REVIEW ARTICLE

Remimazolam: The future of its sedative potential

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ABSTRACT

Remimazolam (CNS 7056) is a new drug innovation in anesthesia. It combines the properties of two unique drugs already established in anesthesia – Midazolam and remifentanil. It acts on GABA receptors like midazolam and has organ-independent metabolism like remifentanil. It is likely to be the sedative of the future, as preliminary phase II trials have shown minimal residual effects on prolonged infusions. It has potential to be used as a sedative in ICU and as a novel agent for procedural sedation. Unlike most rapidly acting intravenous sedatives available presently, the propensity to cause apnea is very low. Availability of a specific antagonist (flumazenil) adds to its safety even in cases of overdose. The present review discusses remimazolam's potential as a new drug in anesthesia along with the presently available literary evidence.

Key words: *CNS 7056, newer sedatives in anesthesia, remimazolam, soft chemistry in anesthesia*

INTRODUCTION

Although anesthesiology, as a specialty, has come a long way since the first public demonstration of ether anesthesia, the search for an elusive ideal anesthetic is still on. In the last 15-20 yrs, the field of intravenous anesthesia and sedation seems to have made significant strides in filling this void. It is unlikely that a single drug would ever be found that would meet all the pharmacological and safety requirements. However, there is increasing realization that an existing Gama Aminobutyric Acid (GABA) agonist with suitable molecular modification might be the next logical step. Propofol has significant limitations, especially with prolonged infusion. Pain on injection is sometimes the only event patients remember. Propofol infusion syndrome, although extremely rare, is sometimes fatal and enough to deter some anesthesiologists from using it as an infusion, especially in pediatric population. Additionally, as per American Society of Anesthesiologists (ASA) guidelines, practitioners with insufficient airway skills are discouraged from using propofol. Given the pharmacokinetic and pharmacodynamic variability, the later restriction on the use of propofol seems to be appropriate. Additionally, target-controlled infusion (TCI) devices are currently unavailable for propofol in USA and this is unlikely to change. In view of the above, a suitable alternative to propofol, at least in some situations, seems to be desirable. Remimazolam with its suggested pharmacological benefits might be the answer for at least some of these propofol shortcomings. It has emerged from its initial animal experiments, and human studies are underway to determine its place in anesthesiologists armamentarium.[1-4] A word of caution to tamper the optimism is warranted. Anesthesia literature is rich with "promising" drugs, rapacuronium, mivacuronium, althesin are just a few examples. It is hoped that remimazolam will not meet the same fate.

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Chemistry and formulations

Midazolam is the parent compound of remimazolam. As the name indicates, this new drug is midazolam incorporating pharmacokinetic properties of remifentanil. The structure of midazolam, remifentanil, and remimazolam is

presented in Figure 1. Like many drugs used in anesthesia, introduction of a carboxylic ester linkage makes the drug suitable for metabolism by non-specific tissue esterases in the blood. Other anesthetic drugs demonstrating similar kinetics and metabolized by blood esterases are mivacurium and remifentanil.

Like other benzodiazepines, remimazolam acts on GABA receptor, specifically GABA-alpha.[5] Other drugs acting on GABA receptors are propofol (GABA-beta), etomidate (GABA-alpha), and thiopentone (GABA-alpha), all commonly used anesthetics. GABA is the main inhibitory neurotransmitter in the central nervous system. The actions of benzodiazepines on GABA receptors are dose-dependent, lower does are anxiolytic and with increasing doses, sedative and hypnotic effects dominate. As a result, at appropriate doses suitable, benzodiazepines can be used as anesthetics.

Pharmacokinetics and metabolism

Remimazolam undergoes dose-independent ester hydrolysis. In the clinical doses, the enzymes are unlikely to be saturated and as a result, there is no accumulation reported.[6,7] In other words, the rate of reaction continues to follow first order kinetics and is unlikely to change to zero order in the recommended doses. As a result, increasing doses or prolonged infusions are unlikely to have prolonged or residual effects. Due to organ-independent elimination, it can be safely used in patients with hepatic or renal impairment. Additionally, age-related deterioration of hepato-renal drug handling is less likely to have impact on remimazolam's clinical profile. Initial study has shown a mean clearance of 70.3 ± 13.9 L/h and a mean steady state volume of distribution of 34.8 ± 9.4 L.[7] It has a context sensitive halftime of 7-8 minutes after a 2-hour infusion. Needless to say, that for midazolam, they are significantly higher. However, the duration is still significantly longer than remifentanil (another drug metabolized by esterases following similar kinetics). Used as a continuous infusion for similar periods, propofol has also a similar context-sensitive halftime. It is yet to be demonstrated if the decrement times of remimazolam as hypothesized actually remain the same with increments in infusion doses.

