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Remimazolam: Five Years of Clinical Experience Since Its First-in-World Approval in Japan

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Abstract

Background: Remimazolam besylate, an ultra-short-acting benzodiazepine anesthetic, received its first-in-world approval in Japan in January 2020, marking a significant milestone in anesthetic drug development. Five years of clinical experience have provided substantial evidence on its clinical utility and safety profile, offering unprecedented insights into the practical application of this novel agent across diverse patient populations and clinical scenarios. **Methods:** This narrative review synthesized published literature from PubMed-indexed sources, focusing on Japanese clinical trials, international studies, and post-marketing surveillance data to evaluate remimazolam's clinical performance over the five years since its approval. The analysis encompassed randomized controlled trials, observational studies, case reports, and pharmacovigilance data, to provide a comprehensive assessment of clinical outcomes, safety profiles, and practical considerations for its clinical use. **Results:** Clinical trials demonstrated remimazolam's non-inferiority to propofol for general anesthesia, with superior cardiovascular stability and reduced injection site pain. Japanese researchers led pivotal Phase III trials showing drug efficacy in both standard and high-risk (ASA III) patients, establishing a robust evidence base for its clinical implementation. Post-marketing surveillance revealed rare but serious adverse events, including anaphylaxis and circulatory collapse, particularly in elderly patients, while simultaneously demonstrating excellent overall tolerability. Notably, remimazolam showed no increased risk of postoperative delirium in cardiovascular surgery patients, distinguishing it from other benzodiazepines, and suggesting potential cognitive advantages. **Conclusions:** Five years of clinical experience confirm that remimazolam is a valuable addition to the anesthetic armamentarium, with particular advantages in terms of hemodynamic stability and reversibility. While the overall safety profile remains favorable, vigilance for rare, albeit serious allergic reactions is warranted, especially in older patients. The accumulated evidence supports judicious use of remimazolam in selected clinical scenarios

where traditional agents may be suboptimal.

Keywords

Remimazolam, Benzodiazepine, General Anesthesia, Japan, Clinical Experience, Safety

1. Introduction

The development and approval of new anesthetic agents represent a rare, but profoundly significant advancement in perioperative medicine, occurring perhaps once in a generation. In January 2020, Japan achieved a historic milestone by becoming the first country worldwide to approve remimazolam besylate (Anerem®) for general anesthesia, culminating decades of meticulous research and clinical development that began in the laboratories of Glaxo Wellcome in the late 1990s [1]. This ultra-short-acting benzodiazepine, bearing the original research designation CNS-7056, represents a unique pharmacological approach that successfully combines the familiar and well-understood receptor profile of benzodiazepines with revolutionary metabolic properties specifically designed to overcome the traditional limitations that have long constrained this drug class [2].

The significance of Japan's pioneering regulatory approval extends far beyond mere administrative precedence, reflecting the country's substantial intellectual contribution to the drug's development. Japanese investigators, led by distinguished researchers such as Doi, Masui, and Yamakage, conducted many of the foundational clinical studies that established remimazolam's efficacy and safety profile through rigorous scientific investigation [3] [4]. The prescient observation by Masui in his landmark 2020 editorial captures the essence of this achievement: "A novel anesthetic, remimazolam, would be desired to have advantages beyond existing anesthetics such as inhalation anesthetics, propofol, and midazolam" [1]. This statement proved remarkably prophetic as subsequent clinical experience has validated many of these anticipated advantages. The Japanese clinical development program strategically targeted patient populations and surgical contexts that were particularly relevant to Japan's healthcare landscape and demographic profile. Initial trials focused on elderly patients undergoing elective surgery, reflecting Japan's rapidly aging society where nearly 30% of the population is over 65 years old. The emphasis on cardiovascular procedures and patients with multiple comorbidities (ASA-PS class III) aligned with the prevalent healthcare challenges in Japan, where age-related cardiovascular disease represents a major perioperative risk factor. This targeted approach ensured that remimazolam's clinical evidence would be directly applicable to the patient populations most encountered in Japanese anesthetic practice, facilitating evidence-based adoption and optimal clinical implementation [3] [4].

The temporal milestone of five years since this landmark approval now provides sufficient clinical experience to conduct a comprehensive and meaningful assessment of remimazolam's place in modern anesthetic practice. The accumulated ex-

perience spans diverse patient populations, varied surgical procedures, and multiple clinical contexts, offering insights that extend well beyond the controlled conditions of initial clinical trials. The present review synthesizes this wealth of available evidence, with particular emphasis on the pioneering Japanese clinical experience, while incorporating valuable international perspectives and crucial post-marketing surveillance data that have emerged during this formative period.

2. Development History and Pharmacological Profile of Remimazolam

2.1. Historical Development and Corporate Evolution

The genesis of remimazolam can be traced to the British pharmaceutical company, Glaxo Wellcome, in the late 1990s, where researchers, buoyed by the remarkable success of remifentanil development, embarked upon an ambitious project to identify novel sedatives with short and highly predictable durations of action [5]. The pharmaceutical development landscape of this era was marked by growing recognition of the clinical limitations inherent to existing anesthetic agents, creating both scientific opportunity and commercial incentive for innovation. The compound that would eventually become remimazolam, initially designated GW502056 and subsequently CNS-7056, emerged as the lead candidate through systematic medicinal chemistry efforts, although its path to clinical reality proved both circuitous and prolonged [6].

The compound's developmental journey reflects the complex realities of modern pharmaceutical innovation, involving multiple corporate transitions and strategic realignments that are characteristic of drug development in the contemporary era. Following initial promise at Glaxo Wellcome, the project underwent various corporate transitions before ultimately reaching clinical development under the guidance of PAION AG (Aachen, Germany) in 2008, demonstrating the persistence required for novel anesthetic development [6]. Simultaneously, a parallel and strategically independent development program was initiated by Jiangsu Hengrui Pharmaceutical Co. Ltd. in China, utilizing a different salt formulation (tosylate) in what appears to have been a calculated maneuver to circumvent existing patent protection while advancing clinical availability [6]. This dual development pathway ultimately contributed to remimazolam's eventual global availability in multiple formulations, each optimized for different regulatory and clinical contexts.

