Anaesthesia with dexmedetomidine and remifentanil in a child with mitochondrial myopathy

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Keywords: dexmedetomidine, malignant hyperthermia, mitochondrial myopathy

Abstract

Patients with mitochondrial disorders have complex physiological issues which create a challenging scenario with regard to the safe provision of anaesthetic care. Within the spectrum of mitochondrial disorders, patients can be susceptible to multiple adverse effects and drug reactions from medications used during general anaesthesia. Although recent evidence suggests that inhalational anaesthetic agents may be used in patients with mitochondrial disorders, there is still a preference among some anaesthesia providers to use total intravenous anaesthesia (TIVA). In most scenarios, when TIVA is chosen, propofol is a major component. However, as a result of using propofol, patients with mitochondrial disorders may be susceptible to an acute metabolic crisis. It has been postulated that propofol, especially when given in large dosages, or when infused for prolonged periods of time, can adversely affect the function of the abnormal mitochondria that are present in patients with mitochondrial disorders.

We present our experience with the use of dexmedetomidine as the primary component of a general anaesthetic regimen in a 10-year-old girl with a mitochondrial disorder and dystonia, who required anaesthetic care during a urological procedure. Previous reports on the use of dexmedetomidine as part of TIVA in patients susceptible to malignant hyperthermia are reviewed, and its benefits in patients with mitochondrial disorders, discussed. Additional concerns regarding the perioperative care of patients with mitochondrial disorders are deliberated.

Ⓟ **Peer reviewed. (Submitted: 2010-10-28, Accepted: 2011-03-08) ©SASA** **South Afr J Anaesth Analg 2011;17(3):262-264**

Introduction

Mitochondrial disorders are related to mutations in either nuclear or mitochondrial DNA.[1-5] This change in the genetic code results in alterations in the function of the mitochondria and respiratory chain. Usually, mitochondrial disorders present in childhood and can affect one or multiple organ systems. Clinical symptoms are often variable, and can be difficult to classify into specific mitochondrial cytopathies (syndromes). Common manifestations of these disorders include myopathy, encephalopathy, and cardiomyopathy. Although recent evidence suggests that inhalational anaesthetic agents may be used in patients with mitochondrial disorders,[1-3] there is still a preference among some anaesthesia providers to use total intravenous anaesthesia (TIVA). In most scenarios, when TIVA is chosen, propofol is a major component. However, as a result of using propofol, patients with mitochondrial disorders may be susceptible to an acute metabolic crisis. It has been postulated that propofol, especially when given in large dosages, or when infused for prolonged periods of time, can adversely affect the function of the abnormal mitochondria that are present in patients with mitochondrial disorders. We present the case study of a 10-year-old girl with a mitochondrial disorder and myopathy, who presented for a bilateral ureteral implant, with cystoscopy and cecostomy tube placement. Given the associated mitochondrial disorder, there was a relative contraindication to the administration of propofol, and, therefore dexmedetomidine was included as a major component of the intraoperative general anaesthetic. To our knowledge, there are no previous reports in the literature regarding the use of dexmedetomidine in patients with mitochondrial disorders. Previous reports of the use of dexmedetomidine, as part of TIVA, in patients susceptible to malignant hyperthermia (MH) are reviewed, and its benefits in patients with mitochondrial disorders, discussed. Additional concerns regarding the perioperative care of patients with mitochondrial disorders are deliberated.

Case study

Approval for the retrospective review of this case and presentation of the material in this format was provided by the Nationwide Children's Hospital Institutional Review Board, Columbus, Ohio. The patient was a 10-year-old, 42-kg female with a past medical history that included a previously diagnosed mitochondrial disorder, as well as dystonia and

myopathy. She was scheduled to undergo a bilateral ureteral implant with cystoscopy and cecostomy tube placement. Taking into account the patient's history of an uncharacterised mitochondrial disorder, it was decided not to use propofol as part of the anaesthetic regimen. Furthermore, given the clinical manifestations of myopathy and dystonia, it was decided that a non-triggering anaesthetic technique would be most appropriate.

The anaesthesia machine was prepared by a 60-minute high-flow gas flush at 10 l/minute, removal of the vapourisers, and replacement of the soda lime. The patient was held nil per os for six hours, and transported to the operating room with existing intravenous access in place. Routine American Society of Anesthesiologists' monitors were erected. Preoperative haemodynamic data included blood pressure (BP) 110/77 mmHg and heart rate (HR) 139 beats/minute.

