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Case Report

J Clin Med Res. 2024;16(6):319-323

The Use of Remimazolam During Awake Craniotomy for Seizure Foci Resection in Adolescents: A Case Series

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Abstract

Remimazolam is a novel benzodiazepine with sedative, anxiolytic, and amnestic properties similar to midazolam. Metabolism by tissue esterases results in a short clinical half-life of 5 - 10 min and a limited context sensitive half-life. We present initial retrospective clinical experience with the use of remimazolam as an intraoperative adjunct to sedation during awake craniotomy in a cohort of three adolescent patients. A remimazolam infusion was added to a combination of dexmedetomidine and remifentanil to deepen the level of sedation during surgical incision, craniotomy, duraplasty, and surgical dissection for exposure of the seizure foci. The remimazolam infusion was discontinued 30 min prior to the planned awake assessments and electrophysiology testing. The patients emerged calmly and were able to follow commands for intraoperative testing. Our anecdotal experience supports the efficacy of remimazolam for awake craniotomy and tumor resection using a standard asleep-awake-asleep technique. We noted adequate sedation, maintenance of spontaneous respiration, rapid awakening, and no limitations to intraoperative neuromonitoring or awake assessment in our three patients.

Keywords: Remimazolam; Awake craniotomy; Pediatric anesthesiology; Procedural sedation

Introduction

Awake craniotomy is a surgical technique that allows direct intraoperative testing during resection of seizure foci and tumors in eloquent areas of the brain that control vital motor or speech functions [1, 2]. Due to the inter-individual variability in the representation of specific motor and speech functions within the cortex, cortical mapping while the patient is awake allows the delineation of specific areas for resection while potentially avoiding neurologic deficits [3]. Various anesthetic regimens have been described using short-acting agents such as propofol, dexmedetomidine, and opioids to provide sedation and anesthesia during surgical incision and craniotomy while allowing for rapid awakening and verbal interaction during cortical mapping [4, 5]. In the pediatric-aged patients, awake craniotomy may be performed with or without a native airway [4, 5]. Regardless of the agents used, the goal is to generally maintain spontaneous ventilation and allow for the rapid return of consciousness during key portions of the procedure.

Remimazolam is a pharmacologic derivative of the intravenous benzodiazepine, midazolam, with similar sedative, anxiolytic, and amnestic properties [6, 7]. Remimazolam undergoes hydrolysis by tissue esterases which results in a short duration of action with a limited context-sensitive half-life. These pharmacologic properties result in a deep level of sedation while allowing for rapid awakening when its administration is discontinued. Following FDA approval for use in adults in 2020, initial clinical trials demonstrated its efficacy for sedation of adults during invasive procedures, primarily gastrointestinal endoscopy and bronchoscopy [8-12]. In general, these trials have demonstrated that remimazolam can provide effect on sedation and amnesia during these procedures, and efficacy in limiting adverse effects on respiratory function, thereby allowing for the maintenance of spontaneous ventilation with a native airway. Additional benefits have included a benign impact on hemodynamic function, lack of pain with intravenous administration, reduction of post-procedure nausea and vomiting (PONV), and a rapid return to baseline neurologic function. Anecdotal and retrospective clinical experience has demonstrated its potential utility in awake craniotomy in adults [13, 14]. To date, there are no reports regarding its use in this clinical scenario in pediatric-aged patients. We present initial clinical experience with the use of remimazolam as an intraoperative adjunct to sedation during awake craniotomy in a cohort of three adolescent patients. The use of remimazolam for procedural sedation in pediatric-aged patients is reviewed, dosing regimens reviewed, and potential utility in awake craniotomy discussed.

Case Report

This retrospective review was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). Given the retrospective nature of the study, the need

Manuscript submitted April 9, 2024, accepted May 31, 2024
Published online June 30, 2024

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doi: https://doi.org/10.14740/jocmr5175

for individual written informed consent was waived. However, consent was obtained for anesthetic care and the use of de-identified information for publication.

Remimazolam was added to the operating room (OR) formulary of our hospital in January 2022. For clinical use, remimazolam was reconstituted from the lyophilized powder in a single vial, using normal saline. Dilution resulted in a final concentration of 20 mg/8 mL (2.5 mg/mL). For intraoperative administration, the medication was provided to the anesthesia team in a syringe. Based on our routine clinical practice for continuous intravenous infusions, administration was calculated in µg/kg/min and not mg/kg/h, using an infusion pump.