2.2. Pharmacological Characteristics and Molecular Innovation

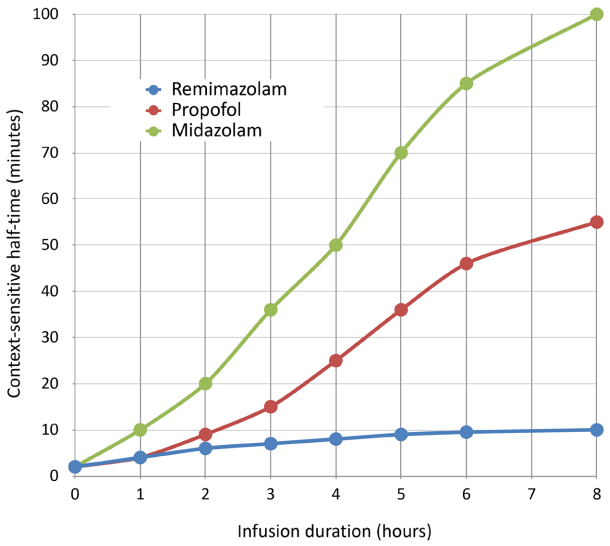
Remimazolam possesses a sophisticated imidazobenzodiazepine structure, distinguished by a carefully engineered ester side chain attached to the diazepine ring, representing a masterful example of rational drug design [2]. This structural modification, seemingly minor from a chemical perspective, enables rapid and predictable hydrolysis by tissue esterases, primarily carboxylesterase 1 (CES1), to produce CNS-7054, an inactive carboxylic acid metabolite characterized by approximately 300 - 400 fold lower receptor affinity compared to the parent compound [6]. This remarkable difference in receptor affinity ensures that metabolism truly

represents pharmacological inactivation rather than merely redistribution or chemical transformation into an equipotent metabolite.

The comprehensive pharmacological profile of remimazolam encompasses several remarkable characteristics that distinguish it from existing benzodiazepines. The compound demonstrates high affinity for GABA-A receptor benzodiazepine binding sites with a Ki value of approximately 30 nM, ensuring robust pharmacological activity at clinically relevant concentrations. The kinetic profile is characterized by rapid onset and offset, with an effect-site equilibration half-life ranging from 1 - 5 minutes, allowing clinicians to exert precise temporal control over anesthetic depth. The terminal elimination half-life of approximately 0.75 hours, combined with linear pharmacokinetics and minimal accumulation potential, ensures predictable recovery characteristics even following prolonged administration [6].

The formulation represents another triumph of pharmaceutical science, with remimazolam presented as a water-soluble besylate salt with a molecular weight of 567.5 Da, eliminating many of the formulation challenges that have historically complicated benzodiazepine administration, such as poor aqueous solubility and the need for organic solvents. The protein binding of 92% ensures appropriate tissue distribution, while maintaining sufficient free drug concentrations for pharmacological activity [6]. The metabolic pathway of remimazolam through tissue esterases represents a fundamental advantage over traditional hepatic cytochrome P450-dependent metabolism, potentially reducing drug interactions and providing more predictable pharmacokinetics across patient populations with varying hepatic function [2] (**Figure 1**).

Parameter	Remimazolam	Propofol	Midazolam
Elimination half-life (h)	0.75	4-7	1.5-2.5
Primary metabolism	Tissue esteraces (CES1)	Hepatic (CYP2B6, CYP2C9)	Hepatic (CYP3A4/5)
Active metabolites	No (CNS-7054)	No	Yes (α-hydroxymidazolam)
Context-sensitive half-life	Minimal increase	Increases with infusion time	Marked increase with infusion time
Pharmacokinetic profile	Linear	Non-linear	Linear
Recovery predictability	High	Moderate	Low
Characteristics	Organ-independent metabolism	Affected by liver dysfunction	Drug interaction & variability



Linear pharmacokinetics with predictable recovery characteristics regardless of infusion duration distinguish remimazolam from the hepatic cytochrome P450-dependent sedative midazolam. The table demonstrates the pharmacokinetic effects of the organ-independent metabolism of remimazolam versus the hepatic metabolism of propofol and midazolam, with implications for drug interactions and recovery predictability [11] [12]. The graph represents a comparison of the pharmacokinetic parameters of the three drugs, showing remimazolam's ultra-short elimination half-life (0.75 hours) and tissue esterase-mediated metabolism via CES1 to inactive metabolite CNS-7054 [2] [6].

Figure 1. Pharmacokinetic comparison: remimazolam, propofol, and midazolam.

3. Clinical Development of Remimazolam: Foundational Studies in Japan

3.1. Early Clinical Investigation and Phase I Studies

Japanese investigators assumed a crucial and ultimately decisive role in remimazolam's clinical development, contributing scientific rigor and clinical insight that proved essential for regulatory approval and clinical implementation. Doi's comprehensive 2014 review of early clinical data established many fundamental principles that remain relevant and applicable even today, providing a scientific foundation upon which subsequent clinical experience has been built [2]. The initial Phase I studies conducted in healthy volunteers demonstrated several remarkable pharmacological characteristics that would later prove clinically significant.

These early investigations revealed a single-dose elimination half-life ranging from 39 - 53 minutes, confirming the rapid clearance anticipated from the compound's molecular design. Perhaps most significantly, universal loss of consciousness occurred at the modest dose of 0.2 mg/kg, demonstrating both potency and consistency of effect across study participants. The pharmacokinetic parameters exhibited dose-independence, a characteristic that greatly simplifies clinical dosing and reduces the potential for unexpected accumulation or prolonged effect. Throughout these studies, subjects maintained a stable cardiovascular profile during anesthesia, demonstrating one of remimazolam's most clinically valuable characteristics [2].

The transition from Phase I to Phase II studies marked remimazolam's first clinical application for general anesthesia, representing a pivotal moment in anesthetic drug development. This landmark Phase II trial involved 85 carefully selected patients, comprising 55 non-elderly and 30 elderly subjects, and demonstrated average maintenance infusion rates of 1.02 mg/kg/h in non-elderly patients and 0.72 mg/kg/h in elderly patients. These findings suggested age-related pharmacokinetic differences that would require clinical consideration. Recovery times from infusion cessation to eye opening averaged 14 minutes in non-elderly and 11 minutes in elderly patients, indicating rapid and predictable emergence across age groups [2].

