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REVIEW

Safety of Remimazolam in Vulnerable Populations

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Abstract: Vulnerable populations require careful consideration in drug selection due to their unique physiological conditions. Remimazolam, an innovative ultra-short-acting benzodiazepine, presents several advantages, including rapid onset, brief duration of action, and high predictability. Despite the extensive literature on remimazolam, few studies have specifically evaluated its safety in vulnerable patient populations. This review offers a comprehensive analysis of the safety profile of remimazolam in vulnerable populations, including cardiovascular diseases, neurological disorders, hepatic and renal dysfunction, respiratory conditions, metabolic disorders, rare diseases, and special groups such as the elderly and pediatric patients. It assesses recovery outcomes, hemodynamic stability, and adverse events such as respiratory depression and delirium. In our view, the prophylactic potential of remimazolam in these aspects may not be inferior to traditional anesthetic drugs (propofol, sevoflurane, etomidate, etc). and shows a trend of surpassing them in some aspects.

Keywords: hemodynamic stability, recovery outcomes, respiratory depression, delirium

Introduction

In the medical field, "vulnerable population" typically refers to groups that experience significant disadvantages in accessing healthcare services and facing disease risks, or achieving positive medical outcomes due to a confluence of physiological, psychological, social, or systemic healthcare factors. According to World Health Organization (WHO) statistics, patients with conditions such as heart disease, diabetes, and chronic lung disease account for 74% of global deaths.[1] An investigation revealed that one in four men and one in five women worldwide are afflicted by hypertension, while over 10% of the population grapples with various renal disorders.[2] In the United States, about 27.2% of adults are burdened by multiple chronic conditions.[3] Rare diseases impact nearly 300 million people globally.[4] Presently, around 2 billion people worldwide are classified as overweight, with the obese population reaching 600 million.[5] The above diseases result in varying degrees of impairment in organ function. Patients with cardiovascular disease may experience significant hemodynamic instability due to the sympatholytic effects of anesthetic agents, which suppress sympathetic nervous system activity. Patients with cerebrovascular disease are predisposed to reductions in cerebral blood flow and elevated intracranial pressure. Patients with hepatic or renal disease exhibit significant alterations in the distribution, protein binding, and metabolism of anesthetic drugs, resulting in delayed emergence from anesthesia. Patients with a history of malignant hyperthermia are at risk of triggering this life-threatening condition upon exposure to specific anesthetic agents. Patients with respiratory disease demonstrate markedly increased sensitivity to the respiratory depressant effects of anesthetics, leading to varying degrees of respiratory inhibition. Obese patients, in addition to facing challenges related to altered drug pharmacokinetics, are also susceptible to adverse events involving the cardiovascular and respiratory systems. Similarly, children and the elderly exhibit reduced tolerance to anesthesia and surgical interventions due to their distinct physiological states. Moreover, the risk of chronic diseases escalates with advancing age in elderly patients. In pediatric patients, common adverse events include hypoxia, decreased cardiac output, and delayed emergence from anesthesia. Elderly patients, conversely, are predisposed to hypotension, respiratory depression, delirium, and postoperative cognitive dysfunction (POCD). These adverse events pose significant challenges,

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leading to an increased risk of poor patient outcomes, prolonged hospital stays, and elevated healthcare costs. Generally, it is imperative for clinicians to prioritize strategies aimed at mitigating risks for vulnerable populations and minimizing the adverse effects of pharmacological treatments on these patients.

Propofol, sevoflurane, and etomidate are widely used anesthetics in clinical practice, with well-established efficacy and safety profiles. The recent introduction of remimazolam has further expanded the horizons of anesthesiology, offering a novel therapeutic option. As a novel ultra-short-acting benzodiazepine, remimazolam has gained considerable acclaim among anesthesiologists since its approval for use in numerous countries worldwide in 2020. It has advantages like rapid onset, brief duration of action, and high predictability. Meta-analyses suggested that remimazolam may serve as an excellent alternative to propofol and demonstrates more stable hemodynamics, reduced incidence of respiratory depression and a lower rate of injection pain. Moreover, the occurrence of nausea and vomiting is comparable between the two agents. However, remimazolam takes relatively longer to induce loss of consciousness.[6]

Currently, remimazolam has been applied in a diverse array of vulnerable populations, including individuals with cardiovascular diseases, neurological disorders, psychiatric conditions, hepatic and renal impairments, respiratory ailments, rare diseases, obesity, as well as the elderly and pediatric patients. Nonetheless, existing reviews, both domestically and internationally, predominantly approach these populations through the perspectives of surgical interventions and fail to provide a focused summary of the safety profile of remimazolam for these groups. This review synthesizes evidence on the safety of remimazolam in vulnerable populations, with focused evaluation of recovery profiles, hemodynamic stability, and critical adverse events including respiratory depression and delirium, to guide evidence-based clinical decision-making (Table 1 and Figure 1).

Search Strategy

A systematic literature search was conducted using the keywords "remimazolam" AND ("anesthesia" OR sedation) across the following databases: Web of Science, PubMed, China National Knowledge Infrastructure and Wanfang Database. The search was limited to articles published in the past five years. Inclusion criteria were defined as follows:

Study Type: Clinical trials OR case reports.

Study Population: Patients meeting at least one of the following criteria: Diagnosed with any systemic disease (eg, cardiovascular, cerebrovascular, respiratory, hepatic, renal, metabolic); Aged < 18 years (pediatric population); Aged ≥ 60 years (geriatric population); Critically ill.

Intervention: Administration of remimazolam as part of the anesthetic regimen.

Outcome Measures: Reporting of at least one of the following: blood pressure, heart rate, respiratory parameters (eg, respiratory rate, oxygen saturation, apnea), postoperative delirium (POD), emergence time, and postoperative nausea and vomiting (PONV).

Following the initial search and application of inclusion/exclusion criteria, the included studies were categorized into predefined subgroups based on patient characteristics (eg, specific systemic diseases, pediatric, geriatric) and study design.

Pharmacological Characteristics

Pharmacodynamics

Remimazolam is a benzodiazepine that exerts its primary effects through high-affinity binding to gamma-aminobutyric acid (GABA) receptors. Upon activation of GABAA receptors, a pronounced influx of chloride ions occurs, leading to neuronal membrane hyperpolarization and reduced neuronal excitability. The mechanism facilitates various effects like sedation, anterograde amnesia, and anticonvulsant properties.[17] Notably, these effects can be effectively antagonized by the specific benzodiazepine receptor antagonist flumazenil. In healthy adults, remimazolam demonstrates rapid onset of action and a significant dose-response relationship. Maximum sedation is typically attained within three minutes following a single injection, with effective doses for loss of consciousness (ED50 and ED95) recorded at 0.11/0.19 mg/kg and 0.14/0.27 mg/kg, respectively. These values closely correlate with the patient's age. Recommended dosages for various age demographics are as follows: 0.25–0.33 mg/kg for individuals under 40 years old, 0.19–0.25 mg/

