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Case Report

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Remimazolam as a Primary Agent for Brief Invasive and Noninvasive Procedures: A Case Series

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Abstract

Remimazolam is a novel benzodiazepine with sedative and amnestic properties similar to midazolam. Ester metabolism results in a half-life of 5 - 10 min and a limited context sensitive half-life. We present preliminary retrospective experience with its use as a primary agent for procedural sedation for brief invasive and noninvasive procedures. The study cohort included seven patients, ranging in age from 14 to 51 years. Remimazolam administration included bolus dosing in two patients and a combination of bolus dosing followed by an infusion in the other five patients. The initial bolus dose of remimazolam ranged from 2.5 to 5 mg. Starting doses for the infusion ranged from 10 to 30 µg/kg/min with titration of the continuous infusion during the procedure, ranging from 10 - 30 µg/kg/min. Median dose infusion requirements were 15 - 20 µg/kg/min. One procedure was completed with remimazolam as the sole anesthetic agent while the other six patients received adjunctive agents. Changes in blood pressure or oxygen saturation were noted which resolved with minimal interventions such as a decrease in remimazolam infusion rate or an increase in supplemental oxygen administration. Our anecdotal experience provides further support for the efficacy of remimazolam as an agent for procedural sedation.

Keywords: Remimazolam; Benzodiazepine; Procedural sedation

Introduction

Remimazolam is an ester metabolized intravenous benzodiazepine [1, 2]. Although it has sedative and amnestic properties similar to midazolam, remimazolam undergoes hydrolysis by tissue-esterases with a reported half-life of 5 - 10 min and a limited context sensitive half-life. These properties allow for its administration by bolus and/or continuous infusion, with the attainment of a deep level of sedation while allowing for rapid awakening when its administration is discontinued. Following the Food and Drug Administration (FDA)-approval for use in adults in 2020, initial clinical trials demonstrated its efficacy for sedation of adults during invasive procedures such as gastrointestinal endoscopy and bronchoscopy [3-7]. These trials have demonstrated its efficacy with limited adverse effects on respiratory and hemodynamic function, a lack of pain with intravenous administration, reduction of post-procedure nausea and vomiting (PONV), and a rapid return to baseline neurologic function. We present initial experience with remimazolam as a primary agent for sedation during various invasive and noninvasive procedures with an emphasis on its use in the cardiac catheterization suite with patients requiring sedation during transesophageal echocardiogram (TEE), placement of a pericardial drain, cardioversion or placement of an automatic implantable cardioverter-defibrillator (AICD).

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This retrospective study was approved by the Institutional Review Board (IRB) of Nationwide Children's Hospital (IRB ID: MOD00014747) and conducted in accordance with the guidelines of the Declaration of Helsinki. As a retrospective study, the need for individual written informed consent was waived. Data collected during this study were stored in a secure location and only collaborators directly involved in the study had access. All electronic files were stored on a secure, password protected network.

Remimazolam was added to the hospital operating room formulary in January 2022 with preliminary use recommended for patients ≥ 12 years of age and ≥ 40 kg in weight. As part of an ongoing departmental quality assurance project, patients who received remimazolam in the main operating room were documented and audited by the pharmacy department. This list of patients was used as the basis for the retrospective review. From the list, we identified patients who received remimazolam as the primary agent for procedural sedation. As they were included in a separate study cohort, patients undergoing hemodynamic and/or interventional cardiac catheterization were not included in this review.

For clinical use, remimazolam was reconstituted in normal saline from a lyophilized powder using the manufacturer provided vial size to a final concentration of 20 mg/8 mL (2.5 mg/

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Table 1. Summary of Patient Demographics and Preoperative Comorbid Conditions

Patient number and procedure	Demographic data (age, gender, weight)	Patient comorbid conditions
1. EGD	27, male, 62 kg	Congenital heart disease including d-TGA status post Fontan procedure, hepatic cirrhosis, paroxysmal atrial flutter, amiodarone-induced hyperthyroidism, listed heart transplant candidate for failing Fontan physiology
2. Placement of pericardial drain	14, female, 87.5 kg	Recurrent idiopathic pericardial effusion, obesity
3. Cardioversion, TEE	28, male, 117.8 kg	Tricuspid atresia status post Fontan procedure, atrial flutter, permanent pacemaker, obesity
4. CT imaging	19, female, 47.3 kg	Oral-facial-digital syndrome, Dandy-Walker syndrome, cleft palate, partial epilepsy, global developmental delay, chronic lung disease, hydrocephalus with ventriculoperitoneal shunt, obstructive sleep apnea, bilateral sensorineural hearing loss, end-stage renal disease on hemodialysis, obesity
5. AICD placement	27, male, 60 kg	Becker's muscular dystrophy, dilated cardiomyopathy, obstructive sleep apnea
6. Halo removal	16, male, 64.1 kg	Polytrauma secondary to motor vehicle accident with C2 fracture, left vertebral artery injury, traumatic brain injury, lumbar spine transverse process fractures, pelvic fracture
7. Cardioversion	51, male, 71 kg	Tetralogy of Fallot status post BTT shunt and repair, atrial flutter, severe pulmonary regurgitation and tricuspid regurgitation status post valve replacement, intra-atrial re-entrant tachycardia, complete heart block with dual chamber pacemaker/AICD

