ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2024 July 16; 16(7): 376-438

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 16 Number 7 July 16, 2024

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Clinical Trials Study

Observational Study

CASE REPORT

World Journal of Gastrointestinal Endoscopy

Monthly Volume 16 Number 7 July 16, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Jayanta Samanta, MD, DM, Associate Professor, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. invincible.doc@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGE* as 1.4; JIF without journal self cites: 1.4; 5-year JIF: 1.7; JIF Rank: 111/143 in gastroenterology and hepatology; JIF Quartile: Q4; and 5-year JIF Quartile: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee, JooYoung Cho

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
July 16, 2024

PUBLISHING PARTNER
Digestive Endoscopy Center of West China Hospital, SCU

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://www.cd120.com/index.html

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2024 July 16; 16(7): 385-395

DOI: 10.4253/wjge.v16.i7.385

ISSN 1948-5190 (online)

MINIREVIEWS

Remimazolam for sedation in gastrointestinal endoscopy: A comprehensive review

Dushyant Singh Dahiya, Ganesh Kumar, Syeda Parsa, Manesh Kumar Gangwani, Hassam Ali, Amir Humza Sohail, Saqr Alsakarneh, Umar Hayat, Sheza Malik, Yash R Shah, Bhanu Siva Mohan Pinnam, Sahib Singh, Islam Mohamed, Adishwar Rao, Saurabh Chandan, Mohammad Al-Haddad

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Kitamura K, Japan

Received: March 30, 2024
Revised: May 5, 2024
Accepted: June 4, 2024
Published online: July 16, 2024
Processing time: 99 Days and 8.9 Hours

Dushyant Singh Dahiya, Division of Gastroenterology, Hepatology & Motility, The University of Kansas School of Medicine, Kansas City, MO 66160, United States

Ganesh Kumar, Syeda Parsa, Department of Internal Medicine, Chandka Medical College, Sindh 77280, Pakistan

Manesh Kumar Gangwani, Department of Gastroenterology and Hepatology, University of Arkansas For Medical Sciences, Little Rock, AR 72205, United States

Hassam Ali, Division of Gastroenterology, Hepatology and Nutrition, East Carolina University/Brody School of Medicine, Greenville, NC 27858, United States

Amir Humza Sohail, Department of Surgery, University of New Mexico School of Medicine, Albuquerque, NM 87106, United States

Saqr Alsakarneh, Department of Internal Medicine, University of Missouri-Kansas City, Kansas City, MO 64108, United States

Umar Hayat, Department of Internal Medicine, Geisinger Wyoming Valley Medical Center, Wilkes Barre, PA 18711, United States

Sheza Malik, Department of Internal Medicine, Rochester General Hospital, Rochester, NY 14621, United States

Yash R Shah, Department of Internal Medicine, Trinity Health Oakland/Wayne State University, Pontiac, MI 48341, United States

Bhanu Siva Mohan Pinnam, Department of Internal Medicine, John H. Stroger Hospital of Cook County, Chicago, IL 60612, United States

Sahib Singh, Department of Internal Medicine, Sinai hospital, Baltimore, MD 21215, United States

Islam Mohamed, Department of Hepatology, University of Missouri, Columbia, MO 65211, United States

Adishwar Rao, Department of Internal Medicine, Guthrie Robert Packer Hospital, Sayre, PA 18840, United States

Saurabh Chandan, Division of Gastroenterology and Hepatology, Creighton University School

of Medicine, Omaha, NE 68131, United States

Mohammad Al-Haddad, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN 46202, United States

Corresponding author: Dushyant Singh Dahiya, MD, Doctor, Division of Gastroenterology, Hepatology & Motility, The University of Kansas School of Medicine, 2000 Olathe Blvd, Kansas City, MO 66160, United States. dush.dahiya@gmail.com

Abstract

Worldwide, a majority of routine endoscopic procedures are performed under some form of sedation to maximize patient comfort. Propofol, benzodiazepines and opioids continue to be widely used. However, in recent years, Remimazolam is gaining immense popularity for procedural sedation in gastrointestinal (GI) endoscopy. It is an ultra-short-acting benzodiazepine sedative which was approved by the Food and Drug Administration in July 2020 for use in procedural sedation. Remimazolam has shown a favorable pharmacokinetic and pharmacodynamic profile in terms of its non-specific metabolism by tissue esterase, volume of distribution, total body clearance, and negligible drug-drug interactions. It also has satisfactory efficacy and has achieved high rates of successful sedation in GI endoscopy. Furthermore, studies have demonstrated that the efficacy of Remimazolam is non-inferior to Propofol, which is currently a gold standard for procedural sedation in most parts of the world. However, the use of Propofol is associated with hemodynamic instability and respiratory depression. In contrast, Remimazolam has lower incidence of these adverse effects intra-procedurally and hence, may provide a safer alternative to Propofol in procedural sedation. In this comprehensive narrative review, highlight the pharmacologic characteristics, efficacy, and safety of Remimazolam for procedural sedation. We also discuss the potential of Remimazolam as a suitable alternative and how it can shape the future of procedural sedation in gastroenterology.

Key Words: Remimazolam; Endoscopy; Sedation; Outcomes; Efficacy; Safety; Pharmacokinetics

Core Tip: Procedural sedation is a key component of diagnostic and therapeutic gastrointestinal (GI) procedures. It maximizes patient comfort and improves procedural outcomes. Propofol is currently a gold standard for procedural sedation in most parts of the world. However, in recent years, Remimazolam, an ultra-short acting benzodiazepine sedative, is gaining popularity among anesthesiologists and endoscopists for its favorable pharmacology, efficacy, and safety profile. In contrast to other sedatives, particularly Propofol, Remimazolam has lower incidence of intra-procedural hemodynamic instability and respiratory depression. This comprehensive review highlights how Remimazolam can shape the future of GI endoscopy.

Citation: Dahiya DS, Kumar G, Parsa S, Gangwani MK, Ali H, Sohail AH, Alsakarneh S, Hayat U, Malik S, Shah YR, Pinnam BSM, Singh S, Mohamed I, Rao A, Chandan S, Al-Haddad M. Remimazolam for sedation in gastrointestinal endoscopy: A comprehensive review. *World J Gastrointest Endosc* 2024; 16(7): 385-395
URL: https://www.wjgnet.com/1948-5190/full/v16/i7/385.htm
DOI: https://dx.doi.org/10.4253/wjge.v16.i7.385

INTRODUCTION

Worldwide, gastrointestinal (GI) endoscopy is routinely performed for diagnostic and therapeutic interventions for various GI pathologies, both in an inpatient and outpatient setting[1,2]. However, if performed without sedation, endoscopy can be uncomfortable for patients due to intra-procedure complications such as gagging, coughing and choking during upper GI examination, and abdominal pain, abdominal discomfort and bloating during lower GI examination[3]. Hence, all endoscopies are routinely performed under procedural sedation to improve outcomes by minimizing patient discomfort, allowing endoscopists to carry out a safe and thorough examination[2,4,5]. The ultimate goal of procedural sedation is to increase patient satisfaction and improve their willingness to undergo future procedures, if deemed necessary[3]. Some of the commonly used sedating agents for endoscopy include Propofol, Midazolam, and opioids[6]. Across the globe for many decades, Propofol has been the agent of choice for procedural sedation during endoscopy[7,8]. However, the utilization of Propofol has been associated with numerous adverse effects such as hemodynamic and respiratory instability, and potential for aspiration events[9,10]. This has driven researchers to develop potential alternative to Propofol.

Remimazolam is a benzodiazepine agent with full agonist activity at γ-aminobutyric acid type A (GABA-A) receptor [11]. Since its first approval by the Food and Drug Administration (FDA) in 2020, Remimazolam has gained significant traction for use in both general and procedural anesthesia to good effect[12-14]. It is an ultra-short-acting sedative owing

to its rapid and non-specific metabolism by tissue esterases to inactive metabolites[11,15]. For sedation during GI procedures, Remimazolam has demonstrated good efficacy compared to its counterpart including Propofol and Midazolam[16]. Furthermore, it has shown a favorable safety profile including a lower incidence of hemodynamics and respiratory stability, reduction in incidence of injection site pain, lower rates of postoperative nausea and vomiting, and rapid return to full neurological awareness, compared to Propofol[17,18].