Table 1 Clinical Summary of Remimazolam Use in Vulnerable Populations

Categories	Recommended Dosage	Key Advantages	Precautions	Evidence Strength
Cardiovascular Diseases	Induction 6 mg/kg/h; maintenance 0.3–0.7 mg/kg/h (severe cases: vasopressors ready)	More stable hemodynamics; less hypotension; faster emergence	Insufficient data for NYHA IV; vigilance for hypotension during induction	Moderate to High
Neurological Disorders	Induction 6–12 mg/kg/h; maintenance 1–2 mg/kg/h	Reduced intraoperative hypotension; faster emergence; no increased POD risk	High concentrations may induce neuronal apoptosis; caution with flumazenil in epileptic patients due to potential seizures	Moderate
Liver Dysfunction	Child-Pugh A: Induction 0.2 mg/kg; maintenance ≤2 mg/kg/h (B/C: reduced)	Stable hemodynamics in Child-Pugh A; faster emergence than propofol	Limited data for Child-Pugh B/C; possible delayed emergence	Low to Moderate
Renal Dysfunction	No adjustment needed	No impact on emergence; no exacerbation of renal injury	Insufficient data for non-renal surgeries	Moderate
Respiratory Diseases	Induction 0.2 mg/kg; additional 0.05 mg/kg	Less respiratory depression in compensated patients (vs propofol/dexmedetomidine)	Avoid in decompensated stages; lack of data for long-term intubation	Moderate
Obesity	1.0–2.0 mg/kg/h	Fewer cardiovascular/respiratory adverse events than dexmedetomidine	Need to monitor cardiopulmonary function	Low
Rare Diseases	Start with a low dose and gradually increase	No severe adverse reactions reported	Based solely on case reports; extremely small sample size	Very Low
Pediatric Patients	Induction 12 mg/kg/h maintenance 1–2 mg/kg/h Intranasal 1.09–1.57 mg/kg	Faster emergence; less POD; reduced risks with combination therapy	High doses may affect short-term memory; significant mucosal irritation with intranasal administration	Moderate
Elderly Patients	60-69 years: 0.12 mg/kg; 70–85 years: 0.09 mg/kg	Stable hemodynamics; less hypotension/respiratory depression; faster early cognitive recovery	High incidence of hypotension in patients over 80; inconsistent findings on POD/POCD	Moderate to High
Critically Ill Patients	Sedation: 0.125–0.15 mg/kg/h; anesthesia: 0.2 mg/kg/h	Safe for short/long-term sedation; no risk of propofol infusion syndrome	High doses may affect liver/kidney function; vigilance for acute tolerance	Moderate

Notes: Employ GRADE (Grading of Recommendations Assessment, Development and Evaluation) for grading the levels of evidence.
Abbreviations: NYHA, New York Heart Association; POD, Postoperative Delirium; POCD, Postoperative Cognitive Dysfunction.

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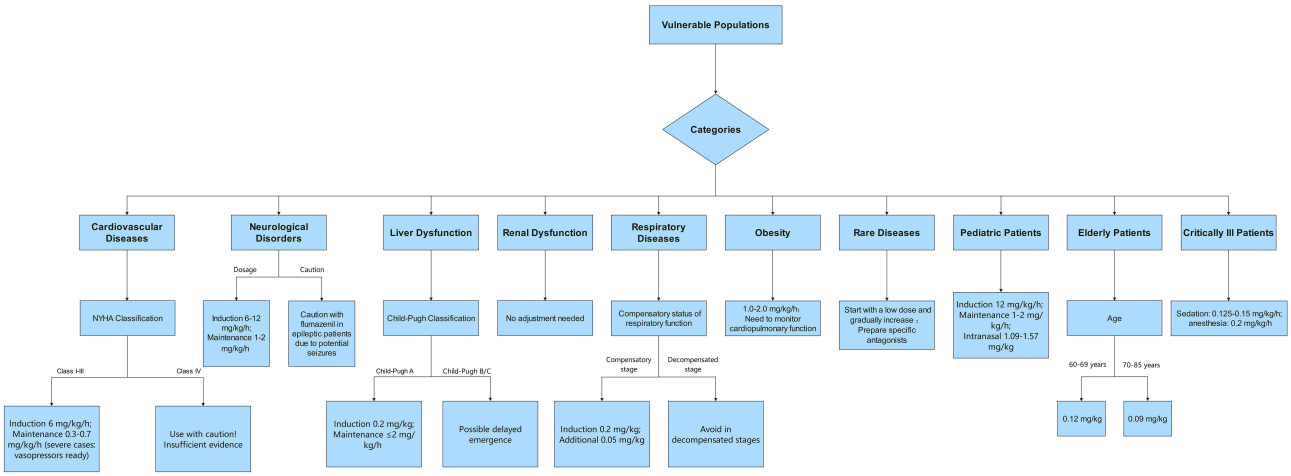

Figure 1 Visual clinical pathway of the remimazolam in vulnerable populations.

kg for those aged 60–80 years old, and 0.14–0.19 mg/kg for patients over 80 years old.[18,19] When administered by continuous intravenous infusion, the onset time for remimazolam is approximately five minutes, with the ED50 and ED95 for loss of consciousness being 0.07 mg/kg/min and 0.10 mg/kg/min, respectively.[20]

Pharmacokinetics

A standout pharmacological characteristic of remimazolam is its rapid clearance. Firstly, its volume of distribution at steady-state (Vdss) is approximately 35 L, which is merely one-tenth that of propofol. It suggests that there is minimal drug accumulation in the body during administration and results in a reduced quantity that requires elimination post-discontinuation.[21] Secondly, the systemic clearance rate of remimazolam is recorded at (70.3 ± 13.9) L/h, substantially surpassing that of propofol. Thirdly, the metabolism of remimazolam predominantly occurs via tissue esterases, particularly carboxylesterase 1 (CES 1), which hydrolyzes the drug's ester bonds to yield the inactive metabolite CNS7054. The metabolite is subsequently excreted by the kidneys following its conjugation with endogenous compounds.[22] Remimazolam exhibits a three-compartment pharmacokinetic model. In a Phase I clinical trial, following a continuous infusion of remimazolam for four hours, the simulated concentration-dependent half-life was determined to be 6.8 ± 2.4 minutes, with complete recovery of consciousness observed 19 ± 7 minutes after cessation of the drug.[20]

Safety of Remimazolam in Various Diseases

Cardiovascular Diseases

Remimazolam provides relatively stable hemodynamics and a reduced incidence of respiratory depression for patients with cardiovascular diseases, particularly in critically ill individuals, while ensuring adequate sedation and anesthesia levels during surgical procedures. Besides, it may assist in mitigating the occurrence of POCD and delirium.[23] Notably, during isovolemic hemodilution procedures, remimazolam maintains hemodynamic stability. Such phenomenon may be attributed to the absence of binding sites for the γ subunit of GABAa receptors in the human heart, resulting in negligible negative inotropic effects.[24] In addition, a study suggested that remimazolam may prevent POD via the HMGB1-TLR4-NF-κB pathway, effectively inhibiting neuro inflammation and facilitating M2 polarization of microglia.[25,26]

Patients with hypertension may experience substantial fluctuations in blood pressure during anesthesia due to factors such as diminished vascular elasticity and organ impairment of the heart and kidneys. One study showed that in patients with well-controlled hypertension for over six months, the use of remimazolam, in comparison to propofol, was associated with a reduced incidence of intraoperative hypotension (37.5% vs 64.6%, $P = 0.014$). Although the heart rate was elevated in the remimazolam group ($P < 0.0001$), the occurrence of sinus bradycardia did not differ significantly ($P = 1.000$).[27] A further clinical study corroborated these findings, but the researchers predominantly concentrated on the

induction phase as their primary observational endpoint.[28] Current evidence indicates that remimazolam provides superior hemodynamic stability compared to propofol in hypertensive patients.

