PACCJ

Use of remimazolam as an adjunct to general anesthesia for an adolescent with MELAS syndrome

N. Gyurgyik[1], J. Warren[2], R. Miketic[1,3], J. D. Tobias[1,3]

[1]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio
[2]Heritage College of Osteopathic Medicine - Dublin Campus, Dublin, Ohio and Ohio University, Athens, Ohio
[3]Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio

Corresponding author: J. D. Tobias, Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio. Email: Joseph.Tobias@Nationwidechildrens.org

Keypoints

1. The acronym, MELAS, first reported as a specific clinical entity in 1984, refers specifically to the hallmark clinical and pathophysiologic features including *m*itochondrial *e*ncephalo-myopathy, *l*actic *a*cidosis, and *s*troke-like episodes.
2. Abnormal mitochondrial function with impaired oxidative phosphorylation impairs the function of tissues dependent on high energy output including the skeletal muscle, the heart, and the central nervous system.
3. In addition to the perioperative implications related to the end-organ involvement of MELAS syndrome, the volatile anesthetic agents and propofol may be relatively or absolutely contraindicated in this patient population dependent on the exact cellular or genetic abnormality.
4. Remimazolam provides sedation, amnesia, and anxiolysis through the gamma-aminobutyric acid (GABA) system. As an ester-based benzodiazepine, it is hydrolyzed quickly with a more rapid offset than midazolam and a limited context-sensitive half-life.

Abstract

MELAS syndrome is an acronym so named because of the characteristic clinical and pathophysiologic features including *m*itochondrial *e*ncephalo-myopathy, *l*actic *a*cidosis, and *s*troke-like episodes. As the disorder impacts mitochondrial function and oxidative phosphorylation, clinical symptoms characteristically involve tissues and organ systems with high energy requirements including the skeletal muscle, the heart, and the central nervous system. Classically considered in the group of disorders known as mitochondrial myopathies, specific perioperative concerns must be considered in such patients given the effect of various anesthetic agents including propofol or the volatile anesthetic agents on patients with myopathic conditions or disorders of mitochondrial function.

We report an 1-year-old with MELAS syndrome who required anesthetic care during eye muscle surgery. Due to potential concerns with volatile anesthetic agents and propofol, we used the novel benzodiazepine, remimazolam, with dexmedetomidine and remifentanil to provide maintenance anesthesia. Previous reports of anesthetic care in patients with MELAS syndrome are reviewed and the use of the novel benzodiazepine, remimazolam, is discussed.

Keywords

Mitochondrial myopathy, oxidative phosphorylation, MELAS syndrome, lactic acidosis

