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Review article

Benefits of remimazolam as an anesthetic sedative for older patients: A review

Ning Jin, Zhiqiang Xue *

Department of Anesthesiology, Benxi Central Hospital, Benxi, 117000, Liaoning Province, China

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ABSTRACT

Owing to the decreased levels of receptors in the peripheral and central nervous systems, the functions of various organ systems decline in older patients. When administering anesthesia to older patients, it is necessary to consider the effects of medication on the homeostatic balance. Remimazolam, a new benzodiazepine, was recently developed as an anesthetic drug that has shown promise in clinical anesthesia application owing to its molecular structure, targets, pharmacodynamics, and pharmacokinetic characteristics. Remimazolam exhibits a rapid onset and metabolism, with minor effects on liver and kidney functions. Moreover, the drug has a specific antagonist, flumazenil. It is safer to use in older patients than other anesthetic sedatives and has been widely used since its introduction. Comparisons of the pharmacokinetics, metabolic pathways, effects on target organs, and hemodynamics of different drugs with those of commonly used anesthetic sedative drugs are useful to inform clinical practice. This article elaborates on the benefits of remimazolam compared with those of other anesthetic sedatives for sedation in older patients to demonstrate how it offers a new option for anesthetics in older patients. In cases involving older patients with increased clinical complexities or very old patients requiring anesthesia, remimazolam can be selected as the preferred anesthetic sedative, as outlined in this review.

1. Introduction

Traditionally, the term "older" refers to individuals who are aged ≥65 years. The aging population is likely to encompass 22% of the total population by 2050 [1]. Choosing suitable anesthetics has become an important issue as many older people undergo surgical treatment. The incidence of postoperative complications and mortality is high in older patients owing to age-related physical changes and various accompanying chronic diseases. Older individuals are often prescribed multiple medications that affect the bioavailability of anesthetic medications [2,3]; moreover, they are more prone to blood–brain barrier damage than younger individuals [4]. This is more pronounced in patients with mild cognitive impairment, particularly in the hippocampus [4].

Most anesthetic sedative medications enter the brain through the blood–brain barrier to elicit pharmacological effects; these medications include benzodiazepines, propofol, and dexmedetomidine. Studies on rodents have shown that several anesthetics have harmful effects on the blood–brain barrier [5,6]. The central nervous system and peripheral receptors exhibit reduced function in older patients, and regular doses of anesthetics cause more potent respiratory and circulatory inhibition in older than younger patients due to the reduced number of receptor sites in the target organs [7]. As age increases, so does the use of polypharmacy, which may lead to

* Corresponding author.
E-mail address: zxyyxzq@126.com (Z. Xue).

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drug interactions in older patients. Changes in drug distribution caused by alterations in body composition can lead to prolonged half-lives or higher plasma concentrations of many medications [8]. Therefore, when administering medications, the decline in drug metabolism in older patients, intake of multiple medications, and organ dysfunction should be considered [9]. Furthermore, comorbidities and multidrug use are common in the older population. On average, older individuals take 2–5 prescription medications regularly, and 20–50% of patients receive multidrug treatment [2]. Therefore, it is necessary to consider the interactions between medications and bioavailability of drugs and carefully select sedative medications for older patients [10].

Remimazolam, a newly developed benzodiazepine, has many pharmacological characteristics suitable for anesthesia in older patients. It has a rapid onset and independent esterase metabolism and only slightly affects hemodynamics; thus, it is safe for older patients who require sedation and maintenance under general anesthesia [11]. Remimazolam has obvious advantages over the widely used medications midazolam and propofol. There are several reports on the application of remimazolam in older patients; however, its application has not been systematically compared with that of propofol and midazolam in older patients. This article reviews the benefits of the newly developed benzodiazepine drug, remimazolam, compared with those of midazolam and propofol for anesthesia and sedation in older patients.

