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**Title**: Remimazolam – current knowledge on a new benzodiazepine intravenous anesthetic agent

**Short title**: Remimazolam

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Remimazolam – current knowledge on a new benzodiazepine intravenous anesthetic agent

Running title: Remimazolam
Abstract

Intravenous anesthetic agents, such as midazolam, propofol or ketamine are routinely used to provide anesthesia and sedation. They have been shown to effectively induce and maintain amnesia, sedation and hypnosis in various patient groups and different clinical settings. However, all anesthetic agents may cause unwanted side effects, like hemodynamic instability, respiratory depression or slow recovery due to prolonged post-procedural sedation. Remimazolam, a recently approved benzodiazepine for general anesthesia and procedural sedation in Korea, has been successfully used to provide general anesthesia and sedation. Based on the data available to date inconclusive knowledge has been gained on the use of remimazolam in different patient populations and under various surgical conditions. With respect to the specific pharmacokinetic and pharmacodynamic characteristics of remimazolam, an increasing number of administrations of remimazolam to provide safe general anesthesia and sedation can be expected. It is the aim of this review to provide an overview of the specific basic and clinical pharmacology of remimazolam and to compare it to midazolam and propofol.

Keywords: Amnesia; Anesthesia; Benzodiazepine; Hypnosis; Remimazolam; Sedation.
Introduction

Remimazolam is a rapidly metabolized benzodiazepine (BZD) and has been approved for general anesthesia and procedural sedation in 2021 in Korea. It shows a typical pharmacodynamic profile of other BZDs like midazolam, but in contrast has a high organ-independent elimination clearance. It is rapidly metabolized by unspecific esterases [predominantly carboxylesterase 1A (CES 1A)] mainly localized in the human liver to CNS7054, a so-called inactive metabolite with a 300 to 400 times reduced binding affinity at the γ-aminobutyric acid (GABA) type A receptor. After its administration, plasma concentrations of remimazolam predictably and rapidly decrease and with adequate dosing there is no prolonged sedative effect. After approval in Korea for general anesthesia, further clinical experience with the use of remimazolam as well as evidence-based approaches for dosing and drug handling are needed to use remimazolam safely and efficiently in different patient populations and in various clinical conditions. The intention of this review article therefore is to provide an overview of the specific pharmacodynamic and pharmacokinetic characteristics of remimazolam relevant for its clinical use as a modern intravenous sedative and anesthetic agent.

Basic knowledge on intravenous anesthetic agents

1. Mechanism of action of intravenous anesthetic agents

There is no doubt that the introduction of general anesthesia was a revolutionary achievement in medical history, but to date the mechanism of action of anesthetic agents has still not been fully elucidated. In general, the concept that anesthetic agents produce neuro-depression in specific areas of the central nervous system by enhancing the effect of inhibitory neurotransmitters, especially GABA, and reducing the effect of excitatory neurotransmitters, as well as suppressing specific neuronal network activity necessary for consciousness and arousal, has been accepted [1, 2]. The GABA receptor system is the main inhibitory receptor population in the human central nervous
system and is the main target receptor for intravenous anesthetic agents inducing general anesthesia [1]. Most of the intravenous anesthetic agents such as barbiturates, BZDs, propofol and etomidate, bind to GABA type A receptors, except for ketamine, that mainly acts via the N-methyl-D-aspartate (NMDA) receptor besides other receptor types. All intravenous anesthetic agents can induce amnesia, hypnosis, sedation, unconsciousness and immobility (muscle-suppressing activity), although immobility is achieved to a lesser extent as with inhalational anesthetic agents. Intravenous anesthetic agents may also induce cardiovascular depression, respiratory depression or pain on injection.