Introduction

MELAS syndrome, first reported in 1984 by Pavlakis et al, is a multisystem disorder characterized by stroke-like episodes, mitochondrial dysfunction with lactic acidosis, ragged-red fibers on muscle biopsy, and at least two of the following clinical features: focal or generalized seizures, dementia, recurrent headaches, or vomiting.[1] The acronym, MELAS, refers specifically to the hallmark clinical and pathophysiologic features including *m*itochondrial *e*ncephalo-myopathy, *l*actic *a*cidosis, and *s*troke-like episodes. As a disorder affecting mitochondrial function, clinical symptoms characteristically involve tissues and organ systems dependent on high energy output via oxidative phosphorylation including the skeletal muscle, the heart, and the central nervous system. MELAS is the result of point or microdeletion mutations in mitochondrial DNA.[2] As the majority of mitochondrial DNA is maternally derived during initial fertilization, inheritance follows the maternal lineage. The most common mutation associated with MELAS syndrome is a single point mutation (adenine to guanine) in the MT-TL1 gene encoding for mitochondrial tRNA. Impairment of mitochondrial translation and protein synthesis affects mitochondrial function and the mitochondrial electron transport chain leading to impaired mitochondrial energy production. The inability of dysfunctional mitochondria to generate sufficient energy to meet the needs of various high energy tissues results in the multi-organ dysfunction observed in MELAS syndrome. Deficient energy production in the mitochondria or smooth muscle and endothelial cells of small blood vessels leads to impairment of the microvasculature including deficient nitric oxide production causing angiopathy and stroke-like episodes. Given the multi-organ involvement of MELAS syndrome, surgical interventions may be required to address associated comorbid organ system involvement. In such cases, effective perioperative care mandates the identification of associated organ involvement and selection of anesthetic agents based on the potential impact of the underlying disruption of mitochondrial function. We report a 12-year-old girl with MELAS syndrome who required anesthetic care during eye muscle surgery. Previous reports of anesthetic care are reviewed, options for choice of anesthetic agent discussed, and use of the novel benzodiazepine, remimazolam, is discussed.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). A 12-year-old, 52.6 kg child presented for anesthetic care during right eye surgery (resection of the lateral and medial rectus muscle) due to alternating exotropia and diplopia. The patient has a family history of MELAS syndrome and she was diagnosed with having the MELAS pathogenic variant (m.3243A>G) in a blood sample showing a 56% heteroplasmic state. She had been clinically asymptomatic and had no developmental concerns, but underwent genetic testing for MELAS syndrome as her brother was diagnosed at 9 years of age when he presented with a stroke. Additional pertinent past medical history included insomnia, cystic fibrosis carrier (found on a newborn screening), and an unvaccinated condition due to parental refusal. At 5 years of age, the patient had been hospitalized for treatment of *streptococcus pneumoniae* pneumonia, which was complicated by a pleural effusion requiring tube thoracostomy. Current medications that the patient took included Miralax® (polyethylene glycol), Zyrtec® (cetirizine), and nasal Flonase® (fluticasone). The patient had no allergies, other than medication alerts due to the associated MELAS syndrome (see below).

Preoperative vital signs revealed temperature 36.8°C (98.2°F), pulse rate 62 beats/minute, respiratory rate 18 breaths/minute, blood pressure (BP) 105/62 mmHg, and room oxygen saturation 100%. The pre-operative physical exam revealed a thyromental distance of more than 3 fingerbreadths, adequate mouth opening, and a Mallampati grade 2. Respiratory and cardiovascular examination were unremarkable. The patient's most recent

echocardiogram and electrocardiogram were unremarkable. The patient was held nil per os for 8 hours. She was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. Additionally, a depth of anesthesia monitor (bispectral index or BIS) was placed. After the inhalation of 50% nitrous oxide in oxygen, a peripheral intravenous catheter was placed. Anesthesia was induced with dexmedetomidine (0.2 µg/kg), remifentanil (1 µg/kg), and etomidate (0.3 mg/kg). Glycopyrrolate (0.2 mg) was administered prophylactically to prevent an oculocardiac reflex during eye muscle retraction. Endotracheal intubation was facilitated by the administration of rocuronium (25 mg). Maintenance of anesthesia included infusions of dexmedetomidine (0.5-1 µg/kg/hr), remifentanil (0.3-0.4 µg/kg/min), and remimazolam (5-10 µg/kg/min). A second dose of glycopyrrolate (0.2 mg) was administered intraoperatively following a brief episode of significant bradycardia (heart rate 30 beats/minute) during retraction on the eye muscle. After the administration of the second dose of glycopyrrolate, the patient had an exaggerated blood pressure response with a blood pressure of 140/ 90 mmHg. During this time, no change was noted in the BIS number. Blood pressure was controlled by the administration of midazolam (2 mg) and fentanyl (100 µg). No other intraoperative concerns were noted. The surgical procedure lasted approximately 60 minutes. Ondansetron (4 mg) was administered for the prevention of postoperative nausea and vomiting. Postoperative analgesia was provided by hydromorphone (0.5 mg). Residual neuromuscular blockade was reversed with sugammadex (200 mg). Intraoperative fluids included normal saline (600 mL). The patient's trachea was extubated in the operating room and she was transported to the post-anesthesia care unit (PACU). The remainder of her postoperative course was unremarkable and she was discharged home.

