

New sedatives and analgesic drugs for gastrointestinal endoscopic procedures

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Procedural sedation has become increasingly common in endoscopy. Sedatives and analgesics induce anxiolysis and amnesia. In addition, an appropriate level of sedation is necessary for safe procedures including therapeutic endoscopy. Midazolam and propofol are the most commonly used drugs in sedative endoscopy. In recent years, the need to ascertain the safety and effectiveness of sedation has increased in practice. Therefore, new sedatives and analgesic drugs for optimal sedative endoscopy, have recently emerged. This article reviews the characteristics of sedatives and analgesics, and describes their clinical use in gastrointestinal endoscopy.

Keywords: Analgesics; Conscious sedation; Endoscopy; Hypnotics and sedatives

INTRODUCTION

Endoscopy plays a significant role in the diagnosis and treatment of gastrointestinal diseases. Sedation has been used in clinical practice to make the procedure more comfortable, and

improve patient satisfaction by helping patients rest during the procedure. Although sedation is widely used for these benefits, it continues to pose some potential risks, requiring medical teams to closely monitor patients during the procedure. Currently, the most widely used agents for endoscopic sedation in Korea are midazolam and propofol.¹ Propofol is commonly used for intravenous anesthesia in outpatient surgeries and examinations, due to advantages such as rapid induction and early return of consciousness. However, propofol also has disadvantages as it decreases both cardiovascular and respiratory parameters and lacks antagonists.² The side effects of midazolam include hypoxemia, paradoxical responses, and delayed recovery. Therefore, there is a need for alternatives.³

Recently, newer sedatives that overcome these drawbacks have been discovered and subsequently applied in endoscopic

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sedation. New drugs such as etomidate, dexmedetomidine, and remimazolam, have emerged, and the benefits of ketamine and remifentanyl have also been highlighted.^{4,5} This review will therefore discuss etomidate and other new sedatives that are receiving attention in clinical practice.

ETOMIDATE

Etomidate is a short-acting intravenous anesthetic that is indicated for the induction of anesthesia and sedation during short procedures. It is an imidazole derivative that acts as a gamma-aminobutyric acid (GABA)-A receptor agonist in the central nervous system to induce sedation. The drug is mainly distributed by binding to albumin in blood plasma, inducing the opening of the chlorine ion permeation channels of GABA-A receptors and amplifying the action of GABA for rapid sedation.⁶ Although etomidate is often compared with propofol, it was widely used in the field of general anesthesia even before the development of propofol. Its duration of action is slightly shorter than that of propofol because etomidate is redistributed to peripheral tissues such as muscles, and is metabolized by hepatic and plasma esterases. The resulting carboxylate metabolites are mostly excreted through the urine and bile, exhibiting an elimination half-life of 2–5 hours. Etomidate has an onset of action of 30–60 seconds, with peak effect at approximately 1 minute. Additionally, its action lasts for approximately 3–5 minutes, showing pharmacokinetic properties similar to those of propofol. When using etomidate, initial studies have recommended an induction dose of 0.1–0.2 mg/kg with additional 0.05 mg/kg every 3–5 minutes for maintenance. Although there are no dosage recommendations for etomidate in endoscopic sedation, sedation is mainly achieved using intermittent injections with an induction dose of 0.05 mg/kg, and additional 0.03–0.05 mg/kg for maintenance, in adult patients. In clinical practice, etomidate is mainly used in intensive care units and emergency medicine because it has a lower risk of respiratory depression or hypotension than other intravenous anesthetics.^{7–9} Thus, the advantages of etomidate include fast recovery, reduced impact on the cardiovascular system, and reduced respiratory failure. However, its disadvantages include pain associated with the injection as well as myoclonus. Additional administration of midazolam (0.015 mg/kg), magnesium sulfate, fentanyl (100–500 µg), or remifentanyl (1 µg/kg) with etomidate may reduce the risk of myoclonus.⁷ The combination of propofol and etomidate can reduce the adverse effects of propofol or

etomidate alone.^{10,11} Etomidate was approved in February 1999 by the US Food and Drug Administration (FDA) as an anesthetic agent.

DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α_2 agonist used for sedation in various procedures. It is 7–8 times more selective for the α_2 receptor than clonidine.¹² It is an anxiolytic, sedative, and pain reliever with an elimination half-life of approximately 2 hours and a distribution half-life of approximately 6 minutes. Dexmedetomidine activates 2-adrenoceptors and causes a decrease in sympathetic tone, with associated attenuation of neuroendocrine and hemodynamic responses to anesthesia; it also reduces anesthetic and opioid requirements. There are several review articles and meta-analyses of dexmedetomidine in the field of endoscopic sedation.^{13–16} The usual dose used for sedation is 1 µg/kg for 6–10 minutes, followed by an intravenous infusion of 0.5–0.8 µg/kg/hr. However, some patients may require combined sedation with midazolam (0.5–1 mg).¹⁷ Dexmedetomidine is considered safe for administration to patients with spontaneous breathing, while ensuring that chin lift maneuvers are performed to maintain their stable breathing. Patients receiving dexmedetomidine are easy to arouse and are less likely to develop delirium than those receiving midazolam.¹⁸ However, it still has adverse effects, including bradycardia and hypotension. Therefore, caution should be exercised when administering it to patients with bradycardia, arrhythmia, heart failure, and/or hypotension.¹⁹ In some cases, maintenance doses are prescribed without a loading dose. Although dexmedetomidine has fewer adverse effects on respiratory function than propofol, it bears the risk of inducing insufficient sedation during endoscopic procedures.^{14,15,20} In summary, dexmedetomidine may be useful for diagnostic endoscopy; additional agents, such as midazolam or fentanyl, may be required for more time-consuming procedures such as therapeutic endoscopy. Considering all of these, dexmedetomidine was approved in December 1999 by the FDA as a short-term sedative and analgesic.

REMIMAZOLAM

Remimazolam is a short-acting benzodiazepine used to induce and maintain procedural sedation. Remimazolam modulated the effects of GABA-A receptors to enhance the effects of GABA. The half-life of remimazolam is not prolonged after

discontinuing continuous infusion.²¹ Therefore, the use of remimazolam as an analgesic in intensive care units offers some advantages over fentanyl. Unlike other sedatives that are mainly metabolized in the liver, remimazolam is metabolized by tissue esterases, regardless of their location in the body. Thus, it may be administered regardless of body weight, rapidly metabolizing in blood plasma and tissues.²² Remimazolam was observed to be well tolerated and effective after a single dose of 0.1–0.2 mg/kg or an initial dose of 5.0 mg during endoscopic procedures.^{23,24} If necessary, supplemental doses of 2.5 mg can be administered. However, at least 2 minutes must have elapsed after the initial dose, prior to the administration of any supplemental dose. Its onset of action is 1–3 minutes and its half-life is 7–8 minutes, which is slightly shorter than that of midazolam, and remains consistent even during continuous intravenous infusion. As such, patients recover quickly after discontinuation of remimazolam infusion. Notably, the benzodiazepine receptor antagonist flumazenil can be used to reverse the sedative effects associated with overdosing. Although the sedative efficiency of remimazolam is higher than that of midazolam, it is slightly lower than that of propofol.²⁵ In a meta-analysis comparing remimazolam and midazolam, the remimazolam group showed excellent results in terms of procedure success rates, proper sedation maintenance, and use of antagonistic drugs.²⁶ However, apnea or chest stiffness was observed in rare cases. In severe cases, chest or thoracic stiffness may affect jaw muscles. Remimazolam was approved for use by the FDA in July 2020; however, it should be used with caution, even during sedation, due to the risk of respiratory failure and hypoxia.

