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Advances in The Assessment of the Sedative Effect of Remimazolam

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Abstract

Purpose of Review: Remimazolam is a new short-acting benzodiazepine in the final stages of clinical development. The methods of monitoring sedation and assessing the depth of anesthesia for benzodiazepine sedative drugs have been fraught with controversy in clinical work. As a newly released short-acting anesthetic sedative drug that can be continuously pumped, appropriate anesthetic monitoring and sedation depth assessment tools can better help anesthesiologists make clinical decisions and reduce the emergence of perioperative complications in patients.

Recent Findings: Clinical trials of remimazolam have been completed at home and abroad in various phases, and much progress has been made, but the effective sedation monitoring means of remimazolam are still not conclusive.

Summary: Remimazolam has a rapid onset of action and a high rate of metabolism in the body; tissue accumulation and delayed awakening are rare. At the same time, it can be safely applied to elderly patients with a low cardiopulmonary function inhibition rate, accurate anesthesia effect, and satisfactory quality of awakening. By comparing various methods of sedation depth monitoring, the data correlation is high, which can be of significant importance for remimazolam sedation depth monitoring.

Keywords

Anaesthesia, Midazolam, Propofol, Remimazolam, Sedation

Introduction

Remimazolam (CNS 7056) is a novel ultra-short-acting benzodiazepine drug whose parent compound is midazolam. Based on the chemical structure of midazolam, a carboxylic ester bond has been introduced to make it easier to be metabolized in vivo by plasma non-specific tissue enzymes, and an inactive metabolite CNS 7054 has been found to be catalyzed in the liver by CES1 as a result of the increasing pharmacokinetic studies of remimazolam. These two metabolic mechanisms allow for a rapid metabolism of remimazolam, and the metabolism of the drug has been shown to be very rapid in vitro. Meanwhile, according to an in vitro hepatic cell exposure study, although part of the metabolic pathway of remimazolam is metabolized by hepatic carboxylesterase, no deleterious alteration of hepatic cells was observed. Therefore, as a sedative drug, remimazolam, which combines the dual features of midazolam and remifentanil, has become the focus of research and application of new anesthesia drugs [1-3]. It is a new type of anesthesia drug.

Clinical Studies of Remimazolam

In a drug study program of remimazolam in Chinese healthy volunteers [4], the recommended drug dosage of remimazolam for single sedation versus continuous pumping was obtained. The results of this study showed that when remimazolam was injected in a single dose, a sedative effect could be observed at 0.05 mg/kg of remimazolam, and the sedative effect peaked 1-2 minutes after ≥0.075 mg/kg of remimazolam was injected. Satisfactory sedation was achieved at a continuous pumping induction dose of 0.2 mg/kg/min and a maintenance dose of 1 mg/kg/h. This study is the first to obtain the optimal sedative dose of remimazolam in healthy volunteers. Since this study is a healthy volunteer study, it is affected by the physiological state of the patients in actual clinical work, so this dose still needs to be verified in subsequent clinical and experimental trials.

A team from Korea conducted a study [5,6]. The study evaluated the safety and efficacy of intravenous remimazolam and obtained the ED_{50} and ED_{95} of remimazolam in causing loss of consciousness and respiratory depression in patients, which were 0.11/0.19 mg/kg and 0.14/0.27 mg/kg, respectively. The study also obtained the optimal dose of remimazolam according to the patient's age for patients less than 40 years old, 40-80 years old, and more than 80 years old, which asked 0.25-0.33 mg/kg, 0.19-0.25 mg/kg, and 0.14-0.19 mg/kg, respectively. The study successfully evaluated the safety and efficacy of remimazolam and provided a safer anesthesia idea for rational clinical application of remimazolam. This study still has the limitation that the adverse effects of intravenous anesthetics include circulatory depression, hepatic, and renal impairment in addition to respiratory depression, so the ED_{50} and ED_{95} of different doses of remimazolam leading to different sedation-related adverse events still need to be confirmed by clinical practice.