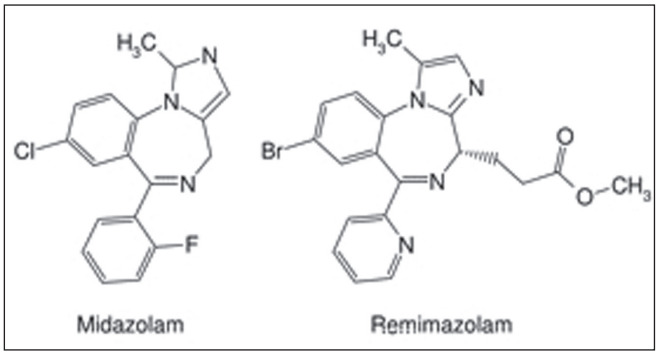

Figure 1: Structural comparison between midazolam and remimazolam

Dosages and clinical use

The possible clinical uses of remimazolam (from an anesthesia practitioner standpoint) fall into four broad areas

1. Single dose for premedication
2. Bolus followed by supplemental doses for procedural sedation.
3. Intravenous anesthetic along with an opioid (as part of total intravenous anesthesia)
4. Intensive care unit (ICU) sedation

Remimazolam as a single dose for premedication

As a premedicant or pre-induction sedative, remimazolam is unlikely to turn out to be superior to midazolam. An onset time of 1-3 min after a dose of 0.075 mg/Kg is no different than midazolam.[7] The short offset time is hardly an advantage either with a single dose or infusion. A longer clinical duration may be desirable for an anxious patient waiting for induction. Either the anxiolysis must be administered just prior to transferring to operating room, as in case of children, or may be used as infusion. A scenario where this short offset may be used to clinical advantage may be in patients requiring short-term sedation or where longer acting sedatives may be potentially hazardous. Morbidly obese patients are often denied sedation during short procedures like epidural catheter placement or central line insertion. These procedures are often technically challenging in morbidly obese and are further complicated by patient-related anxiety. Titration to a desired level of sedation with limited risk of airway obstruction is likely to be easier with remimazolam (unlike propofol, which is a high ceiling anesthetic).[8] The availability of an antidote (flumazenil) for both is another advantage over propofol. The eventual clinical utility will be further guided by cost-benefit ratio that is ultimately determined by factors outside clinicians use.

Remimazolam — As an infusion for procedural sedation

Many gastrointestinal (GI) endoscopic procedures like diagnostic gastro-duodenoscopy or screening colonoscopy can be completed with a short-acting benzodiazepine along with short-acting opioid like fentanyl. Recently, in a phase IIa clinical trial where remimazolam was evaluated for procedural sedation in patients undergoing upper gastrointestinal endoscopy, the time to recovery was found to be shorter than midazolam.[9] Occasionally, addition of a sedative anti-histamine like diphenhydramine hydrochloride was necessary. In addition to the quality of sedation, success of the procedure depends on many factors like skill of the gastroenterologist and patient's pain tolerance. However,

while caring for these patients, turnover is important. Slow onset of action of remimazolam (1-3 min, which is same as midazolam) is a significant handicap, when trying to expedite the process. While readers might think that 1-3 minutes is short, this should be seen in the context of most diagnostic gastro-duodenoscopies that have a procedure time (from the insertion of gastroscope to its removal) of 2-3 min. A failure rate of 56 percent even with high dose (0.2 mg per Kg of body weight) is a significant drawback. The same study had a mean procedure time of 3.3 to 4.3 minutes. Addition of propofol to achieve procedural success beats the very purpose of the drug, which is supposed to replace propofol. The need of the hour is a drug with very fast and predictable onset of action. Propofol will remain the drug of choice in these situations. Although onset of action of remimazolam can be accelerated with larger doses or combining with fentanyl, it is likely that incidence of respiratory depression will increase. In patients who underwent colonoscopy,[10] some suffered hypotension and low oxygen saturation. Considering these complications are rare even in patients undergoing endoscopic retrograde cholangio pancreatography (ERCP) with propofol.[11] Colonoscopy could not be completed in 11/44 subjects mainly due to failed sedation. This would be seen as a very high failure rate. These patients cannot be administered propofol as they need to be consented again. Considering that bowel preparation for colonoscopy is tedious and unpleasant, re-scheduling these patients pose significant moral and logistical problems. Patient satisfaction can be severely dented. This could be one of the reasons for the popularity of propofol for colonoscopy in many centers around USA.

