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Remimazolam: A New Ingress in Cardiac Surgical Intensive Care Unit

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ABSTRACT

Remimazolam is a novel intravenous ultrashort acting benzodiazepine that has a potential for safe and effective sedative. This recent addition in anesthesia armamentarium has a great role in procedural sedation and general anesthesia which is well-approved. The main beauty of this drug is, if needed its effects can be reversed by flumazenil which allows prompt termination of sedation. Remimizolam has fast predictive effect and recovery time, high procedural success rate, and minor respiratory and hemodynamic fluctuation when used for procedural sedation and general anesthesia. Although has a great potential for sedation in patients admitted to intensive care unit (ICU), some randomized trials are necessary to prove its long-term efficacy and safety in patients admitted to ICU.

Keywords: Remimazolam, Sedation, Intensive care unit

INTRODUCTION

Post-operative sedation is an essential component in recovery of patients undergoing cardiac surgery. The method of sedation gradually shifted from high-dose narcotic-based anesthetic to shorter-acting drugs. Propofol, fentanyl, dexmedetomidine, and benzodiazepines (BDZ) are the common agents. Comparison of BDZ versus non-BDZ regime showed a shorter duration of mechanical ventilation and intensive care unit (ICU) stay by non-BDZ regime. However, none of the studies emphasized on which alternative is best. Use of inotropes, vasodilators, and vasoactive medications makes sedation after cardiac surgery unique in comparison with the requirement for other ICUs.

Remimazolam besylate is a water-soluble, ultrashort acting γ-aminobutyric acid, GABA-A agonist, a recent addition to anesthetic armamentarium.[1] It was approved for sedation during gastroscopy in 2019 in China. Subsequently, it was approved in United States in 2020 and South Korea and the European Union in August 2021.[2,3] Its approval as a general anesthetic happened in Japan in 2020 and China in 2021.[4] In August 2020, remimazolam was used as a compassionate medication for ICU sedation in Belgium.[5]

In this mini-review, we want to bring in remimazolam as a novel sedative which can be safe and useful in ICU sedation for cardiac surgical patients.

COMMON SEDATIVE AGENTS IN CARDIAC SURGICAL ICU

Early extubation is always a cornerstone of management in patients undergoing cardiac surgery. To facilitate this early extubation, "light" or "cooperative" sedation is a requisite. Now question

arises, what is the ideal sedative for this patient population? In general, an ideal sedative would keep the patient comfortable without anxiety or recall of care requirements that can be unpleasant. Most importantly, it would effectively provide adequate sedation, but also allow neurologic evaluation of the patient, without stopping the administration of the drug. It would have minimal hemodynamics and respiratory depressant effect, a rapid onset and offset of action without any accumulation, easily titratable, allowing rapid recovery and not associated with any additional adverse outcome. Although such a magic drug is not always available, remimazolam can fulfill some of the criteria to a great extent.

Propofol, is an effective sedative due to its pharmacologic profile. There are reports of acute kidney injury in ICU patients who received propofol sedation than those who received midazolam.[6] Propofol is a myocardial depressant and also causes delayed weaning due to its respiratory depressant effect.[7] *Dexmedetomidine* is a centrally active sympatholytic, sedative, and amnestic agent, has a slower onset of action, extremely metabolized in liver. Its clearance is also dependent on cardiac output and hepatic blood flow which potentially could escalate its duration of action in patients with compromised cardiac function. The inactive metabolite of dexmedetomidine may accumulate in patients with impaired renal function.[8] With preservation of respiratory drive in clinically effective doses, sedation with continuous infusion of dexmedetomidine does not delay the normal course of ventilator weaning and extubation.[9] In spite of a favorable agent for ICU sedation, bradycardia and hypotension are common during its infusion.[10] *Opioids* though provide effective sedation and analgesia cause respiratory depression and consequent delayed extubation with prolong stay in ICU and hospital. Therefore, minimizing opioid use is a critical component of early extubation after cardiac surgery. It is also associated with increased risk of hypotension and bradycardia.[11] *BDZ* use in ICU sedation always remains controversial. The commonly used BDZ midazolam is rapidly acting with minimal respiratory and cardiovascular suppressant effects. Nonetheless, the offset of this drug is slow and delayed with accumulation.[12] Critically ill patients at times present with an altered mental state caused by a neurological event, for example, seizure, infarction, hypoxic encephalopathy, or intracranial hemorrhage. This situation is challenging when it is essential to distinguish this real neurological emergency from the after-effect of BDZ. Acute kidney injury and chronic renal failure are not uncommon in cardiac surgical ICU. Acute metabolite of midazolam can accumulate in these patients and lead to prolong sedation, as conjugate metabolites of midazolam have significant pharmacological activity.[13]