2. Remimazolam and remimazolam tosylate (RT)

2.1. Mechanism of action

Remimazolam and RT are recently developed ultra-short-acting benzodiazepines. In July 2020, the Food and Drug Administration approved the intravenous (IV) administration of remimazolam (Byfavo; Acacia Pharma, Indianapolis, IN, USA) for procedural sedation during short diagnostic and surgical procedures lasting $\leq$30 min [11]. Owing to the instability of the free molecule of remimazolam (which can only be stored at the low temperature of 5 °C), it must be salted to improve its physical and chemical properties. In 2013, Jiangsu Hengrui Medical Co., Ltd. (Jiangsu, China) developed a more stable benzodiazepine drug, RT, based on its chemical composition [12]. After the completion of clinical trials on its use, the Chinese National Drug Administration approved RT in December 2019 as a new drug for anesthesia and sedation, with no restriction on the duration of RT administration (unlike remimazolam) [13,14]; Jiangsu Hengrui Medical Co., Ltd. holds the intellectual property rights to the RT formulation.

Over the last two decades, there have been no changes in anesthesia induction and maintenance medications; the development of remimazolam and RT has thus brought new changes to the academic field of anesthesia. Benzodiazepines are characterized by sedation, hypnosis, and anterograde amnesia. The sedative effect is mild, and the time to induce sleep is shortened. Commonly used medications include diazepam, lorazepam, and midazolam. Midazolam was the first benzodiazepine drug approved for clinical use in 1985 and has been widely used since [15]. The mechanism of action of benzodiazepines is to stimulate the γ-aminobutyric acid A-type (GABAA) receptor, an inhibitory transmitter of the ascending reticular activation system in the brain (Table 1). This enhances the inhibition and blocking of cortical and limbic arousal, thus exerting sedative and hypnotic effects [16]. The ionic GABA receptor comprises five subunits that form complete chloride channels. The GABA receptor/ion channel is a compound of many anesthetic and relaxant molecules [17]. Anesthetics exert sedative effects by binding to GABAA and glycine-gated ion channels and enhancing their inhibitory activity [18].

Benzodiazepines act on GABAA receptors and are mainly responsible for inhibitory neurotransmission in the central nervous system. Their signal transduction mechanism involves coupling with the G protein; the α1 receptor mediates sedation, anterograde amnesia, and anticonvulsion, while anxiety resolution and muscle relaxation seem to be mediated by the α2 GABAA receptor [19]. Two main disadvantages of the benzodiazepines currently used for sedation are that they lack analgesic effects and remain effective for a considerable period after surgery. Additionally, midazolam has an active metabolite with pharmacological activity that generally prolongs patients' recovery time [11,20]. Studies have shown that remimazolam has a high specific affinity for all benzodiazepine GABAA receptor subtypes and does not show selectivity [21]; additionally, the metabolites show no measurable affinity for any of the detected off-target sites. Remimazolam is a high-affinity and selective ligand for benzodiazepine sites on GABAA receptors and can effectively inhibit the discharge of neurons. The maximum discharge inhibition of old benzodiazepine drug pairs in the substantia nigra pars reticularis was reported to be only 40–50% of the baseline discharge rate, compared with 80% for remimazolam [22]. This indicates that the sedative effect of remimazolam was stronger than that of older benzodiazepines.

Table 1
Pharmacokinetic comparison of three medications.

Items	Drug		
	Remimazolam	Propofol	Midazolam
Receptors in the brain	All subtypes of GABAA receptors inhibit central nervous system neurotransmission	GABAA receptor inhibits neurotransmission in the central nervous system NMDA receptor	GABAA receptor inhibits neurotransmission in the central nervous system
Effect on blood–brain barrier	Unknown	Injured	Injured
Antagonist	Flumazenil	None	Flumazenil

GABAA, γ-aminobutyric acid A-type; NMDA, N-methyl-D-aspartate.

By acting on the GABAA receptor, remimazolam and RT increase the permeability of the chloride channel on the nerve cell membrane. Chloride ions enter the cell along the concentration gradient, and the intracellular membrane potential increases to produce hyperpolarization, inhibiting neuronal electrical activity and producing a sedative effect [23]. Remimazolam and RT have the characteristics of rapid induction and recovery, and have a minimal effect on patients' respiration and hemodynamics during anesthesia (Table 1) [24].

