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\textsubscript{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 \(\gamma\)-aminobutyric acid type A receptors (GABA\textsubscript{A} receptor complex) in postsynaptic membranes. Gamma-aminobutyric acid (GABA) released from the presynaptic neuron binds to postsynaptic GABA\textsubscript{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.
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 | Premedicant | Induction | General Anesthesia Maintenance* | Sedative Maintenance° |
|----------------|---------------|-------------------------|-------------|-----------|---------------------------------|-----------------------|
| Midazolam      | Short         | 1-5                     | Oral 0.25 - 0.5 mg/kg i.v. 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. 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/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.
°Mixed with opioids, ketamine, or halogenated anesthetics.
*Procedures done under sedation plus local anesthesia.

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<sub>A</sub> brain receptors, without having found selectivity GABA<sub>A</sub> receptor subtypes. It acts enhancing the activity of GABA<sub>A</sub> 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 reticulate 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].

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     |
| Etorphine      | 5     | 11    | 17    | 22    |
| Propofol       | 8     | 9     | 11    | 12    |
| Midazolam      | 27    | 27    | 27    | 27    |
| Remifentanil   | 3     | 3     | 3     | 3     |
| Fentanyl       | 35    | 131   | 217   | 256   |

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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 resedation. Pambianco et al. [36] studied 162 patients of both sexes, aged 18-70 years 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%, 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 30 mg/ 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-remifentanil 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,
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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 remifentanil and midazolam having organ-independent metabolism like remifentanil and acting in GABA receptors like midazolam. Similar to remifentanil, 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 induction, 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 inexpert in managing the airway.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Tan KR, Rudolph U, Lascher C (2010) Hooked on benzodiazepines: GABAA receptors subtypes and addiction. Trends Neurosci 34(4): 188-197.
2. Daile JW (2004) Sedative-hypnotic and anxiolytic drugs. In: Craig CL, Sitzel R, Modern pharmacology with clinical application, Lippincott Williams & Wilkins, USA, pp. 355-363.
3. Vaessen HH, Knape JT (2016) Considerable variability of procedural sedation and analgesia practices for gastrointestinal endoscopic procedures in Europe. Clin Endosc 49(1): 47-55.
4. Pambianco DJ, Harli R (2011) The debate for non anesthesiologist-administered propofol sedation in endoscopy rages on. Gastroint Endosc 74(2): 449.
5. Coté GA (2011) The debate for non anesthesiologist-administered propofol sedation in endoscopy rages on: who will be the “King of Prop”? Gastroint Endosc 73(4): 773-776.
6. Gin T (2013) Hypnotic and sedative drugs—anything new on the horizon? Curr Opin Anaesthesiol 26(4): 409-413.
7. Upton RN, Somogyi AA, Martinez AM, Colvill J, Grant C (2010) Pharmacokinetics and pharmacodynamics of the short-acting sedative CNS 7056 in sheep. Br J Anaesth 105(6): 798-809.
8. Upton RN, Martinez AM, Grant C (2009) Comparison of the sedative properties of CNS 7056, midazolam, and propofol in sheep. Br J Anaesth 103(6): 848-857.
9. Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM (2012) 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 115(2): 274-283.
10. Rogers WK, McDowell TS (2010) Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. I Drugs 13(12): 929-937.
11. Trudell JR, Bertaccini E, Maciver MB (2012) Teaching an old GABA receptor new tricks. Anesth Analg 115(2): 270-273.
12. Rudolph U, Davies MF, Barr J (2011) Benzodiazepines. In: Alex SF, Mervyn Maze, Evan D Kharaesch Anesthetic Pharmacology, 2nd edn, Cambridge University Press. Cambridge University Press, USA, pp. 465-477.
13. Goodchild CS (1993) GABA receptors and benzodiazepines. Br J Anaesth 71(1): 127-133.
14. Sheen MJ, Chang FL, Ho ST (2014) Anesthetic premedication: new horizons of an old practice. Acta Anaesthesiol Taiw 52(3): 134-142.
15. Schwender D, Golling W, Klaing S, Fabzer-Zulig E, Poppel E, et al. (1994) Effects of surgical stimulation on midlatency auditory evoked potentials during general anaesthesia with propofol/fentanyl, isoflurane/fentanyl and flunitrazepam/fentanyl. Anaesthesia 49(7): 572-578.
16. Whizar LV, Ávila CR, De Lille FR, Ramírez AJ (1978) Flunitrazepam como agente inductor de la anestesia general y su uso en anestesia de rotura uterina. Rev Mex Anest 1: 23-28.
17. Ramírez AJ, Whizar LV, García B, López HG (1978) Injectable lorazepam as premedication in general anesthesia. Sedative effect and safety compared to diazepam. Rev Invest Clin (Mex) 31(4): 369-376.
18. No author listed (2010) International nonproprietary names for pharmaceutical substances (INN). WHO Drug Information 24(3): 259-290.
19. Buchwald P, Bodor N (2014) Recent advances in the design and development of soft drugs. Pharmazie 69(6): 403-413.
20. Johnson KB (2012) New horizons in sedative hypnotic drug development: fast, clean, and soft. Anesth Analg 115(2): 220-222.
21. Willshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM (2012) 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 115(2): 284-296.

