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Case Report

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Remimazolam for Sedation During Fiberoptic Intubation in an Adolescent

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Abstract

In specific clinical scenarios, fiberoptic intubation (FOI) may be the preferred technique for airway management and endotracheal intubation. In addition to topical anesthesia of the airway, sedation is frequently necessary, especially in younger patients, to facilitate the procedure. The goal is to facilitate the procedure by providing sedation, anxiolysis, and analgesia with maintenance of spontaneous ventilation. Remimazolam is a novel benzodiazepine with a short half-life and limited context sensitive half-life that can be titrated by continuous infusion. These novel properties may make it a suitable agent for sedation during FOI of the trachea. We report the novel use of a combination of remimazolam and remifentanil infusions to provide sedation during FOI in an adolescent. The basic pharmacology of remimazolam is presented and previous reports of its use for sedation during FOI are reviewed.

Keywords: Remimazolam; Benzodiazepine; Fiberoptic intubation; Difficult airway

Introduction

Airway management with endotracheal intubation is a key component in various clinical scenarios including perioperative anesthetic care, the intensive care unit (ICU) setting, and during resuscitation. Failure to establish an effective airway with the provision of oxygenation and ventilation can rapidly result in cardiac arrest and death [1]. Although the incidence of problematic airway management, defined as difficulties with mask ventilation or failure to achieve endotracheal intubation, is rare; its impact on outcome is significant as the Perioperative Cardiac Arrest (POCA) registry reports that adverse respiratory events remain the second most common cause for perioperative cardiac arrest in children [2, 3]. Given these concerns, there remains significant emphasis on airway assessment with identification of physical features that may result in problematic airway management, alternative techniques of endotracheal intubation other than direct laryngoscopy, as well alternative means to provide oxygenation and ventilation when bag-valve-mask ventilation and endotracheal intubation are unsuccessful.

In specific clinical scenarios, an awake technique such as fiberoptic intubation (FOI) may be preferred for airway management and endotracheal intubation [4]. Although effective topical anesthesia of the airway may improve the tolerability and success of the technique, some degree of anxiolysis or sedation is frequently necessary, especially in younger patients. As with other types of procedural sedation, the goal is to facilitate the procedure by providing sedation, anxiolysis, and analgesia with maintenance of spontaneous ventilation. Remimazolam is a novel benzodiazepine with a short half-life and limited context sensitive half-life that can be titrated by continuous infusion. These novel properties may make it a suitable agent for sedation during FOI of the trachea. We report the novel use of a combination of remimazolam and remifentanil infusions to provide sedation during FOI in an adolescent.

Case Report

Investigations

The patient was a 12-year-old male who presented for the release of burn scar contractures, selective photothermolysis and fractional ablative laser fenestrations of burns and traumatic scars for functional improvement.

Diagnosis

The preoperative physical exam revealed a thyromental distance of less than three finger-breadths, micrognathia, and limited mouth opening with scars on the neck and lower aspect of the chin. During a previous anesthetic procedure, an awake FOI was performed by the pediatric otolaryngology team. Al-

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though the trachea was intubated, the patient was uncomfortable and not able to cooperate during the awake procedure. After tracheal intubation, a grade 3 - 4 view was able to be obtained with direct laryngoscopy. The cardiac and respiratory examinations were unremarkable. Given the previous intubation experience, FOI with sedation was planned for the current anesthetic.

Treatment

The patient was held *nil per os* for 8 h and transported to the operating room where routine American Society of Anesthesiologists monitors were placed. Midazolam (2 mg) was administered intravenously to provide preoperative anxiolysis and glycopyrrolate (0.4 mg) as an anti-sialagogue. Once the patient was positioned on the operating room table, continuous infusions of remimazolam (15 µg/kg/min) and remifentanil (0.05 µg/kg/min) were started. The airway was topicalized with nebulized 4% lidocaine. The remifentanil infusion was increased to 0.1 µg/kg/min. After it was sprayed with additional lidocaine with oxymetazoline, an 18 French split nasopharyngeal airway (NPA) was placed in the right nare. The fiberoptic bronchoscope was advanced through the NPA, the nasal passage, the vocal cords, and into the trachea. The NPA was removed, and the endotracheal tube (ETT) was threaded over the fiberoptic bronchoscope into the trachea. During this time, the patient was sedated and cooperative. Correct placement was confirmed by auscultation and the presence of end-tidal carbon dioxide. The provision of sedation and FOI of the airway required approximately 15 min.