Remimazolam as an intravenous anesthetic along with an opioid

Anesthesiologists have traditionally relied on different drugs to address diverse aspects of anesthesia. As a result, we have sedatives, hypnotics, opioids, and muscle relaxants to address various components of anesthesia. Many anesthesiologists practice and teach administration of a combination of a benzodiazepine, opioid, inhalational agent, and a muscle relaxant. However, advent of total intravenous anesthesia (TIVA) has changed the landscape. TIVA aims to achieve the twin elements (hypnosis and analgesia) with propofol and an analgesic, usually remifentanil. Experience with millions of anesthetics and research suggests that incidence of awareness with total intravenous anesthesia is similar to inhalational anesthesia. Cases of awareness due to delivery system malfunction cannot be blamed on the technique. Like propofol, remimazolam is a GABA agonist and produces dose-dependent and measurable hypnosis. Its unique metabolism (ester-dependent hydrolysis) would ensure that accumulation will not occur after prolonged infusion. It is also reversed by flumazenil. These aspects of clinical safety and efficacy for use as a general anesthetic are presently under investigation. Patient recruitment is in progress for phase II trial evaluating, efficacy, safety, and pharmacokinetics of remimazolam, compared with propofol and sevoflurane, during the induction and maintenance of general anesthesia.

Propofol, the most commonly used component of TIVA, has some significant drawbacks. Pain on injection is still to be addressed to the satisfaction of all patients and anesthesia providers. The fear of propofol infusion syndrome might act as a significant deterrent to some of the anesthesiologists, especially for long surgeries. Most importantly, there is accumulation of propofol with pronged infusion due to the nature of its metabolism. Use of propofol with a target-controlled infusion (TCI) pump is unlikely to be ever realized in USA. An alternative to propofol is clearly justified. Remimazolam might be ideally placed to succeed in this regard. As a new drug, it is hoped that it will be approved for administration with a TCI device in USA.

However, the cost of the drug needs to be taken into account. Although the drug is not released into the market, the manufacturers will try to realize the costs (of research and development) and acquire profits while the patent is on. Due to its unique metabolism, infusion doses are likely to be large for anesthesia maintenance. If priced appropriately for infusion requirements, it might turn out to be cheap for bolus needs. Another factor is the volume of infusion. The manufacturers have not indicated the concentration of the drug for marketing. Any drug with ester hydrolysis will be consumed rapidly and require larger quantities for equipotent clinical effects. This is seen with both remifentanil and mivacurium.

Remimazolam as an infusion for ICU sedation

Recent evidence suggests that sedation-free intervals in ICU enhance the likelihood of early extubation. Often, critically-ill patients have essential organ dysfunction (hepatic or renal). Most sedatives used presently require hepatic metabolism followed by renal clearance. Thus, although sedation is stopped, the altered pharmacokinetics of excretion or metabolism is an issue. Furthermore, most drugs (other than propofol) have significantly long pharmacological half-life. The ideal drug of choice in such a scenario would be a short-acting agent with metabolism independent of liver or kidney, which are actually the properties of remimazolam. Presently, trials on ICU sedation involving remimazolam are not available, but its prospects of becoming preferred drug are very bright.

Future

The "soft chemistry" (self-metabolizing, organ-independent drugs) in anesthesia and critical care has been the focus of modern research.[12] The initial mammoth task of designing

and manufacturing this unique benzodiazepine is achieved. The drug has undergone preliminary testing in humans and shown favorable results. Many phase II human trials evaluating its safety and efficacy for sedation are already underway. The challenge for all of us is to find the right niche for this drug in clinical practice.

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