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Review Article

Anaesthesia Section

Remimazolam (CNS 7056): an Emerging Sedative and General Anaesthetic

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ABSTRACT

Remimazolam is a newer drug in the field of anaesthesia. It combines the properties of midazolam and remifentanil. As the name indicates, midazolam is the parent compound of remimazolam which incorporates the pharmacokinetic properties of remifentanil. Remimazolam is an ultra short acting anaesthetic agent/sedative which rapidly shows its effect after injection and also wears off expeditiously after cessation. Therefore, remimazolam's dosage can be ideally controlled. Since it acts on benzodiazepine receptors, availability of specific antagonist (flumazenil) further adds to its safety in case of overdose.

Keywords: Anaesthesia, Benzodiazepine, Midazolam, Propofol, Sedative

INTRODUCTION

In the ancient times, various non pharmacological (cold, concussion, carotid compression, nerve compression, bloodletting and hypnosis) and pharmacological measures (alcohol, opium, hyoscine, cocaine) were used to produce anaesthesia. With passing time various new agents and technologies have been introduced in the field of medicine including anaesthesia and changed the way of clinical practice. Procedures once performed only in hospitals are now commonly conducted in outpatient settings and demand such type of drugs which produce faster and predictable effect with easy reversibility of action and lesser side effect profile. Drugs currently under development are CNS-7056, THRX-918661, Methoxycarbonyl-etomidate (MOC-etomidate) and melatonin analogs [1,2].

Remimazolam (CNS-7056) is an emerging intravenous sedative which is developed by rational drug designing. One of the approaches in rational drug designing is the modification of a known drug to create an analog with improved pharmacokinetic properties. Remimazolam has been developed after the incorporation of metabolically labile ester moiety into the benzodiazepine core. This modification makes the remimazolam highly susceptible to hydrolysis by plasma esterases. Because of its organ-independent metabolism, rapid and predictable onset and recovery, remimazolam appears to have potential advantages over other currently available short-acting sedatives-midazolam and propofol [3,4,5].

Chemistry and Mechanism of Action

Remimazolam (CNS 7056) is an innovative short-acting benzodiazepine derivative which combines the properties of two commonly used drugs in anaesthesia-midazolam and remifentanil. As the name indicates, midazolam is the parent compound of remimazolam which incorporates the pharmacokinetic properties of remifentanil [6].

Remimazolam binds to brain benzodiazepine receptors with high affinity and does not show any affinity for a range of other receptors [7]. 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 subunit. After combining with its receptor benzodiazepines facilitate the opening of GABA activated chloride channels i.e., increase in chloride conductance and hyperpolarisation and thus, decrease the firing rate of neurons and produce inhibitory response. The action of benzodiazepines on GABA receptors are dose dependent, lower doses act as anxiolytic whereas higher doses produce sedative and hypnotic effect. As a result, at an appropriate dose benzodiazepine acts as suitable anaesthetic agents.

Pharmacokinetics

Remimazolam (CNS 7056) is a methyl ester which undergoes dose independent ester hydrolysis by tissue esterases and converts into inactive metabolite CNS 7054. CNS 7054 has low activity at the GABA-A receptor. The conversion of remimazolam (CNS-7056) to CNS 7054 is an important mechanism which limits the duration and intensity of sedative effect of remimazolam. The plasma clearance of CNS 7056 is approximately three times more rapid than the clearance of midazolam [8]. Preclinical studies show 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). Due to organ independent elimination, it can be safely used in patients with hepatic or renal impairment. High extra hepatic clearance also confers little scope for metabolic interactions with other drugs in the liver. Remimazolam follows first order kinetics. As a result on prolonged infusion or on increasing dose no drug accumulation occurs and thus no residual effects observed [6,8,9].

Remimazolam as General Anaesthetic Agent

General anaesthesia is a reversible loss of consciousness and includes amnesia, analgesia, loss of sensation, muscle relaxation and loss of various reflexes. Currently available intravenous sedatives for general anaesthesia include propofol, midazolam, dexmedetomidine. Propofol is used because of the short duration of sedative action and early recovery, but it has safety issues such as decrease of blood pressure, respiratory depression, [10] vascular pain [11] and high susceptibility of bacterial growth [12]. It also lacks a reversal agent. Midazolam has a weaker circulatory suppressive effect than that of propofol, but it is rarely used for the induction and maintenance of general anaesthesia because of its long duration of action and less control of sedation [10].

Phase III study was carried out to compare the efficacy and safety of remimazolam with propofol in 375 surgery patients (2 groups with induction speed at 6 mg/kg/hour and 12 mg/kg/hour, 150 subjects per group (remimazolam/CNS 7056) and 75 patients (propofol), respectively) undergoing general anaesthesia. Study result showed that general anaesthetic effect was observed in all the patients of each group. However, remimazolam showed a clinically meaningful advantage regarding cardiodepressive/hypotensive effects compared

to propofol. (The incidence rates of decrease in blood pressure were 35.3%, 34.7% and 60.0% in the 6 mg/kg/hour and 12 mg/kg/hour remimazolam and propofol groups, respectively). The other benefit of remimazolam over propofol is that it does not produce injection site pain which is common in propofol. Propofol is often co-administered with lidocaine as it causes pain on injection site, to avoid patient discomfort. No other significant adverse events of concern were observed [13,14].