3.2. Landmark Phase III Trials: Establishing Clinical Efficacy

The definitive Phase IIb/III multicenter trial conducted by Doi *et al.* represents perhaps the most significant single study in remimazolam's clinical development, providing unequivocal evidence of its clinical efficacy and establishing the foundation for regulatory approval [7]. This meticulously designed study randomized 375 surgical patients to receive either remimazolam at induction doses of 6 or 12 mg/kg/h, followed by maintenance at 1 mg/kg/h, or propofol according to standard protocols. The study's primary endpoint was a composite measure designed to capture the essential elements of successful anesthesia: absence of intraoperative awakening or recall, no requirement for rescue sedatives, and absence of purposeful body movements.

The results exceeded expectations, with a remarkable 100% success rate achieved in all treatment groups for the composite endpoint, definitively establishing rem-

imazolam's clinical efficacy. The statistical demonstration of non-inferiority to propofol, confirmed by a 95% confidence interval of −0.0487 to 0.0250, provided regulatory authorities with the evidence needed for approval decisions. However, the study's most clinically significant findings may have been the safety advantages demonstrated by remimazolam compared to propofol [7].

The safety profile revealed several remarkable differences favoring remimazolam. The overall incidence of adverse events was substantially lower, with remimazolam groups experiencing rates of 39.3% - 42.7% compared to 61.3% in the propofol group. More specifically, the incidence of hypotension, a common and clinically significant adverse event associated with anesthesia induction, occurred in only 20.0% - 24.0% of remimazolam patients compared to 49.3% of propofol patients. Perhaps, most notable from a patient comfort perspective, injection site pain, reported in 18.7% of propofol patients, was completely absent in the remimazolam group [7].

The study also revealed important kinetic differences that inform clinical practice. The time to loss of consciousness was longer with remimazolam compared to propofol, reflecting different pharmacological mechanisms and suggesting the need for modified induction techniques. Similarly, extubation times were prolonged in the remimazolam group, although this difference must be interpreted in the context of overall recovery quality and patient satisfaction [7].

3.3. High-Risk Patient Populations: Studies of Remimazolam in ASA-PS Class III Patients

Building upon the success of the drug in standard patient populations, Doi *et al.* conducted a subsequent investigation specifically targeting American Society of Anesthesiologists-physical status (ASA-PS) class III patients, a population traditionally considered at elevated risk for anesthetic complications [8]. This study, involving 67 carefully selected high-risk patients, compared two remimazolam induction regimens (6 vs. 12 mg/kg/h), and proved particularly significant in establishing the agent's safety profile in vulnerable patient populations.

The study achieved a remarkable 100% anesthesia success rate across both dosing regimens, demonstrating that remimazolam's efficacy extends to patients with significant medical comorbidities. The adverse event profiles were manageable and comparable between dose groups, suggesting that higher-risk patients do not experience disproportionate complications with remimazolam use. This finding proved crucial for its clinical adoption, as it provided evidence-based support for remimazolam use in precisely those patients who might benefit most from its favorable hemodynamic profile [8].

4. International Clinical Experience and Global Regulatory Development

4.1. Regulatory Approvals and Global Implementation

Following Japan's pioneering approval, remimazolam underwent a carefully or-

chestrated global regulatory campaign that reflected both the compound's clinical promise and the complex realities of international drug development. The pattern of approvals revealed important strategic considerations, with general anesthesia indications approved in Japan in January 2020 and South Korea in 2021, while procedural sedation applications gained approval in the United States in July 2020, the European Union in 2021, and China in 2021. This staggered approval pattern reflects different regulatory priorities and clinical needs across global markets [6].

The approval for intensive care unit sedation in Belgium through compassionate use protocols represented an important expansion of remimazolam's clinical applications, although this indication remains limited compared to its general anesthesia and procedural sedation uses. These varied regulatory pathways demonstrate the flexibility of remimazolam's clinical profile and its potential applicability across different clinical contexts [6].

4.2. Procedural Sedation Applications

International clinical trials, particularly those conducted under the leadership of Rex *et al.*, established compelling evidence of remimazolam's efficacy in procedural sedation applications, complementing the general anesthesia data generated by Japanese investigators [9]. The pivotal Phase III colonoscopy study demonstrated the superior efficacy of remimazolam compared to both placebo and midazolam controls, while simultaneously revealing faster recovery times and reduced respiratory depression compared to traditional agents. These findings proved particularly significant given the large volume of colonoscopic procedures performed worldwide, and the growing emphasis on the efficiency of ambulatory care.

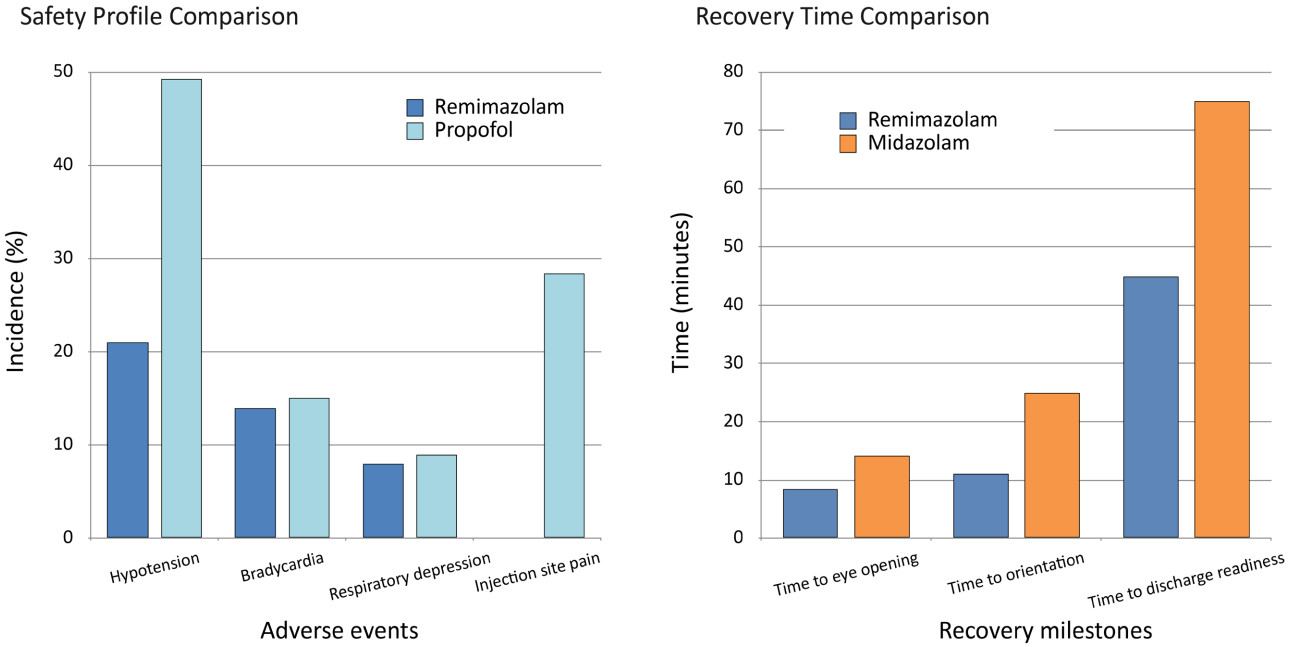
Similar benefits were observed in bronchoscopy procedures, with particular advantages noted in elderly and high-risk patients who traditionally pose greater challenges for procedural sedation [10]. The consistency of these findings across different procedures and patient populations provided strong evidence for remimazolam's versatility and reliability in ambulatory settings, where rapid, predictable recovery is paramount.

