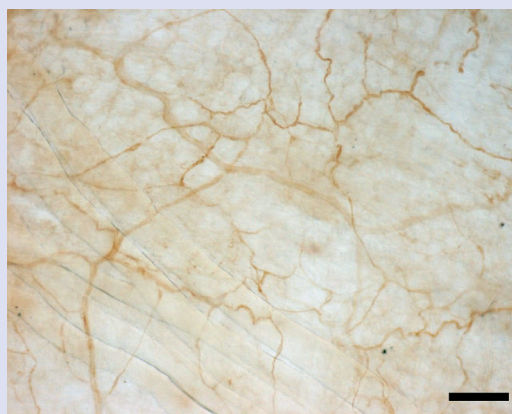


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EDITORIAL

Remimazolam: back to the future

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In an era that seeks to limit the use of benzodiazepines due to potential neurological complications in elderly patients undergoing surgery¹ and in critically ill patients admitted to the intensive care unit,² a new and promising benzodiazepine – remimazolam – appears to spread, with excellent results, high level of satisfaction and a renewed attraction to benzodiazepines, the use of these molecules among clinicians in various clinical settings, including procedural sedation, anesthesia, and intensive care.

It is important to note that, to date, remimazolam, has been licensed for procedural sedation in the USA, China, Europe, South Korea and Taiwan, induction and maintenance of anaesthesia in Japan, South Korea and Europe (in Italy, remimazolam besilate 20 mg is commercialized only for procedural sedation in adults), China, Taiwan and Philippines.^{3, 4}

Clinical research and investigations on remimazolam conducted from 2015 to 2024 have primarily focused on comparing this new benzodiazepine with midazolam and propofol in terms of pharmacokinetics (PK) and pharmacodynamics (PD) (especially onset and offset times), and safety profile (cardiovascular and respiratory effects).^{3, 5-11}

The new meta-analysis of randomized controlled trials published by Xue *et al.*¹² in this issue of *Minerva Anestesiologica* highlights an interesting addition to the comparison between remimazolam and propofol. By analyzing 10 randomized controlled trials (five conducted in

China, four in Korea, and one in Japan) involving 1077 patients, the authors investigated a previously uncovered outcome – the postoperative subjective quality of recovery. As a primary outcome, remimazolam demonstrated comparable quality of recovery scores to propofol (evidence of non-inferiority) on postoperative days one, two, and three. Secondary outcomes showed no significant differences in recovery time for consciousness, extubation duration, incidence of postoperative nausea and vomiting, or length of hospital stay between the remimazolam and propofol groups.

The PD and PK of remimazolam are likely the strengths and baseline characteristics that have generated considerable enthusiasm among clinicians regarding the widespread use of this new benzodiazepine.^{5, 10, 11}

As a soft drug (a medication with a high therapeutic index that is metabolized predictably to inactive metabolites after exerting its therapeutic effect), remimazolam is metabolized by carboxylesterase-1, which is abundant in the liver and also is present in the lungs and brain. Even with multiple administrations and continuous infusion, remimazolam is not associated with accumulation or increased plasma concentration, thus maintaining a consistently low context-sensitive half-time.⁵ Due to these characteristics, remimazolam is an ultra-short-acting benzodiazepine with rapid onset and offset times, organ-independent metabolism, and a high safety profile. Numerous clinical trials have demonstrated its

efficacy in procedural sedation and general anesthesia, demonstrating a favorable safety profile with minimal cardiovascular and respiratory depression.^{3, 5-11}

Over the past 30 years, the pharmacological armamentarium in anesthesiology has been enriched with a few milestone drugs that have dramatically changed clinical practice in operating theaters, intensive care units, and non-operating room anesthesia suites: propofol, midazolam, remifentanyl, and sugammadex have substantially improved patient safety and satisfaction for both patients and healthcare providers. It appears that remimazolam is poised to write new important chapters in anesthesia, intensive care, and sedation practices.

Remimazolam has been shown to cause less hypotension, require less treatment for hypotension, and result in lower rates of respiratory depression during endoscopic procedures compared to propofol, according to a large systematic review and meta-analysis that included 15 trials and 4516 patients.¹⁰ Moreover, the superiority of remimazolam in terms of cardiovascular and respiratory function was associated with non-inferiority in clinical efficacy (defined as the successful completion of the endoscopy procedure without requiring an alternative sedative, rescue sedative, or both) and high satisfaction among both endoscopists and patients.¹⁰

Compared to midazolam, remimazolam exhibits generally superior PK and PD properties, including lower onset time, faster offset time, decreased volume of distribution, and shorter time to alertness.^{3, 11}