Discussion

The mitochondria are double membrane organelles that are present in all nucleated human cells. The inner mitochondrial membrane harbors the electron transport chain complexes that transfer electrons, translocate protons, and produce ATP through oxidate phosphorylation. The mitochondrial myopathies included respiratory chain deficiencies; mitochondrial DNA mutations that include mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), mitochondrial neuro-gastrointestinal encephalopathy (MNGIE) and myoclonic epilepsy with ragged red fibers (MERRF) syndrome; and mitochondrial deletions such as Kearns-Sayre syndrome.[1,2] Mitochondria contain their own extra-chromosomal DNA (mitochondrial or mDNA) which is maternally derived during fertilization as the mitochondria reside in the cytoplasm, which is derived primarily from the oocyte. Although only a small proportion of mitochondrial proteins are encoded by mDNA, significant mitochondrial dysfunction can occur due to mutations in mDNA resulting in disorders classified as mitochondrial myopathies.

Our patient's diagnosis of MELAS syndrome was based on the clinical manifestation of the disorder in her sibling who had a stroke followed by subsequent genetic testing to identify the point mutation in the mitochondrial DNA. Clinical symptoms most commonly (65-76% of affected individuals) manifest before 20 years of age with seizures, recurrent headaches, failure to thrive, cortical vision loss, muscle weakness, recurrent vomiting, and stroke-like episodes. With multiple organ systems affected, there are a myriad of clinical, biochemical, radiological, and histological findings. As the syndrome progresses, at least 90% of affected patients develop dementia, epilepsy, lactic acidosis, skeletal muscle involvement with exercise intolerance, and continued stroke-like episodes. Other common manifestations of MELAS include cardiac involvement (cardiomyopathy, conduction disturbances, arrhythmias), endocrine dysfunction (diabetes, thyroid disorders), hepatic dysfunction, and peripheral

neuropathy. Biochemical features include elevated serum lactate, creatinine kinase, and alanine. Additionally, there are elevated levels of lactate and alanine in the CSF. Radiological features include basal ganglia calcifications, cerebral atrophy and cortical infarcts. Histological features seen under electron microscopy of muscle biopsy include ragged red fibers and mitochondrial proliferation. To date, treatment options are limited, generally including daily oral arginine supplementation.[3]As with all anesthetic care, the initial step is a thorough preoperative examination with identification of the acute and chronic end-organ involvement of the primary disorder. Primary concerns with MELAS include cardiac involvement manifesting with arrhythmias including Wolf-Parkinson-White syndrome, conduction disturbances with various degrees of atrioventricular blockade, and depressed myocardial function. The most prevalent cardiac complication is hypertrophic cardiomyopathy. Although, currently not completely understood, it is hypothesized that the development of hypertrophic cardiomyopathy is a compensatory measure due to mitochondrial metabolic alterations resulting in ATP deficiency.[4,5] Given these concerns, a thorough preoperative cardiac evaluation is indicated including a 12-lead electrocardiogram and echocardiogram to evaluate structure and function. Various factors may impact respiratory function during the perioperative period in patients with mitochondrial dysfunction including respiratory depression from the residual effects of anesthetic agents and the associated myopathic condition and skeletal muscle weakness.[4,5] These respiratory concerns may be compounded by poor cough effort, chronic aspiration or recurrent pneumonia. Given these concerns, whenever feasible, short-acting anesthetic agents are recommended to allow for rapid awakening and limited impact on postoperative upper airway and respiratory function. The potential for perioperative respiratory failure may be increased by pre-existing respiratory dysfunction from hypotonia, poor cough effort, chronic aspiration or recurrent pneumonia. Given these concerns, continuous postoperative monitoring of

