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# Rapidly Metabolized Anesthetics: Novel Alternative Agents for Procedural Sedation

**Joseph Colao and Daniel Rodriguez-Correa***

*Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, NJ, USA*

***Corresponding author:** Daniel Rodriguez-Correa MD., PhD. Assistant Professor, Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, NJ, USA, Tel: 973-972-9457; E-mail: dtr38@njms.rutgers.edu

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**Abstract**

The increased demand for procedural sedation in the ambulatory setting has prompted the development of anesthetic agents that anesthesiologists and non-anesthesiologists could administer easily and safely. In this article, we discuss novel short-acting agents in development or in clinical trials that may serve as alternatives to current anesthetics for procedural sedation.

## Introduction

Propofol and midazolam are the most commonly used agents for intravenous sedation and induction of anesthesia in a wide variety of surgical and nonsurgical procedures. Though both agents exert their effects by interacting with inhibitory GABA-A receptors in the central nervous system, they have different advantages and adverse effects. Midazolam is a short-acting benzodiazepine, which has sedative effects that are pharmacologically reversible by administration of flumazenil. However, midazolam has a relative long onset to produce sedation and its active metabolite, α1-hydroxymidazolam, may prolong recovery [1-3]. This can both decrease procedural efficiency and increase the risk of adverse effects, such as respiratory depression. Propofol is a sedative-hypnotic agent that is advantageous because it has a rapid onset of sedation and recovery, compared to midazolam [4-6]. It has a narrow therapeutic range and steep dose-response curve; therefore, a small increase in dose can quickly cause a large increase in depth of sedation [7]. Propofol can cause apnea and significant cardiovascular depression if too large of a dose is administered. There is no clinically available agent that can reverse its effects. Because propofol also has low solubility in aqueous solution, it is often prepared as an emulsion, which supports bacterial growth and may lead to bacteremia [8]. Propofol also produces pain on injection and it is often co-administered with lidocaine to reduce patient discomfort [9].

There has been an increase in the number of procedures requiring deep sedation, including minimally invasive surgeries and nonsurgical procedures commonly performed in outpatient settings such as upper gastrointestinal endoscopy, colonoscopy, and bronchoscopy [10]. Procedural sedation is also common in emergency departments for dislocated joint reduction, fracture care, and cardioversion, among others [11,12]. In those settings, etomidate and ketamine are agents of choice in addition to midazolam and propofol [11]. The use of propofol for sedation in these procedures is growing, and current guidelines recommend for it to be administered by anesthesiologists [13]. However, the demand for anesthesiologists' services in these procedures has exceeded anesthesiologists' availability in many clinical settings [7,10]. As a result, non-anesthesiologist administration of propofol (NAAP) by endoscopists and registered nurses is on the rise, with favorable safety data, especially for upper gastrointestinal endoscopy and colonoscopy [14-16]. Though NAAP has been supported by both American and European anesthesiology guidelines for certain procedures with low risk patients, the practice remains controversial due to concern for adverse effects occurring without a trained anesthesiologist present to manage the patient [13,17]. Ideally, anesthetic agents used for these procedures would produce rapid onset of sedation and recovery with minimal adverse effects so that anesthesiologists and non-anesthesiologists could administer them easily and safely. There is no drug approved for clinical use that possesses all of these properties. However, multiple rapidly metabolized anesthetic agents with those characteristics are currently in pre-clinical and clinical trials. This review summarizes the most recent developments in these drugs, which could shape the future of procedural sedation.