Additionally, some authors have hypothesized that remimazolam's pharmacological effects on the central nervous system may lead to a lower incidence of postoperative cognitive disorders compared to propofol in older patients, although this difference requires confirmation through prospective randomized studies.¹³ Furthermore, a pediatric double-blind randomized trial involving 120 children aged one to six years who received remimazolam in conjunction with sevoflurane for laparoscopic surgery under processed electroencephalography-guided anesthesia demonstrated a significant reduction in the occurrence of emergence delirium.¹⁴

Therefore, remimazolam's favorable safety profile stems from its dual characteristics as a benzodiazepine and a soft drug. These properties position this molecule as a first-choice option for various clinical applications: induction and maintenance of anesthesia, sedation in intensive care units, and deep and moderate sedation for procedures. Due to its PK and PD characteristics, remimazolam appears to be the ideal sedative agent, even for non-anesthesia personnel such as gastroenterologists, radiologists, cardiologists, and nurses.^{10, 15, 16}

This aspect is of primary importance, as we are witnessing a dramatic increase in the volume of non-operating room anesthesia cases involving older and medically complex patients with multiple comorbidities, alongside a contemporary shortage of anesthesia personnel.¹⁵⁻¹⁸

For many anesthesia healthcare services, this expanding field of non-operating room anesthesia presents a new dimension of patient care for anesthesiology teams. Safe sedatives managed by supervised non-anesthesia physicians (*e.g.*, certified anesthesia nurses, gastroenterologists, radiologists, cardiologists), adequately trained and supervised by physician anesthesia providers, are essential for prioritizing the safety of both patients and operators.

Based on these observations, remimazolam can be considered a new anesthetic and sedative drug with broad prospects for use in various procedures across multiple clinical settings, including operating theaters, intensive care units, and non-operating room suites. It seems to have an excellent profile in terms of safety and efficacy for use by anesthesiologists, non-anesthesia physicians, and non-physician anesthesia providers.

References

1. Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, *et al.* Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand* 2016;60:289-334.
2. Devlin JW; Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:825-73.
3. Sneyd JR, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and

- the case for remimazolam: a narrative review. *Br J Anaesth* 2021;127:41–55.
4. European Medicine Agency. Byfavo [Internet]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/byfavo> [cited 2024, Nov 7].
 5. Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. *Pharmacotherapy* 2016;36:1021–7.
 6. 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;115:274–83.
 7. Wiltshire HR, 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 II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg* 2012;115:284–96.
 8. Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, *et al.*; PAION Investigators. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest* 2019;155:137–46.
 9. Rex DK, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D. Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. *Dig Liver Dis* 2021;53:94–101.
 10. Barbosa EC, Espírito Santo PA, Baraldo S, Meine GC. Remimazolam versus propofol for sedation in gastrointestinal endoscopic procedures: a systematic review and meta-analysis. *Br J Anaesth* 2024;132:1219–29.
 11. Pantos MM, Kennedy DR, Nemeč EC. Remimazolam: A Novel Option for Procedural Sedation in High Risk Patients. *J Pharm Pract* 2023;36:149–54.
 12. Xue RT, Sun RH, Wang M, Guo H, Chang J. Comparison of remimazolam and propofol on postoperative subjective quality of recovery in patients undergoing general anesthesia: a meta-analysis of randomized controlled trials. *Minerva Anestesiol* 2025;91:191–200.
 13. Yuan Q, Dai M, Han L, Wang X. Effects of remimazolam on cognitive function. *Asian J Surg* 2024;S1015-9584:01045–5.
 14. Cai YH, Zhong JW, Ma HY, Szmuk P, Wang CY, Wang Z, *et al.* Effect of Remimazolam on Emergence Delirium in Children Undergoing Laparoscopic Surgery: A Double-blind Randomized Trial. *Anesthesiology* 2024;141:500–10.
 15. Goudra B, Singh PM, Lichtenstein GR. Medical, Political, and Economic Considerations for the Use of MAC for Endoscopic Sedation: Big Price, Little Justification? *Dig Dis Sci* 2020;65:2466–72.
 16. Nagrebetsky A, Gabriel RA, Dutton RP, Urman RD. Growth of Nonoperating Room Anesthesia Care in the United States: A Contemporary Trends Analysis. *Anesth Analg* 2017;124:1261–7.
 17. Külling D, Rothenbühler R, Inauen W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. *Endoscopy* 2003;35:679–82.
 18. Abouleish AE, Pomerantz P, Peterson MD, Cannesson M, Akeju O, Miller TR, *et al.* Closing the Chasm: Understanding and Addressing the Anesthesia Workforce Supply and Demand Imbalance. *Anesthesiology* 2024;141:238–49.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Both authors read and approved the final version of the manuscript.

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