Acute and Critical Care

Acute and Critical Care 2022 May 37(2):151-158
https://doi.org/10.4266/acc.2022.00619

| pISSN 2586-6052 | eISSN 2586-6060

Review of remimazolam and sedatives in the intensive care unit

Hey-Ran Choi[1,2], In-Ae Song[3,4]

[1]Department of Anesthesiology and Pain Medicine, Inje University College of Medicine, Busan; [2]Department of Anesthesiology and Pain Medicine, Inje University Seoul Paik Hospital, Seoul; [3]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam; [4]Department of Anesthesiology and Pain Medicine, Seoul National University College of Medicine, Seoul, Korea

Remimazolam is a novel intravenous ultra-short acting benzodiazepine that has the potential of being a safe and effective new sedative for use in intensive care unit (ICU) settings. Because remimazolam metabolizes rapidly by being hydrolyzed to an inactive metabolite (CNS 7054) through non-specific tissue esterase activity, specific dosing adjustment for older adults and for patients with renal or hepatic impairment patients (except for those with severe hepatic impairment) is not required. In addition, research has shown that remimazolam may be reversed by administration of flumazenil, as its half time was sufficiently short compared to flumazenil. It shows a lower incidence of cardiorespiratory depression, less injection pain, and no fatal complications such as propofol infusion syndrome and malignant hyperthermia of inhalational anesthetics. Future studies to study the suitability of remimazolam for managing the sedation of ICU patients who need sedation for a long time over several days is required.

Key Words: critical care; flumazenil; midazolam; remimazolam

Review Article

Received: May 8, 2022
Revised: May 20, 2022
Accepted: May 23, 2022

Corresponding author
In-Ae Song
Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7499
Fax: +82-31-787-4063
E-mail: songoficu@outlook.kr

INTRODUCTION

Remimazolam besylate (Byfavo injection, Korea) is a water-soluble, fast-acting γ-aminobutyric acid A GABA-A agonist commonly used as an intravenous (IV) benzodiazepine (BDZ). Remimazolam was initially developed as a "soft drug" of the BDZ class to enhance GABA-A receptor activity through adding a carboxylic ester moiety into the BDZ. Metabolization of remimazolam shows that it is rapidly hydrolyzed to an inactive metabolite (CNS 7054) through non-specific tissue esterase activity. This drug is expected to be relatively safe with regard to potential risk of cardiovascular depression complications and does not require specific reduced dosing for older adults or for patients with renal or hepatic impairment patients except for those with severe liver dysfunction. Additionally, it can be reversed by flumazenil.

Remimazolam was recently approved as a general anesthetic for adults in January 2021 in South Korea, and for use in procedural sedation for less than 30 minutes in August 2021 [1,2]. This drug is now widely used in other countries, as it was approved as a general anesthetic in January 2020 in Japan, as a procedural sedative in July 2020 in the United States and China

and in March 2021 in Europe, and as compassionate use medication in intensive care unit (ICU) sedation in August 2020 in Belgium [3]. In this review, we will introduce remimazolam as a novel BDZ to be predictive to be useful and safe in the ICU sedation, especially deep sedation.

ICU SEDATION

Sedation can be problematic in terms of delirium. No or light sedation seems to be related to improved patient outcomes, more days free of mechanical ventilation, and shorter hospital stays [4,5]. However, light sedation protocol could cause accidental extubation of endotracheal tubes and loss of other important instruments, as well as aggravate anxiety, pain, and post-traumatic stress disorder [6]. Pain control has been thought to proceed sedation in the ICU because inadequate analgesia was related with worsening stress, sleep deprivation, delirium, cognitive dysfunction, and extreme anxiety [7,8].

Deep sedation with or without using neuromuscular blocking agents in the ICU has been used for anxiolysis and amnesia in mechanically ventilated patients, particularly those with acute respiratory distress syndrome (ARDS) [9,10]. However, deep sedation might lead to over-sedation, which can be associated with prolonged duration of mechanical ventilation [9].

The use BDZ for sedation in the ICU remains controversial. BDZs are well-established drugs that are inexpensive and provide powerful anxiolysis and amnesia. However, sedation using non-BDZ drugs has been shown to improve the clinical outcome of critically ill patients better than BDZs in terms of incidence of delirium and prolonged, and unpredicted sedation [11,12]. We compared sedatives that can be used for deep sedation in the ICU in Table 1.

