

Clinical Application and Research Progress of Remimazolam for Pediatric Patients

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Abstract: Remimazolam is a novel ultrashort-acting benzodiazepine that allosterically modulates γ -aminobutyric acid type A (GABAA) receptors to exert sedative effects. Remimazolam has the properties of controllable sedation, rapid onset, and a short duration of action, along with minor depression of circulation and respiration. Remimazolam has been approved for clinical use since 2020 in Japan, and it has been applied for procedural sedation, general anesthesia induction and maintenance, and sedation in ICU patients, and has been proven to be safe and effective. Currently, no consensus has been reached on the clinical application of remimazolam in pediatric patients. This review introduces the clinical research progress and limitations of remimazolam in recent years, aiming to supply scientific guidance and a theoretical reference for the application of remimazolam in pediatric anaesthesia.

Keywords: remimazolam, sedation, pediatric patient, clinical anesthesia

Introduction

With the popularization of comfortable medical services, optimizing perioperative medication, reducing the occurrence of adverse events, and promoting early recovery has always been a goal in pediatric anesthesia. Perioperative traumatic experiences increase the risk of long-term psychological problems in children.¹ Therefore, adequate sedation is vital for pediatric patients. The commonly used sedative drugs for children, including propofol, dexmedetomidine, midazolam and sevoflurane, produce different types of adverse reactions, which restrict their applications. The incidence of propofol injection pain and respiratory depression is high, and prolonged sedation with propofol has been associated with propofol infusion syndrome (PRIS).^{2,3} Circulatory depression and a slow onset of action are common for dexmedetomidine.⁴ The incidence of hypoxemia and tachycardia is higher with midazolam.⁵ For sevoflurane, malignant hyperthermia (MH), intraoperative airway and circulatory adverse effects and emergence agitation on postoperative recovery reduce perioperative safety in pediatric patients.^{6,7} Remimazolam, an ester analogue of midazolam, is another product based on the concept of “soft drugs” (Figure 1). Remimazolam produces no injection pain and minor respiratory and circulatory depression, and does not increase the risk of postoperative nausea and vomiting (PONV), suggesting that it could play a role in pediatric anesthesia.² This paper presents the pharmacological properties and advantages of remimazolam in pediatric patients and reviews the current status and limitations its clinical applications to provide a reference for medication safety and subsequent research.

Pharmacokinetics and Pharmacodynamic Characteristics of Remimazolam

Remimazolam is a midazolam derivative, mainly including two salt forms of benzenesulfonate and toluenesulfonate (Figure 2). Due to the introduction of a methyl propionate side chain, it can be hydrolysed by carboxylesterase (CES) in the liver and eliminated by first-order kinetics to produce the inactive metabolite CNS7054 (Figure 3).⁸ Remimazolam has a high affinity for GABAA receptors (inhibition constant (K_i) = 30 nmol/L) and no selectivity among receptor subtypes. Remimazolam can weakly inhibit the tail current of the ether-a-go-go related gene (hERG) channel and act by a positive allosteric modulation of the GABAA receptor–chloride channel complex, which then hyperpolarizes the

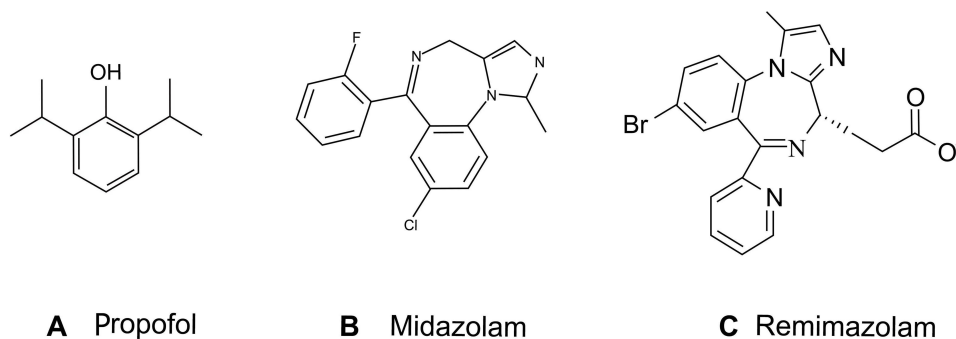


Figure 1 Chemical structures of propofol (A), midazolam (B), and remimazolam (C).