This narrative review aims to provide comprehensive evidence on the utilization of Remimazolam for procedural sedation during GI endoscopy. We discuss pharmacologic characteristics, efficacy, and safety of Remimazolam for procedural sedation, while comparing it to other sedatives. Furthermore, we also highlight the potential of Remimazolam to become a suitable alternative to currently utilized sedatives and how it can shape the future of procedural sedation in gastroenterology.

Sedation is defined as a decreased level of consciousness by the administration of a sedating agent[19,20]. Currently, it is routine practice in endoscopy as it increases the overall tolerance for the procedure[19,20]. However, a few decades ago, unsedated endoscopy was a common clinical practice[21]. Hence, the utilization of sedation during endoscopy has been the subject of ongoing debate as it delays patient recovery and can cause numerous cardiovascular and respiratory-related adverse effects[22]. Despite these known risks, procedural sedation has become increasingly popular because it results in greater patient satisfaction and meets their expectations for a painless procedures[22].

Over the years, there have been ongoing advancements in the types of agents used for sedation during endoscopy in gastroenterology[21]. This dates back to the 1960s when phenobarbital was introduced along with trans-tracheal xylocaine injections[22]. After this, meperidine was used as an analgesic, but eventually diazepam gained popularity as studies demonstrated higher patient satisfaction with diazepam[21]. With time, midazolam started gained acceptability for procedural sedation as it was far more effective and had a shorter duration of action than diazepam. Furthermore, it was also noted that midazolam induced more amnesia compared to diazepam, further increasing patient satisfaction. Hence, it started to be increasingly utilized for procedural sedation with or without opioids and became widely recognized as a traditional sedative[22].

The introduction of Propofol as a sedating agent changed the landscape of procedural sedation due to its pharmacokinetic and pharmacodynamic properties. It was considered better than midazolam because of its faster onset and shorter duration of action[22]. Although Propofol is currently the gold standard for sedation in GI endoscopy across the globe, its use has been associated with several adverse effects, including injection site pain, hypotension, and other cardiovascular and respiratory complications[7,23]. This prompted the search for a safer alternatives[7,23,24]. In recent years, Remimazolam has emerged as an alterative to propofol for procedural sedation[23].

LEVELS OF SEDATION

The American Society of Anesthesiologists (ASA) has described four levels of sedation which include minimal sedation, moderate sedation or conscious sedation, deep sedation, and general anesthesia[4,20,25]. In routine endoscopy, the most levels of sedation include moderate sedation, also known as conscious sedation, and deep sedation. Benzodiazepines and opioids are typically administered for moderate sedation, while Propofol is used for deep sedation. In moderate sedation, the patient can be awakened by verbal and tactile cues, their cardiovascular function is maintained, adequate ventilation is present, and airway support is not required. In deep sedation, the patient's responsiveness is limited to noxious stimuli or strong verbal stimuli, and in almost all cases, airway support is necessary[3,20,25]. In rare cases, general anesthesia may be used, which requires intubation and can be induced by nitrous oxide and ketamine[3].

HISTORY OF REMIMAZOLAM AS A SEDATING AGENT

Remimazolam is a benzodiazepine that goes by several names, including GW502056, CNS 7056, CNS 7056B, CNS 7056BS, ONO-2745, and HR 7056[26]. In the late 1990s, an initiative was brought up by Glaxo Wellcome which focused on discovering an ester-based benzodiazepine agent that would be broken down by a non-specific esterase, thereby providing a short and predictable duration of action[26-28]. This led to the identification of Remimazolam as a novel sedative agent owing to its rapid onset of action, aqueous solubility, and overall short duration of action[26,29]. The first Phase 1 study for Remimazolam on healthy human volunteers was registered after FDA approval in 2008 and the results were reported in 2011[26,30]. However, prior to this, several preclinical animal studies were carried out to evaluate the dosage, pharmacokinetics, and pharmacodynamics of Remimazolam with promising results[29,31,32].

Remimazolam was first approved in China for sedation during esophagogastroduodenoscopy (EGD) and colonoscopy in December 2019 and June 2020, respectively[33]. It was later approved in the United States by the FDA in July 2020 and by the European Union and South Korea in August 2021 for use in procedural sedation including GI endoscopy and bronchoscopy[16,33]. Furthermore, remimazolam was first approved for general anesthesia on 23 January, 2020 in Japan, and then in China in November 2021[12,33]. In August 2020, it was approved for intensive care unit sedation in Belgium [26].

MECHANISM OF ACTION OF REMIMAZOLAM

Remimazolam, like other benzodiazepines, is a full agonist at GABA-A receptor[11]. It binds to the receptor and induces the influx of chloride ions leading to membrane hyperpolarization and inhibition of neural activity[34,35]. The properties of this new benzodiazepine can be compared to midazolam in terms of its structure and pharmacokinetic properties which has inspired its name[33,36]. It contains the ring structure of Midazolam with the addition of a carboxylic ester side group[33,36]. This ester group is hydrolyzed by the non-specific esterases into an inactive metabolite CNS7054 which has 300 times lower affinity for the GABA-A receptor as compared to the original compound CNS7056 L[30,33,36]. This unique structure confers an ultra-short duration of action to Remimazolam[37]. Furthermore, like any other benzodiazepine, the actions of Remimazolam can be reversed easily at any stage with flumazenil[35,38].

PHARMACOKINETICS AND PHARMACODYNAMICS OF REMIMAZOLAM

Remimazolam is an ideal anesthetic. It is a water-soluble compound that follows first-order kinetics[11,36,39,40]. It undergoes metabolism by non-specific tissue esterase to an inactive compound CNS7054, independent of the dose and has a short terminal half-life (70 ± 10 minutes) (Table 1)[36,39-43]. This allows for administration of increasing doses of the drug and prolonged continuous infusions without the possibility of enzyme saturation[36]. Hence, the drug accumulation within the body and associated prolonged residual effects are prevented[11,36]. It has minimal drug-drug interactions as well because of its hepatic cytochrome p450 independent metabolism[33,41,44]. Hence, Remimazolam can be safely administered in patients with kidney and liver dysfunction because of its organ-independent elimination[33,36,44,45].

Moreover, the total body clearance of Remimazolam is independent of the body weight[11,46]. The total body clearance of Remimazolam was noted to be significantly higher than that of midazolam and slightly lower than that of Propofol. However, Propofol follows organ-dependent elimination and needs cautious administration in patients with hepatic impairment. The steady-state volume of distribution for Remimazolam was found to be 35L in contrast to 400L for Propofol, which is 10 times higher[9,41,47]. The smaller volume of distribution for Remimazolam prompts faster elimination, recovery, and negligible drug accumulation in the body[9].

The pharmacokinetic properties of Remimazolam are unaffected by age, race, gender, and ASA class. However, it is recommended to consider lower doses of infusion in susceptible elderly patients, and those with ASA class 3 or more[33,39,41,48,49]. Some degree of caution should be observed in patients with hepatic impairment as a few studies have reported variation in the half-life, volume of distribution, and recovery times in such patients compared to those with normal hepatic function[33,45].

From a pharmacodynamic standpoint, remimazolam has dose-dependent properties. In the initial trials on pharmacodynamics, the rapid onset of sedation (Table 1) was first observed at a dose of 0.05 mg/kg[33,50]. The peak sedation with the drug was observed within 1-2 minutes after administration of ≥ 0.075 mg/kg dose (Table 1)[33,50]. With higher doses ≥ 0.25 mg/kg, the recovery times were observed to be significantly higher (approximately 50 minutes), rendering these doses unsuitable for short-term procedural sedation; however, ideal for induction of general anesthesia[30,33,50].