A multicenter clinical study of the safety and efficacy of remimazolam in general anesthesia for patients with ASA classification III was conducted in Japan [7]. The investigators used 6 mg/kg/h (group A) and 12 mg/kg/h (group B) of remimazolam for maintenance anesthesia and observed the time to loss of consciousness, patient BIS scores, and the incidence of adverse events. The study found that the time to loss of consciousness in group B was significantly less than that in group A at the two different doses, but there was no significant difference in the BIS scores, and there was no statistically significant difference in the incidence of adverse events in the patients. The team concluded that the dose of remimazolam was positively correlated with the time to loss of consciousness and that the safety profile of remimazolam remained high under conditions of continuous pumping at a dose of 12mg/kg/h. This study is the first to evaluate the drug safety of remimazolam general anesthesia applied to ASA class III patients at high risk of anesthesia and strongly demonstrates that remimazolam's mild inhibition of respiratory and circulatory function can be safely applied to sedate critically ill patients in the perioperative period.

Clinical Applications of Remimazolam

As an anesthetic induction drug, remimazolam is unlikely to be superior to midazolam. The onset of action is 1-3 minutes after 0.075 mg/kg, which is not significantly different from that of midazolam. Although the shorter elimination time is a prominent advantage of remimazolam, anesthetic drugs with longer metabolism times may be more beneficial for pre-anesthetic induction in special populations such as anxious patients, children, etc., to alleviate the patient's pre-anesthetic stress response. However, short-acting anesthetic drugs, represented by remimazolam and remifentanil, may be more beneficial for populations that are inherently at high risk for sedation, such as morbidly obese patients who are often denied sedation during short-term procedures such as epidural catheter placements or central catheterization, which are often technically challenging for morbidly obese patients and are further complicated by the patient's anxiety. With remimazolam, it may be easier to achieve a satisfactory level of sedation with a low risk of airway obstruction. Flumazenil is another advantage of benzodiazepines [1,2,8].

Many gastrointestinal (GI) endoscopic procedures can be accomplished with short-acting benzodiazepines along with short-acting opioids such

as fentanyl. In a phase IIa clinical trial [2], remimazolam was evaluated for procedural sedation in patients undergoing upper gastrointestinal endoscopy and was found to have a shorter recovery time than midazolam. However, due to the uncertainty of gastroscopy procedure times and differences in the proficiency of endoscopic technicians, the advantages of remimazolam are difficult to realize, and therefore propofol remains the most preferred sedative drug for gastrointestinal endoscopy. Mean procedure times in this study ranged from 3.3 to 4.3 minutes. It does not make sense to add propofol to remimazolam dosing for procedural success. Although larger doses or combinations with fentanyl may accelerate and prolong the effects of remimazolam, the incidence of respiratory depression is likely to increase. Hypotension and hypoxemia were seen in some of the patients who underwent colonoscopy. Failure to complete colonoscopy in 25% of subjects due to failure of sedation and a severe decrease in patient satisfaction may be one of the reasons why propofol is more commonly used for colonoscopy in many healthcare organizations in the United States [9,10].

Studies have shown that interval-free sedation in the intensive care unit (ICU) increases the likelihood of early extubation. Critically ill patients often have varying organ dysfunction. A significant proportion of commonly used sedatives require hepatic metabolism followed by renal clearance. Therefore, even if sedation is discontinued, altered pharmacokinetics of excretion or metabolism are problems that cannot be ignored. In addition, most drugs (with the exception of propofol) have significantly longer pharmacologic half-lives. In this case, the ideal drug choice would be a short-acting drug whose metabolism is not dependent on the liver or kidney [11].

BIS for Intraoperative Sedation with Remimazolam

The Bispectral Index (BIS), bispectral index monitoring, is a widely used index for the assessment of clinical anesthesia and sedation, mainly reflecting cortical excitatory or inhibitory states and sedative-hypnotic information [12,13]. BIS is a widely used indicator for clinical anesthesia and sedation assessment. By analyzing and processing this information, it is possible to understand the patient's immediate state of consciousness, thus helping the anesthesiologist to dynamically change the anesthesia plan.

Professor Matsuyuki Doi's team from Japan applied BIS monitoring to assess the sedative effect of different doses of remimazolam against continuous pumping of propofol in a phase III multicenter clinical trial evaluating the safety and efficacy of remimazolam [7]. The trial included 375 patients who were divided into three groups: a continuously pumped low-dose remimazolam group, a continuously pumped high-dose remimazolam group, and a continuously pumped propofol group. The time of loss of consciousness of the patients was assessed by BIS monitoring in relation to the drug dose. The results of the trial showed similar sedation effects in the 6 mg/kg/h, 12 mg/kg/h remimazolam, and 2.0-2.5 mg/kg propofol groups. As the primary sedation level monitor, it is emphasized that BIS values showed adequate depth of anesthesia in all groups, suggesting a higher degree of objectivity in the results of this trial.