The anesthetic risks associated with valvular disease are particularly pronounced during the induction phase, which is highly susceptible to various malignant hemodynamic fluctuations. Research showed that remimazolam provides superior hemodynamic stability during the induction phase of valve replacement surgery in patients with severe heart valve disease, particularly when compared to etomidate and propofol.[29,30] A study on 20 elderly patients with a mean age of 86 suffering from severe aortic stenosis found no significant cardiovascular events during the induction phase with remimazolam.[31] Another investigation indicated that remimazolam maintains its advantages not only during induction but also throughout the maintenance phase of general anesthesia.[32] Studies suggested that remimazolam does not significantly influence the occurrence of POD (30.3% vs 26.6%, risk difference, 3.8%; 95% confidence interval −11.5% to 19.1%; $P = 0.63$).[33] Further research indicated that remimazolam may facilitate earlier extubation following valve replacement surgery when compared to sevoflurane [6.5 (5.1–8.1) min vs 14.2 (10.9–15.9) min; difference in medians, −6.9 min; 95% confidence interval, −8.7 to −5.0; $P = 0.001$].[34] Collectively, current evidence demonstrates that remimazolam enhances hemodynamic stability during both induction and maintenance phases of anesthesia in patients with valvular heart disease, while providing faster emergence profiles without increasing the incidence of POD.

In patients with severe coronary artery disease, the anesthetic induction phase poses a significant risk of myocardial ischemia or even acute myocardial infarction due to hypotension. Researchers conducted a comparative study on the safety of an anesthesia regimen utilizing remimazolam alongside propofol and sevoflurane in patients undergoing coronary artery bypass grafting for severe coronary heart disease.[35] In the experimental group, anesthesia was induced with remimazolam at a rate of 6 mg/kg/h and maintained at 1–2 mg/kg/h. In comparison, the control group received propofol at 1.5 mg/kg for induction, followed by maintenance with 1–1.5% sevoflurane. The findings proved that the perimental group experienced a lesser degree of blood pressure reduction ($P = 0.014$), alongside a decreased frequency of intraoperative vasopressor administration (60% vs 88%, $P = 0.001$). However, it is important to note that the study did not include patients classified as New York Heart Association (NYHA) IV. Current evidence regarding remimazolam in this specific population remains limited, with only one study involving 46 cases. Furthermore, in this study, all patients were routinely administered nitroglycerin for the prevention of coronary spasm, which significantly increased the incidence of intraoperative hypotension and thus interfered with the observation of actual results. Based on available pharmacological profiles and preliminary clinical data, remimazolam may offer potential benefits. However, given the non-negligible risk of hypotension observed in extant studies, we strongly recommend implementing proactive hemodynamic safeguards—including preemptive vasopressor availability—during its clinical administration.

In summary, in patients with cardiovascular comorbidities, remimazolam demonstrates superior hemodynamic stability compared to propofol and sevoflurane, significantly reducing the incidence of major adverse cardiovascular events.remimazolam demonstrates a commendable safety profile in patients with cardiovascular diseases and indicates promising prospects for clinical application. Nonetheless, the existing studies are marked by significant limitations. Firstly, investigations into emergency surgeries in patients with poorly controlled hypertension have yet to be explored. Secondly, clinical studies focusing on individuals with severe coronary artery disease remain scarce. Thirdly, there is a notable absence of research concerning patients with congenital heart disease who do not present with Eisenmenger syndrome. Fourthly, the lack of clinical controlled studies on Recommendations 1:

For patients with hypertension/valvular heart disease: the induction dose is 6 mg/kg/h, and the maintenance dose is 0.3–0.7 mg/kg/h;

Be vigilant about the risk of hypotension during the induction phase in patients with severe coronary heart disease, and have vasoactive drugs ready.

Rare cardiovascular conditions is likely attributable to challenges in sourcing adequate samples. As patients with diverse cardiovascular ailments continues to rise, future research in these areas may reveal superior clinical treatment strategies and propel advancements in the field of anesthesiology.

Neurological Disorders

Research concerning the neuroprotective and toxic effects of remimazolam remains notably limited. Some studies indicate that remimazolam may mitigate neuronal damage, neurological dysfunction, and cerebral infarction size after ischemia/reperfusion injury by inhibiting NLRP3 inflammasome-dependent pyroptosis.[36] Furthermore, other investigations points out that remimazolam can attenuate oxidative stress and cellular apoptosis during cerebral ischemia/reperfusion injury via the AKT/GSK-3β/NRF2 signaling pathway.[37] However, it is also noted that high concentrations of remimazolam may suppress neuronal viability and induce neuronal apoptosis through glutamate-mediated excitotoxicity, ultimately resulting in memory deficits.[38]

Cerebrovascular diseases can induce significant alterations in cerebral blood flow and its regional distribution, rendering precise blood pressure management during anesthesia critically imperative. Monitoring results from a study involving 65 patients with moyamoya disease undergoing cerebral vascular bypass surgery indicated that the administration of remimazolam significantly diminished both the incidence (73.5% vs 38.7%) and duration (7.5 vs 0 minutes) of intraoperative hypotension when compared to propofol. Furthermore, the remimazolam cohort required lower doses of deoxyepinephrine.[39] Another investigation revealed that during the induction phase, despite a 17% reduction in mean arterial pressure and an 11% decrease in cerebral blood flow velocity (CBFV), cerebral blood flow remained stable due to the mechanisms of cerebral autoregulation.[40] However, a study examining patients with carotid artery stenosis undergoing carotid endarterectomy found no significant differences between propofol and remimazolam in their effects on cerebral oxygen saturation and cerebral blood flow velocity during the induction phase.[41]

Moreover, a study examining patients with intracranial aneurysms and cerebrovascular malformations revealed that remimazolam was associated with a shorter emergence time compared to propofol [16.1 (10.4) min in the remimazolam group vs 19.0 (11.2) min in the propofol group. The group difference was − 2.9 min (95% CI −6.5, 0.7)(P = 0.003 for non-inferiority)], while also exhibiting more stable hemodynamics during surgery [rate of hypotension during induction (11.3% vs 25.4%, P=0.03); use of vasopressors during surgery (29.6% vs 62.0%, $P < 0.001$)]. There were no significant differences in the incidence of delirium at 30 and 90 days postoperative.[42] In a randomized controlled trial involving patients with ruptured intracranial aneurysms, remimazolam demonstrated superior hemodynamic stability during surgical interventions when compared to propofol [the total phenylephrine dose: 0.0 (0.0–30.0) vs 30.0 (0.0–205.0) ug, P = 0.001; hypotensive events: 11 (28.9%) vs 23 (60.5%), P = 0.001]. Furthermore, with the administration of flumazenil for reversal, remimazolam yielded improved emergence times [270.0 (121.5–439.5) vs 96.0 (67.0–161.5)] and overall quality.[43] Overall, remimazolam significantly reduces the risk of intraoperative hypotension in patients with cerebrovascular diseases compared to propofol, shortens recovery time, ensures intraoperative cerebral perfusion, and does not increase the incidence of POD.

