Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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VERY LONG-CHAIN ACYL-COENZYME A DEHYDROGENASE DEFICIENCY AND PERIOPERATIVE MANAGEMENT IN ADULT PATIENTS.

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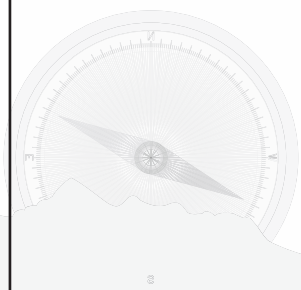

Abstract

Surgery and anaesthesia pose a threat to patients with very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), because prolonged fasting, stress, and pain are known risk factors for the induction of metabolic derangement. The optimal perioperative management in these patients is unknown and the use of volatile agents and agents dissolved in fatty acids have been related to postoperative metabolic complications. However, the occurrence of metabolic derangement is multifactorial and depends, amongst others, on the severity of the mutation and residual enzyme activity. Current guidelines suggest avoiding both volatile anaesthetics as well as propofol, which seriously limits the options for providing safe anaesthesia. Therefore, we reviewed the available literature on the perioperative management of patients with VLCADD. We concluded that the use of some medications, such as volatile anaesthetics, in patients with VLCADD might be wrongfully avoided and could in fact prevent metabolic derangement by the adequate suppression of pain and stress during surgery. We will illustrate this with a case report of an adult VLCADD patient undergoing minor surgery. Besides the use of remifentanil, anaesthesia was uneventfully maintained with the use of sevoflurane, a volatile agent, and continuous glucose infusion. The patient was monitored with a continuous glucose meter and creatinine kinase measurements.

Introduction

In patients with a very long-chain acyl-CoA dehydrogenase deficiency (VLCADD; EC # OMIM201475) the enzyme responsible for one of the first steps in the metabolism of fatty acids is deficient (Leslie et al. 1993; Redshaw and Stewart 2014). VLCADD is an autosomal recessive disorder with an estimated prevalence of 1:31,500–1:85,000 (Lindner et al. 2010; Arnold et al. 2009). The disorder is highly variable, and ranges from severe infantile disease to completely asymptomatic elderly individuals. Since the introduction of worldwide newborn screening, it has become clear that a significant number of the identified newborns with VLCADD actually have a very low risk for metabolic decompensation and may even remain fully asymptomatic if left untreated. The pathophysiology of VLCADD is complex. As in other fatty acid oxidation defects, a combination of hypoglycaemia and toxicity of fatty acid intermediates can result in liver, brain, and heart injury. There is evidence of more general mitochondrial dysfunction in these disorders, including generation of reactive oxygen species and calcium imbalance (Wajner and Amaral 2015). During catabolic circumstances such as prolonged fasting, stress, illness, and surgery, metabolic derangement can occur, resulting in hypoglycaemia, myopathies (including cardiomyopathy), metabolic acidosis, and rhabdomyolysis (Leslie et al. 1993; Redshaw and Stewart 2014). Current treatment consists of avoiding catabolism with regular feedings and in some patients a restriction of long chain fatty acids, supplementation of medium chain triglycerides, and frequent carbohydrate intake to prevent activation of fatty acid metabolism (Arnold et al. 2009; Das et al. 2010). The metabolic derangement during surgery depends, amongst others, on disease severity, which is related to residual enzyme activity. Nonsense mutations in the encoding gene (ACADVL) may result in a severe and early presentation of the disorder, but the more frequent missense mutations are associated with both severe and attenuated presentations. Perioperative care in patients with VLCADD should thus be individualized, but the evidence is scarce and the literature is conflicting (Table 1). The use of volatile agents and agents dissolved in a fatty solution is controversial, since they have been related to metabolic derangement (Fierobe et al. 1998). This limits the option to provide safe and stress-reducing anaesthesia. The available evidence might however be biased by reports of symptomatic patients and consequently concern more severe presentations of VLCADD. Thus, a critical review of the available perioperative management is needed, as adequate management of VLCADD patients during surgery is crucial to prevent metabolic deterioration. We will highlight this by presenting a case report and critically review the available literature on perioperative management of patients with VLCADD.