Using the pharmacy and OR records, patients undergoing awake craniotomy who received remimazolam for intraoperative care were identified. Demographic data obtained included age, weight, comorbid conditions, and gender. Sedation regimen information included the medications administered and the doses used for both bolus administration and continuous infusions. Specific information regarding remimazolam dosing included the dose, changes in dosing during intraoperative administration, the mode of administration (intermittent or continuous), and duration of the infusion. The electronic medical records were further reviewed for adverse effects that required a pause or decrease of the remimazolam infusion rate. Intraoperative and postoperative adverse effects including hypotension, bradycardia, respiratory arrest, apnea, or hypoventilation were also identified. Additionally, the use of rescue medications including anticholinergic or vasoactive agents (epinephrine, phenylephrine, vasopressin, or ephedrine) was noted. 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).

We identified three adolescents who received remimazolam during awake craniotomy and seizure focus resection. The three patients maintained spontaneous ventilation with a native airway during the procedure. Table 1 summarizes patient and procedure characteristics including demographic data, remimazolam dosing, and the use of additional analgesic and sedative medications. Remimazolam was used as an adjunct to a dexmedetomidine-remifentanil technique.

In all three patients, a peripheral intravenous cannula was placed preoperatively. Standard *nil per os* guidelines were followed and the patients were transported to the operating where standard American Society of Anesthesiologists' monitors were placed along with continuous end-tidal carbon dioxide ($ETCO_2$) monitoring from a nasal cannula. Dexmedetomidine was administered as a loading dose and then an infusion along with remifentanil. A propofol infusion at 20 µg/kg/min was used in patient 1 during infiltration of the scalp with a local anesthetic agent. The propofol infusion was discontinued before surgical incision. For the three patients, bilateral scalp blocks were placed along with additional local anesthetic agent at the site of pin insertion for the Mayfield holder. Following the achievement of an adequate level of sedation, two peripheral intravenous cannulas and a radial arterial cannula were placed. One peripheral intravenous site was utilized solely for the remimazolam infusion. Sedation medications are summarized in Table 1.

Remimazolam was added to the dexmedetomidine and remifentanil infusions to achieve a deeper level of sedation during surgical incision, craniotomy, duraplasty, and surgical dissection for exposure of the seizure foci. The starting dose was 10 µg/kg/min in two patients and 5 µg/kg/min in one patient. Infusions varied from 2.5 to 15 µg/kg/min. The remimazolam infusion was discontinued 30 min prior to the planned awake assessments and electrophysiology testing for each patient. During this time, the dexmedetomidine and remifentanil infusions were continued. Spontaneous patient arousal was noted 5 - 8 min after discontinuation of these medications. The patients emerged calmly and were able to follow commands for intraoperative testing. Remimazolam was kept in line post-resection, but all three patients were adequately sedated with remifentanil and dexmedetomidine without further need for remimazolam for both surgical closure and the post-procedure magnetic resonance imaging (MRI). The dexmedetomidine and remifentanil infusions were discontinued last after resection of the seizure focus and closure of the surgical incision.

During intraoperative care, all patients maintained adequate spontaneous ventilation without clinical signs of respiratory depression or upper airway obstruction. No additional airway supports were required. An arterial blood gas was obtained after sedation was started and before the initial surgical incision to assess adequacy of ventilation with the nasal cannula in place and a native airway (Table 2). Intraoperative respiratory and hemodynamic parameters remained stable (Table 3).

During assessment and direct stimulation to the motor cortex by the electrophysiologist, patient 1 had a self-aborting focal seizure with left-hand clonic movements. Resection was therefore avoided in this area. On continued awake assessment, she exhibited difficulty with movement of her left upper and lower extremities. Neurosurgery attributed this to tumor involvement of the superior associative motor cortex. One year postoperatively, she has minor left finger weakness and is seizure-free.

With electrocorticography stimulation of patient 2, areas of speech were noted on the cortical surface in the inferior frontal gyrus in the region near the lesion. No intraoperative seizures occurred. Postoperatively, he developed expressive aphasia, left gaze preference, right facial droop, and right sided hemiparesis in the setting of new diffusion restriction noted on postoperative MRI in the left periventricular deep white matter along the superior and medial aspect of the operative bed. These symptoms have improved with physical therapy.

Patient 3 had functional cortical stimulation mapping performed in the OR during the awake state which demonstrated difficulty with visual processing of pictures with stimulation of the left angular gyrus. Word generation was slowed, but was without errors. No seizures were noted intraoperatively and there were no postoperative deficits. He has been seizure-free since his resection.

