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Remimazolam in Modern Anesthesia: Mechanisms, Organ-Independent Pharmacokinetics, Clinical Evidence, and Safety

Jiansheng He[1], Shunlian Li[1], Qiao Li[1], Hang Zhang[1], Junze Deng[1], Wei Gao[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
**Correspondence Author*

Abstract: ***Remimazolam is an ultra‑short-acting benzodiazepine that positively modulates GABA_A receptors and is rapidly hydrolyzed by nonspecific tissue carboxylesterases to an inactive metabolite, yielding organ-independent clearance, rapid onset and offset, and generally stable hemodynamics; its effects are promptly reversible with flumazenil. Accruing evidence across "painless" endoscopy, perioperative general anesthesia, and ICU sedation shows non-inferior procedural success to propofol or midazolam—with fewer hypotensive and respiratory events and faster cognitive recovery in gastrointestinal endoscopy—and emerging feasibility in ambulatory gynecologic procedures and awake neurosurgery. Practical considerations include the absence of intrinsic analgesia (necessitating opioid co-administration), heightened pharmacodynamic sensitivity in older or frail patients, reduced clearance in severe hepatic impairment, and the potential for re-sedation after antagonism. Adverse events largely mirror class effects (hypoxemia, blood-pressure perturbations), while serious hypersensitivity and clinically meaningful effects on cardiac repolarization appear rare at therapeutic exposure. This review integrates mechanism, pharmacokinetics, dosing strategies, clinical efficacy, and safety to guide rational use of remimazolam in modern, comfort-oriented anesthesia, and highlights priorities for rigorous trials in organ dysfunction and critical illness where putative anti-inflammatory actions remain to be validated.***

Keywords: Remimazolam, Benzodiazepines, General anesthesia, Endoscopy.

1. Introduction

Sedation underpins contemporary anesthetic care across procedural sedation, general anesthesia, and diagnostic interventions, with benzodiazepines remaining foundational owing to reliable anxiolysis and anterograde amnesia [1]; yet the prototypical agent, midazolam, can accumulate with prolonged use, yielding delayed emergence and respiratory depression. Propofol, the current workhorse for "painless" procedures, offers rapid onset but is limited by dose-dependent hypotension, respiratory depression, injection pain, and rare infusion-related toxicity [2]. Remimazolam—an ultra-short-acting benzodiazepine introduced into clinical practice in 2020—addresses several of these constraints: as a positive allosteric modulator of the GABA_A receptor, it is rapidly hydrolyzed by nonspecific tissue carboxylesterases to an inactive metabolite, providing organ-independent clearance, fast onset, a brief context-sensitive half-time, and predictable titratability with generally stable hemodynamics and minimal injection discomfort; importantly, its effects are promptly reversible with flumazenil [3]. Across Phase III trials in gastrointestinal endoscopy, including colonoscopy spanning ASA I–IV risk strata, remimazolam has demonstrated non-inferior procedural success versus propofol or midazolam with lower rates of hypotension and respiratory events and faster cognitive recovery, and early data in ambulatory gynecologic hysteroscopy and awake craniotomy suggest comparable feasibility with improved tolerability [4, 5]. At induction, both infusion and bolus strategies are effective, with older or frail patients often requiring lower exposure; during maintenance, remimazolam's limited accumulation favors rapid recovery, though clearance can decrease in severe hepatic impairment, and re-sedation may follow flumazenil, warranting vigilant monitoring [6, 7]. Safety considerations include the usual risks of sedative-hypnotics (hypoxemia, blood-pressure perturbations), rare hypersensitivity, and minimal clinically meaningful impact on cardiac repolarization at therapeutic concentrations [8]; remimazolam lacks intrinsic analgesia and should be paired with appropriate opioids. Emerging preclinical evidence hints at anti-inflammatory effects relevant to critical illness, but human data remain insufficient [9]. This review synthesizes pharmacology, dosing strategies, and clinical evidence for remimazolam in endoscopy, general anesthesia, and ICU sedation, critically appraising efficacy, safety, and limitations to guide rational, evidence-based adoption in modern, comfort-oriented anesthesia practice.