KEY MESSAGES

- Remimazolam is a novel intravenous ultra-short acting benzodiazepine, which can be reversed by flumazenil.
- Dosing adjustment for older adults and for patients with renal or liver impairment patients (except for those with severe hepatic impairment) are not required because remimazolam is rapidly metabolized by tissue esterase.
- Use of remimazolam results in a lower incidence of cardiorespiratory depression and less pain at injection site, as well as no fatal adverse effects such as propofol infusion syndrome and malignant hyperthermia of volatile anesthetics.

IV SEDATIVES AND DEEP SEDATION IN ICU

Propofol

Propofol is a sedative-hypnotic medication used for sedation in the ICU; it has various sedative, anxiolytic, and anticonvulsant properties, and its use has been shown to help reduce intracranial pressure [13,14]. Propofol provides a rapid onset of action within seconds after administration and a short duration of action up to 15 minutes. However, propofol has several risks. First, its formulation must be prepared in a lipid solution, which increases the risk of bacterial contamination and could be associated with fatal infectious disease [15,16]. Second, patients have been reported to experience pain on IV injection. Third, propofol is associated with a higher risk of cardiorespiratory depression compared to other IV sedatives like dexmedetomidine, ketamine, and midazolam. Finally, propofol has been associated with fatal "propofol infusion syndrome (PRIS)" [17]. PRIS is a rare syndrome which affects patients undergoing long-term treatment with high doses of propofol and causes cardiac and renal failure, rhabdomyolysis, metabolic acidosis. The safe dose of propofol infusion is

Table 1. Characteristics of sedatives

	Onset	Offset	Respiratory suppression	Cardiac suppression	Injection pain	Reverse	Severe adverse effect
Propofol	Very rapid	Rapid	++ to +++	++ to +++	++	None	Septicemia due to contamination of formula, and propofol infusion syndrome
Midazolam	Rapid	Slow and delayed with accumulation	+ to ++	+ to ++	0	Flumazenil	-
Remimazolam	Very rapid	Rapid	+ to ++	0	0	Flumazenil	-
Dexmedetomidine	>10 min	Slow	0 to +	+ to ++	0	None	-
Sevoflurane (inhalational anesthetics)	Very rapid	Rapid	+ to ++	++	-	None	Malignant hyperthermia

considered to be 1–4 mg/kg/hr for sedation in intensive care. However, fatal cases of PRIS have been reported after infusion doses as low as 1.9–2.6 mg/kg/hr. Propofol can be relatively safe and an ideal anesthetics for several minute up to several hours of surgery, but physicians must keep in mind that propofol infusion can cause PRIS in cases of prolonged continuous infusion in the ICU [18].

Midazolam

Midazolam is an amnesic and sedative BDZ, and had been shown to have an onset of 3–5 minutes and a recovery period of 2 hours before remimazolam approval. It is considered safe to use, and the risk of cardiorespiratory depression caused by the use of midazolam is much lower than that of propofol. However, midazolam accumulation can occur via repeated injection or prolonged continuous infusion, leading to unpredictably prolonged sedation associated with delirium [19]. Critically ill patients also sometime present with an altered mental state caused by a neurological event such as intracranial hemorrhage, infarction, or seizure. Intensivists could face challenging situations distinguishing this "real neurological emergency" from the after-effects of prolonged sedation with classic BDZs.

Critically ill patients also commonly have chronic renal failure and experience acute kidney injury. Active metabolites of midazolam can accumulate in patients with renal failure and lead to longer-than-expected sedation of these patients, as conjugated metabolites of midazolam have significant pharmacological activity [20]. Prolonged sedation can occur due to active metabolites of midazolam and an impaired metabolism on the liver enzyme cytochrome P450 3A4 [21].