2.2. Pharmacokinetics

Remimazolam is an inactive metabolite that is independently metabolized by tissue esterases and eliminated through first-order pharmacokinetics. There is no clear relationship between body weight and elimination clearance [25]. A two-stage randomized double-blind study found that body weight and cardiac output had no significant effects on the pharmacokinetic parameters of remimazolam (CNS7056) and midazolam during upper gastrointestinal endoscopy [26]. Therefore, there are no guidelines regarding drug accumulation during the long-term infusion of remimazolam and RT [27]. These two medications play an essential role in the induction and maintenance of general anesthesia [24]. Remimazolam has the advantages of a rapid onset, complete metabolism, and no drug accumulation; therefore, it is advantageous for the induction and maintenance of general anesthesia and assisted sedation [11]. Unlike other benzodiazepines, remimazolam has a carboxyl ester bond that rapidly decomposes into inactive metabolites [28]. Injection of a lower dose (3 mg over 15 or 60 s), with an interval of at least 2s for a few minutes, is sufficient to maintain the sedative effect in most patients. This indicates that remimazolam has a more accurate maintenance dose than slower-acting medications [26]. Remimazolam is an inactive metabolite; after injection, it is converted into the inactive metabolite CNS7054 under the action of tissue carboxylesterase. CNS7054 is an inactive metabolite excreted through the kidneys after hydroxylation and glucuronidation. The average onset time is 1–3 min after a 2 h stimulated infusion [29]. More than 91% of remimazolam is bound to plasma proteins after IV injection, and the peak plasma concentration is reached in 1 min. The elimination half-life after administration is 37–53 min, and the average half-life of the drug is 0.5–2 min. The clearance rate is 54–75 L/h, and the distribution volume is 0.76–0.98 L/kg (Table 2) [30]. Remimazolam has no advantage over propofol regarding onset speed; however, the drug can be eliminated faster than propofol in vitro owing to its unique metabolic pathway [31].

The kidneys are the main routes for IV drug excretion. Between 30 and 90 years of age, the weight of normal kidneys decreases by 30%-60%, or more with glomerular reduction, accompanied by patchy renal tubular atrophy, interstitial fibrosis, and arteriosclerosis. Therefore, even without kidney disease, the glomerular filtration rate and renal blood flow are reduced [32]. If a drug is cleared by renal elimination, its effects may be prolonged [33]. Studies have shown no difference in remimazolam metabolism between older and younger patients, or between patients with normal renal function and end-stage renal failure [23]. The safety of remimazolam has also been confirmed in patients with renal dysfunction. Its metabolism does not change with kidney damage, and it is safer than midazolam as its active metabolite — α-hydroxy midazolam glucuronide — can damage liver and kidney functions [34]. Another IV anesthetic, propofol, can also damage liver and kidney functions [34]. Some clinical trials have concluded that remimazolam is safe and effective for procedural sedation [35–37]; even in high-risk patients with American Society of Anesthesiologists (ASA) scores of III and IV, remimazolam can be safely used as an anesthetic sedative [38].

3. Comparison of the applications of remimazolam and other sedative medications in older patients

3.1. Propofol

Propofol is an anesthetic drug commonly used in clinical practice; like most anesthetics, it is a GABA receptor agonist that exerts its hypnotic effect by enhancing the activity of the inhibitory neurotransmitter GABA. Propofol enhances the GABA-activated inward chloride current at low concentrations, and directly activates channel opening at higher concentrations [39]. Simultaneously, it enhances the GABAA receptor and blocks the N-methyl-D-aspartate receptor to produce an antianxiety effect [40]. Owing to its high lipophilicity, it quickly passes through the blood–brain barrier to exert its efficacy within a short period after injection. The time of

Table 2
Pharmacodynamic comparison of three medications.

Items	Drug		
	Remimazolam	Propofol	Midazolam
Onset time	1–3 min	30 s	3–5 min
Half-life of distribution	0.5–2 min	2–4 min	6–15 min
Elimination half-life	0.75 h	6.75 h	1.7–3.5 h
CL	0.9–1.25 L/min	2.2 L/min	0.34–0.64 L/min
Main metabolic pathways	Independent metabolism of tissue esterase	Liver uridine 50-diphosphate glucuronosyltransferase CYP450 enzymes	Intrahepatic CYP3A enzyme
Metabolites (presence of pharmacological activity)	CNS7054 (+)	Propofol glucuronide (+) 4-hydroxypropofol (+)	Glucuronidated α-hydroxymidazolam (+)
Discharge pathway	Kidneys	Kidneys	Kidneys

CL, clearance rate.

drug redistribution to the surrounding tissues is 30 s, the distribution time is 2–4 min [41], the time to awakening is 10–20 min, and the drug can be rapidly metabolized after withdrawal [42]. It is therefore widely used in clinical practice owing to its drug effect [43,44].

