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Case Report

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Remimazolam for Sedation During Upper Gastrointestinal Endoscopy in an Adolescent

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Abstract

Remimazolam is a short-acting benzodiazepine that has recently received approval from the US Food and Drug Administration (FDA) for procedural sedation in adults. Similar to other benzodiazepines such as midazolam, remimazolam has sedative, anxiolytic, and amnestic properties. Rapid metabolism by plasma esterases results in a half-life of 5 - 10 min and a limited context sensitive half-life. Preliminary data from adult studies have demonstrated favorable hemodynamic stability, no pain on injection, and limited impact on ventilatory function. To date, its use as the primary agent for procedural sedation in pediatric-aged patients has been limited, as previous published reports of its use have detailed its administration as an adjunct to general anesthesia. We report anecdotal experience with the use of remimazolam for procedural sedation during an upper gastrointestinal endoscopy in a 15-year-old adolescent with multiple drug and food allergies. The role of remimazolam in procedural sedation is discussed, previous reports of its use in pediatric-aged patients are reviewed, and dosing algorithms are presented.

Keywords: Remimazolam; Total intravenous anesthesia; Procedural sedation; Benzodiazepines

Introduction

Pediatric patients typically require general anesthesia or deep sedation for upper endoscopy procedures including for esophagogastroduodenoscopy (EGD) [1-4]. When procedural sedation is chosen, there are several agents available including some combination of opioids, benzodiazepines, or propofol administered by intravenous bolus dosing or continuous infusions. In routine clinical practice, total intravenous anesthesia (TIVA) with the continuous infusion of propofol remains the most commonly used technique with a native airway and the maintenance of spontaneous ventilation [5-7]. Although generally safe and effective, specific patient-associated comorbid conditions or procedure-related requirements may mandate the use of alternative agents [8].

Remimazolam is a novel, ester-metabolized benzodiazepine that has been used for the sedation of adults during invasive medical procedures including gastrointestinal endoscopy and bronchoscopy. To date, its use in pediatric-aged patients has been anecdotal with limited information regarding its use as the primary agent for procedural sedation. We report the use of remimazolam for procedural sedation in an adolescent during EGD with biopsy and an EndoFLIP® procedure. The role of remimazolam in procedural sedation is discussed, previous reports of its use in pediatric-aged patients are reviewed, and dosing algorithms are presented.

Case Report

Investigations

The patient was a 15-year-old, 62.3 kg adolescent who presented for EGD with biopsy and an EndoFLIP® procedure [9]. The patient had a past medical history of eosinophilic esophagitis with painful dysphagia, esophageal dysmotility, central hypothyroidism, conversion disorder, anxiety, depression, and asthma. Since infancy, the patient had experienced symptoms of dysphagia, severe abdominal pain, gastro-esophageal reflux, and occasional emesis with most foods leading her to exercise a variety of dietary restrictions. The patient had been closely followed by an allergist and had more than 20 documented allergies to several foods, food products, and medications.

Diagnosis

During an EndoFLIP® procedure, balloon dilation is used to measure esophageal pressures. As volatile anesthetic agents and nitrous oxide may affect manometry readings and interfere with balloon dilation measurements during the procedure,

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TIVA is generally recommended to avoid impacting data collection.