Dexmedetomidine

Dexmedetomidine, a high-affinity adrenergic agonist of the alpha2 receptor, provides light sedation and pain relief in patients in the ICU. Dexmedetomidine is associated with more days free of mechanical ventilation, a shorter time in a coma-like state, and less risk of delirium [22-24]. Additionally, dexmedetomidine has been shown to reduce the incidence of delirium, prevent delirium, and improve mortality [25-28]. However, hypotension and bradycardia are common side effects of dexmedetomidine [29-31]. Dexmedetomidine can be used a sole anesthetic for deep sedation or general anesthesia with a higher dose (5–10 times the maximum recommended dose for procedural sedation). However, deep sedation with a large dose of dexmedetomidine is rarely applied generally due to its associated risks of hypotension and bradycardia, particularly in critically ill patients [32].

Volatile Agents

Inhalational anesthetic agents are often used for general anesthesia, as they are potent sedatives which show a fast elimination, limited hepatic metabolism, and no accumulation [33]. Volatile sedation in the ICU has been tried more frequently after solving technical problems since the development of inhalational anesthetic devices, such as AnaConDa (SEDANA Medical, Uppsala, Sweden) and Mirus (Pall Medical, Dreieich, Germany) [33,34]. In a systematic review and meta-analysis of randomized controlled trials showed that ICU sedation with volatile anesthetic agents relative to classic IV sedatives, like propofol or midazolam, reduced the awakening time from sedation by 80minutes and the extubation time by 196 minutes. Despite such benefits, no reductions in the length of stay in the ICU or hospital were reported [34].

However, the use of inhalational sedation in the ICU remains limited. The reasons for this limited usage may be associated with the unfamiliarity of medical staff to inhalational agents and their methods of administration; patients' higher risk of agitation, nausea, and vomiting after awakening; potential atmospheric contamination; and a rare, but fatal, complication known as malignant hyperthermia. Malignant hyperthermia is a life-threatening reaction to potent inhalation agents (such as halothane, isoflurane, sevoflurane, and desflurane), and the depolarizing muscle relaxant succinylcholine. Malignant hyperthermia show a hypermetabolic crisis such as extremely high body temperature, rigid muscles or muscle spasms, hyperkalemia, high oxygen consumption, high CO_2 production, multiple vital organ failure, and disseminated intravascular coagulation [35].

DRUG INFORMATION AND MECHANISM OF ACTION OF REMIMAZOLAM

Mechanism of Remimazolam Action

Remimazolam has a high affinity on GABA-A receptors to bind at the interface between the alpha and gamma subunits, inducing a highly inhibitory central nervous system. It binds to receptors to make the intracellular concentration of chloride ions increase; this is followed by cellular membrane hyperpolarization and inhibitory conduction of the neuron action potentials to enhance the effects of GABA [36].

Pharmacokinetics

Remimazolam is characterized by pharmacokinetics (PK) profiles, specifically a high clearance, a small steady-state volume of distribution, a short elimination half-life, a short context-sensitive half-life, and first-order linear PK. Time after administration to onset of remimazolam is 1–3 minutes; this is faster than that of midazolam [37], and the half time of remimazolam is 7–8 minutes, which is much less than that of midazolam [36].

In a phase 1 PK study with healthy volunteers who were given a single dose of remimazolam, the mean residence time for remimazolam was 0.50 hours and the mean residence time for midazolam was 3.56 hours, as the systemic clearance of midazolam is about one-third that of remimazolam and the volume of distribution is more than twice that of midazolam [38,39]. This difference in PK between remimazolam and midazolam could explain one factor in patients' rapid recovery after receiving remimazolam. There is no clear relationship between body weight and systemic clearance of remimazolam within the studied body weight range (60–100 kg) [39]. There may be no significant benefit for dosing by body weight compared to fixed doses [39], The PK profiles were similar to those in a single-dose phase 1 PK study with continuous infusion of remimazolam and midazolam [40].

Carboxylesterase enzymes can be found in the cytosol and the rough endoplasmic reticulum of tissues [41], and remimazolam is metabolized by this tissue esterase (particularly, the liver) to an inactive carboxy acid metabolite, CNS 7054 [5,12,13]. CNS 7054 has a PK profile with a smaller volume of distribution, slower clearance rate, and a longer mean residence time in comparison to remimazolam [42], and has a 400-fold lower affinity for the GABA-A receptor [43]. An additional study found that there was no significant difference between older adults (median age, 66.0 years) versus younger adults (median age, 21.0 years) in terms of PK profile of remimazolam [44].

