Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

RESEARCH REPORT

# A retrospective review of anesthesia and perioperative care in children with medium-chain acyl-CoA dehydrogenase deficiency

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**What is already known**

- Surgery, fasting, and anesthesia may trigger decompensation in children with medium-chain acyl-CoA dehydrogenase deficiency and propofol may be potentially harmful.

**What this article adds**

- Administering glucose perioperatively is important for preventing hypoglycemia and decompensation, but hyperglycemia is a relatively common complication.
- Propofol as a single bolus at induction appears safe in children with well-controlled medium-chain acyl-CoA dehydrogenase deficiency.

**Keywords**
medium-chain acyl-CoA dehydrogenase; anesthesia; child; humans; lipid metabolism; inborn errors; blood glucose

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Section Editor: Francis Veyckemans

Accepted 31 October 2016

doi:10.1111/pan.13065

## Summary

**Background:** Medium-chain acyl-CoA dehydrogenase deficiency is the most common genetically determined disorder of mitochondrial fatty acid oxidation. Decompensation can result in hypoglycemia, seizures, coma, and death but may be prevented by ensuring glycogen stores do not become depleted. Perioperative care is of interest as surgery, fasting, and infection may all trigger decompensation and the safety of anesthetic agents has been questioned. Current guidelines from the British Inherited Metabolic Disease Group advise on administering fluid containing 10% glucose during the perioperative period.
**Aim:** To review the management of anesthesia and perioperative care for children with medium-chain acyl-CoA dehydrogenase deficiency and determine the frequency and nature of any complications.
**Method:** A retrospective review of case notes of children with medium-chain acyl-CoA dehydrogenase deficiency undergoing anesthesia between 1997 and 2014.
**Results:** Fourteen patients underwent 21 episodes of anesthesia. In 20 episodes, the patient received a glucose-containing fluid during their perioperative fast, of which eight received fluid containing 10% dextrose throughout the entire perioperative period. No episodes of hypoglycemia or decompensation occurred, but perioperative hyperglycemia occurred in five episodes. A propofol bolus was administered at induction in 16 episodes and volatile agents were administered for maintenance of anesthesia in all episodes without any observed complications. In one episode, delayed offset of atracurium was reported.

**Conclusions:** Perioperative metabolic decompensation and hypoglycemia appear to be uncommon in children who are well and receive glucose supplementation. Hyperglycemia may occur as a consequence of surgery and glucose supplementation. Propofol boluses and volatile anesthetic agents were used without any apparent complications. Prolonged action of atracurium was reported in one case, suggesting that nondepolarizing muscle relaxants may have delayed offset in this patient group. We do not recommend any particular approach to anesthesia but would advise administering glucose supplementation according to current guidelines, frequent monitoring of blood glucose perioperatively, and monitoring of neuromuscular blockade.

## Introduction

Medium-chain acyl-CoA dehydrogenase deficiency is the most common genetically determined disorder of mitochondrial fatty acid oxidation. $\beta$-oxidation of fatty acids is an important process for providing energy when hepatic glycogen stores become depleted, for example, during periods of fasting. Fatty acids are metabolized to ketones which become a major energy source for the body after exhaustion of glycogen stores. Failure of this process, as occurs in medium-chain acyl-CoA dehydrogenase deficiency (MCADD), can result in accumulation of fatty acids and an inadequate supply of ketones. Deficiency of the ketone beta-hydroxybutyrate can lead to severe hypoglycemia, and the accumulation of fatty acids and corresponding acylcarnitines can lead to toxic effects on the liver, muscle, and central nervous system (1).

Medium-chain acyl-CoA dehydrogenase deficiency is inherited in an autosomal recessive pattern. It is most prevalent in northern European Caucasians, in whom the incidence is approximately 1/12 000 newborn infants (2). Cases present when challenged with insufficient food intake, usually within the first 2 years of life (3), with the mean age of onset being 12 months (4). However, some patients may live for many years without symptoms, and delayed presentation in adulthood has been reported (5). Typically, presentation is precipitated by a period of fasting or increased energy demand, for example, due to a minor illness or perioperatively. Decompensation usually occurs after 12–16 h of fasting, when glycogen stores become depleted and ketones would usually become the major fuel source.

