JPPT

CASE REPORT

Dexmedetomidine as Part of Balanced Anesthesia Care in Children With Malignant Hyperthermia Risk and Egg Allergy

Elisabeth Dewhirst, MD,[1] Aymen Naguib, MD,[1] and Joseph D. Tobias, MD[1,2]

Departments of [1]Anesthesiology and [2]Pediatrics, Nationwide Children's Hospital and The Ohio State University, Columbus, Ohio

Malignant hyperthermia is an acute hypermetabolic crisis triggered in susceptible patients by the administration of succinylcholine or a volatile anesthetic agent. When anesthesia care is provided to malignant hyperthermia-susceptible patients, a total intravenous anesthesia technique with propofol is frequently chosen. However, coexisting allergies to egg and soybeans may contraindicate the use of propofol. We present our experience with the use of dexmedetomidine as part of the anesthesia regimen in 3 patients with family histories of malignant hyperthermia and personal histories of egg or soybean allergies. In 2 patients, dexmedetomidine was used as part of a general anesthesia regimen and for sedation during spinal anesthesia in the third patient. Previous reports of the use of dexmedetomidine in patients susceptible to malignant hyperthermia are reviewed, and its benefits in such patients are discussed.

INDEX TERMS balanced anesthesia, dexmedetomidine, egg allergy, malignant hyperthermia

ABBREVIATIONS BIS, bispectral index; $ETCO_2$, end-tidal carbon dioxide; FDA, Food and Drug Administration

J Pediatr Pharmacol Ther 2011;16(2):113–117

INTRODUCTION

Malignant hyperthermia is an acute hypermetabolic crisis triggered in susceptible patients by the administration of succinylcholine or a volatile anesthetic agent. Although the incidence of malignant hyperthermia is only 1 case in 15,000 patients in the pediatric population, if it is untreated, the mortality exceeds 80%.[1] The primary defect responsible for malignant hyperthermia lies in the calcium release channel of the sarcoplasmic reticulum (the ryanodine receptor).[2] More than 30 mutations in 6 loci of the ryanodine receptor (*RYR1*) gene have been implicated in those who develop malignant hyperthermia; however, the pattern of inheritance, initially thought to be autosomal dominance with variable penetrance, is under investigation. Following the patient's exposure to a triggering agent (e.g., inhalational anesthetic agents or succinylcholine), excessive calcium is released into the cytoplasm, which produces myofibrillar contraction, depletion of high-energy phosphate compounds, lactic acid and carbon dioxide, metabolic acidosis, and generation of heat. Damage to cell membranes results in rhabdomyolysis, with the release of potassium and myoglobin. Ongoing muscle contraction and hypermetabolism lead to clinical signs and symptoms including muscle rigidity, metabolic acidosis, tachycardia, hypercarbia, and elevated temperature (i.e., increase of central temperature by more than 2°C/hr). Treatment includes elimination of the triggering agent, administration of dantrolene, and treatment of the results of the hypermetabolic state.[3] More commonly, anesthesia providers are faced with providing anesthesia for patients who have a family history of malignant hyperthermia. In such cases, total intravenous (IV) anesthesia can be provided, generally by using propofol. In even rarer cases, coexisting egg or soybean allergies may preclude the use of propofol.

Address correspondence to: Joseph D. Tobias, MD, Chairman, Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, The Ohio State University, 700 Children's Drive, Columbus, OH 43205, e-mail: Joseph.Tobias@Nationwidechildrens.org
© 2011 *Pediatric Pharmacy Advocacy Group*

Dexmedetomidine (Precedex, Hospira Pharmaceuticals, Lake Forest, IL) is an α_2-adrenergic agonist that initially received Food and Drug Administration (FDA) approval in the United States in 1999 for the sedation of adults during mechanical ventilation. In 2009, dexmedetomidine subsequently received FDA approval for monitored anesthesia care. Although it was FDA approved only for use in adults, dexmedetomidine has been shown to be efficacious in several different clinical scenarios in infants and children, including sedation during mechanical ventilation, procedural sedation, supplementation of postoperative analgesia, prevention of emergence delirium, and treatment of withdrawal.[4] We present 3 patients who presented with a family history of malignant hyperthermia and allergy to egg and/or soy beans, who received dexmedetomidine as part of a balanced anesthesia technique.