After preoxygenation, anaesthesia was induced with intravenous dexmedetomidine (1 µg/kg), midazolam (0.05 mg/kg), and ketamine (1.2 mg/kg). Rocuronium (0.5 mg/kg) was administered to facilitate endotracheal intubation. Following anaesthetic induction, an arterial cannula was inserted. Maintenance anaesthetic consisted of a dexmedetomidine infusion titrated at between 0.5 and 1.0 µg/kg/hour, and a remifentanil infusion titrated at between 0.2 and 0.4 µg/kg/minute. Intraoperatively, the HR varied from 88-140 beats/minute. The BP was well maintained during the intraoperative course (BP 81-134/42-97 mmHg), except for one episode of hypotension with a BP of 58/32 mmHg. During this episode, minimal lower pelvic manipulation was performed. When traction was released, there was no change in the BP, and there had been no significant blood loss throughout the case to account for the hypotension. The HR remained at 100-110 beats/minute during the period of hypotension. No abrupt change in oxygen saturation or end-tidal carbon dioxide, suggestive of an air embolism, was noted. The remifentanil and dexmedetomidine infusions were temporarily discontinued. A bolus dose of phenylephrine (0.25 µg/kg) was administered, as well as isotonic fluids (20 ml/kg of crystalloid and 50 ml of 5% albumin). Three bolus doses of ketamine (0.25 mg/kg) were also administered to ensure that an adequate depth of anaesthesia was maintained. Haemodynamic stability was achieved with a gradual return of the BP to baseline over a period of five to six minutes. As there was a slow, yet consistent increase in the BP from a nadir of 58/32 mmHg back toward baseline, no other interventions were deemed necessary. The dexmedetomidine and remifentanil infusions were restarted at 0.5 µg/kg/hour and 0.2 µg/kg/minute respectively, and eventually titrated back to their initial infusion rates. The surgical procedure lasted approximately four hours. At the end of the procedure, the dexmedetomidine and remifentanil infusions were discontinued, and residual neuromuscular blockade was reversed with glycopyrrolate and neostigmine. The patient's trachea was extubated to nasal cannula without complication. The patient was transitioned from the post-anaesthesia care unit to the paediatric intensive care unit (PICU). The remainder of her postoperative course was unremarkable and she was discharged from the PICU the following day, and to home on postoperative day three.

Discussion

The potential impact of the anaesthetic regimen on the outcome of such patients is illustrated in a case report by Casta et al, who described white matter degeneration, central nervous system dysfunction, and eventual death in a 13-month-old following anaesthetic care for cholescystectomy.[6] The patient, although not carrying a specific diagnosis, had chronically elevated urine and serum pyruvate levels, as well as Kreb's cycle intermediates, suggestive of a mitochondrial disorder. Prior to the anaesthetic care and surgical procedure, the patient was interactive and happy. Anaesthetic care included premedication with midazolam, anaesthetic induction with thiopental, fentanyl and pancuronium, followed by maintenance anaesthesia with isoflurane, nitrous oxide and oxygen. Following the procedure, the patient was agitated, with increased tone, and was unable to recognise his parents. There was progressive neurologic dysfunction and eventual death. Although a direct cause-effect relationship could not be demonstrated definitively, many anaesthetic agents, including the potent inhalational agents, may have variable effects on mitochondrial function.

The intravenous anaesthetic agent, propofol, is commonly chosen as an alternative to inhalational anaesthetic agents when a total intravenous anaesthetic technique is chosen or indicated.[7] Patients with mitochondrial disorders secondary to the disruption of the electron transport chain and the Kreb's cycle, are potentially at increased risk when propofol is used.[4,5,8,9] This potential risk is thought to be secondary to the effects of propofol, with impairment of the mitochondrial function and uncoupling of oxidative phosphorylation. Propofol inhibits the function of the protein complexes within the electron transport chain (complex II and complex IV).[10,11] It constrains the ability of complex II to transfer electrons between each protein complex. Furthermore, propofol impairs the transfer of electrons from cytochrome c to complex IV, ultimately halting the production of ATP. Patients with mitochondrial disorders may have an inherent dysfunction in cellular respiration at baseline, making the patient more susceptible to the inhibitory properties of propofol on oxidative phosphorylation.

Dexmedetomidine is an α_2-adrenergic agonist. In 1999, it initially received Food and Drug Administration (FDA) approval in the USA for the sedation of adults during mechanical ventilation, and subsequently in 2009, for monitored anaesthesia care of adults. Although the FDA approved its use in adults only, it has been used successfully in several different clinical scenarios in infants and children, including sedation during mechanical ventilation, procedural sedation, supplementation of postoperative analgesia, prevention of emergence delirium, control of postanaesthesia shivering, and the treatment of withdrawal.[12] To date, there are limited data regarding the use of dexmedetomidine in patients with myopathic conditions, and from our review of the literature, there have been no reports of its use in patients with mitochondrial disorders.