One study involved the use of a simulated plasma PK after a 10 mg remimazolam bolus, and revealed no significant different in Cmax values among hepatic impairment patients groups [45]. There was no difference between liver dysfunction and healthy subjects in the incidence and duration of loss of consciousness. However, recovery from sedation was delayed by hepatic impairment. This demonstrated that carboxylesterase enzymes–1A in liver must have an important role in metabolism of remimazolam. As recovery from sedation in severely hepatic impaired patients was delayed, specifically reduced dosing for these patients can be considered. In contrast, no dose adjustment is required for patients with mild or moderate hepatic failure [45]. Remimazolam is not metabolized by cytochrome P-450 isozymes, nor does it inhibit cytochrome P-450 metabolism [46].

In one study, 80% of the dose of remimazolam was excreted in urine as an inactive metabolite, and less than 1% of the dose was detected as unchanged 24 hours after remimazolam injection. Remimazolam indicated no accumulation in patients with renal impairment, and was metabolized at the same rate as that of healthy volunteers. There was no need to adjust the dosing of remimazolam in patients with impaired renal function, as renal function does not affect the PK of remimazolam [45].

Pharmacodynamics

To determine a level of sedation in study of anesthetics, researchers use commonly the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) and Bispectral Index (BIS) of electroencephalogram. MOAA/S is scored 0–5, where 5 represents an alert subject who responds promptly to their name spoken in a normal tone, and 0 represents a patient with no response after a painful trapezius squeeze. BIS index which ranges from 0 to 100, where 0 represents the absence of brain activity, and 100 represents the fully awake state. Generally, BIS values between 40 to 60 meant adequate general anesthesia for a surgery [40].

In the phase 1 pharmacodynamic study with healthy volunteers who were given a single dose of remimazolam, the dose was escalated throughout the cohorts until cohort 9 (0.30 mg/kg) was reached and six of 10 subjects (60%) in this cohort experienced loss of consciousness (MOAA/S scores of <2) for a minimum of five minutes, which was the predefined stopping criterion for dose escalation. In contrast, subjects in the placebo group did not experience sedation [39].

In this study, the onset of sedation was fast for both midazolam and remimazolam (at doses of >0.05 mg/kg). The degree and duration of sedation with remimazolam showed dose dependency, and the peak effect of sedation was observed in 1–4 minutes following the start of the infusion. Administration of a 0.10–0.20 mg/kg dose of remimazolam resulted in deeper sedation and faster recovery from sedation in comparison with administration of a 0.075 mg/kg dose of midazolam [39].

Subjects showed no sedation, or very minimal sedation, at 0.01 and 0.025 mg/kg, and showed small reductions in MOAA/S scores (to 4) and BIS scores (to 75) at 0.05 mg/kg. Doses of

0.075 mg/kg and higher resulted in deeper sedation, as evidenced by MOAA/S scores of <2 and mean BIS scores of 60 [39].

SAFETY DATA

Blood pressure decreased (24%±6%) and heart rate increased (28%±15%) during remimazolam infusion. The Spo_2 decreased during the first 5 minutes of remimazolam infusion, but this was successfully treated by oxygen administration through a nasal cannula with a median duration of 42 minutes, or by chin lift with a median duration of 26 minutes. No significant effect of remimazolam on the PR interval and on QRS duration was observed from the analysis of the 12-lead Holter electrocardiogram. Involuntary movements, psychomotor hyperactivity, cough, hiccup, sneezing, and apnea (lasting 0.9 minutes) were also observed. All adverse events were classified as mild or moderate (not severe) [38,40].

Remimazolam may enhance the central nervous system depressant activities of other BDZs, barbiturates, ketamine, propofol dexmedetomidine, inhalational anesthetics, haloperidol, tricyclic antidepressants, anticonvulsants, or opioids, such as remifentanil and fentanyl. The therapeutic efficacy of Remimazolam decreases when used in combination with Aminophylline or theophylline [47]. Since remimazolam contains dextran 40, it is contraindicated in patients with a history of severe hypersensitivity to dextran 40 [48]. Remimazolam reacts with Ringer's acetate or lactate solution and forms a precipitate; thus, it is recommended that Remimazolam be used only in combination with saline. In addition, when co-administration is essential, using a low concentration of remimazolam and a high injection rate of Ringer's solution is preferred [49].