COMPARISON OF EFFICACY AND COST OF REMIMAZOLAM TO OTHER SEDATION AGENTS

Remimazolam is a highly effective for procedural sedation for GI endoscopy, regardless of the patient's baseline characteristics[9]. It provides adequate sedation in most cases and is comparable to Propofol in terms of overall procedure success[5,17,18,39]. In the study by Guo *et al*[39] which consisted primarily of an elderly cohort undergoing endoscopy, the authors noted that there was no difference and a 100% sedation success rate was achieved with both Remimazolam and Propofol (P = 0.350). At a lower dose of Remimazolam (0.2 mg/kg), Cui *et al*[17] reported significantly higher efficacy (82% *vs* 100%) in the Propofol group (2 mg/kg), but at progressively higher doses (0.3 mg/kg and 0.4 mg/kg) of Remimazolam, both groups provided comparable success rates (96%, 98% in Remimazolam group *vs* 100% in Propofol group) during sedation for endoscopy.

Literature reports significantly better efficacy and sedation success rates for Remimazolam compared to midazolam for GI endoscopy[6,9,51-54]. Rex *et al*[6] assessed the efficacy of Remimazolam compared to midazolam and placebo at 3 sites in the United States. The authors noted that Remimazolam (87.1%) had superiority in procedure success rates compared to midazolam (13.3%, P < 0.00001), and placebo (0.0%, P < 0.00001)[9]. Similar results were reported by Zhang *et al*[54] in a Phase III trial at 12 different sites in the United States. Overall, patients who received Remimazolam had higher rates of adequate sedation, greater procedure success, shorter time to the start of the procedure, lower requirement for rescue medication, and fewer top-up doses compared to those who received midazolam for procedural sedation[6,52-54].

The time to loss of consciousness and achieving adequate sedation is longer with Remimazolam compared to Propofol [18,39,51,55,56]. Additionally, more supplemental doses are required with Remimazolam to achieve adequate sedation compared to Propofol which is more successful in achieving sedation with only one dose[18,39,56]. According to the study by Chen *et al*[18], 94.97% of patients in the Propofol group achieved adequate sedation with the initial dose, while only 54.89% of patients in the Remimazolam group achieved the same level of sedation. This suggests that the time for adequate sedation may be extended for patients receiving Remimazolam[18].

Numerous studies have produced conflicting results regarding the recovery time from sedation, including the time to emerge from sedation and the time to become fully alert, while comparing Remimazolam and Propofol. Some studies, such as those conducted by Chen *et al*[18], Zhang *et al*[55], Cao *et al*[56], and Xiao *et al*[57], reported faster recovery times

Table 1 Half-life and sedation (onset and recovery) time of remimazolam

Characteristics	Value (minute)
Half-life	70
Sedation	
Onset	1-2
Recovery	8-40

in the Remimazolam compared to Propofol group. However, other studies, such as those conducted by Hu *et al*[51], Dong *et al*[58], and Zhu *et al*[59] reported longer recovery times in the Remimazolam compared to the Propofol cohort. One study by Guo *et al*[39] found no significant difference in recovery times between the two sedatives for GI endoscopy, particularly in elderly patients. Hence, additional large prospective studies are needed to fully assess recovery times, an important metric for endoscopy, for Remimazolam.

Remimazolam was found to be as effective as Propofol in terms of the time required for discharge readiness[51,60]. However, patients who received Remimazolam reported higher satisfaction with the procedure compared to those who received Propofol[58,60]. There was no difference in the endoscopists' satisfaction with either of these sedatives[39,58].

Propofol is known to provide a deeper level of sedation [Modified Observer's Alertness/Sedation scale (MOAA/S) = 1] compared to Remimazolam (MOAA/S = 3)[18]. Sedation provided by Remimazolam is usually sufficient for routine GI endoscopic procedures as they are relatively short and do not require such deep sedation[18]. The lowest MOAA/S score or time to peak sedation with Remimazolam can be achieved in a median of 3 minutes (95%CI: 2.0-3.0) before the first top-up dose[9]. However, the need for rescue sedatives was greater for Remimazolam compared to Propofol[6,53,55]. Zhang *et al* reported that the group receiving Remimazolam (19.1%) required more rescue sedation (7.7%) compared to the propofol cohort (P = 0.007)[55].

Compared to Propofol, Remimazolam is associated with lower costs for patients and insurers due to a lower effective dose (ED)[9,61]. Sun *et al*[62] studied the ED of Remimazolam for sedation during GI endoscopy and reported an ED50 of 0.153 mg/kg (95%CI: 0.151-0.154 mg/kg) and an ED95 of 0.164 mg/kg (95%CI: 0.160-0.166 mg/kg). Cao *et al*[63] reported an ED50 and ED95 of Remimazolam with adjuvant sufentanil in patients with hepatic cirrhosis undergoing endoscopic screening for varices as 0.097 mg/kg (95%CI: 0.004–0.099 mg/kg) and 0.107 mg/kg (95%CI: 0.103–0.336 mg/kg), respectively. In a recent multicenter randomized controlled trial (RCT), it was reported that 0.2 mg/kg of Remimazolam has non-inferior efficacy for GI endoscopic procedural sedation compared to 1.5 mg/kg of Propofol[51].

COMPARISON OF SAFETY OF REMIMAZOLAM TO OTHER SEDATION AGENTS

The most frequently used sedative agents for GI endoscopy include Propofol, midazolam, and opioids[9]. Numerous studies have demonstrated that Remimazolam offers a superior safety profile compared to these sedatives agents[23,64]. Remimazolam has demonstrated excellent safety for procedural sedation during general anesthesia, EGD, colonoscopy, bronchoscopy, and endoscopic retrograde cholangiopancreatography (ERCP)[23,58,64].

Propofol is a widely accepted anesthetic for procedural sedation, particularly among anesthesiologists, owing to its shorter half-life and speedy recovery[39]. Despite its favorable properties, it can elicit serious adverse effects which are more frequently observed in elderly and high-risk patients[6,39]. The common side effects of Propofol include pain at the injection site, hypotension, hypoxia, and respiratory depression[39]. Propofol infusion syndrome is a rare but extremely feared complication associated with its use[65].

The occurrence of pain at the injection site can be frustrating for patients. Studies have indicated that Remimazolam, in comparison to Propofol, exhibits a lower incidence of pain at injection sites[23,39,66,67]. For elderly patients, a study explored the use of Remimazolam tosilate and etomidate-Propofol in outpatient colonoscopies[68]. The authors noted that the administration of etomidate-Propofol resulted in a higher incidence of pain at the injection site[68].

Hypotension is the most commonly reported adverse effect associated with Propofol sedation with an incidence rate as high as 50%[69-72]. It is important to note that a mean arterial pressure of less than 80 mmHg may lead to permanent organ injury or ischemia[73]. Hemodynamically, Remimazolam has shown favorable safety[17,67,74]. In literature, Remimazolam, as a sedative, has been shown to significantly reduce the incidence of hypotension by approximately more than 50% as compared to patients who receive Propofol[23,39,69,72]. In a recent multicenter RCT which included elderly patients, the authors noted a higher occurrence of hypotension in the Propofol group (69.6%) in comparison with the Remimazolam group (36.5%)[74]. Recently another trial that compared different doses of Remimazolam and Propofol, reported a significantly lower incidence of hypotension with Remimazolam tosilate compared to Propofol[17].