## Remimazolam

Remimazolam (CNS 7056) (Figure 1) is a rapidly metabolized midazolam analogue developed by PAION for which Phase II clinical trials have recently been completed. The major shortcoming of midazolam use in sedation is that patients have prolonged recoveries due to midazolam's liver-dependent metabolism by cytochrome P450 3A4 and the accumulation of the drug's active metabolites [18]. This requires additional monitoring of patients during recovery. Remimazolam contains a carboxylic ester linkage that allows it to undergo rapid, dose-dependent hydrolysis by non-specific tissue esterases, rather than primarily by liver enzymes as with midazolam. This organ-independent metabolism allows for faster, more predictable elimination and greater procedural efficiency. Like midazolam and other benzodiazepines, remimazolam produces sedative effects by interacting with GABA-A receptors. Its carboxylic acid metabolite (CNS 7054) also has affinity for GABA-A receptors, but it is 400-fold less than remimazolam *in vitro* [19]. CNS 7054 has a terminal half-life 4 times greater than that of remimazolam but is considered inactive [20]. Phase I clinical trials demonstrated that remimazolam had a dose-dependent duration of sedation with a median time to fully alert of 10 minutes, compared to a 40 minutes for midazolam, following 1-minute IV infusions of equihypnotic doses of each drug. Remimazolam had similar adverse effects to midazolam; they were most commonly headache and somnolence. There were no significant effects on heart rate, blood pressure, respiratory rate, temperature,

ECG, or laboratory values [18]. The effects of remimazolam were easily reversed with administration of flumazenil [20]. An additional finding of note was the lack of a clear relationship between systemic clearance of remimazolam and body weight, which could suggest that dosing by body weight would not be advantageous [18].

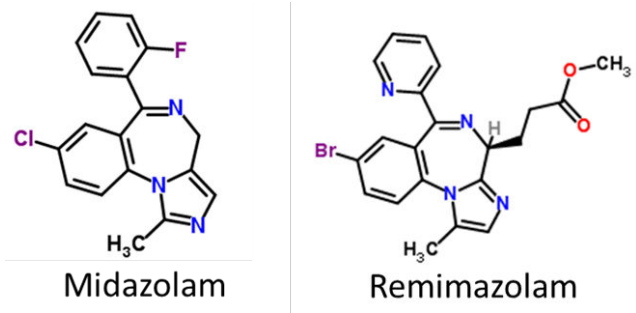


**Figure 1:** Molecular structures of remimazolam and midazolam.

The randomized, double-blind Phase II clinical trials, published in 2015, evaluated the safety and efficacy of remimazolam versus midazolam in upper GI endoscopy and colonoscopy to define doses for procedural sedation in future trials. In the Phase IIa trial, patients received a single dose of either remimazolam (0.10, 0.15, or 0.20 mg/kg) or midazolam (0.075 mg/kg) for an upper GI endoscopy [21]. The 0.15 and 0.20 mg/kg remimazolam study groups had greater procedure success rates (56.0% and 64.0% respectively) than the midazolam group (44.0%). The 0.10 mg/kg remimazolam group had a lower success rate of 32.0%. In all four study groups, procedure failure was solely due to the need for a rescue sedative of either propofol, midazolam, or both propofol and midazolam if sedation could not be maintained after the single dose administration. 51 of the 100 total patients in the study required rescue sedative. The percentage of patients who received rescue sedatives varied greatly from 8.3% to 78.6% among the several different clinical sites at which the procedures were performed. This likely resulted from each site waiting a different amount of time to administer the rescue sedative, which primarily determined the procedural success rates. Additionally, 25 of the recruited patients, who were evenly distributed across the four study groups, received topical anesthetic for the procedure, and only 2 (8%) of these patients required rescue sedative in comparison to the overall study rate of 51%. The authors advised for topical anesthetic administration to be standardized for all patients' in future upper GI endoscopies. All three remimazolam groups had faster onsets of sedation (1.5 to 2.5 minutes) and faster mean recoveries from of sedation (6.8 to 9.9 minutes) than the midazolam group (5 minute onset, 11.5 minute recovery). These results excluded patients who required rescue sedatives. The incidence of adverse events occurring after sedative administration was similar among all 4 study groups with the remimazolam groups (40% to 48%) having slightly less incidences than the midazolam group (52%). Both compounds had stable vital sign profiles and low risk of adverse respiratory events, suggesting that remimazolam has a typical benzodiazepine adverse effect profile, but this must be confirmed by further studies.