Table 1. Clinical Patient Data and Remimazolam Dosing

Demographic data	Neurologic history and concerns	Remimazolam and sedative/analgesic medication dosing	Outcomes
Gender: female Age: 15 years Weight: 103.9 kg Height: 161.2 cm BMI: 39.98 kg/m^2 Handedness: left	History of previous resection of a dysembryoplastic neuroepithelial tumor creating motor seizures. One previous traditional craniotomy resulted in left extremity weakness. Awake craniotomy was chosen to avoid surgical impact on the motor cortex.	Dexmedetomidine: loading dose 20 µg followed by infusion at 1 - 1.5 µg/kg/h. Propofol infusion: 20 - 50 µg/kg/min started only during scalp block with local anesthetic. Remifentanil infusion: 0.01 - 0.09 µg/kg/min. Remimazolam infusion started at 10 µg/kg/min without a bolus, increased to 15 µg/kg/min after 25 min and stopped after 129 min. Intraoperative anesthetic events: none. Total procedure time: 338 min.	PACU recovery time: 83 min. Postoperative course: uncomplicated. PICU LOS: 1 day.
Gender: male Age: 16 years Weight: 99.5 kg Height: 183 cm BMI: 29.71 kg/m^2 Handedness: right	History of left inferior frontal mixed glial neuronal tumor/ganglioglioma and associated focal seizures presents for awake craniotomy for language mapping. Seizures result in aphasia followed by right facial contraction with post-ictal slurred speech. Additionally, the patient has bilateral tonic-clonic seizures in the setting of missed medication doses.	Dexmedetomidine: loading dose 40 µg followed by an infusion at 0.4 - 1.5 µg/kg/h. Remifentanil infusion: 0.01 - 0.5 µg/kg/min. Remimazolam infusion started at 5 µg/kg/min without a bolus, titrated from 2.5 - 5 µg/kg/min and stopped after 25 min of procedure time. Intraoperative anesthetic events: none. Total procedure time: 434 min.	PACU recovery time: 20 min. Postoperative course: uncomplicated. PICU LOS: 2 days.
Gender: male Age: 15 years Weight: 72.3 kg Height: 182.3 cm BMI: 21.76 kg/m^2 Handedness: right	History of seizure foci within the left inferior posterior temporal gyrus, abutting the superior and inferior angular gyrus. Seizures result in full body stiffening, tonic-clonic movements in the upper and lower extremities followed by upper extremity (left > right) weakness without aphasia. Atypical language representation, with anterior/expressive language areas demonstrating predominantly left-sided activation and posterior/receptive language areas demonstrating bilateral to right sided activation on functional MRI. Therefore, awake craniotomy was pursued.	Dexmedetomidine: loading dose 40 µg followed by an infusion at 0.8 - 1.5 µg/kg/h. Remifentanil infusion: 0.04 - 0.15 µg/kg/min. Remimazolam infusion started at 10 µg/kg/min without a bolus for 36 min and then decreased to 5 µg/kg/min. Infusion was stopped after 184 min of procedure time. Intraoperative anesthetic events: none. Total procedure time: 323 min.	PACU recovery time: 46 min. Postoperative course: uncomplicated. PICU LOS: 1 day.

BMI: body mass index; PACU: post-anesthesia care unit; PICU: pediatric intensive care unit; LOS: length of stay.

Table 2. Arterial Blood Gas Analysis

	Patient 1	Patient 2	Patient 3
End-tidal CO_2 (mm Hg)	47	41	56
pH	7.30	7.29	7.30
$PaCO_2$ (mm Hg)	52	54	57
PaO_2 (mm Hg)	88	196	129
HCO_3 (mmol/L)	26	26	28
Base deficit (mmol/L)	1.1	1.7	0.2
O_2 saturation (%)	97	100	99
Sodium (mmol/L)	139	134	139
Potassium (mmol/L)	4.0	4.6	4.0
Ionized calcium (mmol/L)	1.27	1.33	1.24
Glucose (mg/dL)	129	134	112
Hemoglobin (g/dL)	11.3	14.1	14.3

Discussion

Remimazolam provides sedation, amnesia, and anxiolysis through the gamma-aminobutyric acid (GABA) system via pathways that parallels that of other benzodiazepines such as midazolam. As an ester-based medication, it undergoes rapid metabolism by tissue esterase with a limited context-sensitive half-life thereby allowing for control of the depth of sedation by adjustment of the continuous infusion. Although not currently FDA-approved for use in pediatric-aged patients, there is increasing anecdotal and clinical experience with its use as a primary agent for sedation and as an adjunct for sedation and general anesthesia in children and adolescents [15-18]. Its adverse effect profile on hemodynamic and respiratory function appears to parallel that of midazolam. Of note, there is one report of an apparent anaphylactoid reaction to remimazolam in a patient who had previously received midazolam [19].