Respiratory depression is a serious concern with sedation, and it is commonly reported with Propofol. However, literature reports lower incidence of respiratory depression during sedation for GI endoscopic procedures with Remimazolam[39,51,67]. Dong *et al* reported that when Remimazolam is administered with alfentanil for procedural sedation, there are significantly fewer cases of hypoxia compared to when Propofol and alfentanil are used[58]. Another study conducted in elderly patients undergoing endoscopy to compare the incidence of respiratory depression between the Remimazolam tosilate group and the Propofol group noted that the Remimazolam tosilate group had a significantly lower incidence of respiratory depression compared to the Propofol group (9.8% *vs* 17.9%, P = 0.042)[51]. Furthermore,

obese patients are at a higher risk of developing respiratory complications and airway management can be challenging during procedural sedation[75]. In a RCT conducted to evaluate the safer sedation strategy for obese patients, Remimazolam combined with esketamine was deemed safer than Propofol combined with esketamine, as the former group was associated with a lower incidence of hypoxia[55].

With age, the likelihood of developing GI diseases increases, resulting in a higher need for GI endoscopy[76]. Studies have shown that the use of Propofol in elderly patients can lead to adverse effects such as tachycardia, bradycardia, arrhythmia, hypoxemia, and respiratory arrest more frequently than in younger patients[39,77,78]. A RCT comparing Remimazolam tosilate with Propofol for endoscopy in elderly patients found that the use of Remimazolam tosilate led to significantly fewer hemodynamic events (6/39 *vs* 17/38, $P = 0.005$) and fewer respiratory depression (2/39 *vs* 9/38, $P = 0.026$) compared to Propofol[39].

In terms of postoperative events such as nausea, vomiting, vertigo, and gait abnormalities, studies have demonstrated comparable safety of Remimazolam and Propofol[64,67]. However, in a study conducted in 2022, the group receiving Remimazolam besylate combined with alfentanil reported significantly fewer events of nausea, abdominal pain, dizziness, and fatigue within 24 hour of the procedure compared to the control group receiving Propofol combined with alfentanil[79].

Current literature also reports a better safety profile for Remimazolam compared midazolam[9,43]. A phase III clinical trial was conducted to compare Remimazolam and midazolam for outpatient colonoscopy and the authors concluded that Remimazolam has faster neuropsychiatric function recovery compared to midazolam[9]. Additional, hypotension was also far less frequent in patients receiving Remimazolam than in those receiving midazolam[9]. A meta-analysis of RCT s involving 528 patients also established Remimazolam as a safer alternative than midazolam for GI endoscopy[54].

REMIMAZOLAM IN UPPER, LOWER, AND PANCREATICOBILIARY ENDOSCOPY

In the upper and lower GI endoscopic procedures, Remimazolam has shown excellent efficacy. In the RCT by Zhu *et al* [59], it was established that 0.2 mg/kg dose of Remimazolam provided adequate and non-inferior sedation as compared to propofol (1.5 mg/kg) in upper GI endoscopy with a superior safety profile. Furthermore, Ye *et al*[80] also noted that the ED95 of 0.2039 mg/kg (95%CI 0.1753-0.3896) for Remimazolam was consistent with previous published literature. Similarly for lower GI endoscopic procedures, Zheng *et al*[81] noted that Remimazolam achieved adequate sedation in 95% of the patients in the subgroup with initial dose of 0.2 mg/kg dose. Hence, the authors concluded that dose of Remimazolam for both upper and lower GI endoscopy tend to be comparable[81].

ERCP is a therapeutic intervention which has revolutionized management of pancreaticobiliary diseases[82]. As patients undergoing ERCP need to be in a prone to semi-prone position for a prolonged period, it causes physiological changes in hemodynamics and respiration leading to challenges in management of the respiratory tract during the procedure[83]. Hence, Remimazolam can be considered as an alternative to the traditional sedating agents such as propofol due to its lower rates of respiratory depression[59,84]. Tan *et al*[84] calculated the ED50 and ED95 of Remimazolam for adequate sedation in ERCP, which were found to be 0.196 mg/kg (95%CI: 0.187–0.206 mg/kg) and 0.239 mg/kg (95%CI: 0.221–0.297 mg/kg), respectively. Furthermore, as ERCP can be painful, a sedative alone is usually never sufficient in such a procedure, it is usually combined with an opioid analgesic such as sufentanil and the combination of 0.239 mg/kg of Remimazolam with a 0.1 mg/kg of sufentanil is sufficient to provide adequate sedation with analgesia for the procedure[84]. However, the patients need to be observed for positive reactions such as a cough response or body movements which may be an early indication for the need of additional sedation in some cases[84].

USE OF REMIMAZOLAM IN DIFFERENT PATIENT POPULATIONS

Remimazolam has been established to be a safe sedating agent for various patient populations, especially young adults. However, as the incidence of adverse events for sedation is generally higher in the elderly populations, primarily due to organ function decline and co-morbid conditions, and pregnant women, it requires a special focus.

In a multi-center RCT by Lu *et al*[74], the Remimazolam group showed a significant reduction when compared to propofol in the incidence of hypotension (36.5% *vs* 69.6%; $P < 0.001$), vasoactive drug use (12.0% *vs* 38.5%; $P < 0.001$), bradycardia (1.5% *vs* 8.5%; $P < 0.001$), respiratory depression (4.5% *vs* 10.0%; $P = 0.034$), and overall adverse effects (41.0% *vs* 70.5%; $P < 0.001$). Additionally, a significantly lower incidence of hemodynamic instability and respiratory depression with Remimazolam has been reported in the elderly population as compared to its counterparts such as propofol[68]. In pharmacokinetic studies of Remimazolam, sedation was achieved in young adults with a 0.2 mg/kg dose of Remimazolam while in older adults, it was obtained at 0.1 mg/kg dose[85]. Hence, a low dose (0.15 mg/kg and supplemental doses of 0.5 mg/kg) Remimazolam may be considered in elderly patients, especially those with decline in liver function[23,39].

Although Remimazolam has been used to good effect in hysteroscopy for low-risk non-pregnant women, the data on its use in procedural sedation in pregnant women and its placental transfer is fairly limited[86,87]. As Remimazolam shares structural and functional characteristics with midazolam, it is expected to cross the placenta[87]. Since fetuses have a significantly inferior metabolizing capacity and levels of carboxylesterases, extreme care should be taken with the use of any anesthetic in pregnancy[88]. Additional studies are warranted to investigate the safety, dosage, placental transfer, and pharmacological characteristics of Remimazolam in pregnant women and neonates.

CAUTION WHILE USING REMIMAZOLAM AS A SEDATING AGENT

Through clinical trials, Remimazolam has emerged as an appropriate alternative sedative for GI endoscopy, with minimal potential for adverse effects when comparison to traditional sedatives. However, caution needs to be practiced with higher doses of Remimazolam. With increasing doses, Remimazolam has shown the potential to increase the risk of post-operative vertigo and delayed recovery from the sedation[17].

Sedation may result in cognitive dysfunction in elderly patients. Therefore, selecting a sedating agent with lower impact on their cognitive abilities is vital to help them return to their baseline. In a study conducted on 99 patients who were randomly assigned to one of three groups, namely Remimazolam 1 (0.1 mg/kg RT), Remimazolam 2 (0.2 mg/kg RT), or the Propofol group, the authors noted that Remimazolam, at higher doses, is more likely to cause short-term cognitive impairment compared to Propofol[89].

Caution should also be taken while administering the increasing doses of Remimazolam in ASA class 3 or more patients and those with the impairment of liver function[33,39,45]. However, additional large multi-center studies are still needed to confirm these findings.

REMIMAZOLAM AND FUTURE OF GI ENDOSCOPY

Owing to its safety and efficacy, Remimazolam can become ideal anesthetic for GI endoscopy. Its rapid metabolism and elimination offer a significant advantage for sedation during short procedures. It can be considered as a potential alternative to traditional sedatives like Propofol and midazolam, especially in patients susceptible to hemodynamic and respiratory adverse effects of Propofol. Unlike Propofol, the administration of Remimazolam doesn't require additional airway management since Remimazolam has proven to reduce the risk of respiratory depression. Due to this, non-anesthesiologists can also administer Remimazolam with proper training. Remimazolam is also a great option for patients and insurers due to lower costs compared to Propofol.

