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Remimazolam: Revolutionizing Tiva

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Abstract: ***Drugs having a short duration of action and early recovery are often the preferred choice for sedation. Propofol fits into this category but it has safety issues such as decrease of blood pressure, respiratory depression, vascular pain and a high susceptibility of the drug to bacterial growth.(1,2) It also lacks a reversal agent. Midazolam has a weaker circulatory suppressive effect than propofol, but it is rarely used for the induction and maintenance of general anaesthesia because of its longer duration of action (40 min), variable onset and offset of sedative effect. (3, 4, 5). Remimazolam (CNS 7056, $C_{21}H_{19}BrN_4O_2$) is a novel benzodiazepine created out of a soft drug development technique known as rational drug designing. It is an ultrashort-acting intravenous sedative-anesthetic currently in Phase III clinical trials as a safe and effective option for procedural sedation. Remimazolam does not produce injection site pain. Its safety of clinical use is further increased by the availability of benzodiazepine antagonist Flumazenil. High extra hepatic clearance also confers little scope for metabolic interactions with other drugs in the liver and its propensity to cause apnea is very low.(6)***

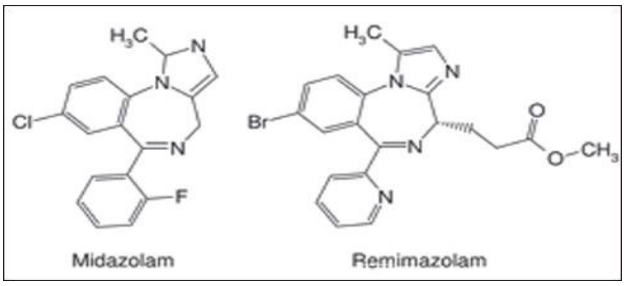
Keywords: Remimazolam, TIVA

1. Pharmacokinetics and Metabolism

Total body clearance of remimazolam (~4 litre/minutes) is much higher than the hepatic blood flow-indicating significant extra hepatic metabolism (~2.6 litre/minutes) . The incorporation of a metabolically labile carboxylic ester moiety into the benzodiazapine core of remimazolam renders it susceptible to hydrolysis by non-specific tissue and plasma esterases. The drug undergoes organ-independent metabolism to an inactive metabolite CNS-7054 that has low activity at the GABA-A receptor. In the clinical doses, the plasma esterase enzymes are unlikely to be saturated and also, because remimazolam follows first-order pharmacokinetics, there is no accumulation reported even after prolonged infusions or higher doses. This makes it favorable for use as an intravenous anesthetic and for sedation in the intensive care unit. 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. It has a context sensitive halftime of 7-8 minutes after a 2-hour infusion. Onset time is 1-3 minutes after the dose of 0.075 mg/kg with peak sedative effect of 4 minutes and its duration of sedation being 10 minutes. (7,8,9)

2. Mechanism of Action

Remimazolam binds to brain benzodiazepine receptors with high affinity and does not show any affinity for a range of other receptors. The benzodiazepine receptors are present on GABA-A BZD receptor chloride channel complex. This receptor channel complex is comprised of alpha, beta and gamma subunits (pentameric assembly) surrounding the chloride channel present in the centre. Benzodiazepine binding requires alpha and gamma subunits. After combining with its receptor, it facilitates the opening of GABA activated chloride channels i.e. an increase in chloride conductance and hyperpolarisation, decreasing the firing rate of neurons and producing an inhibitory response. This action of benzodiazepines on GABA receptors is dose dependent, lower doses acting as an anxiolytic and higher doses producing sedative, hypnotic or anesthetic effect. (10, 11, 12)



Structural comparison between midazolam and remimazolam

2.1 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 (13)

2.2 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 as onset time is similar. 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 awaiting induction. The anxiolytic must be administered just prior to transferring of the patient into the operating room (as in case of children) or used as an infusion. A short offset may be advantageous 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. 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. The availability of an antidote (flumazenil) 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.(14)

2.3 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. With remimazolam, the time to recovery is shorter than midazolam. The quality of sedation and success of the procedure depends on factors like skill of the gastroenterologist and patient's pain tolerance. The slow onset of action of remimazolam (1-3 min, same as midazolam) is a significant handicap, when trying to expedite the process. While readers might think that 1-3 minutes is short, most diagnostic gastro-duodenoscopies have a procedure time just 2-3 min. Propofol remains the drug of choice in these situations. A larger dose of remimazolam or combining with fentanyl is likely to increase the likelihood of respiratory depression. In colonoscopic procedures, 25% of patients administered remimazolam had transient hypotension and desaturation and procedure could not be completed. Considering that bowel preparation for colonoscopy is tedious and unpleasant, re-scheduling these patients poses additional problems. Remimazolam is considered unsuited for endoscopic procedural sedation.(15,16)

2.4 Remimazolam as an infusion for ICU sedation

TIVA aims to achieve the twin elements (hypnosis and analgesia) with propofol and an analgesic. 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. Propofol, is associated with pain and its infusion with accumulation. A life threatening situation can occur due to direct mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by propofol in high doses. 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.(17)

Sedation-free intervals in ICU enhances 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. Remimazolam has prospects of becoming a preferred drug for ICU in the future.

3. Conclusion

The “soft chemistry” concept of self-metabolizing, organ-independent drugs in anesthesia and critical care has become a shot-in-the-arm for anesthesiologists and intensivists. Research in the field has resulted in several short-acting agents with metabolism independent of liver or kidney. Remimizolam has all the prospects of becoming a preferred drug in the near future.

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