KETAMINE

Ketamine is a phencyclidine derivative that was first used in clinical practice in 1965.²⁷ It is a rapid-acting general anesthetic and N-methyl-D-aspartate receptor antagonist. In terms of pharmacokinetics, ketamine fits a two-compartment model. Plasma concentration after intravenous infusion decreases rapidly at the early stage, which results in a slow elimination and distribution period that is suitable for endoscopy.²⁸ Ketamine is mainly metabolized in the liver and its major metabolite is norketamine. It has an onset of action of less than 1 minute, reaching its peak effect at approximately 1 minute. Its action lasts for approximately 10–15 minutes, and the recommended induction dose is 0.5 mg/kg. Additional doses may be admin-

istered to patients after observing their degree of sedation. Ketamine is beneficial in preserving breathing and airway reflexes during endoscopy. The anesthetic state it produces has been termed “dissociative anesthesia” as it appears to selectively interrupt association pathways of the brain before producing a somesthetic sensory blockade. Ketamine also has anti-vagal effects; it increases the secretion of endogenous catecholamines, leading to excellent cardiopulmonary stability. Despite these advantages, the usefulness of ketamine as a sedative is limited because 10%–30% of patients experience hallucinations, visual distortions, and the sensation of floating during the recovery period. It is also associated with a 0.3% incidence of laryngospasms during endoscopic procedures. In the field of anesthesia, ketamine is usually administered with diazepam or midazolam. Currently, a combined administration of ketamine and midazolam is recommended for sedation rather than ketamine alone.²⁹ In clinical practice, ketamine is considered as a useful drug with a low risk of apnea during pediatric sedation.³⁰ The combination of midazolam and ketamine was most commonly used for pediatric endoscopic procedures. In procedural sedation for pediatric endoscopy, the sedation with midazolam 0.03 mg/kg + ketamine 0.65 mg/kg + propofol 2.5 mg/kg performed by an anesthesiologist was deeper and safer with fewer complications.³¹

FOSPROPOFOL

Fospropofol is a sedative-hypnotic agent used for monitored sedation during anesthesia care. It is a water-soluble prodrug of propofol, which is metabolized into propofol, formaldehyde, and phosphate by endothelial alkaline phosphatase.³² Due to these pharmacokinetic properties, it exhibits the same rise in blood concentration as propofol. However, the effect of fospropofol persists for 15–30 minutes, and its excretion is slightly slower than that of propofol. Its disadvantages include the risk of cardiovascular and respiratory failure, which are similar to those of propofol. Additionally, side effects include itching and perineal pain. Some studies have been conducted on its use in endoscopic sedation, with one study attempting sedation with various concentrations (2, 5, 6.5, or 8 mg/kg) in colonoscopic procedures.³³ This study showed a high success rate for moderate sedation in patients who received 6.5 mg/kg, and the results were positive in terms of doctor and patient satisfaction. Although the FDA approved the use of fospropofol in May 2008, it was later required in December 2008 that it be used only by individuals trained in the administration of general anesthesia.

Therefore, it is usually indicated for monitored anesthesia care sedation.

REMIFENTANIL

Remifentanyl is a short-acting opioid analgesic and μ -opioid receptor agonist. It is metabolized by plasma and tissue esterases, and it has a short context-sensitive half-life of approximately 1–20 minutes.⁵ The metabolism of remifentanyl is unaffected by changes in renal function; therefore, it is easier to predict its clinical action and corresponding recovery period of the patient. It typically induces slight amnesic effects. The optimal induction dose of remifentanyl is 0.1–0.2 $\mu\text{g}/\text{kg}$ for 2 minutes, and its maintenance dose is 0.025–0.1 $\mu\text{g}/\text{kg}/\text{min}$. Administering 0.5–2 mg of midazolam 2–3 minutes before remifentanyl administration may lead to better sedative and amnesic effects. Its sedative effect persists for 3–6 minutes, and several studies have shown that it is effective in reducing pain during endoscopy, especially when it is necessary for the patient to remain conscious during colonoscopy.³⁴ The opioid activity of remifentanyl is antagonized by opioid antagonists such as naloxone. Compared to midazolam and meperidine for sedation during colonoscopy, remifentanyl shows increased hemodynamic stability, reduced respiratory inhibition, faster recovery, and shorter discharge times.³⁵ Considering these, remifentanyl was approved by the US FDA in July 1996.

