

Remimazolam: A New Ultra Short Acting Benzodiazepine

Research Article

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Abstract

Remimazolam (CNS 7056) is a novel molecule, water soluble, ultra-short-acting intravenous BDZ under human research in protocols phase II-III. This new BDZ is a designed soft drug, ester-based, intended to undergo rapid hydrolysis by esterase enzymes to inactive metabolites. It acts on GABA_A receptors containing gamma subunits, initiating cell membrane hyperpolarization and therefore inhibition of the neural activity via rising chloride influx. After intravenous infusion it rapidly induces sedation for a short period of time with no serious side effects. It has been investigated in the induction and maintenance of general anesthesia, for sedation in gastrointestinal endoscopies, and in the critically ill patient. Like other BDZs, remimazolam can be reversed with flumazenil in order to rapidly terminate sedation if necessary. Because of its organ-independent metabolism, rapid and predictable onset and recovery, remimazolam appears to be the next sedative drug.

Keywords: Benzodiazepines; Remimazolam; Sedation; General anesthesia

Introduction

Benzodiazepines (BDZs) are prescribed for anxiety, insomnia, epileptic seizures, and to treat muscle spasms. They also elicit anterograde amnesia, an effect that is very useful in clinical anesthesia. Chlordiazepoxide was the first discovered BDZ in 1955; since then more than 2000 BDZs have been synthesized, but only 30 have been marketed for clinical use [1,2]. Benzodiazepines are an important part of the armamentarium in anesthesiology and intensive care, they have had an interesting development. From the old and well known diazepam to the short acting midazolam, anesthesiologists have been using BDZs alone or in combination for premedication, as induction, in the maintenance of anesthesia, for sedation and anxiolysis, in intensive care unit (UCI), and even in chronic pain patients. Although unsafely, some non-anesthesiologist colleagues use sedative drugs for procedures inside and outside of the operating room, a practice that has been recently debated [3-5].

Remimazolam (CNS 7056) a new rapidly metabolized BDZ has been developed by PAION using molecular level procedures and introduced in clinical research protocols. It has promising attributes as a sedative medicine to be used successfully in clinical anesthesia due to its rapid onset of action, ultra short duration, and fast recovery time, without serious side effects [6-10]. This review provides an update of the pharmacology and clinical uses of remimazolam in proved clinical settings and briefly mention for possible uses in unstudied clinical situations.

Benzodiazepines

Benzodiazepines are classified according to their pharmacokinetic characteristics as short, intermediate or long-acting drugs. The pharmacological characteristics of remimazolam could label it as ultra-short acting BDZ. The basic chemical structure of BDZs is a benzene ring coupled to a seven member heterocyclic structure containing two nitrogens at position 1 and 4 (Figure 1). They bind γ -aminobutyric acid type A receptors

(GABA_A receptor complex) in postsynaptic membranes. Gamma-aminobutyric acid (GABA) released from the presynaptic neuron binds to postsynaptic GABA_A receptors, leading to a chloride influx, which precedes hyper polarization of the postsynaptic neuron, making this neuron less excitable [11-13].

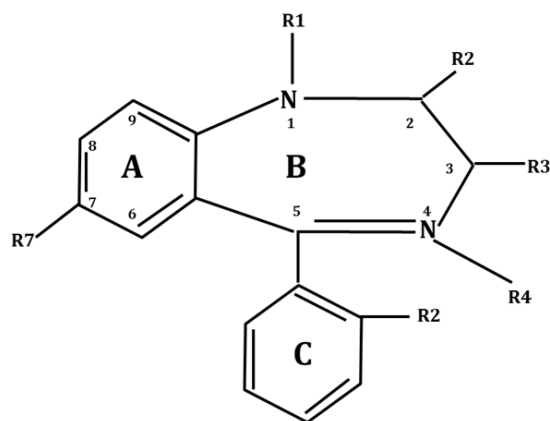


Figure 1: Benzodiazepine nucleus.

Of the 30 available BDZs for clinical use, only a few are used frequently by the anesthesiologist; diazepam, flunitrazepam, lorazepam and midazolam (Table 1). Its use varies from country to country, preferences of the anesthesiologists, its availability, and the clinical setting. Benzodiazepines most common use is for premedication, although they are frequently used in the induction and maintenance of general anesthesia or conscious sedation [14-17]. Midazolam is the most used BDZ for sedation and anesthesia induction because of its rapid onset of action and short duration. This drug is metabolized by cytochrome P450 (CYP) 3A4, which favors prolonged sedation in patients taking

selective serotonin reuptake inhibitors antidepressant drugs (fluoxetine, sertraline, paroxetine), macrolide antibiotics, calcium channel blockers (verapamil, diltiazem) and grapefruit juice that inhibit this enzyme. Prolonged sedation with midazolam can

also happen after infusion for several days in patients with liver failure. Moreover, a resistance to midazolam has been described in patients taking anticonvulsants, some glucocorticoids and Saint John's wort [10].

