orphanaesthesia

Anaesthesia recommendations for

Timothy syndrome

Disease name: Timothy syndrome

ICD 10: 145.8

Synonyms: LQT8, Long QT syndrome type 8, Long QT syndrome-syndactyly syndrome

Disease summary: Timothy Syndrome is one of the many syndromes causing long QT and is referred to as Long QT Syndrome type 8. It was first described by Timothy et al in 2004 and is a rare genetic disorder.

It has a broad spectrum of characteristics that include:

- cardiac arrhythmias (prol. QT/QTc interval, bradycardia, 2:1 AV block, T-wave alternans)
- congenital cardiac defects (PDA, PFO, VSD, tetralogy of Fallot, HOCM)
- syndactaly (variably involving the index, middle, ring and little fingers)
- bilateral cutaneous syndactaly of the second and third toes

The following features have also been described:

- craniofacial characteristics
- immunodeficiency
- neurodevelopment delay
- a tendency to hypoglycaemia
- autistic spectrum disorders

Two forms of Timothy syndrome exist. Type 1 includes all of the characteristic features. Type 2 causes a more severe form of long QT syndrome (LQTS) but does not appear to cause the fusion of interdigital skin.

All cases of Timothy syndrome arise from a mutation if the CACNA1C gene which is located on the short arm of Chromosome 12. This gene encodes the L-type Ca(v)1.2 calcium channel protein. The gene mutation causes a reduction in the inactivation of the calcium channels during the plateau phase of the cardiac action potential. The result is that the calcium channels never close properly allowing excess calcium to influx into the cell. This in turn leads to prolongation of the plateau phase and thus the QT/QTc interval. The clinical implications of this are: an increased risk of spontaneous ventricular tachyarrhythmia, especially tornadoes de points (TdP) and sudden death.

A recent study identified five variants in the CACNA1C gene associated with long QT syndrome, however not all were associated with the phenotypical manifestations of Timothy

syndrome. Timothy syndrome is inherited in an autosomal dominant manner, however, most cases arise as spontaneous mutations rather than from direct parental inheritance.

Tachyarrhythmia is the leading cause of death, followed by infection and complications of intractable hypoglycaemia. The life expectancy of a patient with Timothy Syndrome is 2.5 years, however, as may patients live for much longer, anaesthetists may need to provide anaesthesia to patients of a variety of ages with Timothy syndrome.

ECG findings:

Patients with Timothy syndrome may exhibit a variety of ECG changes as described above. As the QT interval varies with heart rate the QTc is calculated using Bazette's equation:

$$QTC = QT/\sqrt{RR}$$

The QT interval is usually measured in lead II as the T-wave end is usually discrete and the QT interval itself has good correlation with the maximal QT measurement across the entire 12 lead ECG.

T-wave alternans is a pathognomonic feature of LQTS. However, this beat to beat variation in T-wave amplitude has high specificity but very low sensitivity for LQTS.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Corrective cardiac surgery; insertion of implantable automated defibrillator or pacemaker; plastic surgery for the correction of syndactyly.

Type of anaesthesia

There are reports about the use of volatile anaesthetics as well as all intravenous anaesthetics without preference.

The use of ketamine is not recommended.

All types of regional anaesthesia have been described.

During surgery, drugs known to increase the QTc and induce TdP should be avoided. The list of potential drugs is long. A resource providing an up to date list of medications should be regularly consulted, e.g.: www.qtdrugs.org.

Necessary additional pre-operative testing (beside standard care)

Pre-operative planning is of paramount importance and should involve a multidisciplinary team comprising the relevant paediatric surgeon, anaesthetist and paediatric cardiologist.

Pre-operative evaluation must include an ECG. Whilst the calculation of the resting heart rate, QTc interval and recognition of other electrical abnormalities is essential, no recommendations are published regarding the specific cut-offs which may contraindicate surgery. Ambulatory ECG monitoring can be considered to identify the presence, frequency and duration of paroxysmal arrhythmic episodes.

Any pacemaker of implanted internal defibrillator must be checked preoperatively and surgical teams must consider the effect diathermy may have on the device.

Echocardiography should be performed to identify previously undiagnosed congenital structural cardiac defects and to assess cardiac function.

