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Case Report

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Remimazolam in a Pediatric Patient With a Suspected Family History of Malignant Hyperthermia

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Abstract

Malignant hyperthermia (MH) is an acute hypermetabolic crisis, triggered in susceptible patients by the administration of succinylcholine or a volatile anesthetic agent. When providing anesthetic care for MH-susceptible patients, a total intravenous anesthetic technique with propofol or other sedative hypnotic is frequently chosen. Remimazolam is a novel benzodiazepine which, like midazolam, has sedative, anxiolytic, and amnestic properties. Ester metabolism results in a half-life of 5-10 min and a limited context sensitive half-life. We present anecdotal experience with its use as an adjunct to propofol anesthesia in a patient with a suspected family history of MH. Previous reports of the use of remimazolam in MH-susceptible patients are reviewed and its potential role in such patients discussed.

Keywords: Malignant hyperthermia; Remimazolam; Total intravenous anesthesia

Introduction

Malignant hyperthermia (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 1) [1]. Following exposure to triggering agents, excessive calcium release into the cytoplasm of skeletal muscle fibers results in myofibrillar contraction, depletion of high energy phosphate compounds, lactic acid and carbon dioxide production, and hyperthermia. Ongoing muscle contraction and hypermetabolism leads to tachycardia, muscle rigidity, hypercarbia, respiratory and metabolic acidosis, and rhabdomyolysis. Treatment includes elimination of triggering agents, administration of dantrolene, and supportive treatment of the consequences of the hypermetabolic state [2, 3].

Though 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 will be considered MH-susceptible. A "non-triggering" anesthetic can be provided to those patients who are MH-susceptible by using a total intravenous anesthetic (TIVA) technique. Although propofol is commonly used, benzodiazepines are also considered safe in this patient population. Remimazolam is a novel benzodiazepine which undergoes ester metabolism with a half-life of 5-10 min and a limited context sensitive half-life [4]. We present anecdotal experience with its use as an adjunct to propofol anesthesia in a patient with a suspected family history of MH. 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-year-old, 24.3 kg girl who presented for a dental rehabilitation procedure under general anesthesia. The patient had no significant past medical history and no prior surgical procedures.

Diagnosis

The family history indicated an anesthesia event concerning for possible MH in the paternal grandfather. After receiving succinylcholine, he was paralyzed and unable to wake for 5 h. He recalled requiring mechanical ventilation for 6 h postoperatively, related to the anesthetic. The parents of the patient specifically used the term "malignant hyperthermia" when discussing anesthesia concerns. Additionally, the patient's father

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also relayed that several family members had received general anesthesia with "MH-precautions." As family anesthetic records were not immediately available, it was decided to proceed with a general anesthetic using non-triggering agents and departmental-based procedures for patients with MH susceptibility.

Treatment

The patient was assigned an American Society of Anesthesiologists (ASA) physical status II. She was *nil per os* for greater than 8 h. The anesthesia machine was prepared per department policy for MH-susceptible patients. The patient was transported to the operating room and routine ASA monitors were placed. After placement of a topical anesthetic cream, a peripheral intravenous cannula was placed, and anesthesia was induced by the administration of intravenous propofol (4 mg/kg). The trachea was intubated with a 5.0 mm cuffed endotracheal tube via the nasal route. Anesthesia was maintained by the administration of infusions of remimazolam (5 - 7 µg/kg/min) and propofol (50 µg/kg/min). The doses of propofol and remimazolam were adjusted based on the clinical and hemodynamic response to the procedure. Analgesia was provided by morphine (1 mg) and ketorolac (0.5 mg/kg). Prophylaxis against postoperative nausea and vomiting was provided by dexamethasone and ondansetron. Total surgical time was 75 - 80 min. Intraoperative fluids included 350 mL of lactated Ringer's. After the completion of the surgical procedure, the patient's trachea was extubated while spontaneously breathing and she was transported to the post-anesthesia care unit (PACU).

Follow-up and outcomes

She was observed and monitored for 75 min postoperatively in the PACU. Her postoperative course was unremarkable, and she was discharged home.