Follow-up and outcomes

The remainder of the surgical procedure and the postoperative course were unremarkable.

Discussion

Remimazolam is an ester metabolized derivative of the intravenous benzodiazepine, midazolam [5, 6]. It received the Food and Drug Administration (FDA) approval for procedural sedation in adults in 2020. While it has similar sedative, anxiolytic, and amnestic properties to midazolam, metabolism by tissue esterases results in a half-life of 5 - 10 min and a limited context-sensitive half-life. Preliminary clinical experience in adults has demonstrated its efficacy as a primary agent for procedural sedation, as the primary agent to provide general anesthesia, and as an adjunct to general anesthesia [7, 8]. Remimazolam was added to the formulary of our pediatric operating rooms in January 2022. Based on a review of its reported clinical experience, we initially recommended use in patients ≥ 12 years of age and ≥ 40 kg in weight. When requested for clinical use, remimazolam was reconstituted in normal saline from a lyophilized powder. Using the manufacturer provided vial (8 mg), the lyophilized powder is provided in a syringe, reconstituted to a final concentration of 2.5 mg/mL. The medication is administered using a programmed syringe pump with dosing calculated in µg/kg/min.

Various medications or combinations of medications may be chosen to provide sedation during FOI of the airway in patients with a potentially difficult airway. Of paramount importance in this clinical scenario is the preservation of spontaneous ventilation and the potential to rapidly reverse or allow the sedation effects to dissipate should tracheal intubation fail, and an alternative technique be required. In this scenario, preliminary clinical experience suggests the potential utility of remimazolam including preliminary trials demonstrating its ability to provide sedation and maintain spontaneous ventilation during procedural sedation for upper and lower gastrointestinal endoscopy, as well as airway procedures such as bronchoscopy [9-11]. In a prospective trial involving 346 adults presenting for upper gastrointestinal (GI) endoscopy, remimazolam was equally as effective as propofol with a lower incidence of adverse respiratory effects including a respiratory rate less than 8 breaths/min or an oxygen saturation less than 90% [12]. Overall, the incidence of respiratory depression with remimazolam was 9.8% compared to 17.9% with propofol ($P = 0.042$). When compared to a combination of dexmedetomidine and remifentanil for sedation during bronchoscopy, a combination of remimazolam and remifentanil provided equivalent efficacy, a more rapid onset and recovery time, and a lower incidence of hemodynamic effects [13].

Bekker et al reported anecdotal experience with the use remimazolam for sedation during FOI of the trachea in a 70-year-old woman with oropharyngeal squamous cell carcinoma [14]. Flexible fiberoptic laryngoscopy had previously revealed a mass at the base of the tongue extending to the midline and into the hypopharynx. On physical examination, the patient had a left-sided neck mass extending from the ear to the submental region, with minor tracheal deviation to the right. There was limited range of motion of the neck, 1 cm mouth opening, a Mallampati score of IV, and a thyromental distance of three finger-breadths. Therefore, the plan for airway management included sedated FOI of the trachea. Topical anesthesia of the airway was provided by nebulizing 5 mL of 4% lidocaine, and the patient was transported to the operating room. Additional topical anesthesia of the oropharynx was provided by topical benzocaine spray (Cetacaine®). Following pre-oxygenation, sedation and analgesia was provided by intravenous fentanyl (25 µg) and remimazolam (4 mg times two for a total of 8 mg). While the patient was still spontaneously breathing, an Ovassapian airway was placed in the mouth. The fiberoptic bronchoscope was advanced through the oropharynx into the airway. Once the vocal cords were visualized, additional remimazolam (7 mg) was administered and the bronchoscope and ETT advanced into the airway. Correct ETT placement was confirmed via direct visualization by the bronchoscope, auscultation, and end-tidal carbon dioxide. Fentanyl (75 µg), remimazolam (5 mg), propofol (40 mg), and rocuronium (30 mg) were administered followed by maintenance anesthesia with sevoflurane. The remainder of perioperative care was unremarkable. Alternatively, Zeng et al report successful use of intravenous remimazolam for for sedation during direct laryngoscopy and endotracheal intubation in an adult trauma victim

following failed FOI of the airway [15].