Treatment

The patient's physical examination was unremarkable with a Mallampati class I airway and a thyromental distance of more than three finger breadths. There was no history of recent illnesses or symptoms, obstructive sleep apnea, or sleep-disordered breathing. Her *nil per os* status was confirmed as 8 h. A 20-gauge peripheral intravenous cannula was placed in dorsum of the right hand in the preoperative holding area. The patient was transported to the operating room and routine American Society of Anesthesiologists monitors were placed. A nasal cannula was placed to administer supplemental oxygen during the procedure and monitor end-tidal carbon dioxide. After a safety timeout was completed between the anesthesia and procedural team, a bolus dose of remimazolam besylate (Byfavo®) (0.03 mg/kg, 2 mg) was administered followed by a continuous infusion at a rate of 20 µg/kg/min into the peripheral intravenous cannula in her right hand. Subsequently, a second 20-gauge peripheral intravenous cannula was placed into the dorsum of her left hand without reaction from the patient to obtain blood for ongoing clinical care laboratory studies as requested by her treating physicians. The procedure was started approximately 10 min later. Anesthesia adjuncts for the procedure included two boluses of fentanyl (25 µg). One bolus of fentanyl was given along with the remimazolam bolus, and an additional bolus of fentanyl was given approximately 9 min after the remimazolam infusion was started but prior to the procedure start time to ensure that the patient had adequate analgesia for scope insertion given her history of painful dysphagia. A bolus of propofol (30 mg followed by 60 mg) was administered at the start of the procedure into her right-hand intravenous line after the patient moved with insertion of the endoscope. However, some resistance was noted when attempting to administer the propofol, and it was noted that the right hand peripheral IV, through which the remimazolam was infusing, had infiltrated for an unknown period of time. The proceduralist was able to continue the procedure during this time without the administration of other sedative agents as there was a clinically insignificant reaction to the procedure. The remimazolam infusion was then switched to the peripheral intravenous cannula in the left hand. No additional boluses of remimazolam or changes to the infusion rate were required to prevent movement during this time period. Prophylaxis against postoperative nausea and vomiting (PONV) was provided by ondansetron (4 mg). The remimazolam infusion was decreased to 10 µg/kg/min approximately 15 min into the procedure in order to expedite emergence time, and it was discontinued approximately 5 min prior to procedure end-time. The patient remained spontaneously breathing for the duration of the procedure. The patient's baseline vitals intraoperatively prior to medication administration or procedure start were a heart rate of 111, noninvasive blood pressure monitoring reading of 121/66, end-tidal carbon dioxide reading of 37 as measured using an end-tidal sampling line via nasal cannula, and an oxygen saturation of 100%. From the time of the procedure start to procedure finish, her noninvasive blood pressure readings ranged from 96 - 106/54 - 73, heart rate of 67 - 72, end-tidal carbon dioxide readings of 31 - 48, and oxygen saturation of 97-100% on 2 L of oxygen by nasal cannula.

Follow-up and outcomes

The remimazolam infusion was administered for a total of 37 min. The patient was transported to the post-anesthesia care unit (PACU) 9 min after stopping the infusion. On arrival to the PACU, the patient was responsive and able to answer questions. At the time of handoff in the PACU, the patient was fully awake, alert, and spontaneously ventilating without supplemental oxygen. She was discharged from the recovery room after 15 min of observation. Her postoperative course was unremarkable. She denied any recall of the procedure.

Discussion

Remimazolam is an ester-metabolized benzodiazepine that received initial approval by the FDA in July 2020 for sedation of adult patients during invasive medical procedures, including gastrointestinal endoscopy and bronchoscopy, lasting ≤ 30 min [10-12]. Similar to other benzodiazepines, remimazolam induces inhibitory effects on the central nervous system by binding to gamma-aminobutyric acid A receptors. As an ester-based medication, it is hydrolyzed quickly with a more rapid offset than midazolam and a limited context-sensitive half-life. 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 PONV, and a rapid return to baseline neurologic function [10-14].

In prospective trials for sedation in adults during gastrointestinal endoscopy and bronchoscopy, remimazolam has been shown to be more efficacious and have a more favorable adverse effect profile than other commonly used sedative agents, including propofol and midazolam. In a prospective, randomized trial comparing bolus dosing of remimazolam and propofol in 384 adults presenting for colonoscopy, procedure success rate was similar in the two groups (97% with remimazolam and 100% with propofol) [10]. Sedation was titrated to achieve adequate sedation as assessed using a standard clinical sedation scale (modified observer's assessment of alertness/sedation score ≤ 3). Remimazolam was dosed with an initial bolus of 5 mg followed by subsequent bolus doses of 2.5 mg as needed while propofol was administered as an initial bolus of 1.5 mg/kg followed by 0.5 mg/kg as needed. The time to achieve adequate sedation was slightly longer with remimazolam (average time of 101 versus 75 s). No difference was noted in the time for the patient to become fully alert or time to discharge. Patients receiving remimazolam were less likely to experience administration site pain, hypotension, bradypnea, or desaturation than those patients who received propofol. Similar findings were noted by the same group of investigators when comparing sedation using remimazolam versus propofol

Table 1. Previous Reports of Remimazolam Administration in Pediatric-Aged Patients