Table 3. Hemodynamic and Patient Data Immediately Before Discontinuation of the Remimazolam Infusion

Parameter	Patient 1	Patient 2	Patient 3
Heart rate (beats/min)	63	57	65
Blood pressure (mm Hg)	119/61	122/52	125/71
Respiratory rate (breaths/min)	14	11	9
Oxygen saturation (pulse oximeter %)	98%	98%	99%
End-tidal carbon dioxide (mm Hg)	41	43	54
Temperature (°C)	35.6	36	35.6
Fraction of inspired oxygen	0.23	0.25	0.21

Given its pharmacokinetic properties, remimazolam was a useful adjunct to our routine sedation technique of dexmedetomidine and remifentanil infusions for awake craniotomy procedures in adolescents. Remimazolam did not inhibit the use of direct cortical stimulation or blunt seizure activity upon electrocorticography (ECoG) monitoring. Although previous reports have described the use of depth of anesthesia monitoring to allow objective titration of the remimazolam infusion, this was not feasible in our patients given the site of the surgical incision and potential interference with the sterile field. When questioned on postoperative day 1, none of the patients reported intraoperative awareness except for the awake portion of the procedure. The negative cardiorespiratory effects of propofol administration were avoided and a native airway with a nasal cannula and spontaneous ventilation was feasible despite achieving a deep plane of sedation which allowed for the most invasive aspects of the procedure. Mild to moderate hypercarbia was noted in our patients during spontaneous ventilation with $PaCO_2$ values varying from 52 to 57 mm Hg.

A retrospective evaluation compared efficacy and recovery profiles of remimazolam or propofol infusion during the asleep phase of 36 adult patients undergoing awake craniotomy using a standard asleep-awake-asleep technique [13]. In the 15 patients who received remimazolam, anesthesia was induced with a remimazolam infusion starting at 12 mg/kg/h and then decreased to 1 mg/kg/h once there was loss of consciousness. In the remaining 21 patients, propofol was administered to a concentration of 3 µg/mL using a target-controlled infusion (TCI). Fentanyl (50 - 100 µg) and a remifentanil infusion (0.1 µg/kg/min) were used as adjuncts for anesthesia induction in both groups. A laryngeal mask airway (LMA) was placed and anesthesia was then maintained during the asleep phase with remimazolam (0.5 - 1.0 mg/kg/h) or propofol (TCI at 2.4 - 3.5 µg/mL) plus remifentanil (0.1 - 0.15 µg/kg/min) to maintain the bispectral index at 40 - 60. Drug infusions were discontinued after dural opening for the awake phase of the procedure with awake intraoperative neurologic assessment during tumor resection. Recovery time defined as the interval between stopping the infusions (propofol or remimazolam and remifentanil) and removal of the LMA was similar between the two groups (21 ± 6 min for remimazolam versus 19 ± 7 min for propofol). The recovery time for remimazolam was increased in eight patients treated with flumazenil (14.8 ± 2.6 min) without precipitation of agitation or seizures. There was an increase in the incidence of intraoperative nausea without vomiting in the patients who received remimazolam.

In adults, both intermittent bolus doses and continuous infusions have been used as the sole agent during procedural sedation and as a supplement to volatile anesthetic agents during general anesthesia. Bolus dosing in adults has generally included 2.5 - 5 mg doses (repeated as needed) for procedural sedation while maintaining spontaneous ventilation up to 0.2 mg/kg for the induction of general anesthesia. Infusions, titrated to effect, have varied from 1 to 2 mg/kg/h. Remimazolam was used as an adjunct in our patients and therefore slightly lower doses were required with the infusion started at 5 - 10 µg/kg/min and then maintained at 15 µg/kg/min in one patient and 2.5 - 5 µg/kg/min in the other two. As remimazolam is a sedative hypnotic, additional agents may be needed to supplement analgesia for painful procedures. In our patients, remifentanil provided analgesia.

In summary, remimazolam is a novel sedative agent that received FDA approval for procedural sedation in adults in 2020. To date, it has no FDA-approved indication in pediatric-aged patients, although initial clinical experience has demonstrated its potential efficacy in various clinical scenarios in children and adolescents including procedural sedation and as an adjunct to general anesthesia. Remimazolam is an ultra-short-acting benzodiazepine that undergoes rapid metabolism by tissue esterases to inactive metabolites. Clinical studies have demonstrated a rapid onset, a limited context-sensitive half-life, and generally rapid recovery with limited impact on hemodynamic and respiratory function. These properties may make it a useful agent for awake craniotomy and tumor resection using a standard asleep-awake-asleep regimen. Our anecdotal experience supports its efficacy for these procedures in pediatric-aged patients. We noted adequate sedation, maintenance of spontaneous respiration, rapid awakening, and no limitations to intraoperative neuromonitoring or awake assessment in our three patients. However, as we present only anecdotal and preliminary clinical information, additional clinical work and research is needed to better define doing parameters for both bolus dosing and continuous infusions. Additionally, more information is needed regarding the value of depth of anesthesia monitors to guide its administration.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained for anesthetic care and the use of de-identified information for publication.

Author Contributions

AS: preparation of initial, subsequent, and final drafts and clinical care of the patients; JDT: concept, writing, and review of all drafts; SK: case reviews and preparation, review of drafts including final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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