Table 1: Characteristics of the most commonly used BDZs in anesthesiology compared to remimazolam.

Benzodiazepine	Acting Profile	Elimination half-life h	Premedication	Induction	General Anesthesia Maintenance ^o	Sedative Maintenance ^o
Midazolam	Short	1-5	Oral 0.25- 0.5 mg/kg i.v. 50 µg/kg	0.2-0.35 mg/kg	0.05 mg/kg/h	0.05 mg/kg/h
Lorazepam	Long	10-18	Oral 1-2 mg i.v. 2- 4 mg	2 - 4 mg or	0.05-0.1 mg	0.05 mg/kg
Diazepam	Intermediate	20-100	Oral 5-20 mg i.v. 5-10 mg	0.2 - 0.5 mg/kg	0.1-0.2 mg/kg	0.25 mg/kg
Flunitrazepam	Long	18-26	Oral 1-2 mg i.v. 0.015- 0.03 mg/kg	0.01 mg/kg	1.2 mg/h-1	0.009- 0.01 mg/kg
Remimazolam	Ultra short	0.75	No reports	0.1- 0.3 mg/kg	0.72-3 mg/kg/h	0.72-3 mg/kg/h?

*Doses for adults. Dosage can vary.

^oMixed with opioids, ketamine, or halogenated anesthetics.

^oProcedures done under sedation plus local anesthesia.

Remimazolam

Remimazolam was discovered by Glaxo Smith Kline and developed by PAION. It is the newest BDZ, developed to allow better sedative profile to current similar drugs. This new chemical water soluble product is a ultra short acting imidazobenzodiazepine (Methyl 3-[(4S)-8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-4-yl]propanoate) with the addition of a carboxylic ester linkage to the BDZ ring (Figure 2). It has a molecular formula C₂₁H₁₉BrN₄O₂, average mass 439.305 Da, and monoisotopic mass 438.069122 Da. Designed as a soft drug ester-based, it is rapidly hydrolyzed in the body by tissue esterases in the blood to an inactive carboxylic acid (CNS 7054), its major metabolite [10,18]. As a soft designed drug it undergoes a predictable and controllable metabolic deactivation after exerting its sedative effect [7-10,19,20]. The context-sensitive half time profile of remimazolam allows rapid removal, even after prolonged infusions as seen in Table 2 [21,22]. It has a mean clearance 70.3±213.9 L/h and a mean steady state volume of distribution of 34.8±9.5 L [9].

Remimazolam has a high-affinity and selective ligand for the BDZ site on the GABA_A brain receptors, without having found selectivity GABA_A receptor subtypes. It acts enhancing the activity of GABA_A receptors containing gamma subunits, initiating cell membrane hyperpolarization and therefore inhibition of the neural activity via rising chloride influx [10]. In rodents it inhibits the substantia nigra pars reticulata firing [23,24]. A single dose of 0.25 mg of remimazolam produces significant sedation for a short period of time. As with any other BDZ, remimazolam sedative effects can be reversed with flumazenil. Most preliminary reports have found that this novel BDZ is safe, without significant side effects, although some investigators reported mild hypoxemia resolved using a chin lift maneuver. No supplemental oxygen or manual ventilation was required [9].

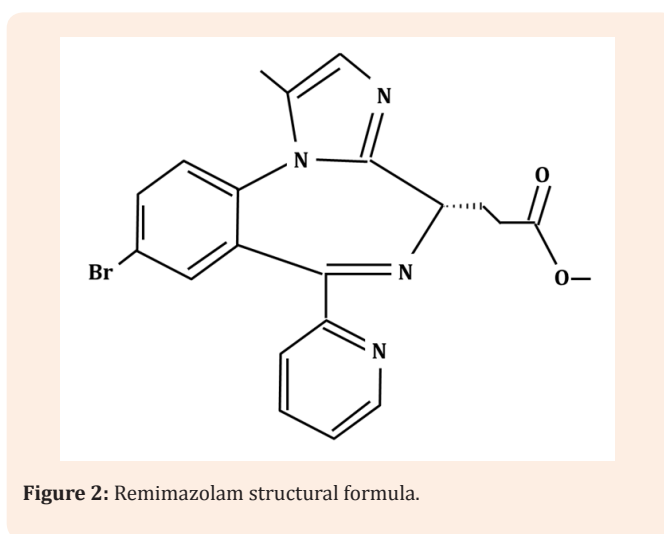


Figure 2: Remimazolam structural formula.