Volatile anaesthetics have easy dose adjustment, shorter extubation time, and stable hemodynamics. However, they cause respiratory depression, hypotension in some compromised patients, increased risk of delirium, and reduced mobility. In a systemic review and meta-analysis of randomized and controlled trials, the authors showed that ICU sedation with volatile anesthetic agents relative to classic intravenous sedative like propofol or midazolam reduced awakening time from sedation by 80 min and extubation time by 196 min. In spite of such benefits, no reduction in length of stay in ICU or hospital was reported.[14] The limited use of volatile anesthetics in ICU is probably due to unfamiliarity of medical staff with inhalational agents and their method of administration, atmospheric contamination, and higher risk of agitation, nausea, and vomiting after awaking.

REMIMAZOLAM, IS IT AN UPCOMING BLESSING?

Remimazolam besylate (CNS 7056) is a recent ultrashort acting intravenous BDZ developed by the pharmaceutical company PAION AG. It has the properties of both midazolam and fentanyl. It was initially developed as a "soft drug" of BDZ class to enhance GABA-A receptor activity by adding a carboxy ester moiety into BDZ. Remimazolam has fast onset, short, and predictive duration of sedative action, short recovery time, insignificant accumulation after long-term infusion, and less serious side effects when compared with currently used BDZ for procedural sedation and general anesthetic.[15,16] These characteristics render remimazolam a promising sedative for use among a wide range of patient population, including those who are critically ill ones.

Pharmacokinetics (PK)

After administration, the onset time of Remimazolam is 1–3 min which is much shorter than midazolam. Remimazolam has high clearance rate, a small steady state volume distribution, short elimination half-life, short context sensitive half-life, and first order linear PK. When compared with midazolam in Phase I PK study in healthy volunteers who were given single dose of remimazolam/midazolam, it was observed that the mean residence time for remimazolam was 0.50 h and mean residence time for midazolam was 3.56 h.[16] There was no clear relationship between body weight and systemic clearance of remimazolam within the studied body weight range 60–100 kg. This means that there is no significant benefit for dosing by body weight compared to fixed doses.[17] With 1 min intravenous dose of 0.01–0.3 mg/kg remimazolam, the maximum effect of sedation was achieved within 3 min.[16,17] This Phase I PK trial also revealed that the clearance rate of remimazolam was approximately 3 times greater than midazolam {0.075 mg/kg ([70.3 ± 13.9] L/h vs. [23.0 ± 4.5] L/h)} whereas its steady state volume of distribution was 50% of that of midazolam ([34.8 ± 9.4) L vs. (81.8 ± 27.1] L) and its terminal half-life

(t1/2) was also shorter than that of midazolam (0.75 ± 0.15 vs. 2.89 ± 0.65 h).[17] The context sensitive half time (the time required for the plasma level of the drug decreased by 50% after the infusion is stopped) of remimazolam (50 mg/h) was significantly lesser than those of midazolam (0.075 mg/kg/h).[16] Remimazolam can reach a steady state value of 7–8 min after an infusion of 2 h and appears to not be affected by the infusion duration.[16,18] It is metabolized by tissue carboxylase enzyme particularly in liver to an inactive carboxy acid metabolite CNS 7054.[19]

Stöhr *et al*. used 10 mg of remimazolam bolus and found no significant difference in Cmax (time taken for the drug to reach the maximum concentration after administration) values among hepatic impairment patient group.[20] They did not find any difference between the liver dysfunction patients and healthy subjects in the incidence and duration of consciousness. About 80% of the dose of remimazolam was excreted in urine as an inactive metabolite as demonstrated in one of the studies. This implies no accumulation in patients with renal impairment; therefore, no need to adjust the drug in patients with impaired renal function.[20]

Remimazolam has little clinical effect on heart rate (HR), blood pressure (BP) electrocardiogram, and respiratory rate. According to one of the animal studies, it does not have any burst suppression patterns and isoelectric encephalogram. It also reduces the incidence of delirium and post-operative cognitive dysfunction.[21,22]