4.3. Pharmacokinetic Validation across Populations

International pharmacokinetic studies conducted by Schuttler *et al.* and other investigators provided crucial validation of remimazolam's pharmacological consistency across diverse patient populations [11] [12]. These investigations confirmed that the favorable pharmacokinetic properties observed in initial Japanese studies were maintained across different ethnic populations, with minimal effects of age, sex, race, and obesity status on drug disposition. Such consistency represents a remarkable achievement in drug development, where population-specific pharmacokinetic differences often complicate clinical implementation and dosing recommendations.

These findings proved instrumental in supporting remimazolam's global regulatory approvals and clinical implementation, providing evidence-based reassur-

ance that dosing recommendations developed in one population could be safely applied across diverse patient groups. The pharmacokinetic predictability observed across populations also supported the development of standardized dosing protocols that could be implemented globally without extensive population-specific modifications [11] [12] (**Figure 2**).



Integrated efficacy and safety outcomes were evaluated in pivotal trials. Japanese Phase III studies demonstrated 100% composite endpoint success with non-inferiority to propofol, significantly reduced hypotension (20.0% - 24.0% vs. 49.3%) and complete elimination of injection site pain [7] [8]. High-risk ASA-PS class III patients experienced equivalent efficacy of remimazolam as healthy subjects [8]. International procedural sedation trials confirmed superior outcomes of remimazolam versus midazolam, with faster and more predictable recovery profiles in bronchoscopy and colonoscopy procedures [9] [10]. Enhanced hemodynamic stability represented a consistent finding across all major clinical trials.

Figure 2. Summary of major clinical trials on remimazolam.

5. Five Years of Clinical Experience: Comprehensive Safety Assessment

5.1. Overall Safety Profile and Clinical Tolerability

Five years of increasingly widespread clinical use have provided unprecedented insight into remimazolam's safety profile under real-world conditions, confirming and extending the favorable findings observed in controlled clinical trials. The most commonly reported adverse events continue to align closely with expected benzodiazepine pharmacology, including hypotension, nausea, vomiting, and transient respiratory depression. However, the critical clinical observation is that the incidence of these events typically equals or falls below that observed with comparative agents, confirming remimazolam's favorable risk-benefit profile across diverse clinical applications [6] [13].

The accumulation of clinical experience has also provided valuable insights into patient factors that may influence adverse event risk, dosing requirements, and

clinical outcomes. Age-related differences in drug sensitivity and clearance have become more clearly defined through clinical observation, while the influence of comorbid conditions on drug response has been better characterized through case reports and clinical series.

5.2. Post-Marketing Surveillance: FAERS Database Analysis

The recent comprehensive analysis of the FDA Adverse Event Reporting System (FAERS) database, covering the period from 2020-2023, provides the most systematic assessment of remimazolam's post-marketing safety profile currently available [14]. However, it is important to acknowledge the inherent limitations of spontaneous adverse event reporting systems. FAERS data are subject to significant reporting bias, with serious and unexpected events more likely to be reported than common or well-recognized adverse effects. The database cannot establish causal relationships between drug exposure and adverse events, as temporal association does not prove causation. Additionally, underreporting is common, particularly for non-serious events, and the quality and completeness of individual reports vary considerably. Despite these limitations, this analysis, encompassing 67 cases with 161 adverse drug events, offers valuable insights into the real-world safety experience that extends beyond the controlled conditions of clinical trials [15].

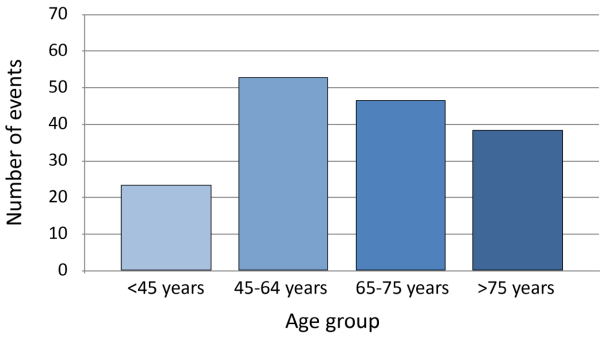
The FAERS analysis revealed several important patterns that inform clinical practice. A higher incidence of adverse events was observed in patients over 45 years of age, with particular concentration in those over 65 years, suggesting that advanced age represents a risk factor for remimazolam-related complications. The analysis identified notable signals for serious adverse events, including allergic reactions, respiratory arrest, cardiac arrest, and vascular access occlusion, emphasizing the need for enhanced monitoring protocols in elderly patients and continued post-marketing surveillance [14].

