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CASE REPORTS/CASE SERIES

Ventricular tachycardia after ondansetron administration in a child with undiagnosed long QT syndrome

Tachycardie ventriculaire après l'administration d'ondansétron chez une enfant souffrant d'un syndrome du QT long congénital non diagnostiqué

Kyle McKechnie, MD · Alison Froese, MD

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Abstract

Purpose *To describe a case of ventricular tachycardia after co-administration of ondansetron and dimenhydrinate to a child with occult congenital QT prolongation.*

Clinical features *A previously healthy 11-yr-old girl presented for surgical excision of a thyroglossal duct cyst under general anesthesia. Induction and maintenance of anesthesia were unremarkable, and the surgery was carried out without incident. Prior to emergence, ondansetron 0.1 mg·kg^{-1} and dimenhydrinate 0.4 mg·kg^{-1} were administered. Within approximately two minutes, polymorphic premature ventricular contractions developed and, subsequently, polymorphic ventricular tachycardia ensued. A 12-lead electrocardiogram revealed a profoundly prolonged QT interval that decreased but failed to normalize completely postoperatively. Our patient was diagnosed subsequently with congenital QT prolongation.*

Conclusion *The QT interval is prolonged by the administration of ondansetron in a manner similar to that seen with droperidol, whereas dimenhydrinate is not considered to exert significant effects on the QT interval. Individuals with occult QT prolongation are at risk of experiencing malignant dysrhythmias when ondansetron is administered, especially in conjunction with anesthetic agents that also prolong the QT. The incidence of congenital QT prolongation in the general population has been estimated to be 1:2,500, and it may be undiagnosed preoperatively, especially in pediatric patients.*

K. McKechnie, MD (✉) · A. Froese, MD
Department of Anesthesiology and Perioperative Medicine,
Kingston General Hospital, 76 Stuart St, Victory 2, Kingston,
ON K7L 2V7, Canada
e-mail: kylemckechnie@gmail.com

Résumé

Objectif *Décrire un cas de tachycardie ventriculaire après l'administration concomitante d'ondansétron et de dimenhydrinate à une enfant souffrant d'une prolongation du QT congénitale occulte.*

Éléments cliniques *Une enfant de 11 ans auparavant en bonne santé s'est présentée pour l'excision chirurgicale d'un kyste du canal thyréoglosse sous anesthésie générale. L'induction et le maintien de l'anesthésie étaient sans particularité, et la chirurgie a été réalisée sans incident. Avant le réveil, de l'ondansétron 0,1 mg·kg^{-1} et du dimenhydrinate 0,4 mg·kg^{-1} ont été administrés. Dans un intervalle de deux minutes environ, des contractions ventriculaires prématurées polymorphes se sont manifestées, et une tachycardie ventriculaire polymorphe est apparue par la suite. L'électrocardiogramme à 12 dérivations a révélé un intervalle QT profondément prolongé qui a diminué mais n'est pas complètement retourné à la normale après l'opération. Par la suite, une prolongation du QT congénitale a été diagnostiquée chez notre patiente.*

Conclusion *L'intervalle QT est prolongé par l'administration d'ondansétron d'une façon semblable à ce que l'on peut observer avec le dropéridol, alors que le dimenhydrinate n'est pas considéré comme exerçant des effets significatifs sur l'intervalle QT. Les personnes souffrant d'une prolongation occulte du QT courent le risque de souffrir de dysrythmies malignes lors de l'administration d'ondansétron, particulièrement s'il est administré simultanément à d'autres agents anesthésiques qui prolongent également l'intervalle QT. L'incidence de prolongation du QT congénitale dans la population générale a été estimée à environ 1: 2500, et cette pathologie pourrait ne pas être diagnostiquée avant l'opération, particulièrement chez les enfants.*

Both ondansetron and dimenhydrinate are used extensively for the prophylaxis and treatment of postoperative nausea and vomiting (PONV) in children, and they have well-established safety records in this respect.[1,2] Prior to the implementation of the Federal Drug Administration's (FDA) black box warning in 2001, droperidol was also commonly used for this purpose. The rationale behind the restriction of droperidol administration was largely related to its QT-prolonging effect. Ironically, ondansetron, which was popularized as a safe alternative to droperidol, elicits similar changes in the QT interval.[3] This issue becomes an important consideration in the anesthetic management of patients with baseline congenital or acquired causes of QT prolongation. In contrast, dimenhydrinate is not considered to have significant effects on the QT interval.[4] We report a case of intraoperative ventricular tachycardia in an anesthetized child with previously undiagnosed congenital prolonged QT syndrome after the co-administration of ondansetron and dimenhydrinate. Consent for publication of this report was received in writing from the child's mother.

