Review

Sedation outcomes for remimazolam, a new benzodiazepine

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Abstract: Remimazolam is a new ultrashort-acting benzodiazepine with fast onset, quick recovery, and few side effects, such as hypotension and respiratory depression. It is expected to be safe and effective for a wide range of patients undergoing intravenous sedation for dental procedures. The aim of this literature review was to evaluate clinical and sedation outcomes for remimazolam, including method of administration, level of sedation at the dose required, and clinical adverse events. An electronic literature search of databases was conducted, and eight articles were selected for inclusion in this review. Onset time from drug administration to optimal sedation level was faster for remimazolam (around 1.5-6.4 min) than for midazolam. Recovery time was significantly shorter for remimazolam than for midazolam and propofol. A study comparing various doses of remimazolam with midazolam found no significant difference in safety. Comparison of a remimazolam group with a propofol group showed that incidences of hypotension (13.0% vs 42.9%, respectively) and respiratory depression (1.1% vs 6.9%, respectively) were significantly lower for remimazolam. Remimazolam appears to be an ideal sedative.

Keywords; benzodiazepine, clinical, complication, remimazolam, sedation

Introduction

Dental procedures, including minor oral surgeries, often result in patient anxiety, fear, and physical or emotional stress due to the possibility of pain; such distress can lead to systemic complications. To minimize these unpleasant conditions and complications, intravenous sedation has been widely used [1-3].

Although current dental sedation strategies include the use of propofol or midazolam, both have drawbacks. Propofol is the most commonly used intravenous anesthetic. It has a rapid onset of action (15-40 s) [4] and a very short half-life, which results in rapid awakening and quick recovery of cognitive functions. The drawbacks include possible hypotension and respiratory depression, particularly in older adults [5]. Furthermore, pain on injection, metabolic acidosis, egg and soy allergies, and propofol infusion syndrome have been reported [6,7].

Midazolam is a short-acting γ -aminobutyric acid A (GABA_A) receptor agonist with an onset of action of 3 to 5 min and potent amnesic effect, and is the most frequently used benzodiazepine [8]. However, its long half-life (1.8-6.4 h) results in longer sedation and less-predictable recovery from sedation [9]. Thus, the need remains for a safe anesthetic with a fast onset of action and rapid recovery.

Remimazolam, a new ultrashort-acting GABA_A receptor agonist, was approved for induction and maintenance of general anesthesia in adults, on January 23, 2020 in Japan [10,11]. In addition, it was approved by the US Food and Drug Administration, on July 3, 2020, for injection to achieve induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 min or less, and by the Chinese National Medical Products Administration, on July 20, 2020, for use in procedural sedation.

Elimination of remimazolam is organ-independent, like remifentanyl, and it acts on the same receptor as midazolam— γ -aminobutyric acid. Thus, its name is combined from the names of those drugs. The sedative effect of remimazolam is caused by modulation of the γ -aminobutyric acid receptor, like most sedative-hypnotic agents. Although its structure is similar to that of midazolam, remimazolam has an ester-linked side chain to the diazepine ring, making it an ultrashort-acting intravenous drug that is metabolized rapidly, mainly by liver tissue esterases. Another important difference is that the hepatic drug-metabolizing enzyme CYP is not involved in metabolism and the metabolites are not active [12,13]. Furthermore, remimazolam metabolites have a lower affinity for benzodiazepine receptors than does the midazolam metabolite, α -hydromidazolam (1/400 vs 1/8) [12]. This mechanism explains the ultrashort action of the drug. A study using population pharmacokinetic and pharmacodynamic (PK-PD) models to assess remimazolam 0.01 to 0.03 mg/kg infused over 1 min found a population kinetic model with a clearance of 66.7 L/h, an apparent volume of distribution at steady state (V_{dss}) of 37 L, a terminal half-life of 0.92 h, and a mean residence time of 0.57 h [14]. These characteristics suggest that remimazolam will be safe and effective for a wide range of patients undergoing intravenous sedation for dental procedures, including older adults and patients with unstable circulation.