Propofol results in the rapid loss of consciousness, sometimes within the time required for the drug to pass through the blood circulation [45]. However, propofol can induce blood–brain barrier defects in human stem cell-derived blood–brain barrier models, resulting in damage to the barrier integrity [46]. Thirty minutes after injection, blood and brain concentrations reach equilibrium, with a ratio of total blood to cerebrospinal fluid propofol of 0.01–0.02 [47]. The average clearance rate of propofol is approximately 2.2 L/min [48]; for short-term infusion (3 h), the 80% reduction time is 50 min, whereas for long-term infusion (12 h), the reduction time increases to 3.5 h [49]. Subsequent elimination is biphasic; the first stage has a half-life of 45 min, and terminal elimination occurs with a half-life of approximately 405 min [50]. The initial distribution volume of propofol in older patients is lower than in younger patients; therefore, the propofol concentration immediately after injection is higher in the older group. Additionally, the total clearance rate of propofol is lower in older than younger patients [51].

The liver is the main site of propofol metabolism. Most (70%) propofol binds to propofol glucuronide through uridine 50-diphosphate glucuronosyltransferase. Approximately 29% of propofol is hydroxylated to 2,6-diisopropyl-1,4-quinol (4-hydroxypropofol) [52]. After metabolism, 88% of propofol is excreted in urine within 5 days [53], and only 0.3% of the substances recovered from the urine are present as unchanged medications [54]. Approximately 60–70% of propofol metabolism after injection occurs through the renal pathway, accounting for one-third of the total propofol metabolism [55].

Propofol inhibits apoptosis and inflammatory responses and regulates neuroprotection-related protein and ion homeostasis [56]. It reportedly inhibits astrocyte activation and the release of interleukin (IL)-6 and tumor necrosis factor-α in the central nervous system [57]. It downregulates the expression of proinflammatory cytokines involved in the nuclear factor-κB (NF-κB) pathway, as well as the *TICAM1*, *IRF3*, and *NFKB1* genes involved in the NF-κB pathway [58]. An animal experiment showed that 4 h of light propofol anesthesia could be used to treat stroke in rats, leading to improved functionality [59].

Although propofol has rapid induction and metabolism, it cannot inhibit the cough response, and affects the circulatory and respiratory systems during use. A meta-analysis [60] reported that the degree of bradycardia during induction was highly correlated with propofol injection. It is noteworthy that 42.4% of patients in the propofol group experienced induced hypotension after anesthesia induction, while such patients in the remimazolam group comprised only 27.2%. Moreover, remimazolam causes less pain during injection [60]. With an increase in dosage, propofol has the side effect of inhibiting the respiratory and cardiovascular systems. In a randomized controlled trial of painless bronchoscopy in older patients, it was found that the incidence of hypoxemia and hypotension in patients in the remimazolam group was lower than that in the propofol group, regardless of whether it was combined with dexmedetomidine [61]. Perioperative hypotension can lead to insufficient perfusion of essential organs, thus leading to acute and chronic irreversible organ damage. Perioperative hypotension is associated with an increased incidence of postoperative myocardial injury, ischemic stroke, postoperative mental disorders, acute kidney injury, and postoperative mortality [62–64].