Case report

A previously healthy 11-yr-old girl (weight, 35 kg) presented for surgical excision of a thyroglossal duct cyst. She had no drug allergies but reported rashes with citric acid ingestion. Her exercise tolerance was normal and she regularly participated in physical activity. There was no family history of sudden death or dysrhythmias. A soft tissue ultrasound revealed a 12 × 8 mm inhomogeneous mass in her submandibular suprahyoid triangle within the midline, in keeping with an infected thyroglossal duct cyst. As the child was afebrile, had normal vital signs, and did not appear toxic, no other investigations were performed preoperatively.

During her preoperative assessment, our patient and her family expressed concerns regarding the potential for PONV. As such, it was decided to incorporate PONV prophylaxis into the anesthetic plan. No premedication was administered. An inhalational induction was performed with 4% sevoflurane in 50% nitrous oxide and 50% oxygen. Subsequently, nitrous oxide was discontinued, intravenous access was established, and remifentanil 50 μg (1.4 $\mu g \cdot kg^{-1}$) along with rocuronium 10 mg (0.3 $mg \cdot kg^{-1}$) were administered prior to an uneventful tracheal intubation with a cuffed 5.5 endotracheal tube. Dexamethasone 3.5 mg (0.1 $mg \cdot kg^{-1}$) was then administered for PONV prophylaxis. Anesthesia was maintained with 2% sevoflurane in 50% oxygen. A normal end-tidal CO_2 concentration was maintained by means of positive pressure ventilation. No baseline abnormalities were appreciated on the 5-lead electrocardiogram (ECG).

The surgery proceeded as planned, and excision of the cyst was completed without any difficulties. Although blood loss was minimal, crystalloid 700 mL (20 $mL \cdot kg^{-1}$) was administered during the 70 min procedure. As the incision was being closed, ondansetron 0.1 $mg \cdot kg^{-1}$ (as per our institution's protocol for pediatric patients) and dimenhydrinate 0.4 $mg \cdot kg^{-1}$ were administered for further PONV prophylaxis. Residual neuromuscular blockade was ruled out by eliciting a five-second tetanic contraction of abductor pollicis using a nerve stimulator at 50 Hz, and our patient was allowed to ventilate spontaneously. Within approximately two minutes, she began to experience frequent polymorphic premature ventricular contractions (PVCs) that rapidly degenerated into polymorphic ventricular tachycardia (PVT). Unfortunately, no rhythm strip was printed. One hundred percent oxygen was administered and the surgical team was asked to verify the presence of a carotid pulse. Polymorphic ventricular tachycardia persisted for approximately ten seconds before spontaneous conversion to sinus rhythm, again with polymorphic PVCs. Less than one minute later, as our patient was about to be connected to the defibrillator, she experienced another episode of PVT lasting approximately ten seconds. Subsequently, lidocaine 1 $mg \cdot kg^{-1}$ was administered; a 12-lead ECG was performed, and complete blood count, electrolytes (including calcium, magnesium, and phosphate), blood urea nitrogen, creatinine, blood glucose, and arterial blood gasses were sent for immediate analysis.

The ECG demonstrated normal sinus rhythm with a profoundly prolonged corrected QT (QTc) interval (590 msec) (see the Figure 1). In the event of further dysrhythmia, magnesium 50 $mg \cdot kg^{-1}$ was prepared for administration but was not administered. Blood tests were normal, with the exception of the arterial blood gas, which revealed a respiratory acidosis (pH 7.29, $PaCO_2$ 51 mmHg). This result was not unexpected, as our patient had been ventilating spontaneously in preparation for emergence from general anesthesia. No episodes of desaturation occurred prior to the dysrhythmias.