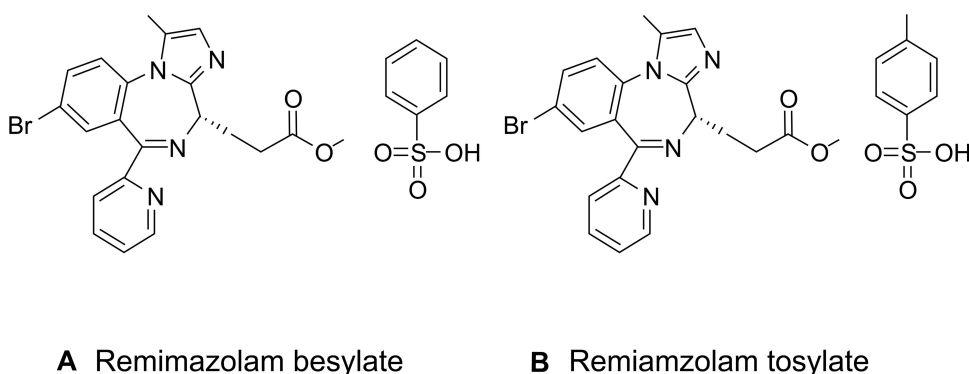


Figure 2 Chemical structures of remimazolam besylate (A), remimazolam tosylate (B).

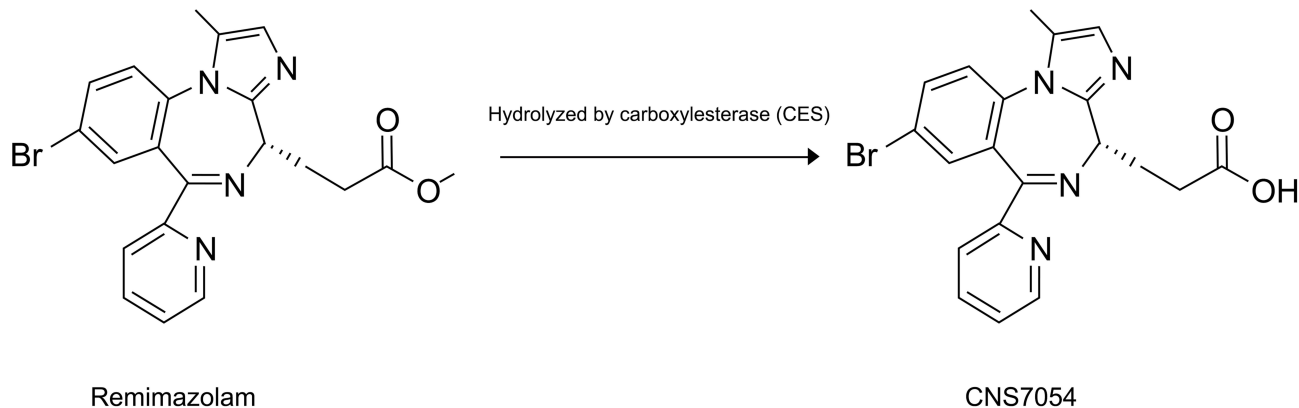


Figure 3 Catabolic process remimazolam and the carboxylic acid metabolite CNS7054.

membrane through the influx of chloride ions, resulting in sedation, anticonvulsant effects, and anterograde amnesia.^{9,10} Animal experiments have also shown that remimazolam can produce sedative effect by dose-dependently inhibiting the firing of substantia nigra pars reticulata neurons which receive a prominent GABAergic innervation by striatonigral afferents.¹¹ Population pharmacokinetic studies indicate that factors such as age and weight have no effect on remimazolam metabolism.⁸ Gao et al¹² used a three-compartment model to analyse the pharmacokinetics of remimazolam and CNS7054 in arterial blood samples from 24 children aged 3 to 6 years. The results show that remimazolam has high clearance rates of 15.9 [12.9–18.2] mL/kg/min (median [IQR]), a small volume of distribution of 0.11 [0.08–0.14] L/kg and a short terminal half-life of 67 [49–85] min. The 4-hour context-sensitive half-time (CSHT) of remimazolam in children is 17 [12–21] min, which is comparable to that of propofol, indicating that remimazolam has a rapid decay curve

similar to that of propofol. Notably, the weight-corrected pharmacokinetic characteristics of remimazolam in children are similar to data from previous studies in adults.¹³ In addition, Masui et al⁸ found that the blood remimazolam concentration in adult women was higher than that in men during the initial and maintenance periods of administration, which may be related to higher CES activity in adult women. Due to the restricted use of remimazolam in children, no current trial has explored sex differences in the blood concentrations of remimazolam in pediatric patients.

