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Review

J Clin Med Res. 2025;17(3):125-135

Clinical Experience With Remimazolam in Neuroanesthesiology and Neurocritical Care: An Educational Focused Review

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Abstract

Remimazolam is an ultrashort-acting benzodiazepine, approved for clinical use by the United States Food & Drug Administration in 2020. Similar to other benzodiazepines, its clinical effects of sedation, anxiolysis, and amnesia are mediated through the gamma-aminobutyric acid A ($GABA_A$) receptor. A unique metabolic pathway via tissue esterases results in a rapid elimination, a limited context-sensitive half-life, and prompt dissipation of its effect when administration is discontinued. Preliminary clinical experience has demonstrated its efficacy in the adult and pediatric population as a primary agent for procedural sedation or as an adjunct to general anesthesia. Given its rapid onset and recovery, preliminary clinical experience has demonstrated its potential utility in neuroanesthesia including procedural sedation for neuroimaging as well as a primary agent and adjunct for general anesthesia during neurosurgical procedures including awake craniotomy. This narrative review outlines the pharmacological properties of this unique medication, reviews previous published reports of its role in neuroanesthesia and neurocritical care, and discusses dosing parameters and clinical use in this population.

Keywords: Benzodiazepine; Procedural sedation; Neuroanesthesiology; Remimazolam; Neurosurgery; Awake craniotomy

Introduction

Remimazolam is an ultra-short acting benzodiazepine, which like midazolam and other medications in the benzodiazepine class, enacts its effects as an agonist on the gamma-aminobutyric acid A ($GABA_A$) receptor resulting in sedation, anxiolysis, and amnesia. Remimazolam is unique in that its structural modifications allow for organ-independent rapid metabolism via tissue esterases resulting in a rapid onset, a brief duration of sedation, and a predictable duration of action [1, 2]. The desirable properties of rapid onset and elimination, a limited context-sensitive half-life, predictable timing, and lower occurrence of hypotension, respiratory depression, and pain on injection compared to other hypnotic agents, such as propofol, have led to its use in various clinical scenarios as a primary agent or adjunct for the induction and maintenance of anesthesia and procedural sedation [3-6]. Following Food & Drug Administration (FDA) approval for use in adults in 2020, initial clinical trials demonstrated its efficacy for sedation during endoscopic procedures in adults including gastrointestinal endoscopy and bronchoscopy [7-9]. In general, these trials have demonstrated that remimazolam provides effective sedation and amnesia with a wide safety margin and limited adverse effects on respiratory and hemodynamic function. Given its favorable properties, remimazolam has the potential to play a role in neuroanesthesia in various clinical scenarios. This narrative outlines the pharmacologic properties of remimazolam, reviews previous published reports of its role in neuroanesthesia and neurocritical care, and discusses dosing parameters and clinical uses in this population.

A systematic search using PubMed® was conducted using the search terms remimazolam, neuroanesthesia, and neurocritical care (December 2024). The abstracts from the publications were reviewed and those pertaining to pediatric-aged patients were included for further review. In addition to the electronic search, a manual search was performed to identify potentially relevant studies from the reference lists of the included articles and published review articles.

Pharmacokinetics and Neurophysiological Effects

Remimazolam is a high affinity benzodiazepine ligand that acts at the $GABA_A$ receptor, specifically targeting the A_1, A_2, A_3, and A_5 $GABA_A$ subtypes. The selectivity to GABA receptors, without affinity for other receptors such as dopamine, adenosine, muscarinic, nicotinic, opiate, or serotonin allows in part for the predictable clinical effects of sedation, anxiolysis,

Manuscript submitted February 1, 2025, accepted March 5, 2025
Published online March 10, 2025

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doi: https://doi.org/10.14740/jocmr6193

and amnesia [2]. The effects on the $GABA_A$ receptor increases membrane permeability to chloride leading to hyperpolarization and inhibition of neuronal activity. Although its clinical effects have not been specifically characterized, remimazolam also increases cytosolic calcium through G protein-coupled receptors on the endoplasmic reticulum [10].

One of the more unique properties of remimazolam is its metabolic pathway. Unlike midazolam and other benzodiazepines that undergo metabolism by hepatic cytochrome P450 isoenzymes, remimazolam undergoes rapid hydrolysis by non-specific tissue esterases (predominantly carboxy-esterases) into an inactive carboxylic acid metabolite CNS 7054. Studies in an adult male evaluating the metabolite profile of remimazolam in plasma and urine following intravenous administration have demonstrated that 2 h following its administration, the plasma contains 0.33% remimazolam and 99.67% CNS 7054 [11, 12].

When compared to midazolam, remimazolam demonstrated systemic clearance approximately three times faster with a half-life of 8 - 10 min [2]. Clinical trials investigating the pharmacokinetics and pharmacodynamics profile of remimazolam have included both continuous infusion and single bolus administration [6]. In summary, these trials have demonstrated that remimazolam exhibits a high clearance, a small steady-state volume of distribution, a short elimination half-life, and a short context-sensitive half-time (CSHT) [1]. It demonstrates first-order and linear pharmacokinetics [6, 12]. The first-order and linear pharmacokinetics remain consistent in both bolus injections and continuous infusions. Like other benzodiazepines, the sedative effects can be reversed using the competitive antagonist, flumazenil.