OLICERIDINE

Oliceridine is a new μ -opioid receptor agonist that avoids beta-arrestin pathways and enhances G-protein-coupled signaling pathways to exert analgesic effects.³⁶ It acts through downstream signaling pathways to exert anti-nociceptive analgesia in patients experiencing severe acute pain. Oliceridine is primarily metabolized hepatically by CYP3A4 and CYP2D6.³⁷ It shows significant analgesic benefits within 5–20 minutes of administration, with a half-life of approximately 1.3–3 hours. No dose adjustment was required for patients with renal impairment. Additionally, regardless of the patient's body weight, sex, and age, the recommended dose is 1–3 mg by intravenous administration. If necessary, supplemental doses of 1 mg may be administered 15 minutes after the loading dose, for maintenance. Its onset of action of approximately 5 minutes is slightly slower than that of fentanyl. Oliceridine offers analgesic effects and has a reduced propensity to cause side effects associated

Table 1. Characteristics of sedative and analgesic drugs for gastrointestinal endoscopic procedure

Drug	Initial dose	Repeat dose	Onset	Duration	Pros	Cons	Reversal agent	Analgesic effect
Etomidate	0.15 mg/kg	0.05 mg/kg q 2 min	30–60 sec	3–5 min	Fast onset of action Hemodynamic stability Low risk of respiratory depression	Myoclonus Adrenal suppression	-	-
Dexmedetomidine	1 $\mu\text{g}/\text{kg}$	Continuous infusion of 0.2–0.7 $\mu\text{g}/\text{kg}/\text{hr}$	1 min	2–4 hr	Ability to preserve spontaneous ventilation	Slow onset and slow offset of effect	Atipamezole	++
Remimazolam	0.05–0.075 mg/kg	0.2 mg/kg	30–60 sec	3–5 min	Fast onset of action Short recovery time		Flumazenil	-
Ketamine	1–2 mg/kg IV	0.5 mg/kg q 2 min	30–120 sec	15–30 min	Analgesic effect Ability to preserve spontaneous ventilation	Hallucination Increased salivation	-	++
Fospropofol	6.5 mg/kg	1.6 mg/kg	4–8 min	2–16 min	Aqueous formulation	Currently not available	-	-
Remifentanyl	0.1–0.3 $\mu\text{g}/\text{kg}$	0.025–0.1 $\mu\text{g}/\text{kg}/\text{min}$	30–60 sec	3–6 min	Hemodynamic stability Low risk of respiratory depression Short recovery time		Naloxone	+++
Oliceridine	1–3 mg	1 mg	5–20 min	1–3 hr	No dose adjustment Low risk of respiratory depression	Slightly slow onset	Naloxone	+++

-, none; +, weak; ++, moderate; +++, strong; IV, intravenous.

with conventional opioids, including nausea, vomiting, respiratory failure, and/or constipation.³⁸ Respiratory depression after administration of oliceridine is rare, particularly when using small doses. When administered with propofol as a sedative agent, it maintains sedation and reduces the required amount of propofol, thereby lowering the risk of cardiovascular side effects and respiratory failure. The combination of oliceridine and remimazolam is expected to have positive effects during colonoscopy. Its distribution tends to increase in patients with hepatic impairment, but this does not seem to have any effect on excretion.³⁹ Therefore, oliceridine may be used in patients with hepatobiliary diseases. Oliceridine received the FDA's breakthrough therapy designation in 2016 and was approved by the FDA in August 2020.³⁷

CONCLUSIONS

Table 1 summarized the characteristics of sedative and analgesic drugs for gastrointestinal endoscopic procedure.