Discussion

Remimazolam is an ester-metabolized benzodiazepine that received approval by the United States Food & Drug Administration (FDA) in July 2020 for sedation of adult patients during invasive medical procedures that last ≤ 30 min, such as colonoscopy or bronchoscopy. Approval for remimazolam followed three clinical trials involving approximately 1,000 patients who received remimazolam for procedural sedation [5, 6]. Similar to other benzodiazpines, remimazolam induces inhibitory effects on the central nervous system by binding to gamma-aminobutyric acid-A ($GABA_A$) receptors and modulating the transmembrane movement of chloride. As an ester-based medication, it hydrolyzes quickly for a more rapid onset and offset than midazolam. Potential clinical applications include premedication prior to anesthetic care, procedural sedation for endoscopic procedures, sedation in the intensive care unit (ICU), and as an adjunct for intraoperative anesthetic care. Initial clinical experience in adults has demonstrated its efficacy for procedural sedation as well as an acceptable safety profile that includes limited effects on hemodynamic function, lack of pain with intravenous administration, organ-independent metabolic clearance, a reduced incidence of postoperative nausea and vomiting (PONV), and a rapid return to baseline neurologic function [7, 8].

Both intermittent bolus dosing and continuous infusions have been used as the sole-agent during procedural sedation and as a supplement to volatile anesthetics during general anesthesia in adults [7-10]. In a prospective randomized trial of 384 adults presenting for colonoscopy, comparing remimazolam and propofol (both administered by bolus dosing), procedure success rate was similar in the two groups (97% with remimazolam and 100% with propofol) [7]. Remimazolam was dosed with an initial bolus of 5 mg followed by subsequent bolus doses of 2.5 mg. Patients receiving remimazolam were less likely to experience administration site pain, hypotension, bradypnea, or desaturation than those patients who received propofol. The time to achieve adequate sedation was slightly longer with remimazolam (average time of 101 s versus 75 s). No difference was noted in the time for the patient to become fully alert or time to discharge. Similar findings were reported by the same investigators when comparing bolus dosing of remimazolam versus propofol for sedation during upper endoscopy [8].

In a prospective, randomized, multi-center trial, remimazolam was compared to open-label midazolam and placebo for sedation during adult bronchoscopy [9]. Following an initial dose of fentanyl (25 - 75 µg), placebo (n = 60), midazolam (1.75 mg, n = 60), or remimazolam (5 mg, n = 300) was administered in up to five doses to achieve a Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) score of 3/5. The success rate of completion of the procedure without the need for rescue sedatives was 80.6% with remimazolam, compared to 32.9% with midazolam, and 4.8% with placebo. Bronchoscopy was initiated sooner, and recovery times were shorter with remimazolam than with placebo or midazolam.

Following the successful use of remimazolam as the primary agent for procedural sedation, there has also been preliminary experience with its use as a supplement to general anesthesia during intraoperative care [11-15]. In a prospective, double-blinded, randomized controlled trial, sufentanil and remifentanil were paired with either remimazolam or propofol for the induction and maintenance of general anesthesia during adult urologic surgery [11]. In the remimazolam group, anesthesia was induced with remimazolam (0.2 - 0.3 mg/kg) and sufentanil (0.3 - 0.5 µg/kg) and then maintained with remimazolam (1 - 2 mg/kg/h) and remifentanil (0.2 - 0.3 µg/kg/min). In the propofol group, anesthesia was induced with propofol (2 - 3 mg/kg) and sufentanil (0.3 - 0.5 µg/kg) and then maintained with propofol (4 - 10 mg/kg/h) and remifentanil (0.2 - 0.3 µg/kg/min). Neuromuscular blockade was provided by cis-atracurium. Anesthetic depth was adjusted to maintain the bispectral index (BIS) at 40 - 60. Using a standardized recovery score (Quality of Recovery-15 scale), remimazolam patients had lower scores in emotional state and physical comfort categories on postoperative day 1, indicating a small decline in recovery rate as compared to propofol; however, no differences

