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EDITORIAL

Remimazolam: an ultrashort-acting intravenous anesthetic suitable for general anesthesia

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Currently, the use of intravenous (i.v.) benzodiazepines is recommended for procedural, perioperative, or intensive care sedation, with diazepam reserved for the treatment of seizures. Midazolam is the principal hypnotic used for procedural sedation;[1] it replaced diazepam because it is water-soluble and does not cause pain on injection. It is usually employed as premedication in patients undergoing surgery, mainly because it has a rapid onset and for inducing amnesia;[2] moreover, it presents synergistic interactions with both propofol and opioids,[3] and its active metabolite, α-hydroxy-midazolam, contributes substantially to enhance its effects.[4]

After the introduction of midazolam, there were further efforts to identify a new short-acting benzodiazepine with rapid onset and offset,[5, 6] albeit neither compound was believed to have sufficient advantages over midazolam to worth additional developments. Remimazolam, a novel ultrashort-acting γ-aminobutyric acid (GABA) A receptor agonist benzodiazepine, was approved for induction and maintenance of general anesthesia in adults, in January 2020, in Japan[7] and in January 2021 in South Korea.[8] It was also approved by the US Food and Drug Administration, in July 2020, for induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less, and, in July 2020 by the Chinese National Medical Products Administration for use in procedural sedation.[9] In Europe, it has been licensed for procedural sedation in March 2021. Remimazolam is designed from soft drug development, a strategy in which active compounds are specifically designed to be vulnerable to rapid biotransformation into inactive metabolites,[10] allowing favorable pharmacokinetic profiles and consequently a broad therapeutic use.[11] Remimazolam binds with high affinity to the GABA A receptor, and the enhancement of GABA effect is similar to that produced by midazolam, with slightly greater potency and maximum effect.[12] In addition, the principal metabolite of remimazolam, CNS-7054, has a lower affinity for benzodiazepine receptors than does the midazolam metabolite α-hydromidazolam (1/400 *vs*. 1/8); furthermore, remimazolam metabolites are considered inactive, explaining the ultrashort action of the drug.[9, 12] Another significant aspect is that the hepatic drug-metabolizing enzyme CYP is not involved in the metabolism of remimazolam.[12, 13] Some characteristics are owned by both remifentanil and remimazolam; as remifentanil, which is rapidly metabolized by nonspecific esterases distributed throughout the body, remimazolam is rapidly metabolized by carboxylesterases in the liver.[14] Another similarity is that elimination is organ-independent. Hence the name remimazolam.[9] A conventional mamillary model superseded the original recirculatory and weight-independent pharmacokinetic model.[15] Simulations of context-sensitive half-time and time to peak effect demonstrates the characteristic of remimazolam. In particular,

onset of remimazolam appears slightly slower than propofol but faster than midazolam. Swift hydrolysis of remimazolam is reflected in its context-sensitive half-time; offset is faster than midazolam but more similar to propofol than remifentanil.[8] The degree and duration of sedation using remimazolam are dose-dependent; consequently, prolonged infusions or higher doses are unlikely to result in accumulation and extended effect.[10]

In this issue of *Minerva Anestesiologica*, Dai *et al.*[16] present a topic of radical innovation in terms of both cultural interest and clinical practice: safety and efficacy of remimazolam compared with propofol in induction of general anesthesia. The study represents a valuable advance in the clinical use of remimazolam; furthermore, the authors conduct a randomized trial to evaluate whether remimazolam is superior to propofol during anesthesia induction in terms of efficacy and safety.

