

## General

# A comprehensive review of remimazolam for sedation

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Benzodiazepines are one of the most commonly used medications in the field of anesthesia. They offer excellent anxiolytic and amnestic properties ideal for the perioperative period when patient anxiety is understandably heightened. Remimazolam has presented a favorable alternative to some of the common intravenous anesthetic agents used given its fast onset of action, high safety profile, and reasonably short duration of action.

The drugs within the four classes of benzodiazepines, 2-keto-benzodiazepines, 3-hydroxy-benzodiazepines, triazolo-benzodiazepines, and 7-nitro-benzodiazepines provide varying degrees of anxiolysis, sedation, and amnesia. This is provided by the benzodiazepine molecule binding and causing a conformational change to the chloride ion channel to cause hyperpolarization and thus inhibition of the central nervous system. Each type of benzodiazepine has a preferred role within the realm of medicine. For instance, diazepam is used for the treatment of seizures and anxiety. Midazolam's anxiolytic and anterograde amnestic properties are taking advantage of during the perioperative period. Lorazepam is beneficial for anxiety and status epilepticus.

Remimazolam, currently in phase II and III clinical trials, has demonstrated a very short duration of action and low context-sensitive half-time, allowing for its rapid removal even during a prolonged infusion. Much of its properties may be credited to being a soft drug, meaning it is a metabolically active drug that is rapidly inactivated in the body. This provides anesthesiologists and other practitioners administering it with a more predictable sedative. These properties have the potential to push it towards becoming the drug of choice for premedication during the perioperative period and sedation in the ICU.

Furthermore, remimazolam does not seem to rely on any specific organ to be metabolized. The drug's ester moiety makes it a substrate for non-specific tissue esterase enzymes, meaning its metabolism and elimination are not impaired in patients with hepatic and/or renal disease. Its addictive potential closely resembles that of its parent compound, midazolam. Reports of its adverse reactions include headache and somnolence after an involuntary movement during infusion.

Benzodiazepines are a great adjunct to anesthetic care. Remimazolam's safety profile, pharmacokinetics, pharmacodynamics, and potential practical use make it quite favorable in this regard. It has the potential to equip anesthesiologists and other medical practitioners with a more predictable medication that has a good safety profile. However, further large clinical trials will provide us with a better understanding of the advantages and disadvantages of remimazolam.

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## INTRODUCTION

Remimazolam is a benzodiazepine drug that is a recent innovation in the field of anesthesia.<sup>1</sup> Benzodiazepines are a class of drugs that directly interact with gamma-aminobutyric acid (GABA) and modifiable chloride channels through polysynaptic pathway inhibition.<sup>2</sup> In anesthesia, the anxiolytic properties of benzodiazepines make them useful as sedatives, which are loosely defined as the middle ground between naturally relaxed, and an unconscious state as one would be under general anesthesia.<sup>3</sup> In terms of intravenous hypnotic agents, propofol has long been thought of as the “ideal agent” since the first administration of its current formulation (Diprivan) and its subsequent debut into clinical usage in 1986. However, scientists and clinicians continue to question how ideal propofol is due to certain risks. For example, its requirement for formulation in a lipid solution introduces the risk of bacterial contamination from open air. There have also been reports of pain on intravenous injection, aside from its most well-known risk of cardiorespiratory depression.<sup>4,5</sup> Midazolam is also not an optimal anesthesia drug, as although its effects of cardiorespiratory depression are less, it comes with the risk of excessive sedation. It can accumulate in situations such as renal impairment and prolonged infusion. Individual variability in cytochrome P450-3A4 activity can cause the drug’s onset and duration to fluctuate unpredictably. Propofol has a fast onset of 9-51 seconds and recovery of 10 minutes but comes with a considerably unattractive safety profile; midazolam is safer and is the shortest acting benzodiazepine currently available on the US market but has an onset of 3-5 minutes and a recovery period of 2 hours. Remimazolam displays a fast onset of action, good safety profile, and short recovery time in comparison to intravenous (IV) sedatives commonly used in anesthesia, such as propofol and midazolam, and it is, therefore, a promising combination of the advantages of Propofol and midazolam.<sup>6,7</sup>