When considering its specific neurophysiological effects including sedation, amnesia, and anxiolysis, remimazolam is slightly more potent at the A_1 $GABA_A$ subtype than midazolam. The A_1 subtype of the $GABA_A$ receptor is postulated to play a primary role in the sedative effects of benzodiazepines by inhibiting substantia nigra pars reticularis (SNpr) cell firing in the substantia nigra pars reticulata. By acting as a more potent agonist at the A_1 subtype, remimazolam achieves greater inhibition of neuronal depolarization. Despite these effects, recovery to baseline SNpr cell firing was noted within 7 min following cessation of administration compared to 30 - 50 min with other benzodiazepines [13].

Applications in Neuroanesthesia and Neurocritical Care

The initial clinical experience in adults has demonstrated that remimazolam is an effective pharmacological agent for procedural sedation during upper and lower gastrointestinal (GI) endoscopy. Remimazolam has a rapid onset, limited impact on hemodynamic and respiratory function, a predictable half-life, and minimal pain on injection. When compared with propofol for procedural sedation in adults, remimazolam has been reported to have a more favorable adverse effect profile with a decreased incidence of hypotension and hypoxemia [7-9]. These clinical properties have led to its preliminary and anecdotal use for sedation and general anesthesia during computed tomography (CT) imaging, magnetic resonance imaging (MRI), neuroangiography, awake craniotomies, and other neurological related surgeries.

Imaging and neuroradiological procedures

The various reports outlining the use of remimazolam for neuroradiological imaging and other related procedures are summarized in Table 1 [14-16]. Recent institutional pilot programs have been developed to evaluate the efficacy and safety profile of remimazolam for procedural sedation during neuroimaging in pediatric-aged patients [14]. Using an open label, retrospective design, Hirano et al reported their experience with the use of remimazolam for procedural sedation in a cohort of 48 children (average age of 7 years). Procedures included CT, MRI, radiation therapy, and intravenous angiography. Remimazolam was administered as a continuous infusion with a starting rate of 12 mg/kg/h and then decreased to 1 - 2 mg/kg/h once the desired level of sedation was achieved (Ramsay sedation score of 3). Remimazolam boluses of 0.2 mg/kg were administered as needed to sustain the desired sedation level. The use of adjunctive agents (ketamine, fentanyl, or propofol) was left to the discretion of the provider resulting in 95% of patients receiving remimazolam in combination with one of these other agents. Given the combined anesthetic regimen, it was difficult to attribute changes in blood pressure, heart rate, and other vital signs to a single agent. However, none of the patients required pharmacological intervention to manage hemodynamic changes. The authors concluded that remimazolam, when supplemented with propofol or ketamine, offers a safe and effective pathway for procedural sedation in pediatric patients.

Additional case reports have provided further anecdotal information regarding the potential utility of remimazolam for procedural sedation with reports of its use during MRI and other neuroradiological procedures. Villalobos et al reported the successful sedation of a 9-month-old, 8.72 kg toddler with a comorbid COVID-19 infection, higher fever, and a seizure requiring MRI [15]. In order to prevent aerosolization and postoperative respiratory complications due to an acute COVID-19 infection, remimazolam was used to provide sedation and maintain spontaneous ventilation with a native airway. Remimazolam dosing included a continuous infusion starting at 15 µg/kg/min without a bolus dose. Two bolus doses of dexmedetomidine (4 µg) were administered and the remimazolam infusion was increased to 20 µg/kg/min. Adequate sedation was achieved and the infusion continued for approximately 60 min during imaging. The patient successfully completed the imaging procedure while maintaining an oxygen saturation of 97-99% with supplemental oxygen administered via a nasal cannula at 2 L/min. Additional anecdotal information and case reports have documented the successful use of remimazolam by bolus or infusion for sedation during CT imaging and halo removal [16].

Awake craniotomy

To allow for optimal tumor resection with preservation of

Table 1. Reports of Remimazolam Administration for Procedural Sedation During Neuroimaging and Related Procedures

Author and reference	Demographic and surgical/imaging procedure	Dosing and outcome
Hirano et al [14]	Cohort of 48 children with median age of 7 years for CT, MRI, angiography, and radiation therapy	Remimazolam administered as a continuous infusion (12 mg/kg/h) and decreased to 1 - 2 mg/kg/h once the desired level of sedation was achieved (Ramsay sedation score of 3). Bolus doses (0.2 mg/kg) were administered as needed to sustain the desired sedation level. Adjunctive agents (ketamine, fentanyl, or propofol) were used in 95% of the patients. None of the patients required pharmacological intervention to manage hemodynamic changes. The authors concluded that remimazolam, when supplemented with propofol or ketamine, was a safe and effective agent for procedural sedation.
Villalobos et al [15]	A 9-month-old, 8.72 kg toddler for MRI. Comorbid conditions included viral infection (COVID), high fever, and seizure.	Remimazolam titrated from 15 to 20 µg/kg/min without a bolus dose. Two supplemental doses of dexmedetomidine (4 µg). Successful completion of MRI with a native airway, spontaneous ventilation, and no respiratory concerns.
Yeh et al [16]	Case series of a 19-year-old, 47.3 kg patient undergoing CT imaging and a 16-year-old, 64.1 kg patient for halo removal	Patient 1 received four individual bolus doses of remimazolam (2.5 mg each) without adjunctive agents. Adequate sedation achieved with a native airway and spontaneous ventilation. Brief episode of hypotension and one episode of apnea, both of which resolved without intervention. Second patient received initial bolus of 5 mg followed by three additional doses of 2.5 mg. Single dose of fentanyl (50 µg fentanyl). Adequate sedation with spontaneous ventilation and a native airway.