Patients with epilepsy may face an elevated risk of seizure activity in the postoperative period due to the effects of flumazenil reversal. In a comprehensive retrospective study involving 19,105 patients, researchers analyzed 12,033 patients who received remimazolam-flumazenil total intravenous anesthesia alongside 432,275 patients administered propofol.[44] They determined that there was no significant difference in seizure incidence between the two groups in non-neurosurgical procedures, with both rates remaining below 1%. Furthermore, some scholars posited that remimazolam, owing to its more rapid onset and emergence times compared to midazolam, may be better suited for the diagnosis of non-convulsive epilepsy.[45] However, the hypothesis currently lacks clinical evidence. Collectively, current evidence suggests that compared to propofol, remimazolam reduces intraoperative hypotension risk, shortens emergence time, maintains adequate cerebral perfusion pressure, and does not increase POD incidence in patients with cerebrovascular diseases.

Due to potential abnormalities in neurological function and structure, as well as variations in neurotransmitter levels, receptor activity, and hepatic enzyme function, there can be substantial modifications in the pharmacodynamics and pharmacokinetics of medications administered to patients with intellectual disabilities. Currently, there is only one small-sample study addressing patients with intellectual disabilities.[46] The study included 54 adults with intellectual disabilities scheduled for dental treatment, who were divided into two groups. Anesthesia for both groups predominantly employed target-controlled infusion of propofol at 3.0–5.0 ng/mL for induction, maintained at a central concentration of 1.5–5.0 μg/mL, in conjunction with remifentanil at 0.1–4.0 ng/mL. However, in the remimazolam group, propofol was substituted

with a continuous infusion of remimazolam at a rate of 1.0–2.0 mg/kg/h one hour prior to the conclusion of anesthesia, followed by intravenous administration of flumazenil at 0.5 mg postoperatively. The findings revealed that the remimazolam group experienced shorter times to eye-opening (mean difference, 5.4 min; 95% CI, 3.3–8.1; $P < 0.001$), extubation (mean difference, 5.5 min; 95% CI, 3.6–7.9; $P < 0.001$), and recovery in the PACU [mean difference, 8.7 min; 95% CI, 3.3–14.2, $P = 0.002$]. Notably, there were no statistically significant differences between the two groups concerning hemodynamic stability, depth of anesthesia, PONV, or modified Aldrete scores. Nonetheless, the study has limitations. Firstly, the classification of patients with intellectual disabilities into congenital and acquired categories, each potentially accompanied by various comorbidities, may have influenced the trial outcomes; however, the researchers did not implement appropriate management measures for these variables. Secondly, the method of drug administration employed in the trial deviated from the conventional approach of utilizing remimazolam for both induction and maintenance. Lastly, the study did not evaluate the incidence of POD or agitation.

In patients with neurological comorbidities, remimazolam exhibits a favorable safety profile characterized by rapid emergence, hemodynamic stability, and enhanced recovery quality—particularly when combined with flumazenil antagonism—without increasing the risk of neurological adverse events. At present, investigations into remimazolam concerning neurological diseases are predominantly confined to the realm of cerebrovascular disorders, with limited number of studies available. One research team is conducting a comparative analysis of remimazolam versus propofol for anesthesia in patients undergoing thrombectomy for ischemic stroke, with the objective of assessing both its safety and its implications for patient prognosis. Furthermore, some researchers are preparing to explore the effects of remimazolam on POD in individuals with neurovascular conditions. However, there is a significant gap in research regarding the exacerbation of postoperative psychiatric symptoms in patients with schizophrenia, the impact of intracranial pressure in those with intracranial tumors, and the safety profiles for patients experiencing emergency intracranial hemorrhage. Advancements in this area of research could potentially yield substantial benefits for these populations.

Recommendations 2:

For patients with cerebrovascular diseases: remimazolam is administered at 6–12 mg/kg/h (adjusted according to age) during the induction phase of general anesthesia, with a maintenance dose of 1–2 mg/kg/h;

For patients with epilepsy: vigilance is required regarding the potential risk of convulsions when using flumazenil for antagonism (though the incidence is low);

For patients with intellectual disabilities: continuous infusion of remimazolam (1.0–2.0 mg/kg/h) may be switched to at the end of operation.

Liver Disease

Common liver diseases include viral hepatitis, alcoholic liver disease, and autoimmune liver disease. Regardless of the specific type, liver function is invariably compromised to varying extents. Anesthesiologists concentrate on two primary considerations. Liver dysfunction significantly impacts the metabolism of anesthetic agents while these anesthetic drugs may further exacerbate the already impaired liver function. A pharmacokinetic study involving patients with liver impairment discovered that while the maximum blood concentration of remimazolam remains unchanged following intravenous administration, the clearance rate in individuals with severe liver dysfunction decreased by 38.1%. Consequently, the time to recovery was doubled compared to healthy subjects (16.7 minutes vs 8.0 minutes).[47] The prolonged emergence time may be attributed to the continued production of certain tissue esterases within the liver.

Currently, research regarding the application of remimazolam in patients with liver disease remains sparse. One clinical study previously compared the safety profiles of remimazolam and propofol in patients with cirrhosis undergoing endoscopic variceal ligation.[48] The researchers found that those receiving remimazolam exhibited shorter emergence times (67.1 ± 9.6 s vs 503.3 ± 59.6 s) and lower incidences of hypotension (5.3% vs 23.7%) and hypoxemia (0% vs 15.8%) compared to their counterparts treated with propofol, indicating that remimazolam may offer a greater safety advantage for this population. However, it is noteworthy that this trial excluded patients classified as American Society of Anesthesiologists (ASA) IV. Another study assessing painless gastroscopy in cirrhotic patients demonstrated that the emergence time with remimazolam was significantly shorter than that with propofol.[49] However, the study was also confined to patients classified as Child-Pugh grade A.

As liver disease progresses, patients exhibit worsening Child-Pugh classification. Current evidence indicates that remimazolam demonstrates an acceptable safety profile in Child-Pugh A patients, with preserved hemodynamic stability, minimal respiratory depression, and predictable emergence time. However, for Child-Pugh B/C patients, the absence of large-scale randomized trials necessitates cautious clinical application, where flumazenil antagonism may provide therapeutic benefit. These findings underscore the limited clinical research on the use of remimazolam in patients with liver disease. Future investigations can examine the emergence times and recovery quality for these individuals and explore the occurrence of postoperative complications.

Recommendations 3:

Child-Pugh A: Remimazolam can be used at standard doses (0.2 mg/kg for induction; maximum allowable infusion rate during the maintenance phase: 2 mg/kg/h), with a favorable safety profile (stable hemodynamics, minimal respiratory depression, and predictable recovery time);

Child-Pugh B/C: Caution is advised! Clearance is significantly reduced, leading to delayed recovery. Dose reduction is recommended, and consideration should be given to antagonism with flumazenil to accelerate recovery. Closely monitor recovery time.