FLUMAZENIL REVERSAL

Flumazenil was approved as a reversal of BDZ, an antagonist to the positive allosteric modulator effects of BDZs at the GABA-A receptor. The presences of a reversal agent enhanced a safety in cases of overdose or adverse events. However, flumazenil has a shorter half-life and duration of action than most classic BDZ drugs. Therefore, in cases of prolonged sedation by classic BDZ drugs, flumazenil was used for distinguishing the oversedation by BDZ and other significant neurological injury or impairment because re-sleeping after several minutes occurred after reversal of flumazenil [50].

As the half time of remimazolam was thought to be sufficiently short to be reversed by a single dose of flumazenil, use of flumazenil for reversal of remimazolam or to control sedation levels by remimazolam was expected. However, re-sleeping issue was demonstrated as case reports for remimazolam after flumazenil reversal. In particular, further study into the efficacy of flumazenil reversal of remimazolam following long duration ICU sedation is required.

CLINICAL USE

Procedure Sedation

Remimazolam had a sufficiently safe and sedative effect to use for procedures like endoscopy. Induction doses of 5 mg were administered intravenously over a period of 1 minute and 2.5 mg supplemental doses for 15 seconds can be administered within a least 2-minute interval [51]. Compared with the other sedatives, remimazolam demonstrated a higher sedative efficiency than that of midazolam and lower than that of propofol [52-56]. Remimazolam showed a lower incidence of hypotension than midazolam, and no significant differences were observed in hypoxia, bradycardia, nausea, vomiting, and injection site pain. Compared with propofol, remimazolam showed a significantly lower incidence of hypotension, hypoxemia, and pain at injection site; however, there were no differences in the incidence of bradycardia, nausea, and vomiting [57,58].

General Anesthesia

Remimazolam was used as a general anesthetic, using induction doses of 6 and 12 mg/kg/hr and maintenance rates of 1 mg/kg/hr. Remimazolam was superior to propofol in terms of its efficacy for general anesthesia, and it showed a significantly lower incidence of hypotension and other adverse events [37,59,60].

Sedation of Patients in ICUs

Phase II trial of Ono pharmaceutical company about 49 ICU patients sedated with remimazolam, all patients were reported to be sedated successfully and have no significant adverse events, and seven out of 49 ICU patients were sedated with remimazolam for >24 hours. However, on analyzing samples 24 hours or more after starting the continuous infusion, a higher concentration of remimazolam was observed than expected [61]. The suitability and safety of remimazolam for prolonged sedation of ICU patients' needs to be tested in the future. A few clinical trials on sedating patients in ICUs with remimazolam are ongoing or completed to recruit patients.; however, the re-

sults of the trials have not been published yet (national clinical trial number: NCT04611425, NCT04815265) [62]. One study involving general anesthesia (5 hours) and postoperative sedation (18 hours) using remimazolam showed that postoperative sedation with a continuous infusion of 0.25 mg/kg/hr remimazolam with infusion of remifentanil provided optimal sedation of ICU patients [47].

CONCLUSION

Remimazolam is very promising as a safe and effective sedative in ICU patients. It is expected that remimazolam can be used for not only light sedation for general ICU patients and but also deep sedation for severe ARDS, although studies for dosing adjustments for the specific medical conditions of ICU patients are required. As remimazolam is metabolized rapidly by tissue esterase, dose adjustment for age and for renal and hepatic impairment (except for severe liver dysfunction) was not required. This drug has a lower incidence of cardiovascular collapse and respiratory distress, and no fatal complication such as PRIS of propofol and malignant hyperthermia of volatile anesthetics have been reported. This profile seems to be suitable for critically ill patients, although future studies are required.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Hey-Ran Choi https://orcid.org/0000-0002-9899-0158
In-Ae Song https://orcid.org/0000-0002-7814-4253

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Methodology: all authors. Project administration: all authors. Visualization: all authors. Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES

1. Keam SJ. Remimazolam: first approval. Drugs 2020;80:625-33.
2. Masui K. Remimazolam besilate, a benzodiazepine, has been approved for general anesthesia!! J Anesth 2020;34:479-82.
3. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. Front Pharmacol 2021;12:690875.
4. Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev 2014;2014:CD009176.
5. Brush DR, Kress JP. Sedation and analgesia for the mechanically ventilated patient. Clin Chest Med 2009;30:131-41.
6. DAS-Taskforce 2015, Baron R, Binder A, Biniek R, Braune S, Buerkle H, et al. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine: revision 2015 (DAS-Guideline 2015)-short version. Ger Med Sci 2015;13:Doc19.
7. Martin J, Parsch A, Franck M, Wernecke KD, Fischer M, Spies C. Practice of sedation and analgesia in German intensive care units: results of a national survey. Crit Care 2005;9:R117-23.
8. Meiser A, Laubenthal H. Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. Best Pract Res Clin Anaesthesiol 2005;19:523-38.
9. Shinotsuka CR, Salluh JI. Perceptions and practices regarding delirium, sedation and analgesia in critically ill patients: a narrative review. Rev Bras Ter Intensiva 2013;25:155-61.
10. Schweickert WD, Kress JP. Strategies to optimize analgesia and sedation. Crit Care 2008;12(Suppl 3):S6.
11. Kress JP, Pohlman AS, Hall JB. Sedation and analgesia in the intensive care unit. Am J Respir Crit Care Med 2002;166:1024-8.
12. Temesgen N, Chekol B, Tamirie T, Eshetie D, Simeneh N, Feleke A. Adult sedation and analgesia in a resource limited intensive care unit: a systematic review and evidence based guideline. Ann Med Surg (Lond) 2021;66:102356.
13. Barr J. Propofol: a new drug for sedation in the intensive care unit. Int Anesthesiol Clin 1995;33:131-54.
14. Hall RI, Sandham D, Cardinal P, Tweeddale M, Moher D, Wang X, et al. Propofol vs midazolam for ICU sedation : a Canadian multicenter randomized trial. Chest 2001;119:1151-9.
15. Zorrilla-Vaca A, Arevalo JJ, Escandón-Vargas K, Soltanifar D, Mirski MA. Infectious disease risk associated with contaminated propofol anesthesia, 1989-2014(1). Emerg Infect Dis 2016;22:981-92.
16. Bennett SN, McNeil MM, Bland LA, Arduino MJ, Villarino ME, Perrotta DM, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med

1995;333:147-54.
17. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM. Propofol infusion syndrome in adults: a clinical update. Crit Care Res Pract 2015;2015:260385.
18. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia 2007;62:690-701.
19. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. Crit Care Med 1998;26:947-56.
20. Bauer TM, Ritz R, Haberthür C, Ha HR, Hunkeler W, Sleight AJ, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 1995;346:145-7.
21. Wandel C, Böcker R, Böhrer H, Browne A, Rügheimer E, Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth 1994;73:658-61.
22. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53.
23. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99.
24. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.
25. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016;315:1460-8.
26. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium: a randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018;197:1147-56.
27. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care 2010;14:R38.
28. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: a randomized clinical trial. JAMA 2017;317:1321-8.
29. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med 2009;37:3031-9.
30. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380:2506-17.
31. Jalowiecki P, Rudner R, Gonciarz M, Kawecki P, Petelenz M, Dziurdzik P. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. Anesthesiology 2005;103:269-73.
32. Scott-Warren VL, Sebastian J. Dexmedetomidine: its use in intensive care medicine and anaesthesia. BJA Educ 2016;16:242-6.
33. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Volatile anesthetics: is a new player emerging in critical care sedation? Am J Respir Crit Care Med 2016;193:1202-12.
34. Kim HY, Lee JE, Kim HY, Kim J. Volatile sedation in the intensive care unit: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e8976.
35. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis 2015;10:93.
36. Goudra BG, Singh PM. Remimazolam: the future of its sedative potential. Saudi J Anaesth 2014;8:388-91.
37. Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: pharmacologic considerations and clinical role in anesthesiology. Pharmacotherapy 2016;36:1021-7.
38. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056). Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. Anesth Analg 2012;115:284-96.
39. Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056). Part I. Safety, efficacy, and basic pharmacokinetics. Anesth Analg 2012;115:274-83.
40. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers. Part I. Pharmacokinetics and clinical pharmacodynamics. Anesthesiology 2020;132:636-51.
41. Birgenheier NM, Stuart AR, Egan TD. Soft drugs in anesthesia: remifentanil as prototype to modern anesthetic drug development. Curr Opin Anaesthesiol 2020;33:499-505.
42. Stafford JA, Pacofsky GJ, Cox RF, Cowan JR, Dorsey GF Jr, Gonzales SS, et al. Identification and structure-activity studies of novel ultrashort-acting benzodiazepine receptor agonists. Bioorg