Subsequently, fentanyl 0.5 $\mu g \cdot kg^{-1}$ was administered for analgesia and sevoflurane was discontinued. Emergence from anesthesia was uneventful, and our patient was transported to the recovery room where she was continuously monitored. Serial ECGs were performed, which demonstrated only partial resolution of the prolonged QTc (nadir 510 msec). Pediatric cardiology was consulted, and our patient was transferred to the pediatric step-down unit for continued cardiac monitoring. The following day, the QTc remained prolonged (490 msec) and the cardiologist made a diagnosis of congenital QT prolongation. This was later confirmed with genetic testing. Ironically, our patient suffered from significant PONV in the step-down unit, despite having received dexamethasone, ondansetron, and

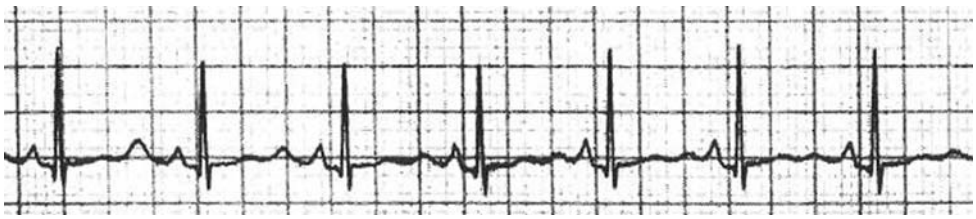

Fig. 1 Rhythm strip (lead II) from our patient's 12-lead electrocardiogram, which was performed after her intraoperative dysrhythmias

dimenhydrinate for prophylaxis. Prior to discharge, beta blockade was initiated with nadolol 20 mg *po* once daily. Following discharge, her family underwent evaluation by cardiology, and our patient's mother was found to be affected on the basis of genetic testing, although she had been asymptomatic her entire life.

Discussion

The prevalence of congenital QT prolongation in the general population is approximately 1 in 2,500-5,000 people.[5,6] It arises as the result of inherited or spontaneous mutations in genes encoding cardiac ion channels responsible for ventricular repolarization. Three particular genes, LQT1, LQT2, and LQT3, are responsible for the majority of cases.[7] Inherited mutations typically follow an autosomal dominant pattern of inheritance, leading to heterozygosity and the Romano-Ward syndrome. However, autosomal recessive mutations may also cause QT prolongation in homozygotes, who usually suffer from congenital deafness. These individuals are referred to as having Jervell and Lange-Nielsen syndrome. In either case, affected individuals are at risk of developing torsades de pointes, syncope, and sudden death, which can sometimes be triggered by emotional or physical stress.[7]

Unfortunately, many of these patients are completely unaware of their condition, and sudden death can be the presenting symptom that leads to diagnosis.[8] In a recent retrospective review of pediatric patients with prolonged QT syndrome, only 17% of cases identified through family screening had experienced any symptoms prior to being diagnosed.[9] With this in mind, it may be prudent to inquire about a family history of serious dysrhythmias during the routine pre-anesthetic assessment. An ECG would be a simple and relatively inexpensive test to perform in individuals with a positive family history, although the resting ECG may still be normal in some individuals with prolonged QT syndrome.[8,10] Unfortunately, a negative family history is an insensitive screening tool for ruling out this condition.[8]

It is well known that individuals with normal cardiac ion channels can also acquire a prolonged QT interval, usually as a consequence of consuming one or more of a host of QT-prolonging medications.[11] In 2001, the FDA issued a black box warning regarding droperidol, on the basis that it prolonged the QT interval, thereby increasing the risk of malignant dysrhythmias such as torsades de pointes. This warning was met with protest by the anesthesiology community, given droperidol's effectiveness as an antiemetic, its low cost and its established safety record when used at antiemetic doses. In fact, a review of 273 adverse events, which were related to droperidol and reported to the FDA from 1997 to 2002, revealed that only ten of these cases were associated with an antiemetic dose of 1.25 mg or less, and most of these cases contained confounding factors that made it impossible to implicate droperidol as the cause of the event.[12] Paradoxically, subsequent to the FDA warning on droperidol, ondansetron became adopted as a widely accepted, albeit far more costly substitute, despite the fact that it was also known to prolong the QT interval.[13,14] More recently, ondansetron and droperidol have been shown to have almost identical effects on the QT intervals of patients being treated for PONV in the recovery room.[3] The mechanism by which ondansetron prolongs QT is via blockade of the human ether-a-go-go-related gene (HERG) potassium channel in the myocardium, leading to disruption of the rapid delayed rectifier potassium current (I_{kr}).[14] This characteristic is shared by several other medications that are better known for their QT prolonging effects, including class III antidysrhythmics, cisapride, and droperidol.[11]