In contrast to the endoscopy study, the patients in the Phase IIb clinical trial received an initial body-weight-independent dose of either remimazolam (8.0, 7.0, or 5.0 mg) or midazolam (2.5 mg) for a colonoscopy [22]. The patients also received a maximum of 6 top-up boluses of their initial drug for maintenance of sedation throughout the procedure (3.0, 2.0, or 3.0 mg for the remimazolam groups respectively or 1.0 mg for the midazolam group). Supplemental oxygen and 100 μg of fentanyl were administered to all patients prior to the procedure. Procedure success was significantly greater in the remimazolam groups (92.5% to 97.5%) than in the midazolam group (75.0%), though the greater success of the 8.0 mg remimazolam group was not statistically significant. Among the 3 remimazolam groups, the success rate increased with decreasing initial dose; the 5.0 mg group had the greatest success rate of 97.5%. All procedure failures were again due to the need for a rescue sedative if sedation could not be maintained after 2 minutes after using all 6 available top-ups. Onset of sedation was faster for the remimazolam groups (2.35 to 3.03 minutes) than for the midazolam group (4.80 minutes). Over 82.5% of the remimazolam patients were sufficiently sedated to start the procedure after the initial dose, compared to 46.3% of midazolam patients. In addition, the remimazolam groups (1.43 to 2.35) required less top-ups on average than the midazolam group (2.48). Mean recovery time was similarly short among all four study groups (11.3 to 15.2 minutes), but this is likely due to the 25% of midazolam patients who received propofol as a rescue sedative while very few remimazolam patients received rescue sedatives. The 5.0 mg remimazolam group had the best safety profile of the 4 study groups with no incidences of hypoxia, respiratory depression, or severe hypotension, which each occurred in at least 2 of the other 3 study groups. Some of these adverse events occurred shortly after fentanyl administration, so the benzodiazepines may not have been the primary cause. With the superior success rate and safety profile, a 5.0 mg initial dose of remimazolam with 3.0 mg top-ups to maintain sedation proved to be the most effective dose to pursue in future clinical trials.

Remimazolam has shown great potential among new rapidly metabolized anesthetics as a safe sedative with fast onset and short duration of action. This allows for faster procedure times and decreased risk of prolonged sedation in comparison to midazolam, the current drug of choice. The drug has made the most progress in clinical trials, and its success thus far necessitates further investigation in Phase III studies, which are ongoing.

## Etomidate Analogues

### Cyclopropyl-methoxycarbonyl metomidate (ABP-700)

ABP-700 (Figure 2), also known as cyclopropyl-methoxycarbonyl metomidate (CPMM), is a rapidly metabolized etomidate analogue developed by the Massachusetts General Hospital Department of Anesthesia that has recently completed Phase I clinical trials. The parent compound, etomidate, is a GABA-A receptor agonist that produces variable hypnotic recovery times after intravenous infusions and also produces adrenocortical steroid suppression that persists much longer than its hypnotic effect due to inhibition of the cytochrome P450 enzyme β-11 hydroxylase, which is necessary for cortisol, corticosterone, and aldosterone synthesis [23]. To improve recovery times and avoid adrenocortical suppression, the research team at Massachusetts General Hospital developed methoxycarbonyl etomidate (MOC-etomidate), an ester-linked etomidate analogue that is rapidly metabolized by nonspecific esterases to a significantly less potent carboxylic acid metabolite in a similar way as remimazolam [24,25]. MOC-etomidate had a significantly shorter duration of hypnotic effect and adrenocortical suppression than etomidate in animal studies, but it was determined to be too short acting for clinical

use [26,27]. The research team then developed a series of MOC-etomidate analogues by incorporating various chemical groups into the compound to sterically protect the ester moiety from hydrolysis by esterases, prolonging the duration of action to a clinically useful length. CPMM (ABP-700) was the most promising of the analogues synthesized [27].