A cohort study¹⁴ involving 418 children (4.6 ± 4.52 years) (mean $\pm$ SD) showed that after 109.4 ± 83.1 min intravenous infusion, the mean time of remimazolam (induction dose 12 mg/kg/h, maintenance dose 1–2 mg/kg/h) from ceasing administration to spontaneous eye-opening was 34.3 ± 15.8 min, which was longer than the time in adults (average 19 min).¹⁵ The discrepancy may have been due to differing degrees of sedation in the presence or absence of endotracheal intubation between children and adults in the abovementioned studies. Research results show that whether it is a solid form or a solution, intranasal remimazolam administration (dose 0.2–0.4 mg/kg) can produce significant sedation, and the onset and peak of effects (5 min, 10 to 20 min) are prolonged compared with intravenous administration in adults.¹⁶ The onset of effects for children after intranasal administration (initial dose 0.5 mg/kg) was 5.00 ± 1.47 min (toddlers) and 4.68 ± 1.33 min (preschool children), in accord with the results of previous adult studies.⁸ The ED₉₅ of remimazolam for relieving preoperative anxiety in toddlers and preschool children was 1.57 mg/kg and 1.09 mg/kg, respectively.¹⁷

Current Status of Applications of Remimazolam

General Anesthesia

The availability of remimazolam for general anesthesia in adults has been widely established. The advantages of remimazolam in inhibiting the systemic inflammatory response, reducing perioperative stress, and balancing autonomic nervous activity make it a sedative with a wide range of applications.^{18–20} General anesthesia is the preferred choice for pediatric patients. However, inhalation anaesthetics combined with mask induction may further cause preoperative anxiety in children. Therefore, total intravenous anesthesia (TIVA) is more suitable for pediatric patients.²¹ Remimazolam can not only effectively relieve preoperative anxiety but also reduce the risk of postoperative delirium and mania in children after sevoflurane anesthesia, which contributes to shortening hospitalization, reducing the medical burden, and improving parent satisfaction.^{6,22} Remimazolam has not been approved by the FDA for use in pediatric patients and was first approved in 2020 for general anesthesia in adults (Figure 4). At present, remimazolam is only used in a few licenced health care facilities. Yu - Bo Fang et al²³ designed a multicentre, single blind, randomized controlled study to explore the non inferiority of remimazolam tosylate versus propofol used to reduce the incidence of adverse events during general anesthesia in preschool children (3–6 years). However, current research is at the stage of patient enrolment. The ultrashort-acting sedative effect of remimazolam may have unique value for reducing the incidence of postoperative delirium and emergence agitation in pediatric patients. A prospective, double-blind, randomized, placebo-controlled study showed that the risk of delirium after anesthesia with sevoflurane was reduced by the intraoperative administration of remimazolam (0.2 mg/kg) before the end of surgery in children aged 3 to 7 years undergoing adenotonsillectomy, without prolonging recovery time in the postanesthesia care unit (PACU).²² Mo et al⁶ found that a low of remimazolam (0.1 mg/kg) significantly reduces the incidence of emergence agitation without affecting recovery



Figure 4 The milestones in the development of remimazolam.

Note: Data from Kilpatrick GJ. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. *Front Pharmacol.* 2021; '90875. Published 2021 Jul 20. Doi: 10.3389 / fphar. 2021.690875.¹⁰ and Kimoto Y, Hirano T, Kuratani N, et al. Remimazolam as an Adjunct to General Anesthesia in Children: Adverse Events and Outcomes in a Large Cohort of 418 Cases. *J Clin Med.* 2023; '3930. Published 2023 Jun 8. Doi:10.3390/jcm12123930.¹⁴

and improves the safety of preschoolers undergoing day surgery after discharge. The dose–response relationship and long-term effects of remimazolam on reducing the incidence of postoperative delirium and emergence agitation after anesthesia with sevoflurane need further assessment in the future.