Table 1. Summary of the statements of the articles included.

	Kleemann (1986)	Vellekoop (2011)	Redshaw (2014)
Preoperative care	Heptabarbital, morphine, promethazine	Adequate premedication recommended, (benzodiazepines)	Benzodiazepines: safe to use
Peroperative care	Volatile agents: recommended	Volatile agents: avoid Propofol: avoid Etomidate: avoid	Volatile agents, thiopentone and opiates: safe to use Propofol: caution Etomidate: not recommended
Glucose infusion (recommended)	**x**	Age and weight based (infants: 6 - 8 mg kg^{-1} min^{-1})	Age and weight based (adults: 2 mg kg^{-1} hr^{-1})
Laboratory measurements (recommended)	**x**	Pre- (during) and postoperative monitoring of glucose and CK	If decompensation is considered: extensive laboratory measurements
Postoperative care (recommended)	**x**	**x**	Maintaining glucose infusion until normal oral intake Prophylaxis with anti-emetics Prevent catabolism by monitoring early signs of infection, pain and surgical complications

Case Report

Our patient is a 24-year-old woman with relatively mild VLCADD, diagnosed at the age of 16 months after severe hypoglycaemia caused by metabolic derangement (ACADVL mutations c. 104delC (p.Pro35LeufsX26) and c.848T>C (p.Val283Ala); lymphocyte enzyme activity <0.15 (1.84–4.8); fibroblast enzyme activity 0.24 (1.8–5.24) IcFAO flux (([9,10-3H(N)]-oleic acid oxidation rate)) 37% of normal). Later she was diagnosed with mild psychomotor retardation. She was admitted for a surgical removal of a cyst in the neck. We used the following strategy: The patient was scheduled as the first patient of the elective program. Glucose 10% was started at a rate of 2,500 ml 24 h^{-1} (~2 mg kg^{-1} min^{-1}), in a solution containing 0.45% NaCl and 10 mmol KCl per 500 ml. We inserted a continuous intravenous glucose monitor for glucose measurements (Fig. 1). Premedication consisted of temazepam 10 mg the evening prior to surgery and clonidine 150 mcg, paracetamol 1,000 mg, and esomeprazole 40 mg the morning of the procedure. Anaesthesia was induced with thiopental 4.5 mg kg^{-1}, remifentanil infusion 0.3 mcg kg^{-1} min^{-1}, and rocuronium 40 mg. For maintenance of anaesthesia we used remifentanil 0.19 mcg kg^{-1} min^{-1} and sevoflurane 1.6 vol.% end-tidal. At the end of the procedure 3

mg of morphine was administered as a loading dose for postoperative pain relief. Dehydrobenzoperidol 0.625 mg and dexamethasone 4 mg were administered to prevent postoperative nausea and vomiting. The procedure was uneventful and took 60 min. The patient was extubated before leaving the operation room. Creatinine kinase (CK) before and after surgery was 61 mcg l^{-1} and 36 mcg l^{-1}, respectively. The patient was discharged from the recovery room after resuming oral intake. Her stay on the surgical department was also uneventful and the same evening she was discharged home.