Since, remimazolam undergoes ester dependent hydrolysis the chances of accumulation of drug after prolonged infusion is also less and thus the chances of development of syndrome like "propofol infusion syndrome" are also rare. The safety of remimazolam is further increased by the availability of benzodiazepine antagonist Flumazenil [6]. Both drugs remimazolam and midazolam showed onset time of 1-3 minutes after the dose of 0.075 mg/kg with peak sedative effect of 4 minutes and 10 minutes respectively. Remimazolam also showed better control of sedative effect along with markedly shorter duration of sedation (10 minutes) as compared to midazolam (40 minutes) [15,9].

Remimazolam as Procedural Sedative

In US, remimazolam is developed as an agent for procedural sedation. According to American Society of Anaesthesiologists (ASA) presence of anaesthesiologist is must, if the procedure is carried out under propofol sedation due to its variable pharmacokinetics and pharmacodynamics property [10]. Unlike propofol, an anaesthesiologist does not need to be present under the sedation with midazolam, as midazolam is very safe agent for providing conscious sedation but the disadvantages of midazolam are its longer duration of action and variable onset and offset of sedative effect. This results in reduced numbers of procedures with midazolam as compared to propofol. The high number of procedures in a doctor's surgery/clinic is not only necessary to manage the facility's business but also to fulfil the social mission to screen as many patients as possible, as colonoscopies are the only proven method for early detection and prevention of colon cancer. So, there is a need of drug that incorporates the desirable properties of both propofol and midazolam i.e., rapid and shorter duration of action as propofol and safe as midazolam.

Being a benzodiazepine, remimazolam is as safe as midazolam and also shows a controllable sedative and anaesthetic effect with rapid onset and offset. An exploratory study was carried out in patients to assess the safety and efficacy of remimazolam in different single doses for procedural sedation. A single dose of remimazolam resulted in a successful procedure in 32%, 56%, and 64% of patients in the low (0.10 mg/kg), middle (0.15 mg/kg), and high (0.20 mg/kg) dose groups compared with 44% of patients in the midazolam (0.075 mg/kg) dose group. The onset of sedation was 1.5 to 2.5 minutes in the remimazolam dose groups compared with five minutes for midazolam [16]. A Phase Ib study was carried out to assess the feasibility of remimazolam in maintaining suitable sedation during colonoscopy. Study result showed that remimazolam produced adequate sedation in 33 out of 44 patients undergoing colonoscopy which is quite encouraging for a new sedative drug. Failures were due to inability to sedate or due to adverse events like hypotension (BP80/40) and low partial pressure of oxygen (SpO_2<90%) [17]. Since the trial was conducted in small number of population it is possible that few adverse effects of remimazolam might be observed later on.

Remimazolam can also be used as procedural sedative in morbidly obese patients because of its rapid onset, short duration of action and body weight independent clearance which could provide an increased safety margin during vulnerable operative times, such as induction, emergence, and recovery from anaesthesia [9].

Remimazolam as a Preanaesthetic Medication

Benzodiazepines (diazepam, lorazepam, midazolam) are used commonly as a pre anaesthetic medication in clinical practice. These drugs possess useful anxiolytic and sedative activity. Midazolam is preferred over other benzodiazepines because of rapid and shorter duration of action and low frequency of venous irritation [18,19,20]. Phase I study was carried out to compare the safety, efficacy and pharmacokinetics properties of intravenous remimazolam with intravenous midazolam. Remimazolam was well tolerated and no serious Adverse Events (AEs) were reported. Three AEs of mild (SpO_2 85%-88%) haemoglobin desaturation (2 in the remimazolam groups and 1 in the midazolam group) resolved spontaneously, and 1 AE of moderate hemoglobin desaturation (SpO_2 75%) resolved with a chin lift in the remimazolam group. Study result also suggested that the duration of sedative effect of remimazolam (10 minutes) is markedly less as compared to midazolam (40 minutes) [11,9]. This shorter duration of sedative effect of remimazolam hardly has any advantage over midazolam because longer clinical duration is required for anxious patient waiting for induction. In such case either anxiolysis should be given along with remimazolam or it should be administer as a infusion. However, shorter duration of remimazolam is particularly helpful in patients requiring short term sedation or in patients where long acting sedative is potentially hazardous [6].

Remimazolam as an Infusion for ICU Sedation

Remimazolam is expected to be a good sedative agent for ICU patients. Often, patients in ICU have multiple diseases with major organ dysfunction (hepatic or renal). So, the sedatives which are eliminated by the body either by hepatic or renal route would have long pharmacological half life. The ideal drug of choice would be remimazolam, a short acting agent with metabolism independent of liver or kidney. A phase 2 clinical trial was carried out in 90 postoperative patients to assess the efficacy and safety of remimazolam for sedation during mechanical ventilation in the Intensive Care Unit (ICU). However, the trial was discontinued early because of higher plasma level of remimazolam in few patients. The manufacturers concluded remimazolam, may occasionally exhibit higher concentration in the blood of patients with typical ICU complications (blood loss, fluid imbalance or the reduction of several important organ functions). However, higher plasma concentration of remimazolam can be prevented by using therapeutic drug monitoring. Still, there is dilemma regarding the use of remimazolam as an infusion in ICU sedation [6].

CONCLUSION

Remimazolam is a novel ultra short acting benzodiazepine which incorporates the ester moiety in its structure. Due to the presence of ester moiety, it is hydrolysed by tissue esterases and shows organ independent metabolism and thereby safe in hepatic and renal failure patients. Although some side effects of remimazolam are similar to midazolam like headache, somnolence, changes in heart rate, blood pressure but its effects are reversed by flumazenil. Researchers have tried to develop remimazolam as a potential anaesthetic and sedative agent; however, more studies are required to establish the drug in the clinical practice.

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