Kidney Disease

Patients suffering from various forms of kidney disease frequently exhibit differing degrees of renal dysfunction, which can result in a delay in the excretion of drug metabolites. Conversely, anesthetic agents may indirectly compromise residual kidney function by impacting hemodynamics. Because the metabolites of remimazolam are largely inactive, and the plasma clearance rate in individuals with renal impairment is comparable to that of healthy subjects, the emergence time does not seem to be adversely affected.[48] A study demonstrated that remimazolam can effectively inhibit the expression of pro-inflammatory and pro-fibrotic molecules following folic acid-induced renal injury.[50]

A research team conducted a randomized controlled trial on 113 patients with end-stage renal disease undergoing kidney transplantation.[51] The participants were classified into two groups: the remimazolam group (n = 56) and the propofol group (n = 57), each receiving the designated anesthetic agent. The trial results showed that patients in the remifentanil group demonstrated more stable hemodynamics ($P < 0.001$). However, no significant differences in post-operative renal function were observed between the two cohorts.

Despite the limited research data on the use of remimazolam in patients with kidney disease, both pharmacological models and extant clinical evidence indicate that remimazolam stabilizes hemodynamic parameters, demonstrates no observed deterioration in renal function, and accelerates emergence time—even without flumazenil reversal. Future investigations could focus on exploring the efficacy and safety of remimazolam in patients with renal impairment undergoing non-renal surgical procedures.

Recommendations 4:

Its metabolites are inactive, and pharmacokinetics are not significantly affected.

Hemodynamics remain stable, with rapid recovery (even without flumazenil), so it can be used safely.

Respiratory System Diseases

Patients afflicted with respiratory system diseases exhibit markedly heightened sensitivity to the respiratory depressant effects of anesthetic agents due to obstructive or restrictive ventilatory dysfunction. Previous studies have validated the efficacy and safety of remimazolam in patients classified as ASA I to III undergoing bronchoscopy, and demonstrated faster emergence times in comparison to midazolam.[52] Researchers employed the Common Terminology Criteria for Adverse Events version 5.0 to evaluate the safety profile of remimazolam in this context, revealing no significant difference in the incidence of respiratory depression when compared to propofol.[53] Conversely, another study found that the combination of remimazolam and alfentanil was superior in maintaining spontaneous respiration and reducing the occurrence of respiratory depression relative to propofol (13.5% vs 39.6%, $P < 0.001$).[54] Additional research discovered that remimazolam was associated with a lower rate of respiratory depression than dexmedetomidine (14.3% vs 44.2%, $P < 0.05$); however, this study excluded patients with chronic obstructive pulmonary disease (COPD) and asthma.[55]

The aforementioned clinical studies were confined to patients whose respiratory function remained within compensatory limits, all undergoing non-intubated general anesthesia. The current evidence suggests that in patients with compensated respiratory diseases, remimazolam demonstrates non-inferiority to propofol and midazolam regarding hemodynamic stability and reduction of respiratory depression rates. However, insufficient data preclude definitive conclusions about its safety superiority over dexmedetomidine in this population. It remains uncertain whether remimazolam can ensure adequate safety in patients whose respiratory function is decompensated despite preoperative respiratory interventions. Moreover, there is currently a notable absence of relevant reports or studies addressing patients with respiratory diseases undergoing prolonged intubated general anesthesia. This is particularly pertinent in scenarios involving acute exacerbations requiring emergency surgery, or in cases such as lung cancer patients undergoing total lung resection, where postoperative repercussions on respiratory function are substantial.

Recommendations 5:

For patients with compensated respiratory function undergoing non-intubated anesthesia, remimazolam may be considered; co-administration with alfentanil is preferable, and close monitoring of respiratory and circulatory status is required;

For patients with decompensated respiratory function despite interventions, it is not recommended temporarily;

For patients requiring prolonged intubated anesthesia, blind use should be avoided due to limited research; priority should be given to other regimens with enhanced monitoring.

Metabolic Diseases

Metabolic diseases commonly refer to diabetes, hyperlipidemia, gout, hyperthyroidism, and obesity. To date, there's only one study primarily focused on the safety of remimazolam in obese patients. Obese patients commonly present with a range of pathophysiological alterations in the cardiovascular and respiratory systems. The study included 60 obese individuals classified as ASA I and II undergoing gastrointestinal surgery and revealed that the incidence of postoperative adverse reactions, such as nausea, vomiting, sinus bradycardia, hypotension, and respiratory apnea, was 13.33% for remimazolam compared to 36.67% for dexmedetomidine.[56] However, the study lacks clarity regarding whether the gastrointestinal surgeries were performed laparoscopically or as bariatric procedures. Furthermore, it is confusing that, despite the administration of muscle relaxants during intubated general anesthesia, the researchers concluded that there were notable differences in respiratory rate and oxygen saturation throughout the anesthesia period.

Furthermore, several clinicians documented two cases in which remimazolam was employed for awake craniotomy in obese patients. Utilizing a pharmacokinetic simulation system, both patients experienced no intraoperative complications. In addition, another physician reported a case involving a patient with a BMI of 44.8 kg/m² undergoing an analgesic gastroscopy. Although the patient's oxygen saturation temporarily fell to 92% on two occasions during the procedure, straightforward interventions effectively restored it to normal levels. Lastly, a case report concerning a patient with a BMI of 60.6 kg/m² undergoing bariatric surgery highlighted that induction with remimazolam resulted in exceptionally stable hemodynamics.

Available evidence suggests that remimazolam may reduce the incidence of cardiovascular and respiratory adverse events in obese patients; However, the current quantity and quality of evidence are insufficient. But researchers are in the process of preparing safety trials to evaluate the use of remimazolam, either in conjunction with or independent of opioid analgesics, for analgesic gastrointestinal endoscopy. Moreover, there is a notable absence of large-scale studies investigating postoperative respiratory and hemodynamic outcomes in patients undergoing intubated general anesthesia. Additionally, research into the alterations in cardiac function following surgery in this demographic is similarly lacking. Therefore, undertaking studies in these domains would substantially enhance the assessment of remimazolam's safety profile.

Recommendations 6:

Due to insufficient evidence, caution is advised when using remimazolam in obese patients. Dosage should be individually adjusted based on the patient's specific conditions; if conditions permit, consideration may be given to using pharmacokinetic simulation methods;

Throughout the procedure, close monitoring of respiratory function and hemodynamic indicators is required, especially in patients with extreme obesity (BMI $\geq$ 40 kg/m²).

Rare Diseases

Rare diseases are generally defined as conditions with extremely low prevalence, marked by complex clinical presentations and significant challenges in diagnosis and treatment. Notably, many of these conditions may have intricate relationships with anesthetic agents.

It is rare to encounter patients requiring anesthesia for such conditions in clinical practice, thus current knowledge being largely derived from case reports. One study demonstrated that clinical doses of remimazolam do not elevate intracellular calcium concentrations in the muscle cells of patients with malignant hyperthermia, indicating that remimazolam may be safely administered to this population.[57] There was a report of remimazolam being successfully utilized in a patient with malignant hyperthermia harboring a heterozygous RYR1 mutation.[58] Other case reports covered patients with various neuromuscular disorders, including Duchenne muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic dystrophy, amyotrophic lateral sclerosis, mitochondrial encephalomyopathy, mitochondrial cardiomyopathy, immune-mediated necrotizing myopathy, and hereditary angioedema, all of which reported no severe adverse events occurring either intraoperatively or postoperatively (Table 2).[7–16]

Unlike propofol, sevoflurane, and succinylcholine, no reports of serious adverse events associated with remimazolam use have been observed in multiple rare disease populations. Due to the challenges associated with conducting large-scale studies, the investigation of remimazolam's application in patients with rare diseases is likely to remain predominantly laboratory-based. The continuous emergence of new case reports and experimental results will provide valuable insights to inform clinical medication strategies.