Serum electrolytes, especially potassium, magnesium and calcium, should be measured and corrected. Low levels of these electrolytes predispose to delayed ventricular depolarisation and therefore prolongation of the QT interval.

Patients with proven LQTS require pre-operative treatment; beta blockade is the usual form of pharmacological intervention. Beta blockers maintain QT interval stability and suppress cardiac sympathetic stimulation. Beta blockers should be continued up to and including the morning of surgery. The acute use and effectiveness of beta blocker therapy during and acute arrhythmic crisis during surgery is currently unknown.

As with any anaesthetic candidate, a thorough respiratory history and examination should be performed. In addition to assessing for respiratory sequelae of cardiac function abnormalities, signs of intercurrent infection must be looked for as this may influence the preoperative course.

Particular preparation for airway management

No specific recommendations beside standard care.

Particular preparation for transfusion or administration of blood products

There are no specific recommendations regarding the transfusion or administration of blood products. The maintenance of tissue oxygen delivery should be considered especially in the context of congenital cardiac comorbidity.

Particular preparation for anticoagulation

There are no prerequisites for anticoagulation for the syndrome itself, and no coagulopathies have been described.

However there may be indications for anticoagulation specific to congenital cardiac abnormalities and their subsequent correction.

Particular precautions for positioning, transportation and mobilisation

There are no specific precautions for the mobilisation and positioning of patients with Timothy syndrome.

The transportation of the anaesthetised patient with Timothy syndrome should be performed with the same care as with any anaesthetised patient with full, continuous, invasive monitoring and easy access to emergency resuscitation drugs and equipment. Particular attention must be paid to ensuring an adequate depth of anaesthesia, gentle handing and maintaining a temperature controlled environment.

Interactions of chronic disease and anaesthesia medications

Bradycardia related to adequate beta blockade is common; however, the use of chronotropic drugs may increase the QTc and therefore should be used with caution.

Anaesthetic procedure

Precautions should begin during the immediate pre-operative period and should focus on minimising the stress associated with the impeding surgery. The patient should be kept in a warm, quiet and supportive environment. The application of topical local anaesthetic creams to potential venipuncture sites is advised. There is also a suggestion that sedation prior to venepuncture and cannulation should be considered as the act of venipuncture has been documented to induce arrhythmias.

Adequate sedation and analgesia reduces catecholamine release. Midazolam is considered an appropriate drug for providing sedation as it has no effect on the QTc in healthy adults.

Midazolam reduces sympathetic activity in unstimulated patients, however it does not blunt the haemodynamic response to oral or nasal intubation. Fentanyl and morphine are commonly used analgesics and, whilst the effects of fentanyl on the QTc are conflicting, fentanyl and morphine have been used in patients with congenital LQTS without any adverse effects.

Some literature has advocated the administration of magnesium sulphate prophylactically, even in the presence of normal serum magnesium levels.

Positive pressure ventilation strategies should ensure that sustained high intra thoracic pressures are avoided as this mimics a valsalva manoeuvre, which can lengthen QT intervals in patients who are not fully beta blocked.

The use of central and regional neuroblockade has been described and, if successful, provides excellent analgesia and sympatholysis. However, should any block fail, additional analgesia would be required. Epidural anaesthesia with the gradual establishment of the sympathetic block is preferred to single dose spinal anaesthesia due to the associated lower risk of hypotension with the need for vasopressors. Due to the young age of patients, epidural catheters are placed following the induction of general anaesthesia.

Induction agents:

Induction of anaesthesia can be performed using either halogenated volatile anaesthetics or with intravenous agents. Many anaesthetic drugs are known to prolong the QTc, nevertheless all anaesthetic agents have been successfully used. Halothane, enflurane, isoflurane, desflurane and sevoflurane all prolong the QTc, even if the data available for some of these agents is controversial. Propofol infusion is an alternative to inhaled anaesthetic gases for the maintenance of anaesthesia and is a drug with which most anaesthetists are very familiar.

Ketamine should be avoided in patients with LQTS as its sympathomimetic properties may precipitate the onset of TdP.