However, there are no current guidelines on the utilization of Remimazolam in GI endoscopy. Therefore, as a first step, standard guidelines will need to be drafted to efficiently incorporate the sedative into clinical practice. Professional training and education of the healthcare providers involved in endoscopy is warranted to ensure patient safety and favorable procedural outcomes. This comprehensive training must include basic pharmacology, including knowledge about pharmacokinetics and pharmacodynamics of the drug, pre-procedural, intra-procedural, and post-procedural monitoring and care, and management of possible complications. The trained staff should be competent in handling emergencies or any serious adverse effects that may arise during sedation. The staff performing the procedure and sedation should be certified in life support techniques like basic life support, and advanced cardiac life support. In addition, practice-based training in addition to theoretical courses will need to be introduced to provide hands-on experience and real-time exposure in managing these critical situations.

CONCLUSION

Remimazolam is an ultra-short-acting benzodiazepine sedative that can serve as an ideal anesthetic for short procedural sedation. It has comparable efficacy and a better safety profile compared to Propofol. Furthermore, is associated with decreased risk of adverse effects such as hemodynamic instability, respiratory depression, and injection site pain. The rapid onset and offset of action, rapid metabolism, organ-independent elimination, smaller volume of distribution, and water solubility make it an ideal sedating agent with the potential to revolutionize procedural sedation during GI endoscopic procedures. However, literature available on Remimazolam is still limited, and additional research and clinical evidence is warranted before it becomes a mainstream sedative in clinical practice.

FOOTNOTES

Author contributions: Dahiya DS, Kumar G, Parsa S, Chandan S, and Al-Haddad M contributed to conception and design; Dahiya DS and Kumar G contributed to administrative support; Dahiya DS, Kumar G, Parsa S, Gangwani MK, Ali H, Sohail AH, Alsakarneh S, Chandan S, and Al-Haddad M contributed to provision, collection, and assembly of data; Dahiya DS, Kumar G, Parsa S, Gangwani MK, Ali H, Sohail AH, Alsakarneh S, Hayat U, Malik S, Shah YR, Pinnam BSM, Singh S, Mohamed I, Rao A, Chandan S, and Al-Haddad M contributed to review of literature and drafting the manuscript; Dahiya DS, Kumar G, Parsa S, Gangwani MK, Ali H, Chandan S, and Al-Haddad M contributed to revision of key components of the manuscript and final approval of manuscript; Dahiya DS, Kumar G, Parsa S, Gangwani MK, Ali H, Sohail AH, Alsakarneh S, Hayat U, Malik S, Shah YR, Pinnam BSM, Singh S, Mohamed I, Rao A, Chandan S, and Al-Haddad M are accountable for all aspects of the work.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Country of origin: United States

ORCID number: Dushyant Singh Dahiya 0000-0002-8544-9039; Manesh Kumar Gangwani 0000-0002-3931-6163; Hassam Ali 0000-0001-5546-9197; Umar Hayat 0000-0003-3484-1994; Sahib Singh 0000-0001-5660-782X; Saurabh Chandan 0000-0002-2661-6693; Mohammad Al-Haddad 0000-0003-1641-9976.

Corresponding Author's Membership in Professional Societies: American Gastroenterological Association; American Society for Gastrointestinal Endoscopy.

S-Editor: Lin C
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Skiljic S**, Budrovac D, Cicvaric A, Neskovic N, Kvolik S. Advances in Analgosedation and Periprocedural Care for Gastrointestinal Endoscopy. *Life (Basel)* 2023; **13** [PMID: 36836830 DOI: 10.3390/life13020473]
2 **Thompson R**, Seck V, Riordan S, Wong S. Comparison of the Effects of Midazolam/Fentanyl, Midazolam/Propofol, and Midazolam/Fentanyl/Propofol on Cognitive Function After Gastrointestinal Endoscopy. *Surg Laparosc Endosc Percutan Tech* 2019; **29**: 441-446 [PMID: 31135712 DOI: 10.1097/SLE.0000000000000679]
3 **Lin OS**. Sedation for routine gastrointestinal endoscopic procedures: a review on efficacy, safety, efficiency, cost and satisfaction. *Intest Res* 2017; **15**: 456-466 [PMID: 29142513 DOI: 10.5217/ir.2017.15.4.456]
4 **Kochhar GS**, Gill A, Vargo JJ. On the Horizon: The Future of Procedural Sedation. *Gastrointest Endosc Clin N Am* 2016; **26**: 577-592 [PMID: 27372779 DOI: 10.1016/j.giec.2016.03.002]
5 **American Association for Study of Liver Diseases**; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates, Vargo JJ, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, Nuccio S, Rex DK, Schiller LR. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastrointest Endosc* 2012; **76**: e1-25 [PMID: 22624793 DOI: 10.1016/j.gie.2012.03.001]
6 **Rex DK**, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D. Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. *Dig Liver Dis* 2021; **53**: 94-101 [PMID: 33243567 DOI: 10.1016/j.dld.2020.10.039]
7 **Goudra B**, Singh PM. Oliceridine and its potential to revolutionize GI endoscopy sedation. *Saudi J Anaesth* 2020; **14**: 349-354 [PMID: 32934628 DOI: 10.4103/sja.SJA_813_19]
8 **Inadomi JM**, Gunnarsson CL, Rizzo JA, Fang H. Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. *Gastrointest Endosc* 2010; **72**: 580-586 [PMID: 20630511 DOI: 10.1016/j.gie.2010.04.040]
9 **Rex DK**, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, Barish CF, Pruitt R, Cash BD, Quirk D, Tiongco F, Sullivan S, Bernstein D. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2018; **88**: 427-437.e6 [PMID: 29723512 DOI: 10.1016/j.gie.2018.04.2351]
10 **Cooper GS**, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* 2013; **173**: 551-556 [PMID: 23478904 DOI: 10.1001/jamainternmed.2013.2908]
11 **Kim SH**, Fechner J. Remimazolam - current knowledge on a new intravenous benzodiazepine anesthetic agent. *Korean J Anesthesiol* 2022; **75**: 307-315 [PMID: 35585830 DOI: 10.4097/kja.22297]
12 **Keam SJ**. Remimazolam: First Approval. *Drugs* 2020; **80**: 625-633 [PMID: 32274703 DOI: 10.1007/s40265-020-01299-8]
13 **Zhang J**, Cairen Z, Shi L, Pang S, Shao Y, Wang Y, Lu Z. Remimazolam versus propofol for procedural sedation and anesthesia: a systemic review and meta-analysis. *Minerva Anestesiol* 2022; **88**: 1035-1042 [PMID: 36326772 DOI: 10.23736/S0375-9393.22.16817-3]
14 **Yang JJ**, Lei L, Qiu D, Chen S, Xing LK, Zhao JW, Mao YY, Yang JJ. Effect of Remimazolam on Postoperative Delirium in Older Adult Patients Undergoing Orthopedic Surgery: A Prospective Randomized Controlled Clinical Trial. *Drug Des Devel Ther* 2023; **17**: 143-153 [PMID: 36712948 DOI: 10.2147/DDDT.S392569]
15 **Sneyd JR**, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and the case for remimazolam: a narrative review. *Br J Anaesth* 2021; **127**: 41-55 [PMID: 33965206 DOI: 10.1016/j.bja.2021.03.028]
16 **Garrett A**, Flowers J, Ng V, Tobias JD. Remimazolam for Sedation During Upper Gastrointestinal Endoscopy in an Adolescent. *J Med Cases* 2022; **13**: 495-498 [PMID: 36407860 DOI: 10.14740/jmc4013]
17 **Cui X**, Cheng Z, Li H, Zhang X, Luan H, Zhao Z, Zhu P. Efficacy and Safety of Different Doses of Remimazolam Tosilate Applied in Upper Gastrointestinal Endoscopy: A Prospective Randomized Controlled Double-Blind Trial. *Drug Des Devel Ther* 2023; **17**: 2889-2896 [PMID: 37750066 DOI: 10.2147/DDDT.S422531]
18 **Chen SH**, Yuan TM, Zhang J, Bai H, Tian M, Pan CX, Bao HG, Jin XJ, Ji FH, Zhong TD, Wang Q, Lv JR, Wang S, Li YJ, Yu YH, Luo AL, Li XK, Min S, Li L, Zou XH, Huang YG. Remimazolam tosilate in upper gastrointestinal endoscopy: A multicenter, randomized, non-inferiority, phase III trial. *J Gastroenterol Hepatol* 2021; **36**: 474-481 [PMID: 32677707 DOI: 10.1111/jgh.15188]
19 **Moon SH**. Sedation regimens for gastrointestinal endoscopy. *Clin Endosc* 2014; **47**: 135-140 [PMID: 24765595 DOI: 10.5946/ce.2014.47.2.135]
20 **Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy**, Lichtenstein DR, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, Fanelli RD, Gan SI, Harrison ME, Ikenberry SO, Shen B, Stewart L, Khan K, Vargo JJ. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008; **68**: 815-826 [PMID: 18984096 DOI: 10.1016/j.gie.2008.09.029]
21 **Goudra B**, Singh PM, Lichtenstein GR. Medical, Political, and Economic Considerations for the Use of MAC for Endoscopic Sedation: Big Price, Little Justification? *Dig Dis Sci* 2020; **65**: 2466-2472 [PMID: 32671589 DOI: 10.1007/s10620-020-06464-3]