2. An ideal intravenous anesthetic agent and soft drug

An ideal intravenous anesthetic agent (Table 1) has not been developed yet. All available intravenous anesthetic agents can cause undesirable side effects. Therefore, balanced anesthesia using a combination of the different anesthetic agents with the lowest possible dose of each to achieve adequate anesthesia in the past has been used to minimize side effects of anesthetic agents in daily practice. Modern anesthetic agents therefore should be effective, efficient and well tolerated. For improved usability new intravenous anesthetic agents should also offer a predictable and rapid onset and offset of drug effect. Drug development programs have been searching for intravenous anesthetic agents specifically structured to undergo rapid biotransformation into inactive metabolites. This type of drug is called “soft drug”, and remifentanil is a well-known prototype. Remimazolam, which is the newest “soft drug”, has been developed based on the midazolam molecular structure (Fig. 1 and Fig. 2) and is a structural analogue with an added ester side chain. After stopping the administration of a soft drug, the effects rapidly disappear, as the parent compound is fast converted to inactive or much less active metabolites [3]. Anesthetic soft drugs can be further characterized by pharmacologic efficiency, that is easy dosing schemes with a superior quality of care to treatment cost ratio, rapid restoration of protective reflexes, rapid return of spontaneous ventilation and a reduced need for postoperative care monitoring. [3]
Midazolam, a well-known BDZ, is metabolized by hepatic cytochrome P450 enzymes and glucuronide conjugation [4]. However, in contrast to remimazolam the metabolites of midazolam are active. The sedative or anesthetic effect of midazolam and its metabolites can be prolonged due to its organ-dependent and much lower drug clearance rate, especially after prolonged drug administration, in patients with advanced age, in patients with reduced hepatic or renal function. Midazolam in contrast to remimazolam cannot be called a soft drug, and to date the use of midazolam for anesthesia and sedation has been limited mainly to postoperative intensive care unit (ICU) sedation. Midazolam is no longer in use for the maintenance of intravenous anesthesia.

**Remimazolam**

1. **Basic pharmacology of remimazolam**

When administering remimazolam depending on the plasma and effect site concentration (biophase), the effects of amnesia, sedation and hypnosis, unconsciousness and some grade of immobility can reliably be achieved. In comparison to midazolam remimazolam does not cause prolonged sedative effects after discontinuing the administration, because remimazolam is rapidly metabolized by unspecific tissue esterases to CNS7054, the only active metabolite with a 300 times lower affinity for the GABA type A receptor and with no clinically relevant effect at the GABA type A receptor [5]. Remimazolam is a “soft drug” with the pharmacodynamic characteristic of a BZD. Remimazolam shows some characteristics of an ideal intravenous anesthetic agent. It is water-soluble, it has a high and organ-independent clearance rate and it shows more benign hemodynamic and respiratory side effects when compared to propofol.

The pharmacokinetics of remimazolam have been described with non-compartmental and compartmental modeling approaches as well as a recirculatory model[6–8]. In these pharmacokinetic models the total body clearance was independent from body weight, which is remarkable. In a clinical
trial Lu Z. et al [9] has estimated a body-weight independent single dose of 11.43 mg of remimazolam as a dose achieving a 90% (ED$_{90}$) probability for adequate sedation during colonoscopy. This study illustrates body weight independent and simple dosing concepts for remimazolam. Total body clearance values have been estimated as $70.3 \pm 13.9$ L/h [8] by Antonik et al., as $66.7 \pm 2.59$ L/h by Wiltshire et al. [7] and as $69 \pm 7.2$ L/h by Schuttler et al. [6]. The total body clearance of midazolam has also been measured by Wiltshire et al. as $22.6 \pm 8.36$ L/h in the cited publication [7]. The clearance of midazolam is nearly one third of the total body clearance of remimazolam. The total body clearance for propofol has been measured as $102 \pm 18$ L/h by Gepts at al. [10] in a rather historical but still used data set, which is incorporated as the “Marsh model” [11] still in commercially available target-controlled infusion (TCI) systems for propofol. The estimated total body clearance rate of propofol therefore is around 25 to 30 percent higher than the clearance rate of remimazolam, but the clearance of propofol is organ-dependent and can be reduced in hepatic disease. In contrast, Stöhr et al. [12] have shown that neither hepatic nor renal dysfunction impairs the clearance of remimazolam. A total volume of distribution at steady state (Vdss) of around 35 L has been described for remimazolam [6, 8], whereas for propofol Vdss has been estimated at around 400 L [10], which is about 10 times higher than the Vdss of remimazolam. A smaller Vdss speeds up drug elimination and patient recovery, as less drug has accumulated in the body during the administrations, and so that less drug has to be cleared after the administration has been stopped. Based on pharmacokinetic simulations context-sensitive decrement times of a 50% decrease in the plasma and effect site concentration of remimazolam are very comparable to the simulated times for propofol (Fig. 3 and Fig. 4). In these simulations the pharmacokinetic data set of Gepts/Marsh et al. [11] for propofol and the pharmacokinetic data set of Schuttler et al. [6] for remimazolam have been used. The decrement time is shorter for remimazolam when we look at the decrease in plasma concentration, but it is around 3 to 4 min longer, when we look at decrease in effect site concentration. This is in better agreement...
with the clinical finding that recovery times after remimazolam anesthesia tend to be around 1 to 5 min longer when directly compared to propofol [13].