Features of decompensation include hypoketotic hypoglycemia, lethargy, coma, cardiac arrhythmias vomiting, seizures, and sudden death. Patients may develop acute liver impairment with hepatomegaly and abnormal liver function tests, and encephalopathy may occur with features resembling Reye's syndrome (4,6,7). A period of metabolic decompensation carries a mortality rate of up to 25%, and survivors have a significant risk of developmental disability and long-term illness (7).

Neonatal screening for MCADD is now routine in the UK after being introduced in February 2009 (8,9). If MCADD is diagnosed early and treated effectively, patients have an excellent prognosis. The mainstay of treatment is to avoid of any periods of prolonged fasting and ensure caloric intake is maintained during periods of illness.

Medium-chain acyl-CoA dehydrogenase deficiency has important implications for anesthetists as fasting, surgery, and infection can all trigger decompensation. The surgical stress response may be deranged, and there is also concern about the effects of anesthetic agents on fatty acid metabolism and liver function. Guidelines are available from the British Inherited Metabolic Disease Group (BIMDG) about the management of children with disorders of fatty acid oxidation who undergo surgery (10). The guidelines advise that an infusion of 10% glucose/0.45% saline should be commenced preoperatively and continued until normal feeding is recommenced. This should provide adequate amounts of carbohydrate and minimize catabolism. One case report demonstrated that infusion of 5% glucose may not be sufficient to prevent hypoglycemia (11).

Authors have questioned the safety of propofol in MCADD and other fatty acid oxidation disorders due to the effect of the drug on lipid metabolism and also the fatty acid content of its preparation in soybean oil (12,13). There is also some uncertainty about the safety of inhalational agents in fatty acid oxidation disorders, as they may cause an increase in circulating free fatty acids (13,14). Caution has also been advised when using muscle relaxants, as patients with fatty acid oxidation disorders may demonstrate hypotonia and the action of some muscle relaxants may also be prolonged if hepatic impairment if present (11).

Our center is a tertiary referral center in the North West of England for children with metabolic diseases. We hold a database of all patients with MCADD who have been treated at our center. We conducted a

 

retrospective review of patients with MCADD who had undergone general anesthesia. We aimed to audit perioperative glucose management against current guidelines and assess the adequacy of glycemic control. We examined the choice of anesthetic agents and aimed to identify any complications or episodes of metabolic decompensation.

## Method

We undertook a retrospective audit of patients with MCADD that had undergone general anesthesia for surgery. The audit was approved by the local clinical audit department. Patients with MCADD were identified from our metabolic database. A computerized database search then enabled us to identify which patients had undergone a surgical procedure within our Trust during the last 20 years. We collected data through reviewing the case notes of these patients. For each episode, we recorded starvation times, perioperative fluid regimes, perioperative blood glucose levels, drugs administered during anesthesia, perioperative events, and details of any postoperative complications.

## Results

We identified 15 patients with MCADD who had undergone general anesthesia. Case notes were available for 14 of these patients, who underwent a total of 21 episodes of general anesthesia. Data presented are for these 21 episodes. In two episodes, the patient did not have a diagnosis of MCADD at the time of anesthesia.

The patient demographics are shown in Table 1 and the surgical procedures performed are shown in Table 2. The median duration of anesthetic time was 45 min (range 20 min–5 h).

Of the 21 episodes, 17 were elective and 4 were urgent. There were no emergency cases requiring anesthesia before completing a period of fasting. All patients were starved of food for at least 6 h and clear fluids for at least 2 h before anesthesia. The mean documented actual fasting times were 10 h (range 6–17 h) for food and 8 h (range 2–14 h) for clear fluids. In two episodes, a glucose polymer drink was administered preoperatively. A range of perioperative fluid regimes were used but intravenous fluids containing glucose were given at some point during the perioperative period in all episodes.

