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FAST, PREDICTABLE, REVERSIBLE: A COMPREHENSIVE REVIEW OF REMIMAZOLAM

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ABSTRACT

Remimazolam is a new, ultra–short-acting benzodiazepine whose unique chemical structure—the introduction of an ester moiety into the benzodiazepine core—enables rapid hydrolysis by non-specific tissue esterases to an inactive metabolite (CNS7054). This modification, analogous to that used in remifentanil, ensures an exceptionally rapid onset and equally rapid offset of sedation, organ-independent metabolism, and a highly predictable pharmacokinetic profile. The drug is intended exclusively for intravenous administration, which—according to the summary of product characteristics—eliminates gastrointestinal absorption and avoids the first-pass effect.

Pharmacodynamically, remimazolam exerts its sedative effect through allosteric enhancement of the inhibitory action of GABA at the GABA-A receptor. Remimazolam may be administered as a bolus or continuous infusion, and its dosing varies depending on the indication, country, patient condition, and concomitant medications. Compared with midazolam, it is characterized by a faster onset, deeper sedative effect, and shorter duration of action.

In comparison with propofol, remimazolam does not shorten recovery time but offers a more favorable safety profile—it significantly less frequently causes post-induction hypotension, bradycardia, respiratory depression, or injection pain. An additional advantage is the availability of a specific antidote—flumazenil. Although remimazolam reduces the risk of postoperative nausea and vomiting (PONV) compared with inhalational anesthetics, it may be associated with a higher incidence of vomiting when compared directly with propofol. However, the drug may offer benefits in terms of postoperative patient comfort.

Methodology: This review paper is based on data derived from peer-reviewed scientific articles and reports published in recognized databases and journals, including PubMed, Clinical Pharmacokinetics, and Anaesthesiology Intensive Therapy. It includes clinical studies and review articles published between 2015 and 2025 in English or Polish.

KEYWORDS

Remimazolam, Benzodiazepines, GABA-A, Procedural Sedation, General Anesthesia, Propofol

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1. Introduction

General anesthesia constitutes a fundamental pillar of modern medicine, enabling the performance of complex diagnostic and surgical procedures by inducing a state of reversible unconsciousness while maintaining basic systemic homeostasis. The appropriate selection of anesthetic agents is crucial for patient safety, the course of surgery, and the recovery process. Therefore, in anesthesiology and intensive care, there is a continuous search for an ideal sedative agent that would combine a rapid onset of action with hypnotic-sedative properties, be characterized by a high therapeutic index, and carry a minimal risk of adverse effects. A response to these challenges may be remimazolam – a relatively new benzodiazepine that, due to its unique pharmacological properties, is gaining increasing interest in the field of general anesthesia. Its specific profile predisposes it to the role of a drug with exceptionally predictable and short-lasting action. [1, 2]

2. Mechanism of action

The GABA receptor system constitutes the main population of inhibitory receptors in the human central nervous system and is a key target site for intravenous anesthetic agents inducing general anesthesia. Most of these drugs – including barbiturates, benzodiazepines, propofol, and etomidate – exert their effects by binding to the GABA type A receptor. Ketamine is an exception, as its mechanism of action is primarily based on antagonism at the N-methyl-D-aspartate (NMDA) receptor, although it also interacts with other receptor types.

Remimazolam, similarly to midazolam, enhances the activity of the GABA type A receptor. This leads to hyperpolarization of the neuronal cell membrane and, consequently, through increased chloride ion influx, inhibits neuronal activity. However, remimazolam was designed by the deliberate introduction of a carboxylic

ester moiety into the benzodiazepine core. This structural modification, analogous to that used in remifentanil, results in rapid hydrolysis of remimazolam to a pharmacologically inactive metabolite via non-specific tissue esterases. As a consequence, sedation has an exceptionally rapid onset and offset, with a highly predictable duration of action. Importantly, as with other benzodiazepines, the sedative effect of remimazolam can be reversed when necessary with flumazenil.