CASE REPORTS

These patients were cared for at the University of Missouri (Columbia, Missouri). The retrospective review of these cases and presentation of the material in this format were approved by the institutional review board at the University of Missouri. Following our protocol for managing malignant hyperthermia, the operating room was prepared in the same manner for all 3 children. Each patient was scheduled as the first case of the day. The anesthesia machine was prepared by performing a 1-hour high gas flush at 10 L/min, removal of the vaporizers, and replacement of the soda lime to ensure removal of any residual inhalational anesthetic agent.

Patient 1

A 6-year-old boy weighing 27 kg presented for adenotonsillectomy. His family history was positive for malignant hyperthermia, since his father had been diagnosed by muscle biopsy results. The child also had a history of anaphylaxis to egg protein, documented by provocative skin test results. Following premedication with 5 mg/kg oral ketamine (Ketalar, JHP Pharmaceuticals, Rochester, MN) and 0.5 mg/kg oral midazolam (midazolam syrup; Roxane, Columbus, OH), the patient was transported to the operating room, where routine American Society of Anesthesiologists' monitors were placed (for continuous electrocardiography, pulse oximetry, noninvasive blood pressure device, end-tidal carbon dioxide [$ETCO_2$], and temperature). Nitrous oxide (70%) in oxygen was administered for 3 minutes, and a peripheral IV cannula was placed. Dexmedetomidine was administered at a loading dose of 1 mcg/kg over 10 minutes, followed by a 1 mcg/kg/hr continuous infusion. The bispectral (BIS) index decreased from 72 to 54 with the administration of dexmedetomidine. Neuromuscular blockade with rocuronium (0.3 mg/kg; Zimuron, Merck-Schering-Plough, Whitehouse Station, NJ) was used to facilitate tracheal intubation. Maintenance anesthesia consisted of 70% nitrous oxide in oxygen, 0.1 mg/kg IV morphine (Astramorph; APP Pharmaceuticals, Schaumburg, IL), and the dexmedetomidine infusion. Antiemetic prophylaxis included 0.5 mg/kg IV dexamethasone (Decadron, APP Pharmaceuticals, Schaumburg, IL) and 0.15 mg/kg IV ondansetron (Zofran, Sandoz Pharmaceuticals, Princeton, NJ). An acetaminophen suppository (40 mg/kg; Actavis, Lincolinton, NC) was administered at the beginning of the case to provide additional postoperative analgesia. The BIS index during the maintenance anesthesia varied from 38 to 52. The surgical procedure lasted 40 minutes. At the completion of the procedure, the dexmedetomidine infusion and the nitrous oxide were discontinued. Morphine (0.05 mg/kg IV) was administered for postoperative analgesia. Residual neuromuscular blockade was reversed with glycopyrrolate (Robinul, Baxter, Deerfield, IL) and neostigmine (Prostigmin, Baxter, Deerfield, IL). Ten minutes after the dexmedetomidine infusion was discontinued, the patient's trachea was extubated. His postoperative course was uneventful, and after 2 hours of temperature monitoring, he was discharged home.

Patient 2

A 12-year-old boy weighing 52 kg presented for placement of a femoral nail for treatment of a traumatic femur fracture. His mother had been diagnosed with malignant hyperthermia, which had been found by muscle biopsy results; and the patient had a history of anaphylaxis to egg and soybean proteins, documented by provocative skin testing results. The IV cannula was present and fully functional on arrival to the preoperative holding area. Following premedication with IV midazolam (2 mg), the patient was transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. A BIS monitor was placed, which read 84 to 90. Dexmedetomidine was administered at a loading dose of 1 mcg/kg over 10 minutes, followed by continuous infusion of 1 mcg/kg/hr. The BIS index decreased from 84 to 90 to 50 to 60 with the administration of dexmedetomidine. Supplemental oxygen (2 L/min) was administered, and $ETCO_2$ was monitored via a nasal cannula. The patient was placed in the left lateral decubitus position. The lumbar area was