The transfer constant \( k_{e0} \) (1/min) describes the speed of drug exchange between the central compartment and the effect compartment or biophase. A \( k_{e0} \) of around 0.25 min\(^{-1}\) has been estimated for remimazolam using the modified observer’s alertness and sedation score (MOAA/S score) as parameter of the electroencephalogram (EEG) in volunteers of both sex by Wiltshire et al. [7]. A \( k_{e0} \) value of 0.33 has been described by Eisenried et al. [14] in young male healthy volunteers using the beta-ratio of the EEG as pharmacodynamic parameter. A larger \( k_{e0} \) value would speed up substance exchange between the effect compartment and the central compartment and thus shorten induction and recovery times. To date from a scientific point of view insufficient data have been published for an exact estimation of the \( k_{e0} \) value of remimazolam for the BIS. This is the clinically most relevant EEG parameter when remimazolam is administered to induce and maintain general anesthesia or sedation.

Interaction modeling between opioids and remimazolam during general anesthesia has only been described for remifentanil in a publication of Zhou et al. [15] with the BIS as the pharmacodynamic effect parameter. This published interaction model for remimazolam and remifentanil during general anesthesia is inconclusive, as the interaction only shows a relevant effect and a weak interaction up to a remifentanil dosing of 0.5 \( \mu \)g/kg/min, and with higher dosages of remifentanil the interaction is further reduced. This might be explained with the study designs of the reevaluated trials, as the whole range of clinically relevant remifentanil and remimazolam concentration had not been studied [15]. Even more relevant for the clinical use of remimazolam is its anesthetic drug potency compared to propofol, which is described by the parameter half-maximal effective concentration (EC\(_{50}\)). EC\(_{50}\) is the plasma concentration at the time when 50 % of the maximal effect for a pharmacodynamic parameter like the BIS is achieved. In the study of Wiltshire et al. [7] a 50% decrease of the maximum
BIS decrease was achieved with a remimazolam effect site concentration of 0.259 µg/ml, whereas for propofol the EC$_{50}$ value for the BIS was estimated as 1.78 ± 0.67 µg/ml in a publication by Mourisse et al. [16]. Considering these published EC$_{50}$ values remimazolam is much more potent than propofol regarding the effect site concentrations estimated for the same effect on the BIS. This may be an explanation for slightly prolonged recovery times of remimazolam compared to propofol, as a decrease of the effect site concentration of propofol by 50% reduces the anesthetic effect more than a reduction in the effect site concentration of remimazolam by 50%.

In summary, although most accurate pharmacokinetic parameters of remimazolam have been described, this is not true for pharmacodynamic parameter like the EC$_{50}$ and the transfer constant $k_{0e}$. Further studies are needed to access and validate these important pharmacologic parameters of remimazolam.

