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New horizons for sedation: The ultrashort acting benzodiazepine remimazolam

Daniel J. Pambianco[a,1,2,*], Brooks D. Cash[b,2]

[a] Charlottesville Medical Research, 325 Winding River Lane, Suite 102, Charlottesville, Virginia 22911
[b] Digestive Health Center, University of South Alabama, Mobile, Alabama

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ABSTRACT

Procedural sedation is used in 98% of endoscopies performed in the United States. The predominant agents used are benzodiazepines, opioids, and propofol. The optimal sedation depends on the procedure being performed and its duration. An ideal sedative would allow for flexible, rapid onset and offset of sedation with predictable short duration of action with minimal cardiopulmonary risk factors. Remimazolam is a novel "soft drug" with the characteristics of a benzodiazepine and organ-independent metabolism. Remimazolam binds selectively and with high affinity to the gamma-aminobutyric acid receptor, with no off-target activities. In animal studies, remimazolam has a short, initial phase half-life and high volume of distribution, indicating extensive tissue distribution, minimal tissue accumulation, and rapid elimination. Remimazolam is hydroxylated to an inactive metabolite, and its effects can be reversed with flumazenil. In clinical studies for procedural sedation, remimazolam was well tolerated with no serious adverse events. Times to onset or offset of sedation were shorter with remimazolam versus active control. All remimazolam-related adverse reactions are well known to clinicians and can be managed by trained staff. This article summarizes the preclinical and clinical data on the efficacy and safety or remimazolam for endoscopic sedation. Remimazolam is in clinical development for procedural sedation, general anesthesia, and sedation in the intensive care unit. Remimazolam is a promising new sedative or anesthetic agent with scientific support for continued clinical development. Phase III studies with remimazolam for procedural sedation are underway.

1. Introduction

Since the advent of fiberoptic endoscopy, in the mid 1950s, the diagnosis and treatment of gastrointestinal (GI) disorders has been transmogrified by the use of this modality to become the primary tool used in colon cancer screening and prevention, as well as the investigation of abdominal pain, anemia, altered bowel habits, GI blood loss, and abnormal imaging [1]. Currently our armamentarium includes the use of not only routine diagnostic and therapeutic esophagogastroduodenoscopy and colonoscopy but also advanced endoscopic procedures such as endoscopic ultrasound, double balloon enteroscopy, and endoscopic retrograde cholangiopancreatography. Simultaneously, there has been a logarithmic growth in the use of and need for sedation, allowing for greater patient comfort and safety in the evolution of these erstwhile nonsurgical procedures. As the number and complexity of endoscopic procedures increase, the role of sedation has been integral in patient and physician satisfaction. Presently, 98% of endoscopic procedures in the United States are performed with sedation administered by gastroenterologist or anesthesia professionals [2]. However, unlike surgery that requires general anesthesia, optimal sedation requirements for endoscopy need to be matched to patient comfort, comorbidity risks, the anticipated procedural discomfort, and the length of the procedure in order to minimize the unnecessary risk of deeper sedation or general anesthesia [3]. Most of the patients require moderate sedation for relatively short procedures for which the ideal agent or administration model is still being sought.

This article focuses on the unmet needs of our current sedation practices and the evolution and potential of the novel compound, remimazolam, an ultrashort acting benzodiazepine.

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* Corresponding author.
E-mail address: djp@cvillemedresearch.com (D.J. Pambianco).

[1] Guarantor of article.

[2] Contributed equally to the concept for the review article, provided substantial feedback on previous drafts and approved the final, submitted version of the manuscript.

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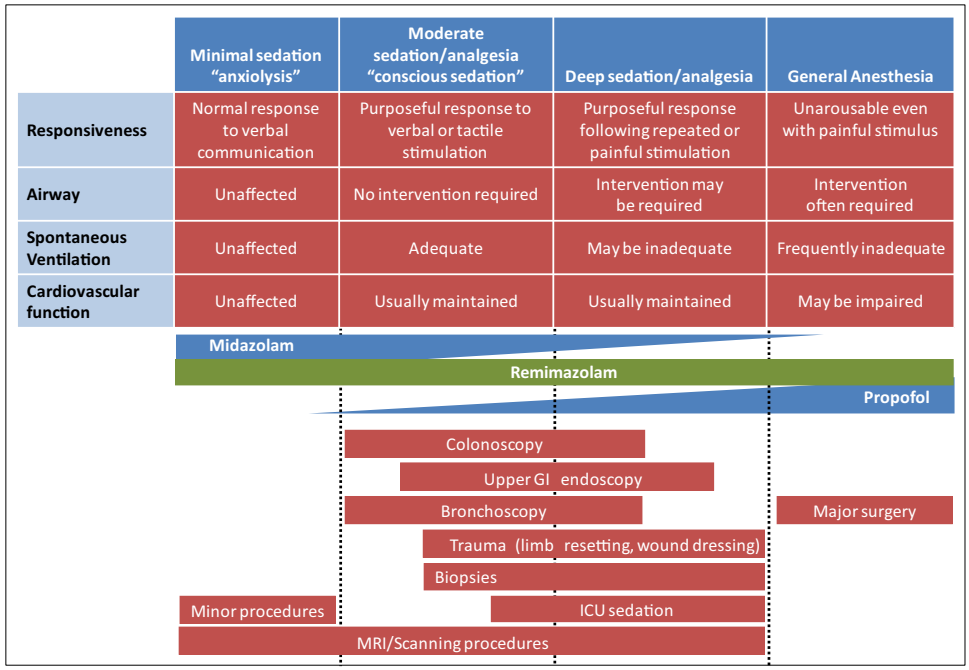