CT: computed tomography; MRI: magnetic resonance imaging.

neurological function, awake craniotomy with electrocortical mapping and functional monitoring has become standard practice in the adult population [17]. These procedures offer a unique anesthetic challenge as they require intermittent neurological examinations with intraoperative electrocorticography in an awake phase. Various regimens have been used for these techniques, most commonly a combination of propofol with an opioid infusion which allows for an asleep-awake-asleep pattern where the patient is asleep for surgical incision and opening, awake for tumor mapping and resection, and then asleep again for surgical closure. Given the reported predictable and rapid onset and offset of remimazolam, several investigators have evaluated it in this clinical scenario.

In a retrospective study, Sato et al reviewed the clinical course of 36 patients who underwent awake craniotomy receiving either propofol (n = 21) or remimazolam (n = 15) [18]. In 15 patients, anesthesia was induced with remimazolam at 12 mg/kg/h and then maintained at 1 mg/kg/h (0.5 - 1.5) after loss of consciousness. The propofol group (n = 21) received a target-controlled infusion (TCI) to achieve a plasma concentration of 3 µg/mL (2.4 - 3.5 µg/mL). Following the induction of general anesthesia, a laryngeal mask airway (LMA) was placed and all patients received remifentanil (0.1 - 0.15 µg/kg/min) in addition to either propofol or remimazolam to achieve the needed depth of anesthesia, maintaining the bispectral index (BIS) at 40 - 60. When it came time for the awake phase of the surgery, there was no significant difference in time to removal of the LMA between patients receiving propofol and remimazolam. The number of patients experiencing nausea was higher with remimazolam than with propofol, although there were no significant differences observed in the frequency of vomiting and other intraoperative adverse events. Regression analysis revealed that the use of remimazolam contributed to increased intraoperative nausea (odds ratio 14.4, P = 0.04). Flumazenil (0.2 mg) was administered to eight of 15 patients in the remimazolam group to facilitate the transition to the awake portion of the case. These patients showed a faster recovery time compared to the remaining seven patients receiving remimazolam who did not get flumazenil. Given the prospect of a reversal agent facilitating an even faster recovery time from the asleep to the awake state, the authors postulated that remimazolam has potential as an alternative medication during awake craniotomy. These findings inspired the researchers to subsequently execute a prospective trial comparing propofol and remimazolam with flumazenil in awake craniotomy surgery.

The subsequent study included 26 patients who received remimazolam and 26 patients with propofol administered to achieve a plasma concentration of 3 µg/mL using TCI [19]. Remimazolam was administered as an induction dose of 12 mg/kg/h and then reduced to 1 - 2 mg/kg/h after loss of consciousness. Fentanyl and remifentanil were administered to both groups. Anesthesia was maintained with a remimazolam dose of 0.5 - 1.0 mg/kg/h or propofol 2.5 to 4.5 µg/mL of TCI. Both were titrated to maintain a BIS between 40 and 60. When it came time for the awake portion of the case, patients who received remimazolam and flumazenil were aroused at a median time of 890.8 s (95% confidence interval (CI): 793.9 - 987.6) versus 1075.4 s (95% CI: 947.2 - 1203.6, P = 0.013) with propofol. Patients who had received remimazolam also performed significantly better during intraoperative task performance and language assessment further pointing to its utility in cases like these vs. traditionally used propofol.

Table 2 summarizes an additional five anecdotal case reports of remimazolam for awake craniotomy surgery in adults [20-24]. These five case reports outline a total of six adult patients who underwent successful awake craniotomy using an asleep-awake-asleep technique with remimazolam and opioid infusion (remifentanil). One used a remimazolam bolus (4