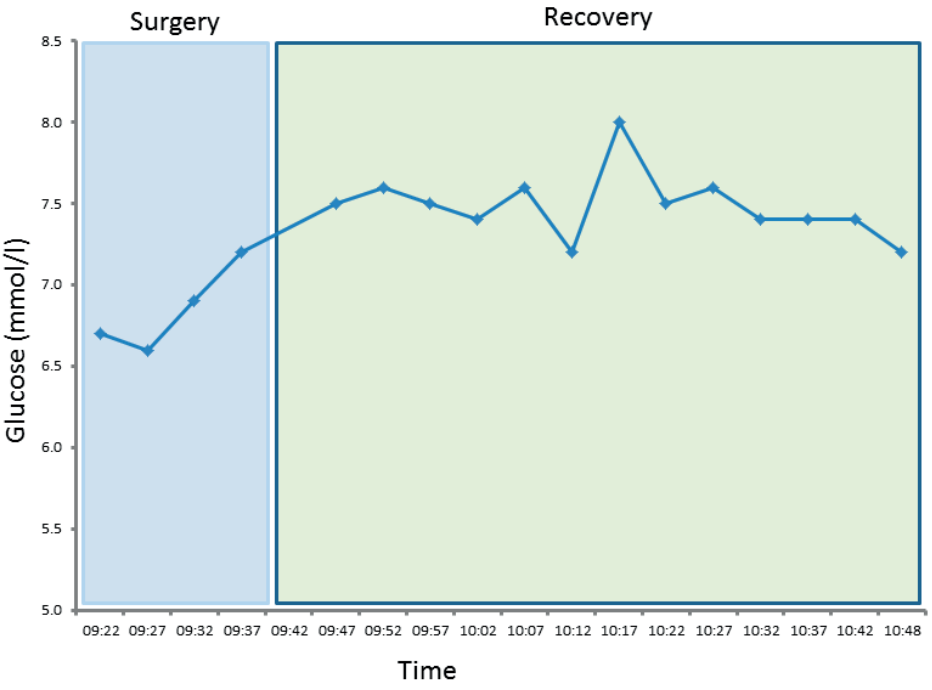

Figure 1. The results of the continuous intravenous glucose monitor

Principles of Perioperative Management

Preoperative Care

Stress prior to surgery is a known trigger for metabolic derangement (Vellekoop et al. 2011; Redshaw and Stewart 2014). Preventing stress with the use of premedication could be effective. However, the available literature that addresses premedication to prevent preoperative stress is inconclusive. Kleemann et al., who investigated the levels of free fatty acids as a sign of stress prior, during, and after surgery, claim that premedication did not prevent a stress-induced rise of free fatty acids, using heptabarbital on the preoperative night and morphine with promethazine prior to the transfer to the

operating room (Kleemann et al. 1986). However, evidence towards the uneventful use of benzodiazepines such as midazolam is also available (Steiner et al. 2002; Schmidt et al. 2009). Despite the conflicting and scarce literature, premedication is not likely to result in additional harm for the patient and as mentioned above, some data indicate that it is possibly helpful in reducing the perioperative stress response. Patients should be planned as early as possible to minimize the fasting period and thereby reducing the period at risk of deterioration. Finally, measuring the fatty acid oxidation flux predicts the clinical severity of VLCAD deficiency, and could be useful to predict severity of the disease before surgery (Diekman et al. 2015).

Peroperative Care

The principal aim of anaesthetizing VLCADD patients is minimizing the surgical stress response, using regional and general anesthesia where considered appropriate. Some anaesthetic medication is discussed separately.

Volatile Agents

According to several authors, volatile agents should be avoided, because they are associated with a significant rise of free fatty acid concentrations and this could lead to metabolic derangement (Leslie et al. 1993; Steiner et al. 2002; Vellekoop et al. 2011). However, the assumption is based on the study of Kleeman et al., who investigated plasma concentrations of free fatty acids as the marker of catabolism secondary to stress at multiple points during surgery in a small cohort. They showed that the induction of anaesthesia caused a statistically significant rise in free fatty acids, which can be attributed to stress prior to surgery and not to the anaesthetic used. Kleeman et al. even showed a decrease of free fatty acids 10 min after the administration of enflurane and concluded that enflurane provides adequate protection against stress during minor surgery. Another mentioned risk of volatile agents is malignant hyperthermia, which could cause rhabdomyolysis (Fierobe et al. 1998; McKenney and Holman 2002; Vellekoop et al. 2011; Rosenberg et al. 2015). Malignant hyperthermia is a hereditary disorder that is characterized by a rise of body temperature (1C 5 min^{-1}) and can be fatal if not timely detected and treated (Vanholder et al. 2000; Rosenberg et al. 2015). The incidence of malignant hyperthermia during anaesthesia is between 1:10,000 and 1:250,000 (Rosenberg et al. 2015). It can be triggered by all inhalation anaesthetics except nitrous oxide (Rosenberg et al. 2015). The risk of malignant hyperthermia could be important in VLCADD patients, since the risk of rhabdomyolysis is already increased. However, although both diseases share some symptoms, the aetiology is different. And to our knowledge, there are no reports about an association of VLCADD with malignant hyperthermia. Thus, the risk for malignant hyperthermia in patients with VLCADD is presumably comparable to patients without VLCADD.