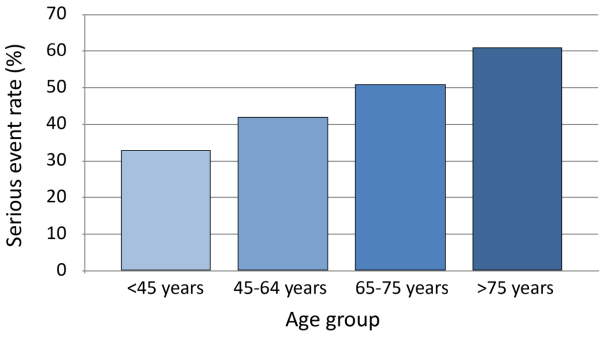
These findings underscore the importance of systematic post-marketing surveillance in detecting rare but potentially serious adverse events not evident in clinical trials, particularly in elderly patients (**Figure 3**).

5.3. Rare but Serious Adverse Events: Clinical Characterization

Japanese case reports have provided detailed clinical characterization of rare but potentially life-threatening anaphylactic reactions associated with remimazolam administration [16]. These reports describe a distinctive clinical pattern of the reaction, characterized by rapid onset within minutes of drug administration, severe hypotension with systolic blood pressure falling to 30 - 40 mmHg, and, notably, the absence of typical cutaneous or respiratory symptoms that usually characterize anaphylactic reactions. The circulatory collapse observed in these cases required aggressive management with epinephrine for hemodynamic stabilization, as other conventional vasopressors (e.g., phenylephrine or ephedrine) were ineffective.

These case reports have raised important questions about the mechanisms underlying these severe reactions, with some evidence suggesting a possible role of





Adverse Event Type	Frequency	% of Total	Age Association
Hypotension	42	26.1	Strong (>65 years)
Respiratory depression	36	22.4	Moderate
Bradycardia	29	18.0	Strong (>75 years)
Anaphylactic reaction	4	2.5	None
Other events	50	31.0	Variable

Anaphylactic reactions present as rapid-onset circulatory collapse without typical allergic manifestations

- Onset typically within minutes of remimazolam administration
- Absent or minimal cutaneous manifestations (urticaria, erythema)
- Primary presentation: Sudden hypotension and cardiovascular collapse
- Potential association with dextran component of formulation

Post-marketing surveillance analysis of 67 cases with 161 adverse events from the FDA Adverse Event Reporting System database showed clear age-related risk stratification [14]. Patients >65 years old exhibit significantly higher serious adverse event rates, with hypotension (26.1%), respiratory depression (22.4%), and bradycardia (18.0%) showing strong age associations. Rare anaphylactic reactions (2.5%) present as rapid-onset circulatory collapse without typical allergic manifestations, with onset typically within minutes of remimazolam administration, potentially associated with the dextran component of the formulation [16].

Figure 3. Adverse events profile by age group: FAERS database (2020-2023).

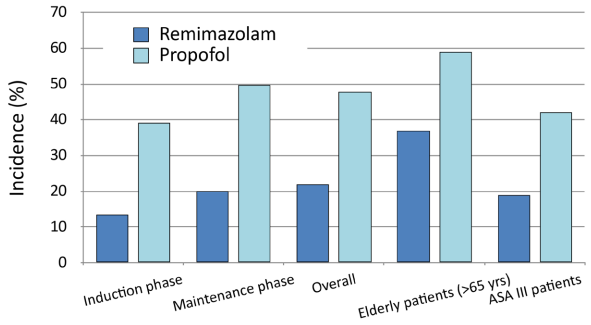
formulation additives, such as dextran 40, rather than the active pharmaceutical ingredient itself [15]. This mechanistic uncertainty has important implications for patient management and risk assessment, as conventional allergy testing may not reliably predict the risk of these severe reactions. Currently, the commercially available remimazolam formulation (Anerem®) contains dextran 40 as a stabilizing excipient, and alternative dextran-free formulations are not yet available for clinical use. However, pharmaceutical manufacturers are actively investigating alternative formulation strategies that could eliminate dextran 40 while maintaining drug stability and efficacy. Until dextran-free alternatives become available, clinicians should maintain heightened awareness of this potential risk factor, particularly in patients with known dextran sensitivity or previous unexplained intraoperative hypotensive episodes. The development of dextran-free formulations represents a high priority for improving remimazolam's safety profile and could potentially eliminate this rare but serious adverse event risk.

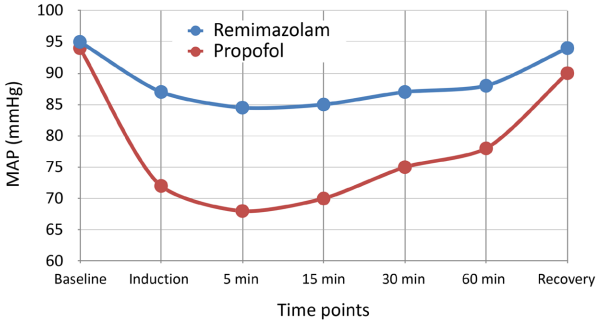
The clinical presentation of remimazolam-associated anaphylaxis, characterized primarily by cardiovascular collapse without classic allergic manifestations, represents a unique challenge for clinical recognition and management. These cases emphasize the critical importance of readiness for anaphylactic emergencies in all patients receiving remimazolam, regardless of prior allergy history, and highlight the need for immediate access to epinephrine and advanced resuscitation capabilities.

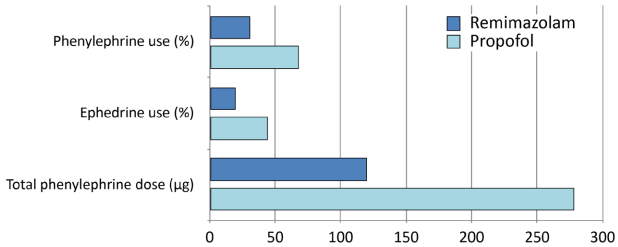
5.4. Cardiovascular Considerations and Paradoxical Responses

While remimazolam generally promotes hemodynamic stability compared to other anesthetic agents, isolated case reports have documented unexpected hypertensive responses during cardiac surgery procedures [17]. These reports suggest the potential for atypical cardiovascular reactions in specific clinical contexts, particularly in patients with underlying cardiovascular diseases, or during procedures involving significant physiological stress.