2. Clinical pharmacology of remimazolam

The hemodynamic stability of remimazolam, especially when compared to propofol, is remarkable. Intravenous anesthetic agents, except ketamine, show dose-dependent cardiovascular depressive effects. These cardiovascular effects can be explained by a dose-dependent decrease in systemic vascular resistance as well as a dose-dependent decrease of cardiac contractility. The effects of remimazolam on the intracellular calcium homeostasis in endothelial and neuronal have not been fully elucidated. Urabe T. et al. [17] have studied and shown the effect of remimazolam on the intracellular calcium concentration. They have described that remimazolam can increase the calcium concentration in endothelial and neuronal cells via a G-protein coupled receptors (GPCRs)-inositol 1,4,5-triphosphate (IP$_3$) pathway. They discuss that the effect is reversible whereas this effect is different and not reversible, when propofol is administered. This might be a first step to explain the different hemodynamic effects of remimazolam compared to propofol possibly modulated by different effects on the intracellular calcium homeostasis of endothelial cells.
Decreased blood pressure with a mean arterial pressure below 65 mm Hg for more than 1 min duration is known to be associated with an increased incidence of postoperative myocardial injury or acute kidney injury [18]. As remimazolam is a BZD a better hemodynamic stability when compared to propofol can be expected. Frölich et al. compared the hemodynamic effects of three different intravenous anesthetic agents: propofol, midazolam and dexmedetomidine. They found that dexmedetomidine and propofol reduced the arterial blood pressure in a dose-dependent manner. Whereas systolic blood pressure (SBP) and diastolic blood pressure (DBP) were maintained in the midazolam group during induction of mild to moderate sedation in American Society of Anesthesiologists Physical Status (ASA PS) I human volunteers of both sexes, a significant decrease in SBP and DBP did occur with the use of propofol [19]. Lim et al. has compared the cardiovascular effects of a midazolam co-administration of 0.03 mg/kg and a reduced dose of propofol of 0.8 mg/kg to a propofol dose of 1.2 mg/kg, each combined with remifentanil for induction of anesthesia in ASA PS I to II patients of both sexes of more than 65 years of age. The co-administration of midazolam and the lower dose of propofol reduced the time to loss of consciousness, and the decrease in mean arterial blood pressure decrease before, just after and 3 min after intubation was significantly smaller [20]. The hemodynamic effects of remimazolam are comparable to midazolam, so that a co-administration of remimazolam and propofol in a reduced dose should also reduce the decrease in mean arterial blood pressure during anesthetic induction. As the speed of induction and recovery as well as awakening times are fairly comparable to propofol, there is no longer a clinically relevant pharmacokinetic advantage in using propofol for total intravenous anesthesia.

Concentration of intravenous anesthetic agents and so anesthetic effects over time can be more accurately controlled with the use of a TCI compared to a manually controlled infusion. Several research groups have investigated and described pharmacokinetic and pharmacodynamic models for remimazolam. Sufficient pharmacokinetic data have been published to further develop and test a TCI.
system for remimazolam in the near future. Insufficient data have been published describing the concentration-effect relationship of remimazolam on typical EEG parameters like the BIS during general anesthesia and in co-administration with an opioid in patients [6, 14, 15]. Further clinical investigations are necessary to clearly define the pharmacodynamic interaction of remimazolam and different opioids in a clinical setting. The parameter “$k_{e0}$” is important to calculate the speed of an increase and decrease in the effect site concentrations of remimazolam. This parameter is necessary for a TCI-system to directly model and target effect site concentrations and to increase adjustability of drug effect over time, especially to shorten recovery times by adequate dosing.

3. Remimazolam for anesthetic induction and maintenance

For the use of anesthesia induction and maintenance, remimazolam should be compared to propofol. Propofol has some disadvantages when used for anesthetic induction and maintenance: 1) pain on injection, 2) decrease in blood pressure, 3) decrease in heart rate, 4) respiratory depression and 5) propofol infusion syndrome (very rare). In the following we present clinical trial results comparing remimazolam and propofol for induction and maintenance of general anesthesia.

Dai et al. evaluated the safety and efficacy of remimazolam for anesthetic induction compared with propofol. A sufentanil bolus dose of 0.3 to 0.5 µg/kg was given 1 min before anesthetic induction. Anesthesia was successfully induced with 0.2 mg/kg (group R1), 0.3 mg/kg (group R2) and 0.4 mg/kg (group R3) of remimazolam in 89%, 94% and 100% of patients. Induction rates were not significantly different between R2, R3 and P. Dai et al. also compared the hypotension rate of these three induction doses of 0.2, 0.3, and 0.4 mg/kg remimazolam or an induction dose of 2 mg/kg propofol (group P) all administered within ≤ 1 minute in these 190 ASA I or II patients. Hypotension during induction, defined as a mean arterial blood pressure below 65 mm Hg or a systolic blood pressure decrease to less than 70% of baseline values, occurred in 13% of patients of R1 and 24% of patients of R2, and occurred significantly less often in R1 and R2 than in group P (44%). Hypotension rates for group R3

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and group P were not significantly different. BIS values decreased more rapidly in group P, so that the anesthetic effect over time was not exactly comparable between the three remimazolam groups and propofol. Also, sufentanil dosing was not standardized. Still in this trial during anesthetic induction remimazolam co-administered with sufentanil has shown superiority in hemodynamic stability. Heart rates were not significantly different between the groups. Pain on injection was not reported in this trial for all three remimazolam groups, in contrast it was reported in 27% of patients who had received propofol [21].