The combination of favorable properties – rapid onset, organ-independent metabolism, short duration of action, predictable recovery, availability of a specific antidote, and a hemodynamic safety profile similar to other benzodiazepines – suggests that remimazolam may have a significant advantage over currently used short-acting sedatives. [3,4] It was recently approved for use as a general anesthetic (January 2020 in Japan and January 2021 in South Korea) and for procedural sedation (July 2020 in the USA and China, March 2021 in Europe, and August 2021 in South Korea) in adult patients. [5]

3. Pharmacokinetics

3.1 Absorption

Remimazolam is intended exclusively for intravenous administration, which – according to the summary of product characteristics – eliminates gastrointestinal absorption and avoids the first-pass effect. Two studies evaluated the off-label intranasal and oral administration of remimazolam. In one study, after intranasal administration of a non-optimized formulation, the bioavailability of remimazolam powder derived from the intravenous preparation was 49%, whereas administration of a solution prepared from the same formulation (23 mg/ml in water for injection) reduced bioavailability to 26%. [6] In another study evaluating oral bioavailability, a dose of 0.14 mg/kg demonstrated low bioavailability ranging from 1.2% to 2.2%. [7]

3.2 Distribution

Based on pharmacokinetic analysis conducted in healthy volunteers, the volume of distribution of remimazolam was found to be 0.8–0.9 L/kg. Both remimazolam and its main metabolite (CNS7054) exhibit a high degree of plasma protein binding, exceeding 91% for remimazolam, with albumin being the primary binding protein. The mean distribution half-life in healthy individuals ranges from 0.5 to 2 minutes, but is prolonged in patients with hepatic impairment, as the drug is primarily metabolized by hepatic carboxylesterase. [8]

3.3 Metabolism

Preliminary studies in animal models (rats, monkeys) demonstrated that remimazolam undergoes hydrolysis to an inactive metabolite under the influence of tissue carboxylesterases. In 2018, using ultra-performance liquid chromatography coupled with mass spectrometry, five metabolites of remimazolam – three phase I and two phase II – were identified in human plasma and urine. [9]

An in vitro study using human cells and tissues confirmed that hepatic metabolism is the main metabolic pathway of remimazolam. Liquid chromatography coupled with proton nuclear magnetic resonance spectroscopy in human liver microsomes identified metabolites formed through hydroxylation, carboxylation, and cleavage of the imidazole ring – both for remimazolam and CNS7054. In pooled urine samples collected over 12 hours following intravenous administration, the peak area of metabolites accounted for approximately 2.3% of the CNS7054 peak area. Further in vitro experiments suggest that remimazolam is primarily a substrate of esterase CES1A1, with minimal metabolism via CES2A1. CNS7054 remains the only clinically relevant metabolite, even after several hours of continuous infusion. In vitro cellular models indicate a dominant role of hepatic metabolism, with minimal contribution of renal clearance to metabolite elimination. [8] These findings are consistent with earlier research showing higher peak concentrations of remimazolam in patients with hepatic impairment (Child-Pugh score ≥10), whereas renal impairment did not affect this parameter. [10]

No significant inhibition of cytochrome P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), induction of isoenzymes 1A2, 2B6, and 3A4, or effects on human drug transporters (OAT3, OCT2, OATP1B1, OATP1B2, OAT1, BCRP) have been observed. [11] After oral administration, remimazolam demonstrates very low bioavailability and undergoes extensive first-pass metabolism. [12]

3.4 Elimination

In healthy volunteers, the mean elimination half-life ranges from 7 to 11 minutes, and the terminal half-life from 37 to 53 minutes. Remimazolam clearance is high at 68 ± 12 L/h. A negligible fraction of the drug (approximately 0.003–0.1%) is excreted unchanged in the urine, whereas 97% of the administered dose is eliminated in the urine as the main metabolite CNS7054. [12]

3.5 Special populations

The pharmacokinetic profile of remimazolam does not differ significantly between young and elderly individuals (mean age 21 vs. 66 years, respectively). Similar pharmacokinetic properties are observed in patients with normal renal function and those with end-stage renal disease (eGFR > 90 vs. < 15 ml/min), as well as in patients with normal hepatic function compared to those with mild or moderate hepatic impairment (Child-Pugh class A and B). [13]

4. Pharmacodynamics

Evaluation of the pharmacodynamic profile of remimazolam using the bispectral index (BIS), electroencephalography (EEG), the Narcotrend index, and the modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale confirmed a rapid onset of short-lasting sedative effects, with intensity dependent on the administered dose. Studies in healthy volunteers demonstrated that a single intravenous dose of 5 mg of remimazolam produces rapid and transient sedation as assessed by the MOAA/S scale. [14]

Intravenous administration of remimazolam at doses of 0.075–0.20 mg/kg was associated with a faster onset of action, a deeper sedative effect (MOAA/S < 2) compared to midazolam 0.075 mg/kg (MOAA/S 3–4), and a shorter mean duration of sedation (5–20 minutes vs. 40 minutes).