respiratory function may be indicated following prolonged surgical procedures. In our patient, we choose to use remifentanil and remimazolam to allow for the intraoperative titration of an appropriate depth of anesthesia while allowing for a rapid recovery given their rapid metabolism and limited context-sensitive half-life. Hypotonia can significantly impact the choice of neuromuscular blocking agents (NMBAs). Patients with pre-existing hypotonia related to mitochondrial disorders may be sensitive to the effects of non-depolarizing NMBAs.[6] Although we chose to use rocuronium to facilitate endotracheal intubation, even in the setting of hypotonia, sugammadex offers the potential to effectively reverse significant residual neuromuscular blockade in patients with neuromyopathic conditions.[7] Additional CNS concerns include the presence of seizures, dementia, the potential increased risk of perioperative strokes, and residual CNS effects from previous strokes. Preoperative management to limit perioperative seizures includes optimizing anticonvulsant medications prior to the surgical procedure and continuation of routine anticonvulsant medications during the perioperative period. There is limited evidence-based medicine to identify advantages of any specific agents for the induction and maintenance of anesthesia in this population.[8] Endocrine involvement is also a frequent sequela of MELAS syndrome with accelerated apoptosis of pancreatic β-islet cells leading to diabetes mellitus, the most prevalent endocrine abnormality. Thyroid dysfunction (hyperthyroidism or hypothyroidism) and hepatic involvement are common during the course of the disease. Blood glucose, hepatic function tests, and coagulation parameters should be monitored perioperatively. Since lactate metabolism is impaired and production increased in patients with MELAS syndrome, intravenous fluids containing sodium lactate such as lactated Ringer's should be avoided. The metabolic conversion of lactic acid to bicarbonate via the Cori cycle is required for lactate to act as a buffer. As this process is impaired, the metabolism of the additional lactate may not be feasible. Given these concerns, we chose to use 0.9% saline

as the isotonic fluid for intraoperative administration. When more aggressive intraoperative fluid resuscitation is required, isotonic fluids such as Normosol® or Plasma-lyte® with alternative buffering agents (acetate or gluconate) can be used to maintain a neutral pH and avoid the dilutional acidosis which may occur with the administration of larger volumes of 0.9% saline.[9,10] Altered glucose metabolism is also commonly seen in MELAS syndrome. Although diabetes mellitus and hyperglycemia is commonly seen later in the course of the disease process, hypoglycemia may also occur in patients with mitochondrial dysfunction and impaired oxidative phosphorylation. Hypoglycemia is most commonly encountered during acute illnesses or prolonged fasting without the administration of exogenous glucose. To avoid hypoglycemia, NPO times should be limited and glucose containing fluids administered during prolonged surgical procedures. Additionally, given the potential for hypoglycemia as well as hyperglycemia related to pancreatic dysfunction, periodic perioperative monitoring of serum glucose is recommended. One of the challenges when designing an appropriate anesthetic for patients with mitochondrial myopathies is that these disorders may potentially be related to a myriad of different genetic and cellular defects. As such, when selecting specific agents for the induction and maintenance of anesthesia in these patients, there is generally limited evidence-based medicine to guide optimal agent selection.[4,5,11] One of the most challenging aspects of providing anesthetic care in the setting of a mitochondrial myopathy is that there are the potential theoretical concerns with the administration of both volatile anesthetic agents and propofol.[5,11] While not absolutely contraindicated, both propofol and the volatile agents have the ability to depress oxidative phosphorylation. Volatile anesthetic agents suppress oxidative phosphorylation in a dose-dependent manner by impacting complex I, coenzyme Q, and complex V of the mitochondrial respiratory chain.[5,11-13] Additionally, patients with MELAS syndrome and mitochondrial dysfunction may have a heightened sensitivity to the effect