Although recent evidence suggests that inhalational anaesthetic agents may be used in patients with mitochondrial disorders,[1-3] there is still a preference among some anaesthesia providers to use total intravenous anaesthesia (TIVA) in this patient population. Furthermore, when there is a question or doubt regarding a diagnosis, a non-triggering anaesthetic technique may be indicated in the unlikely event that the co-morbid condition may be associated with a risk of MH. As there is no interaction between the mechanism of action of dexmedetomidine and the pathophysiology of MH, or effects on mitochondrial function, we postulated that it would be a safe and effective agent in this patient population. Furthermore, norepinephrine and epinephrine may trigger MH, so the sympatholytic effect of dexmedetomidine may be an additional benefit of this agent.[13,14]

In our case, dexmedetomidine was used in conjunction with remifentanil in a patient that had an unspecified mitochondrial disorder and associated myopathy. The co-morbid mitochondrial disorder was a relative contraindication to the use of propfol. Alternative intravenous anaesthetic agents for these patients may have included ketamine or barbiturates as the primary agent. The main disadvantage of these agents is a prolonged recovery time.

As with any anaesthetic agent, adverse effects on haemodynamic and respiratory function may be experienced with dexmedetomidine. Haemodynamic effects generally include bradycardia or hypotension.[12] These effects are more likely in scenarios when the negative chronotropic effects of dexmedetomidine may be exaggerated (hypothermia, or during vagotonic procedures such as laryngoscopy), following large or rapid bolus doses of dexmedetomidine, or in patients with co-morbid cardiac conduction disorders. In our patient, we noted a five-to-six minute period of hypotension during the co-administration of dexmedetomidine and remifentanil. As this hypotension could not be attributed to surgical manipulation, hypovolaemia, or a primary disturbance of myocardial contractility, it was likely to result from the haemodynamic effects of these two agents. Although the decrease in BP was significant, there was an immediate response, noted to the discontinuation of the two agents and administration of a small dose of phenylephrine. As there was a continued increase of the BP back to its baseline value over the ensuing five to six minutes, no further therapy was considered necessary. Given the magnitude of the event, if there had not been an immediate response to these interventions, more aggressive therapy (epinephrine) would have been considered.

In general, patients with mitochondrial disorders can present unique challenges to the anaesthesia provider.[1-5] Specific attention to intraoperative fluid management is necessary in these patients. Preoperative fasting should be limited, as patients with mitochondrial disorders may develop lactic acidosis, especially during periods of stress, including fasting and surgical trauma. When these patients are held nil per os, supplemental glucose-containing fluids should be administered. Given the propensity for the development of lactic acidosis, lactate-containing fluids should be avoided. Stresses which may provoke increased energy requirements (inadequate anaesthesia, pain or hypothermia) should be prevented. An aggressive pain management plan should be part of the perioperative plan. Although the literature documents the safe use of opioids in these patients, alternative techniques, including regional anaesthesia or adjunctive agents (acetaminophen or nonsteroidal anti-inflammatory agents), should be used to limit the opioid dose.

Conclusion

In summary, patients with disorders of mitochondrial function may be extremely susceptible to medications that alter mitochondrial function, such as propofol. This case exhibits the effective use of a dexmedetomidine-based TIVA in a patient with an unspecified mitochondrial disorder. Our anecdotal experience suggests that dexmedetomidine is a safe and effective agent in these patients, and can be used as an alternative to inhaled or other intravenous anaesthetic techniques.

References

1. Dhananjay DN, Sundar S, Thomas KP, et al. Anaesthetic challenges in a patient with mitochondrial cytopathy undergoing surgery. Indian J Anaesth. 2007;51:47-49.
2. Driessen JJ. Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist. Curr Opin Anaesthesiol. 2008;21:350-355.
3. Footitt EJ, Sinha MD, Raiman JAA, et al. Mitochondrial disorders and general anaesthesia: a case series and review. Br J Anaesth. 2008;100:436-441.
4. Ross AK. Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child. Pediatr Anaesth. 2007;17:1-6.
5. Driessen J, Willems S, Derksen S, et al. Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects. Pediatr Anaesth. 2007;17:16-21.
6. Casta A, Quackenbush EJ, Houck CS, Korson MS. Perioperative white matter degeneration and death in a patient with a defect in mitochondrial oxidative phosphorylation. Anaesthesiology. 1997;87:420-425.
7. Smith I, White PF, Nathanson M, et al. Propofol: an update on its clinical use. Anaesthesiology. 1994;81:1005-1043.
8. Ortiz-Gomez JR, Souto-Ferro JM. Anesthesia for a patient with mitochondrial respiratory chain complex III deficiency. Rev Esp Anestesiol Reanim. 2006;53:575-579.
9. Cheam EW, Critchley LA. Anesthesia for a child with complex I respiratory chain enzyme deficiency. J Clin Anaesth. 1998;10:524-527.
10. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia. 2007;62:690-701.
11. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet. 2001;24;357:606-607.
12. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Paediatr Crit Care Med. 2007;8:115-131.
13. Mukhtar AM, Obayah EM, Hassona AM. The use of dexmedetomidine in pediatric cardiac surgery. Anaesth Analg. 2006;103:52-56.
14. Haggendal J, Jonsson L, Hohansson G, et al. Disordered catecholamine release in pigs susceptible to malignant hyperthermia. Pharmacol Toxicol. 1988;63:257-261.