Although propofol is widely used in clinical applications, some limitations should be addressed with caution in older patients [65]. Propofol lacks analgesic effects and specific antagonists, which increases the risk of propofol infusion syndrome and bacterial contamination. When combined with opioids, it can easily cause metabolic acidosis and increase the risk of hypoxia and cardiovascular and respiratory depression [66]. Remimazolam reduces the stress response in patients by decreasing hemodynamic fluctuations. In a study of hip replacement in older patients, remimazolam maintained a more stable heart rate and mean arterial pressure (MAP) after induction, which was beneficial for relieving the stress response in older patients during anesthesia. At the same time, it can avoid the excessive and long-term sedation associated with propofol anesthesia and has a mild inhibitory effect on the central nervous system of patients [67]. A study found that compared with the lactic acid and glucose levels of patients who received propofol, there were no significant changes in patients who received remimazolam before and after tracheal intubation; additionally, there was no hypoxia or excessive stress leading to tissue perfusion dysfunction during the induction process [68]. Some researchers report that the increase in epinephrine and cortisol levels was significantly lower in the remimazolam than propofol group 2 h after cardiac surgery [69]. There were no significant differences in serum inflammatory factor levels between the two groups, and it was concluded that remimazolam was safer than propofol in patients who underwent cardiac surgery. During drug research, it was found that although remimazolam can cause respiratory depression and hypotension, the degree of these respiratory and cardiovascular effects is mild to moderate. Based on reasonable clinical management standards, clinical intervention was not required. Moreover, remimazolam did not affect each organ's average perfusion or cardiac output. The effects of remimazolam on cerebral blood flow and sympathetic tone were insignificant [70], which may also explain the slight effect of remimazolam on circulation and respiration.

Remimazolam is considered an alternative to propofol owing to its lack of CYP3A4 drug interactions, short elimination half-life, small distribution volume, rapid onset, and fast recovery [71]. Additionally, remimazolam-induced postoperative nausea and vomiting is considerably less severe than when induced by inhaled anesthetics [72]. In patients undergoing laparoscopic surgery, remimazolam maintains total IV anesthesia to provide a better quality of recovery than conventional balanced anesthesia. It can also be used for the induction and maintenance of anesthesia, and its efficacy is not inferior to that of propofol [73].

In a phase III clinical trial, it was found that remimazolam had more stable hemodynamics and a lower incidence of hypotension (46 [23.71%] vs. 97 [51.05%]) and respiratory depression (6 [3.09%] vs. 32 [16.84%]) than propofol during painless gastrointestinal endoscopy. A study on valve replacement surgery found that the incidence of hypotension caused by remimazolam during anesthesia induction was lower than that due to propofol [72]. Unlike propofol, specific drug antagonists are available for remimazolam, and the metabolism of remimazolam does not affect liver and kidney functions. Although there was no significant difference in the incidence of postoperative nausea and vomiting between propofol and remimazolam, remimazolam was more suitable for anesthesia in patients with complex or high-risk conditions from the perspective of hemodynamics and drug metabolism [74].

3.2. Midazolam

Midazolam is a traditional benzodiazepine with rapid onset, sedation, and hypnosis effects that acts as a positive allosteric modulator of GABAA [75]. After injection, it rapidly passes through the blood–brain barrier, resulting in a short period of anterograde memory loss [76]. Benzodiazepines bind to specific sites of the GABAA receptor, increasing the chloride ion current generated by GABAA at the benzodiazepine-binding site and exerting a sedative effect [16]. Although both midazolam and propofol act on GABAA receptors, they occupy different receptor-binding sites and have synergistic effects when combined [77]. After injecting a large dose of benzodiazepines, the drug is redistributed from the receptor to a nonspecific site of action in the body, thereby enhancing recovery after anesthesia [78]. The onset time of midazolam is 3–5 min, and the plasma disappearance curve was fitted to a two- or three-compartment model; the elimination half-life is 1.7–3.5 h [78,79]. After IV administration, midazolam is rapidly distributed, with a distribution half-life of 6–15 min [80]. The plasma clearance rate of midazolam is 5.8–9 mL/min/kg in healthy individuals and decreases in older individuals [81]. Its active metabolite, glucuronidated α-hydroxy midazolam, has significant pharmacological effects and can penetrate the blood–brain barrier. Its affinity for brain benzodiazepine receptors is approximately 10 times weaker than that of midazolam or uncoupled α-hydroxy midazolam [82]; this can lead to prolonged postoperative sedation, especially in patients with renal or liver dysfunction [83]. After injection, midazolam is metabolized by the CYP3A enzyme [84], which can lead to variability in metabolic activity (approximately five times) and many drug–drug interactions [7]. This drug interacts significantly with CYP3A4 inhibitors, possibly leading to prolonged sedation due to reduced midazolam clearance [85]. During continuous infusion, the concentration of midazolam increases 2–3 times due to the potent inhibition of CYP3A4 [86]. Owing to changes at the pharmacodynamic level, older patients exhibit higher sensitivity to this drug (indicated by a decrease in the EC50 value for the sedative and hypnotic effects of midazolam) [87]. Administering midazolam for the premedication and induction of anesthesia in older patients should therefore be performed with caution [88].