Table 2. Reports of Remimazolam for Awake Craniotomy in Adult Patients

Author and reference	Demographic and surgical procedure	Remimazolam dosing and outcome
Sato et al [20]	A 37-year-old, 58 kg man for awake craniotomy and tumor resection	Induction with remimazolam (12 mg/kg/h), remifentanil (0.1 µg/kg/min), and fentanyl (75 µg) followed by rocuronium (20 mg) and LMA placement. Anesthesia maintained with remimazolam (1 mg/kg/h) and remifentanil (0.12 - 0.15 µg/kg/min). Twenty-six minutes after discontinuation of medications, the patient was fully awake and cooperative for language mapping. No adverse effects noted.
Murata et al [21]	A 45-year-old, 39 kg woman for awake craniotomy and tumor resection	Induction with remimazolam (4 mg) over 1 min and remifentanil infusion (1 µg/kg/min) followed by rocuronium (20 mg) and LMA placement. Anesthesia was maintained with remimazolam (1.0 - 1.2 mg/kg/h, then reduced to 0.1 µg/kg/min for last 5 min before discontinuation) and remifentanil (0.1 - 0.3 ug/kg/h). Flumazenil (0.05 mg) to speed recovery for language mapping. No adverse effects.
Yoshida et al [22]	A 48-year-old man for awake craniotomy and tumor resection	Induction with remimazolam (6 mg/kg/h) and remifentanil (100 µg) followed by LMA placement. Anesthesia maintained with remimazolam (0.75 - 1 mg/kg/h) and remifentanil (0.1 µg/kg/min). Following discontinuation of remimazolam and flumazenil bolus (0.3 mg), the patient awoke 3 min later and was able to follow commands.
Sato et al [23]	A 78-year-old, 47.2 kg woman for awake craniotomy and tumor resection	Induction with remimazolam (12 mg/kg/h) and remifentanil (0.15 µg/kg/min) followed by rocuronium (20 mg) and LMA placement. Anesthesia maintained with remimazolam (0.3 - 0.7 mg/kg/h). Remimazolam discontinued and flumazenil (0.5 mg) administered for awake phase. Patient was able to perform language tasks with no adverse effects.
Sato et al [24]	Two male patients, 44 and 54 years of age, weighing 98.4 and 90.7 kg, for awake craniotomy for tumor resection	Induction with remimazolam (12 mg/kg/h) and remifentanil (0.1 - 0.15 µg/kg/min) followed by LMA placement. Anesthesia maintained with remimazolam (0.5 - 0.6 mg/kg/h) and remifentanil (0.1 - 0.15 µg/kg/min). Following discontinuation of both agents, one patient received flumazenil (0.5 mg). Both patients awoke and performed intraoperative tasks without adverse effects.

LMA: laryngeal mask airway.

mg) for induction while the others used a high infusion rate induction technique (6 or 12 mg/kg/h). This was followed by maintenance of anesthesia with remimazolam (0.3 - 0.12 mg/kg/h) and a remifentanil infusion. In most patients, awakening was facilitated by the administration of flumazenil. Successful intraoperative language mapping and tumor resection were achieved. No adverse hemodynamic or respiratory effects related to remimazolam were noted.

The feasibility and practicality of performing awake craniotomy surgery in the pediatric-aged patients remains in question, largely due to the concern for adequate patient cooperation, potential for emotional or psychological distress, and lack of widely established anesthetic protocols [25]. The most common anesthetic technique has included a combination of a propofol infusion, remifentanil or fentanyl, scalp nerve blockade, and occasionally the addition of dexmedetomidine. While these anesthetic techniques have generally been reported to be successful, Bhanja et al reported that 20.6% of their patient cohort had difficulty completing monitoring tasks intraoperatively [17]. This is an area in which the limited CSHT, fast onset and offset, and quick return to baseline neurological function of remimazolam may play a role.

To date, the only report of the use of remimazolam in pediatric awake craniotomy surgery has included a cases series of three patients (two 15 years of age and one 16 years of age) [26]. These patients underwent awake craniotomy with remimazolam as part of their anesthetic regimen while all maintaining spontaneous ventilation and no additional airway support. All three patients received a dexmedetomidine loading dose followed by a continuous infusion of dexmedetomidine along with remifentanil infusion and bilateral scalp blockade. In one patient, a propofol infusion was used during infiltration of the scalp with the local anesthetic agent. Remimazolam was added to the existing sedation regimen of dexmedetomidine and remifentanil to achieve a deeper level of sedation during surgical incision, craniotomy, duraplasty, and surgical dissection for exposure of the seizure foci (asleep phase of the asleep-awake-asleep technique). The starting dose of remimazolam was 10 µg/kg/min in two patients and 5 µg/kg/min for the third with eventual infusion rates ranging from 2.5 to 15 µg/kg/min during the procedure. The remimazolam infusions were discontinued approximately 30 min before the start of the awake assessment, while the dexmedetomidine and remifentanil infusions were discontinued 10 - 15 min before the awake assessment. All three patients emerged calmly and were able to properly follow commands for the intraoperative testing. Following the awake portion of the procedure, the patients were re-sedated with dexmedetomidine and remifentanil for surgical resection and post-surgical MRI. Following successful completion of the three cases, the authors noted that remimazolam appeared to be a useful adjunct to their routine sedation regimen of dexmedetomidine and remifentanil for awake craniotomy seizure and seizure focus resection. They reported adequate sedation, maintenance of spontaneous ventilation, rapid awakening, and no limitations to intraoperative neuromonitoring or awake assessment with the addition of remimazolam. The limited case

Table 3. Remimazolam During Intraoperative Neuromonitoring in Pediatric and Adult Patients