EGD: esophagogastroduodenoscopy; d-TGA: dextro-transposition of the great arteries; TEE: transesophageal echocardiogram; CT: computed tomography; AICD: automatic implantable cardioverter-defibrillator; BTT: Blalock-Thomas-Taussig.

mL). The medication was provided in a syringe and administered by an infusion pump during intraoperative care. Based on our routine clinical practice for continuous intravenous infusions, administration was calculated in µg/kg/min and not mg/kg/h.

For the retrospective review, the following demographic data were obtained: age, weight, body mass index, associated comorbid conditions, and gender. Procedural information included the type of procedure, surgical duration, sedative and analgesic agents used in addition to remimazolam, their dose, and mode of administration (continuous or intermittent). Intraoperative and postoperative adverse effects including hypotension, bradycardia, respiratory arrest, apnea, bradypnea, or oxygen desaturation were identified. Hypotension was defined as a systolic blood pressure (SBP) < 90 mm Hg or a greater than 20% decrease from the patient's preoperative baseline if the baseline SBP was less than 90 mm Hg [8, 9]. Bradycardia was defined as a heart rate < 60 beats per minute. Bradypnea was defined as a respiratory rate (RR) < 12 breaths per minute [10]. Oxygen desaturation (SpO_2) was defined as peripheral oxygen saturation measured by pulse oximetry ≤ 90% or a decline greater than 5% from the preoperative baseline if the starting room SpO_2 was less than 90% [11]. Additionally, the use of rescue medications including anticholinergic agents (atropine or glycopyrrolate) or vasoactive agents (epinephrine, phenylephrine, vasopressin, or ephedrine) was noted.

Information regarding remimazolam dosing included the dose, changes in dosing during the intraoperative period, mode of administration (intermittent or continuous), and duration of the infusion. The electronic medical records were further reviewed for adverse effects as noted above that were specifically related to remimazolam, which required a pause or decrease of the infusion rate. Efficacy was determined by a review of subjective assessments from the electronic medical record, data from depth of sedation monitors (bispectral index) when available, dosing of adjunctive sedative and analgesic agents, and the ability to complete the procedure successfully. Anesthesia recovery times were assessed as the time from the last bolus dose or infusion stop time of remimazolam to documentation of the patient's conscious state ranging from "arousable to verbal stimuli" to "awake and alert", as well as the time until patients were ready for discharge from post anesthesia care unit (PACU). As a retrospective descriptive study, data are presented as the number with range or mean ± standard deviation (SD).

The study cohort included seven patients ranging in age from 14 to 51 years and in weight from 47.3 to 117.8 kg. Demographic data, remimazolam dosing, use of adjunctive agents, and procedural data are listed in Tables 1 and 2. Procedures included esophagogastroduodenoscopy (EGD), pericardial drain placement, cardioversion and TEE, computed tomography (CT) imaging, AICD placement, and halo removal. Five patients had pre-existing respiratory concerns including one receiving bilevel positive airway pressure (BiPAP), two requiring nasal cannula, and two with baseline SpO_2 less than 90% on room air. Three patients had comorbid cardiovascular concerns including an arrhythmia requiring cardioversion, a pericardial effusion, and depressed myocardial function requiring hemodynamic support with milrinone at 0.25 µg/kg/min.