Med Chem Lett 2002;12:3215-8.
43. Kilpatrick GJ, McIntyre MS, Cox RF, Stafford JA, Pacofsky GJ, Lovell GG, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. Anesthesiology 2007;107:60-6.
44. Nakanishi T, Sento Y, Kamimura Y, Tsuji T, Kako E, Sobue K. Remimazolam for induction of anesthesia in elderly patients with severe aortic stenosis: a prospective, observational pilot study. BMC Anesthesiol 2021;21:306.
45. Stöhr T, Colin PJ, Ossig J, Pesic M, Borkett K, Winkle P, et al. Pharmacokinetic properties of remimazolam in subjects with hepatic or renal impairment. Br J Anaesth 2021;127:415-23.
46. Pambianco DJ, Cash BD. New horizons for sedation: the ultrashort acting benzodiazepine remimazolam. Tech Gastrointest Endosc 2016;18:22-8.
47. Zhou J, Leonowens C, Ivaturi VD, Lohmer LL, Curd L, Ossig J, et al. Population pharmacokinetic/pharmacodynamic modeling for remimazolam in the induction and maintenance of general anesthesia in healthy subjects and in surgical subjects. J Clin Anesth 2020;66:109899.
48. Zinderman CE, Landow L, Wise RP. Anaphylactoid reactions to Dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. J Vasc Surg 2006;43:1004-9.
49. Sasaki H, Hoshijima H, Mizuta K. Ringer's acetate solution-induced precipitation of remimazolam. Br J Anaesth 2021;126:e87-9.
50. Yamamoto T, Kurabe M, Kamiya Y. Re-sleeping after reversal of remimazolam by flumazenil. J Anesth 2021;35:322.
51. Rex DK, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. Gastrointest Endosc 2018;88:427-37.
52. Sneyd JR, Rigby-Jones AE. Remimazolam for anaesthesia or sedation. Curr Opin Anaesthesiol 2020;33:506-11.
53. Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, et al. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest 2019;155:137-46.
54. Rex DK, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D. Safety and efficacy of remimazolam in high risk colonoscopy: a randomized trial. Dig Liver Dis 2021;53:94-101.
55. Borkett KM, Riff DS, Schwartz HI, Winkle PJ, Pambianco DJ, Lees JP, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. Anesth Analg 2015;120:771-80.
56. Chen SH, Yuan TM, Zhang J, Bai H, Tian M, Pan CX, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, phase III trial. J Gastroenterol Hepatol 2021;36:474-81.
57. Zhu X, Wang H, Yuan S, Li Y, Jia Y, Zhang Z, et al. Efficacy and safety of remimazolam in endoscopic sedation: a systematic review and meta-analysis. Front Med (Lausanne) 2021;8:655042.
58. Lee A, Shirley M. Remimazolam: a review in procedural sedation. Drugs 2021;81:1193-201.
59. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. J Anesth 2020;34:543-53.
60. Sneyd JR, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and the case for remimazolam: a narrative review. Br J Anaesth 2021;127:41-55.
61. Whizar-Lugo V, Garnica-Camacho C, Gastelum-Dagnino R. Remimazolam: a new ultra short acting benzodiazepine. J Anesth Crit Care 2016;4:1-5.
62. de Nantes CH. REmimazolam infusion in the context of hypnotic shortage in the critical care unit during the pandemic of COVID-19: the non-randomized, non-controlled, pilot, open, mono-centric REHSCU study. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 [cited 2022 May 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT04611425.