Author and reference	Demographic and surgical procedure	Remimazolam dosing and outcome
Tanaka et al [28]	Cohort of nine adult patients, 63 ± 9 years of age, undergoing aneurysm clipping, carotid endarterectomy, and tumor resection	VEPs and SSEPs during TIVA with remifentanil and either remimazolam (0.8 to 1.0 mg/kg/h) or propofol (4 - 6 mg/kg/h). VEPs were higher with remimazolam while SSEPs were comparable between remimazolam and propofol.
Kondo et al [29]	Two patients of 76 and 70 years age undergoing laminoplasty for cervical spondylotic myelopathy and anterior cervical discectomy and fusion with intraoperative MEP monitoring	Induction with remimazolam (6 or 12 mg/kg/h) with remifentanil (0.3 µg/kg/min). Following NMBA and tracheal intubation, anesthesia maintained with remimazolam (0.5 - 1.5 mg/kg/h) and remifentanil (0.2 - 0.5 µg/kg/min). Successful intraoperative MEP monitoring with no significant changes compared to preoperative baseline.
Arashiro et al [30]	A 17-year-old, 64.5 kg woman with Alstrom syndrome for posterior spinal fusion for functional scoliosis. Alstrom syndrome is a rare genetic disorder with dilated cardiomyopathy, liver dysfunction, and scoliosis.	Inhalation induction followed by maintenance of anesthesia with remimazolam (0.5 - 1 mg/kg/h) and remifentanil (0.3 µg/kg/min). Posterior spinal fusion and successful MEP monitoring.
Kamata et al [31]	A 12-year-old, 55 kg adolescent with egg hypersensitivity for craniotomy with direct cortical MEP monitoring	Induction with remimazolam at 6 mg/kg/h and maintenance of anesthesia with remimazolam (1.5 mg/kg/h) and remifentanil (0.5 µg/kg/min). Successful MEP monitoring.
Hughes et al [32]	Cohort of 40 adolescents with mean age of 15.3 years old undergoing posterior spinal fusion	Remimazolam started at 2.5 - 10 µg/kg/min (median 5 µg/kg/min) with maintenance doses at a median of 8 µg/kg/min added to baseline anesthesia with either desflurane, propofol, or dexmedetomidine/ketamine. This was combined with an opioid infusion (sufentanil or remifentanil). Successful neurophysiological monitoring (MEP and SSEP). Remimazolam decreased requirements for volatile agent or propofol requirements by at least 15-30%.
Aoki et al [33]	A 57-year-old woman for open repair of a thoracic descending aortic aneurysm	Induction with remimazolam (12 mg/kg/h). Maintenance of anesthesia with remimazolam (0.2 - 1 mg/kg/h) and remifentanil. No significant changes in MEP with remimazolam administration.

MEP: motor evoked potential; NMBA: neuromuscular blocking agent; SSEP: somatosensory evoked potential; TIVA: total intravenous anesthesia; VEP: visual evoked potential.

series highlights the potential utility of remimazolam and its potential over propofol given its limited impact on hemodynamic and respiratory function [26].

Neuromonitoring and spine surgery

Evoked potential monitoring is frequently employed during spine and intracranial surgery to allow for early identification of neurological damage related to surgical intervention. However, the validity and integrity of both somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) may be impacted by the anesthetic technique [27]. Despite the favorable qualities of remimazolam, there remains limited information regarding its use during neuronal monitoring procedures (Table 3) [28-33].

The initial report regarding the impact of remimazolam on neuromonitoring (visual evoked potential (VEPs) and SSEPs) included a cohort of nine adult patients undergoing aneurysm clipping, carotid endarterectomy, and tumor resection [28]. VEPs and SSEPs were recorded during anesthesia with remifentanil and either remimazolam (0.8 to 1.0 mg/kg/h) or propofol (4 - 6 mg/kg/h). VEPs were higher with remimazolam, while SSEPs were comparable between remimazolam and propofol.

Anecdotal experience with remimazolam during neuromonitoring in spine or intracranial surgery has been reported in three reports, totaling four patients [29-31]. Kondo et al reported two adult patients aged 76 and 70 years old undergoing laminoplasty for cervical spondylotic myelopathy and anterior cervical discectomy and fusion, respectively. Both patients required intraoperative MEP monitoring. The induction dose of remimazolam was 6 or 12 mg/kg/h along with 0.3 µg/kg/min remifentanil followed by neuromuscular blocking agent (NMBA) and tracheal intubation. For maintenance of anesthesia to sustain a BIS value of 40 - 60, remimazolam was titrated between 0.5 and 1.5 mg/kg/h and remifentanil 0.2 - 0.5 µg/kg/min. The authors reported that at both a fixed dose of 0.5 mg/kg/h and an increasing dose from 0.5 to 1.5 mg/kg/h of remimazolam, MEP signals were not affected and could successfully be measured intraoperatively [29]. Within the pediatric population, Arashiro et al described a case of a 17-year-old, 64.5 kg adolescent requiring posterior spinal fusion for functional scoliosis and intraoperative MEP monitoring [30]. Of note, this patient had Alstrom syndrome which complicated the anesthetic regimen due to associated comorbid conditions including dilated cardiomyopathy,

type 2 diabetes mellitus, hepatic dysfunction, and hypertriglyceridemia. Given these comorbidities and the need for MEP monitoring, following inhalation induction, remimazolam (0.5 - 1.0 mg/kg/h) and remifentanil (0.3 µg/kg/min remifentanil) were chosen for maintenance of anesthesia. The authors reported stable intraoperative hemodynamic parameters along with successful MEP monitoring with no variation of MEP amplitude as the remimazolam dose was titrated intraoperatively. Finally, a single pediatric case report outlined the use of remimazolam (induction dose of 6 mg/kg/h followed by a maintenance dose of 1.5 mg/kg/h) in a 12-year-old patient during direct cortical MEP monitoring with stable cardiovascular status [31].