Remimazolam administration included bolus dosing in two patients and a combination of bolus dosing followed by an infusion in the other five patients. The initial bolus dosing of remimazolam ranged from 2.5 to 5 mg. In the two patients who received intermittent bolus dosing only, subsequent boluses were 2.5 mg, to a maximum total dose of 12.5 mg of remimazolam. In the five patients who received bolus doses and a continuous infusion, starting doses for the infusion ranged from 10 to 30 µg/kg/min with titration of the continuous during the procedure also

Table 2. Summary of Remimazolam Dosing, Procedure Times, and Outcomes

Patient number and procedure	Remimazolam dosing (bolus and infusion)	Anesthesia duration (minutes in OR)	Procedure duration (min)	Outcomes
1. EGD	Bolus dose: 2.5 mg Infusion: 10 µg/kg/min; titrated up to 30 µg/kg/min	41 min	4 min	Adjunct medications: fentanyl 100 µg, etomidate 10 mg for LMA placement Preoperative SpO_2 85% on room air Period of apnea associated with oxygen desaturation down to SpO_2 70%; resolved with supplemental oxygen via mask and subsequent LMA placement Time from PACU arrival to ready for discharge: 20 min
2. Placement of pericardial drain	Bolus dose: 5 mg Infusion: 30 µg/kg/min; titrated down to 10 - 15 µg/kg/min using the BIS	78 min	29 min	Adjunct medication: fentanyl 100 µg Native airway maintained with NC Oxygen desaturation to 89%; resolved with increased O_2 via NC Lowest BP 72/55 mm Hg; resolved with decrease in remimazolam infusion rate Time from PACU arrival to ready for discharge: 74 min
3. Cardioversion, TEE	Bolus dose: 5 mg Infusion: 10 µg/kg/min; titrated up to 20 µg/kg/min. Brief pause of infusion and then restarted at 10 µg/kg/min	52 min	31 min	Adjunct medication: fentanyl 100 µg Remimazolam infusion rate adjusted and paused based on the BIS number Native airway maintained with NC Preoperative SpO_2 84-91% on room air Oxygen desaturation down to 76%; resolved with supplemental O_2 flow via NC Time from PACU arrival to ready for discharge: 38 min
4. CT imaging	Total of 4 bolus doses of 2.5 mg throughout the procedure. No infusion.	37 min	47 min	No adjunct medications Native airway maintained with NC Intraoperative hypotension, lowest BP 79/44 at the end of the case; resolved without intervention Periods of bradypnea RR 5 - 6 and one period of apnea. All episodes resolved without intervention or with temporary increase in O_2 flow via NC. Time from PACU arrival to ready for discharge: 11 min

Table 2. Summary of Remimazolam Dosing, Procedure Times, and Outcomes - *(continued)*

Patient number and procedure	Remimazolam dosing (bolus and infusion)	Anesthesia duration (minutes in OR)	Procedure duration (min)	Outcomes
5. AICD placement	Initial bolus: 3 mg	133 min	107 min	Adjunct medication: fentanyl 100 µg, dexmedetomidine 16 µg
	Infusion started at 20 µg/kg/min			Patient on BiPAP preoperatively, continued throughout the case
	Second bolus 3 mg			Milrinone 0.25 µg/kg/min preoperatively, continued throughout the case
	Infusion decreased to 15 µg/kg/min, increased back to 20 µg/kg/min, decreased to 10 µg/kg/min			Preoperative BP range 77/45 - 87/52 mm Hg
				Two episodes of intraoperative hypotension. The first coincided with remimazolam infusion increase to 20 µg/kg/min and dexmedetomidine 8 µg bolus dose and resolved with surgical stimulation. The second episode of hypotension resolved without intervention.
				Time from PACU arrival to planned discharge back to CTICU: 19 min
6. Halo removal	Initial bolus: 5 mg followed by 3 subsequent boluses of 2.5 mg	38 min	21 min	Nitrous oxide for placement of intravenous cannula
				Adjunct medication: fentanyl 50 µg
				Native airway maintained with NC
				No intraoperative adverse effects
				Time from PACU arrival to ready for discharge: 21 min
7. Cardioversion	Bolus 3.5 mg	50 mins	19 min	Adjunct medication: fentanyl 100 µg
	Infusion: 20 µg/kg/min, titrated down to 15 µg/kg/min then to 10 µg/kg/min			Native airway maintained with NC
				Six intermittent periods of apnea/bradypnea. All episodes resolved with decrease in remimazolam infusion rate and supplemental O_2 via NC.
				Time from PACU arrival to ready for discharge: 4 min

EGD: esophagogastroduodenoscopy; LMA: laryngeal mask airway; SpO_2: peripheral oxygen saturation; PACU: post anesthesia care unit; BIS: bispectral index; BP: blood pressure; TEE: transesophageal echocardiogram; RR: respiratory rate; CT: computed tomography; AICD: automatic implantable cardioverter-defibrillator; BiPAP: bilevel positive airway pressure; CTICU: cardiothoracic intensive care unit; NC: nasal cannula; OR: operating room.

ranging from 10 to 30 µg/kg/min. Median dose requirements were 15 - 20 µg/kg/min. All of the procedures were successfully completed without the need for conversion to general anesthesia.