of the volatile anesthetic agents on myocardial and CNS function.[13,14] For prolonged or involved surgical procedures, depth of anesthesia monitoring, as was used in our case, may be indicated. Regardless of the agents chose, short-acting intravenous and volatile agents offer the advantage of ease of titration based on CNS and hemodynamic effects as well as rapid awakening with limited postoperative effects. Propofol alone has been shown to inhibit complexes I, II, and IV of the respiratory chain. Specifically, propofol acts on complex I and IV inhibiting mitochondrial function and uncoupling oxidative phosphorylation of fatty acids. This inhibition of mitochondrial function by propofol may lead to the classic findings of propofol infusion syndrome including renal failure, rhabdomyolysis, myocardial dysfunction, and metabolic acidosis.[15] With these concerns in mind, we chose to use total intravenous anesthesia (TIVA) with dexmedetomidine, remifentanil, and remimazolam. Dexmedetomidine is a α2-adrenergic agonist which has been approved by the United States Food & Drug Administration (FDA) in 1999 for the sedation of adults during mechanical ventilation and in 2009 for monitored anesthesia care (MAC) or procedural sedation. Although not formally FDA-approved for use in children, there is significant clinical experience with its use for various perioperative clinical scenarios.[16,17] While anecdotal experience suggests the efficacy of a combination of dexmedetomidine and remifentanil for intraoperative anesthetic care, a potential concern includes lack of firm data demonstrating the amnestic effects of dexmedetomidine.[18-20] To ensure amnesia, we chose to add the ester metabolized benzodiazepine, remimazolam as part of the TIVA regimen for our patient. Following FDA-approval for use in adults in 2020, initial clinical trials have demonstrated the efficacy of remimazolam for sedation of adults during invasive procedures such as gastrointestinal endoscopy and bronchoscopy.[21-23] These trials have demonstrated its efficacy for procedural sedation as well as an acceptable safety profile with limited effects on hemodynamic function, lack of pain with intravenous administration, reduction of

post-procedure nausea and vomiting (PONV), and a rapid return to baseline neurologic function. Similar to other benzodiazepines, remimazolam provides sedation, amnesia, and anxiolysis through the gamma-aminobutyric acid (GABA) system. As an ester-based medication, it is hydrolyzed quickly with a more rapid offset than midazolam and a limited context-sensitive half-life. A previous case also outlines the combination of remimazolam and remifentanil for general anesthesia (TIVA) in a 54-year-old woman with MELAS syndrome undergoing a cochlear implant.[24] Anesthesia was induced by the intravenous administration of a bolus of remimazolam (0.2 mg/kg)followed by maintenance anesthesia with continuous infusions of remimazolam (1 mg/kg/hr) and remifentanil (0.2 µg/kg/min). Neuromuscular blockade was provided by intermittent doses of rocuronium with train-of-four monitoring. Remimazolam dosing was titrated by depth of anesthesia monitoring (SEDLine®, patient state index). The patient's trachea was extubated 8 minutes after discontinuation of the remimazolam infusion. Recovery of consciousness was accelerated by the administration of flumazenil. To date, there is limited anecdotal experience with its use in children.[25-27] In our patient, we chose to use etomidate for induction of anesthesia given the potential followed hemodynamic compromise in patients with MELAS. Maintenance anesthesia included an infusion of remimazolam, titrated from 5-10 µg/kg/min to maintain the BIS value at 50-60 along with infusions of dexmedetomidinie (0.5-1 µg/kg/hr) and remifentanil (0.3-0.4 µg/kg/min). Adequate intraoperative anesthetic conditions were maintained without adverse effects. An episode of bradycardia was noted; however, this was attributed to an oculocardiac reflex with eye muscle retraction. While many different anesthetic techniques and agents have been administered safely in patients with mitochondrial disease, there remain anecdotal reports of life-threatening complications and death following anesthetic care and surgical procedures, regardless of the anesthetic regimen. As a result, it is generally perceived that these patients are at increased risk following surgery.

During the perioperative period, the primary implications of mitochondrial disorders include the potential for respiratory failure, depressed myocardial function, and cardiac conduction defects. Alterations in glucose homeostasis (hypoglycemia or hyperglycemia) and acidosis may occur related to surgical stress, hypothermia, postoperative nausea and vomiting or prolonged fasting. Theoretical concerns exist that may contraindicate the use of both propofol and the volatile anesthetic agents which prompted the use of remimazolam in our patient. Other medications are relatively or absolutely contraindicated in patients with MELAS as they may impact mitochondrial function including metformin, valproic acid, and linezolid.