The largest study to date outlining the use of remimazolam during neurophysiological monitoring retrospectively reviewed the perioperative course of 40 pediatric patients ranging in age from 11 to 35 years who presented for posterior spinal fusion surgery [32]. The primary anesthetic was a volatile agent (desflurane) in 27 patients, propofol (total intravenous anesthesia (TIVA)) in 11, and dexmedetomidine/ketamine in two. The patients also received an opioid infusion (sufentanil or remifentanil) plus a single intraoperative dose of methadone (0.1 - 0.15 mg/kg). The median starting of remimazolam was 5 µg/kg/min with a maintenance dose of 8 µg/kg/min. The depth of anesthesia was titrated with either the volatile agent or propofol to maintain the BIS at 40 - 60. The authors noted that with the addition of remimazolam, the required inspired concentration of desflurane decreased from 3.5-4% to 2-2.6% and the propofol infusion rate was decreased from 150 - 200 to 70 - 100 µg/kg/min. There were also no observed adverse hemodynamic effects. The authors opined that the administration of remimazolam decreased the dose requirements of the volatile agent, thereby facilitating neurophysiological monitoring, and also decreased the dose requirements of propofol which may limit the prolonged awakening related to its CSHT.

Interventional neurological procedures

The applications of interventional neuroradiological procedure have grown significantly due to its efficacy and less invasive approach, thereby providing a more rapid recovery and hospital discharge. As the variety of neuroradiological procedures and interventions expands, so does the complexity and involvement of anesthetics used. The choice between procedural sedation and general anesthesia in neurointerventional procedures presents a critical decision for anesthetists and neurointerventionists, allowing for a broad range of anesthetic and pharmacological approaches. Most neuroradiologists prefer general anesthesia over sedation to ensure an immobile patient to improve imaging quality, therapeutic efficacy, and patient comfort; however, this prevents the ability to perform neurological assessments during the procedure. To date, the most commonly used agents include propofol or an inhalational anesthetic agent (desflurane or sevoflurane), with limited data demonstrating the superiority of any specific technique [34].

To date, only one study has evaluated the use of remimazolam in this clinical setting. Adult patients (n = 76) presenting for elective endovascular embolization were randomized to receive propofol or remimazolam [35]. The remimazolam group (n = 38) received remimazolam at 12 mg/kg/h and remifentanil via a TCI to achieve serum concentration of 3 ng/mL. The propofol group (n = 38) received a TCI to achieve a propofol concentration of 4 µg/mL and remifentanil of 3 ng/mL. Following NMBA administration and tracheal intubation, both groups were maintained at a BIS level of 40 - 60 with either propofol or remimazolam. Outcomes included recovery times and hemodynamic stability. To evaluate hemodynamic stability, the primary outcome was the total phenylephrine dose required to maintain blood pressure and number of hypotensive events (mean arterial pressure less than 80% of baseline). After completion of the case, the continuous infusions (remifentanil-remimazolam or remifentanil-propofol) were discontinued and residual neuromuscular blockade reversed with sugammadex. Flumazenil (0.2 mg) was administered to patients receiving remimazolam when the BIS reached 75 during emergence. The total phenylephrine dose was significantly lower in the remimazolam group (0, 0 - 30) versus the propofol group (30, 0 - 205; P = 0.001). Similar findings were noted in the number of hypotensive events recorded between the two groups. The number of hypotensive episodes, grouped as 0, 1 - 2, 3 - 4, and ≥ 5 were also higher in the propofol group (15, 6, 3, and 14 versus 27, 5, 5, and 1, respectively, P = 0.001). Recovery times (time to spontaneous breathing, time to eye-opening, time to tracheal extubation, and time to orientation) were all significantly shorter in the remimazolam group than in the propofol group. The authors concluded that remimazolam was preferred over propofol given its beneficial hemodynamic stability which maintained cerebral perfusion and a faster recovery to allow neurological assessment following the procedure. Although this study was conducted only in patients undergoing coil embolization for unruptured cerebral aneurysms, the hemodynamic stability and timing advantages associated with remimazolam are likely broadly applicable across other neuroradiological interventions.

Patients with comorbid neurological disorders

Various neurological or neuromyopathic conditions may be associated with increased perioperative morbidity. In several different comorbid conditions, anecdotal experience has been reported with the use of remimazolam as an alternative to volatile anesthesia agents or customary TIVA techniques (Table 4) [36-44]. These anecdotal experiences in both pediatric and adult patients used varying dosing regimens in a variety of clinical scenarios. Comorbid conditions included immune-mediated necrotizing myopathy, Duchenne muscular dystrophy, myotonic dystrophy, stiff person syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, and malignant hyperthermia (MH) susceptibility. In the majority of these cases, anesthesia was induced and maintained with remimazolam, often in conjunction with a remifentanil infusion.