Table 2: The context-sensitive half time in minutes for some sedative and opioids for continuous infusions [21,22].

Drug	Infusion duration			
	2 h	4 h	6 h	8 h
Remimazolam	6	6.5	7	7
Etomidate	5	11	17	22
Propofol	8	9	11	12
Midazolam	27	27	27	27
Remifentanyl	3	3	3	3
Fentanyl	35	131	217	256

Clinical uses

Remimazolam is a BDZ undergoing clinical investigation whereby available information is still scarce. Goudra and Singh considered four clinical scenarios for remimazolam use [25]; a) As a premedication drug, b) Bolus followed by supplemental doses with or without opioids for sedation during some procedural like endoscopies, c) Intravenous combined with opioids as in total intravenous anesthesia technique, and d) Sedation for critical care patients. It also should be considered to induce general anesthesia and for conscious sedation. Until today remimazolam has been investigated for procedural sedation, for induction and maintenance of general anesthesia with no serious side effects [9,10,23,26]. Its pharmacological and pharmacokinetic characteristics confer certain advantages over the previous marketed BDZs, included midazolam.

Sedation in gastrointestinal endoscopy

Although propofol continues to be the drug of choice for endoscopies of the digestive tract there is a debate about safety and who must administer this drug [10,27-30]. In a retrospective study of 73,029 gastrointestinal endoscopies, Goudra et al. [31] found a higher incidence of cardiac arrest and death on those patients receiving propofol versus those receiving midazolam-fentanyl sedation (8.07 and 4.28 per 10,000 vs. 0.67 and 0.44 respectively), where 72% were related to difficulty in managing the airway. About 90% of all cardiac arrests occurred in patients who received propofol. On the other hand, it is well known that sedation with BDZs have proven to be very useful and safe in patients undergoing endoscopic procedures of the digestive tract. They are used as anti-anxiety before the procedures or during endoscopies [32,33]. Initial studies have shown that remimazolam could be a new drug to sedate patients during endoscopy of the gastrointestinal tract, and perhaps for bronchoscopy.

An exploratory research done in patients programmed for upper gastrointestinal endoscopy using three different single doses of remimazolam (0.10, 0.15 or 0.20 mg/kg) showed that higher doses produced better sedation and were more effective (32 vs. 56 vs. 64 % respectively), compared with 44% of those patients receiving midazolam 0.075 mg/kg. Onset sedation was faster with remimazolam compared with midazolam (1.5-2 min vs. 5 min). Also recovery from sedation was faster in those patients treated with remimazolam, but was affected by the choice of rescue medication. Both BDZs were equal regarding safety [34]. Worthington et al. [35] did the first study using multiple dose of remimazolam to assess feasibility for appropriate sedation during colonoscopy, and reversing the sedative effects with flumazenil; they injected fentanyl before remimazolam 0.04, 0.075, or 0.10 mg/kg, plus remimazolam top-up doses to provide sedation during 30 minute period. These authors also investigated the reversion of remimazolam with flumazenil. Sedation was effective in >70% of subjects, with a rapid recovery after colonoscopy (median <10 minutes). One patient developed hypotension 80/40 and low SpO₂ (<90%). Sedative effects were easily reversed in 6 studied subjects without re-sedation. Pambianco et al. [36] studied 162 patients of both sexes, aged 18-70years undergoing routine colonoscopy. They compared remimazolam versus midazolam supplemented with oxygen and fentanyl to keep an appropriate sedation and/or analgesia (Modified Observer's Assessment of

Alertness/Sedation score ≤ 3). They found adequate sedation with a better success rate in the remimazolam group compared with midazolam (>92% vs. 75%, $P=0.007$). None of the patients required mechanical ventilation, and failures procedures were related to the rescue sedatives.

In this clinical scenario, remimazolam has advantages over propofol and midazolam as the possibility of respiratory failure is almost zero, which is very useful benefit when sedation is administered by a non-expert colleague in the management of the airway.

Premedication

The BDZs are used to premedicate patients before anesthesia in order to decrease their anxiety and produce anterograde amnesia. For this purpose, BDZs are usually given orally, and seldom i.v. There is no remimazolam for oral administration. The short duration of remimazolam is not ideal for traditional premedication. Mouth or nasal administration could be used in infants, as is done with midazolam and ketamine. There are no studies on the usefulness and safety in this clinical situation.