One procedure was completed with remimazolam as the sole anesthetic agent while the other six patients received adjunctive agents. Four patients received fentanyl (50 - 100 µg), one patient received fentanyl and dexmedetomidine, and one patient received a single dose of etomidate and fentanyl, which were used to facilitate placement of a laryngeal mask airway (LMA). The addition of a bolus of fentanyl was chosen to provide analgesia for the painful aspects of the procedures. Five procedures were accomplished with a native airway supplemented with oxygen administered via nasal cannula, one used an LMA, and one used BiPAP, which was in place preoperatively and was continued throughout the procedure.

A decrease in the intraoperative SBP below the pre-determined threshold value of 90 mm Hg occurred in three patients (patient number 2, 4, and 5 (Table 1)). Patient 2 had a single

episode of a blood pressure (BP) of 72/55 mm Hg that resolved with a decrease in the remimazolam infusion rate from 30 to 15 µg/kg/min. The lowest BP reading for patient 4 was 79/44 mm Hg at the end of the procedure and resolved without intervention. Patient 5 had a preoperative BP ranging from 77/45 to 87/52 mm Hg while on a milrinone infusion at 0.25 µg/kg/min which was continued intraoperatively. This patient had two episodes of a low intraoperative BP (lowest BP was 62/52 mm Hg). One episode coincided with an increase in the remimazolam infusion rate from 15 to 20 µg/kg/min and a dexmedetomidine bolus dose of 8 µg. The low BP resolved with surgical incision. The second episode resolved without intervention.

Apnea, bradypnea, or oxygen desaturation occurred intraoperatively in five of the patients (patient number 1, 2, 3, 4, and 7). Patient number 1 had a preoperative oxygen saturation of 85% on room air. This patient experienced a period of apnea and decrease in SpO_2 to 70% which followed a bolus dose of fentanyl 100 µg and an increase in the remimazolam infusion rate from 20 to 30 µg/kg/min. The episode resolved with supplemental oxygen and LMA placement. Patient 2 was receiving supplemental oxygen (2 L/min) prior to the procedure with a baseline SpO_2 of 95%. The episode of oxygen desaturation down to 89% resolved with an increase of the supplemental oxygen via nasal cannula. Patient 3 had a preoperative SpO_2 of 84-91% on room air and had a brief decline in the SpO_2 to a low of 76% which resolved with supplemental oxygen. Patient number 4 experienced five intermittent periods of apnea or bradypnea intraoperatively. The lowest oxygen saturation associated with any of the five episodes was 90% and all episodes were either self-limiting or resolved with an increase in supplemental oxygen. Patient 7 experienced six intermittent periods of apnea or bradypnea. One episode was associated with cardioversion and an adenosine push resulting a low SpO_2 of 74%. Another episode was associated with cardioversion only and oxygen desaturation to 90%. Both episodes resolved with a decrease in the remimazolam infusion rate from 20 to 15 and eventually 10 µg/kg/min and an increase in supplemental oxygen. The other episodes resolved without intervention or with an increase in supplemental oxygen.

All of these intraoperative adverse events were either self-limiting, resolved with a decrease in the remimazolam infusion rate, or resolved with the administration of or an increase in supplemental oxygen. No rescue medications (anticholinergic or vasoactive agents) were administered. There were no adverse events during the postoperative period. Consciousness was assessed upon arrival to PACU and then every 5 - 15 min until discharge from PACU. Two patients were awake and alert upon arrival to PACU and four patients were arousable to verbal stimulation on arrival. Patient number 1 who received etomidate and LMA placement intraoperatively arrived to PACU still asleep. Times from the last bolus dose of remimazolam or cessation of the remimazolam infusion to the patient being arousable to verbal stimulation ranged from 13 to 25 min. PACU discharge times ranged from 4 to 74 min.

Discussion

Similar to other benzodiazepines, remimazolam provides sedation and amnesia through the gamma-aminobutyric acid (GABA) system. As an ester-based medication, it undergoes rapid metabolism by tissue esterase with a limited context-sensitive half-life, thereby allowing control of the depth of sedation by adjustment of the continuous infusion. Following FDA-approval for use in adults in 2020, remimazolam has been shown to be effective in adults for sedation during invasive procedures including gastrointestinal endoscopy and bronchoscopy [3-5]. These trials have demonstrated not only its efficacy, but also an acceptable safety profile with limited effects on hemodynamic function, lack of pain with intravenous administration, reduction of post-procedure nausea and vomiting, a limited context-sensitive half-life, and a rapid return to baseline neurologic function [3-5, 12-14].