The current application of remimazolam in pediatric patients additionally includes several clinical cases. Yamadori et al²⁴ reported a case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) in a 10-year-old girl undergoing gastrostomy who was safely treated with remimazolam for the induction and maintenance of general anesthesia. Previous reports have identified the risks of several anaesthetics in patients with mitochondrial diseases, including PRIS, MH, and seizure-like symptoms, especially in pediatric patients.^{3,7} The antiepileptic effects of remimazolam have the potential to provide a new sedative option for MELAS in epilepsy patients. Additionally, remimazolam may have good application value in MH-susceptible patients. A previous *in vitro* experiment showed that remimazolam did not promote caffeine-mediated increases in intracellular calcium concentrations in human embryonic kidney 293 (HEK-293) cells, even at concentrations 100 times higher than those used in clinical practice.²⁵ Petkus et al²⁶ safely used remimazolam (infusion rate 5–7 µg/kg/min) for maintenance of anesthesia in a 6-year-old child with a family history of MH who was undergoing dental surgery. Moreover, the amplitude of the motor evoked potential (MEP) is reduced by inhaled anaesthetics such as sevoflurane and desflurane, which may affect the detection of neurological function.²⁷ Therefore, TIVA is recommended for spinal surgery. A case report of a 17-year-old girl with Alström syndrome undergoing orthopedic surgery for scoliosis showed that remimazolam may have high application value for the sedation with of patients with Alstrom syndrome who are at risk of hypertriglyceridaemia and hepatic insufficiency. Research has shown that varying the administration rate of remimazolam from 0.5 mg/kg/h to 1.0 mg/kg/h has no effect on the MEP amplitude.²⁸ In addition, Kamata et al²⁹ showed that remimazolam could be used as an alternative sedative agent to propofol for MEP monitoring in neurosurgery, even for immature toddlers with neurodevelopment. Inhalation anaesthetics or a prolonged infusion of propofol will reduce the capacity for fatty acid utilization and mitochondrial activity, and thus increase the risk of rhabdomyolysis. Studies of adults have shown that remimazolam and its antagonist flumazenil have no significant effects on fatty acid metabolism and are good options for anesthesia management in children with muscular dystrophy and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.^{30–32} In conclusion, remimazolam is suitable for patients who need MEP monitoring and avoid inhaled anaesthetics.

Sedation Outside the Operating Room

The demand for pediatric patients to receive endoscopy and imaging examinations has increased significantly. Adequate sedation can relieve children's anxiety and improve the accuracy of examinations. The efficacy and safety of remimazolam for procedural sedation in adults have been documented, but the application of remimazolam in pediatrics remains limited.

Gastrointestinal Endoscopy

Some patients are at higher risk of drug accumulation and delayed recovery from propofol, which lacks effective antagonists. The safety and efficacy of remimazolam for gastroscopy or colonoscopy in pediatric patients looks comparable to propofol. A study investigating the safety and efficacy of remimazolam during painless gastroscopy in 60 children aged 1 to 6 years showed that compared with the propofol (initial dose 2 mg/kg; supplemental dose 0.5 mg/kg) group, the onset time in the remimazolam (initial dose 0.2 mg/kg; supplemental dose 0.05 mg/kg) group was significantly longer (129.28 ± 45.27 s vs 80.35 ± 37.29 s), but the emergence time under remimazolam was shorter ($8.8.6 \pm 2.05$ min vs $11.93.7 \pm 2.29$ min). The success rate of sedation was 100% in both groups.³³ A study of a 15-year-old child with multiple drug and food allergies who underwent oesophagogastrroduodenoscopy showed that low-dose of remimazolam besylate (initial dose 0.03 mg/kg; maintenance dose 20 µg/kg/min) was equally safe under spontaneous ventilation and a natural airway.³⁴ In addition, remimazolam significantly reduced the incidence of injection pain based on the phenol structure and improved the comfort of children undergoing gastroscopy, consistent with previous studies.³⁵