were noted during the remainder of the study. When evaluating postoperative adverse effects, the incidence of nausea and vomiting, somnolence, and emergence delirium were higher in the remimazolam group, while the incidence of perioperative blood pressure instability was higher in the propofol group. Remimazolam demonstrated similar hemodynamic stability in a prospective trial of 67 adults, ASA physical status III surgical patients undergoing general anesthesia [12]. When compared to propofol, Doi et al reported less hypotension in adult surgical patients receiving remimazolam. Hypotension occurred in only 20.0% and 24.0% of patients treated with 6 and 12 mg/kg/h of remimazolam, respectively, compared to 49.3% of patients receiving propofol [13]. Additionally, injection site pain was reported in 18.7% of propofol patients, but was not reported in those receiving remimazolam.

The primary cellular defect responsible for MH has been identified as the calcium release channel of the sarcoplasmic reticulum, leading to excessive calcium release in response to triggering agents [1]. In an *in vitro* experiment, the responsiveness to caffeine was compared in HEK-293 cells expressing wild-type *RYR1* with that of mutant *RYR1* following perfusion with remimazolam or propofol [16]. 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 investigation is supported by an anecdotal report of the use of remimazolam in a 26-year-old with a suspected prior MH reaction [17]. Anesthesia was induced and maintained with fentanyl, remifentanil, and an infusion of remimazolam starting at 12 mg/kg/h. Neuromuscular blockade was provided by rocuronium and his trachea was intubated. The remimazolam infusion was reduced to 1.5 mg/kg/h for maintenance anesthesia during the 3 h surgical procedure. The infusions of remimazolam and remifentanil were discontinued at the conclusion of the procedure followed by reversal with sugammadex and flumazenil. The patient did not display any signs of acute MH crisis through the second postoperative day. Additional anecdotal clinical work has suggested the safety and efficacy of remimazolam in various myopathic conditions including myotonic dystrophy and Duchenne muscular dystrophy [18, 19]. Similar to MH-susceptible patients, TIVA is generally chosen in these patients due to concerns regarding the administration of volatile anesthetic agents.

Although propofol is generally used during TIVA, remimazolam may offer specific advantages, as it is associated with a significantly lower incidence of injection pain and fewer adverse hemodynamic effects (hypotension and bradycardia) [20]. Because propofol is lipophilic and insoluble in water or other aqueous medium, it is formulated as an intravenous emulsion with 10% lipid containing soybean oil and egg lecithin. Potential concerns with the lipid component include anaphylactoid reactions in patients with egg or lipid allergies as well as hypertriglyceridemia during prolonged or high dose infusions [21, 22]. Propofol infusion syndrome is a potentially lethal complication of propofol administration, described exclusively during prolonged administration, especially in children [23]. Its occurrence is linked to the impact of propofol on mitochondrial function and oxidative phosphorylation in susceptible patients, which may result in lactic acidosis, cardiac dysfunction, electrolyte disturbances, and rhabdomyolysis. Although it has not been shown to be of clinical concern during short-term intraoperative infusions, Cravens et al reported a higher incidence of metabolic acidosis when comparing patients anesthetized with propofol infusions during radiofrequency ablation versus case-matched controls [24]. Furthermore, the use of propofol as the sole anesthetic agent during TIVA may be associated with unfavorable surgical conditions, the need for the administration of rescue anesthetic agents, as well as longer emergence and recovery times. Wu et al compared 3% sevoflurane to propofol (50 - 150 µg/kg/min) in pediatric patients during surgical procedures lasting less than 1 h [25]. Patients receiving propofol TIVA had a significantly higher incidence of intraoperative movement and required more rescue dosing with ketamine than those receiving sevoflurane. Moreover, patients receiving propofol had longer recovery times. Although the impact of propofol-based TIVA on emergence and time to tracheal extubation has been contradictory, the higher doses of propofol required to prevent movement during surgical stimulus may result in longer emergence compared to short-acting volatile agents, given the context-sensitive half-life of propofol [26-28]. The use of remimazolam as an adjunct, as demonstrated in our patient, may result in lower propofol requirements, and may mitigate these concerns.

