International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 13, No. 3, 2026

Research Progress on the Application of Remimazolam as a Novel Sedative-Anesthetic Agent

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Abstract: Remimazolam is a novel, ultra-short-acting benzodiazepine characterized by its rapid onset of action. It has been approved for procedural sedation and general anesthesia, exhibiting typical pharmacodynamic profiles akin to other benzodiazepines, such as midazolam. The drug demonstrates high organ-independent clearance and acts primarily on the γ-aminobutyric acid type A (GABA-A) receptors. It is rapidly metabolized by nonspecific esterases, predominantly carboxylesterases, into inactive metabolites with significantly reduced binding affinity—approximately 300 to 400 times lower for GABA-A receptors compared to the parent compound. Following administration, plasma concentrations of remimazolam decline predictably and rapidly; at adequate doses, no prolonged sedative effects are observed. Currently, remimazolam has been successfully employed in endoscopic procedures as well as for the induction and maintenance of general anesthesia, offering rapid and predictable onset and recovery, minimal impact on respiratory and hemodynamic parameters, and an absence of severe drug-related adverse events. Moreover, its effects can be reversed by flumazenil. Although remimazolam holds considerable potential for sedation in patients requiring anesthesia, further research is needed to evaluate its efficacy and safety in broader sedative applications. This review aims to outline the pharmacokinetic profile of remimazolam, its current clinical utility, and future directions in clinical practice.

Keywords: Remimazolam; Novel Sedative-Anesthetic Agent; γ-aminobutyric Acid Type A.

1. Introduction

While the introduction of general anesthesia represents a revolutionary achievement in the history of anesthesiology, the mechanisms of action of anesthetic agents remain incompletely understood [1]. The GABA receptor system serves as the primary inhibitory receptor in the human central nervous system and is a major target for intravenous anesthetics used to induce general anesthesia [2]. Most intravenous anesthetics, such as barbiturates, propofol, and etomidate, bind to GABA receptors. However, all anesthetics carry the potential for undesirable side effects, including hemodynamic instability, respiratory depression, injection pain, hypotension, bradycardia, myoclonus, nausea and vomiting, or delayed recovery due to prolonged postoperative sedation [3]. The ideal intravenous anesthetic has yet to be developed, as most available agents may cause adverse side effects. Consequently, combinations of different anesthetics have been used to achieve adequate anesthesia at the lowest possible doses, aiming to minimize side effects in daily practice [4]. Thus, modern anesthetics must be effective, efficient, and well-tolerated. To improve usability, new intravenous anesthetics should also provide a predictable drug effect with both rapid onset and offset.

Remimazolam, a structural analogue of midazolam developed by adding an ester side chain, represents one of the latest pharmacological advances [5]. It exhibits several characteristics of an ideal intravenous anesthetic: it is water-soluble, has a high organ-independent clearance, acts rapidly, and demonstrates a more favorable hemodynamic and respiratory side-effect profile compared to propofol [6, 7]. Moreover, its effects dissipate rapidly upon discontinuation because the parent compound is quickly metabolized into compounds with very low activity [8-10]. Compared to other sedatives, this drug allows for rapid recovery of protective reflexes and spontaneous respiration, reducing the need for postoperative monitoring. Recent studies indicate that remimazolam, when combined with opioids, is non-inferior to propofol in providing adequate sedation as well as in the induction and maintenance of general anesthesia. Its hemodynamic and respiratory stability compared to propofol is notable [11-13]. Additionally, a significant advantage of remimazolam is that its effects can be specifically reversed with flumazenil. These properties suggest that remimazolam may, in the future, at least partially replace propofol as a standard intravenous anesthetic for general anesthesia. To date, however, evidence regarding its use in different patient populations and under various surgical conditions remains inconclusive.