Propofol

The use of propofol in patients with VLCADD is controversial (Leslie et al. 1993; Steiner et al. 2002; Vellekoop et al. 2011; Redshaw and Stewart 2014). Propofol is dissolved in a solution containing 0.1 g fat ml^{-1}. The amount administered depends on the age and weight of a patient. For the induction of anaesthesia in adults, 2–3 mg kg^{-1} of propofol is used; to maintain anaesthesia, a continuous infusion of 4–10 mg kg^{-1} h^{-1} is administered, depending on the administration of other agents. During a one-hour procedure, the minimum dosage fat within propofol may equate a sixth of the daily fat allowance of an adult. Since VLCADD patients may have a fat restricted diet to prevent organ lipidosis and the accumulation of fat oxidation intermediates, it is recommended to avoid the use of propofol, to improve long-term morbidity and mortality (Redshaw and Stewart 2014). A case report of a child without VLCADD suggests that propofol can lead to depression of the mitochondrial respiratory chain by disruption of fatty acid oxidation (Wolf et al. 2001). This could mean that patients with VLCADD might be at greater risk for the propofol infusion syndrome when using a continuous infusion of propofol. However, there is no data to support the latter assumption. Additionally, cases demonstrating the uneventful use of propofol have been described as well (Vellekoop et al. 2011; Martin et al. 2014; Redshaw and Stewart 2014). Most likely, induction with propofol will not lead to immediate problems when sufficient glucose is provided (explained below) and its use in VLCADD is therefore only relatively contraindicated. However, low fat induction agents, e.g., thiopental, are available and perhaps preferable. For maintenance of anaesthesia we still would recommend using volatile agents, unless contraindicated, especially for long procedures.

Other Agents

As discussed above, benzodiazepines are safe. In addition, opiates are considered safe in patients with fatty acid metabolic disorders (Steiner et al. 2002; Vellekoop et al. 2011; Redshaw and Stewart 2014). For the lipid formulation of etomidate (e.g., Etomidaat-®Lipuro, B. Braun, Melsungen, Germany), the same considerations apply as with propofol. Prophylaxis of postoperative nausea and vomiting with anti-emetics is important, as this reduces not only the stress from postoperative nausea and vomiting, but also promotes early restart of oral intake.

Glucose Infusion and Laboratory Measurements

Patients with fatty acid metabolic disorders are unable to address their fatty acids when the available glucose storage becomes depleted. Therefore, patients in need of surgery should receive constant supply of glucose from the moment they fast to prevent cell damage, especially in muscles. The amount of glucose infusion depends on various factors such as residual enzyme activity (the type of VLCADD), the type of procedure