Zhang et al. compared an induction dose of 0.2 mg/kg of remimazolam for anesthesia induction and 1.0 mg/kg/h for anesthesia maintenance to an induction dose of propofol of 2 to 2.5 mg/kg and a propofol maintenance dose of 3-6 mg/kg/h in ASA PS I to II patients undergoing hysteroscopy. Analgesia was achieved with a remifentanil using a TCI with an effect site target concentration of 1.5 μg/ml in both groups. The remifentanil infusion was started after the induction with remimazolam or propofol. Based on their definitions of adverse events the authors reported significantly less low peripheral oxygen saturation values of ≤ 95%, injection pain (2.4% vs. 80.5%) and less postoperative dizziness (0 vs. 24.4%), when remimazolam instead of propofol was used [22]. They concluded that remimazolam was “a safer alternative for anesthesia during hysteroscopy”. However, although times of awakening were longer in the remimazolam groups (199 ± 80 s vs. 60 ± 12 s) in this trial, the post-anesthetic care unit (PACU) length of stay was shorter in the remimazolam group (5.44 ± 1 min vs. 6.3 ± 1.9 min). Depth of anesthesia was monitored using the Modified Observer's Alertness/Sedation scale (MOAA/S). Furuta et al. presented a case report of successfully inducing and maintaining general anesthesia with remimazolam during total mastectomy in an 81 yrs. old female patient with severe aortic valve stenosis. They concluded that general anesthesia using remimazolam preserved cardiac output in this patient and that remimazolam might be safely used to avoid cardiac suppression in patients with severe aortic valve stenosis [23].
Liu et al. compared two groups of 30 patients each, that were induced with remimazolam 0.3 mg/kg as a constant rate infusion of 1.8 mg/kg/h or propofol as a TCI with a target plasma concentration of 2.5 µg/ml scheduled for valve replacement cardiac surgery. All patients also received a sufentanil dose of 1 µg/kg as an infusion rate of 0.1 µg/kg/min. After 7 min, patients were relaxed and after 10 min or after the BIS decreased below 60, the patients were intubated. The primary outcome was the maximum change in heart rate values to baseline as well as the maximum change in mean arterial blood pressure values to baseline values were compared. This study did not find a significant difference in maximum heart rate changes between groups, but the authors reported a significantly reduced delta in mean arterial pressure decrease compared to baseline values during induction in the remimazolam group. They concluded that remimazolam may be an alternative to propofol and was safe and effective for anesthetic induction in patients with cardiac valve disease [13].

As remimazolam is a BZD the specific reversal agent flumazenil is available and can be used in clinical practice to further speed up recovery times or specifically treat prolonged postoperative sedation. This offers a valuable substance benefit compared to propofol because the clinician can easily discriminate between prolonged sedation or other postoperative pathologies, i.e. postoperative stroke, which will also impact the speed of postoperative recovery to full awareness. However, routine use of flumazenil for the reversal of remimazolam should be prospectively evaluated regarding possible side effects and safety in further studies. The main differences between remimazolam and propofol are summarized in table 2.

4. Precipitation

Sasaki et al. reported the precipitation of remimazolam after bolus administration of 0.2 mg/kg with Ringer’s acetate solution [24]. Yoshida et al. reported that an intravenous line occlusion of Ringer’s acetate solution occurred when using remimazolam in a concentration of 2 mg/ml [25]. The solubility of remimazolam is higher in low pH than in high pH and solubility is higher in normal saline than in
Ringer’s solution. Therefore, precipitation can occur when Ringer’s solution is co-administered. The risk of precipitation of remimazolam is increased when a solution with a high remimazolam concentration and a low infusion rate are combined.