In summary, remimazolam is a novel, rapidly metabolized benzodiazepine characterized by rapid onset, an ultra-short duration of action, quick recovery, an absence of severe drug-related adverse events, and good tolerability. As a safe and effective sedative agent, further research is still needed to evaluate its efficacy and safety for long-term sedation in clinical practice. This review aims to provide updated information on the pharmacokinetics and current clinical applications of remimazolam as a new sedative-anesthetic, offering a theoretical foundation for its further clinical use.

2. Pharmacokinetics

Remimazolam is the latest benzodiazepine agent,

combining properties of both midazolam and remifentanil. It acts as a high-affinity selective ligand for the benzodiazepine binding site on GABA receptors, with no significant affinity for other receptor sites [14]. Researchers synthesized this novel ultra-short-acting sedative-anesthetic by introducing a carboxylate ester side chain into the chemical structure of midazolam. In vivo, this carboxylate ester is rapidly cleaved by tissue esterases into inactive metabolites.

Studies have found that the systemic clearance of remimazolam is approximately three times that of midazolam. Its pharmacokinetics exhibit linearity over the therapeutic dose range, and clearance appears independent of body weight within the 65–90 kg range [15]. A steady-state concentration is achieved within 7–8 minutes after a 2-hour infusion, and this appears unaffected by the duration of infusion. Furthermore, remimazolam has no significant effect on PR interval or QRS duration. Consequently, no clinically relevant cardiac effects have been observed during anesthesia with remimazolam. The drug shows no clinically meaningful impact on heart rate, electrocardiogram parameters, blood pressure, or respiratory rate.

Additionally, the metabolism of remimazolam is organ-independent. It is rapidly hydrolyzed by tissue esterases—primarily catalyzed by carboxylesterases in the liver—into an inactive carboxylic acid metabolite. Since remimazolam is eliminated renally without accumulation, and its metabolites are pharmacologically inactive and do not affect hepatic or renal function, it can be safely used in patients with impaired liver or kidney function.

3. Clinical Application

3.1. Efficacy of Remimazolam in Patients Undergoing Total Hip Arthroplasty

Total hip arthroplasty is primarily performed under general anesthesia. However, as the patients undergoing this procedure are mostly elderly individuals with multiple underlying comorbidities, the anesthesia carries a high risk of circulatory depression, which affects hemodynamics and compromises surgical safety. Furthermore, the operative process induces a stress response, leading to the aggregation and activation of a large number of inflammatory cells in myocardial tissue, consequently elevating serum levels of interleukin-6 and tumor necrosis factor-α. Additionally, intraoperative anesthesia affects the patient's central nervous system, causing astrocyte damage and increasing serum levels of central nervous system-specific proteins, thereby impairing cognitive function.

Propofol offers advantages such as rapid induction and significant anesthetic effect, but it also has limitations, including injection pain and a propensity to cause respiratory depression and arrhythmias. Particularly at higher doses, it influences hemodynamic fluctuations, thereby increasing surgical risk for elderly patients. Both anesthesia and various intraoperative manipulations can induce abnormal hemodynamic fluctuations in elderly patients, potentially triggering cardio-cerebrovascular accidents. Propofol anesthesia induces peripheral vasodilation and reduces myocardial contractility, leading to a decrease in cardiac output. While it has a relatively minor impact on blood pressure and heart rate, this is not conducive to the stability of hemodynamic parameters. Moreover, propofol anesthesia can cause nausea, vomiting, metabolic acidosis, and other side effects, compromising anesthetic safety.

Remimazolam possesses favorable water solubility, causes no injection pain, and helps alleviate patient discomfort. Furthermore, this drug offers advantages such as non-reliance on hepatic and renal metabolism, rapid metabolic excretion, and no accumulation, resulting in fewer adverse reactions. Additionally, remimazolam can inhibit sympathetic nerve excitation and promote acetylcholine secretion. Acetylcholine, in turn, can suppress the expression of peripheral inflammatory factors, mitigate their cytotoxic responses, thereby reducing the release of inflammatory factors and lessening the associated damage to cognitive function. This creates favorable conditions for postoperative recovery.