2. Pharmacological Mechanism of Remimazolam

Remazolam is a novel drug designed by combining midazolam and remifentanil. It incorporates a carboxylate moiety into the midazolam structure and undergoes structural modifications similar to remifentanil [10]. Remimazolam is a short-acting GABA_A receptor agonist. Similar to classic benzodiazepines (midazolam), it exhibits high affinity and comparable activity for all four GABA_A receptor subtypes (α1, α2, α3, α5) [11]. Additionally, by amplifying GABA currents in cells expressing GABAA receptor subtypes, it increases intracellular chloride concentration, leading to membrane hyperpolarization. This inhibits the propagation of action potentials in neurons, elevates inhibitory activity in the central nervous system, and produces sedative effects [12]. Flumazenil is a benzodiazepine receptor antagonist that efficiently binds to central benzodiazepine receptors, competitively inhibiting GABA-benzodiazepine recognition of benzodiazepine receptor drugs[13]. This reduces GABA release and reverses the central inhibitory effects induced by

GABA release. Pingel Lasse et al. found that flumazenil effectively reverses the sedative effects of remimazolam and reduces metabolic recovery time. Remimazolam is an ester-based drug with a molecular weight of 439 kD [14]. It undergoes rapid hydrolysis by plasma non-specific esterases, swiftly converting to the inactive metabolite zolpidem propionate without relying on hepatic or renal metabolism. Its elimination kinetics follow first-order kinetics. The carboxylic acid metabolite exhibits 300–400 times weaker affinity for GABA_A receptors than remimazolam (Ki = 10,000 nmol·L^{-1}) and possesses negligible pharmacological activity. Rimazolam bypasses hepatic and renal metabolism. Masui Kenichi found minimal pharmacokinetic impact in patients with hepatic or renal impairment (excluding severe hepatic impairment), necessitating no dose adjustment [15]. Furthermore, Zhou Leguang et al. demonstrated that remimazolam reduces proinflammatory cytokine release and alleviates neuroinflammatory pain by inhibiting NF-κB translocation, inactivating B1-type bradykinin receptor signaling, and suppressing autophagolysosome formation both in vivo and in vitro [16].

3. The Use of Remimazolam in General Anesthesia

Preoperative premedication is routinely used to attenuate anxiety, facilitate amnesia, smooth the transition to induction, and reduce the dose requirements of induction agents. Benzodiazepines are frequently chosen because they reliably produce anxiolysis and anterograde amnesia via positive allosteric modulation of the GABA_A receptor [10]. Remimazolam presents distinct practical considerations for this purpose. Its oral bioavailability is low and the drug's pronounced bitter taste undermines acceptability, limiting the utility of oral dosing. Intranasal administration can cause local irritation and discomfort, which constrains feasibility outside select settings [12]. Pharmacokinetically, remimazolam is ultra–short-acting: a single intravenous bolus is rapidly hydrolyzed by nonspecific tissue esterases to an inactive metabolite, yielding brief sedation that may dissipate during the often-variable preoperative waiting period unless redosing is planned [11]. Importantly, remimazolam lacks intrinsic analgesia, and re-sedation may occur after flumazenil reversal; caution is warranted in patients with severe hepatic impairment, in whom clearance can be reduced [1, 3]. Given these attributes, longer-acting alternatives—such as oral or intranasal midazolam, or α2-agonists (e.g., dexmedetomidine or clonidine) where appropriate—may better sustain pre-induction anxiolysis. If remimazolam is nevertheless selected, a carefully titrated intravenous strategy (small incremental boluses or a low-dose continuous infusion) could maintain stable, light sedation while preserving the option of rapid reversal with flumazenil [6]. Such an approach remains hypothesis-generating and warrants prospective evaluation of dose–response targets, timing relative to operating-room transfer, impacts on induction requirements and patient-reported anxiety, and workflow effects. Protocols should predefine sedation endpoints (e.g., OAA/S or Ramsay scores), incorporate non-pharmacologic measures, and ensure vigilant respiratory monitoring—especially in patients at elevated risk of airway obstruction or hypoventilation (e.g., obstructive sleep apnea, frailty, or hepatic dysfunction) [17]. Overall, agent selection for premedication should be individualized, balancing the need for durable anxiolysis against the advantages of rapid titratability and hemodynamic stability.

