



## REVIEW ARTICLE ON DRUG REMIMAZOLAM

## Anaesthesiology

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## ABSTRACT

Remimazolam is a new drug innovation in anesthesia. 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. 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.

## KEYWORDS

## INTRODUCTION

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 results in 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. Given the pharmacokinetic and pharmacodynamic variability, the later restriction on the use of propofol seems to be appropriate. 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). Midazolam is the parent compound of remimazolam. As the name indicates, this new drug is midazolam incorporating pharmacokinetic properties of remifentanyl. 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 remifentanyl. Like other benzodiazepines, remimazolam acts on GABA receptor, specifically GABA-alpha.(5) The actions of benzodiazepines on GABA receptors are dose-dependent, lower doses are anxiolytic and with increasing doses, sedative and hypnotic effects dominate.

## 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  $70.3 \pm 13.9$  L/h and a mean steady state volume of distribution of  $34.8 \pm 9.4$  L.(7) It has a context sensitive half-time of 7-8 minutes after a 2-hour infusion.

## 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.

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 remifentanyl. 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.

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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