Prof. Sheng's team applied remimazolam to the pharmacokinetics and pharmacodynamics of healthy volunteers in China [4]. Prof. Sheng's team conducted a pharmacokinetic and pharmacodynamic study of remimazolam in Chinese healthy volunteers, relying on BIS to monitor the depth of sedation in combination with blood concentration measurements in volunteers, and concluded that remimazolam can be safely used in Chinese healthy volunteers with a predictable PK profile and dose-dependent PD profile. Based on several clinical studies, it was concluded that remimazolam may have a stronger sedative effect and shorter recovery time than midazolam. Thus, the application of BIS for intraoperative sedation with remimazolam has very considerable clinical value and research potential.

Advances in the Use of PSI for Intraoperative Sedation with Remimazolam

Patient State Index (PSI) is a tool for monitoring the depth of anesthesia in clinical settings and the level of consciousness in intensive care units. Unlike BIS, PSI

does not rely on any sedative drugs but rather on a large collection of EEGs from people in different states of consciousness, forming a huge database from which different PSI scores can be obtained based on the existing image information. The information of the images in the database can be used to obtain different PSI scores in order to assess the state of consciousness of the subjects [14-18]. The PSI scores are obtained by using the image information already in the database.

Based on the premise that the BIS value of remimazolam is relatively high during general anesthesia, Dr. Kazuhiro Shirozu's team from Japan designed a single-arm clinical trial to compare the magnitude and correlation between BIS and PSI during general anesthesia with remimazolam [19]. The trial included 30 patients undergoing breast surgery under elective general anesthesia, and the results of the trial showed that the mean intraoperative BIS and PSI of all patients were 50.6±9.1 and 43.0±11.8, respectively, suggesting that the use of PSI to guide the intraoperative dosage of remimazolam might be more reliable. However, this trial has obvious shortcomings: 1, the effectiveness of remimazolam was not compared with other anesthetics. Therefore, the superiority of remimazolam over other anesthetics cannot be directly discussed. Second, the dose of remimazolam may not be correctly adjusted when the BIS value is not less than 60. There are few trials and studies on the monitoring of the means of intraoperative sedation of remimazolam, so the application of PSI to the monitoring of the degree of intraoperative sedation of newer drugs, such as remimazolam, has strong scientific value.

Progress in the Use of the MOAA/S Sedation Score for Intraoperative Sedation with Remimazolam

The Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) is the most commonly used index for clinical sedation evaluation (**Table-1**), and its good correlation with different levels of patient sedation has been demonstrated in many other studies. In the phase I, II, and III clinical trials of remimazolam, MOAA/S scores were used to assess the degree of sedation of patients at different drug doses [20].

As an ultrashort-acting benzodiazepine sedative, although remimazolam is nowadays widely used for intraoperative sedation in various anesthetic modalities, its best indication is currently intraoperative sedation for non-airway-managed general anesthesia for short procedures, such as gastroenteroscopy, hysteroscopy, and manipulation and repositioning of dislocated long bones. Therefore, the MOAA/S score remains the preferred modality for assessing the degree of intraoperative sedation with remimazolam.

Comparison of BIS and PSI for Intraoperative Sedation Assessment

Dr. Xiaoguang Chen's research team from the Department of Anesthesiology at the University of Texas Southwestern Medical Center attempted to validate the sensitivity of PSI versus BIS for monitoring the degree of intraoperative sedation of two different classical anesthetic drugs [13]. The study included 20 patients undergoing surgical treatment under elective general anesthesia, and through correlation analysis with ROC curves comparing sensitivity, the results showed that both PSI and BIS could successfully differentiate between awake and anesthetized states of patients. They concluded that PSI may have higher sensitivity and specificity in assessing consciousness at the time of induction and awakening from general

Table-1: Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale

Scale	MOAA/S Scale
0	Does not respond to painful trapezius squeeze
1	Responds only after painful trapezius squeeze
2	Responds only after mild prodding or shaking
3	Responds only after name is called loudly and/or repeatedly
4	Lethargic response to name spoken in normal tone
5 (alert)	Responds readily to name spoken in normal tone

anesthesia, and that PSI was also able to monitor changes associated with the use of isoproterenol and desflurane during maintenance. The study also found that PSI was less affected than BIS during intraoperative electrosurgical manipulation with the electrosurgical knife. Additionally, the team found that PSI values were consistently lower than BIS values when anesthesia was supplemented during maintenance, and never returned to pre-induction baseline values as the patient regained orientation, suggesting potential differences in sensitivity to residual (subhypnotic) levels of anesthesia and/or "drift" in PSI values during surgery.