## COMMON USE OF BENZODIAZEPINES

Benzodiazepines primarily exert their effects in the amygdala and reticular activating system via direct interaction with GABA and modifiable chloride channels to cause polysynaptic pathway inhibition.<sup>2</sup> GABA-A, one of three GABA receptor subtypes, is the site of action for benzodiazepines.<sup>8</sup> This receptor has five subunits and is a ligand-gated, chloride-selective ion channel that forms a pocket between its two alpha and two gamma subunits. Benzodiazepines act as positive allosteric modulators where they bind at this pocket.<sup>2</sup> Under normal circumstances, two GABA molecules bind the GABA-A receptor, whereas one benzodiazepine molecule occupies the entire binding site.<sup>9</sup> This induces a conformational change in the chloride channel, causing it to hyperpolarize, leading to the desired effect of inhibiting the central nervous system.<sup>10</sup>

The most common use of benzodiazepines is for sedation, as well as for adjuvants to general anesthetics.<sup>2</sup> Due to their ability to cause various responses in different pa-

tients, reduced potency, slow onset, and long-lasting residual effects, benzodiazepines are not used as primary induction agents.<sup>11</sup> When used as IV induction agents or sedatives, these drugs have advantages, such as water solubility, anxiolytic effects, and amnesia, as seen with midazolam. On the other hand, benzodiazepines such as diazepam are used primarily to manage conditions such as seizures and anxiety and are not used in perioperative settings due to their slow offset and ability to be a venous irritant.<sup>2,12</sup> Benzodiazepines are classified by duration of action, elimination half-life, and/or chemical structure. Short-acting refers to a duration of fewer than 24 hours, while long-acting implies a duration of action greater than 24 hours. Factors that contribute to the duration of action include rate and degree of drug distribution, elimination profile following distribution, and the active metabolites produced upon drug breakdown.<sup>2</sup>

Four groups of benzodiazepines are classified based on chemical structure and half-life: 2-keto-benzodiazepines, 3-hydroxy-benzodiazepines, triazolo-benzodiazepines, and 7-nitro-benzodiazepines. The 2-keto-benzodiazepines include diazepam, chlordiazepoxide, flurazepam, and many other early benzodiazepines. Diazepam is considered the prototype benzodiazepine drug, as it is low potency with a long half-life due to its extensive biotransformation before elimination from the body. It is hydroxylated at the three position to become temazepam, which is then demethylated to form oxazepam, both active drugs and members of the second class 3-hydroxy-benzodiazepines. Another member of this class is lorazepam, which is an exception to the low potency of the other 3-hydroxy-benzodiazepines. Oxazepam has the slowest onset of action and the lowest risk of dependency on the drugs in this class. The 3-hydroxy-benzodiazepines are good for detoxifying inpatients at risk for serious alcohol withdrawal or those with decreased hepatic function with the potential for liver failure.

Additionally, lorazepam can be administered intravenously or intramuscularly to provide a rapid onset of action when this effect is needed, such as for status epilepticus. Drugs in the triazolo-benzodiazepine class have an added ring structure, allowing them to be more ring soluble and have a shorter half-life and greater likelihood of withdrawal. Alprazolam, a member of this class, can do a cross-taper for patients administered clonazepam, as these two agents have similar benzodiazepine binding sites. In contrast, alprazolam has a considerably longer half-life that permits such a taper. The only member of the final class, 7-nitro-benzodiazepines, widely used in the United States, is clonazepam. It has a longer half-life, so once-daily administration is effective to reach target concentrations.<sup>13</sup>