Fig. 1. Continuum of sedation: definition of general anesthesia and levels of sedation/analgesia (ASA, 1999—modified) [19] and intended use of remimazolam. (Color version of figure is available online.)

2. Sedation background

The goals of sedation are to balance patient comfort and tolerability with the risks of drug-related side effects and over sedation. It is intended to reduce patient anxiety and discomfort for procedures that may need to be repetitive while allowing the endoscopist patient stability to perform a thorough examination [4].

Sedation has been defined as a drug-induced suppression of consciousness that is a continuum from anxiolysis (minimal) to conscious sedation (moderate) to unconsciousness (general anesthesia). The American Society of Anesthesiologists (ASA) has developed and defined the continuum of sedation for medical procedures of varying invasiveness (Figure 1). The ability to achieve and maintain the balance of appropriate necessary depth of individualized sedation with minimal adversity is a combination of expertise and pharmacology.

Currently, midazolam and propofol are the most commonly used intravenous (IV) sedatives used for procedural sedation often in conjunction with IV opioids [5], however each agent has disadvantages.

Propofol, an anesthetic alkylphenol, is an IV sedative or hypnotic that is used for sedation and general anesthesia in higher doses. Among its major advantages for brief procedural sedation such as endoscopy are its exceptional sedative properties with fast induction and extremely short half-life, allowing for rapid recovery from sedation and rapid discharge from the endoscopy suite. However, there are some safety and tolerability concerns, including injection site pain, susceptibility to bacterial contamination, and cardiovascular and respiratory depression. The induction or maintenance dosing to effect-site concentration is not linear owing to tissue compartment variability, and repeated or prolonged administration can lead to unpredictable clinical consequences, predominantly apnea, and hypotension. As a result of this potential narrow therapeutic window, rapid progression to respiratory depression and hypoxia can cause the potential need for respiratory rescue with endotracheal intubation. Consequently, the presence of an anesthesia professional is required to monitor the patient and manage the level of sedation for the endoscopic procedure [6,7].

Benzodiazepines were discovered in the 1950s with the vanguard of chlordiazepoxide and later diazepam, the latter of which was widely used for endoscopic sedation until the advent of midazolam in the 1980s. Owing to midazolam's water solubility, which eliminated pain on injection and its shorter half-life, it usurped the use of diazepam [8].

Midazolam is considered a safe and effective sedation agent. The mean elimination half-life of midazolam is about 3 hours (range: 1.8-6.4 hour), and it is metabolized by cytochrome P450-3A4. It is well established that individual variability in P450 activity and interactions with drugs that inhibit or activate the 3A4 system can contribute to the unpredictability in onset or duration of midazolam's sedative effects. As such and similar to propofol, plasma effect-site concentration after an IV dose and its relationship to pharmacodynamic measures (ie, reaction time, eye movement, sedation depth) have shown extensive intersubject variability [9].

Moreover, midazolam is hydroxylated into active and inactive metabolites, which can increase the risk of excessive sedation by drug interactions. About 60%-70% of the biotransformation product is 1-hydroxy-midazolam (alpha-hydroxy-midazolam), which is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam [9]. Midazolam accumulates with renal impairment, prolonged infusion, and after repeated single dose infusions—a common dosing schedule during short, conscious sedation administration. Owing to these variable pharmacokinetic and pharmacodynamic effects, midazolam can be difficult to titrate and may produce prolonged sedation, thus delaying recovery. These characteristics make midazolam a suboptimal candidate as a sedative or anesthetic agent.

The development of new sedative and anesthetic drugs over the last decade has been driven by the changing demands of clinical practice, where procedures once performed in the hospital are now performed in ambulatory settings, on an increasingly