Authors and citation	Clinical scenario	Remimazolam dosing and outcomes
Horikoshi et al, 2021 [16]	4-year, 16 kg boy for laparoscopic herniorrhaphy, diagnosed with Duchenne muscular dystrophy due to elevated creatine phosphokinase	Anesthesia was induced with remimazolam (3 mg) and fentanyl (100 µg) followed by infusions of remifentanil (1 µg/kg/min) and remimazolam (15 mg/h). Neuromuscular blockade was provided by rocuronium followed by sugammadex for reversal at the completion of the procedure. The remimazolam infusion was reduced to 5 mg/h, 30 min prior to the end of the surgery. Emergence from anesthesia was slightly prolonged (20 min). Postoperative course was uncomplicated.
Kamata et al, 2022 [17]	12-year-old, 55 kg adolescent for brain tumor resection with cortical motor-evoked potential (MEP) monitoring	Remimazolam chosen instead of propofol, due to the patient's egg hypersensitivity. General anesthesia was induced with remimazolam at 6 mg/kg/h and remifentanil at 0.5 µg/kg/min. After loss of consciousness, remimazolam infusion was reduced to 1.5 mg/kg/h and rocuronium administered to facilitate endotracheal intubation. Neither additional rocuronium nor sugammadex was administered during MEP monitoring. Adequate maintenance anesthesia with MEP monitoring with infusions of remimazolam (0.9 - 1.5 mg/kg/h) and remifentanil (0.3 - 0.4 µg/kg/min).
Petkus et al, 2022 [18]	6-year-old, 24 kg girl with a family history of malignant hyperthermia	Remimazolam (5 - 7 µg/kg/min) administered as an adjunct to propofol (50 µg/kg/min) for maintenance anesthesia during dental surgery. Analgesia was provided by morphine (1 mg) and ketorolac (0.5 mg/kg). No intraoperative concerns were noted, and recovery was rapid.

during upper gastrointestinal endoscopy [11]. The authors noted equal efficacy with fewer adverse effects on hemodynamic and respiratory function in patients receiving remimazolam.

Shi et al prospectively compared general anesthesia with remimazolam or propofol in a cohort of 88 adult patients presenting for endoscopic ligation of esophageal varices [15]. Remimazolam was administered as a bolus of 0.2 mg/kg followed by an infusion of 1 - 2 mg/kg/h while propofol was administered as a bolus of 2 mg/kg followed by an infusion of 4 - 10 mg/kg/h. Adequate anesthesia with successful completion of the procedure was accomplished in all patients in both groups. When comparing outcomes between remimazolam and propofol, the time to loss of consciousness was longer (66 versus 46 s) with remimazolam compared to propofol. However, time to return of consciousness (67 versus 503 s), time to tracheal extubation (116 versus 525 s), and PACU stay were longer with propofol (860 versus 370 s) compared to remimazolam. Of note, flumazenil was routinely administered to patients who received remimazolam. Additionally, the incidence of hypotension and postoperative low oxygenation was greater in the propofol group.

To date, there are only three previous reports regarding the administration of remimazolam in pediatric-aged patients (Table 1) [16-18]. These reports describe the use of remimazolam in combination with remifentanil or propofol for TIVA during surgical procedures with endotracheal intubation, rather than as a primary agent for procedural sedation with a native airway as in our case report. These anecdotal reports suggest the potential benefits of remimazolam including a favorable hemodynamic profile, a rapid onset, predictable half-life with a rapid offset, and limited pain on injection. Despite the potential advantages outlined above when comparing remimazolam to other agents commonly used for procedural sedation or as adjuncts to general anesthesia, remimazolam has not received FDA approval for use in children. There are currently at least five ongoing studies registered at clinicaltrials.gov investigating its use in pediatric-aged patients, but results of these trials have not yet been released. We present the first case of its use as the primary agent for procedural sedation with a native airway and spontaneous ventilation in a pediatric-aged patient undergoing upper gastrointestinal endoscopy. Despite technical issues with an infiltrated intravenous infusion, remimazolam was effective during upper gastrointestinal endoscopy as a bolus dose of 0.03 mg/kg followed by an infusion of 20 µg/kg/min.

Learning points

Remimazolam received FDA approval for procedural sedation in adults in 2020. It is an ultra-short-acting benzodiazepine that undergoes rapid ester hydrolysis to inactive metabolites. Clinical studies have demonstrated a rapid onset and generally rapid recovery with limited impact on hemodynamic and respiratory function. There are currently at least five ongoing studies registered at clinicaltrials.gov investigating its use in pediatric-aged patients, but results of these trials have not yet been released contributing to the scarcity of data for the pediatric population. It is anticipated that these trials will provide valuable clinical information regarding efficacy, dosing regimens, and adverse effect profile in children and adolescents. Preliminary clinical experience suggests its role a primary agent for procedural sedation or as an adjunct to general anesthesia in combination with propofol or remifentanil.

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Financial Disclosure

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 deidentified for publication.

Author Contributions

AG provided clinical care for the patient, performed the initial manuscript preparation, literature review, and editing of revisions. JF participated in manuscript preparation, aided in the literature review, and assisted with editing of revisions. VN provided clinical care for the patient and participated in manuscript preparation. JDT participated in manuscript preparation (initial draft, revisions, and final version).

Data Availability

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

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