An important clinical consideration for prescription use of benzodiazepines is associated with liability for abuse and dependence. Physicians should be aware that triazolo-benzodiazepines pose the greatest risk of abuse and dependence due to their high lipophilicity and rapid absorption. When it comes to pharmacological management of certain disorders, panic disorder and other chronic anxiety conditions are similar to epilepsy, may warrant benzodiazepines in their management. Despite their sedation effects, how-

ever, benzodiazepines do not make good sleeping aids due to the ability for circulating levels to persist after the individual awakens, impairing alertness and reaction time.<sup>13</sup> In anesthesia, benzodiazepines are the standard drugs chosen for most procedural sedation regimens, regardless of the intended depth or route of administration. While they have little effect on cardiorespiratory function at doses recommended for at-home use for minimal sedation purposes, doses used in anesthesia for moderate or deep sedation reduce ventilation significantly, primarily by depressing hypoxic drive and decreasing muscle tone in the upper airway.<sup>14</sup>

Several newer benzodiazepines could be clinically useful in the future. Among these is remimazolam, one of the most promising and currently in phase II and III clinical trials.<sup>2</sup> This agent is known to be very short-acting as it is metabolized to an inactive carboxylic acid metabolite that is rapidly removed even during prolonged infusions.<sup>7</sup> Its potential clinical uses include premedication for anesthesia, procedural sedation for endoscopic procedures, and sedation in ICU settings.<sup>2</sup> Other new benzodiazepines include clonazepam, adinazolam, 3-hydroxyphenazepam, and 4-chlorodiazepam. Clonazepam is a derivative of clonazepam and alprazolam. It is a highly potent amnesic and sedative benzodiazepine. Its main uses are as a potent amnesic and sedative.<sup>2</sup> When administered, it can have anxiolytic and muscle relaxant effects, making it appropriate in the initial treatment of generalized seizures.<sup>15,16</sup> Adinazolam is a benzodiazepine derivative with anxiolytic, anticonvulsant, sedative, and antidepressant properties. It is used in the treatment of panic disorder, depression, and generalized anxiety disorder.<sup>2</sup> Additionally, it can decrease catecholamine levels, which benefit patients with high levels such as those with pheochromocytomas, heart failure, or myocardial infarction.<sup>17</sup> 3-hydroxyphenazepam is another new benzodiazepine, mainly used recreationally. However, its sedative properties are rarely used to treat epilepsy, alcohol withdrawal, and insomnia. It mimics lysergic acid diethylamide (LSD) and has similar effects as its parent compound, diazepam, with fewer myorelaxant effects.<sup>2</sup> 4-chlorodiazepam is a derivative of diazepam currently in the research phase. Unlike the benzodiazepines previously discussed, it has no affinity for GABA-A receptors, giving this atypical drug effects.<sup>2</sup> It inhibits oxidative stress and decreases cholesterol accumulation in the mitochondria during coronary reperfusion; thus, it has cardioprotective abilities.<sup>18</sup> Additionally, it can decrease pro-inflammatory mast cell functions and can suppress LPS-induced TNF activity.<sup>19,20</sup>

## DRUG INFORMATION AND MECHANISM OF ACTION

Remimazolam besilate (CNS 7056) was designed as a soft drug, metabolically active in its native form, and converted to an inactive compound rapidly. This is not to be confused with a prodrug, which is the converse (inactive metabolite predictably converted to an active metabolite).<sup>21</sup> The advent of soft drugs is of particular importance to the field of

anesthesia, as these new compounds give more control and predictability to anesthesiologists.

Remimazolam is a short-acting GABA-A receptor agonist. Its molecular formula is  $C_{21}H_{19}BrN_4O_2$ , with an average mass of 439.305 Da. The structure of remimazolam is analogous to that of midazolam but with the addition of an ester moiety. It is water-soluble, and consequently, there is less pain at injection sites.<sup>22</sup>

## MECHANISM OF ACTION

Remimazolam has a high affinity for the benzodiazepine (BDZ) site on GABA (A) brain receptors. It binds at the interface between alpha ( $\alpha$ ) and gamma ( $\gamma$ ) subunits and acts to augment inhibitory activity in the central nervous system. This is achieved by increasing the intracellular concentration of chloride ions, leading to membrane hyperpolarization and subsequent inhibition of the neuron action potential conduction. Unlike some benzodiazepines, remimazolam does not display selectivity between the GABA-A receptor subtypes. However, it was observed to be slightly more potent at the  $\alpha_1$ -containing subtypes than midazolam. This is notable because  $\alpha_1$ -containing subtypes of GABA-A are thought to mediate sedation.<sup>23</sup>