Chen et al [3] compared remimazolam and propofol, both administered by intermittent boluses, in a prospective, randomized trial of 384 adults presenting for colonoscopy. Remimazolam dosing included 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. There was a similar procedural success rate with the two agents (97% with remimazolam and 100% with propofol) with a shorter time to achieve adequate sedation with propofol (average time of 75 versus 101 s). No difference was noted in awakening or discharge times. Adverse effects including administration site pain, hypotension, bradypnea, or oxygen desaturation that were less common with remimazolam. Similar outcomes were noted by the same investigators when comparing remimazolam versus propofol for sedation during upper gastrointestinal endoscopy [4].

In addition to its efficacy for procedural sedation, preliminary clinical data suggest a lower adverse effect profile than propofol [15, 16]. In a prospective trial that included a total of 346 adults presenting for upper endoscopy, patients were randomized to sedation with an initial bolus dose of remimazolam (0.2 mg/kg) or propofol (1.5 mg/kg). Supplemental sedation was provided by one-third of the initial bolus dose up to a total of five doses. There were no statistically significant differences between the two groups in terms of sedation success rates, time to discharge, efficacy of sedation as judged by the proceduralist and the anesthesia provider. Adverse effects were less with remimazolam compared to propofol including a lower incidence of respiratory depression, defined as a respiratory rate less than eight breaths per minute or an SpO_2 less than 90%. The incidence of respiratory depression was 9.8% with remimazolam compared to 17.9% with propofol ($P = 0.042$). Additionally, the incidence of hypotension (50.9% vs. 32.4%, $P = 0.001$) and hypotension requiring treatment (5.8% vs. 1.7%, $P = 0.031$) were also significantly higher with propofol.

We present additional anecdotal experience with the use of remimazolam as the primary agent for sedation during a heterogeneous group of invasive and noninvasive procedures. Of note, four of the procedures occurred in the cardiac catheterization suite including AICD placement, placement of a pericardial drain, TEE, and cardioversion. Several of the patients had cardiac or respiratory comorbidities. Although remimazolam was used as the primary agent by intermittent bolus dosing or a continuous infusion, supplemental sedation of analgesia was required in six patients including fentanyl, etomidate, or dexmedetomidine. All adverse events were either self-limiting or improved with a

decrease in the remimazolam infusion rate or with supplemental oxygen. Most cases were completed by maintaining the patient's native airway with supplemental oxygen via a nasal cannula. BiPAP which was in use preoperatively in one patient was continued during procedural sedation while an LMA was used in one patient. The patients were either awake and alert or arousable to verbal stimulation on arrival to the PACU with the exception of the patient who received etomidate for LMA placement. PACU discharge was rapid on all patients and the postoperative course was unremarkable. Dosing for remimazolam varied from 2.5 to 5 mg for intermittent bolus dosing and from 10 to 30 µg/kg/min for a continuous infusion. These are consistent with dosing from previous report [1-3, 14].

In addition to its retrospective study design, another limitation of this study is that dosing was not specifically standardized and there was variability in the choice of adjunctive agents. These clinical variables were derived from previous reports in the literature regarding the use of remimazolam in various clinical scenarios as well as our own clinical experience. Additional, prospective investigations are needed to more clearly define optimal dosing regimens (bolus and infusion rates) as well as the use of adjunctive agents. The study cohort was heterogeneous with variation in patient age, weight, and comorbid conditions. Likewise, the procedure types were varied. However, the majority of the population were cared for in the cardiac catheterization suite, representing a not uncommon cohort of patients requiring procedural sedation in that clinical location.

In summary, remimazolam is a novel sedative agent that 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. Preliminary clinical experience suggests its role a primary agent for procedural sedation or as an adjunct to general anesthesia [15]. Remimazolam by either intermittent bolus dosing or continuous infusion provided effective sedation during various invasive and noninvasive procedures. Changes in BP or oxygen saturation resolved with minimal interventions such as a decrease in remimazolam infusion rate or an increase in supplemental oxygen administration. Our anecdotal experience provides additional evidence for the efficacy of remimazolam as an agent for procedural sedation.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

As a retrospective study, the need for individual written informed consent was waived.

Author Contributions

Case review and preparation of manuscript: JY. CM and KC provided clinical care of the patients and review of the final manuscript. 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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