Midazolam also inhibits immune responses. It inhibits the secretion of IL-10, thereby downregulating the inflammatory immune response [89] and human macrophage activation. Midazolam can simultaneously inhibit the activation of NF-κB/AP-1 and MAPK pathways, as well as exert anti-inflammatory effects on lipopolysaccharide-stimulated macrophages, thereby reducing the activation of proinflammatory genes [90].

Remimazolam differs from other benzodiazepines in its carboxyl ester bonds. Plasma esterases rapidly metabolize remimazolam after injection, decomposing it into inactive metabolites [86]. The average terminal elimination half-life of remimazolam is 0.75 h, and the average terminal elimination half-life of midazolam is 4.3 h [26]. A pharmacokinetic model showed that remimazolam had a higher clearance rate and smaller distribution volume than midazolam [26]; additionally, previous studies have shown that the half-life of remimazolam is approximately 1/5 of that of midazolam after 3 h of continuous infusion [74]. In a study using midazolam as a control, the researchers found that the average time until the Modified Observer's Assessment of Alertness and Sedation scale reached 3 points was 6 min in patients in the remimazolam group and 12 min in the midazolam group; the time to wake up was only half that of midazolam [74]. Moreover, a trial of remimazolam in patients with impaired liver and kidney functions showed that there was no need to adjust the drug dose when infusing remimazolam in these patients [63]. The respiratory depression produced by CNS7056 was consistent with the level of sedation achieved. The greater inhibition produced by CNS7056, rather than midazolam and lower doses of propofol, was mainly because it is a more powerful sedative at the dose used [28]. Some studies have pointed out that remimazolam has outstanding advantages regarding the recovery of neuropsychiatric function and the average length of hospitalization [70]. Compared with midazolam, remimazolam has prominent advantages regarding onset time, drug metabolism, dosage, and liver and kidney injury [36,91]. Remimazolam thus seems more suitable for high-risk patients (Table 3) [92].

Table 3
Inflammatory reactions and clinical applications of three medications.

Items	Drug		
	Remimazolam	Propofol	Midazolam
Inflammatory reaction	Unknown	Inhibits the activation and release of IL-6 and TNF-a by astrocytes in the central nervous system.	Inhibits the secretion of IL-10 that downregulates inflammatory immune responses.
		Downregulation of expression of proinflammatory cytokines involved in the NF-κB pathway and of *TICAM1*, *IRF3*, and *NFKB1* genes involved in the NF-κB pathway.	Inhibition of NF-κB/AP-1 and MAPK pathway activation.
Respiratory and circulatory system effects	Slightly affected	Inhibits respiratory and circulatory systems after injection	Slightly affected
Application in anesthesia	Induction and maintenance of general anesthesia	Induction and maintenance of general anesthesia	Induction and maintenance of general anesthesia
Application in older patients	Distribution rate and clearance rate remain unchanged.	Reduced distribution and clearance rates	Reduced distribution and clearance rates

IL, interleukin; TNF, tumor necrosis factor; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase.

4. Administering remimazolam and its applications in older patients

Owing to the age-related changes in essential organs, the pharmacodynamics and pharmacokinetics of medications in older population are altered [93]. The sensitivity of the central nervous system to the effects of benzodiazepines and midazolam is increased in older patients [94,95]; thus, the clinical effects of benzodiazepines — such as sedation, memory loss, and psychomotor disorders — are not due to their plasma concentrations [96]. The age-related reasons for this discrepancy may include reduced tolerance, increased brain concentration due to changes in blood–brain barrier permeability, enhanced benzodiazepine receptor binding, improved receptor function, and decreased steady-state reserves, which may develop with increased age [97].

