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Case Report

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Remimazolam as an Adjunct to General Anesthesia During Surgery for Congenital Heart Disease in a Pediatric Patient With a Family History of Malignant Hyperthermia

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Abstract

Malignant hyperthermia (MH) is an inherited disorder of muscle physiology, triggered by various pharmacologic agents including succinylcholine or the volatile anesthetic agents. In susceptible patients, intraoperative care may be provided by total intravenous anesthesia (TIVA) with propofol or other sedative-hypnotic agents. Remimazolam is a novel benzodiazepine which possesses sedative, anxiolytic, and amnestic properties similar to those of midazolam. Metabolism by tissue esterases results in a half-life of 5 - 10 min, a limited context sensitive half-life, which may make it a suitable agent for continuous administration during TIVA. We present anecdotal experience with the use of remimazolam as an adjunct to general anesthesia during the intraoperative care of a 6-month-old patient undergoing surgery for congenital heart disease with cardiopulmonary bypass. Previous reports regarding the use of remimazolam in MH-susceptible patients are reviewed, and its role in this clinical scenario is discussed.

Keywords: Malignant hyperthermia; Remimazolam; Total intravenous anesthesia; Congenital heart disease; Pediatric anesthesiology

Introduction

Malignant hyperthermia (MH) is a familial disorder of muscle metabolism and physiology that results in an acute hypermetabolic syndrome, triggered by the administration of succinylcholine or a volatile anesthetic agent [1, 2]. The primary cellular defect has been identified in the calcium release channel of the sarcoplasmic reticulum known as RYR1 or the ryanodine receptor. A defect in the receptor leads to excessive cytosolic calcium following exposure to a triggering agent with ongoing skeletal muscle contraction and hypermetabolism leading to tachycardia, muscle rigidity, hypercarbia, respiratory and metabolic acidosis, and rhabdomyolysis. Treatment includes supportive care of the metabolic derangements and hyperthermia, discontinuation of triggering agents, and the administration of dantrolene. Most importantly, avoidance of triggering agents is mandatory in patients with a personal or family history of MH. For patients requiring general anesthesia, alternatives to volatile anesthetic agents generally include use of a total intravenous anesthetic (TIVA) technique with continuous infusions of intravenous agents such as propofol and synthetic opioids [3]. However, in patients with comorbid cardiac conditions, there may be deleterious effects of propofol on cardiovascular function including depressed myocardial contractility, a decrease in systemic vascular resistance (SVR), and bradycardia [4, 5].

Remimazolam is an ultra-short-acting benzodiazepine that acts as a positive allosteric modulator of the $GABA_A$ receptor and, unlike traditional benzodiazepines or propofol, it is metabolized by tissue esterases and therefore is not dependent on hepatic or renal pathways [6]. In addition, remimazolam has been shown to have fewer adverse hemodynamic effects compared to propofol [7]. We present anecdotal experience with its use as an adjunct to propofol anesthesia in a pediatric patient with a suspected family history of MH, who presented for cardiac surgery with cardiopulmonary bypass (CPB). Previous reports of the use of remimazolam in MH-susceptible patients are reviewed and its potential role in such patients discussed.

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio).

Case Report

Investigations

The patient was a 6-month-old, 5.9-kg female infant who was born at term with a history significant for complete atrioventricular canal defect (AVCD), who presented for operative repair.

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Diagnosis

The patient had no prior anesthetic history; however, the family history was notable for a first-degree relative (father) with a history of MH. The patient's father endorsed having an MH episode after an elective tonsillectomy at 1 year of age. The medical record was not available; however, the history was confirmed by the paternal grandmother.

