

EDITORIAL VIEW

PERIOPERATIVE MEDICINE

Remimazolam besylate; overview of a novel benzodiazepine for general anesthesia

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Abstract

Remimazolam, a novel, ultra-short-acting intravenous anesthetic, belongs to the benzodiazepine class of drugs and was approved for as a general anesthetic. Its pharmacological action is similar to that of midazolam. However, the differences in the metabolic pathway and pharmacokinetic profiles of its metabolites contribute to the faster offset of the action of remimazolam than midazolam. The context-sensitive half time (CSHT) is as short as 6.8 ± 2.4 min. An advantage of remimazolam over other intravenous anesthetics, such as propofol, is the presence of antagonists. Remimazolam-induced sedation is reversed by flumazenil, a benzodiazepine antagonist. Moreover, lower prevalence of injection site pain and less reduction in blood pressure in the are the advantages of remimazolam over propofol. Although our knowledge is limited at present, remimazolam may be useful for general anesthesia. We look forward to the future possibilities of this new anesthetic agent.

Key words: Anesthesia, General; Anesthesia, Intravenous; Benzodiazepine; Remimazolam

Citation: Morimoto Y. Remimazolam besylate; overview of a novel benzodiazepine for general anesthesia. *Anaesthesia, pain intensive care* 2022;26(3):277-279; DOI: [10.35975/apic.v26i3.1819](https://doi.org/10.35975/apic.v26i3.1819)

Received: February 01, 2022; **Reviewed:** May 04, 2022; **Accepted:** May 07, 2022

THE history of general anesthesia is also the history of the development of general anesthetics. However, no new general anesthetic has been developed in recent years. Propofol is the last developed widely used intravenous anesthetic. No intravenous anesthetic developed over the last 25 years, has been superior to propofol.

Remimazolam, a novel, ultra-short-acting intravenous anesthetic, belongs to the benzodiazepines and was approved in Japan in 2020 for use as a general anesthetic.

¹ It was later approved in the United States in 2021 for sedation during endoscopy and has since been approved in various other countries. The potential of remimazolam as a general anesthetic is currently unknown because it has only just been approved, and its use as a general anesthetic is limited in Japan and Korea. This editorial summarizes the current findings on remimazolam as a potential agent for general anesthesia. To understand the use of remimazolam for short surgical procedure sedation, please refer to my other manuscript. ²

Remimazolam is a novel, fast-acting benzodiazepine with a shorter duration of action than other agents. Its pharmacological action is similar to that of midazolam.

However, remimazolam differs from midazolam in two respects. With regard to its metabolic pathway, midazolam is metabolized via cytochrome P450, and remimazolam by hepatic tissue esterases. Additionally, alpha-hydroxymidazolam, a metabolite of midazolam, shows 1/8th of the sedative effect of midazolam, whereas CNS7054, a metabolite of remimazolam, shows 1/400th of its sedative effect. ³ These differences in the metabolic pathway and pharmacokinetic profiles of its metabolites contribute to the rapid offset of the action of remimazolam.

An advantage of remimazolam over other intravenous anesthetics, such as propofol, is the presence of antagonists. Remimazolam-induced sedation is reversed by flumazenil, a benzodiazepine antagonist. Anesthesiologists are now able to use antagonistic general anesthetics for the first time. The advent of sugammadex as a muscle relaxant antagonist has

contributed to the efficiency and safety of general anesthesia. Similarly, remimazolam has the potential to dramatically alter general anesthesia management.

An understanding of pharmacokinetics is essential for the use of intravenous anesthetics. Single injection of remimazolam showed dose-dependent sedative action, with the onset of sedation within 60 sec of administration.^{4,5}

The pharmacokinetics of continuous intravenous infusion of remimazolam have also been investigated by Schuttler et al.⁶ Twenty healthy male volunteers received the following doses: 5 mg/min for 5 min, 3 mg/min for the next 15 min, and 1 mg/min for a further 15 min. Pharmacokinetics was best described by a three-compartment model. Remimazolam showed high clearance, small steady-state volume of distribution, and short terminal phase half-life. The context-sensitive half time (CSHT) calculated using the pharmacokinetic parameters obtained in this study was as short as 6.8 ± 2.4 min. These results suggest that remimazolam is characterized by fast onset and fast recovery after both single and continuous injection.