## METABOLISM

Unlike its parent compound (midazolam), remimazolam is not metabolized by cytochrome P-450 isozymes, nor does it inhibit cytochrome P-450 metabolism.<sup>6</sup> The ester moiety of remimazolam is a substrate for non-specific tissue esterase enzymes, meaning it can be metabolized without the need of any particular organ. It has been suggested that this will make it a valuable drug for people with hepatic or renal compromise.<sup>22</sup>

The metabolic profile of remimazolam was elucidated with the use of ultra-high-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS). A total of five significant metabolites were characterized, of which three were phase I (oxidation, reduction, or hydrolysis of the parent drug), and two were phase II (conjugation by coupling the drug or its metabolites to another molecule) metabolites.<sup>24</sup> Carboxylesterase enzymes are the most important players in remimazolam metabolism and can be found in the cytosol and the rough endoplasmic reticulum of tissues.<sup>25</sup> Once acted upon by an esterase, the remimazolam is converted to its major inactive metabolite (CNS7054) that has a 400-fold lower affinity for the GABA-A receptor.<sup>23</sup>

## ADDICTION

When investigating a new benzodiazepine, it is always important to quantify the addictive capacity of the drug. Studies have confirmed equipotency when comparing remimazolam and midazolam with comparable levels of addictive potential. Both drugs have poor oral bioavailability and pose little risk of addiction when administered IV.<sup>26</sup>

## ADVERSE REACTIONS

A few adverse events have been reported in conjunction with remimazolam administration. One study reported that the most common adverse events that occur after recovery post-infusion were headaches and drowsiness.<sup>27</sup> Additionally, another study reported involuntary movement as the most notable adverse event during infusion.<sup>28</sup>

## REMIMAZOLAM USE

The use of remimazolam will become especially beneficial, given that there is an ongoing problem in the United States because it has become standard for all patients undergoing GI endoscopic sedation to be administered propofol. This paradigm requires that an anesthesia provider be present, which is an unnecessary added cost to the patient and is unsustainable.<sup>29</sup> Alternatives to Propofol are especially sought out by gastroenterologists, as the use of propofol during procedures is legally binding due to the directive set out by the American Society of Anesthesiologists (ASA) "PropofolHealthcare providers must only use propofol with specialized training in airway management."<sup>30</sup> Since most physicians beyond anesthesiologists and emergency physicians lack additional training in airway management, there is a need for an anesthesiologist to be present during procedures in which propofol is administered.<sup>31</sup>

For procedures such as EGD (esophagogastroduodenoscopy) and ERCP (endoscopic retrograde cholangiopancreatography), remimazolam, when it becomes available, has the potential to be administered with oliceridine. Oliceridine is a mu-receptor agonist proposed to achieve adequate analgesia with the major benefit of reduced opioid-related adverse events, such as nausea and vomiting, compared to standard analgesics, like fentanyl.<sup>32</sup> Additionally, oliceridine has a reduced potential to cause respiratory depression, with a minor drawback of an approximate five-minute increase in clinical onset of action.<sup>33</sup>

Although still under investigation in phase III trials, remimazolam has many properties that could deem it suitable for procedural sedation. Currently, trials are still ongoing to study the effects of these properties and how they compare to those of the frequently used propofol and midazolam. Remimazolam undergoes rapid metabolism by abundantly available plasma and tissue esterases, has organ independent metabolism, and a first-order pharmacokinetic profile independent of body weight and elimination clearance, while maintaining a similar safety profile to that of midazolam.<sup>7,34</sup>