Pharmacodynamics

In Phase I pharmacodynamic study, the onset of sedation was fast for remimazolam and the peak effect was observed within 1–2 min of injection at a dose of ≥0.075 mg/kg.[23] A dose of 0.2 mg/kg revealed a greater sedation effect while still maintaining a shorter recovery time, as compared to midazolam. The duration of sedation and the median time for patients to be fully awake were shorter than those of midazolam (8 vs. 12 min and 5.5–20 vs. 40 min). Subjects who received remimazolam showed no sedation or slightest sedation at 0.01 and 0.025 mg/kg dose and small reduction in bispectral index (BIS) scores (to 75) at 0.05 mg/kg[16] Doses of ≥0.075 mg/kg resulted in deeper sedation as evidenced by BIS score of 60.[16]

REMIMAZOLAM SAFETY AND EFFICACY DATA

A clinical trial by Liu *et al*. compared the safety and efficacy of remimazolam with that of etomidate and propofol for procedural sedation. They emphasized that remimazolam is superior to etomidate-propofol in onset time, procedural success rate time, to become fully alert, and time to hospital discharge. They also found a higher safety profile when remimazolam-fentanyl combination was used than etomidate-propofol.[24] Rex *et al*. also demonstrated its safety as a sedative regime among high risk patients with American Society of Anesthesiologists (ASA) III/IV class undergoing colonoscopy.[25] Remimazolam decreased the BP to 24 ± 6% and increased HR to 28 ± 15% as noted in few studies.[17,18] The SpO_2 decreased in initial few minutes of drug administration which was successfully treated by oxygen administration and chin lift. There were involuntary movements, psychomotor activity, hiccough, cough, sneezing, and apnea (lasting for <I min) were observed by the authors. They described all these events as mild-to-moderate and easily controllable. Chen *et al*. compared the safety and efficacy of remimazolam to that with dexmedetomidine for sedation in ASA I-II patients who were undergoing bronchoscopy. Both efficacy and safety of remimazolam were found to be non-inferior than dexmedetomidine.[26]

The report on the use of remimazolam in pediatric population is scanty.[27-29] Despite its significant advantage to maintain cardiovascular stability as a general anesthetic in children with Duchenne muscular atrophy, supratentorial glioma resection, myopathy, encephalopathy, lactic acidosis and stroke like (MELAS) syndrome, mitochondrial myopathy, encephalopathy, and lactic acidosis, it is still not approved as a sedative agent in children.

The central nervous system activity of remimazolam may be enhanced by central nervous system depressants such as barbiturate, opioids, benzodiazepines (BDZ), ketamine, dexmedetomidine, haloperidol, inhaled anesthetics, anticonvulsants, and antidepressants. The efficacy of remimazolam is decreased with aminophylline group of drugs and it is contraindicated in patients who are allergic to dextran.[30,31] It is used only in combination with normal saline as it forms precipitate in ringer lactate solution.

REMIMAZOLAM AS ICU SEDATIVE

The first use of remimazolam as ICU sedative was approved in August 2020 at Belgium during COVID-19 crisis.[10] Because this drug follow first-order kinetics, have inactive metabolite, less burden on liver and kidneys, and no significant adverse effects is much suitable for ICU sedation. Petersen *et al*.[32] administered remimazolam as continuous infusion (>24 h) in 49 ICU patients. Adequate sedation was achieved in all patients without any significant adverse effects. One group of researchers evaluated the long-term (>28 days) sedative effect of the drug in a pig model and reported that the 0–3 fold increase in remimazolam dose was lower than that of midazolam (2–4 fold increase). This tolerance of remimazolam after 28 days of sedation was much lesser than that of midazolam.[33] Some clinical trials are underway for evaluating the safety and efficacy of this drug for ICU sedation.[34-37]

CONCLUSION

Overall, remimazolam is safe with little influence on cardiorespiratory system, easy reversal with flumazenil, no fatal or severe effect during infusion, and well tolerated by the patients in all available studies. Its efficacy in procedural and ICU sedation indicate its potential for long-term sedation in ICU for both pediatric and adult population. However, further studies are essential to evaluate its long-term efficacy and safety in a large group of population as well as to determine the optimal dose in different comorbid situations.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

Dr. Minati Choudhury is one of the members of Associate Editors and Dr. Poonam Malhotra Kapoor is Editor-In-Chief of the Journal.

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