**Table 1** Patient demographics

| | | |
|---|---|---|
| Gender | M | 11 |
| | F | 9 |
| Age (years) | 0–3 | 9 |
| | 4–7 | 9 |
| | 8–11 | 0 |
| | 12–16 | 2 |
| Weight (kg) | 0–10 | 5 |
| | 11–20 | 10 |
| | 21–30 | 3 |
| | 31–40 | 0 |
| | 41–50 | 0 |
| | >51 | 2 |

**Table 2** Surgical procedure performed

| | |
|---|---|
| Tonsillectomy/adenoidectomy | 4 |
| Dental extraction | 3 |
| Circumcision | 2 |
| Esophago-gastro-duodenoscopy | 1 |
| Hernia repair | 1 |
| Manipulation under anesthesia of finger | 1 |
| Correction of buried penis | 1 |
| Insertion of testicular prosthesis | 1 |
| Laparoscopy and exploration of undescended testis | 1 |
| Secondary cleft palate repair | 1 |
| Orchidopexy | 1 |
| MUA and K-wire to elbow | 1 |
| Gastrostomy, rigid bronchoscopy, and central line insertion | 1 |
| Repair of esophageal atresia | 1 |

Fluid containing 10% glucose was given preoperatively in 18 episodes, and fluid containing 5% glucose in one episode. No preoperative fluids were given in two episodes. One episode involved a patient who had not been diagnosed with MCADD at the time of anesthesia. The second episode involved a different patient who was not given preoperative fluids due to parental request and instead received a glucose polymer drink. Preoperative infusions started at a mean of 8 h (range 2–15 h) before induction of anesthesia. Infusions were usually commenced at the start of preoperative fasting; however, this was not always possible in patients admitted on the day of surgery. In all episodes, fluid was administered at maintenance rates according to the Holliday Segar formula (24 hourly rate of 100 $ml \cdot kg^{-1}$ for the 1st 10 kg of weight + 50 $ml \cdot kg^{-1}$ for the 2nd 10 kg of weight + 20 $ml \cdot kg^{-1}$ for the remaining weight) (15).

Intra-operatively, fluid containing 10% glucose was given in eight episodes, fluid containing 5% glucose was given in seven episodes, and no fluid was documented in six episodes. Postoperatively, glucose-containing fluids were continued until oral diet had resumed in 20 episodes. In 15 of these episodes, the fluid contained 10% glucose and in three episodes, it contained 5% glucose. There were two episodes where the patient returned to intensive care postoperatively. In these cases, glucose-containing fluids were administered but fluid regimes were frequently changed. In the case where no postoperative fluids were administered, there was no documented reason for their omission.

A bolus of propofol was given at induction in 16/21 episodes. Volatiles were used for maintenance of anesthesia in all episodes, and no propofol infusions were given. A range of other drugs were given intra-operatively, as shown in Table 3.

Blood glucose was measured perioperatively in 19 episodes. There were five episodes where hyperglycemia (defined as blood glucose >11 mmol·l$^{-1}$) occurred. In these episodes, the median peak blood glucose was 17 mmol·l $^{-1}$ (range 12.5–20 mmol·l$^{-1}$). Blood glucose was within the normal range in the remaining 14 cases, with no episodes of hypoglycemia. There were two episodes where no perioperative blood glucose measurement was recorded. One of these episodes involved a child who had not been diagnosed with MCADD at the time of anesthesia and is later described in more detail. The second episode involved a 16-year old who had a general anesthetic lasting 30 min for insertion of a testicular prosthesis and had an uneventful perioperative period.

There were two cases where an additional perioperative event occurred: in one case, bronchospasm and hemodynamic instability occurred, and in another delayed offset of neuromuscular blockade with atracurium was reported requiring an increased dose of neostigmine.

**Table 3** Drugs administered intra-operatively

| | | |
|---|---|---|
| Induction | Propofol | 15 |
| | Sevoflurane | 4 |
| | Sodium thiopental | 1 |
| Maintenance | Sevoflurane | 17 |
| | Isoflurane | 3 |
| Opioids | Fentanyl | 9 |
| | Morphine | 8 |
| Analgesics | Paracetamol | 8 |
| | Diclofenac | 1 |
| Neuromuscular blockers | Atracurium | 8 |
| | Mivacurium | 2 |
| | Suxamethonium | 1 |
| Antiemetics | Ondansetron | 7 |
| | Dexamethasone | 3 |
| Antibiotics | Amoxicillin/Clavulanic acid | 4 |
| | Flucloxacillin | 1 |
| | Benzylpenicillin | 1 |
| | Cefuroxime | 1 |
| Local anesthetics | Lidocaine | 4 |
| | Unnamed | 3 |
| | Levobupivacaine | 2 |
| | Bupivacaine | 1 |
| Cardiovascular | Metaraminol | 2 |
| | Atropine | 1 |
| Miscellaneous | Neostigmine/glycopyrronium | 2 |
| | Hydrocortisone | 1 |
| | Magnesium sulfate | 1 |