Many endoscopists are looking for ideal drugs to be used in endoscopic sedation. Drugs such as etomidate, remimazolam, and dexmedetomidine may be useful for endoscopic sedation and may help improve procedural sedation in the future. However, it is also critical to understand the characteristics of these drugs and be aware of their strengths and risks in order to adequately prepare countermeasures. Considering the advantages and disadvantages of old and new drugs, it is necessary to have a thorough understanding of conventional drugs, before considering the introduction and application of new drugs, and to actively cope with recommended changes directed towards the most ideal sedation practice.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

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REFERENCES

1. Conscious Sedation TFT Committee of KSGE. A guidebook on sedation for gastrointestinal endoscopy. Seoul: Medbook; 2015.
2. Training Committee. American Society for Gastrointestinal Endoscopy. Training guideline for use of propofol in gastrointestinal endoscopy. *Gastrointest Endosc* 2004;60:167–172.
3. Waring JP, Baron TH, Hirota WK, et al. Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. *Gastrointest Endosc* 2003;58:317–322.
4. Goudra BG, Singh PM. Propofol alternatives in gastrointestinal endoscopy anesthesia. *Saudi J Anaesth* 2014;8:540–545.
5. Goudra B, Gouda G, Mohinder P. Recent developments in drugs for GI endoscopy sedation. *Dig Dis Sci* 2020;65:2781–2788.
6. Forman SA. Clinical and molecular pharmacology of etomidate. *Anesthesiology* 2011;114:695–707.
7. Han SJ, Lee TH, Yang JK, et al. Etomidate sedation for advanced endoscopic procedures. *Dig Dis Sci* 2019;64:144–151.
8. Lee JM, Min G, Lee JM, et al. Efficacy and safety of etomidate-midazolam for screening colonoscopy in the elderly: a prospective double-blinded randomized controlled study. *Medicine (Baltimore)* 2018;97:e10635.
9. Zhou X, Li BX, Chen LM, et al. Etomidate plus propofol versus propofol alone for sedation during gastroscopy: a randomized prospective clinical trial. *Surg Endosc* 2016;30:5108–5116.
10. Chen L, Liang X, Tan X, et al. Safety and efficacy of combined use of propofol and etomidate for sedation during gastroscopy: systematic review and meta-analysis. *Medicine (Baltimore)* 2019;98:e15712.