During induction of general anesthesia, remimazolam can be delivered either as a continuous intravenous infusion or as a single intravenous bolus. For infusion-based induction, fixed-rate infusions of 6 or 12 mg·kg^{-1}·h^{-1} are commonly described [18]. Loss of consciousness (LOC)—defined as loss of eye opening to command or loss of verbal response—typically occurs at median times of approximately 97.2 s and 81.7 s for 6 and 12 mg·kg^{-1}·h^{-1}, respectively. At a 6 mg·kg^{-1}·h^{-1} induction rate, older adults (e.g., ~75 years) may reach LOC 5–10 s sooner than younger adults (~30 years), consistent with greater pharmacodynamic sensitivity [19]. Although age per se does not mandate dose reduction in most patients, frail older adults may require lower rates and closer titration, as with other hypnotics. Once LOC is achieved, the induction rate should be discontinued and transitioned to a lower, individualized maintenance rate guided by clinical signs (lack of response to incision, stable hemodynamics) and, when available, processed EEG targets (e.g., BIS 40–60)[14, 20]. For bolus induction, remimazolam 0.2–0.4 mg·kg^{-1} administered intravenously produces reliable hypnosis. Reported ED95_{95}95 estimates for remimazolam-based induction are 0.37 mg·kg^{-1} (95% CI 0.28–0.39) in younger adults, 0.37 mg·kg^{-1} (95% CI 0.27–0.39) in middle-aged adults, and 0.25 mg·kg^{-1} (95% CI 0.20–0.29) in older adults. In the referenced observation period, no episodes of hypotension or bradycardia required pharmacologic treatment. Several practical considerations warrant emphasis [21]. First, remimazolam provides hypnosis and anxiolysis but no intrinsic analgesia; co-administration of an opioid (e.g., fentanyl or remifentanil) and a neuromuscular blocker should follow standard practice for the planned surgery. Second, synergism with opioids can deepen sedation; incremental dosing and vigilant respiratory monitoring (capnography, oxygen supplementation, and immediate airway readiness) are advised. Third, because remimazolam is rapidly hydrolyzed by nonspecific tissue esterases, overshoot can be reversed with flumazenil, although re-sedation is possible and patients should be observed accordingly [22]. Finally, in severe hepatic impairment, clearance may be reduced; conservative dosing and careful titration are recommended.

Remimazolam is an ultra–short-acting benzodiazepine increasingly used for maintenance of general anesthesia, where it offers rapid, titratable hypnosis with hemodynamic stability and the option of pharmacologic reversal. In head-to-head evaluations with propofol, maintenance infusions of remimazolam (approximately 0.3–1.0 mg·kg^{-1}·h^{-1}) have been associated with more stable intraoperative blood pressure and heart rate, lower rates of adverse effects, and in some series faster early recovery milestones, while preserving adequate anesthetic depth[23]. In patients with hepatic dysfunction, where traditional agents may accumulate, induction and maintenance with remimazolam have yielded greater hemodynamic stability and fewer adverse reactions than propofol; however, some studies report longer times to loss of consciousness, eye opening, and extubation, despite similar post-anesthesia care unit discharge timing and higher Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores at extubation [24]. Thermoregulatory data during robotic surgery suggest smaller fluctuations in core

temperature with remimazolam and altered vasoconstriction thresholds/onset compared with propofol, yet without a significant difference in the incidence of intraoperative hypothermia [25]. For neurosurgical applications, case series indicate that remimazolam can serve as a feasible alternative to propofol for awake craniotomy, supporting reliable intraoperative arousal. Because remimazolam undergoes rapid organ-independent hydrolysis by tissue carboxylesterases to an inactive metabolite (and thus relies less on hepatic or renal function than many agents), accumulation is minimal during appropriately titrated infusions; nonetheless, clearance can be reduced in severe hepatic impairment, and the drug provides no intrinsic analgesia, necessitating opioid co-administration [26]. Finally, while flumazenil enables prompt reversal after remimazolam maintenance, re-sedation has been observed within approximately 45 minutes in some patients, underscoring the need for careful post-reversal monitoring and judicious dosing. Overall, the available evidence supports remimazolam as a safe and effective maintenance option relative to propofol, with particular promise in patients vulnerable to hemodynamic instability or organ dysfunction, while highlighting areas for further study—including temperature regulation, protocols for intraoperative arousal, and strategies to mitigate adverse events and recurrence of sedation after antagonism.