5. Further evaluation for remimazolam

To be able to precisely titrate remimazolam to a chosen pharmacodynamic effect, accurate pharmacokinetic/pharmacodynamic models are mandatory. Interaction modeling between opioids and remimazolam during general anesthesia so far has only been described for remifentanil in a publication of Zhou et al. [15] with the BIS as pharmacodynamic effect parameter. Further randomized controlled trials exactly describing the pharmacodynamic interaction of remimazolam with remifentanil, sufentanil and fentanyl are necessary for the development of feasible and rational dosing strategies in various clinical settings and for specific patient populations. The development of a TCI system for remimazolam targeting plasma and effect site concentrations would further improve exact dosing to effect. The availability of a TCI system could also reduce recovery times, as time of decrease to an estimated awakening concentration of remimazolam can continuously be calculated and displayed by a modern TCI smart pump system. The use of flumazenil to quickly antagonize any residual sedative or anesthetic effect of remimazolam should be further investigated. Flumazenil will certainly result in shortening of recovery times and may also reduce the incidence of postoperative cognitive deficit (POCD) or cognitive decline shortly after surgery. In a rat model of a cerebral ischemia/reperfusion Shi M. et al. [26] have already shown a protective effect of remimazolam. Other harmful or protective side effect of the administration of general anesthetics like recurrence rates of cancer at the site of resection or an effect on metastatic disease burden, the incidence of postoperative nausea and vomiting or the incidence and severity of POCD should be further investigated.

Conclusion

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It has been conclusively shown that remimazolam is non-inferior to midazolam to provide adequate sedation and when co-administered with opioids is non-inferior to propofol for induction and maintenance of general anesthesia [8, 13]. The hemodynamic and respiratory stability compared to propofol is remarkable, but further well designed randomized controlled clinical trials are needed to confirm and support these findings. Awakening time could be slightly longer than for propofol, but as far as it is known today the difference is only in the range of 1 to 5 min, which might not be rated as clinically relevant in daily practice [13]. Also prolonged recovery can be specifically treated with flumazenil, which is a significant advantage for remimazolam. The risk of precipitation in the infusion line should be recognized, and Ringer’s solution should not be used as maintenance fluid together with remimazolam. Since more than four decades remimazolam is the first new intravenous anesthetic agent that has been successfully introduced into clinical practice mainly supported by a superior hemodynamic safety profile in comparison to propofol. Remimazolam is a soft drug and shows a pharmacological profile that should enable it to at least partially replace propofol as standard intravenous anesthetic agent for general anesthesia in the future.
References


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Table 1. Ideal Intravenous Anesthetic Agents

<table>
<thead>
<tr>
<th>Physical and chemical properties</th>
<th>Pharmacology</th>
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<tbody>
<tr>
<td>Chemically stable</td>
<td>Painless on injection</td>
</tr>
<tr>
<td>Water soluble</td>
<td>Low incidence of thrombophlebitis</td>
</tr>
<tr>
<td>Does not contain additive or require reconstitution</td>
<td>Harmless on extravasation and intraarterial injection</td>
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<tr>
<td>Long shelf-life</td>
<td>Low incidence of adverse reactions</td>
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<tr>
<td>Compatible with other intravenous fluids or drugs</td>
<td>Smooth onset of anesthesia</td>
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<tr>
<td>Bacteriostatic</td>
<td>No unwanted movements</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant, antiemetic and analgesic effects</td>
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<tr>
<td></td>
<td>No cause respiratory depression or act as a bronchodilator</td>
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<tr>
<td></td>
<td>No cardiovascular depression or stimulation</td>
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<td></td>
<td>Predictable recovery</td>
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<tr>
<td></td>
<td>Rapid conversion to non-active metabolites</td>
</tr>
<tr>
<td></td>
<td>No impairment of hepatic or renal functions and no suppression of corticosteroid synthesis</td>
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<tr>
<td></td>
<td>No association with emergence phenomenon</td>
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<tr>
<td></td>
<td>No teratogenic effects</td>
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<tr>
<td></td>
<td>Not much cumulation in body tissues, maintenance of general anesthesia possible</td>
</tr>
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Table 2. Comparison between Remimazolam and Propofol

<table>
<thead>
<tr>
<th></th>
<th>Remimazolam</th>
<th>Propofol</th>
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<tbody>
<tr>
<td><strong>Anesthetic induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>Fast</td>
<td>Fast</td>
</tr>
<tr>
<td>Pain at administration</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Anesthetic maintenance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Less frequent, severe</td>
<td>More frequent, severe</td>
</tr>
<tr>
<td><strong>Emergence from anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed</td>
<td>Fast</td>
<td>Fast</td>
</tr>
<tr>
<td>Reverse agent</td>
<td>Flumazenil</td>
<td>-</td>
</tr>
</tbody>
</table>
Fig. 1. Structure of midazolam.
Fig. 2. Structure of remimazolam.
Fig. 3. Context-sensitive decrement times of the plasma concentration.
Fig. 4. Context-sensitive decrement times of the effect concentrations.