Evidence derived from clinical practice indicates that the ideal sedative is characterized by ease of use, rapid onset of action and recovery, minimal pain on injection, and few side effects, such as respiratory and circulatory depression.[17-20] Unfortunately, no clinical sedative-hypnotic drug owns all these properties. Improvements were achieved by more accurate and sophisticated devices designed to monitor the level of sedation during general anesthesia, for that purpose, in association with the traditional observation of autonomic responses, processed electroencephalogram (EEG) monitors are used to assess the effect of anesthetics, especially intravenous agents.[21] Currently, appropriate ranges of EEG indices for remimazolam anesthesia are unclear; nevertheless it is known that EEG effects of benzodiazepines are predominantly a monotonic beta activation,[22, 23] principally in frontal areas, and these effects map to higher Bispectral Index (BIS) values.[24] However, the correlation of BIS with sedation depth was weaker for benzodiazepines.[9] Remimazolam depresses BIS, although BIS scores during anesthesia could be affected by the synergistic effect of remifentanil.[15] Dai *et al.*[16] showed that BIS values were higher after a single shot of remimazolam compared to propofol during induction. However, the use of BIS for monitoring the depth of remimazolam sedation remains controversial. Improved understanding of the determinants of perioperative morbidity and mortality has spotlighted hypotension as a potent cause of patient harm; therefore, practice must respect this assumption.[8] Hypotension was early identified as an unfavorable condition,[17, 25] even though recent data highlight that hypotension after induction of anesthesia is common[26] and largely associated with adverse outcomes.[27-29] Consequently, hypnotic-induced hypotension should be avoided, especially in those patients in whom perfusion is already compromised.[30] Previous phase I clinical trial for remimazolam, performed in healthy subjects, shown that a 1-minute bolus infusion of remimazolam (0.01-0.30 mg/kg) was scarcely related to hypotensive effects.[31] Moreover, hypotension is frequently observed as a side effect during induction of anesthesia using propofol[32-34] even in healthy subjects.[35] Dai *et al.*[16] demonstrated that the efficacy of a single dose of remimazolam at a concentration of 0.3 mg/kg is appropriate for anesthesia induction, while higher concentrations of remimazolam could induce hypotension. Current perioperative hypnotics agents, without exemption, present a rare propensity to off-target effects.[8] Moreover, idiosyncratic reactions have determined the failure of various hypnotic agents.[36, 37] In the more severe scenarios, anaphylactic shock represents a life-threatening complication of anesthesia. The first case of anaphylaxis during induction of general anesthesia with remimazolam was recently reported in a patient that had received general anesthesia with midazolam four weeks before. Clinical manifestations occurred 2 minutes after starting continuous infusion of remimazolam (6 mg/kg/h) and were recovered by repeated administration of adrenaline. Although no increase of serum tryptase levels was observed, intradermal allergy tests, performed four weeks after surgery, revealed that remimazolam and midazolam were positive, thus suggesting remimazolam as a causative agent for anaphylaxis. The authors hypothesized that midazolam might have caused sensitization.[38] It is known that certain drug-solvent combinations can result in precipitation. As described by a couple of case reports, the combined use of continuous infusion of remimazolam and Ringer's

acetate solution could produce the formation of a precipitate that can clog the i.v. line. In those cases, the examination of the fluid present in the i.v. line, showed white turbidity.[39, 40] Recently, a case of re-sleeping after the reversal of remimazolam occurred in a 62-year-old female patient who became drowsy 45 minutes after antagonizing remimazolam with flumazenil was reported.[41] The authors emphasized that the sedative effect of remimazolam may reappear as the blood concentration of flumazenil decreases.[21] The reversibility by flumazenil is a class characteristic of all benzodiazepines, and the use of the reversal flumazenil would reduce the risk of rebound sedation,[10] even though, human experience of flumazenil reversibility is confined to a few volunteers and some rescues during clinical trials.[8] Moreover, there is no yet recommendation about flumazenil dosage.[41] Currently, there are no detailed pharmacokinetic/pharmacodynamic (PK-PD) data concerning the loss of the effect of flumazenil administered as an antagonist of remimazolam.[42-45] Thus, further PK-PD clinical practice studies are necessary to estimate the ideal dosage of the reversal, especially in patients with organ impairment. Among the most relevant results came from Dai *et al.*[16] study in terms of induction efficacy; higher concentrations of remimazolam demonstrated equivalent effect as same as propofol. Even at a lower concentration, remimazolam proved effective in induction, granting stable BIS and blood pressure values. Injection site pain was not observed with remimazolam, and, most important, no serious adverse events during its use were reported, even at higher doses.

A lot is changed in clinical practice since the early overviews concerning benzodiazepine were published; furthermore, patients are older and frailer, and our surgeons are more ambitious. The most relevant benefits of remimazolam are the short duration of action, the limited accumulation, the minimal risk of respiratory depression, and the availability of a reversal agent; these characteristics should be enough to allow this drug widely appreciated for both sedation and general anesthesia. Although the safety of hypnotic agents, at recommended dosages, is now well established, that experience could not be automatically transferrable to remimazolam, whose safety profile will require demonstration of its values. Albeit remimazolam can provide the hypnotic bases for total intravenous anesthesia, further clinical investigations demonstrating that reliability in clinical practice are needed. In emergency, remimazolam, which has a shorter context-sensitive half time, could represent a preferable option.[46] Future studies aiming to refine the technique for rapid sequence induction, especially in patients with significant comorbidities, are needed; moreover, surveys concerning the safety and efficacy profile of remimazolam in pediatric patients and extreme ages are encouraged. Attention is to be paid to the compatibility of remimazolam with infusion solutions and to clarify the mechanism underlying the presumed incompatibility. Concerning toxicity, future works should investigate the profile of remimazolam regarding the possible cellular determinants of neonatal neurotoxicity, delirium, postoperative nausea and vomiting, postoperative cognitive impairment, and cancer cell behaviors.

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