The purpose of this literature review was to evaluate clinical and sedation outcomes for remimazolam, including method of administration, level of sedation at the dose required, and clinical adverse events.

Materials and Methods

Two of the authors (H.S., M.K.) independently searched PubMed, Cochrane Library, and Web of Science. The electronic search strategy was performed by using the keywords benzodiazepine, clinical, complication, remimazolam, and sedation. Furthermore, additional literature was hand-searched in relevant journals for this review. All English-language articles presented or published between January 2012 and December 2020 were considered. Non-English literature was translated if necessary.

Another 2 authors (H.S., K.T.) screened the article titles and abstracts and selected articles by using the criteria for possible inclusion. A full-text analysis of the selected literature was conducted to identify relevant articles. Disagreements were resolved through discussion. All authors extracted the data and assessed the eligibility of the selected full-text articles.

Results

Figure 1 shows the flow diagram for study selection. The initial search strategy identified 471 records, and 85 articles were evaluated for eligibility by full-text assessment by 2 authors (H.S., R.S.). Ultimately, 8 articles were selected for inclusion in this review, as shown in Table 1.

The procedures requiring sedation were colonoscopy ($n = 5$), bronchoscopy ($n = 1$), and gastrointestinal endoscopy ($n = 2$). The initial dose for remimazolam to induce adequate sedation was 0.04-0.2 mg/kg by a single iv over 1 min or 5 mg by a single bolus iv. Many studies used a top-up dose of 2.5 mg by bolus iv. All studies defined adequate sedation as a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 3.

Remimazolam was compared with midazolam or propofol. In the 2 comparisons with midazolam, onset time from drug administration to optimal sedation, as indicated by sedation score, was faster for remimazolam (around 1.5-6.4 min). Recovery time was significantly shorter in the 3 studies that compared remimazolam with midazolam and in the 2 studies

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that compared it with propofol. Many studies used fentanyl as an analgesic during procedures.

Analysis of the safety of remimazolam revealed hypotension in 24% (11/45) of patients, which quickly recovered to normotension [15]. A study comparing various doses of remimazolam with midazolam [9] found no significant difference in safety. In another study [16], severe hypotension was observed in 1 patient each in the 8/3 mg and 7/2 mg remimazolam groups, but there was no significant difference in heart ability or respiratory rate in relation to remimazolam dose or between remimazolam and midazolam. In a study comparing remimazolam with midazolam and pla-

cebo [17], hypotension was observed in 62% of patients in the midazolam group, as compared with 42% in the placebo group and 39% in the remimazolam group. Treatment-emergent adverse events (AEs) were reported in 35% of patients in the remimazolam group, 25% in the placebo group, and 32% in the midazolam group. The differences were not significant, except hypotension was significantly less likely than in the placebo group [18]. Furthermore, as compared with propofol, remimazolam was significantly associated with a lower risk of pain on injection ($P < 0.001$), a lower risk of bilirubin elevation ($P = 0.019$), a higher respiratory rate ($P < 0.001$), and higher SpO₂ ($P < 0.001$) [19]. In a comparison of a remimazolam group and propofol group, the incidences of hypotension (13.0% vs 42.9%, respectively) and respiratory depression (1.1% vs 6.9%, respectively) were significantly lower in the remimazolam group [20].

Discussion

The present literature review was designed to evaluate clinical and sedation outcomes of remimazolam, namely, method of administration, dose required for adequate sedation level, and AEs.

Existing evidence indicates that the ideal sedative is characterized by ease of use, rapid onset of action and recovery, minimal pain on injection, and few side effects, such as respiratory and circulatory depression [5,21,22]. Unfortunately, no clinical sedative-hypnotic drug has all these properties.

A phase 1 study [23] and the studies included in this review indicate that onset and recovery time are shorter and faster, respectively, for remimazolam than for midazolam [9,15-18,24]. In 2 studies comparing remimazolam with propofol, onset time was significantly slower for remimazolam than for propofol, but recovery time was similar or faster for remimazolam. These findings suggest that remimazolam might have a slower distribution than propofol and that it might be metabolized more rapidly than propofol.