22 **Ferreira AO**, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? *World J Gastrointest Endosc* 2015; **7**: 102-109 [PMID: 25685266 DOI: 10.4253/wjge.v7.i2.102]

23 **Dai G**, Pei L, Duan F, Liao M, Zhang Y, Zhu M, Zhao Z, Zhang X. Safety and efficacy of remimazolam compared with propofol in induction of general anesthesia. *Minerva Anestesiol* 2021; **87**: 1073-1079 [PMID: 34263581 DOI: 10.23736/S0375-9393.21.15517-8]

24 **Finlay JE**, Leslie K. Sedation/analgesia techniques for nonoperating room anesthesia: new drugs and devices. *Curr Opin Anaesthesiol* 2021; **34**: 678-682 [PMID: 34419992 DOI: 10.1097/ACO.0000000000001057]

25 **Goulson DT**, Fragneto RY. Anesthesia for gastrointestinal endoscopic procedures. *Anesthesiol Clin* 2009; **27**: 71-85 [PMID: 19361769 DOI: 10.1016/j.anclin.2008.10.004]

26 **Kilpatrick GJ**. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. *Front Pharmacol* 2021; **12**: 690875 [PMID: 34354587 DOI: 10.3389/fphar.2021.690875]

27 **Pacofsky GJ**, Stafford JA, Cox RF, Cowan JR, Dorsey GF Jr, Gonzales SS, Kaldor I, Koszalka GW, Lovell GG, McIntyre MS, Tidwell JH, Todd D, Whitesell G, Wiard RP, Feldman PL. Relating the structure, activity, and physical properties of ultrashort-acting benzodiazepine receptor agonists. *Bioorg Med Chem Lett* 2002; **12**: 3219-3222 [PMID: 12372538 DOI: 10.1016/S0960-894X(02)00513-9]

28 **Stafford JA**, Pacofsky GJ, Cox RF, Cowan JR, Dorsey GF Jr, Gonzales SS, Jung DK, Koszalka GW, McIntyre MS, Tidwell JH, Wiard RP, Feldman PL. Identification and structure-activity studies of novel ultrashort-acting benzodiazepine receptor agonists. *Bioorg Med Chem Lett* 2002; **12**: 3215-3218 [PMID: 12372537 DOI: 10.1016/S0960-894X(02)00512-7]

29 **Kilpatrick GJ**, McIntyre MS, Cox RF, Stafford JA, Pacofsky GJ, Lovell GG, Wiard RP, Feldman PL, Collins H, Waszczak BL, Tilbrook GS. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology* 2007; **107**: 60-66 [PMID: 17585216 DOI: 10.1097/01.ANES.0000267503.85085.C0]

30 **Antonik LJ**, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg* 2012; **115**: 274-283 [PMID: 22190555 DOI: 10.1213/ANE.0b013e31823f0c28]

31 **Upton R**, Martinez A, Grant C. A dose escalation study in sheep of the effects of the benzodiazepine CNS 7056 on sedation, the EEG and the respiratory and cardiovascular systems. *Br J Pharmacol* 2008; **155**: 52-61 [PMID: 18552878 DOI: 10.1038/bjp.2008.228]

32 **Upton RN**, Martinez AM, Grant C. Comparison of the sedative properties of CNS 7056, midazolam, and propofol in sheep. *Br J Anaesth* 2009; **103**: 848-857 [PMID: 19797247 DOI: 10.1093/bja/aep269]

33 **Hu Q**, Liu X, Wen C, Li D, Lei X. Remimazolam: An Updated Review of a New Sedative and Anaesthetic. *Drug Des Devel Ther* 2022; **16**: 3957-3974 [PMID: 36411859 DOI: 10.2147/DDDT.S384155]

34 **Sigel E**, Buhr A. The benzodiazepine binding site of GABAA receptors. *Trends Pharmacol Sci* 1997; **18**: 425-429 [PMID: 9426470 DOI: 10.1016/S0165-6147(97)01118-8]

35 **Kim KM**. Remimazolam: pharmacological characteristics and clinical applications in anesthesiology. *Anesth Pain Med (Seoul)* 2022; **17**: 1-11 [PMID: 35139608 DOI: 10.17085/apm.21115]

36 **Goudra BG**, Singh PM. Remimazolam: The future of its sedative potential. *Saudi J Anaesth* 2014; **8**: 388-391 [PMID: 25191193 DOI: 10.4103/1658-354X.136627]

37 **Freyer N**, Knöspel F, Damm G, Greuel S, Schneider C, Seehofer D, Stöhr T, Petersen KU, Zeilinger K. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther* 2019; **13**: 1033-1047 [PMID: 31037028 DOI: 10.2147/DDDT.S186759]

38 **Worthington MT**, Antonik LJ, Goldwater DR, Lees JP, Wilhelm-Ogunbiyi K, Borkett KM, Mitchell MC. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg* 2013; **117**: 1093-1100 [PMID: 24108261 DOI: 10.1213/ANE.0b013e3182a705ae]

39 **Guo J**, Qian Y, Zhang X, Han S, Shi Q, Xu J. Remimazolam tosilate compared with propofol for gastrointestinal endoscopy in elderly patients: a prospective, randomized and controlled study. *BMC Anesthesiol* 2022; **22**: 180 [PMID: 35689208 DOI: 10.1186/s12871-022-01713-6]

40 **Wiltshire HR**, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg* 2012; **115**: 284-296 [PMID: 22253270 DOI: 10.1213/ANE.0b013e318241f68a]

41 **Schüttler J**, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part I. Pharmacokinetics and Clinical Pharmacodynamics. *Anesthesiology* 2020; **132**: 636-651 [PMID: 31972655 DOI: 10.1097/ALN.0000000000003103]

42 **Zhou Y**, Hu P, Jiang J. Metabolite characterization of a novel sedative drug, remimazolam in human plasma and urine using ultra high-performance liquid chromatography coupled with synapt high-definition mass spectrometry. *J Pharm Biomed Anal* 2017; **137**: 78-83 [PMID: 28104560 DOI: 10.1016/j.jpba.2017.01.016]

43 **Zhu H**, Su Z, Huai X, Chen C, Zhang X, Zhou J, Su D. Efficacy and safety of remimazolam tosylate for sedation during upper gastrointestinal endoscopy: study protocol for a multicenter randomized controlled trial. *Trials* 2022; **23**: 995 [PMID: 36510290 DOI: 10.1186/s13063-022-06935-0]