11. Kim JH, Byun S, Choi YJ, et al. Efficacy and safety of etomidate in comparison with propofol or midazolam as sedative for upper gastrointestinal endoscopy. *Clin Endosc* 2020;53:555–561.
12. Scheinin H, Aantaa R, Anttila M, et al. Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha2-adrenoceptor antagonist atipamezole: a pharmacodynamic and kinetic study in healthy volunteers. *Anesthesiology* 1998; 89:574–584.
13. Liu W, Yu W, Yu H, et al. Comparison of clinical efficacy and safety between dexmedetomidine and propofol among patients undergoing gastrointestinal endoscopy: a meta-analysis. *J Int Med Res* 2021;49:3000605211032786.
14. Chen YT, Sun CK, Wu KY, et al. The use of propofol versus dexmedetomidine for patients receiving drug-induced sleep endoscopy: a meta-analysis of randomized controlled trials. *J Clin Med* 2021;10:1585.
15. Nishizawa T, Suzuki H, Hosoe N, et al. Dexmedetomidine vs propofol for gastrointestinal endoscopy: a meta-analysis. *United European Gastroenterol J* 2017;5:1037–1045.
16. Nishizawa T, Suzuki H, Sagara S, et al. Dexmedetomidine versus midazolam for gastrointestinal endoscopy: a meta-analysis. *Dig Endosc* 2015;27:8–15.
17. Belleville JP, Ward DS, Bloor BC, et al. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992;77:1125–1133.
18. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;90:699–705.
19. Jalowiecki P, Rudner R, Gonciarz M, et al. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *Anesthesiology* 2005;103:269–273.
20. Zhang F, Sun HR, Zheng ZB, et al. Dexmedetomidine versus midazolam for sedation during endoscopy: a meta-analysis. *Exp Ther Med* 2016;11:2519–2524.
21. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting benzodiazepine. *Anesthesiology* 2007;107:60–66.
22. Goudra BG, Singh PM. Remimazolam: the future of its sedative potential. *Saudi J Anaesth* 2014;8:388–391.
23. Borkett KM, Riff DS, Schwartz HI, et al. 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.
24. Chen SH, Yuan TM, Zhang J, et al. Remimazolam tosylate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, phase III trial. *J Gastroenterol Hepatol* 2021;36:474–481.
25. Zhu X, Wang H, Yuan S, et al. Efficacy and safety of remimazolam in endoscopic sedation—a systematic review and meta-analysis. *Front Med (Lausanne)* 2021;8:655042.
26. Jhuang BJ, Yeh BH, Huang YT, et al. Efficacy and safety of remimazolam for procedural sedation: a meta-analysis of randomized controlled trials with trial sequential analysis. *Front Med (Lausanne)* 2021;8:641866.
27. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther* 1965;6:279–291.
28. Cohen LB, Delegee MH, Aisenberg J, et al. AGA institute review of endoscopic sedation. *Gastroenterology* 2007;133:675–701.
29. Akbulut UE, Saylan S, Sengu B, et al. A comparison of sedation with midazolam-ketamine versus propofol-fentanyl during endoscopy in children: a randomized trial. *Eur J Gastroenterol Hepatol* 2017;29:112–118.
30. Eskander AE, Baroudy NR, Refay AS. Ketamine sedation in gastrointestinal endoscopy in children. *Open Access Maced J Med Sci* 2016;4:392–396.
31. Lee YM, Kang B, Kim YB, et al. Procedural sedation for pediatric upper gastrointestinal endoscopy in Korea. *J Korean Med Sci* 2021;36:e136.
32. Fechner J, Ihmsen H, Jeleazcov C, et al. Fospropofol disodium, a water-soluble prodrug of the intravenous anesthetic propofol (2,6-diisopropylphenol). *Expert Opin Investig Drugs* 2009;18:1565–1571.
33. Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. *Aliment Pharmacol Ther* 2008;27:597–608.
34. Toklu S, Iyilikci L, Gonen C, et al. Comparison of etomidate-remifentanyl and propofol-remifentanyl sedation in patients scheduled for colonoscopy. *Eur J Anaesthesiol* 2009;26:370–376.
35. Mandel JE, Tanner JW, Lichtenstein GR, et al. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanyl versus midazolam/fentanyl for colonoscopy. *Anesth Analg* 2008;106:434–439.
36. Fossler MJ, Sadler BM, Farrell C, et al. Oliceridine (TRV130), a novel G protein-biased ligand at the μ -opioid receptor, demonstrates a predictable relationship between plasma concentrations and pain relief. I: development of a pharmacokinetic/pharmacodynamic model. *J Clin Pharmacol* 2018;58:750–761.
37. Food and Drug Administration (FDA). FDA approved drug products: Olinvyk (Oliceridine) injection [Internet]. Silver Spring (MD): FDA; 2020 [cited 2022 Jan 17]. Available from: https://www.access-data.fda.gov/drugsatfda_docs/label/2020/210730s000lbl.pdf.

38. Singla N, Minkowitz HS, Soergel DG, et al. A randomized, phase IIb study investigating oliceridine (TRV130), a novel μ -receptor G-protein pathway selective (μ -GPS) modulator, for the management of moderate to severe acute pain following abdominoplasty. *J Pain Res* 2017;10:2413–2424.
39. Liang DY, Li WW, Nwaneshiudu C, et al. Pharmacological characters of oliceridine, a μ -opioid receptor G-protein-biased ligand in mice. *Anesth Analg* 2019;129:1414–1421.