When analyzed in the context of the original development process, it would seem that PSI is more objective than BIS in the assessment of sedation for use during anesthesia. However, research by Dr. Paul F. White's team showed [13] that during induction, maintenance, and emergence, PSI and BIS generally performed similarly, with ROC curves obtained between the two monitors showing similar performance in the trial results (PSI 0.98±0.05, BIS 0.97±0.05). Additionally, PSI was associated with the patient's performance at the time of eye opening (PSI r=0.57, BIS r=0.11) and at the time of removal of the endotracheal tube (PSI r=0.72, BIS r=0.33).

Conclusion

In his study of EEG monitoring in anesthesia, Dr. Drummond JC noted that [21] for a means of detecting depth of anesthesia to be considered ideal, the depth of anesthesia monitoring device must satisfy two conditions: 1) there must be a statistically significant difference between the mean values measured by the monitoring device at two different depths of anesthesia, and there should be no overlap between the ranges of values obtained in these two states; and 2) the choice of anesthetic drug should not influence the measurements distinguishing between various depths of anesthesia. With more in-depth research on BIS and EEG, scholars have found that neither of these two sedation assessment tools can fully meet the above two conditions. However, the application of EEG monitoring to sedation monitoring of propofol, benzodiazepines such as midazolam, inhalational anesthetics such as sevoflurane and desflurane, and α2-adrenergic agonists such as dexmedetomidine has also made corresponding progress. Synthesizing relevant domestic and international clinical studies, it can be concluded that although the sensitivity and specificities of different monitoring methods applied to the sedation assessment of different anesthetics vary, overall they significantly reduce the use of anesthetic drugs, and at the same time reduce the incidence of intraoperative awareness and other complications.

The MOAA/S sedation score is simple, reliable, and easy to collect data, making it widely used in clinical sedation assessment. However, its disadvantages include susceptibility to the subjective factors of anesthesiologists and a lag in assessment, which does not allow for dynamic and accurate assessment of the patient's immediate state of consciousness, particularly during deep anesthesia maintenance.

With the gradual expansion of clinical indications for remimazolam, more anesthesiologists have begun to use this ultrashort-acting benzodiazepine sedative in different anesthetic protocols. Therefore, the use of more accurate intraoperative sedation monitoring to optimize the dosing regimen of remimazolam can better maintain perioperative patient's vital organ function and thus reduce the emergence of anesthetic complications. The commonly used BIS, PSI, and MOAA/S sedation scores have different characteristics, advantages, and disadvantages, and possess strong clinical potential and research value. Further studies can be conducted by clinicians and researchers to explore their characteristics.

"Soft chemistry" (self-metabolizing, organ-independent drugs) in anesthesia and intensive care has been a major focus of modern medical research. As the research and application of remimazolam have progressed, the manufacturer's instructions for remimazolam have extended the indications from sedation for gastric and colonoscopy to the induction and maintenance of general anesthesia. Comparison of remimazolam with propofol, etomidate, midazolam, and other drugs in various research institutions has resulted in a lower incidence of adverse effects, more rapid awakening of the patient, and the reversal of the benzodiazepine antagonist flumazenil as a safety

guarantee. Remimazolam has been used safely in clinical anesthesia work.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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References

[1] Zhou Y, Hu P, Jiang J. Metabolite characterization of a novel sedative drug, remimazolam in human plasma and urine using ultra high-performance liquid chromatography coupled with synapt high-definition mass spectrometry. J Pharm Biomed Anal. 2017 Apr 15;137:78-83. [**PMID**: 28104560]

[2] Rogers WK, McDowell TS. Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. IDrugs. 2010 Dec;13(12):929-37. [**PMID**: 21154153]

[3] Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. Pharmacotherapy. 2016 Sep;36(9):1021-27. [**PMID**: 27496519]

[4] Sheng XY, Liang Y, Yang XY, Li LE, Ye X, Zhao X, Cui YM. Safety, pharmacokinetic and pharmacodynamic properties of single ascending dose and continuous infusion of remimazolam besylate in healthy Chinese volunteers. Eur J Clin Pharmacol. 2020 Mar;76(3):383-91. [**PMID**: 31873765]