The first of these cases was a 6-year-old child who developed severe bronchospasm, hemodynamic instability, and hyperglycemia during anesthesia. Anesthesia was not performed at our center but the patient was later transferred to us for intensive care. The patient had an inhalational induction with sevoflurane and did not receive propofol. After induction, she developed severe bronchospasm and hemodynamic instability which was managed with hydrocortisone, magnesium sulfate, metaraminol, noradrenaline, and dobutamine. After these treatments had been administered, she had a blood glucose reading of 20.5 mmol·l$^{-1}$. She had been receiving 10% glucose at a maintenance rate prior to this, which was changed at this point to 5% glucose/0.45% saline. Her blood glucose returned to the normal range and 10% glucose was then recommenced.

In the second case, a 9-month-old child developed hyperglycemia and was reported to have delayed offset of neuromuscular blockade from atracurium. He received 10% glucose/0.45% saline at a maintenance rate preoperatively, which was changed to 5% glucose/0.45% saline intra-operatively and then back to 10% glucose/0.45% saline postoperatively. Postoperatively his blood sugar was 12.5 mmol·l$^{-1}$. The infusion of 10% glucose/0.45% saline was continued until feeding. His blood glucose subsequently returned to normal. It was documented on the anesthetic chart that there was a delay in the offset of atracurium which had been given at induction as a dose of 0.5 mg·kg$^{-1}$. Neostigmine (100 mcg·kg$^{-1}$) and glycopyrronium (20 mcg·kg$^{-1}$) were given 60 min after induction and the child was extubated uneventfully. After emergence from anesthesia, the patient's blood pressure and heart rate were noted to be raised at 125/70 mmHg and 170 b·min$^{-1}$, respectively. These settled to within normal limits within 30 min of observation.

There were two episodes where the patient had not been diagnosed with MCADD at the time of anesthesia. One case involved a child who had a hernia repair lasting 60 min and received propofol for induction of anesthesia. He received no preoperative or postoperative fluids, but did receive 5% glucose/0.45% saline at a maintenance rate intra-operatively. Blood glucose was not checked perioperatively, but no features of hypo or hyperglycemia were reported.

The second case involved a neonate with congenital anomalies of esophageal atresia, atrial septal defect, and ventricular septal defect. His first anesthetic episode, prior to the diagnosis of MCADD, was for a gastrostomy, rigid bronchoscopy, and central line insertion. He was receiving total parenteral nutrition preoperatively and received 5% glucose/0.45% sodium chloride intra-operatively. His perioperative glucose level was within

normal limits. He was diagnosed with MCADD before his second episode of anesthesia which was for repair of esophageal atresia at the age of 4 months. During this episode, he developed perioperative hyperglycemia. He received an infusion of 10% glucose/0.18% saline preoperatively and intra-operatively and had intra-operative blood glucose reading of 19.9 $mmol \cdot l^{-1}$. At this point the intravenous fluids were stopped for 1 h. The blood sugar subsequently dropped to 10.7 $mmol \cdot l^{-1}$, at which point glucose-containing fluids were restarted.

## Discussion

This is the first review which we have identified examining perioperative care in pediatric patients with MCADD. The review covers a broad age range and includes a variety of surgical procedures which are common among patients in this age group. A range of different anesthetic drugs were used and these represent common current practice in pediatric anesthesia. The review has limitations common to retrospective case note reviews: the case notes were incomplete or unavailable in some cases, we are relying upon the accuracy of data recorded in the case notes and in some cases events were described with limited detail.

All patients were well at the time of surgery and all received glucose-containing fluids at some point during the period of perioperative fasting. Only 8/21 children received fluid containing 10% glucose throughout their perioperative fast, which is the recommendation of the BIMDG guidelines. The current edition of these guidelines, however, was only published in 2013. Prior to this, there was advice in the literature that fluid containing 10% glucose should be administered perioperatively to patients with MCADD (16) but formal guidelines may not have been available.