44 **Liu T**, Lai T, Chen J, Lu Y, He F, Chen Y, Xie Y. Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: A randomized, double-blind, controlled trial. *Pharmacol Res Perspect* 2021; **9**: e00851 [PMID: 34390228 DOI: 10.1002/prp2.851]

45 **Stöhr T**, Colin PJ, Ossig J, Pesic M, Borkett K, Winkle P, Struys MMRF, Schippers F. Pharmacokinetic properties of remimazolam in subjects with hepatic or renal impairment. *Br J Anaesth* 2021; **127**: 415-423 [PMID: 34246461 DOI: 10.1016/j.bja.2021.05.027]

46 **Lu Z**, Zhou N, Li Y, Yang L, Hao W. Up-down determination of the 90% effective dose (ED90) of remimazolam besylate for anesthesia induction. *Ann Palliat Med* 2022; **11**: 568-573 [PMID: 35249335 DOI: 10.21037/apm-22-89]

47 **Gepts E**, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; **66**: 1256-1263 [PMID: 3500657]

48 **Lee A**, Shirley M. Remimazolam: A Review in Procedural Sedation. *Drugs* 2021; **81**: 1193-1201 [PMID: 34196946 DOI: 10.1007/s40265-021-01544-8]

49 **Lohmer LL**, Schippers F, Petersen KU, Stoehr T, Schmith VD. Time-to-Event Modeling for Remimazolam for the Indication of Induction and Maintenance of General Anesthesia. *J Clin Pharmacol* 2020; **60**: 505-514 [PMID: 31989598 DOI: 10.1002/jcph.1552]

50 **Sheng XY**, Liang Y, Yang XY, Li LE, Ye X, Zhao X, Cui YM. Safety, pharmacokinetic and pharmacodynamic properties of single ascending dose and continuous infusion of remimazolam besylate in healthy Chinese volunteers. *Eur J Clin Pharmacol* 2020; **76**: 383-391 [PMID:

31873765 DOI: 10.1007/s00228-019-02800-3]

51 **Hu B**, Jiang K, Shi W, Xiao S, Zhang S, Zhang Y, Zhou Y, Tan C, Tan S, Zou X. Effect of Remimazolam Tosilate on Respiratory Depression in Elderly Patients Undergoing Gastroscopy: A Multicentered, Prospective, and Randomized Study. *Drug Des Devel Ther* 2022; **16**: 4151-4159 [PMID: 36506792 DOI: 10.2147/DDDT.S391147]

52 **Borkett KM**, Riff DS, Schwartz HI, Winkle PJ, Pambianco DJ, Lees JP, Wilhelm-Ogunbiyi K. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg* 2015; **120**: 771-780 [PMID: 25502841 DOI: 10.1213/ANE.0000000000000548]

53 **Pambianco DJ**, Borkett KM, Riff DS, Winkle PJ, Schwartz HI, Melson TI, Wilhelm-Ogunbiyi K. A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2016; **83**: 984-992 [PMID: 26363333 DOI: 10.1016/j.gie.2015.08.062]

54 **Zhang L**, Li C, Zhao C, You Y, Xu J. The comparison of remimazolam and midazolam for the sedation of gastrointestinal endoscopy: a meta-analysis of randomized controlled studies. *Afr Health Sci* 2022; **22**: 384-391 [PMID: 36407397 DOI: 10.4314/ahs.v22i2.44]

55 **Zhang K**, Bao Y, Han X, Zhai W, Yang Y, Luo M, Gao F. Effects of opioid-free propofol or remimazolam balanced anesthesia on hypoxemia incidence in patients with obesity during gastrointestinal endoscopy: A prospective, randomized clinical trial. *Front Med (Lausanne)* 2023; **10**: 1124743 [PMID: 37035337 DOI: 10.3389/fmed.2023.1124743]

56 **Cao Y**, Chi P, Zhou C, Lv W, Quan Z, Xue FS. Remimazolam Tosilate Sedation with Adjuvant Sufentanil in Chinese Patients with Liver Cirrhosis Undergoing Gastroscopy: A Randomized Controlled Study. *Med Sci Monit* 2022; **28**: e936580 [PMID: 35706340 DOI: 10.12659/MSM.936580]

57 **Xiao X**, Xiao N, Zeng F, Chen H, Zhang L, He X. Gastroscopy sedation: clinical trial comparing propofol and sufentanil with or without remimazolam. *Minerva Anestesiol* 2022; **88**: 223-229 [PMID: 35072431 DOI: 10.23736/S0375-9393.21.15917-6]

58 **Dong SA**, Guo Y, Liu SS, Wu LL, Wu LN, Song K, Wang JH, Chen HR, Li WZ, Li HX, Zhang L, Yu JB. A randomized, controlled clinical trial comparing remimazolam to propofol when combined with alfentanil for sedation during ERCP procedures. *J Clin Anesth* 2023; **86**: 111077 [PMID: 36764022 DOI: 10.1016/j.jclinane.2023.111077]

59 **Zhu H**, Su Z, Zhou H, Lu J, Wang X, Ji Z, Chen S, Yao M, Lu Y, Yu W, Su D. Remimazolam Dosing for Gastroscopy: A Randomized Noninferiority Trial. *Anesthesiology* 2024; **140**: 409-416 [PMID: 38039392 DOI: 10.1097/ALN.0000000000004851]

60 **Yao Y**, Guan J, Liu L, Fu B, Chen L, Zheng X. Discharge readiness after remimazolam versus propofol for colonoscopy: A randomised, double-blind trial. *Eur J Anaesthesiol* 2022; **39**: 911-917 [PMID: 35796575 DOI: 10.1097/EJA.0000000000001715]

61 **Zhao YR**, Huang KS, Hou G, Yao L, Lu LP, Xu S, Lian YT, Yao Z, Yu Z. Efficacy and safety of remimazolam-based sedation for intensive care unit patients undergoing upper gastrointestinal endoscopy: a cohort study. *World J Emerg Med* 2023; **14**: 31-36 [PMID: 36713335 DOI: 10.5847/wjem.j.1920-8642.2023.020]

62 **Sun H**, Wang T, Xu ZX, Chen XF, Cao JB, Li H. [Effective dose and adverse reactions analysis of Remimazolam for sedation in elderly patients undergoing gastroscopy]. *Zhonghua Yi Xue Za Zhi* 2022; **102**: 332-335 [PMID: 35092973 DOI: 10.3760/cma.j.cn112137-20211111-02509]

63 **Cao YH**, Chi P, Zhou C, Lv WF, Quan ZF, Xue FS. The 50% and 95% effective doses of remimazolam tosilate with adjuvant sufentanil for sedation in patients with liver cirrhosis undergoing oesophagogastric varices screening endoscopy. *J Clin Pharm Ther* 2022; **47**: 2068-2073 [PMID: 36543252 DOI: 10.1111/jcpt.13751]

64 **Peng X**, Liu C, Zhu Y, Peng L, Zhang X, Wei W, Zhu T. Hemodynamic Influences of Remimazolam Versus Propofol During the Induction Period of General Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Pain Physician* 2023; **26**: E761-E773 [PMID: 37976477]

65 **Singh A**, Anjankar AP. Propofol-Related Infusion Syndrome: A Clinical Review. *Cureus* 2022; **14**: e30383 [PMID: 36407194 DOI: 10.7759/cureus.30383]

66 **Shi W**, Cheng Y, He H, Fang Q, Hu Y, Xu X, Shuai Y, Zhang J, Fang X, Wang Z, Zhang Y. Efficacy and Safety of the Remimazolam-Alfentanil Combination for Sedation During Gastroscopy: A Randomized, Double-blind, Single-center Controlled Trial. *Clin Ther* 2022; **44**: 1506-1518 [PMID: 36763995 DOI: 10.1016/j.clinthera.2022.09.014]