[5] Chae D, Kim HC, Song Y, Choi YS, Han DW. Pharmacodynamic analysis of intravenous bolus remimazolam for loss of consciousness in patients undergoing general anaesthesia: a randomised, prospective, double-blind study. Br J Anaesth. 2022 Jul;129(1):49-57. Erratum in: Br J Anaesth. 2022 Nov;129(5):831. [**PMID**: 35562226]

[6] Chae D, Kim HC, Song Y, Choi YS, Han DW. Corrigendum to 'Pharmacodynamic analysis of intravenous bolus remimazolam for loss of consciousness in patients undergoing general anaesthesia: a randomised, prospective, double-blind study' (Br J Anaesth 2022; 129: 49-57). Br J Anaesth. 2022 Nov;129(5):831. Erratum for: Br J Anaesth. 2022 Jul;129(1):49-57. [**PMID**: 36075773]

[7] Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. J Anesth. 2020 Aug;34(4):491-501. [**PMID**: 32303884]

[8] Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. Anesth Analg. 2012 Aug;115(2):274-83. [**PMID**: 22190555]

[9] Worthington MT, Antonik LJ, Goldwater DR, Lees JP, Wilhelm-Ogunbiyi K, Borkett KM, Mitchell MC. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. Anesth Analg. 2013 Nov;117(5):1093-100. [**PMID**: 24108261]

[10] Goudra BG, Singh PM, Sinha AC. Outpatient endoscopic retrograde cholangiopancreatography: Safety and efficacy of anesthetic management with a natural airway in 653 consecutive procedures. Saudi J Anaesth. 2013 Jul;7(3):259-65. [**PMID**: 24015127]

[11] Goudra BG, Singh PM. Remimazolam: The future of its sedative potential. Saudi J Anaesth. 2014 Jul;8(3):388-91. [**PMID**: 25191193]

[12] Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013 Jan;25(1):33-42. [**PMID**: 23027226]

[13] Chen X, Tang J, White PF, Wender RH, Ma H, Sloninsky A, Kariger R. A comparison of patient state index and bispectral index values during the perioperative period. Anesth Analg. 2002 Dec;95(6):1669-74. [**PMID**: 12456436]

[14] Drover D, Ortega HR. Patient state index. Best Pract Res Clin Anaesthesiol. 2006 Mar;20(1):121-28. [**PMID**: 16634419]

[15] Drover DR, Lemmens HJ, Pierce ET, Plourde G, Loyd G, Ornstein E, Prichep LS, Chabot RJ, Gugino L. Patient State Index: titration of delivery and recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology. 2002 Jul;97(1):82-89.

[**PMID**: 12131107]

[16] Jacobsohn E, De Wet C, Tymkew H, Hill L, Avidan M, Levy N, Bruemmer-Smith S. Use of the Patient State Index (PSI) to assist in the diagnosis of perioperative neurological injury and brain death. J Clin Monit Comput. 2005 Jun;19(3):219-22. [**PMID**: 16244845]

[17] Pérez GA, Pérez JAM, Álvarez ST, Morales JAR, Fragoso AML. Modelling the PSI response in general anesthesia. J Clin Monit Comput. 2021 Oct;35(5):1015-25. [**PMID**: 32691283]

[18] Christenson C, Martinez-Vazquez P, Breidenstein M, Farhang B, Mathews J, Melia U, Jensen EW, Mathews D. Comparison of the Conox (qCON) and Sedline (PSI) depth of anaesthesia indices to predict the hypnotic effect during desflurane general anaesthesia with ketamine. J Clin Monit Comput. 2021 Dec;35(6):1421-28. [**PMID**: 33211251]

[19] Shirozu K, Nobukuni K, Funakoshi K, Nakamura T, Sumie M, Higashi M, Yamaura K. The effect of remimazolam on postoperative memory retention and delayed regeneration in breast surgery patients: Rationale and design of an exploratory, randomized, open, propofol-controlled, single-center clinical trial: A study protocol. Medicine (Baltimore). 2021 Dec 3;100(48):e27808. [**PMID**: 35049181]

[20] Pastis NJ, Hill NT, Yarmus LB, Schippers F, Imre M, Sohngen W, Randall O, Callahan SP, Silvestri GA. Correlation of Vital Signs and Depth of Sedation by Modified Observer's Assessment of Alertness and Sedation (MOAA/S) Scale in Bronchoscopy. J Bronchology Interv Pulmonol. 2022 Jan 1;29(1):54-61. [**PMID**: 34238838]

[21] Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. Anesthesiology. 2001 Nov;95(5):1151-59. [**PMID**: 11684984]