No episodes of perioperative hypoglycemia or metabolic decompensation were observed. Hypoglycemia is, however, a late event in decompensating fatty acid disorders and its absence does not preclude other biochemical derangement and onset of intoxication. We cannot exclude biochemical disturbances as there was no monitoring of free fatty acids or acylcarnitines performed.

Hyperglycemia occurred in 5 of the 19 episodes where blood glucose was recorded. All cases were managed by adjusting the fluid regime, and insulin was not given in any cases. Hyperglycemia is likely to be attributable to the combination of glucose infusion coupled with the surgical stress response. In both adult and pediatric patients who are well, blood glucose levels tend to increase intra-operatively, even when glucose-containing fluids are not administered. This glycemic response to surgery is exacerbated by concurrent administration of glucose (17). Infusion of 5% glucose is frequently associated with hyperglycemia (18); therefore, it is not surprising to see hyperglycemia when 10% glucose is administered.

The observed frequency of transient hyperglycemia reinforces the importance of frequent perioperative blood glucose monitoring. It is unclear how hyperglycemia should best be managed in this population; there is however no requirement to use insulin perioperatively and it may be safest to continue to administer glucose containing fluids given the potential consequences of metabolic decompensation. To reduce the extent of hyperglycemia, we would recommend taking steps to minimize the surgical stress response, for example, through employing minimally invasive surgery and providing regional anesthesia or analgesia where possible.

There has been concern about the use of propofol and volatiles in children with MCADD. Propofol has effects on fatty acid metabolism which have been increasingly recognized since the discovery of propofol infusion syndrome. Propofol infusion syndrome is a rare condition related to high-dose propofol infusion, and carries a mortality rate of up to 20% (19). The features include bradycardia, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and fatty liver. The underlying mechanism is thought to be due to propofol causing impaired fatty acid metabolism or inhibiting the mitochondrial respiratory chain (20). The features of propofol infusion syndrome have been likened to those of fatty acid oxidation disorders such as MCADD. This, and the concern about the disturbance of fatty acid metabolism caused by propofol and the fatty acid load associated with propofol preparations, has led to recommendations that propofol should be avoided in fatty acid oxidation disorders (12,13). As previously discussed, the concern about volatile agents relates to their potential to increase circulating free fatty acids.

In this review, 16 patients received propofol as a bolus and all 21 patients received volatile agents without any observed complications. Other than the one case where delayed offset of atracurium was reported, there were no reported complications of other anesthetic drugs. It would be unwise to make recommendations for anesthetic management based on a this small dataset; however, our results suggest there is no case for avoiding volatiles or an induction dose of propofol in children with MCADD who are well. It would seem pertinent, however, to use muscle relaxants judiciously and carefully monitor neuromuscular blockade.

It remains unclear which anesthetic agents would be safe to use in the unwell, decompensated MCADD patient presenting for emergency surgery. In these

 

patients, it may be safest to avoid propofol, even for induction of anesthesia, and use an alternative induction agent such as thiopentone or ketamine. If propofol is needed, using a 2% formulation would reduce the fatty acid load. A high-dose opiate, low-dose volatile technique could then be used for maintenance of anesthesia. Were a patient with MCADD to present for spinal surgery when propofol-based total intravenous anesthesia is routinely used to allow somatosensory evoked potentials to be monitored, the anesthetist would be faced with a particularly difficult conundrum.

This review is limited in size but may provide useful information given the limited literature relating to perioperative care in patients with MCADD. Our findings suggest that perioperative metabolic decompensation and hypoglycemia are uncommon in children with MCADD who are well and receive glucose supplementation during the period of perioperative fasting. When delivering perioperative care to patients with MCADD, we recommend administering perioperative carbohydrate supplementation according to BIMDG guidelines and gaining input from a metabolic specialist if possible. Glycemic control should be carefully monitored and postoperative nausea and vomiting minimized so that feeding can be resumed in a timely manner. Further prospective studies would allow further information about perioperative care in MCADD and may provide further guidance about the optimal way to administer general anesthesia.

## Ethical approval

Ethics approval was not necessary for this study.

## Funding

The study was funded by departmental resources.

## Disclosures

The authors report no conflict of interest.

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