Despite these potential advantages, remimazolam does not hold FDA approval for use in children and, to date, there has been only one previous anecdotal report of its use in a pediatric-aged patient. Horikosi et al reported the use of remimazolam as part of TIVA for a 4-year-old, 16 kg boy with Duchenne muscular dystrophy during inguinal herniorrhaphy and umbilicoplasty [18]. After the intravenous administration of fentanyl (100 µg), continuous infusions of remifentanil (1 µg/kg/min) and remimazolam (15 mg/h) were started. Once general anesthesia was obtained, rocuronium (10 mg) was administered and the trachea was intubated. Anesthesia was maintained with the same doses of remifentanil and remimazolam. The remimazolam infusion was decreased (5 mg/h) 30 min prior to the end of surgery. Residual neuromuscular blockade was reversed with sugammadex. It took approximately 20 min after the discontinuation of remimazolam for the patient to open his eyes to verbal command. A postoperative urine myoglobin examination was negative, and he was discharged home on the second postoperative day. In hopes of expanding FDA approval to the use of remimazolam in children, there are currently four trials registered at ClinicalTrials.gov enrolling pediatric patients for prospective studies to evaluate remimazolam for procedural sedation during magnetic resonance imaging (MRI), for premedication prior to anesthetic care, and as an adjunct to intraoperative anesthetic care [29].

Patients presenting with a suspected family history of MH require anesthetic care with avoidance of triggering agents (succinylcholine and volatile anesthetic agents). Generally, TIVA with propofol is chosen in this patient population. As an ester-metabolized benzodiazepine, remimazolam may offer the benefit of limiting the dose of propofol and, thereby, the impact of propfol's context-sensitive half-life on awakening. Clinical experience with remimazolam as an adjunct to general

anesthesia or as a primary agent for anesthesia or procedural sedation in children has been minimal. In our pediatric patient, remimazolam was effective as an adjunct to propofol during a TIVA used for suspected family history of MH. An infusion of remimazolam at 5 - 7 µg/kg/min allowed for a reduction of the propofol dose to 50 µg/kg/min for maintenance anesthesia. No intraoperative concerns were noted, and recovery was rapid.

Learning points

MH is an acute hypermetabolic syndrome, related to a genetic defect in the calcium release channel of the sarcoplasmic reticulum. It is triggered in susceptible patients by the administration of succinylcholine or a volatile anesthetic agent, resulting in an increase in cytoplasmic calcium and a hypermetabolic response. To prevent an MH crisis during anesthetic care, non-triggering agents including intravenous anesthetic agents such as propofol, ketamine, dexmedetomidine, or opioids are administered. Remimazolam is a novel benzodiazepine which has sedative, anxiolytic, and amnestic properties similar to those of midazolam. As a benzodiazepine compound and as demonstrated by preliminary anecdotal experience and laboratory investigations, remimazolam is theoretically safe and can be used as part of TIVA in patients with MH. Ester metabolism results in non-organ dependent elimination, a half-life of 5 - 10 min, and a brief context-sensitive half-life with rapid awakening [30]. When compared with propofol, clinical trials have demonstrated that remimazolam is associated with less injection pain and fewer hemodynamic events. When compared with midazolam, remimazolam's rapid metabolism and short half-life provides the advantages of easy and rapid titration by continuous infusion as well as rapid recovery when the infusion is discontinued. As it is water-soluble, it avoids concerns regarding the lipid emulsion of propofol. Remimazolam may be a helpful adjunct during TIVA, by limiting the dose of propofol required to achieve ideal surgical conditions and facilitating a rapid recovery.

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None to declare.

Conflict of Interest

The authors deny any conflict of interest.

Informed Consent

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

Author Contributions

HP performed the initial case review and manuscript preparation, literature review, and editing of subsequent revisions. BLW 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 case report are available from the corresponding author upon reasonable request.

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