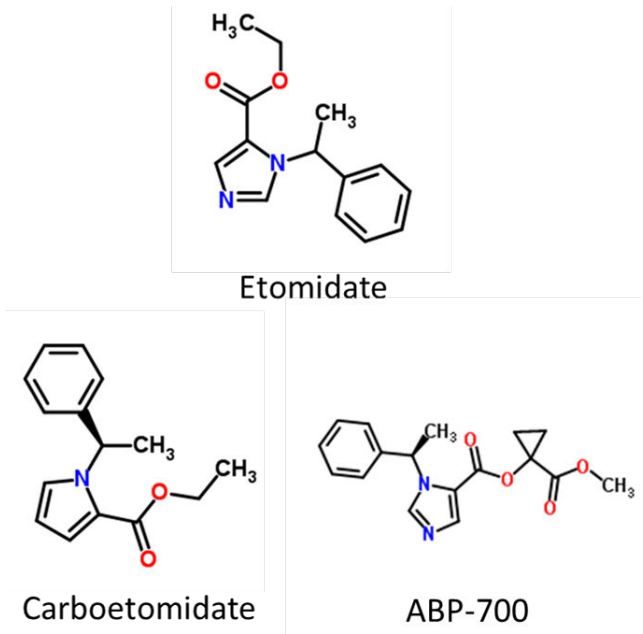


**Figure 2:** Molecular structure on etomidate, caeboetomidate and ABP-700.

A subsequent study comparing the effects of CPMM with those of etomidate in dogs found that single intravenous boluses of CPMM produced dose-dependent durations of sedation with significantly faster clearance than etomidate as indicated by the slopes of the dose-response curves [23]. Hypnotic recovery times after both a single bolus and a single bolus followed by a 2-hour infusion of each drug were also faster for CPMM than for etomidate. Mean recovery time did not differ significantly after single bolus administration (8 ± 3 min) than after 2-hour infusion (11 ± 3 min) demonstrating that recovery time was independent of CPMM infusion duration. In contrast, there was a greater than four-fold increase in mean hypnotic recovery time after etomidate infusion than after single bolus administration. A CPMM metabolite was also found to remain in the blood at high concentrations long after CPMM administration, but the metabolite's hypnotic potency and molecular interactions have not been determined.

Similar to etomidate, CPMM produced adrenocortical suppression during a 2-hour infusion and 30 minutes after termination of the infusion, as indicated by decreased ACTH-induced serum cortisol concentration. Adrenocortical response was normal (compared to vehicle control) 120 minutes after CPMM infusion termination, while cortisol levels remained decreased for greater than 300 minutes after etomidate infusion termination. A similar study in rats receiving infusions of either etomidate or CPMM demonstrated similarly faster adrenocortical responsiveness following CPMM infusion [24]. Adrenocortical responsiveness after a 2-hour infusion of CPMM was also found to be similar to that of propofol within 90 minutes after infusion termination [23]. This indicated that adrenocortical suppression following CPMM administration was likely brief and clinically insignificant, further demonstrating potential for CPMM to advance to human studies. Another study found that CPMM produced reduced elevations of inflammatory cytokines in response to lipopolysaccharide challenge in rats, implicating CPMM as a safer alternative to etomidate in septic patients [28].

In October 2015, The Medicines Company issued a press release briefly summarizing the results of Phase I clinical trials for CPMM, which was renamed ABP-700 [29]. In one double-blind randomized study (ANVN-01), 60 healthy adult volunteers received either a single intravenous bolus of ABP-700 (0.03 to 1.0 mg/kg) or placebo. ABP-700 produced dose-dependent depth and duration of sedation, which was rapidly reversible at all doses. Adverse events were dose-dependent and included tachycardia, hyperventilation, apnea, muscle twitching, and myoclonus [30]. Of note, myoclonus was also observed in a significant portion of subjects in the dog study of CPMM and was reversed rapidly with midazolam administration [23]. There was no significant variance in blood pressure and low incidence of nausea and vomiting in this Phase I study.

Adrenocortical suppression was also evaluated in two separate Phase I trials mentioned in the press release. One trial was the aforementioned placebo-controlled ABP-700 bolus study, and in the other trial, subjects received placebo or 30-minute intravenous infusions of ABP-700 (0.9 to 1.97 mg/kg) or propofol (2.25 mg/kg) [29]. ACTH-induced adrenocortical responsiveness was measured one hour after bolus administration or infusion termination. In both Phase I studies, adrenocortical responsiveness after ABP-700 administration was similar to placebo and propofol, demonstrating that ABP-700 had minimal impact on adrenocortical steroid synthesis after single bolus administration or short-term infusion. These results correlated with those of the previous animal studies.