Phase II/III general anesthesia trials in Japan have demonstrated the action of remimazolam as a general anesthetic to be "non-inferior" to propofol. It is important to note that remimazolam was found to be associated with longer times to loss of consciousness and time to extubation; however, a few seconds is deemed clinically insignificant, and the authors of the study argued that because remimazolam can be effectively reversed with flumazenil, this benefit outweighs the minor cost. Additionally, extuba-

tion time is presumed to be reduced with the implementation of a tapering regimen for remimazolam.<sup>7</sup>

Trials have also demonstrated remimazolam's success over midazolam. In a cohort of 461 colonoscopy patients with randomization to either remimazolam, placebo, or open-label midazolam groups, the rates of successful colonoscopies without rescue medication were 91.3, 1.7, and 25.2, respectively. Furthermore, patients that received remimazolam experienced less hypotension and a faster recovery time than their midazolam counterparts.<sup>35</sup> In a cohort of 446 patients that underwent flexible bronchoscopy, procedural success with the group receiving remimazolam was 80.6%, compared to 32.9% and 4.8% for midazolam and placebo, respectively. An added benefit of remimazolam here was a shorter time to recovery and a shorter time to alertness and restoration of neuropsychiatric function.<sup>36</sup>

Remimazolam provides a similar degree of sedation with similar patient satisfaction and earlier "readiness to discharge" times.<sup>36</sup> Although unlikely to replace propofol in patients undergoing colonoscopy, endoscopists will be able to perform the majority of these procedures with remimazolam alone while spared the fear of delayed discharge. Remimazolam will also be a valuable addition to propofol in advanced endoscopic procedures as it does not delay discharge.<sup>1</sup>

## PHARMACOKINETICS

Remimazolam is generally administered IV, as it has negligible oral bioavailability. It is completely absorbed via the GI tract but then undergoes widespread first-pass metabolism.<sup>37</sup> As previously discussed, remimazolam metabolism is not organ-dependent. Therefore, we may not see the same decline in the inability to metabolize this drug with age as we do with drugs dependent on hepato-renal clearance.<sup>1</sup> Intranasal sedation using remimazolam has also been studied and determined to be a viable alternative for procedural sedation. It may especially have value for pediatric procedures, where IV sedation can prove difficult.<sup>38</sup>

Remimazolam's onset of action was demonstrated to be 1-3 minutes, surpassing the rapidity of midazolam (3-5 minutes).<sup>39</sup> This is clinically significant, as it will ease the administration of accurate maintenance doses.<sup>40</sup> Additionally, the half time of remimazolam is 7-8 minutes, much less than midazolam.<sup>1</sup>

The duration of action remimazolam is eliminated by first-order kinetics at clinical doses. Its volume of distribution is less than that of midazolam. This makes way for rapid elimination without significant accumulation.<sup>40</sup> Additionally, drug clearance seems to be independent of body weight, suggesting that patients can be administered fixed doses of remimazolam.<sup>40</sup>

## PHARMACODYNAMICS

The Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) is frequently used to determine a subject's level of sedation in anesthesia drug studies. It is scored 0-5, where 5 represents an awake and alert subject, and

0 represents a patient under general anesthesia. A study was conducted with continuous infusion of remimazolam, and subjects were assigned scores based on levels of sedation achieved. These scores were then applied to a sigmoid model to better predict the probability of achieving a specific level of sedation for a given concentration of the drug. It was found that there was greater difficulty in achieving moderate levels of sedation (scores 2, 3), and the infusion quickly brought patients from 5 to 0.<sup>28</sup>

Benzodiazepines are often administered with the intent of strengthening the effect of opioid analgesia. The coadministration of inhaled remimazolam with inhaled remifentanyl has been investigated in rodents, and it was found that remimazolam has the power to potentiate remifentanyl's analgesic properties. Additionally, it has been speculated that remifentanyl may work to increase the sedative properties of remimazolam.<sup>41</sup>