Li et al. [16] investigated the effects of remimazolam anesthesia on hemodynamics, recovery quality, and postoperative cognitive function in elderly patients undergoing total hip arthroplasty under general anesthesia. The study enrolled 82 elderly patients, all of whom underwent total hip arthroplasty under general anesthesia. The results indicated that in elderly patients receiving remimazolam general anesthesia for total hip arthroplasty, it was conducive to stabilizing hemodynamics, restoring postoperative cognitive function, improving recovery quality, reducing inflammatory responses, and enhancing anesthetic safety.

Cheng et al. [17] analyzed the effects of remimazolam on recovery outcomes and cognitive function in elderly patients undergoing total hip arthroplasty under general anesthesia. The study involved 118 elderly patients scheduled for total hip arthroplasty. They were divided into a control group and an observation group based on the anesthesia method, with 59 patients in each group. The control group received induction anesthesia with intravenous propofol, sufentanil, and vecuronium, while the observation group received induction with intravenous remimazolam, sufentanil, and vecuronium. The study found that the combination of remimazolam for induction in elderly patients undergoing total hip arthroplasty under general anesthesia offered greater advantages, causing less impact on cognitive function and resulting in a more stable recovery period.

In summary, the use of remimazolam in elderly patients undergoing total hip arthroplasty under general anesthesia is beneficial for stabilizing hemodynamics, improving recovery quality and anesthetic safety. It also promotes the restoration of postoperative cognitive function and reduces inflammatory responses, making it worthy of clinical promotion.

3.2. The Application Effects of Remimazolam in Patients Undergoing Hepatectomy

Hepatectomy is a primary treatment modality for hepatocellular carcinoma and intrahepatic bile duct stones. This surgical procedure is characterized by significant trauma, pronounced stress response, and prolonged operative duration. Similarly, patients undergoing this procedure are predominantly elderly and often present with varying degrees of underlying comorbidities, which to some extent affect the metabolism of anesthetic agents. Consequently, the incidence of perioperative complications is high, including postoperative agitation, delayed emergence, and postoperative cognitive dysfunction. There is a pressing clinical need to stabilize intraoperative hemodynamics, improve the quality of the emergence period, and reduce the occurrence of postoperative complications.

Remimazolam is a short-acting, novel benzodiazepine drug that provides sedative, hypnotic, and anxiolytic effects similar to propofol. It offers advantages such as rapid onset, short

duration of action, and the specific reversibility by flumazenil. Studies have confirmed that remimazolam primarily acts by enhancing inhibitory transmission at the gamma-aminobutyric acid (GABA) receptor gene cluster receptors. This mechanism can inhibit neuronal excitation, improve interneuronal transmission, and alleviate postoperative neurological dysfunction. Furthermore, remimazolam has weaker inhibitory effects on the circulatory and respiratory systems, facilitating an easier return to normal physiological function. Additional research results indicate that the application of remimazolam in hepatectomy leads to rapid onset without drug accumulation, and its metabolites are inactive substances, which is beneficial for reducing patient postoperative awakening time [18].

3.3. Clinical Application of Non-Operating Room Anesthesia

Gastrointestinal endoscopy serves as the gold standard for the early screening and diagnosis of many digestive tract diseases. Intravenous anesthesia technology can alleviate or eliminate discomfort such as pain, nausea, and vomiting during the procedure. It creates better diagnostic and therapeutic conditions for endoscopists, improves the detection rate of early lesions and the complete resection rate of foci. This is of significant importance for alleviating patients' fear of examination and enhancing the success rate of examination and treatment. Therefore, effective anesthetic methods hold positive implications for patients' clinical treatment.

In clinical practice, propofol is used for the induction and maintenance of sedation. When used at induction doses, propofol causes injection pain and can significantly suppress respiratory function. Respiration may show slowed rhythm, reduced depth, or even apnea, compromising anesthetic safety. Furthermore, propofol has a pronounced inhibitory effect on the cardiovascular system. During anesthesia induction, it reduces cardiac output, stroke index, etc., leading to a significant drop in arterial pressure. In contrast, remimazolam is metabolized in the body by plasma esterases, independent of hepatic and renal function. Its metabolites are pharmacologically inactive. It offers advantages such as smooth induction, rapid onset, quick recovery, and minimal impact on the cardiovascular and respiratory systems. In summary, the application of tosilate remimazolam for sedation in gastrointestinal endoscopy has a lesser impact on hemodynamics, reduces procedural time and recovery time, and is associated with a lower incidence of adverse reactions.