Though the complete results of these Phase I studies have not yet been published, ABP-700 has shown great potential to be used in future clinical trials due to its rapid metabolism and maintenance of etomidate's favorable hypnotic effects while producing clinically insignificant adrenocortical suppression, though this effect has not been evaluated for continuous infusions longer than 30 minutes. These characteristics of ABP-700 warrant further investigation into its potential uses in specific clinical procedures and its advantages over the sedative agents that are commonly used in those procedures.

## Carboetomidate and MOC-carboetomidate

Etomidate analogs such as APB-700 and MOC-etomidate were designed to produce less adrenocortical suppression than etomidate through their rapid metabolism, resulting in a shorter duration of adrenocortical steroid production. However, these sedatives still inhibit β-11 hydroxylase by the same proposed mechanism as etomidate. The chemical structures of etomidate and its aforementioned analogs contain an imidazole ring, which has been suggested to inhibit the enzyme through the high-affinity interaction of the of its nitrogen atom with the heme iron in the enzyme's active site [31,32]. In order to create an etomidate analog that does not interact with β-11 hydroxylase, the Massachusetts General Hospital Department of Anesthesia developed carboetomidate (Figure 2), which contains a pyrrole ring rather than an imidazole ring [33]. When equihypnotic boluses of carboetomidate and etomidate were given to rats, there was significantly reduced adrenocortical suppression in those that received

carboetomidate than for etomidate, indicated by a greater than two-fold less ACTH-induced serum corticosterone concentration measured 15 minutes after bolus administration. There was no statistically significant difference in adrenocortical suppression between rats that received carboetomidate and those that received placebo, suggesting that carboetomidate does not inhibit β-11 hydroxylase significantly. In a rat endotoxemia study, carboetomidate produced a smaller increase in inflammatory cytokine production and less adrenocortical suppression than etomidate, demonstrating potential usefulness in anesthetic management of septic patients [34]. However, carboetomidate had a much slower onset time than etomidate (33 ± 22 sec vs. 4.5 ± 0.6 sec), as well 1/7th the hypnotic potency [33].

Carboetomidate was modified to incorporate a metabolically labile ester group into its structure, similar to MOC-etomidate, in order to make it a more rapidly metabolized drug while maintaining its favorable adrenocortical effects. The resulting compound, MOC-carboetomidate, retained the GABA-A receptor agonist property and hemodynamic stability of carboetomidate in a rat study [35]. It had a much shorter half-life (1.3 min) than carboetomidate (>20 min) and etomidate (>20 min) but a longer half-life than MOC-etomidate (0.35 min), which was advantageous as MOC-etomidate was too short acting to be feasible for clinical use. MOC-carboetomidate also produced adrenocortical suppression that was significantly less than etomidate and similar to that of the placebo. However, MOC-carboetomidate had a similar onset time to carboetomidate, indicating that the ester linkage did not make induction of sedation faster than that of etomidate. No additional studies of MOC-carboetomidate have been published at this time. Though the reduced half-life demonstrated that MOC-carboetomidate was metabolized faster than carboetomidate and etomidate, the compound must be modified further to warrant future study as a potentially more reliable alternative to etomidate with faster onset and offset of sedation.