67 **Guo L**, Liu T, Zhang Y, Qi D. Effect of remimazolam versus propofol sedation on the quality of recovery after colonoscopy: A randomised, controlled, noninferiority trial. *Eur J Anaesthesiol* 2022; **39**: 953-955 [PMID: 35875918 DOI: 10.1097/EJA.0000000000001701]

68 **Liu X**, Ding B, Shi F, Zhang Y, Liu L, Sha Y, Zhao T. The Efficacy and Safety of Remimazolam Tosilate versus Etomidate-Propofol in Elderly Outpatients Undergoing Colonoscopy: A Prospective, Randomized, Single-Blind, Non-Inferiority Trial. *Drug Des Devel Ther* 2021; **15**: 4675-4685 [PMID: 34819721 DOI: 10.2147/DDDT.S339535]

69 **Sneyd JR**, Absalom AR, Barends CRM, Jones JB. Hypotension during propofol sedation for colonoscopy: a retrospective exploratory analysis and meta-analysis. *Br J Anaesth* 2022; **128**: 610-622 [PMID: 34916051 DOI: 10.1016/j.bja.2021.10.044]

70 **Skues MA**, Prys-Roberts C. The pharmacology of propofol. *J Clin Anesth* 1989; **1**: 387-400 [PMID: 2697245 DOI: 10.1016/0952-8180(89)90080-9]

71 **Yamagata T**, Hirasawa D, Fujita N, Suzuki T, Obana T, Sugawara T, Ohira T, Harada Y, Maeda Y, Koike Y, Suzuki K, Noda Y. Efficacy of propofol sedation for endoscopic submucosal dissection (ESD): assessment with prospective data collection. *Intern Med* 2011; **50**: 1455-1460 [PMID: 21757829 DOI: 10.2169/INTERNALMEDICINE.50.4627]

72 **Qiu Y**, Gu W, Zhao M, Zhang Y, Wu J. The hemodynamic stability of remimazolam compared with propofol in patients undergoing endoscopic submucosal dissection: A randomized trial. *Front Med (Lausanne)* 2022; **9**: 938940 [PMID: 36004376 DOI: 10.3389/fmed.2022.938940]

73 **Wesselink EM**, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; **121**: 706-721 [PMID: 30236233 DOI: 10.1016/j.bja.2018.04.036]

74 **Lu K**, Wei S, Ling W, Wei Y, Ran X, Huang H, Wang M, Wei N, Liao Y, Qin Z, Pan M, Wei Q, Fu L, Xiong B, Ma C, Jiang J, Huang Y. Remimazolam versus propofol for deep sedation/anaesthesia in upper gastrointestinal endoscopy in elderly patients: A multicenter, randomized controlled trial. *J Clin Pharm Ther* 2022; **47**: 2230-2236 [PMID: 36334013 DOI: 10.1111/jcpt.13797]

75 **Jirapinyo P**, Thompson CC. Sedation Challenges: Obesity and Sleep Apnea. *Gastrointest Endosc Clin N Am* 2016; **26**: 527-537 [PMID: 27372775 DOI: 10.1016/j.giec.2016.03.001]

76 **Travis AC**, Pievsky D, Saltzman JR. Endoscopy in the elderly. *Am J Gastroenterol* 2012; **107**: 1495-501; quiz 1494, 1502 [PMID: 22869323 DOI: 10.1038/ajg.2012.246]

77 **Mönkemüller K**, Fry LC, Malfertheiner P, Schuckardt W. Gastrointestinal endoscopy in the elderly: current issues. *Best Pract Res Clin*

Gastroenterol 2009; **23**: 821-827 [PMID: 19942160 DOI: 10.1016/j.bpg.2009.10.002]

78 **Razavi F**, Gross S, Katz S. Endoscopy in the elderly: risks, benefits, and yield of common endoscopic procedures. *Clin Geriatr Med* 2014; **30**: 133-147 [PMID: 24267608 DOI: 10.1016/j.cger.2013.10.010]

79 **Xu C**, He L, Ren J, Zhou J, Guo H, Chen N, Chen H, Lv Y. Efficacy and Safety of Remimazolam Besylate Combined with Alfentanil in Painless Gastroscopy: A Randomized, Single-Blind, Parallel Controlled Study. *Contrast Media Mol Imaging* 2022; **2022**: 7102293 [PMID: 36263002 DOI: 10.1155/2022/7102293]

80 **Ye E**, Wu K, Ye H, Zhang W, Chu L, Zhang K, Xie G, Jin Y, Fang X. Comparison of 95% effective dose of remimazolam besylate and propofol for gastroscopy sedation on older patients: A single-centre randomized controlled trial. *Br J Clin Pharmacol* 2023; **89**: 3401-3410 [PMID: 37387195 DOI: 10.1111/bcp.15839]

81 **Zheng X**, Ji J, Cheng H, Peng K, Liu L, Ji F. Efficacy and safety of different doses of remimazolam tosylate for colonoscopy: single-center, prospective, randomized, double-blind, parallel trial. *Ann Transl Med* 2022; **10**: 1244 [PMID: 36544645 DOI: 10.21037/atm-22-5133]

82 **Hollenbach M**, Hoffmeister A. Adverse events in endoscopic retrograde cholangiopancreaticography (ERCP): Focus on post-ERCP-pancreatitis. *United European Gastroenterol J* 2022; **10**: 10-11 [PMID: 35134279 DOI: 10.1002/ueg2.12201]

83 **Haytural C**, Aydınlı B, Demir B, Bozkurt E, Parlak E, Dişibeyaz S, Saraç A, Özgök A, Kazancı D. Comparison of Propofol, Propofol-Remifentanil, and Propofol-Fentanyl Administrations with Each Other Used for the Sedation of Patients to Undergo ERCP. *Biomed Res Int* 2015; **2015**: 465465 [PMID: 26576424 DOI: 10.1155/2015/465465]

84 **Tan DD**, Gu J, Li J, Yu WQ, Liu DX, Zhao LJ, Zhu GH, Yang XX, Tian J, Tian Q, Zhu ZQ. The effective doses of remimazolam besylate in the procedural sedation of endoscopic retrograde cholangiopancreatography. *Ibrain* 2023; **9**: 290-297 [PMID: 37786755 DOI: 10.1002/ibra.12072]

85 **Wang M**, Zhao X, Yin P, Bao X, Tang H, Kang X. Profile of Remimazolam in Anesthesiology: A Narrative Review of Clinical Research Progress. *Drug Des Devel Ther* 2022; **16**: 3431-3444 [PMID: 36213379 DOI: 10.2147/DDDT.S375957]

86 **Zhang F**, Chang H, Qing W, Yu R, Liao Q, Tong J. Remimazolam Tosylate Combined with Low-Dose Propofol Improves Sedation and Safety in Hysteroscopy. *Drug Des Devel Ther* 2022; **16**: 4101-4108 [PMID: 36471692 DOI: 10.2147/DDDT.S390403]

87 **Yamamoto S**, Oyama Y, Sasaki M, Miyagoshi M, Matsumoto S, Kitano T. General anesthesia with remimazolam for emergency cesarean section in a patient with acute infective endocarditis: a case report. *JA Clin Rep* 2023; **9**: 53 [PMID: 37612528 DOI: 10.1186/s40981-023-00645-5]

88 **Shi D**, Yang D, Prinssen EP, Davies BE, Yan B. Surge in expression of carboxylesterase 1 during the post-neonatal stage enables a rapid gain of the capacity to activate the anti-influenza prodrug oseltamivir. *J Infect Dis* 2011; **203**: 937-942 [PMID: 21402544 DOI: 10.1093/infdis/jiq145]

89 **Tan Y**, Ouyang W, Tang Y, Fang N, Fang C, Quan C. Effect of remimazolam tosilate on early cognitive function in elderly patients undergoing upper gastrointestinal endoscopy. *J Gastroenterol Hepatol* 2022; **37**: 576-583 [PMID: 34907594 DOI: 10.1111/jgh.15761]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com