Bronchofibroscope

Due to airway hyperresponsiveness during fibreoptic bronchoscopy, children are prone to bronchospasm during bronchoscopic lavage. Therefore, cough, breath hold and bronchospasm caused by lavage must be avoided to recover quickly after

the procedure. Previous studies have shown that moderate sedation with 0.2 mg/kg remimazolam is safe and effective for bronchoscopy in adults.³⁶ Zhao et al³⁵ randomly divided 50 children with a mean age of 5 years into a remimazolam group (induction dose 0.2 mg/kg) and a midazolam group (induction dose 0.05 mg/kg) to explore the safety and efficacy of remimazolam in children undergoing fibreoptic bronchoscopic lavage. In this study, children who received remimazolam had a lower incidence of injection pain than children who received midazolam for anesthesia and no significant differences in haemodynamic indices or postoperative recovery after lavage were detected between groups. Remimazolam has the unique advantages of rapid awakening and reversal, suggesting that it may have special value for bronchoscopy in pediatric patients. In addition, although effective airway surface anesthesia during fibreoptic intubation (FOI) improves children's tolerance, some degree of sedation is necessary. The short CSHT of remimazolam and its ease of titration by continuous infusion may make it an appropriate choice for sedation during FOI in children. Hughes et al³⁷ reported the successful use of remimazolam (15 µg/kg/min) and remifentanyl (0.05 µg/kg/min) for analgesia and sedation in a 12-year-old boy with postburn neck contracture and FOI was completed. This result suggests that the potential of remimazolam to preserve spontaneous breathing and rapidly reverse sedation is extremely important in patients who are difficult to intubate.

Cardiac Ultrasonography

Infants and young children are usually unable to cooperate in completing cardiac ultrasonography during wakefulness. Yang et al³⁸ randomly divided 46 infants aged 5 to 18 months who were undergoing cardiac ultrasound into a remimazolam group (0.3 mg/kg, iv) and a dexmedetomidine group (2 µg/kg, in). The results showed that the fall asleep time (2.05 ± 0.69 min) and awakening time (5.74 ± 1.42 min) of infants who received remimazolam were significantly shorter than those of infants who received dexmedetomidine, and no differences in safety were evident between the two groups. These results revealed that intravenous remimazolam (0.3 mg/kg) can achieve a good sedation outcome, and rapid awakening, and can meet the needs of infants who require sedation to undergo cardiac ultrasonography.

Outpatient Root Canal Treatment

Zhang et al³⁹ found that the administration of remimazolam besylate (induction dose 0.2 mg/kg; maintenance dose 0.3 mg/kg/h) combined with low-dose propofol (induction dose 1 to 3 mg/kg; maintenance dose 6 to 12 mg/kg/h) to 2 to 6-year-old children undergoing root canal treatment with preserved spontaneous breathing can achieve a shorter recovery time, a lower propofol requirement, and a lower incidence of intraoperative hypotension, hypoxemia, and body movement than propofol alone, consistent with previous findings.⁴⁰ The dosing regimen could be the current ideal sedative approach for root canal treatment.

Antagonistic Effect of Flumazenil

Flumazenil can quickly reverse the hypnotic effect of remimazolam, shorten the postoperative extubation time in children, allow spontaneous breathing after failed intubation and avoid delayed awakening in children with congenital metabolic diseases, which improves the safety and controllability of remimazolam anesthesia.^{32,37,41} The FDA-approved doses of remimazolam for benzodiazepine reversal when used for pediatric patients (children 1 year and older and adolescents) receiving conscious sedation or general anesthesia are the initial dose of 0.01 mg/kg given over 15 seconds (up to a maximum dose of 0.2 mg). If no desired return of consciousness is noted after 45 seconds, repeat 0.01 mg/kg (up to 0.2 mg) at 1-minute intervals as needed. The maximum total dose should not exceed 1 mg or 0.05 mg/kg. Shannon et al⁴² confirmed flumazenil quickly and efficiently reverses the sedative effects of midazolam in children (aged 1 to 17 years) undergoing conscious sedation (76% patients experienced an increase of ≥ 2 points in OAA/S score at 10 minutes after flumazenil administration) according to the dosage regimen, with no significant adverse effects. At present, the routine use of flumazenil cannot be recommended. Because the CSHT of flumazenil (50 min) is similar to that of remimazolam (0.75 h), even if the recommended dose of flumazenil is administered, clinicians still need to be alert to the possibility of resedation in pediatric patients and should be monitored for 1 to 2 hours after flumazenil administration.^{42–44} A retrospective study showed no obvious difference in the wake time between children who did and did not receive flumazenil (34.7 ± 11.07 min vs 34.2 ± 15.5 min).¹⁴ In the future, the dosing parameters of flumazenil should be set to determine whether it is beneficial for the recovery of pediatric patients.