In adults, various dosing regimens have been reported including intermittent bolus dosing, bolus dosing followed by a continuous infusion, or use of only a continuous infusion with the rate adjusted to achieve the clinically desired effect. Dosing regimens are impacted by the clinical scenario as well as whether remimazolam is used as the primary agent or an adjunct. In adults, bolus dosing generally includes a 2.5 - 5 mg dose, which is intermittently repeated as needed to provide the desired level of sedation [9, 10, 13]. These doses have been used primarily for procedural sedation while maintaining spontaneous ventilation. When used as the primary agent for the induction of general anesthesia, doses up to 0.2 mg/kg have been reported. Infusions, titrated to effect, have varied from 1 - 2 mg/kg/h, which is similar to our dosing range of 15 µg/kg/min and that reported anecdotally in pediatric patients [16-18]. Given its rapid onset, the clinical effect of sedation can generally be achieved within 10 - 15 minutes of starting the infusion without a bolus dose. When a bolus dose is not used, a higher initial infusion rate may be chosen to speed the onset of the clinical effect. As remimazolam is a sedative hypnotic, additional agents may be needed to supplement analgesia for painful procedures.

As this novel agent does not hold FDA approval for use in children, before adding this medication to the formulary of our operating room, educational initiatives were completed including a presentation and literature review regarding the medication at a faculty and staff meeting and distribution of key published reports regarding its clinical use. Additionally, in cooperation with the pharmacy department, we developed departmental guidelines for medication preparation by the operating room pharmacy, dosing recommendation for intraoperative anesthesia and procedural sedation, and a quality improvement process for quarterly review of cases.

To date, published experience with the use of remimazolam in pediatric-aged patients remains anecdotal, primarily from individual case reports and small case series [16-18]. Dosing in both adults and children has included bolus administration and continuous administration. In our patient, given our clinical experience with this novel agent, preliminary preoperative sedation was provided by intravenous midazolam followed by a continuous infusion of remimazolam at 15 µg/kg/min. This was supplemented by remifentanil at 0.05 - 0.1 µg/kg/min and topical anesthesia of the airway to provide adequate sedation with maintenance of spontaneous ventilation during FOI of the airway in our patient. The rapid onset and short half-life of both remimazolam and remifentanil allowed their rapid titration by continuous infusion to achieve the desired depth of sedation.

In summary, we present anecdotal experience with the use of remimazolam for sedation during FOI of the airway in an adolescent with a difficult airway. Remimazolam is a novel benzodiazepine with a short half-life due to its rapid metabolism by tissue esterases. Preliminary clinical trials in adults have demonstrated its role in both procedural sedation and as an adjunct to general anesthesia. Its rapid onset and offset as well as the potential to reverse its sedative effects with flumazenil suggest that it may be a useful agent in clinical scenarios where maintenance of spontaneous ventilation is necessary.

Learning points

Remimazolam is a novel benzodiazepine that undergoes metabolism by tissue esterases thus resulting in a short half-life and limited context sensitive half-life that can be titrated by continuous infusion. Preliminary clinical experience in adults has demonstrated its efficacy as a primary agent for procedural sedation, as the primary agent to provide general anesthesia, and as an adjunct to general anesthesia. During FOI of the airway in patients with a potentially difficult airway, the preservation of spontaneous ventilation and the potential to rapidly reverse or allow sedative effects to dissipate are essential should tracheal intubation fail, and an alternative technique be required. Remimazolam has been effective in adults to provide sedation and maintain spontaneous ventilation during procedural sedation for upper and lower gastrointestinal endoscopy, as well as airway procedures such as bronchoscopy. Anecdotal experience has also demonstrated its efficacy for sedation during FOI of the airway. We suggest that prospective trials may be indicated with remimazolam in this unique clinical scenario.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, OH). Informed consent was obtained for use of de-identified information for publication.

Author Contributions

Case review and preparation of manuscript: MH. GM provided clinical care, manuscript review, and editing. Manuscript preparation, review, and editing: JDT.

Data Availability

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

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