Ye et al. [19] investigated the efficacy of different doses of remimazolam combined with propofol in elderly patients undergoing painless gastrointestinal endoscopy and its impact on delirium. The study enrolled 120 elderly patients scheduled for painless gastrointestinal endoscopy, who were randomly assigned using a random number table method. Comparisons were made regarding changes in heart rate, blood oxygen saturation, and mean arterial pressure at different time points, as well as anesthesia onset time, supplemental propofol dosage, recovery time, and the incidence and severity of delirium. The results showed that the use of 0.3 mg/kg remimazolam combined with propofol produced significant application effects in elderly patients undergoing painless gastrointestinal endoscopy and also exerted a preventive effect against delirium.

Xu et al. [20] compared the hemodynamic stability of remimazolam versus propofol when used for anesthetic sedation during endoscopic submucosal dissection of the esophagus. The study selected 60 patients undergoing endoscopic esophageal mucosal dissection, who were divided into groups according to a random number table method. The results found that the application of remimazolam in endoscopic submucosal dissection of the esophagus had a lesser impact on hemodynamics. The procedure time, recovery time, and hospital stay were shorter, and the incidence of adverse reactions was lower.

In summary, remimazolam holds advantages over propofol in terms of effects on circulation, respiratory depression, and injection pain. Patients experience no serious adverse consequences, making it worthy of clinical promotion.

4. Discussion

This review summarizes and analyzes the pharmacokinetics of remimazolam and its performance in clinical applications. As a novel, ultra-short-acting benzodiazepine, remimazolam is rapidly hydrolyzed by non-specific esterases into inactive metabolites, demonstrating linear pharmacokinetics independent of hepatic and renal function. This provides a significant pharmacological basis for its use in elderly patients with concomitant organ dysfunction. Clinical evidence consistently indicates that, compared to commonly used anesthetic agents like propofol, remimazolam shows distinct advantages in maintaining hemodynamic stability, reducing respiratory depression, and avoiding injection pain. Particularly in surgeries common among elderly patients, such as total hip arthroplasty and hepatectomy, remimazolam anesthesia not only helps stabilize perioperative circulation but may also positively impact the reduction of surgery-related neuroinflammation and promote early recovery of postoperative cognitive function through its potential anti-inflammatory mechanisms (e.g., promoting acetylcholine release and inhibiting inflammatory factor expression). In non-operating room anesthesia settings like painless gastrointestinal endoscopy, remimazolam similarly exhibits rapid onset and recovery, minimal impact on circulation and respiration, and a possibly reduced incidence of delirium, broadening its clinical application prospects.

However, existing research still possesses certain limitations that warrant further investigation. Although the overall safety profile of remimazolam is favorable, a consensus on its optimal dosing regimen (e.g., loading dose, maintenance infusion rate, combination with different opioids) for various surgery types and patient populations (e.g., those with extreme body weight or severe hepatic/renal impairment) has not been established. The dose-response relationship requires more detailed study. Furthermore, most current clinical studies have limited sample sizes and short follow-up durations. There is a lack of large-scale, multicenter, long-term follow-up randomized controlled trials to comprehensively evaluate its long-term safety, cost-effectiveness, and performance in complex and critical surgeries. Future research should focus on conducting large-sample clinical studies to explore and optimize its individualized dosing strategies for various surgeries and special populations, and to assess the safety of its long-term use and its impact on patients' long-term outcomes. With the continuous accumulation of research evidence, remimazolam is expected to play a more significant role in the field of clinical anesthesia and sedation, leveraging its unique pharmacological advantages.

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