Intensive care unit (ICU) sedation

Sedative agents are essential components of the care plan for

Table 4. Remimazolam in Patients With Comorbid Conditions

Author and reference	Demographic data and surgical procedure	Comorbid condition	Remimazolam dosing
Ogino et al [36]	A 21-month-old, 8.7 kg infant undergoing gastrostomy placement	Immune-mediated necrotizing myopathy	Induction with remimazolam (10 mg/kg/h) and fentanyl (3 µg/kg). NM blockade - rocuronium. Maintenance of anesthesia with remimazolam (1 - 2 mg/kg/h) and intermittent fentanyl.
Horikoshi et al [37]	A 4-year-old, 16 kg toddler undergoing inguinal herniorrhaphy	DMD	Remimazolam (15 mg/hr or 15-16 µg/kg/min) and remifentanil infusion, intermittent fentanyl. NM blockade - rocuronium.
Fukuda et al [38]	A 58-year-old, 68 kg woman undergoing ERCP	Myotonic dystrophy type 1	Induction with remimazolam (12 mg/kg/h) and remifentanil (0.1 µg/kg/min). NM blockade - rocuronium. Maintenance of anesthesia with remimazolam (0.8 - 1.0 mg/kg/h) and remifentanil (0.1 µg/kg/min).
Morimoto et al [39]	A 46-year-old, 60 kg man undergoing phacoemulsification and intraocular lens implantation	Myotonic dystrophy type 1	Induction with remimazolam (6 mg/kg/h). NM blockade. Maintenance of anesthesia with remimazolam (0.25 - 0.5 mg/kg/h) and remifentanil (0.2 µg/kg/min).
Morita et al [40]	A 16-year-old, 23 kg adolescent undergoing intrathecal baclofen pump exchange	Stiff person syndrome	Induction with remimazolam (4 mg) and remifentanil (0.5 µg/kg/min). NM blockade - rocuronium. Maintenance of anesthesia with remimazolam (2 mg/kg/h) and remifentanil (0.1 - 0.3 µg/kg/min). Depth of anesthesia monitored with the BIS.
Yamadori et al [41]	A 10-year-old girl undergoing open gastrostomy	MELAS syndrome	Induction with remimazolam (0.2 mg/kg bolus). NM blockade. Maintenance of anesthesia with remimazolam (1 - 2 mg/kg/h) and remifentanil (0.1 - 0.25 µg/kg/min).
Gyurgyik et al [42]	A 12-year-old, 52.6 kg adolescent undergoing right eye muscle surgery	MELAS syndrome	Maintenance of anesthesia with dexmedetomidine (0.5 µg/kg/min), remifentanil (0.3 - 0.4 µg/kg/min), and remimazolam (5 - 10 µg/kg/min). NM blockade - rocuronium. Depth of anesthesia monitored with the BIS.
Petkus et al [43]	A 6-year-old, 24.3 kg girl undergoing dental rehabilitation	Family history of MH	Induction with propofol. Maintenance of anesthesia with remimazolam (5 - 7 µg/kg/min) and propofol (50 µg/kg/min). Analgesia with morphine and ketorolac.
Kiyokawa et al [44]	A 5-year-old boy undergoing inguinal herniorrhaphy	Medium chain acyl dehydrogenase deficiency	Induction with remimazolam (4 mg bolus). Maintenance of anesthesia with remimazolam (2 mg/kg/h) and remifentanil (0.5 µg/kg/min). NM blockade - rocuronium. Depth of anesthesia monitored with the BIS. Rectus sheath and ilioinguinal nerve blockade.

DMD: Duchenne muscular dystrophy; ERCP: endoscopic retrograde cholangiopancreatography; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MH: malignant hyperthermia.

mechanically ventilated, ICU patients, as they help alleviate discomfort, agitation, and anxiety associated with mechanical ventilation. Choosing the optimal agent to minimize adverse physiological effects or injection pain remains a challenge with commonly utilized agents including propofol, midazolam, dexmedetomidine, and fentanyl. Due to its unique pharmacological properties, remimazolam shows great potential as a sedative agent in ICU patients.

To date, only one trial has investigated the use of remimazolam for sedation of ICU patients during mechanical ventilation [45]. The prospective study cohort consisted of 23 postoperative adult patients with a median age of 63 years (range: 51 - 72 years) who were admitted to the ICU immediately from their surgical procedure, requiring postoperative mechanical ventilation. The Narcotrend index (NTI) and the Richmond Agitation-Sedation Scale (RASS) were used to assess sedation and titrate the dose of remimazolam with a goal NTI value of 65 - 94 (moderate sedation to light sedation) and RASS score of -3 to -1 (moderate sedation to drowsy). Mechanical ventilation was adjusted to allow for spontaneous ventilation using the pressure support ventilation (PSV) mode. Remimazolam was then administered as a bolus dose of 0.02 - 0.05 mg/kg over 1 min, followed by additional bonuses of 0.005 mg/kg until the goal NTI and RASS scores were achieved. At that point, an infusion was started at 0.2 - 0.35 mg/kg/h with titration increments of 0.05 mg/kg/h to maintain sedation goals for the 30 - 120 min study duration. All 23 patients reached adequate sedation levels without adverse physiological effects or changes in hemodynamic and respiratory parameters. One patient required a vasoactive medication to maintain blood pressure during the study.

Additional Neurophysiological Effects of Remimazolam

Remimazolam has the potential to exert additional neurophysi-

ological effects that may be beneficial in the practice of neuroanesthesia and neurocritical care [46]. Preliminary animal data have demonstrated a potential neuroprotective role with reduced brain infarct volume, inhibited neuroinflammatory pathways, and improved neurological outcomes after ischemic injury [47]. Remimazolam has been shown to have little to no impact on postoperative delirium and cognitive dysfunction [48]. In a cohort of 200 adult patients, ≥ 65 years of age, undergoing cardiovascular surgery, the incidence of delirium within 5 days after surgery was 30.3% in patients who received remimazolam versus 26.6% in the control group (risk difference, 3.8%; 95% CI: -11.5% to 19.1%; P = 0.63). Furthermore, a single intraoperative bolus dose of remimazolam (0.2 mg/kg) decreased emergency delirium following tonsillectomy in a cohort of 104 pediatric patients (3 - 7 years of age) [49]. The incidence of emergence delirium was significantly lower in the remimazolam group compared to placebo (12% versus 44%; P < 0.05).