Electroencephalographic (EEG) monitoring, including the bispectral index (BIS) (Medtronic, Minneapolis, MN, USA) and patient state index (PSI) (Mashimo, Irvine, CA, USA), are commonly used to maintain the appropriate hypnotic level. Since the amount of intravenous anesthetic required varies widely among individuals, the use of EEG monitoring is essential. Therefore, it is important to determine whether the hypnotic effect of remimazolam can be evaluated using EEG.

Eisenried et al. evaluated the changes in the blood levels of remimazolam, MOAA/S score, and BIS.⁶ They found that an increase in blood remimazolam concentration was associated with a decrease in the MOAA/S score and BIS, which suggests that the BIS might be a useful indicator for monitoring the sedative effects of remimazolam.

Shirozu et al. monitored BIS and PSI during general anesthesia with remimazolam in 30 patients who underwent breast surgery.⁷ The mean intraoperative BIS and PSI were 50.6 ± 9.1 and 43.0 ± 11.8 , respectively. They found that BIS and PSI were higher during anesthesia with remimazolam than during anesthesia with conventional anesthetics. The usefulness of EEG monitoring during remimazolam anesthesia requires further investigation.

A clinical study on the administration of remimazolam during general anesthesia was conducted by Doi et al. in Japan.⁸ In the phase IIb/III trial, surgical patients (n = 375) were randomized to receive remimazolam starting at 6 or 12 mg/kg/h by continuous intravenous infusion

followed by 1 mg/kg/h to be adjusted as appropriate until the end of surgery or IV propofol. All patients received rocuronium and a continuous infusion of remifentanyl to maintain general anesthesia. No patients experienced intraoperative awakening/recall or body movement, or required rescue sedatives. The time to loss of consciousness was longer in the remimazolam 6 and 12 mg/kg/h groups than in the propofol group. The time to extubation was longer in the remimazolam group than in the propofol group. The incidence of adverse drug reactions was similar between the groups. Decreased blood pressure occurred in 20% and 24% of patients treated with 6 and 12 mg/kg/h remimazolam, respectively, compared with 49.3% of patients receiving propofol. Injection site pain was reported in 18.7% of patients in the propofol group, but not in those receiving remimazolam.

Lower prevalence of injection site pain and less reduction in blood pressure in the study are the advantages of remimazolam over propofol. Regarding arousal after anesthesia, propofol and remimazolam showed nearly the same CSHT; therefore, arousal time after anesthesia should be nearly the same. The longer time to extubation might be due to unfamiliarity with the use of remimazolam. However, the availability of flumazenil (a benzodiazepine antagonist) is a specific advantage of remimazolam. Patients who were administered flumazenil awakened within 2 min in the study. These results demonstrate that remimazolam is non-inferior to propofol in terms of efficacy as a sedative hypnotic for general anesthesia.

The administration of flumazenil (a benzodiazepine antagonist) should be considered in patients with inadequate or delayed arousal. However, a case of re-sedation in a patient who was aroused following flumazenil administration was reported.⁹ Re-sedation is likely to occur following the administration of a large volume of remimazolam during general anesthesia. Further studies are warranted to confirm the optimal timing and dosage of flumazenil.

A case of remimazolam-induced anaphylactic shock was reported.¹⁰ In this case, the patient was sensitized by previously administered midazolam. Remimazolam should not be used in patients with history of benzodiazepine allergy.

This editorial summarized the use of remimazolam as a general anesthetic. Although our knowledge is limited at present, it may be useful for general anesthesia, especially in elderly and high-risk patients. We look forward to the future possibilities of this new anesthetic agent.

Conflict of interest

None declared by the author.

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