## HEMODYNAMICS

In one study, blood pressure and heart rate were monitored during continuous administration of IV remimazolam. Subjects experienced decreases in mean arterial blood pressure (20 mmHg) and increases in heart rate (20 bpm). Additionally, SpO<sub>2</sub> levels were monitored during infusion, and it was concluded that there were only modest decreases that could be remedied with supplemental oxygen by nasal cannula.<sup>28</sup> Another study tested the hemodynamic effects of deep sedation with remimazolam in pigs, sheep, and monkeys. It was found that this drug does not seem to induce an excessive amount of cardiac or respiratory depression.<sup>6</sup>

## ECG

Remimazolam was determined not to prolong the PR interval or the QRS duration on ECG.<sup>28</sup>

## REMIMAZOLAM FOR GENERAL ANESTHESIA

Many studies have been conducted regarding the safety and efficacy of remimazolam use for sedation. One study conducted by Sheng et al. assessed the safety and pharmacokinetic and pharmacodynamic properties of remimazolam following a single ascending dose and continuous infusion in a Chinese population. The study was conducted in a double-blind placebo and midazolam controlled manner with a remimazolam dose of 0.025-0.4 mg/kg. In the study, remimazolam was compared to midazolam and assessed for recovery time, induction dosage, and peak sedation effects. The study concluded that for general anesthesia, an induction dosage of 0.2 mg/kg/min of remimazolam and a maintenance dose of 1 mg/kg/h could be efficacious. In addition, the study observed that remimazolam demonstrated greater sedation and quicker recovery than midazolam.<sup>42</sup> Similarly, another study by Antonik et al. conducted a phase I, double-blind, placebo, and active-controlled study to assess remimazolam use compared to midazolam. In the study, remimazolam doses of 0.01-0.35 mg/kg or placebo were given to 10 participants. The study concluded

that rapid onset and dose-dependent sedation for remimazolam was observed after doses of 0.05 mg/kg and higher. In addition, the researchers observed that 0.075-0.20 mg/kg doses achieved peak sedation with remimazolam with a median recovery time of 10 minutes with remimazolam doses between 0.10-0.15 mg/kg. In addition, as compared to midazolam, remimazolam provided quicker onset and offset compared to midazolam.<sup>27</sup> Overall, much of the studies conducted comparing remimazolam with midazolam show quicker onset and offset no adverse events and greater efficacy than midazolam.

Further studies assessing the use of remimazolam as compared to propofol for induction of general anesthesia were conducted. In a study conducted by Doi et al., a single-blind, randomized, parallel-group trial was conducted to assess the efficacy of remimazolam versus propofol for induction and maintenance of general anesthesia. In the study, 375 surgical patients were randomized to receive 6 or 12 mg/kg/h of continuous IV remimazolam versus 2-2.5 mg/kg of IV propofol followed by 4-10 mg/kg/h after the loss of consciousness. The study concluded that remimazolam was not inferior to propofol, given the efficacy of remimazolam in inducing general anesthesia.<sup>43</sup> Finally, although the use of remimazolam was assessed in ASA I and ASA II patients, less research has been conducted on the use of the sedative for ASA III patients. In another study by Doi et al., 67 surgical patients classified as ASA III were randomized into one group receiving 6 mg/kg/h infusion of remimazolam while the other group received 12 mg/kg/h infusion for maintenance anesthesia. In conclusion, the study found that both infusion regimens were equally safe and efficacious in ASA III surgical patients and was one of the few studies that assessed the use of the sedative in this subset of patients.<sup>44</sup>

## REMIMAZOLAM USE IN COLONOSCOPY, ENDOSCOPY, AND BRONCHOSCOPY

Further studies assessing the use of remimazolam in patients undergoing gastrointestinal procedures such as colonoscopy, endoscopy, and bronchoscopy were conducted. In one study by Worthington et al., the researchers studied the use of remimazolam in volunteers undergoing colonoscopy. In the study, the first part assessed the use of remimazolam during colonoscopy, while the second part assessed the ability to reverse remimazolam with flumazenil. In the study, adequate sedation for colonoscopy was achieved in 33 of 44 subjects and observed that sedation could be rapidly reversed within 1 minute with flumazenil. In addition, after the procedure, subjects recovered with a median time of <10 minutes. Finally, no serious adverse events were reported with the use of the drug.<sup>45</sup> Another study conducted by Pambianco et al. also assessed the use of remimazolam for procedural sedation, specifically for patients undergoing a colonoscopy. In the randomized, double-blind study, active-controlled study, patients received either a dosage of remimazolam or midazolam for sedation before undergoing a colonoscopy. The study found that adequate sedation was obtained for >92% of the remimazolam groups compared with 75% of the midazolam groups with a p-value of 0.007.<sup>34</sup> The study concluded that given the

