occur in the PACU.