Recommendations 7:

When using remimazolam in patients with rare diseases, existing case reports can be used as a reference, especially for populations with limited accumulated cases such as those with malignant hyperthermia and neuromuscular diseases. A comprehensive preoperative evaluation is required, including the triggers of the disease, the patient's cardiopulmonary function, and metabolic status;

Intraoperative close monitoring is also necessary, such as monitoring body temperature, end-tidal CO_2, creatine kinase levels, and neuromuscular function;

Meanwhile, targeted emergency medications (eg, dantrolene, antihistamines) should be kept ready.

Special Populations

Children

Children are in a continuous state of development, characterized by numerous physiological differences from adults, which presents a unique array of challenges in pediatric anesthesia. Firstly, children often display irregular breathing patterns, an elevated diaphragm position, and weakened respiratory musculature, rendering them particularly vulnerable to respiratory depression, and their heightened metabolic rates and low functional residual capacity further increase their vulnerability to hypoxia. Secondly, cardiac output in this population is predominantly reliant on heart rate, and the influence of anesthetic agents on heart rate may lead to a reduction in cardiac output. Thirdly, children possess a higher proportion of body fluids, and their immature hepatic and renal functions can significantly alter drug distribution and metabolism. Lastly, the limited range of cerebral vascular autoregulation in children increases the risk of cerebral ischemia.

The effective dose (ED_{50}) of remimazolam in pediatric patients has been established at 0.19 mg/kg, with studies indicating that its sedative efficacy is 5.8 times that of propofol, thus recommending an induction dose of 0.34 mg/kg.[59] In this demographic, remimazolam exhibits a high clearance rate of 15.9 (12.9, 18.2) mL/kg/min and a relatively shorter terminal half-life of 67 (49, 85) minutes, with a dose-dependent half-life of 17 (12, 21) minutes following a 4-hour infusion.[60] A study also demonstrated that remimazolam may induce apoptosis in hippocampal neurons in mice and diminish the expression of PSD-95 in the hippocampus, potentially impairing short-term learning and memory capabilities. However, such an effect is less pronounced than that associated with midazolam.[61]

Table 2 Main Case Report on the Application of Remimazolam in Patients with Rare Diseases

Ref	Disease	Surgery	Anesthesia Method	Remimazolam Dose	Outcome
[7]	Duchenne Muscular Dystrophy	Orthopedic Fixation	GA (TIVA) + Regional	Maintenance: 1.5 μg/kg/min	Stable hemodynamics, no SAEs, extubated to nasal cannula, discharged
[8]	Duchenne Muscular Dystrophy	Laparoscopic Hernia Repair	GA (TIVA)	Induction: 3 mg; Maintenance: 15 mg/h	Rapid emergence (20 min), negative myoglobin, discharged
[9]	FSHD	Total Laryngectomy	GA (TIVA)	Induction: 12 mg/kg/h; Maint: 1.5–2 mg/kg/h	Stable hemodynamics, spontaneous eye opening in 10 min
[10]	Myotonic Dystrophy	TMJ Reconstruction	GA (TIVA) + Regional	Induction: 10 mg/kg/h; Maint: 0.6–1.0 mg/kg/h	Stable hemodynamics, rapid emergence (3 min), spontaneous respiration, discharged.
[11]	ALS	Open Colectomy	Sedation + Regional	1 mg/min infusion	Spontaneous respiration, stable hemodynamics
[12]	ALS	Tracheostomy	GA (TIVA)	Induction: 6 mg/kg/h; Maint: 0.8–1.2 mg/kg/h	Stable hemodynamics, no emesis, ventilator settings unchanged, discharged
[13]	Mitochondrial Encephalomyopathy	Cochlear Implant	GA (TIVA)	Induction: 0.2 mg/kg; Maint: 1 mg/kg/h	Stable lactate, extubated in 8min, awake in 23min, mild vomiting
[14]	Mitochondrial Cardiomyopathy	Transcatheter Mitral Valve Repair	GA (TIVA)	Induction: 4 mg/kg/h; Maint: 0.35–1 mg/kg/h	Stable hemodynamics, awake in 16min, discharged
[15]	Immune-Mediated Necrotizing Myopathy	Laparoscopic Gastrojejunostomy	GA (TIVA)	Induction: 10 mg/kg/h; Maint: 1–2 mg/kg/h	Spontaneous respiration in 5min, rapid wakefulness, no seizures, discharged
[16]	Hereditary Angioedema	Cervical Laminoplasty	GA (TIVA)	Induction: 6 mg/kg/h; Maint: 1 mg/kg/h	Stable vitals, discharged

Notes: All cases in this table are derived from case reports (evidence level: very low), and clinical application requires careful risk assessment;
Abbreviations: GA, General Anesthesia; TIVA, Total Intravenous Anesthesia; FSHD, Facioscapulohumeral Muscular Dystrophy; ALS, Amyotrophic Lateral Sclerosis.

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Anxiety Management

The majority of children experience varying degrees of anxiety in the preoperative period. Prior research demonstrated that the intranasal administration of remimazolam at doses ranging from 1.09 to 1.57 ug/kg can effectively mitigate preoperative anxiety in pediatric patients.[62] However, another study suggested that while remimazolam is comparably effective to intranasal dexmedetomidine, its sedative efficacy is notably inferior, and it also exhibits significant irritant effects on the nasal mucosa.[63] We suggest that the adverse effects associated with intranasal administration of remimazolam may limit its wider clinical adoption. From an efficacy perspective, dexmedetomidine may represent a preferable alternative.

General Anesthesia

In terms of general anesthesia for children, a comprehensive cohort study was undertaken in Japan.[64] Researchers recruited 418 pediatric patients, with a mean age of 4.6 years, who were scheduled for elective surgical procedures. Anesthesia was induced using remimazolam at a dosage of 12 mg/kg/h, subsequently transitioning to a maintenance dose of 1–2 mg/kg/h following the onset of unconsciousness. The findings revealed that 75.2% of the children experienced fluctuations in mean arterial pressure (MAP) exceeding 20%. Specifically, 25.9% and 42.5% of the patients exhibited MAP reductions of 20–30% and greater than 30%, respectively, while 11.6% and 23.3% experienced MAP increases of 20–30% and greater than 30%, respectively. Meanwhile, 27.8% of the children demonstrated heart rate changes surpassing 30% from baseline. Notably, any declines in heart rate and blood pressure were effectively reversible with the administration of ephedrine. In a subsequent multicenter trial conducted by Chinese researchers, it was observed that among 192 preschool-aged children, induction with 0.3 mg/kg of remimazolam, maintained at 1–3 mg/kg/h, yielded results comparable to those of propofol while exhibiting more stable hemodynamic profiles.[65] Moreover, clinical studies indicated that a single intravenous bolus of remimazolam, administered intraoperatively or at the time of incision, significantly reduced the incidence of POD in children undergoing laparoscopic surgery (continuous infusion (5%) vs bolus injection (7.7%) vs untreated controls (35%)).[66] In summary, for intubated pediatric patients undergoing general anesthesia, remimazolam demonstrates superior hemodynamic stability and reduced incidence of POD compared to propofol. However, significant hemodynamic fluctuations persist. Consequently, close monitoring of vital signs, implementation of individualized dosing regimens, and prompt intervention remain imperative throughout administration to mitigate serious adverse events.