prepped with chlorhexidine, and local infiltration of 1% lidocaine was administered subcutaneously at the third and fourth lumbar ($L_{3–4}$) interspace. A 24-gauge 3.5-inch spinal needle was inserted into the $L_{3–4}$ interspace until free flow of cerebrospinal fluid was obtained. Isobaric bupivacaine (7.5 mg) with epinephrine was then administered into the interspace, and the patient was turned to the supine position. A bilateral T_8 sensory level was obtained. During the 80-minute surgical procedure, the dexmedetomidine infusion was continued at 0.7 to 1 mcg/kg/hr to maintain the BIS index at 50 to 70. The patient slept throughout the surgical procedure. The $ETCO_2$ varied from 42 to 48 mmHg. At the completion of the procedure, the dexmedetomidine infusion was discontinued, and the patient was transported to the Post-Anesthesia Care Unit. His postoperative course was uneventful, and after 2 hours of temperature monitoring, he was discharged to the inpatient ward.

Patient 3

A 4-year-old boy weighing 22 kg was scheduled for craniotomy and resection of a medulloblastoma. His family history was positive for malignant hyperthermia (the father had been diagnosed by positive muscle biopsy results), and the patient had a history of anaphylaxis to egg protein, documented by provocative skin testing results. Following premedication with oral ketamine (0.5 mg/kg) and midazolam (0.5 mg/kg), the patient was transported to the operating room, where routine American Society of Anesthesiologists' monitors were placed. Nitrous oxide (70%) in oxygen was administered for 3 minutes, and a peripheral IV cannula was placed.

Infusions of dexmedetomidine (loading dose of 1 mcg/kg over 10 minutes, followed by an infusion at 1 mcg/kg/hr) and remifentanil (loading dose of 3 mcg/kg, followed by an infusion of 0.2 mcg/kg/min [Ultiva, Hospira, Lake Forest, IL]) were started. The BIS index decreased from 78 to 50 with the administration of dexmedetomidine and remifentanil. Neuromuscular blockade with IV rocuronium (1 mg/kg; Zemuron, Merck-Schering-Plough, Whitehouse Station, NJ) was used to facilitate tracheal intubation. Maintenance anesthesia consisted of 50% nitrous oxide in oxygen, remifentanil at 0.2 to 0.5 mcg/kg/min, and dexmedetomidine at 1 mcg/kg/hr. The BIS index during maintenance anesthesia varied from 36 to 54. The surgical procedure lasted 4 hours 20 minutes. At the completion of the procedure, the dexmedetomidine infusion, the remifentanil infusion, and the nitrous oxide were discontinued. Morphine (0.05 mg/kg IV) was administered for postoperative analgesia. Residual neuromuscular blockade was reversed with glycopyrrolate and neostigmine. Ten minutes after the dexmedetomidine infusion was discontinued, the patient's trachea was extubated, and he was transported to the Pediatric Intensive Care Unit. His postoperative course was uneventful.

DISCUSSION

The IV anesthetic agent propofol is a commonly chosen alternative to inhalational anesthetic agents in patients with susceptibility to malignant hyperthermia.[5] The only contraindication to propofol, listed by its manufacturer, is a known hypersensitivity to the product or its components, which include egg lecithin and soybean oil. Additionally, specific formulations of propofol may be of concern given the use of sodium metabisulfite as the preservative. Although there is no definitive literature to support the potential for allergic reactions following propofol use in patients with egg or peanut oil allergies, many anesthesia providers consider such allergies a contraindication to the use of propofol.