Other antiemetic medications have variable effects on the QT interval. Dimenhydrinate is a first generation H-1 antagonist that has not been linked with significant changes in the QT interval. However, the H-1 antagonist, diphenhydramine, has been infrequently associated with QT prolongation and dysrhythmia, particularly in the setting of overdose.[15,16] Metoclopramide is a central and peripheral dopaminergic receptor antagonist acting at D1 and D2 receptors and is pharmacologically related to the class I antidysrhythmic, procainamide. It has been shown to elicit changes in QT dynamicity and has been associated with cardiac arrest in a critically ill patient with central nervous system pathology.[17,18] The prokinetic agent, domperidone, another D2 receptor antagonist, is more notorious for its QT prolonging effects.[4,17] Prochlorperazine, a phenothiazine antipsychotic, has been shown to block the HERG

potassium channel *in vitro* and has been associated with dysrhythmias in cases of overdose, although toxicity with antiemetic dosages has not been reported.[19,20] Dexamethasone has not been associated with pathologic changes in the QT interval, nor has propofol.[21,22] Of all of the aforementioned antiemetics, only droperidol, ondansetron, and domperidone are listed by the Arizona Center for Education and Research on Therapeutics (qtdrugs.org) as drugs to be avoided for individuals with prolonged QT intervals.[4] Of note, the 5-HT3 receptor blockers, dolasetron and granisetron, and the phenothiazine antipsychotic, chlorpromazine, are also listed.[4]

A number of anesthetic agents are known to prolong the QT interval, notably succinylcholine, sodium thiopental, volatile anesthetics, reversal agents, and opioids such as methadone.[6] As such, prolonged QT intervals have been noted in the recovery room after general anesthesia in up to 20% of patients.[3] When one considers the combined effects of general anesthesia with the considerable emotional and physical stresses of undergoing surgery, individuals with baseline QT prolongation are likely to be particularly vulnerable to dysrhythmias in the perioperative period. At the time we administered ondansetron to our patient, anesthesia was being maintained with sevoflurane, which likely acted synergistically with ondansetron, mild respiratory acidosis, and the stress of undergoing surgery to precipitate the dysrhythmias that occurred.

In cases where prolonged QT has been identified preoperatively, several avenues are available to minimize the risk of perioperative adverse events. The first and foremost strategy is to avoid QT-prolonging medications, which of course mandates careful selection of anesthetic agents. Other options include minimization of sympathetic stimulation and pain and anxiety, perioperative beta blockade, stellate ganglion block on the left side, maintenance of normothermia and normocapnia, magnesium loading, and insertion of an implantable cardiac defibrillator.[6] Regional techniques are safe in these individuals; however, it may be prudent to avoid the addition of epinephrine to local anesthetics. Associated dysrhythmias should be managed according to advanced cardiac life support (ACLS) guidelines.[23] The treatment of choice for torsades de pointes secondary to prolonged QT interval is magnesium sulphate 1-2 g with unsynchronized cardioversion (200 J biphasic, 360 J monophasic, or 1-2 $J \cdot kg^{-1}$ defibrillation in pediatric patients) in cases of hemodynamic instability. Also, lidocaine may be administered at doses of up to 1.5 $mg \cdot kg^{-1}$ with repeated 0.5-0.75 mg doses every five minutes to a maximum dose of 3 $mg \cdot kg^{-1}$. Amiodarone should not be administered, as it prolongs the QT interval. Although isoproterenol may be effective in terminating drug-induced torsades de pointes, it is relatively contraindicated in patients with congenital QT prolongation who may deteriorate with excessive sympathetic stimulation.

In summary, congenital prolongation of the QT interval is a relatively rare condition that increases the risk of perioperative dysrhythmias and sudden death. Affected individuals may be asymptomatic and unaware of their condition. Ondansetron, which was originally marketed as a safe alternative to droperidol for PONV prophylaxis, also prolongs the QT interval, and its administration can precipitate dysrhythmias in susceptible individuals. Current recommendations suggest considering multidrug prophylaxis against PONV that is based on anesthetic, patient, and surgical risk factors.[1] It is prudent to exercise caution when administering multiple agents, given that several of the most commonly used antiemetic agents have the potential to alter the QT interval and that the QT interval is already prolonged in many anesthetized and postoperative patients because of the effects of anesthetic drugs. Since QT prolongation is often a dose-dependent phenomenon, the risk of adverse effects might be reduced by administering the minimal effective dosage of each antiemetic. A comprehensive and up-to-date listing of QT prolonging medications to be avoided in individuals with long QT syndrome can be found at www.qtdrugs.org.[4]

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