Procedural Sedation

Given their immaturity in cognitive development, children often experience significant fear during various diagnostic and therapeutic procedures, leading to diminished cooperation. Pediatric patients frequently undergo procedural sedation to facilitate medical interventions. Prior studies demonstrated that in children undergoing painless gastrointestinal endoscopy, the combination of remimazolam with low doses of esketamine resulted in lower incidences of respiratory depression (9.43% vs 35.85%) and hypotension (18.89% vs 45.28%) compared to propofol.[67] Another investigation revealed that a combination of 0.2 mg/kg remimazolam and 0.5 mg/kg propofol effectively mitigated the respective drawbacks of both agents, which rendered it an outstanding option for painless fiberoptic bronchoscopy.[68]

To date, there is a considerable amount of research regarding the application of remimazolam in pediatric patients. Based on current findings, remimazolam appears suitable for pediatric general anesthesia and procedural sedation. Furthermore, its safety profile can be significantly enhanced when administered as part of a combination therapy strategy. Nonetheless, certain domains remain underexplored, particularly concerning parental apprehensions about the long-term effects of anesthetic agents on children's memory and learning capabilities. Such studies typically require prolonged durations for completion and make them vulnerable to various confounding factors. The potential for elevated loss-to-follow-up rates further complicates their practical application.

Recommendations 8:

For general anesthesia - induction dose is 12 mg/kg/h, and maintenance dose is 1–2 mg/kg/h to maintain anesthesia;

For painless endoscopy - 0.34 mg/kg, when used in combination with low-dose ketamine, can reduce the risk of respiratory depression and hypotension;

Intranasal administration (1.09–1.57 mg/kg) is effective, but its sedative effect is inferior to that of dexmedetomidine, and it may irritate the nasal mucosa.

Elderly Patients

As individuals advance in age, they undergo a series of physiological declines, such as diminished cardiac and pulmonary reserves, reduced central nervous system excitability, impaired autonomic nervous system function, and alterations in body composition. These changes render elderly patients increasingly susceptible to pharmacodynamic and pharmacokinetic variations, as well as adverse events such as hemodynamic instability, respiratory depression, delirium, and cognitive impairment.

To date, many studies have explored the application of remimazolam in elderly patients. Previous studies established that age serves as an independent factor influencing the dosage of remimazolam required to achieve loss of consciousness.[69] For patients aged 60 to 69 years, the effective dose for 95% of individuals (ED_{95}) is 0.118 mg/kg, while for those aged 70 to 85 years, it is 0.09 mg/kg.[70] Meta-analyse comparing remimazolam with propofol showed that remimazolam not only attains sedation effects comparable to those of propofol but also exhibits markedly superior safety profiles.[71]

General Anesthesia

Elderly patients make up a significant proportion of orthopedic patients for various reasons, leading to a concentrated focus on research related to general anesthesia within this demographic, particularly during orthopedic surgeries. Comparative studies between remimazolam and etomidate concluded that remimazolam induces more stable hemodynamics in elderly hypertensive patients undergoing non-cardiac surgical procedures.[72] However, an investigation indicated that the use of remimazolam for anesthesia maintenance in patients over the age of 80 cannot effectively diminish the incidence of hypotension [72.1% (31/43) vs 72.7% (32/44)].[73] And the hemodynamic stability provided by remimazolam does not appear to correlate with a reduced incidence of postoperative acute kidney injury.[74]

In addition, a study proved that remimazolam may mitigate lipopolysaccharide-induced cognitive impairment via the α7nAChR-mediated Nrf2/HO-1 signaling pathway.[75] Interestingly, several randomized controlled trials have produced inconsistent findings regarding POD. One study assessed the incidence of delirium within seven days post-surgery in 100 patients aged 65 and older undergoing radical colon cancer surgery by utilizing the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and found no significant difference in delirium rates compared to propofol.[76] In contrast, a distinct trial that evaluated consciousness scores in elderly patients aged 65 to 85 undergoing spinal surgery suggested that remimazolam could reduce the incidence of POD. However, no statistically significant differences were observed in the incidence of intraoperative hypotension, or PONV, dizziness, and respiratory depression between the two groups.[77] Besides, another study utilizing the Mini-Mental State Examination (MMSE) to assess elderly patients with lower limb fractures indicated a reduction in the prevalence of postoperative cognitive dysfunction, the incidence of hypotension [2 (5.7%) vs 10 (28.6%)] and the incidence of respiratory depression [3 (8.6%) vs 10 (28.6%)] were both lower.[78] The discrepancies in findings across studies may stem from variations in surgical procedures, age cohorts, and assessment methodologies. Moreover, reports stated that the administration of remimazolam can diminish the occurrence of postoperative agitation during the recovery phase following hip replacement surgery in elderly patients.[79] Thus, in elderly patients undergoing general anesthesia, including even advanced geriatric populations, remimazolam demonstrates non-inferiority to propofol regarding hemodynamic stability, airway safety, and prevention of POD.

Procedural Sedation

While the dosage of anesthetic agents utilized in procedural sedation is relatively modest, their impact on the vital signs of elderly patients can be considerable. Previous studies demonstrated that, in the context of sufentanil-assisted procedures, remimazolam offers stable hemodynamics (6/39 vs 17/38, $P = 0.005$) and lower rates of respiratory depression (2/39 vs 9/38, $P = 0.026$) compared to propofol during painless gastrointestinal endoscopy in elderly patients.[80] Likewise, our earlier studies combining remimazolam with esketamine yielded similarly favorable outcomes.[81] A study focused on painless gastrointestinal endoscopy also revealed that the recovery of cognitive function

with remimazolam is comparable to that achieved with propofol.[82] Furthermore, research indicated that in elderly patients undergoing tooth extraction, remimazolam significantly enhances the early restoration of cognitive function, emergence time [12 (12, 13) vs 15 (14, 16) min, median (IQR)] and time to discharge eligibility [17 (17, 18) vs 20 (19, 21) min, median (IQR)] were also shorter.[83]

Based on the comprehensive findings, remimazolam demonstrates a modest reduction in the incidence of hypotension and respiratory depression compared with propofol, and is additionally beneficial for early cognitive recovery in elderly patients. Currently, investigations into the application of remimazolam among elderly patients primarily concentrate on hemodynamic stability, respiratory depression, and POD as key observational indicators. Future studies are expected to prioritize a more in-depth exploration of the long-term effects of this agent on cognitive function in elderly patients.

Recommendations 9:

For patients aged 60–69 years, the recommended dose is 0.12 mg/kg; for those aged 70–85 years, it is 0.09 mg/kg;

Compared with propofol, it reduces hypotension and respiratory depression, but the incidence of hypotension remains relatively high in patients over 80 years old, requiring continuous monitoring;

Research findings on its effects on POD and POCD are inconsistent, but it may be beneficial to early cognitive recovery.