Hofer et al[6] reported the use of propofol and rocuronium for emergent endotracheal intubation in a 14-month-old boy with respiratory failure. The infant had a history of egg, peanut oil, and mold allergies. Shortly after propofol and rocuronium were administered, the patient had an acute reaction, with hypotension and tachycardia, which were attributed to anaphylaxis. The patient's anaphylactic reaction following propofol was rated as a possible adverse drug reaction, using the Naranjo probability scale.[7] Although the association remains controversial, the authors concluded that whenever possible, propofol should be avoided in patients with allergies to egg and/or soybean oil. Egg white proteins are identified as the responsible allergens,[8] while egg lecithin is a yolk protein. Similarly, the soybean oil present in propofol is refined, effectively negating its allergenic protein content.[9] In addition, most egg allergies are mild and spontaneously resolve with age.[8]

Because the patients in our case series had a known anaphylaxis to eggs and/or soybeans, it was decided to pursue alternative IV anesthetic agents. Dexmedetomidine is a centrally acting α_2-adrenergic agonist with sedative, sympatholytic, and analgesic properties. Compared to clonidine, dexmedetomidine has a shorter half-life (2–3 hours versus 12–24 hours, respectively) and a higher affinity for the α_2 than for the α_1 receptor (1620:1 versus 220:1, respectively).[10] Although dexmedetomidine has not been approved by the FDA in the United States for use in pediatric patients, there is

growing experience with its use in the pediatric population in various clinical scenarios.[4] Like all sedative/anesthetic agents, adverse effects on hemodynamic function may be seen with dexmedetomidine. Although we did not note any clinically significant changes in vital signs, bradycardia and hypotension may occur. These effects are more likely in scenarios in which the negative chronotropic effects of a drug may be exaggerated (e.g., hypothermia or during vagotonic procedures such as laryngoscopy) following large or rapid bolus doses or in patients with comorbid cardiac disorders.[4]

To date, there are limited data regarding the use of dexmedetomidine in malignant hyperthermia-susceptible patients. As there is no interaction between the mechanism of action of dexmedetomidine and the pathophysiology of malignant hyperthermia, dexmedetomidine is postulated to be safe in this setting. Because norepinephrine and epinephrine may trigger malignant hyperthermia,[11] the sympatholytic effect of dexmedetomidine has been suggested as an additional benefit of this agent.[11]

There are two previous reports regarding the use of dexmedetomidine in malignant hyperthermia-susceptible patients.[12,13] Unger[12] reported using a combination of dexmedetomidine, propofol, nitrous oxide, and fentanyl to provide anesthesia in a 59-year-old woman with malignant hyperthermia diagnosed by muscle biopsy results. Dexmedetomidine dosing included a loading dose of 1 mcg/kg administered over 10 minutes, followed by an infusion of 0.6 mcg/kg/hr during the procedure and 0.4 mcg/kg/hr for the initial 30 minutes in the Post-Anesthesia Care Unit. The propofol was titrated to maintain a BIS index of 40 to 55. There were no adverse effects related to the anesthesia care, and the patient had an uncomplicated perioperative course.

Hudcova and Schumann[13] reported managing a 35-year-old woman with a family history positive for malignant hyperthermia, who was undergoing removal of two retroperitoneal neuroendocrine tumors. The expected prolonged operative time and the coexisting elevated catecholamine levels from the tumor led to a concern for the risk of propofol infusion syndrome. Therefore, the authors decided to use dexmedetomidine as part of the intraoperative anesthesia care to limit the propofol dose to 50 to 70 mcg/kg/min. Following anesthetic induction, a dexmedetomidine infusion was started at a dose of 0.7 mcg/kg/hr. Fluctuations in blood pressure were noted intraoperatively. Hypertension, which occurred during tumor manipulation, was treated with sodium nitroprusside, esmolol, and phentolamine. Following tumor resection, hypotension was treated with volume resuscitation, phenylephrine, and a decrease in the dexmedetomidine infusion to 0.2 mcg/kg/hr. Following the 10-hour 49-minute surgical procedure, the propofol and dexmedetomidine infusions were discontinued, and the patient's trachea was extubated. The patients' postoperative course was uneventful.