4. The Use of Remimazolam in General Anesthesia

As healthcare increasingly prioritizes patient comfort, demand for “pain-free” procedures—more precisely, procedural sedation and analgesia (PSA)—continues to rise. Propofol remains the workhorse sedative because it provides reliable hypnosis with rapid onset and a brief context-sensitive half-time, enabling fast turnover in ambulatory settings; however, its liabilities are well recognized, including dose-dependent hypotension and respiratory depression, injection-site pain, and—in rare cases with high doses or prolonged infusions—propofol infusion syndrome characterized by otherwise unexplained metabolic acidosis, rhabdomyolysis, and cardiovascular collapse [27]. Remimazolam, a next-generation ultra-short-acting benzodiazepine, has emerged as an attractive alternative for PSA and “painless” endoscopic procedures: it offers rapid, titratable onset and offset; comparatively stable hemodynamics and a lower propensity for apnea at equipotent depths; minimal injection pain; and organ-independent clearance via nonspecific tissue carboxylesterases to an inactive metabolite, permitting predictable recovery and pharmacologic reversal with flumazenil [28]. These advantages are particularly relevant in patients vulnerable to hemodynamic instability or with impaired hepatic or renal function (noting that severe hepatic dysfunction can still reduce clearance and warrants careful titration). As with propofol, remimazolam lacks intrinsic analgesia and should be paired with an opioid when painful stimuli are expected, and clinicians should monitor for possible re-sedation after flumazenil [29]. Overall, accumulating evidence supports remimazolam as a safe, effective, and operationally flexible option for modern comfort-oriented care while highlighting the need for thoughtful agent selection and vigilant physiologic monitoring.

In a Phase III randomized trial of 384 adults undergoing gastrointestinal endoscopy, participants received either remimazolam or propofol with sedation success rate as the primary endpoint; efficacy was comparable, with no statistically significant difference between groups (97.34% for remimazolam vs 100.00% for propofol). Safety favored remimazolam: compared with propofol, it was associated with a markedly lower incidence of intraoperative hypotension (13.04% vs 42.86%), treatment-related hypotension (0.54% vs 5.82%), and respiratory depression (1.09% vs 6.88%), alongside a faster return to full consciousness[30]. Although onset times with remimazolam showed a broader distribution, they remained clinically acceptable, and overall recovery proceeded efficiently. Taken together, these findings indicate that remimazolam provides non-inferior procedural sedation success with a more favorable hemodynamic and respiratory profile and improved patient tolerance relative to propofol, supporting its use for “painless” endoscopic procedures.

In randomized colonoscopy studies, Rex et al. enrolled 461 low-risk adults (ASA I–II) and assigned them to remimazolam, midazolam, or placebo; the prespecified composite success rate for procedural sedation was 91.3% with remimazolam versus 25.2% with midazolam and 1.7% with placebo, and remimazolam was associated with less hypotension, faster recovery of neuropsychological function, and earlier discharge[14, 17]. A separate Phase III trial in higher-risk patients (ASA III–IV) showed a similar efficacy gradient—87.1% with remimazolam, 13.3% with midazolam, and 0% with placebo—with no serious adverse events reported in the remimazolam arm [6]. Taken together, these Phase III data indicate that remimazolam provides effective, titratable sedation for colonoscopy across ASA I–IV risk strata, with a safety profile marked by greater hemodynamic stability and brisk cognitive recovery relative to midazolam; its rapid onset and offset further support its use in ambulatory endoscopy where predictable throughput and patient tolerance are priorities.

Hysteroscopy is a common ambulatory gynecologic procedure for diagnosing and treating intrauterine pathology, and propofol combined with a short-acting opioid remains a frequently used anesthetic strategy; however, remimazolam has emerged as a practical alternative given its rapid, titratable hypnosis and favorable cardiorespiratory profile[31]. In a randomized study by Zhang et al. including 90 patients, Group A received propofol (induction 2 $mg \cdot kg^{-1}$; maintenance 5 $mg \cdot kg^{-1} \cdot h^{-1}$), whereas Groups B and C received remimazolam (induction 0.25 $mg \cdot kg^{-1}$; maintenance 0.48 or 0.60 $mg \cdot kg^{-1} \cdot h^{-1}$); sedation success was 100% across all groups, but remimazolam was associated with absent injection-site pain, attenuated effects on hemodynamics and respiration, and higher-quality emergence. These clinical advantages are consistent with remimazolam’s organ-independent hydrolysis by nonspecific tissue esterases and the option for rapid pharmacologic reversal with flumazenil, features well suited to outpatient hysteroscopy where predictable recovery and throughput are priorities [24]. Because remimazolam lacks intrinsic analgesia, adjuncts such as a short-acting opioid and, when appropriate, paracervical block should be employed to cover nociception [26]. Taken together, the evidence supports remimazolam as a safe and effective anesthetic for hysteroscopy, offering improved tolerability and operational

flexibility compared with propofol-based regimens.