Assessment of Remimazolam-Mediated Sedation

The EEG indicators currently used, such as the bispectral index (BIS), patient state index (PSI), and the Narcotrend index, are methods for assessing the extent of sedation based on EEG algorithms that are used for adult EEG. Thus, their accuracy in children remains to be determined.⁴⁵ Given that the nervous system undergoes significant changes during the development, the anesthetic-induced EEG changes for children may be different from those for adults. Lee et al⁴⁶ showed that propofol-induced EEG oscillations were qualitatively similar among patients aged one year through adulthood (slow and coherent alpha oscillations), but not for children under the age of one (noncoherent alpha oscillations). Age-related changes in remimazolam-induced EEG parameters in children have not been studied. To date, most clinical studies of children have administered remimazolam according to the recommended dose for adults and adjusted the dosing rate according to the BIS value.^{24,32,39} The BIS, however, may be insufficient due to the lack of age-related covariates for assessing the extent of sedation under remimazolam.⁴⁰ A study²³ showed that the modified observer's assessment of alertness/sedation (MOAA/S) scale may be the best index for optimal indices assessing the extent of sedation under remimazolam in adults, but the accuracy remains to be proven in children.

Rational Dosing Strategies for Remimazolam

Oral Route

Currently, the safety and efficacy of oral administration in pediatric patients are not established. In a study of 14 healthy adult subjects, Pesic et al⁴⁷ found that the oral bioavailability of remimazolam was low (1.2% to 2.2%), which means that the sedative effects of remimazolam by oral administration might be limited, and higher doses are needed compared with intravenous route. Remimazolam possesses a specific bitter taste, suggesting that oral administration may be difficult in children.

Intranasal Route

In 1988, Wilton et al⁴⁸ first reported the safety and reliability of the intranasal administration of midazolam for relieving preoperative anxiety in preschool children. However, some studies have reported that some children may present residual drug after intranasal administration. As a midazolam derivative, remimazolam has a short duration of action and inactive metabolites. Long et al¹⁷ found that a single intranasal administration of remimazolam was effective at relieving preoperative anxiety in toddlers and preschool children. Notably, this effect of remimazolam was weakened after 20 minutes postadministration. This finding agrees with those of Antonik et al² regarding the pharmacokinetic parameters of intravenous remimazolam. Furthermore, studies showed that compared with the solution formulation, the retention time of the powder formulation of remimazolam on the nasal mucosa was prolonged, which in turn retarded the peak and action times. In addition, the severe pain associated with administration via the intranasal route in adults may have limited the administration of remimazolam via this route in children.¹⁶ For children who cannot cooperate or in emergency situations in which professionals have difficulty rapidly establishing intravenous access, the intranasal route (especially the solution) can still be used as a backup for administration.

Intravenous Route

Because remimazolam is only approved for adults, the current administered dose of remimazolam in pediatric patients is based on the recommended adult dose in the package insert and the medication experience in case reports. For procedural sedation, remimazolam should be formulated as 1 mg/mL solution with a single intravenous bolus loading dose of 5 mg and an additional dose of 2.5 mg (1 min interval) for adults. When remimazolam is used for general anesthesia, 2 mg/mL solution should be prepared and administered by continuous intravenous infusion using infusion pumps at a rate of 6 mg/kg/h (infusion time ≤ 3 min), and an additional 1 min at a rate of 12 mg/kg/h is allowed. Clinical practitioners can adjust the dosing speed to range between 1 and 3 mg/kg/h according to age and EEG parameters to maintain a suitable depth of anesthesia.⁴⁹ Jeong et al⁵⁰ used the sequential method to explore the ED₉₀ dose of 0.10 mg/kg/min (90% CI: 0.10–0.15 mg/kg/min) for reaching the loss of consciousness (LoC) within 2 minutes of general anesthesia induction with remimazolam in adults. In addition, studies have shown that the recommended dose for a single intravenous injection of remimazolam in adults is 0.075–0.30 mg/kg, and the degree of sedation increases with increasing doses of remimazolam.⁵¹ The bolus dosing