Paralytics:

Succinylcholine is known to prolong the QTc. Rocuronium, vecuronium, atracurium and cisatracurium do not prolong the QTc and are considered safe for use in patients with Timothy syndrome.

Intraoperative analgesia:

Case reports describing the use of remifentanyl infusions have suggested that it is an excellent sympatholytic intra-operatively, and also during the induction if anaesthesia.

Vasopressors and chronotropes:

The use of vasopressors in the management of hypotension is a balance of risk. Epinephrine, norepinephrine, ephedrine and phenylephrine are known to increase QTc, however case reports of their successful use are published. The authors would recommend optimisation of fluid balance together with the use of metaraminol as this is not known to prolong the QTc.

Atropine and glycopyrolate are thought to be safe.

Antiemetics:

Droperidrol, domperidone and the 5-HT3 antagonists (e.g., ondansetron) prolong the QTc and should be avoided. Metoclopramide is not contraindicated. However dexamethasone is considered to represent the safest, most effective option.

Particular or additional monitoring

The need for invasive monitoring of this group of patients is determined by the type of surgery being performed. Every patient undergoing general anaesthesia should have continuous ECG monitoring, non-invasive blood pressure monitoring at regular intervals, pulse oximetry and capnography as standard throughout induction, maintenance and emergence.

Anaesthetists should have a low threshold for invasive monitoring, especially an arterial line, considering the risk of tachyarrhythmia with associated cardiac instability. Arterial access would also allow regular glucose and electrolyte monitoring. Volume status must be carefully monitored as beta-blocked patients tolerate hypovolaemia poorly.

Possible complications

The anaesthetist must be prepared to deal with malignant arrhythmias particularity TdP and be aware that the treatment is still empiric without hard evidence. Electrolyte abnormalities, particularly hypokalaemia, should be corrected.

Magnesium is the drug therapy of choice both for the prevention of repeated and treatment of established TdP. An initial bolus of 30mg/kg should be administered over 2-3 minutes followed by an infusion of 2-4mg/kg/hr. For resistant TdP a further bolus may be given after 15 minutes. Plasma magnesium levels should be monitored to avoid toxicity. Magnesium acts as a calcium channel blocker and also promotes membrane stability by the activation of sodium-potassium ATPase.

Intravenous lidocane is also advocated at a dose of 1-2mg/kg. This may be administered either before or with magnesium and may prevent degeneration of the arrhythmia.

Should magnesium prove ineffective temporary overdrive pacing may be necessary. In one case calcium channel blockers and ranolazine has been found effective.

The most serious sequelae of TdP is the progression to ventricular fibrillation. The anaesthetist must be familiar with advanced paediatric life support algorithms and prepared to deliver asynchronous defribillation and chest compressions.

Post-operative care

In the post-operative period, continuous ECG monitoring in a high dependency environment is advised. The environment should be kept quiet, calm and warm in order to reduce sympathetic stimulation. Senior recovery staff is recommended to care for this cohort of patients. There should be easy access to emergency resuscitation equipment and drugs. The duration of ECG monitoring may be required for up to 24 hours post-surgery.

It is important to rapidly recognise and treat post-operative pain, nausea and vomiting, thus reducing the associated sympathetic stimulation.

Serum glucose levels would be monitored as hypoglycaemia is common and poorly tolerated.

Hypothermia prolongs the QTc, so core temperature should be checked regularly and normothermia maintained. Hypothermia can increase the risk of postoperative infection.

In the longer term, patients required a complete bundle of care including a ventilation strategy if not immediately extubated, plus physiotherapy in order to reduce the risk of pneumonia.

Disease-related acute problems and effect on anaesthesia and recovery

None.

Ambulatory anaesthesia

Cases of ambulatory anaesthesia are not reported, most likely due to the nature of the syndrome and the likely surgical procedures. However, the advantages of early mobilisation of patients post-operatively should not be overlooked.

Obstetrical anaesthesia

There are currently no case reports or descriptions of obstetric anaesthetic procedures for patients with Timothy Syndrome. This is most likely attributable to the high infant mortality rate due to significant cardiac comorbidities. However, multiple case reports do exist for obstetric anaesthesia in patients with congenital LQTS.

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