high success rate with remimazolam and no serious adverse events, further investigation of remimazolam could be conducted. Similar to the study of the drug in patients receiving a colonoscopy, a similar study was conducted in patients undergoing upper endoscopy. In a similar randomized, double-blind study conducted by Borkett et al., patients scheduled to receive an upper endoscopy were randomized to receive either remimazolam or midazolam. In the study, the researchers observed that the onset of sedation with remimazolam was between 1.5-2.5 minutes compared to 5 minutes for midazolam. In conclusion, the study found that patients receiving an upper endoscopy were successfully sedated with a remimazolam dosage of 0.10-0.20 mg/kg without any adverse events.<sup>46</sup> Finally, another study by Chen et al. was conducted to assess the efficacy and Safety of remimazolam compared to propofol in patients undergoing colonoscopy. In this blinded, randomized, active-controlled trial, 384 patients were separated into remimazolam and propofol groups. The study concluded that the efficacy of remimazolam was non-inferior to propofol, and emergent adverse events were decreased in the remimazolam group compared to the propofol group.<sup>47</sup> Similarly, a study conducted by Chen et al. also assessed the use of remimazolam in patients undergoing gastrointestinal endoscopy. In this study, a total of 384 scheduled to receive an endoscopy were randomized assigned to receive remimazolam or propofol. The study concluded that remimazolam allowed for faster recovery after sedation as compared with propofol with lower incidences of adverse events such as hypotension and respiratory depression.<sup>48</sup> Another study conducted by Pastis et al. observed the efficacy and Safety of remimazolam for sedation during flexible bronchoscopy. In the study, the remimazolam was compared with both placebo and midazolam. The study concluded that in the remimazolam group, the success rate was 80.6% compared to 32.9% in the midazolam group. Overall, the remimazolam group had a quicker start time of bronchoscopy, quicker time to full alertness, and superior restoration of neuropsychiatric function with remimazolam.<sup>36</sup> Overall, in all four studies, remimazolam proved to be a far better option than midazolam for a range of endoscopic procedures, such as colonoscopy, endoscopy, and bronchoscopy.

## CONCLUSION

Remimazolam has a quick onset and quick offset with a good safety profile. It does not have a significant effect on hemodynamics, nor is it known to cause cardiac depression, like propofol. These attributes make it a favorable IV anesthetic for a wide array of procedures. A 2020 study by Doi et al. showed non-inferiority when comparing maintenance of general anesthesia with a remimazolam infusion to the control group receiving a propofol infusion in ASA I and II patients. It is still under clinical trials and maybe quite a ways away from replacing our more well-known IV anesthetics, but it has the potential to provide us more predictability and control over our anesthetic. Remimazolam has organ-independent metabolism as it is metabolized

by abundant plasma and non-specific tissue esterases. This makes it advantageous for patients with a history of hepatic and/or renal disease. The medication's addiction profile is very similar to midazolam. Thus there is not an increased risk of addiction with its use. It has many advantages and seemingly few disadvantages. A few of its downsides would be complaints of headaches and somnolence after and involuntary movement during infusions. Involuntary movement can be an obvious issue when immobility is crucial in many surgical procedures. But often, patients undergoing a surgical procedure are given muscle relaxants if no contraindications exist, which can help prevent such involuntary movements. As a recently approved medication, further large clinical trials are still warranted to provide the medical community with a better understanding of its properties. Though it has shown many benefits, it will likely take time before it becomes a commonly used adjunct to other sedatives and analgesics.