## MR04A3

MR04A3 is a 1% aqueous solution of the compound JM-1232(-) (Figure 3) that has been evaluated for its efficacy and safety as a sedative in a human study [36]. JM-1232(-), developed by the Maruishi Pharmaceutical Company, is a water-soluble compound with a non-benzodiazepine structure that, like benzodiazepines, is a GABA-A receptor agonist. It was found to have favorable hypnotic effects in mice, and the effects were inhibited by flumazenil. Due to these results, MR04A3 (the JM-1232(-) preparation) was studied in 69 healthy male volunteers in 2010. MR04A3 produced dose-dependent durations of sedation, measured by time to eyes open on command, after both 1 minute and 10 minute infusions. Mean sedation durations ranged from 5.7 to 67.3 minutes after infusions with doses of 0.075 to 0.8 mg/kg. Ramsay sedation scores were greater with increasing doses of MR04A3. There was also a greater reduction in bispectral index and for a longer duration with larger doses. Heart rate and blood pressure were recorded for 60 minutes after the infusions, and both varied minimally throughout that time. The adverse event profile in volunteers who received MR04A3 was similar to that of those who received the placebo with a small number of volunteers developing upper airway obstruction, which was relieved by simple positional maneuvers. Overall, MR04A3 was well tolerated among the study participants. Its dose-dependent hypnotic effect and low incidence of adverse events during recovery warrant further clinical investigation. Though this study demonstrated faster onset and offset times for MR04A3 than for literature values of midazolam, future studies must compare MR04A3 directly to active control anesthetics, such as midazolam and propofol, rather than only placebo [37]. There was also a JM-1232(-) metabolite, JM-Metabo-3, that was found in increasing arterial concentrations with greater MR04A3 infusion doses [36]. This metabolite must be investigated further to determine the risk of unexpected prolongation of sedation and other potential adverse effects.

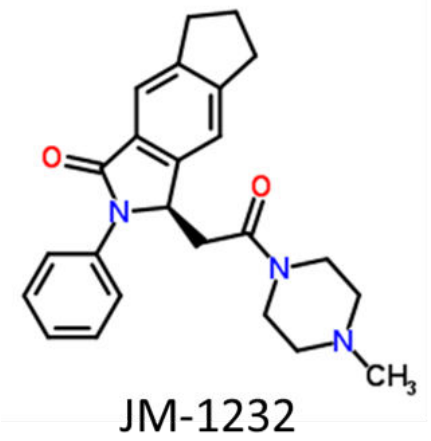


**Figure 3:** Molecular Structure of JM-1232.

More recently, animal studies on the cerebrovacular effects of JM-1232(-) found that intravenous administration of the compound has minimally affected vascular reactivity and further validated its safety [38,39]. However, plans for future evaluation in human studies are unclear.

## Conclusion

The emerging group of rapidly metabolized anesthetics represents both pharmacokinetic and pharmacodynamic modifications to agents used clinically for intravenous induction of anesthesia, such as midazolam and etomidate. The preferred pharmacokinetic modification is an ester linkage, which is found in remimazolam, ABP-700, MOC-carboetomidate, and MOC-etomidate. The ester group allows for rapid, nonspecific metabolism by tissue esterases, leading to faster offset and less significant adverse effects due to the short duration of action. However, rapid metabolism also causes greater production of metabolites, which must be closely evaluated for the potential to prolong sedation unexpectedly and cause adverse effects. Remimazolam, MR04A3, and ABP-700, which have all at least completed Phase I clinical trials, have known metabolites under investigation, though the remimazolam metabolite is considered inactive. In contrast, carboetomidate is a pharmacodynamic modification of etomidate that significantly decreases adrenocortical suppression, which is etomidate's major adverse effect. MOC-carboetomidate is a combination of both pharmacokinetic and pharmacodynamic modifications.

Remimazolam and ABP-700 have the greatest potential to be introduced into clinical practice since they have completed Phase II and Phase I trials, respectively, with favorable results. Further trials that can continue to demonstrate these drugs' more rapid and reliable onsets and offsets of sedation may warrant their use as alternatives to midazolam, especially for short procedures. These favorable properties may also have implications for use of these drugs by non-

anesthetists. While the rapidly metabolized anesthetics were compared to their parent compounds, midazolam and etomidate, an important shortcoming of the clinical trials performed thus far is the lack of direct comparison to other anesthetics commonly used outside of the operating room, such as propofol and ketamine. Inclusion of these agents for comparison in future studies would be useful in demonstrating the advantages of the novel anesthetics in procedural sedation more clearly. The last decade has yielded exciting advances in the development of rapidly metabolized anesthetics. While their exact clinical applications have yet to be defined, these drugs show great potential to produce more reliable sedation while improving procedural efficiency and patient safety.

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