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22. Johnson K, Egan T (2008) Principles of pharmacokinetics and pharmacodynamics: applied clinical pharmacology for the practitioner. In: Longnecker D, Brown D, Newman M, Zapfel E (Eds.), Anesthesiology (1st edn), McGraw Hill, New York, USA, pp. 821-848.

23. Kilpatrick GJ, McIntyre MS, Cox RF, Stafford JA, Pascasio GJ, et al (2007) CNS 7056: a novel ultra-short-acting benzodiazepine. Anesthesiology 107(1): 60-66.

24. Zhou Y, Wang H, Jiang J, Hu P (2015) Simultaneous determination of remimazolam and its carboxylic acid metabolite in human plasma using ultra-performance liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 976-977: 78-83.

25. Goudra BG, Singh PM (2014) Remimazolam: The future of its sedative potential. Saudi J Anaesth 8(3): 388-391.

26. Ilic RG (2015) Fospropofol and remimazolam. Int Anesthesiol Clin 53(2): 76-90.

27. Goudra BG, Singh PM (2014) Propofol alternatives in gastrointestinal endoscopy anesthesia. Saudi J Anaesth 8(4): 540-545.

28. Vaessen HH, Knape JT (2016) Considerable variability of procedural sedation and analgesia practices for gastrointestinal endoscopic procedures in Europe. Clin Endosc 49(1): 47-55.

29. Lee CK, Dong SH, Kim ES, Moon SH, Park HL, et al. (2016) Room for quality improvement in endoscopist-directed sedation: Results from the first nationwide survey in Korea. Gut Liver 10(1): 83-94.

30. Tsai HC, Lin YC, Ko CI, Lou HY, Chen TL, et al. (2015) Propofol versus midazolam for upper gastrointestinal endoscopy in cirrhotic patients: a meta-analysis of randomized controlled trials. PLoS One 10(2): e0117585.

31. Goudra B, Nuzat A, Singh PM, Gouda GB, Carlin A, et al. (2015) Cardiac arrests in patients undergoing gastrointestinal endoscopy: A retrospective analysis of 73,029 procedures. Saudi J Gastroenterol doi: 10.4103/1319-3767.

32. Ramirez J, Whizar-Lugo V, Cruz C, Elizando J (1977) A comparison of intravenous lorazepam and diazepam as endoscopic premedications. Gastroint Endosc 24(2): 80-81.

33. Igea F, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, et al. (2014) Sedation for gastrointestinal endoscopy. Endoscopy 46(8): 720-731.

34. Borkett KM, Riff DS, Schwartz HI, Winke PJ, Pambianco DJ, et al. (2015) A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. Anesth Analg 120(4): 771-780.

35. Worthington MT, Antonik LJ, Goldwater DR, Lees JP, Ogunkiyi K, et al. (2013) A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. Anesth Analg 117(5): 1093-1100.

36. Pambianco DJ, Borkett KM, Riff DS, Winkle PJ, Schwartz HI, et al. (2015) A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. Gastrointest Endosc 83(5): 984-992.

37. Doi M, Morita K, Shimishi Y, Kato T, Kurita T, et al. (2015) Remimazolam dose finding studies for anesthetic/sedative in the indication general anesthesia in Japanese volunteers/patients. Anesthesiology A3011.

38. Sato S, Doi M, Morita K, Takeda J, Sakamoto A, et al. (2015) Remimazolam a new ultra-short acting anesthetic shows similar efficacy and superior hemodynamic stability vs. propofol in general surgery patients with TIVA: Results of a randomized, non-inferiority, phase IIb/III trial. Anesthesiology A5018.

39. Probst S, Bevilacqua C, Eibel S, Müller A, Wohlers S, et al. (2015) Difference in vasopressor use and usage patterns in patients undergoing cardiac surgery with remimazolam versus propofol/ sevoflurane for general anesthesia. Anesthesiology A4025.

40. http://www.paion.com/remimazolam/product-information/clinical-trials/

41. Buchwald P, Bodor N (2014) Recent advances in the design and development of soft drugs. Pharmazie 69(6): 403-413.