These paradoxical cardiovascular responses, while rare, underscore the importance of continuous hemodynamic monitoring during remimazolam administration, and the need for clinicians to remain vigilant for unexpected cardiovascular changes. Several mechanistic hypotheses may explain these atypical responses. First, remimazolam's selective binding to specific GABA-A receptor subunits (α_1, α_2, α_3, and α_5) may produce differential effects in patients with altered receptor expression patterns due to chronic cardiovascular disease [5]. Second, reflex sympathetic activation could occur in response to remimazolam-induced peripheral vasodilation, particularly in patients with impaired baroreceptor sensitivity or pre-existing sympathetic hyperactivity. Third, the stress of cardiac surgery may unmask latent cardiovascular instability that becomes apparent when combined with remimazolam's unique pharmacological profile. These mechanisms highlight the complex interactions between remimazolam's pharmacological effects and the underlying cardiovascular pathophysiology in susceptible patients (**Figure 4**).







Procedure Type	Remimazolam	Propofol	P-value
Cardiopulmonary bypass	87.3% stable	62.1% stable	P < 0.01
Transcatheter interventions	92.5% stable	76.8% stable	P < 0.01
ASA III-IV patients	18.2% hypotension	42.7% hypotension	P < 0.01

Hemodynamic outcomes demonstrating remimazolam's cardiovascular advantages with superior hemodynamic stability during high-risk procedures compared to propofol [7] [8]. Hemodynamic stability was seen in 87.3% of cardiopulmonary bypass procedures with remimazolam versus 62.1% with propofol ($P < 0.01$), while stability was seen in 92.5% versus 76.8% transcatheter interventions, respectively ($P < 0.01$). ASA III-IV patients experienced significantly reduced hypotension rates (18.2% vs. 42.7%, $P < 0.001$), supporting remimazolam's utility in cardiac surgery and high-risk cardiovascular procedures [19]-[21].

Figure 4. Hemodynamic stability: remimazolam versus propofol.

6. Remimazolam in Specialized Populations and for Advanced Clinical Applications

6.1. Elderly Patient Management and Super-Elderly Experience

Japanese investigators have made particularly significant contributions to understanding remimazolam's clinical performance in elderly patients, including groundbreaking case reports documenting its successful use in super-elderly patients exceeding 90 years of age [18]. These reports demonstrate that remimazolam can provide safe and effective anesthesia management in this challenging population without significant hemodynamic perturbation, supporting its potential value in geriatric anesthesia where traditional agents may pose excessive risks.

However, post-marketing surveillance data suggest that increased vigilance is warranted in elderly populations due to reports of higher adverse event rates, creating a nuanced clinical picture that requires careful balance between the potential benefits and recognized risks of remimazolam [14]. This apparent contradiction between case report successes and surveillance data highlights the complexity of elderly patient management and the importance of individualized risk assessment.

Clinical experience in elderly patients has also provided valuable insights into age-related pharmacokinetic and pharmacodynamic differences that influence dosing requirements and recovery characteristics. While the fundamental pharmacological profile remains consistent across age groups, subtle differences in drug sensitivity and clearance may require clinical consideration and potentially modified dosing protocols in very elderly patients.

6.2. Cardiac Surgery Applications and Hemodynamic Advantages

Multiple Japanese case series have documented successful remimazolam implementation across a broad spectrum of cardiac surgical procedures, providing compelling evidence for its utility in this demanding clinical context [19]-[21]. These applications have encompassed complex procedures, including cardiopulmonary bypass operations, transcatheter aortic valve implantations, and MitraClip implantations in patients with advanced heart failure.

The consistent theme emerging from these cardiac surgery reports is remimazolam's primary clinical advantage of maintenance of hemodynamic stability, although the reports also emphasize that careful monitoring remains essential despite this favorable profile [19]-[21]. The hemodynamic stability observed in cardiac surgery patients represents a particularly valuable characteristic, as these procedures often involve patients with compromised cardiovascular reserve who have poor tolerance for anesthesia-induced hypotension or cardiac depression.

The success of remimazolam in cardiac surgery applications has important implications for anesthesia management in high-risk cardiovascular patients across a broader range of procedures. The demonstrated hemodynamic stability in these challenging cases also provides evidence-based support for remimazolam use in other clinical contexts where cardiovascular stability is paramount.

6.3. Postoperative Delirium: A Distinguishing Safety Feature

One of the most clinically significant findings to emerge from the five-year experience with remimazolam usage is the evidence regarding the risk of postoperative delirium. A landmark prospective cohort study involving 200 elderly cardiovascular surgery patients demonstrated that remimazolam administration was not associated with an increased risk of postoperative delirium compared to other anesthetic agents, with delirium rates of 30.3% versus 26.6% respectively ($P = 0.63$) [22].

This finding represents a potentially paradigm-shifting observation that distinguishes remimazolam from other benzodiazepines, which have traditionally been associated with an increased delirium risk in vulnerable populations. The clinical implications of this finding are profound, as postoperative delirium represents a serious complication associated with increased morbidity, mortality, duration of hospitalization, and healthcare costs. The ability to utilize a benzodiazepine-based anesthetic without increased delirium risk could represent a significant clinical advantage of remimazolam, particularly in elderly patients undergoing major surgery [22].

The mechanism underlying this apparent protection against delirium remains unclear, but may relate to remimazolam's unique pharmacokinetic profile and rapid clearance, which may minimize the prolonged central nervous system effects associated with the development of delirium. This finding warrants further investigation through larger, randomized studies to confirm and extend these preliminary observations.

6.4. Complex Medical Conditions: Case Study Evidence

Japanese case reports have documented successful remimazolam implementation across an impressive range of complex medical conditions, providing valuable evidence for its safety and efficacy in challenging clinical scenarios. These conditions have included myotonic dystrophy type 1, where neuromuscular dysfunction creates significant anesthetic challenges [23], amyotrophic lateral sclerosis, where respiratory compromise is a constant concern [24], and hemodialysis patients with compromised fluid and electrolyte balance [25].

Additional case reports have documented successful use of remimazolam in patients with Child-Pugh C liver cirrhosis, where altered drug metabolism creates significant pharmacokinetic concerns [26], MELAS syndrome, where mitochondrial dysfunction affects multiple organ systems [27], and suspected malignant hyperthermia susceptibility, where avoidance of triggers is paramount [28]. The consistent success reported across these diverse and challenging conditions suggests that remimazolam's favorable pharmacological profile translates into clinical benefits across a broad spectrum of medical complexity.