Studies have shown that remimazolam administration can result in stable hemodynamic indicators in older patients; remimazolam may therefore be a valuable choice for anesthesia induction [73,98]. One study found that the timely administration of ephedrine and phenylephrine could be combined with remimazolam for anesthesia induction [98]. Patients' hemodynamics were stable during anesthesia induction and maintenance, and no adverse cardiovascular events occurred. As flumazenil can rapidly antagonize benzodiazepines, remimazolam may be an ideal anesthetic for early recovery. As older and critically ill patients receive general anesthesia during short-term surgery, remimazolam may be a better option.

A highly stable heart rate and mean arterial pressure are maintained after anesthetic induction with remimazolam. Owing to its rapid onset and low dose dependence on the depth of sedation, its effects on the cardiovascular and respiratory systems are consistent with the level of sedation it produces [70]. This is conducive to alleviating the stress response in older patients during anesthesia. Remimazolam is used for anesthetic induction and maintenance in older patients undergoing hip surgery [99], and its analgesic effect in controls is similar to that of propofol. Remimazolam may have certain advantages in awakening, extubating, and inhibiting cognitive dysfunction; moreover, excessive depth of anesthesia is avoided, especially in older patients, and it has a slight inhibitory effect on the central nervous system. Remimazolam has an anesthetic impact similar to that of propofol in older patients who undergo hip replacement. However, the former results in only slight inhibition of the circulatory system, a mild stress response, faster awakening, and higher safety. In noncardiac surgery in older patients with heart diseases, it was found that there was no accumulation or activity of metabolites after the injection of remimazolam.

The drug itself does not affect hemodynamics or inhibit patient respiration. Its specific antagonist, flumazenil, ensures the safety of remimazolam [100], and some researchers have confirmed that remimazolam does not prolong the QT interval during anesthesia or increase the risk of ventricular arrhythmia [101]. From multiple perspectives, the administration of remimazolam under general anesthesia may be safe in older patients [73]. Remimazolam is a promising drug that can achieve stable hemodynamics under general anesthesia, especially in older or critically ill patients, and can be safely used in high-risk older patients, regardless of their ASA grade, during the anesthesia process [102]. The ASA classification of patients did not affect the efficacy or average length of stay after the use of remimazolam.

5. Postoperative cognitive dysfunction (POCD)

POCD is a severe complication that is not yet fully understood and is a common complication in older patients. POCD often occurs in patients after anesthesia, with an incidence of up to 38% [103]. It primarily manifests as one or more cognitive defects after surgery, including defects in verbal memory, comprehension, visual memory, visual space abstraction, attention, and executive function [104]. It is characterized by changes in consciousness and cognitive ability and a rapid onset, resulting in a prolonged hospital stay and poor prognosis [105]. Traumatic stress associated with surgery and anesthesia triggers sympathetic nerve excitement in the body, increasing catecholamine release and triggering a systemic stress response. The immune system activates NF-κB and releases various proinflammatory mediators, eventually damaging the blood–brain barrier and promoting the migration of macrophages to the brain parenchyma through the ruptured barrier, leading to POCD [106,107]. The neuroinflammatory response is regarded as a key factor and initial link in the POCD process [108].

Studies have shown that sedation can lead to cognitive impairment, resulting in high levels of cognitive dysfunction at discharge and the inability to perform complex daily activities. Thus, the risk of injury may increase [109]. Delirium is the most common form of cognitive dysfunction in children. Delirium can result from the interaction between propofol and the muscarinic acetylcholine receptors. Medications targeting these receptors are associated with mental disorders [110]. A previous study reported that 60 of 164 (36.6%) older patients experienced POCD after surgery; the incidences of POCD in the propofol, dexmedetomidine, and midazolam groups were 18.2%, 40.0%, and 51.9%, respectively. In older patients under dexmedetomidine, propofol, and midazolam sedation, propofol slightly affects cognitive function, whereas midazolam has the greatest effect on cognitive function [111]. To prevent delirium completely, reversible factors — including pain and anemia — should be minimized, and appropriate treatment should be established. The rapid elimination of remimazolam may provide some protection, as there is no accumulation in the body, thereby reducing the incidence of delirium. Concurrently, remimazolam has been shown to relieve neuropathic pain, limit the production of proinflammatory factors [112], and reduce cerebral ischemia and reperfusion injury [113]. To some extent, it reduces oxidative stress and inflammation, supporting the maintenance of cognitive brain function [114].