General anesthesia care for patients who are susceptible to malignant hyperthermia includes proper preparation of the operating room as outlined in our case reports and avoidance of triggering agents. In many instances, anesthesia care includes total IV anesthesia with propofol. Each of our 3 patients had a family history that was positive for malignant hyperthermia, with a first-degree relative diagnosed from muscle biopsy results. They also had anaphylaxis to egg and/or soybean that was documented by provocative skin testing results. Two patients required general anesthesia and endotracheal intubation, while spinal anesthesia was used in the third patient. All patients received dexmedetomidine at a loading dose of 1 mcg/kg, followed by a continuous infusion starting at 1 mcg/kg/hr. Our anecdotal experience combined with that in previously reported literature further supports the use of dexmedetomidine as part of a balanced anesthesia for patients who may be susceptible to malignant hyperthermia.

Alternative IV anesthetic agents for these patients may have included ketamine or the barbiturates. The main disadvantage of these agents is a prolonged recovery time. A newly introduced agent, fospropofol disodium, may also be considered in such patients. It is a prodrug of propofol and is water soluble, without the egg and soybean-based emulsion preparation of propofol.[14] However, it is currently not listed on the formulary of many institutions and was not available at the time these patients presented for anesthesia care.

In summary, we present anecdotal experience with the use of dexmedetomidine as part of intraoperative anesthesia care for 3 pediatric patients with a family history of malignant hyperthermia and a personal history of allergy to egg or soybean. In 2 patients, dexmedetomidine was used as part of a general anesthetic in combination with nitrous oxide and an opioid (morphine or remifentanil). In the third patient, dexmedetomidine was used as an agent for monitored anesthesia care during spinal anesthesia. Given its beneficial physiologic effects, dexmedetomidine as been increasingly used in various clinical scenarios in the pediatric population. Because propofol was contraindicated, we specifically used dexmedetomidine; however, propofol, also provides a viable option in many other patient populations as part of a balanced anesthesia regimen.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGEMENT At the time of this review and report, Dr. Tobias was a faculty member at the University of Missouri.

REFERENCES

1. Britt BA, Kalow W. Malignant hyperthermia: a statistical review. *Can Anaesth Soc J*. 1970; 17(4):293-297.
2. Mickelson JR, Gallant EM, Litterer LA, et al. Abnormal sarcoplasmic reticulum ryanodine receptor in malignant hyperthermia. *J Biochem Chem*. 1988;263(19):9310-9316.
3. Harrison GG. Control of the malignant hyperthermic syndrome in MHS swine by dantrolene sodium. *Br J Anaesth*. 1975;47(1):62-67.
4. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med*. 2007;8(2):115-131.
5. Smith I, White PF, Nathanson M, et al. Propofol: an update on its clinical use. *Anesthesiology*. 1994;81(4):1005-1043.
6. Hofer KN, McCarthy MW, Buck, ML, Hendrick AE. Possible anaphylaxis after propofol in a child with food allergy. *Ann Pharmacother*. 2003;37(3):398-401.
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
8. Clark AT, Skypala I, Leech SC, et al. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. *Clin Exp Allergy*. 2010:40(8):1116-1129.
9. Ramazzotti M, Mulinacci N, Pazzagli L, et al. Analytic investigations on protein content in refined seed oils: implications in food allergy. *Food Chem Toxicol*. 2008;46(11):3383-3388.
10. Virtanen R, Savola JM, Saano V, et al. Characterization of selectivity, specificity and potency of medetomidine as an alpha$_2$-adrenoceptor agonist. *Eur J Pharmacol*. 1988:150(1-2): 9-14.
11. Haggendal J, Jonsson L, Hohansson G, et al. Disordered catecholamine release in pigs susceptible to malignant hyperthermia. *Pharmacol Toxicol*. 1988; 63(4):257-261.
12. Unger RJ. General anesthesia with dexmedetomidine in a malignant hyperthermia-susceptible woman. *Acta Anaesthesiol Scand*. 2006;50(10): 1312-1313.
13. Hudcova J, Schumann R. Undiagnosed catecholamine-secreting paraganglioma and coexisting carcinoid in a patient with MH susceptibility: an unusual anesthetic challenge. *J Anesth*. 2007;21(1):80-82.
14. Welliver M, Rugari SM. New drug, forpropofol disodium: a propofol prodrug. *AANA J*. 2009; 77(4):301-307.