All articles in this review used MOAA/S to assess sedation depth. Among the many methods for assessing sedation depth, the Bispectral Index (BIS) was originally developed to measure propofol sedation. However, the correlation of this index with sedation depth was weaker for other benzodiazepines, such as midazolam. MOAA/S is adequate for assessing depth of sedation for remimazolam, and a score of 3, which was used in this review, indicates that the patient “responds only after (his/her) name

Fig. 1 Flow diagram of study selection process

Table 1 Summary of the characteristics of the included studies

Author Year	Age, mean (range)	n (remi) / N (total)	ASA	Intervention	Success rate (%)	Initial dose of remimazolam (mg) or (mg/kg)	Top-up dose (mg) or (mg/kg)	Adverse events (%)	Main adverse events	Onset time (min)	Recovery time (min)	MOAA/S	Comparator product initial dose (mg) or (mg/kg)	Analge- sic	During pain
Worthington MT et al. 2013 [15]	(18-75)	15/45 15/45 15/45	I	Colonoscopy	67 100 64	0.04 0.075 0.1 (mg/kg) for 1min	0.04 (mg/kg) over 15 s	nothing	hypotension (11/45)	1< min	8.0 9.0 7.0	—	—	fentanyl	—
Borkett KM et al. 2015 [9]	41 (18-65)	25/100 25/100 25/100	I-II	Gastrointes- tinal Endoscopy	32 56 64 44	0.1 0.15 0.2 midazolam 44	as rescue midazolam propofol (mg/kg) over 1min	40 48 40 52	SpO ₂ < 90%	1.5-2.0 midazolam 5.0	6.8 9.0 9.9 midazolam 11.5	≤3	Midazolam 0.075 (mg/kg)	—	—
Pambianco DJ et al. 2016 [16]	55 (18-70)	40/160 40/160 40/160	I-III	Colonoscopy	93 95** 98** 75	8.0 7.0 5.0 midazolam 75	3.0 2.0 3.0 (mg) for 15 s	nothing	hypotension after fentanyl	2.2 3.0 2.6 midazolam 4.8	13.6 11.3 13.3 midazolam 15.2	≤3	Midazolam 2.5 (mg)	fentanyl	not significant
Rex DK et al. 2018 [17]	54 (19-80)	296/458	I-III	Colonoscopy	91* vs 25 vs 2 (placebo)	5 (mg) over 1 min	2.5×5 times (mg)	74 vs 91 vs 78 (placebo)	hypotension	5.1* vs 16.9 vs 20.3 (placebo)	7.4* vs 15.8 vs 11.6 (placebo)	≤3	Midazolam 1.75 (mg) < 60 yr 1.0 (mg) > 60 yr	fentanyl	not significant
Pastis NJ et al. 2019 [18]	63 (22-95)	303/431	I-III	Bronchoscopy	81* vs 33 vs 5 (placebo)	5 (mg)	2.5 (mg)	35 vs 32 vs 25 (placebo)	—	6.4* vs 16.3 vs 17.2	6.0* vs 12 vs 13.6	≤3	Midazolam 1.75 < 60 yr 1.0 > 60 yr	—	—
Chen S et al. 2020 [19]	44 (18-65)	194/384	I-II	Colonoscopy	97 vs 100	5 (mg)	2.5×5 times (mg)	49** vs 68	site pain respiratory rate SpO ₂	1.7** vs 1.3	8.1 vs 7.7	≤3	Propofol 1.5 (mg/kg)	—	less pain with remima- zolam
Chen SH et al. 2020 [20]	41	189/378	I-II	Gastro- intestinal Endoscopy	97 vs 100	5 (mg) over 1 min	2.5 (mg)	39** vs 60	hypotension respiratory depression	2** vs 1.3	5.8* vs 6.7	≤3	Propofol 1.5 (mg/kg)	fentanyl	—
Rex DK et al. 2021 [24]	63	31	III, IV	Colonoscopy	87** vs 13	2.5-5.0 (mg)	(1.25-2.5) ×4 times (mg)	90.3 vs 87.6	—	87.8** vs 18.6	3.0** vs 7.0	≤3	Midazolam 1.0, 0.5 (mg)	fentanyl	—

ASA, American Society of Anesthesiologists; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; * $P < 0.05$ compared to placebo; ** $P < 0.05$ compared to comparator products

is called loudly or repeatedly.” This is likely an adequate level of sedation for dental procedures.