In a continuous infusion study, administration of remimazolam at an induction dose of 0.2 mg/kg (1-minute bolus), followed by infusion at 1.0 mg/kg/h for 2 hours, resulted in deeper sedation and faster recovery of consciousness compared with midazolam administered as a 0.15 mg/kg induction bolus (1 minute), followed by continuous infusion at 0.05 mg/kg/h for 2 hours. [15] These findings confirm the rapid onset, potent sedative properties, and short, dose-dependent half-life of remimazolam. [13]

5. Dosing regimen

Remimazolam may be administered as a bolus or continuous infusion, and its dosing varies depending on the indication, country, patient condition, and concomitant medications. [12]

5.1 Dosing in procedural sedation

In procedural sedation, dose adjustment according to patient status and possible opioid co-administration is essential. For example, in the USA, a healthy adult (ASA I) not receiving opioids is initially given 5 mg of remimazolam besylate as a 1-minute bolus. If necessary, 2.5 mg doses may be repeated every 2 minutes. When co-administered with an opioid, reduction of the initial dose is recommended, with at least a one-minute interval between opioid and remimazolam administration.

Regardless of the protocol, the total dose in clinical trials did not exceed 33 mg. Dose reduction is necessary in elderly patients (>65 years), those at higher anesthetic risk (ASA III–IV), or with low body weight (<50 kg), where a 0–50% dose reduction is recommended. [12]

5.2 Dosing in general anesthesia

In general anesthesia, remimazolam is usually administered in combination with an opioid (e.g., remifentanil). For induction, intravenous infusion is initiated at 6 mg/min, with the possibility of increasing up to a maximum of 12 mg/min until loss of consciousness. [16] After induction, the infusion rate is reduced to a maintenance dose of 1 mg/min, which is then adjusted within the range of 0.1–2.5 mg/min depending on clinical assessment (e.g., vital signs) or EEG indices (e.g., BIS, Narcotrend). [16,17] If necessary, up to three additional 6 mg bolus doses may be administered within one hour, maintaining at least 5-minute intervals.

Importantly, studies indicate that remimazolam dosing in general anesthesia may be independent of body weight, simplifying management, particularly in obese patients. [16]

6. Remimazolam vs. Propofol

Compared with propofol, remimazolam does not offer benefits in terms of faster recovery, but demonstrates a more favorable safety and tolerability profile. Meta-analyses and randomized trials have shown no statistically significant differences between the two drugs in key recovery parameters such as time to awakening, eye opening, or readiness for discharge. [19,20,21] An advantage of remimazolam is the availability of a specific antidote – flumazenil – providing an additional safety measure not available with propofol. [18]

The use of remimazolam is associated with a significantly lower risk of cardiovascular complications – it less frequently causes post-induction hypotension [18,19,20] and bradycardia (in surgical procedures) [22] – as well as respiratory depression and postoperative complaints such as pain during intravenous injection and postoperative nausea and vomiting (PONV) in mixed surgical or endoscopic procedures. [18,19,20] However, caution is

warranted in interpreting PONV data. Recent systematic reviews indicate that this risk strongly depends on the comparator drug. While remimazolam reduces the risk of PONV compared with inhalational anesthetics, it may be associated with a higher incidence of vomiting when compared directly with propofol. [23]

Remimazolam may also provide benefits in terms of postoperative patient comfort. Studies indicate reduced physical discomfort and emotional distress on postoperative days 1 and 3 compared with propofol. [22] However, no significant differences have been observed between these agents in the incidence of postoperative delirium in elderly patients. [24]

7. Conclusions

Remimazolam represents a valuable addition to the arsenal of anesthetic agents. Its main advantage over traditional benzodiazepines is rapid, organ-independent metabolism by tissue esterases to an inactive metabolite, resulting in a short and predictable duration of action with rapid onset and offset of sedation. The pharmacokinetic profile remains stable in elderly individuals and in patients with renal impairment or mild to moderate hepatic dysfunction.

Compared with propofol, remimazolam does not accelerate recovery but demonstrates a more favorable safety profile – significantly lower risk of post-induction hypotension, bradycardia, respiratory depression, and injection pain. An additional advantage is the availability of a specific antidote – flumazenil. The dosing regimen depends on the indication, patient condition, and concomitant medications, and in general anesthesia may be independent of body weight.

In summary, remimazolam is a promising agent that may find broad application in anesthesiology, particularly in patients for whom hemodynamic stability and minimization of respiratory complications are crucial. Its unique pharmacokinetic profile and reversibility with flumazenil make it a valuable alternative to propofol in selected patient groups and procedures.

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