and the amount of stress. It is also based on age, because it is presumed that the need for glucose diminishes with aging. According to Vellekoop et al., a glucose infusion of 6 mg kg^{-1} min^{-1} should prevent catabolism in healthy children undergoing minor surgery, therefore they advise an amount of 8 mg kg^{-1} min^{-1} for infants with VLCADD. Nishina and coworkers advise 2 mg kg^{-1} min^{-1} in healthy children who undergo minor surgeries (Nishina et al. 1995). The BIMDG (British Inherited Metabolic Diseases Group) advises 3 mg kg^{-1} min^{-1} for adults with a fatty acid metabolic disorder, including VLCADD (http://www.bimdg.org.uk/guidelines/guidelines-adult.asp). Redshaw and colleagues however advise to give 2 mg kg^{-1} hr^{-1} (Redshaw and Stewart 2014). Thus, recommendations vary widely and for adults there is no clear consensus, which reflects the paucity of data in this patient group. There is however a clear relation between increasing endogenous glucose production (and thus need) during fasting, ranging from above 8 mg kg^{-1} min^{-1} in the newborn to 2 mg kg^{-1} min^{-1} in the adult human (Huidekoper et al. 2014). In our view, the easiest way to prescribe glucose for the adult patient is to use a fixed 10% solution and give 2 mg kg^{-1} min^{-1}. For children however glucose infusion needs to be increased – depending on age – up to 6–8 mg kg^{-1} min^{-1} (Vellekoop et al. 2011). In case of hyperglycaemia (plasma glucose >10 mmol l^{-1}) the amount of glucose should never be diminished, but must be treated with insulin (http://www.bimdg.org.uk/guidelines/guidelines-adult.asp). To be able to monitor whether catabolism is sufficiently suppressed, it is important to monitor glucose and serum CK frequently. An increased CK is a sign of lysis of muscle cells, which could indicate rhabdomyolysis (Vanholder et al. 2000). The latter can even occur despite the administration of glucose, because during stress cortisol and catecholamines are released. According to Nishina et al., this could affect the insulin receptor, which results in insulin resistance in the peripheral tissue. Rhabdomyolysis can thus occur when glucose levels are within normal range. A relative shortage of insulin causes a delay in glucose uptake within the cells, despite a normal glucose level. Insulin resistance is also associated with the accumulation of lipid intermediates such as long chain acyl-coA, which are presumed to be toxic and responsible for metabolic derangement (Morris and Turnbull 1998; Hoy et al. 2009). Thus, in case of an increase in CK, additional glucose needs to be administered. Postoperative Management and Discharge After surgery, the glucose infusion must be maintained until the patient can resume the normal oral intake (http://www.bimdg.org.uk/guidelines/guidelines-adult.asp). As previously mentioned, glucose infusion must be maintained even in case of hyperglycaemia. To prevent catabolism, early signs of infection, pain, and surgical complications should be monitored as well and treated promptly (Redshaw and Stewart 2014).

Summary and Recommendations

After reviewing the literature we performed an uneventful surgical procedure in a patient with VLCADD. Although a rare disease, complications are serious and precautions are necessary. The most important cornerstones of the perioperative care are to minimize the fasting period and surgical stress. In addition, one needs to provide adequate glucose infusion (~2 mg kg^{-1} min^{-1} of glucose 10% in adults) and measure glucose and CK (summary Table 2). Volatile agents can be used safely; propofol and etomidate in a fatty emulsion are relatively contraindicated. Preoperative knowledge on functional fatty acid oxidation despite the VLCADD, e.g., by measuring the fatty acid oxidation flux, could be useful when preparing for surgery.

Take-Home Message

Despite the conflicting literature addressing the perioperative management in patients with VLCADD (very longchain acyl-CoA dehydrogenase deficiency), volatile agents can be used safely if other important precautions are provided, such as an adequate glucose infusion and the minimization of the fasting period and surgical stress, taking into account the severity of the mutation.

Table 2. Our current recommendations according to the available literature

	Our recommendations based on the literature
Preoperative care	Benzodiazepines if needed
Peroperative care	Volatile agents: Preferred Propofol: Relatively contraindicated Etomidate (lipid formulation): Relatively contraindicated
Glucose infusion	Age and weight based (~ 2 ml kg^{-1} hr^{-1} of glucose 10% in adults)
Laboratory measurements	Glucose and CK levels before and after surgery. If surgery > 3 hours sample CK every 3 hours during surgery. Increase glucose infusion if CK increases.
Postoperative care	Maintaining glucose infusion until normal oral intake Prophylaxis with anti-emetics Prevent catabolism by monitoring early signs of infection, pain and surgical complications

References

Arnold GL, van Hove J, Freedenberg D et al (2009) A delphi clinical practice protocol for the management of very long chain acylCoA dehydrogenase deficiency. Mol Genet Metab 96(3):85–90

British Inherited Metabolic Disease Group (2012) Guidelines for adult emergency managementlong chain fatty acid oxidation defects. http://www.bimdg.org.uk/guidelines/guidelines-adult.asp