regimen, however, may cause instability of the concentration and sedative effects, which in turn extend children's recovery time.⁸ Target-controlled infusion (TCI) and computer-assisted sedation (CAS) may have potential value in shortening the postoperative recovery time in children.^{52,53} According to a recent study on children undergoing gastroscopy, the remedial sedation rate of the remimazolam group (initial dose 0.2 mg/kg) was significantly higher than that of the propofol group (initial dose 2 mg/kg) (90% vs 60%),³³ which may be attributed to the small initial dose of remimazolam. Future studies are needed to further determine the appropriate initial dose of remimazolam for pediatric patients.

Furthermore, Hirano et al⁵⁴ found that remimazolam alone may not achieve adequate sedation in some pediatric surgeries. Additionally, anesthesia achieved with multiple agents has been shown to alleviate adverse reactions or enhance the effect of drugs in clinical practice. Remimazolam exerts synergistic effect, and its sedative effect is enhanced when combined with other drugs (such as sedative hypnotics or opioids).⁵⁵ A recent study⁵⁶ has documented the special value of low-dose remimazolam combined with propofol TCI in reducing the dosage of drugs and avoiding delayed recovery from sedation during anesthesia maintenance. In a study of drug–drug interaction effects in cynomolgus monkeys aged 3 years, the extent of the dose reduction of remimazolam was 94% when administered in combination with opioids compared to when administered alone during deep sedation, which is comparable to that of midazolam (98%), and the dose reduction for propofol (61%) was noticeably lower.⁵⁷ However, the extent of reduction in the dose of remimazolam combined with opioids in clinical practice has not been nearly as high as that observed in animal studies. Therefore, when evaluating the dosage of remimazolam during the perioperative period, the effects on the synergy of remimazolam combined with other drugs during the dosage adjustment and recovery of pediatric patients should also be considered.

Adverse Reactions

Although the safety profile of remimazolam seems more favourable than those of other sedative drugs, adverse effects of remimazolam on pediatric patients still occur, such as hypotension,³³ hypoxia, increased secretions, lethargy upon waking,⁶ choking,³⁵ and bradycardia.³⁹ One report showed that remimazolam increased the risk of nausea and vomiting in children, which may be related to the fact that remimazolam does not produce a direct antiemetic effect similar to propofol.¹⁴ In bronchoscopy practices, 2 of the 25 children treated with remimazolam for general anesthesia induction and maintenance experienced intraoperative body movements, while no children treated with midazolam had intraoperative body movements.³⁵ Because the volume distribution of remimazolam is relatively small, a potential risk of overdose exists during rapid infusion in pediatric patients.¹² Anaesthetics currently used in clinical practice cause the nonphysiological activation of neuronal apoptosis programs during the peak developmental period in the brain, resulting in a permanent reduction in neuronal density in animal models.⁵⁸ However, rapid conversion to the inactive metabolite CNS-7054, accuracy of the dose adjustment and reversibility of sedation may reduce the neurotoxicity of remimazolam. Future studies are needed to further explore the short and long-term effects of remimazolam on neurodevelopment in pediatric patients.

Summary and Prospects

In summary, remimazolam, a novel benzodiazepine, has the advantages of a rapid onset, short duration of action, low level of injection pain, and rapid recovery of baseline neurological function. Remimazolam has the potential to become a sedative drug for pediatric patients during the perioperative period. At present, few relevant studies are available on remimazolam use in pediatric patients because remimazolam has not yet been approved by the US Food and Drug Administration (FDA). Future clinical research should focus on more clinically applicable dosing regimens, further clarify the effects of remimazolam on postoperative cognitive and functional recovery in children, continue to explore the potentials and limitations for clinical application when remimazolam combined with other drugs at different developmental stages or administration routes in children, and identify methods to accurately assess the sedative level of remimazolam in children to improve the economy, efficacy and safety of its clinical application.

Disclosure

The authors report no conflicts of interest in this work.

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