References

1. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke- like episodes: a distinctive clinical syndrome. Ann Neurol. 1984;16:481-8.

2. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab. 2015;116:4-12.

3. Koga Y, Akita Y, Nishioka J, et al. L-arginine improves the symptoms of strokelike episodes in MELAS. Neurology. 2005;64:710-2.

4. Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. Anesthesiology. 2002;96:1268-70.

5. Niezgoda J, Morgan PG. Anesthetic considerations in patients with mitochondrial defects. Paediatr Anaesth. 2013;23:785-93.

6. Finsterer J, Stratil U, Bittner R, Sporn P. Increased sensitivity to rocuronium and atracurium in mitochondrial myopathy. Can J Anaesth. 1998;45:781-4.

7. Tobias JD. Current evidence for the use of sugammadex in children. Paediatr Anaesth. 2017;27:118-25.

8. Kofke WA. Anesthetic management of the patient with epilepsy or prior seizures. Curr Opin Anaesthesiol. 2010;23:391-9.

9. Yamamoto T, Miyazawa N, Yamamoto S, Kawahara H. Anesthetic management in mitochondrial encephalomyopathy: A case report. Anesth Prog. 2017;64:235-9

10. King M, Martin D, Miketic R, et al. Impact of intraoperative fluid management on electrolyte and acid-base variable during posterior spinal fusion in adults. Ortho Res Rev. 2020;12:69-74.

11. Ross AK. Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child. Pediatr Anesth. 2007;17:1-6.

12. Muravchick S, Levy RJ. Clinical implications of mitochondrial dysfunction. Anesthesiology. 2006;105:819-37.

13. Hsieh VC, Niezgoda J, Sedensky MM, et al. Anesthetic hypersensitivity in a case-controlled series of patients with mitochondrial disease. Anesth Analg. 2021;133:924-32.

14. Shipton EA, Prosser DO. Mitochondrial myopathies and anaesthesia. Eur J Anaesthesiol. 2004;21:173-8.

15. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. Br J Anaesth. 2019;122:448-59.

16. Tobias JD. Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8:115-31.

17. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res. 2011;5:128-33.

18. Szmuk P, Andropoulos D, McGowan F, et al. An open label pilot study of a dexmedetomidine-remifentanil-caudal anesthetic for infant lower abdominal/lower extremity surgery: The T REX pilot study. Paediatr Anaesth. 2019;29:59-67.

19. Kasuya Y, Govinda R, Rauch S, et al. The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidine and propofol. Anesth Analg. 2009;109:1811-5.

20. Hayama HR, Drumheller KM, Mastromonaco M, et al. Event-related functional magnetic resonance imaging of a low dose of dexmedetomidine that impairs long-term memory. Anesthesiology. 2012;117:981-95.

21. Chen S, Wang J, Xu X, et al. The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: a multicentered, randomized, positive-controlled, phase III clinical trial. Am J Transl Res. 2020;12:4594-603.

22. Chen SH, Yuan TM, Zhang J, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: A multicenter, randomized, non-inferiority, phase III trial. J Gastroenterol Hepatol. 2021;36:474-81.

23. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest. 2019;155:137-46.

24. Suzuki Y, Doi M, Nakajima Y. General anesthesia with remimazolam in a patient with mitochondrial encephalomyopathy: a case report. JA Clin Rep. 2021;7:51.

25. Horikoshi Y, Kuratani N, Tateno K, et al. Anesthetic management with remimazolam for a pediatric patient with Duchenne muscular dystrophy. Medicine (Baltimore). 2021;100(49):e28209.

26. Kamata K, Asagi S, Shimoda Y, et al. Successful recording of direct cortical motor-evoked potential from a pediatric patient under remimazolam anesthesia: a case report. JA Clin Rep. 2022;8:66.

27. Petkus H, Willer B, Tobias J. Remimazolam in a pediatric patient with a suspected family history of malignant hyperthermia. J Med Cases. 2022;13:386-90.