Treatment

The patient was assigned an American Society of Anesthesiologists' physical status of 4. Given the concern for a possible MH reaction, the anesthesia team elected to proceed with an MH-safe anesthetic to include sedation with nitrous oxide in oxygen for placement of an intravenous cannula followed by TIVA using non-triggering anesthetic agents (remifentanil, remimazolam, and dexmedetomidine). The patient was held *nil per os* for 6 h. The anesthesia machine was prepared according to departmental policy for MH-susceptible patients, which included removal of the anesthesia vaporizers, scheduling the case as the first of the day, replacement of the carbon dioxide absorber and anesthesia circuit, and a high-flow (10 L/min) flush of the anesthesia machine for 1 h. Additionally, a supply of dantrolene and other supplies are always present in the operating room on a separate cart designated for the treatment of MH emergencies. Preoperatively, the patient was premedicated with oral midazolam (0.5 mg/kg) following our routine clinical practice and based on the availability of an oral formulation. The patient was transported to the operating room, and routine American Society of Anesthesiologists' monitors were placed. Given the patient's age, processed electroencephalography monitoring with the bispectral index was not used. Following the administration of 70% nitrous oxide in oxygen, peripheral intravenous access was obtained. Anesthesia was induced by infusions of remimazolam (10 µg/kg/min) and dexmedetomidine (0.5 µg/kg/min), which were administered through a dedicated infusion site to prevent inadvertent bolus doses. Once there was loss of consciousness and the lid reflex, endotracheal intubation was facilitated by the administration of fentanyl (25 µg) and rocuronium (5 mg). Following endotracheal intubation, a second peripheral intravenous cannula, an arterial cannula, and a central venous cannula were placed. After the patient was positioned and prepped for surgery, remifentanil was started (0.3 µg/kg/min), the dexmedetomidine was continued (0.5 µg/kg/min), and the remimazolam infusion increased to 12 µg/kg/min and then to 15 µg/kg/min. Following median sternotomy and the administration of heparin, the patient was cannulated for CPB and cooled to 32 °C. To limit effects on cardiac conduction, the dexmedetomidine infusion was discontinued during rewarming per our usual intraoperative pathway. During rewarming, a milrinone infusion was started at 0.25 µg/kg/min and continued for the first postoperative day (POD). Total CPB and aortic cross-clamp time were 149 and 119 min, respectively. To treat hypertension following CPB, several bolus doses of propofol (2 - 4 mg/kg) were administered, along with additional boluses of fentanyl (total 35 µg), and a nitroprusside infusion was briefly required (1 µg/kg/min). Following closure of the surgical incision, residual neuromuscular blockade was reversed with sugammadex (initial dose of 8 mg/kg followed by a second dose of 8 mg/kg). As train-of-four monitoring was not in use for this patient, sugammadex dosing, including the decision to give a second dose, was based on clinical assessment.

Follow-up and outcomes

The patient was transported to the intensive care unit (ICU) intubated due to residual sedation; however, he was extubated to a nasal cannula within 4 h of ICU admission. The oxygen requirement was weaned to room air within the first 24 postoperative hours. No clinical signs or concerns suggestive of MH, such as alterations in body temperature, heart rate (HR), arterial or end-tidal carbon dioxide, or serum potassium concentrations, were noted. No rhythm disturbances other than occasional premature ventricular contractions that did not require therapy, were noted during the perioperative period. The milrinone infusion was discontinued on POD 1. No other vasoactive agents were administered. Pain was well controlled with acetaminophen, ketorolac, and intravenous morphine as needed with transition to oral oxycodone on POD 2 at which time surgical chest tube drains and pacing wires were removed. The patient was transferred to the inpatient ward on POD 2 and discharged home on POD 6.

As shown in Table 1, the perioperative care and key events for the patient are summarized.

Discussion

Although an acute MH crisis is uncommon, anesthesia providers are often required to provide anesthesia for patients who have a family history of MH. Given that mutations in RYR1 are typically autosomal dominant, patients who have relatives with MH are considered MH-susceptible. A "non-triggering" anesthetic can be provided to such patients who are MH-susceptible, using a variety of intravenous anesthetic agents to achieve the triad of anesthesia, analgesia, and amnesia. While propofol has traditionally be used for TIVA and procedural sedation in these scenarios, the hemodynamic effects including peripheral vasodilation and decreased inotropy may limit its use in patients with comorbid cardiac conditions [8, 9]. Additional concerns include an increasing context-sensitive half-life after prolonged infusions, pain with injection, and the potential for propofol infusion syndrome [10, 11].

In contrast, remimazolam, which was approved by the Food and Drug Association (FDA) in 2020 for use in adults, has unique pharmacological properties that may be able to address the shortcomings of propofol as an intravenous anesthetic. Remimazolam has been shown to be safe in both adult and pediatric patients requiring procedural sedation or general anesthesia as both a primary and adjunctive agent [6, 12]. Due to