Das AM, Steuerwald U, Illsinger S (2010) Inborn errors of energy metabolism associated with myopathies. J Biomed Biotechnol: 340849

Diekman EF, Ferdinandusse S, van der Pol L (2015) Fatty acid oxidation flux predicts the clinical severity of VLCAD deficiency. Genet Med 17:989–994

Fierobe L, Nivoche Y, Mantz J, Elalaoui Y, Veber B, Desmonts JM (1998) Perioperative severe rhabdomyolysis revealing susceptibility to malignant hyperthermia. Anesthesiology 88(1):263–265

Hoy AJ, Brandon AE, Turner N et al (2009) Lipid and insulin infusion-induced skeletal muscle insulin resistance is likely due to metabolic feedback and not changes in Irs-1, Akt, or As160 phosphorylation. Am J Physiol Endocrinol Metab 297(1): E67–E75

Huidekoper HH, Ackermans MT, Ruiter AFC, Sauerwein HP, Wijburg FA (2014) Endogenous glucose production from infancy to adulthood: a non-linear regression model. Arch Dis Child 99 (12):1098–1102

Kleemann PP, Jantzen JP, Fenner R, Wiegand UW (1986) Preoperative increase in the plasma concentration of free fatty acids during minor elective interventions using a conventional anesthesia technic with enflurane. Anaesthesist 35(10):604–608

Leslie ND, Valencia CA, Strauss AW, Connor J, Zhang K (1993) Very long-chain acyl-coenzyme a dehydrogenase deficiency. In Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD et al (eds) Genereviews (R). Seattle

Lindner M, Hoffmann GF, Matern D (2010) Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. J Inherit Metab Dis 33(5):521–526

Martin JM, Gillingham MB, Harding CO (2014) Use of propofol for short duration procedures in children with long chain 3- hydroxyacyl-CoA dehydrogenase (Lchad) or trifunctional protein (Tfp) deficiencies. Mol Genet Metab 112(2):139–142

McKenney KA, Holman SJ (2002) Delayed postoperative rhabdomyolysis in a patient subsequently diagnosed as malignant hyperthermia susceptible. Anesthesiology 96(3):764–765

Morris AA, Turnbull DM (1998) Fatty acid oxidation defects in muscle. Curr Opin Neurol 11(5):485–490

Nishina K, Mikawa K, Maekawa N, Asano M, Obara H (1995) Effects of exogenous intravenous glucose on plasma glucose and lipid homeostasis in anesthetized infants. Anesthesiology 83 (2):258–263

Redshaw C, Stewart C (2014) Anesthetic agents in patients with very long-chain acyl-coenzyme a dehydrogenase deficiency: a literature review. Paediatr Anaesth 24(11):1115–1119

Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K (2015) Malignant hyperthermia: a review. Orphanet J Rare Dis 10(1):93

Schmidt J, Hunsicker A, Irouschek A, Kohler H, Knorr C, Birkholz T (2009) Early recovery from anesthesia and extubation in an infant with very long chain acyl-CoA dehydrogenase deficiency using midazolam, mivacurium, and high dose remifentanil. Paediatr Anaesth 19(9):909–910

Steiner LA, Studer W, Baumgartner ER, Frei FJ (2002) Perioperative management of a child with very-long-chain acyl-coenzyme a dehydrogenase deficiency. Paediatr Anaesth 12(2):187–191

Vanholder R, Sever MS, Erek E, Lameire N (2000) Rhabdomyolysis. J Am Soc Nephrol 11(8):1553–1561

Vellekoop P, Diekman EF, van Tuijl I, de Vries MM, van Hasselt PM, Visser G (2011) Perioperative measures in very long chain acylCoA dehydrogenase deficiency. Mol Genet Metab 103(1):96–97

Wajner M, Amaral AU (2015) Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animal studies. Biosci Rep 36(1):e00281

Wolf A, Weir P, Segar P, Stone J, Shield J (2001) Impaired fatty acid oxidation in propofol infusion syndrome. Lancet 357 (9256):606–607