These case reports consistently emphasize hemodynamic stability and predictable recovery as key advantages of the drug in medically complex patients, supporting the theoretical expectations derived from remimazolam's pharmacologi-

cal profile. While individual case reports cannot establish definitive clinical recommendations, the accumulated experience across diverse conditions provides reassuring evidence of remimazolam's safety and utility in challenging clinical scenarios where traditional anesthetic agents might pose excessive risks.

6.5. Considerations in Pediatric Patients and Gaps in Clinical Development

Despite five years of extensive adult clinical experience, the pediatric applications of remimazolam remain significantly limited, representing one of the most important gaps in current clinical knowledge. A recent comprehensive review emphasized that while remimazolam's fundamental pharmacological properties suggest potential pediatric advantages, "routine use in pediatric populations remains underexplored and unestablished" [29]. This limitation reflects both regulatory requirements for pediatric-specific clinical trials, and the challenges inherent to conducting anesthetic research in vulnerable pediatric populations.

Due to the limited availability of pediatric data, the effects of age-related differences in drug metabolism that might significantly influence remimazolam's clinical performance in children are unclear. Particularly concerning is the reduced carboxylesterase 1 (CES1) activity observed in neonates, which may substantially affect remimazolam pharmacokinetics, necessitating age-specific dosing strategies that have yet to be systematically investigated [29]. These metabolic differences could potentially lead to prolonged drug effects or altered recovery characteristics in very young patients, emphasizing the importance of systematic pediatric pharmacokinetic studies before widespread clinical application of the drug in pediatric populations.

The pediatric knowledge gap represents both a clinical limitation and a significant research opportunity. Given remimazolam's favorable safety profile in adult populations and its theoretical advantages in pediatric applications, systematic investigation of its pharmacology and clinical performance in pediatric patients represents a high priority for future research efforts. Such studies could potentially expand remimazolam's clinical utility to encompass the full age spectrum of patients requiring anesthetic care.

7. Comparative Analysis with Existing Anesthetic Agents

7.1. Advantages over Propofol: Clinical Validation

Five years of clinical experience have comprehensively validated the theoretical advantages of remimazolam over propofol that were initially proposed based on pharmacological considerations. The clinical reality has confirmed reduced cardiovascular depression, with a significantly lower incidence of hypotension during anesthesia induction and maintenance. Complete elimination of the injection site pain associated with propofol injection represents a substantial improvement in patient comfort and satisfaction, particularly important in ambulatory settings where patient experience directly influences procedure acceptance [1] [7].

Absence of the risk of propofol infusion syndrome-like effects with remimazolam has proven clinically significant, particularly in intensive care applications where prolonged anesthetic infusions are sometimes required. The water-soluble formulation of remimazolam eliminates the lipid load associated with propofol administration, reducing complications related to hyperlipidemia and bacterial contamination risk. Most significantly, perhaps, availability of a specific antagonist (flumazenil) to remimazolam provides a safety advantage that has proven valuable in clinical practice, offering the ability to rapidly reverse anesthetic effects when clinically indicated [1] [7]. However, clinical use of flumazenil requires careful consideration of several important factors. Flumazenil has a shorter elimination half-life (approximately 1 hour) compared to remimazolam, creating the potential risk of re-sedation if remimazolam plasma concentrations remain elevated after flumazenil effects dissipate. This risk is particularly relevant following prolonged remimazolam infusions or in patients with impaired drug clearance. Additionally, flumazenil administration may precipitate withdrawal symptoms in patients with chronic benzodiazepine use, and can potentially lower the seizure threshold in susceptible individuals. Therefore, while flumazenil represents a valuable safety advantage, its use requires ongoing patient monitoring and readiness for repeat administration if re-sedation occurs [30].

7.2. Advantages over Midazolam: Kinetic Superiority

Compared to midazolam, remimazolam offers substantial pharmacokinetic advantages that have been consistently confirmed through clinical experience. The significantly shorter context-sensitive half-time, approximately one-fifth that of midazolam, ensures more predictable offset characteristics regardless of infusion duration. This kinetic advantage translates into reduced individual variability in recovery times and lower potential for drug interactions, both clinically significant benefits [1] [2].

The clinical implications of these kinetic differences extend beyond simple recovery times to encompass broader aspects of perioperative care efficiency and patient flow in busy surgical and procedural environments. The predictable recovery characteristics associated with remimazolam use facilitate more accurate scheduling and resource allocation, while reducing the risk of prolonged recovery that can complicate ambulatory care pathways.

7.3. Environmental and Sustainability Considerations

As healthcare systems increasingly focus on environmental sustainability and carbon footprint reduction, remimazolam's profile as an intravenous agent offers significant advantages over volatile anesthetics. Elimination of volatile agent emissions reduces the environmental impact and aligns with growing sustainability initiatives within healthcare organizations [1]. This environmental advantage, while perhaps secondary to clinical considerations, represents an important additional benefit that supports remimazolam adoption in environmentally conscious

healthcare systems.

8. Future Directions and Emerging Clinical Applications

8.1. Ongoing Research Initiatives and Clinical Questions

Current research efforts are focused on addressing the most significant knowledge gaps that have emerged during the five years of clinical experience with remimazolam. Pediatric pharmacokinetics and safety studies represent the highest priority, given the substantial pediatric patient population that could potentially benefit from remimazolam's favorable characteristics. Separately, intensive care unit sedation protocols with remimazolam are under active investigation, building upon the favorable hemodynamic profile of the drug observed in surgical applications, to explore its utility in critically ill patients requiring prolonged sedation.

Combination techniques with other anesthetic agents represent another area of active investigation, as clinicians explore methods to optimize anesthetic protocols by leveraging remimazolam's unique properties in conjunction with complementary agents. Health economic evaluations are increasingly important, as healthcare systems seek evidence-based justification for adoption of higher-cost agents, requiring systematic assessment of remimazolam's cost-effectiveness relative to established alternatives.

Long-term neurocognitive effects also represent a particularly important area of ongoing investigation, given the growing recognition of perioperative neurocognitive disorders and the potential for anesthetic agents to influence long-term cognitive outcomes. The preliminary evidence suggesting reduced delirium risk with remimazolam warrants extensive investigation to determine whether this benefit extends to longer-term cognitive outcomes.