Table 1. Summary of Perioperative Care and Events

Phase of care	Interventions
Preoperative preparation	MH-safe anesthetic planned. Anesthesia machine was prepared according to departmental policy, which included removal of the anesthesia vaporizers, a first case of the day start, changing of the carbon dioxide absorber and anesthesia circuit, and a high flow (10 L/min) flush of the anesthesia machine for 1 h.
	Dantrolene and other supplies available on MH cart
Premedication and placement of IV cannula	Oral midazolam (0.5 mg/kg)
	70% nitrous oxide in oxygen for placement of IV cannula
Induction of anesthesia	Remimazolam (10 µg/kg/min) and dexmedetomidine (0.5 µg/kg/min)
	Endotracheal intubation was facilitated by the administration of fentanyl (25 µg) and rocuronium (5 mg).
Pre-CPB maintenance	Remimazolam increased to 12 µg/kg/min and then to 15 µg/kg/min.
	Remifentanil started and continued at 0.3 µg/kg/min.
	Dexmedetomidine continued at 0.5 µg/kg/min.
CPB	Remimazolam and remifentanil continued at same doses.
	Dexmedetomidine discontinued during rewarming.
	Milrinone started at 0.25 µg/kg/min.
Post-CPB	Milrinone continued at 0.25 µg/kg/min.
	Remimazolam 15 µg/kg/min and remifentanil 0.3 µg/kg/min.
	Hypertension following CPB treated with bolus doses of propofol (2 - 4 mg/kg)
	Additional boluses of fentanyl (total 35 µg) and short-term use of a nitroprusside infusion (1 µg/kg/min).
	Residual neuromuscular blockade reversed with sugammadex.
Transport to CTICU	Remifentanil and remimazolam discontinued.
	Milrinone 0.25 µg/kg/min.
	Tracheal intubation and mechanical ventilation continued.
Postoperative course	Tracheal extubation at 4 h postoperatively and oxygen requirement weaned to room air over 24 h.
	No clinical signs concerning for MH.
	No rhythm disturbances other than occasional PVC (no treatment required).
	Milrinone infusion was discontinued on POD 1.
	Discharged to the inpatient ward on POD 2
	Discharged home on POD 6.

MH: malignant hyperthermia; IV: intravenous; CPB: cardiopulmonary bypass; CTICU: cardiothoracic intensive care unit; PVC: premature ventricular contraction; POD: postoperative day.

its predictable metabolism by tissue esterases to inactive metabolites, remimazolam can be safely administered to patients with renal impairment as well as mild to moderate hepatic dysfunction. An additional benefit noted in anecdotal experience is a lack of impact on cardiac conduction function [13].

Both laboratory investigations and anecdotal clinical experience have suggested the safety of remimazolam in MH-susceptible patients. In an *in vitro* experiment, the responsiveness to caffeine was compared in HEK-293 cells expressing wild-type RYR1 with those of mutant RYR1 following perfusion with remimazolam or propofol [14]. Despite exposure to 100-fold higher concentrations than used clinically, neither remimazolam nor propofol promoted the caffeine-induced increase in intracellular calcium concentrations in cells expressing the mutant RYR1 receptor. This laboratory evaluation is further supported by anecdotal case reports outlining the successful use of remimazolam in MH or MH susceptible patients [15-19]. Our case adds another example, in a unique clinical scenario to this limited list. In addition to the paternal history of MH, this case is also unique due to several factors, including the patient's young age (6 months) and the use of CPB during surgery for congenital heart disease.

Given the limited experience with the use of remimazolam in infants and children, dosing parameters are extrapolated from the adult population, supplemented by the growing clinical experience in pediatric-aged patients. In adults, the induc-

tion of general anesthesia has typically been achieved either with a temporary infusion rate of 12 mg/kg/h (0.2 mg/kg per minute) for 1 - 5 min or with intermittent bolus doses of 0.1 - 0.2 mg/kg until loss of consciousness is observed. Maintenance doses range from 1 to 2 mg/kg/h (17 - 33 µg/kg/min), with the higher end of the range being used if remimazolam is the sole agent for general anesthesia and not used to supplement propofol or a volatile anesthetic agent. In our patient, dosing was based not only on published clinical experience from the literature, but also our institutional experience. As we used remimazolam as an adjunct to other agents, dosing varied from 10 to 15 µg/kg/min. However, significant variations in pharmacokinetics may be present during surgery for congenital heart disease including hemodilution, use of CPB, and alterations in body temperature. Additional studies are necessary to better define safe and effective pediatric dosing guidelines in various patient populations.

Learning points

MH is an acute hypermetabolic syndrome, triggered in susceptible patients by the administration of succinylcholine or a volatile anesthetic agent. The primary cellular defect responsible for MH has been identified as the calcium release channel of the sarcoplasmic reticulum (RYR1, ryanodine receptor). Patients with a family history of MH or who are MH susceptible can be safely cared for intraoperatively by the use of non-triggering agents (TIVA). Laboratory and anecdotal clinical experiences support the safety of remimazolam. Remimazolam is an ultra-short acting benzodiazepine, which undergoes metabolism by tissue esterases. It has been used successfully in adult and pediatric patients undergoing both procedural sedation and general anesthesia. Potential advantages of remimazolam over propofol include a more favorable effect on cardiovascular dynamics and a limited context-sensitive half-life.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from a parent for anesthetic care and use of patient data for publication purposes. The patient information was deidentified for publication.

Author Contributions

BB provided clinical care for the patient, performed the initial case review and manuscript preparation, and edited subsequent revisions. CM provided clinical care for the patient and participated in manuscript preparation. JT contributed to literature review and editing of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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