Induction and general anesthesia maintenance

Two studies done at Hamamatsu University Hospital in Japan have investigated the role of remimazolam to induce and maintain general anesthesia. Doi et al. [37] found that loss of consciousness (LoC) was accomplished in 108.0 ± 7.8 , 70.3 ± 11.1 , 65 ± 5.1 and 65.4 ± 11.3 seconds after infusion bolus doses of 6, 12, 21, and 30mg/kg/h in young patients and 115.2 ± 30.9 , 72.5 ± 14.2 , 57.6 ± 11.1 seconds for doses of 4, 8, and 12 mg/kg/h in aged cases. After LoC was achieved, these investigators maintained general anesthesia with an infusion of remimazolam 1 mg/kg/h to accomplish BIS value less than 53 (average infusion 1.02 mg/kg/h in young patients and 0.72 mg/kg/h in elderly cases). Time to extubation was 16.4 and 13.6 minutes respectively. Sato et al. [38] compared remimazolam versus propofol in 375 patients undergoing general surgery with TIVA. Anesthesia was induced with remimazolam 6 or 12 mg/kg/h and an initial dose of 1 mg/kg/h for maintenance with the option to titrate up or down as needed. The other group of patients were induced with propofol 2-2.5 mg/kg and maintenance was achieved with 4-10 mg/kg/h. Time to LoC was shorter in those patients receiving remimazolam 12 mg versus 6 mg/kg/h, (88.7 vs. 102 seconds), but longer compared to propofol (78.7 sec). Time to extubation was longer in those patients managed with remimazolam versus propofol (19.2 vs. 13.1 min). Propofol group patients needed more vasopressors to treat hypotension events. The authors concluded that remimazolam is effective to induce and maintain general anesthesia, particularly in those cases prone to unstable hemodynamics. Probst et al. [39] from Germany did a randomized controlled phase II protocol in 90 patients undergoing elective major cardiac surgery. These authors used same remimazolam doses than Sato and found that patients treated with remimazolam-remifentanyl required significantly less norepinephrine than those who were anesthetized with propofol-sevoflurane.

Sedation in critically ill patients

Benzodiazepine properties, particularly sedation and anti-convulsing effects are useful for critical patients. These types of drugs are used to sedate patients under mechanical ventilation,

to treat anxiety and sleep deprivation, frequent problems on the ICUs. Long-term sedation with midazolam or propofol in critical patients has serious undesirable side effects. Hypothetically, remimazolam fast metabolic degradation by tissue esterases allows this BDZ to sedate critical patients. The fact that multiple organ failure, especially liver and kidney dysfunction, do not interfere with remimazolam metabolism, could allow a rapidly reversible sedation which eases a fast weaning from invasive mechanical ventilation. In severe trauma cases would facilitate neurological evaluation few minutes after its withdrawal, even after prolonged infusions. Although remimazolam pharmacological characteristics are ideal to sedate the seriously ill patient, until today no data are available in this clinical scenario. Ono Pharmaceutical Company, a former PAION's associate did a phase II trial to sedate ICU patients. Although patients were sedated effectively, the investigation was discontinued due to remimazolam high plasma concentration in some patients [40].

Conclusion

Drugs used in anesthesia require a high degree of pharmacological control during the surgical or invasive diagnostic procedures to maintain patient's safety and to end the anesthesia-sedative effect as fast as possible after the procedures are done [41]. Remimazolam combines the characteristics of remifentanyl and midazolam having organ-independent metabolism like remifentanyl and acting in GABA receptors like midazolam. Similar to remifentanyl, remimazolam is a soft designed drug with a sedative profile suitable to be a new alternative to sedate patients undergoing gastrointestinal endoscopies, in the ICU, conscious sedation, to induce anesthesia and to be used during general anesthesia combined with opioids, ketamine, or halogenated anesthetics. This new BDZ is close to the ideal sedative drug due to its fast onset, good sedation, and a fast recovery time, although more studies are needed to find the best dose in different clinical scenarios.

Remimazolam has not yet been approved for clinical use. Licensing studies are ongoing in Europe, Japan and United States of North America. When remimazolam is available for clinical use worldwide, it will be used in various clinical scenarios requiring rapid recovery: conscious sedation in ambulatory or short stay surgery, TIVA, non-surgical invasive procedures, external cardio version, biopsies, as inductor for difficult airway patients, sedation in ICU, sedation for regional anesthesia, sedation in radiology, sedation in odontology, pediatric medical procedures, and so on. Another advantage of this BDZ is that it can be used safely by colleagues inexperienced in managing the airway.

Conflict of Interest

The authors declare no conflict of interest.

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