8.2. Clinical Practice Integration and Optimal Utilization

Five years of clinical experience have begun to define optimal utilization patterns for remimazolam, identifying specific clinical scenarios where its unique properties provide maximum benefit. Hemodynamically unstable patients represent a primary target population, where remimazolam's cardiovascular stability offers clear advantages over alternatives. Elderly patients requiring rapid and predictable recovery constitute another important application, although the use of remimazolam in geriatric patients should be balanced against the increased vigilance required due to an elevated adverse event risk in this population.

Ambulatory procedures requiring predictable offset characteristics represent an ideal application for remimazolam, where the rapid and consistent recovery facilitates efficient patient flow and reduces the risk of delayed discharge. Patients at elevated risk for propofol-related complications, including those with cardiovascular compromise or propofol allergy, represent another important target population in whom remimazolam may offer superior safety profiles.

Cases requiring potential anesthetic reversal represent a unique application of remimazolam, since its reversibility with flumazenil provides a safety advantage

unavailable with other anesthetic agents. This capability may prove particularly valuable in diagnostic procedures where rapid awakening is desired, or in emergency situations where anesthetic reversal might be clinically necessary (Figure 5).

Timeline of major developments since Japan's first-in-world approval in January 2020 [1] [13]. Key regulatory milestones included US FDA approval for procedural sedation (July 2020), EU approval (March 2021), Chinese NMPA approval (September 2021), and South Korean approval (June 2022). Critical safety findings included the FAERS analysis revealing age-related adverse event patterns (January 2022) [14] and documentation of rare anaphylactic reactions (May 2023) [16]. Clinical evidence milestones included hemodynamic advantages during cardiac surgery (December 2022) and confirmation of no increase in postoperative delirium risk (April 2024) [22]. The timeline demonstrates successful translation from pharmacological innovation to established clinical utility across diverse patient populations and clinical applications.

Figure 5. Five years of remimazolam: clinical and regulatory milestones.

8.3. Limitations and Clinical Constraints

Clinical experience has also identified relative limitations that constrain remimazolam's optimal utilization. The slower onset compared to propofol requires modification of standard induction techniques, and may limit its applicability in rapid sequence induction scenarios where immediate loss of consciousness is paramount. The potential for rare anaphylactic reactions, while uncommon, requires preparedness for emergency management, and may influence risk-benefit calculations in certain patient populations.

Its higher acquisition cost compared to generic alternatives may initially appear to limit its adoption in resource-constrained environments, but this must be evaluated within the broader context of healthcare economics and value-based care. The drug's benefits, including faster and more predictable recovery, reduced injection site pain, superior hemodynamic stability, and decreased risk of complications, may translate into significant cost savings through improved operating

room efficiency, reduced recovery time, decreased need for post-operative monitoring, and enhanced patient satisfaction scores. In ambulatory surgery settings, where rapid patient turnover and predictable discharge times are economically critical, remimazolam's reliable pharmacokinetic profile may offset its higher acquisition cost through improved facility utilization and reduced staffing requirements. Therefore, comprehensive health economic evaluations considering total cost of care, rather than drug acquisition cost alone, are necessary to accurately assess remimazolam's cost-effectiveness in specific clinical contexts [31] [32].

9. Conclusions

The five-year milestone since Japan's pioneering approval of remimazolam provides an appropriate temporal vantage point from which to assess this agent's impact on anesthetic practice, and its evolving role in modern perioperative care. The accumulated clinical experience, spanning diverse patient populations, varied surgical procedures, and multiple clinical contexts, has established remimazolam as a valuable and distinctive addition to the anesthetic pharmacopeia. Japanese investigators who pioneered remimazolam's clinical development deserve particular recognition for their foundational contributions to both, initial drug development and the ongoing expansion of clinical understanding through systematic post-marketing investigation.

The evidence strongly supports remimazolam's particular value in clinical scenarios requiring hemodynamic stability, predictable recovery characteristics, and potential for anesthetic reversal. The demonstrated non-inferiority to propofol in terms of anesthetic efficacy, combined with superior cardiovascular stability and elimination of injection site pain, provides compelling clinical advantages that have been consistently validated across multiple studies and diverse patient populations. The unique finding of no increased postoperative delirium risk distinguishes remimazolam from other benzodiazepines, and suggests potential cognitive advantages that warrant further investigation.

Conversely, while the overall safety profile of remimazolam has proven favorable across five years of clinical experience, post-marketing surveillance has identified rare but serious adverse events that require clinical attention and ongoing vigilance. Of particular concern is anaphylactic reactions in elderly patients, which emphasizes the importance of appropriate patient selection, preparation for emergency management, and continued pharmacovigilance efforts. These safety considerations do not negate remimazolam's clinical utility, but rather inform appropriate risk management strategies that can minimize potential complications while preserving its clinical benefits.

The unique pharmacological properties of remimazolam, successfully combining the familiar benzodiazepine receptor profile with ultra-short duration characteristics, have fulfilled the promise articulated by Masui in 2020, of providing "advantages beyond existing anesthetics". The clinical reality has validated these theoretical expectations, demonstrating that rational drug design can successfully ad-

dress long-standing limitations of existing agents while preserving their beneficial characteristics.

As clinical experience continues to accumulate and expand to encompass additional patient populations and clinical applications, remimazolam's role in modern anesthetic practice will likely continue to evolve and expand. The five-year milestone does not represent an endpoint in clinical development, but rather a solid foundation upon which continued advancement in anesthetic care can be built. Future research priorities should emphasize pediatric applications, health economic evaluations, and optimization of clinical protocols to maximize the clinical benefits of remimazolam, while minimizing rare but serious risks.

The success of remimazolam development and implementation also provides valuable lessons for future anesthetic drug development, demonstrating that systematic clinical investigation, international collaboration, and careful post-marketing surveillance can successfully translate pharmacological innovation into meaningful clinical advancement. The Japanese experience with remimazolam serves as a model for evidence-based drug development and implementation that has global relevance and applicability.

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Conflicts of Interest

The author declares that there are no conflicts of interest related to any commercial entities, including those mentioned in this manuscript.

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