Pain on injection is one of the biggest drawbacks of propofol but can be improved to some extent by avoiding small veins and by pretreatment with various drugs such as lidocaine [25]. In this review, pain on injection was similar for remimazolam and midazolam [16,17] but greater for propofol [19].

In a study [19] comparing remimazolam with propofol, patients who received propofol had elevated bilirubin, decreased respiratory rate, and decreased oxygen saturation. These observations may be due to cardio-respiratory suppression by propofol, which is caused by its effect on central chemoreceptor sensitivity. In addition, AEs such as hypotension, hypertension, and bradycardia were observed, regardless of the mode of drug administration [17], most likely because the procedure studied was colonoscopy.

The risk of AEs attributable to sedation differs in relation to the medical procedure. First, analgesic modalities differ by clinical setting. In this review, opioids such as fentanyl were used as analgesics for successful sedation; however, in dental sedation, local anesthetics rather than opioids are used. Opioid use is more likely to induce respiratory depression and hypotension. Second, the duration of dental sedation is often much longer than that required for most medical procedures. In this review, procedure duration (mean $\pm$ SD) was 12.9 ± 14.3 min [16] for colonoscopy, 12.8 ± 11.6 min [18] for bronchoscopy, and 1–18 min [9] for upper gastrointestinal endoscopy. The longer duration of dental procedures could increase incidences of AEs during sedation. Third, ensuring maintenance of adequate sedation is more difficult during dental sedation than during medical procedures such as colonoscopy and upper gastrointestinal endoscopy. This can result in excessive sedation and associated complications. Fourth, there are maneuvers unique to dental procedures, including introduction of water into the oral cavity and use of the fingers to support and push the mandible while treating mandibular teeth. These maneuvers could contribute to obstruction and compromise of the upper airway reflex, resulting in abnormal breathing. Among AEs associated with dental procedures, hypoxemia is the most common cause of death [26].

Very short-acting medications have limitations. An ultrashort-acting sedative such as remimazolam requires numerous top-ups during most procedures. To avoid this, continuous infusion of remimazolam would be useful for sedation during dental procedures. For general anesthesia in adults, the recommended induction dose of remimazolam required to render the patient unconscious is 12 mg/kg/h, and 1 mg/kg/h is used to maintain anesthesia.

Exposure to remimazolam in the intensive care unit for longer than 24 h resulted in higher plasma concentrations in healthy subjects [Petersen KU. *J Jpn Soc Clin Anesth* 37, S202, 2017], which suggests that prolonged exposure under traumatic conditions could promote metabolic changes. However, a recent study reported that remimazolam metabolism was stable during continuous long-term infusion (5 days) and that remimazolam exposure had no harmful effects on the integrity and metabolic activity of hepatocytes [27].

In a study that used a population model to investigate PK-PD after continuous infusion [28], remimazolam was administered via continuous intravenous infusion at a rate of 5 mg/min for the first 5 min, 3 mg/min for the following 15 min, and 1 mg/min for the last 15 min. This drug exhibited high clearance (1.15 ± 0.12 L/min), low steady-state distribution volume (35.4 ± 4.2 L), an elimination half-life of 70 ± 10 min, and a context-sensitive half-time of 6.8 ± 2.4 min after a 4-h infusion. These values are similar to those reported in a previous study [14] in which remimazolam was administered as a bolus over 1 min. Taken together, these results suggest that the effect of remimazolam does not substantially differ in relation to duration of administration.

Although remimazolam seems to be an ideal sedative, few studies have evaluated its use for sedation during dental procedures. To improve patient safety and comfort during dental procedures, additional studies of remimazolam for dental sedation are warranted.

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Conflict of interest

The authors report no conflicts of interest.

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