Studies have indicated that remimazolam and dexmedetomidine are equally beneficial for reducing the incidence of early POCD after radical gastrectomy in older patients, which may be due to the reduction of the inflammatory response [106]. Moreover, because remimazolam undergoes a specific esterase metabolism in the body and has no effect on renal function, there is no difference on the clearance between older and younger patients, or between patients with normal renal function and end-stage renal failure [23]. Therefore, remimazolam is safe for older patients, even those with impaired renal function [115].

6. RT

RT was approved by the National Medical Products Administration in 2019 as a new drug for anesthesia and sedation [116]. Since 2020, pharmacokinetic and pharmacodynamic tests have been performed on healthy Chinese participants [117].

Similar to remimazolam and midazolam, RT also has a short half-life; however, the onset of sedation and recovery after RT administration are faster than those of currently available short-acting sedatives [116]. The pharmacokinetics and pharmacodynamics of RT are similar to those of remimazolam and have the same advantages [67]. In a study of 461 older patients aged 65–85 years with ASA scores I–III and undergoing gastroscopy, it was confirmed that in the presence of fentanyl, the rates of hypotension, bradycardia, and respiratory inhibition were low in older patients treated with RT and propofol. In this study, the hypotension rate was significantly lower in the remimazolam group than in the propofol control group (36.5% vs. 69.6%, $P < 0.001$). The incidence of hypotension (69.6%) in the propofol arm was higher in this trial than in previous studies (e.g., 42.86% in phase III trials on remimazolam and propofol) [118]. For patients undergoing upper gastrointestinal endoscopy, a single dose of RT after injection can provide sufficient sedation with a high success rate (97.34%), suggesting that RT has a wide therapeutic window for endoscopic sedation. RT can meet various operational requirements with different sedation depths [116]. For the endoscopic monitoring of older patients, IV injection of 0.2 mg/kg RT can achieve a good sedative effect; additionally, RT does not affect the storage and extraction stages of the memory process due to its molecular design [119]. The pharmacokinetics of RT show a linear relationship with an increasing dose, and the degree and duration of sedation after RT administration are dose-dependent. Older patients often take multiple medications, which may affect bioavailability [2]. This study showed that 0.1 mg/kg RT was well-tolerated in older patients compared with propofol and achieved better safety [119]. RT can therefore be applied in various surgeries for patient anesthesia based on clinical research indications and its excellent pharmacokinetic effects.

7. Future directions

The development of remimazolam and RT provides anesthesiologists with more choices, and patients undergoing general anesthesia no longer need to rely solely on propofol infusion to maintain anesthesia. In the future, more clinical trials are needed to demonstrate their applications in other fields of anesthesia, such as pediatric anesthesia. Concurrently, exploring the application modes in different age groups and surgical types is necessary. Studies should describe the implications of remimazolam in older and super-centenarian patients and the associated minor complications in older patients. The effects of remimazolam and RT on liver and kidney functions must be further investigated. Further, the association between remimazolam and RT and POCD must be assessed, and their long-term effects on patients must be followed up. Studies have shown that various anesthetic medications, such as propofol and midazolam, have anti-inflammatory and anticytotoxicity functions; however, whether remimazolam has anti-inflammatory effects requires further experimental studies.

8. Conclusion

This review suggests that remimazolam and RT are more suitable than midazolam and propofol for older patients who require sedation during anesthesia. This means that remimazolam can be considered the first option among other anesthetic drugs. Importantly, remimazolam and RT have a faster onset and offset of sedative effects and may have other benefits regarding tolerance and reduced side effects.

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Data availability statement

This is a systematic review; therefore, all data are included in the manuscript.

Ethics statement

An ethics statement is not applicable because this study is based exclusively on published literature.

CRediT authorship contribution statement

Ning Jin: Writing – review & editing, Investigation. **Zhiqiang Xue:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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