5. The Use of Remimazolam in Sedation in the Intensive Care Unit (ICU)

In critically ill patients with hepatic or renal failure, an ideal sedative for intensive care should permit rapid titration and recovery while minimizing reliance on organ clearance; remimazolam, an ultra–short-acting benzodiazepine, fits this profile by undergoing organ-independent hydrolysis via nonspecific tissue carboxylesterases to an inactive metabolite, resulting in minimal accumulation during prolonged infusions and the option for prompt reversal with flumazenil [32]. Pharmacokinetic data suggest that renal failure has little effect on parent-drug exposure (the inactive metabolite may accumulate without known clinical consequence), whereas severe hepatic impairment can reduce clearance, warranting conservative dosing, careful titration, and vigilance for re-sedation after antagonist use. Beyond its practical pharmacology and generally favorable hemodynamic profile relative to many hypnotics, preclinical studies indicate potentially beneficial immunomodulatory effects: in endotoxemic mice, remimazolam improved survival and attenuated lipopolysaccharide-evoked cytokine release (e.g., TNF-α, IL-6, IL-1β), and in acute liver injury models it mitigated inflammatory signaling, plausibly through translocator protein (peripheral benzodiazepine receptor) engagement and inhibition of hepatocyte p38-MAPK phosphorylation [33]. These observations raise the hypothesis that remimazolam could confer advantages in sepsis, particularly when propofol-related hypotension or dexmedetomidine- associated bradycardia are concerns; however, high-quality clinical trials in septic populations are lacking, and any use should align with modern ICU sedation principles—analgesia-first strategies, light-sedation targets (e.g., RASS −2 to 0), continuous cardiorespiratory monitoring, and routine delirium assessment—while recognizing that benzodiazepines can contribute to delirium and respiratory depression at deeper levels of sedation. Overall, remimazolam represents a promising option for ICU patients with organ dysfunction, but its putative anti-inflammatory benefits remain unproven in humans and warrant rigorous prospective evaluation before routine adoption in sepsis care.

6. Safety Analysis of Remimazolam in Clinical Use

During remimazolam-based sedation, the most common adverse responses reflect dose- and co-medication–dependent respiratory and hemodynamic effects—principally hypoxemia and blood-pressure abnormalities—along with somnolence and headache; although QT prolongation has been reported, recent data suggest little to no clinically meaningful effect on cardiac repolarization at therapeutic exposures. Despite its generally favorable safety profile and broad use in general anesthesia, rare serious hypersensitivity events have occurred: for example, a 32-year-old man undergoing hand surgery developed facial flushing followed within 2 minutes of starting a 6 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion by declines in SpO_2 and blood pressure that resolved after epinephrine, with post-operative allergy testing positive for remimazolam and flumazenil effectively reversing hypnosis [34]. The reversibility of remimazolam was further supported in a randomized, double-blind, midazolam-controlled, two-way crossover study of 87 healthy Chinese adults receiving a 2-hour constant-rate infusion: bispectral index values were maintained between 40 and 60 with mean plasma concentrations around 1,000 $ng \cdot mL^{-1}$; emergence at infusion end was faster with remimazolam than with midazolam, and flumazenil shortened the median time to full emergence to approximately 3.5 minutes while reversing cardiovascular and psychomotor effects[35]. Nonetheless, residual psychomotor impairment may persist despite apparent wakefulness—manifesting as impaired postural stability, blurred vision, slowed reactions, or suboptimal judgment—so patients should undergo standardized psychomotor assessment before discharge, be monitored for possible re-sedation after flumazenil, and receive clear activity restrictions (e.g., no driving or operating machinery) until recovery is unequivocal [36].

7. Summary and Outlook

Ramazolam, as a novel sedative agent, exhibits rapid onset and metabolism. Although its sedative potency is lower than propofol, it demonstrates a low incidence of adverse reactions and possesses a specific antagonist, flumazenil. It offers distinct advantages in general anesthesia for short procedures, endoscopic procedures, and outpatient examinations. Furthermore, it exerts minimal effects on respiratory and circulatory functions, demonstrating particular efficacy in elderly patients with hemodynamic instability or frail constitution. Compared to propofol and benzodiazepines, remimazolam exhibits faster onset and metabolism with a lower incidence of adverse reactions. Moreover, remimazolam undergoes rapid hydrolysis by plasma non-specific esterases and does not rely on hepatic or renal metabolism, potentially making it an ideal future option for patients with hepatic or renal impairment. In the eyes of anesthesiologists, remimazolam is regarded as a “soft drug,” combining the efficacy of propofol with the safety profile of midazolam. Clinical studies confirm its outstanding performance in anesthetic efficacy, offering a new therapeutic option for future clinical anesthesia. Therefore, researchers should further explore its potential therapeutic applications and expand studies on remimazolam in clinical anesthesia. This will better meet patient needs for comfortable medical care while providing more guidance for clinical implementation.

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