Conclusion

Remimazolam is a high affinity, ultrashort-acting benzodiazepine acting at the $GABA_A$ receptor to induce sedation, amnesia, anxiolysis, or general anesthesia depending on the dosage. Its unique, rapid metabolism by tissue esterases, independent of end-organ function, allows for its short elimination and limited CSHT. Garnering FDA approval in 2020 for procedural sedation in adults, remimazolam has been used primarily for GI endoscopy, bronchoscopy, and procedural sedation with more recent clinical work demonstrating its efficacy as both a primary agent and an adjunct to general anesthesia. With a rapid onset and offset, no pain upon injection, limited effect on respiratory and hemodynamic function, and little to no impact on postoperative delirium or cognitive dysfunction, it may offer advantages in specific clinical scenarios to other anesthetic and sedative agents. Despite favorable pharmacological properties and positive experiences in the adult population, it lacks FDA approval in the pediatric population.

Remimazolam is provided as a lyophilized powder. It is typically reconstituted using normal saline to achieve a final concentration of 20 mg/8 mL (2.5 mg/mL). Normal saline is generally recommended as the diluent as there is a potential for precipitation when administered with a buffer-containing solution (acetate or lactate) such as Ringer's lactate [50, 51]. The solubility of remimazolam is maximized in environments with a lower pH, making normal saline a preferred diluent over Ringer's lactate solutions. The risk of precipitation rises with higher concentrations of remimazolam, high pH solution, and a reduction in infusion rates. In a simulated Y-site administration study, researchers found remimazolam to be physically compatible with remifentanil, fentanyl, rocuronium, vecuronium, dexmedetomidine, and midazolam [52]. We have previously reported our standard for operating room pharmacy preparation of remimazolam and general recommendations for dosing (bolus and infusions) in pediatric-aged patients [6]. With any new medication, cost constraints must be considered. As with all medications, acquisition prices will vary based on location, pharmacy contracts, and buyer consortiums. The acquisition price of remimazolam is approximately $41.67 per 20 mg vial. In comparison, the cost of a 20 mL vial of propofol (10 mg/mL) is approximately $9-12.

The typical single bolus dose in adult patients ranges from 2.5 to 5 mg for procedural sedation and maintenance of a native airway. Induction of general anesthesia is typically achieved with a temporary high-dose infusion of 12 mg/kg/h (0.2 mg/kg/min) for 1 - 5 min until loss of consciousness is observed. Maintenance doses range from 1 to 2 mg/kg/h (approximately 17 - 33 µg/kg/min) with bolus doses of 0.1 to 0.2 mg/kg as needed. In the absence of universally established pediatric dosing guidelines, most reports adapt dosing from adult data, often converting to µg/kg/min. Due to the largely anecdotal nature of pediatric reports, there is a lack of data on bolus dosing regimens as well as consistent sedation and general anesthesia dosing in this population. Additional studies are necessary to help establish safe and effective pediatric dosing guidelines.

Given the predictable and favorable pharmacological properties, remimazolam may offer unique advantages in the field of neuroanesthesiology and neurocritical care. Use in both pediatric and adult populations is growing in CT or MRI, awake craniotomies, interventional neurological procedures, and ICU sedation. Anecdotal data also support its use in cases requiring VEP, SSEP, and MEP monitoring by providing adequate anesthesia without interference with neurophysiological monitoring. When used as a combined technique with a volatile agent during neuromonitoring, our clinical experience has demonstrated that remimazolam decreases volatile agent requirements and thereby facilitates MEP monitoring. Additional case reports and anecdotal experience have detailed the safe and effective use of remimazolam in patients with complex comorbid neurological or neuromyopathic conditions including MH susceptibility. There are additional areas even within this field, where its application may prove valuable. Of note, there are no studies evaluating the potential role of remimazolam in the management of status epilepticus. Considering that benzodiazepines are routinely utilized for this indication, there is a substantial opportunity for remimazolam to play a role. Given its unique properties, it may offer advantages that surpass those of currently used benzodiazepines. Additionally, given is pharmacodynamic properties, it may have a role in sedation during mechanical ventilation allowing a rapid titration of the depth of sedation and yet a rapid wake-up when its administration is discontinued. Additional studies further stratifying the pharmacokinetics and pharmacodynamics in pediatric and neonate aged patients are warranted to ensure that its metabolism by tissue esterases remains consistent across this age range as well as observations of true recovery time with remimazolam as the sole agent.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

EM: preparation of initial, subsequent, and final drafts; AS: review of all drafts including final draft; JDT: study concept and review of all drafts.

Data Availability

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

Abbreviations

BIS: bispectral index; CNS: central nervous system; CSHT: context-sensitive half-time; CT: computed tomography; FDA: Food & Drug Administration; GABA: gamma-aminobutyric acid; ICU: intensive care unit; MRI: magnetic resonance imaging; NTI: Narcotrend index; RASS: Richmond Agitation-Sedation Scale; SNpr: substantia nigra pars reticulata; SSEPs: somatosensory evoked potentials; VEPs: visual evoked potentials

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