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**Table 1. Remimazolam's Clinical Safety and Efficacy**

| Table 1: Clinical Safety and Efficacy |  |   |   |
|---------------------------------------|--|---|---|
| Author (Year)                         | Groups Studied and Intervention  | Results and Findings  | Conclusions   |
| Sheng et al. (2019)                   | Healthy Chinese patients   | Sedation function was observed at the dose of 0.05 mg/kg remimazolam. Doses of >0.075 exerted a peak sedation effect within 1-2 min after injection. For general anesthesia, an induction dosage of 0.2 mg/kg/min and a maintenance dosage of 1mg/kg/h achieved satisfactory efficacy effect. | Remimazolam was safe and well-tolerated in healthy Chinese participants.  |
| Antonik et al. (2012)                 | Ten cohorts of health subjects randomized to receive a 1-minute IV infusion of remimazolam, midazolam, or placebo                          | Pharmacokinetic behavior of remimazolam linear and its systemic clearance was approximately three times of midazolam. Administration of 0.05 mg/kg and higher doses of remimazolam achieved a rapid onset and dose-dependent sedation.  | Remimazolam provided rapid onset and offset sedation with minimal adverse events. Further studies on the use of remimazolam for sedation can be conducted.  |
| Doi et al. (2020)                     | Surgical patients randomized to remimazolam at 6 or 12 mg/kg/h infusion  | Remimazolam had a longer time to LOC and longer time to extubate but overall was non-inferior compared to propofol  | Remimazolam was well tolerated and non-inferior to propofol for general anesthesia  |
| Worthington et al. (2013)             | Healthy volunteers receiving remimazolam for sedation during colonoscopy   | Over 70% of subjects had successful sedation with remimazolam with a median recovery time of <10 minutes after the procedure  | Remimazolam has success rates comparable to other drugs for induction during colonoscopy. Further studies with the use of remimazolam in patients receiving colonoscopy or other GI procedures can be conducted                       |
| Pambianco et al. (2015)               | 162 patients aged 18-70 scheduled to receive a routine colonoscopy   | Single-dose of remimazolam provided >92% success rate for the remimazolam group compared to 75% for the midazolam group   | Remimazolam provided high levels of success rate for induction during colonoscopy compared to midazolam. Further studies assessing the use of remimazolam for patients undergoing colonoscopy or other GI procedures can be conducted |
| Borkett et al. (2015)                 | Patients scheduled to undergo a diagnostic upper gastrointestinal endoscopy randomized to receive 1 of 3 doses of remimazolam or midazolam | The onset of sedation in remimazolam dose group was 1.5 - 2.5 minutes compared to 5 minutes for the midazolam group   | A single administration of remimazolam with a dosage of 0.10-0.20 mg/kg was able to induce patients undergoing diagnostic upper gastrointestinal endoscopy with a similar safety profile as midazolam                                 |
| Chen et al. (2020)                    | 384 patients undergoing colonoscopy randomized to receive remimazolam or propofol  | Remimazolam was noted to be non-inferior to propofol with similar success rates and induction time of sedation  | Remimazolam is non-inferior in sedation efficacy while safer than propofol in patients undergoing colonoscopy   |
| Chen et al. (2020)                    | 384 patients undergoing upper endoscopy randomized to receive remimazolam or propofol  | Remimazolam was noted to be non-inferior than propofol, with a shorter time to be fully alert and lower incidences of hypotension and respiratory depression  | Remimazolam is non-inferior to propofol and allows for faster recovery from sedation. In addition, it appears to be superior to propofol with adverse events  |
| Pastis et al. (2018)                  | Patients undergoing flexible bronchoscopy  | The success rate in the remimazolam group was 80.6% compared to 32.9% in the midazolam group. In addition, time to full   | Remimazolam was effective and safe for moderate sedation during bronchoscopy and demonstrated a   |

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|  | receiving either remimazolam or midazolam | alertness in the remimazolam group was shorter compared to midazolam. | shorter onset of action and faster neuropsychiatric recovery than midazolam. |
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