Critically Ill Patients

Critically ill patients' physiological functions are exceptionally fragile, and even minimal doses of medication can trigger significant adverse reactions and result in deteriorated prognoses and diminished survival rates. A previous meta-analysis demonstrated that remimazolam is notably safer for patients classified as ASA III–IV, compared to propofol, particularly for those with cardiovascular conditions or hemodynamic instability.[84]

Invasive Ventilation Sedation

Patients in the ICU need a certain level of sedation due to challenges such as difficulty weaning from mechanical ventilation, agitation, and the need for respiratory support. A Phase I drug study revealed that a continuous infusion rate of remimazolam at 0.125 to 0.150 mg/kg/h effectively satisfies the sedation requirements of postoperative non-cardiac surgery patients in the ICU, with no serious adverse events reported.[85] Additionally, dose-response trials displayed that a loading dose of 0.02–0.05 mg/kg, followed by a maintenance dose of 0.20–0.35 mg/kg/h, successfully stabilized the hemodynamics of these patients.[86] What's more, a large-scale randomized controlled trial established that remimazolam can be employed both effectively and safely for short-term and long-term deep sedation in critically ill patients.[87] Other studies confirmed these findings and indicated that remimazolam does not contribute to increased hospitalization costs or elevated mortality rates.[88] Current evidence supports low-dose remimazolam as a safe sedative for critically ill ICU patients. Given the established risk of propofol infusion syndrome with extended propofol infusions, remimazolam emerges as a clinically viable alternative.

Painless Endoscopy

A Phase III clinical trial revealed that in high-risk patients (ASA III–IV) undergoing painless colonoscopy, the incidence of various adverse events associated with remimazolam and midazolam did not exhibit a significant difference, but their effectiveness demonstrated a dramatic disparity (87.1% vs 13.3%).[89] For high-risk patients undergoing colonoscopy, remimazolam demonstrates preserved efficacy and no additional adverse effects based on current data. Nevertheless, adequately powered multicenter Randomized Controlled Trials (RCTs) are warranted to strengthen the evidence base.

General Anesthesia

In an early multicenter, double-blind, randomized controlled trial involving 67 patients classified as ASA III, who were scheduled for elective surgical procedures, participants received remimazolam at infusion rates of 6 mg/kg/h (Group A) and 12 mg/kg/h (Group B) for induction. Following the loss of consciousness, a maintenance infusion at a rate of 1–2 mg/kg/h was initiated.[90] The findings showed that while the incidence of hypotension in Groups A and B was recorded at 54.8% and 67.7%, respectively, there was no statistically significant difference between the two. The occurrence of other adverse events was similarly comparable. When administered without a loading dose, remimazolam

stabilizes hemodynamics in septic shock patients independent of dosing regimens; however, it exhibits a negative correlation with postoperative renal and hepatic function at escalating doses.[91] Therefore, we recommend an infusion rate of 0.2 mg/kg/h for both induction and maintenance of anesthesia. This regimen not only promotes hemodynamic stability but may also improve patient outcomes.

Moreover, certain studies pointed out the emergence of acute tolerance to remimazolam following targeted infusion in healthy volunteers.[92] Future investigations could explore whether analogous responses manifest with the prolonged administration of remimazolam in critically ill patients.

Recommendations 10:

A low-dose continuous infusion (0.125–0.150 mg/kg/h) can meet the requirements without serious adverse reactions;

For long-term use, it can replace propofol (to avoid infusion syndrome);

In high-risk endoscopic examinations, it has adverse reactions comparable to midazolam but with higher efficacy.

It is recommended to start with a small dose (0.1 mg/kg/h) to optimize hemodynamics, potentially improve organ function prognosis, and avoid loading doses.

Current Limitations

This review assesses the safety profile of remimazolam in diverse vulnerable populations, underscoring its favorable safety and promising clinical potential across multiple clinical scenarios. Nevertheless, the current evidentiary foundation is hampered by substantial limitations: First, research in critical domains remains inadequate, with studies often characterized by small sample sizes. For instance, in the context of severe coronary artery disease (only one small-scale trial involving 20 patients), Child-Pugh class B/C liver impairment (a dearth of large-scale randomized controlled trials [RCTs]), and obesity, such inadequacies significantly compromise the quality of evidence. Critically, these small-scale studies are plagued by insufficient statistical power, meaning they lack the statistical rigor to identify clinically meaningful differences in safety outcomes—particularly for adverse events with moderate or low incidence—thereby elevating the risk of Type II errors (eg, failure to detect true effects). Second, data pertaining to rare patient populations are exclusively derived from case reports. While these reports offer valuable preliminary insights, they are inherently susceptible to selection bias (eg, reporting only successful or specific cases), reporting bias, and confounding factors, which severely undermine the reliability of causal inferences and the extrapolation of results. Third, marked heterogeneity exists in outcome metrics. This is particularly evident in the definition of key outcomes—for example, the assessment of POD employs diverse tools such as CAM-ICU or Nu-DESC and varies across time points—rendering meaningful cross-study comparisons and syntheses exceedingly challenging. Fourth, long-term safety data remain scarce. Existing evidence is confined to short-term outcomes during the perioperative period or procedural settings, with a paucity of data on potential long-term effects of remimazolam in these patients, such as neurocognitive impacts (especially following repeated exposure in pediatric populations), the development of tolerance, or dependence. Finally, RCTs have excluded patients with complex comorbidities to mitigate confounding. However, in real-world clinical practice, patients frequently present with multiple concurrent conditions, resulting in complex physiological states and potentially conflicting therapeutic demands. Such stringent exclusion criteria—for example, excluding patients with NYHA class IV heart failure, Child-Pugh class C liver disease, emergency cases, or significant multisystem disorders—substantially constrain the applicability and generalizability of current RCT findings to the high-risk, vulnerable patients with complex pathologies commonly encountered in clinical practice. Additionally, many studies are single-center or non-blinded, introducing risks of performance bias and detection bias. Further, the administration regimens of remimazolam (including loading and maintenance doses) and concomitant medications (eg, opioids, other sedatives) vary widely, leading to significant intervention heterogeneity and further complicating the interpretation of results. Intra-category population heterogeneity—such as the severity of hypertension, valvular disease, or coronary artery disease; Child-Pugh classification; the type and severity of intellectual disability; and the BMI range and associated comorbidities in obese patients—is also often unaddressed or inadequately analyzed in subgroup analyses. Accordingly, we contend that future research should prioritize multicenter, large-scale studies employing standardized outcome metrics, with a specific focus on addressing the aforementioned evidence gaps.

Conclusion

Although research on remimazolam's application in neurological disorders, respiratory diseases, obesity, and rare conditions remains limited, emerging evidence demonstrates favorable safety profiles within therapeutic dose ranges for patients with comorbidities. Compared to conventional anesthetics, it offers rapid emergence, superior recovery quality, reduced respiratory and cardiovascular depression, non-elevated incidence of POD, and enhanced early post-operative cognitive recovery—particularly evident with combination regimens (eg, remimazolam plus esketamine or alfentanil). Beyond intranasal administration, remimazolam demonstrates versatility across multiple clinical scenarios including pediatric, geriatric, and critically ill populations through various delivery methods, without triggering severe adverse events. However, cautious clinical use remains warranted, especially in patients with severe hepatic impairment or critical illness.

Disclosure

The authors report no conflicts of interest in this work.

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