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REVIEW

Recent Developments in Drugs for GI Endoscopy Sedation

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Abstract
Providing sedation for patients undergoing gastrointestinal (GI) endoscopy continues to be a debated topic in both anesthesia and gastroenterology circles. Sedation approaches are widely varied across the globe. While propofol administration is embraced by more endoscopists and patients, its administration evolves controversy. Whereas trained nurses and gastroenterologists are allowed to administer propofol for GI endoscopy sedation in Europe and Asia, it is the sole privilege of anesthesia providers in the USA. However, the costs of anesthesia providers are significant and threaten to derail the screening colonoscopy practice. Efforts were made by both drug and device manufacturers to find alternatives. Fospropofol was one such effort that did not live up to the expectations due to respiratory depressant properties that were similar to propofol. Use of a new tool to administer propofol in the form of Sedasys® was the next experiment that tried to find alternative to anesthesia providers. The device did not succeed due to inadequate sedation. The latest effort is remimazolam, a new benzodiazepine that has quicker recovery profile. In the interim, many drug combinations such as propofol–dexmedetomidine and propofol–ketamine are improving the safety without compromising the quality of sedation. This review attempts to discuss the new drug innovations and drug combinations of existing sedatives for the benefit of readers.

Keywords Sedation · Remimazolam · Oliceridine · Propofol · Dexmedetomidine

Drugs in GI Endoscopy Sedation, What Is New?

Introduction

Sedation for GI endoscopy centers around propofol. However, propofol is fraught with significant limitations including interpatient pharmacokinetic and pharmacodynamic variability, airway compromise, respiratory depression, hypotension, and absence of a reversal agent [1]. Various approaches to overcome these potential drawbacks include dose titration, preemptive airway management techniques, and use of general anesthesia with endotracheal intubation.

Anesthesia providers may also modify their sedation technique by supplementing with other drugs. Such drugs include dexmedetomidine, ketamine, remifentanil, and local anesthetics. The anesthesia community is also eagerly anticipating G-protein-biased μ receptor agonists which can revolutionize the practice of anesthesia and sedation. Oliceridine was recently denied approval by the FDA, however, hopefully similar drugs find success.

Dexmedetomidine

Mechanism of Action

Dexmedetomidine is an α_2-adrenoceptor agonist with far more selectivity than its predecessor clonidine. It is both a sedative and an analgesic [2]. There is adequate literature regarding its use in the field of GI endoscopy. Few drugs used in endoscopy have both sedative and analgesic properties. For example, propofol has no analgesic properties,

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while benzodiazepines are mainly sedatives. Ketamine has analgesic properties; however, its sedative properties are still poorly understood.

Use in GI Endoscopy

In a prospective interventional study, Inatomi et al. demonstrated the safety and efficacy of dexmedetomidine in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). In their experience, when compared to midazolam alone, administration of dexmedetomidine and midazolam was associated with a lower incidence of oxygen desaturation and reduction in the median dose of additional midazolam required for the completion of the procedure. In addition, there was a decreased incidence of respiratory complications. The study patients received 3 μg kg^{-1} h^{-1} of dexmedetomidine as a loading dose over 10 min, followed by 0.4 μg kg^{-1} h^{-1}. In addition, these patients received 2.5 mg midazolam intravenously at the beginning of the procedure. Repeat intravenous injections of 2 mg of midazolam were administered as required. The conventional group of patients received an initial bolus of 2.5 mg of midazolam followed by 2 mg of midazolam as necessary to provide sedation to an acceptable degree. Although the incidence of respiratory complications such as desaturation was lower in the dexmedetomidine group (0%), compared to conventional group (6.9%), the mean lowest heart rate was also lower (62.1 beats min^{-1}) compared to the conventional group where the mean heart rate was 75.4 beats min^{-1}, [3]. Nevertheless, most anesthesia providers might find it easier to treat transient hypotension and bradycardia than hypoxemia caused by hypoventilation.

In a randomized controlled double-blind study of patients undergoing upper gastrointestinal endoscopy, Samson et al. compared three groups. The first group received only midazolam infusion, the second only propofol infusion and the third group received dexmedetomidine infusion. The authors observed better endoscopist satisfaction, greater hemodynamic stability, and faster recovery in the dexmedetomidine group when compared to propofol and midazolam [4].

Advanced endoscopic procedures including endobariatric surgeries are becoming commonplace. In patients undergoing endoscopic submucosal dissection, the efficacy and safety of dexmedetomidine and remifentanil were comparable to propofol and remifentanil. However, dexmedetomidine has the benefit of lower gastric motility and as a result was preferred by the endoscopists [5].

Finally, a meta-analysis of six randomized controlled trials comparing dexmedetomidine to other sedative hypnotics with or without analgesics concluded that the patient satisfaction level was significantly decreased in patients receiving dexmedetomidine (weighted mean difference : − 0.678, 95% confidence interval (CI): − 1.149 to − 0.207, $p = 0.0048$) when compared to dexmedetomidine [6].

Conclusion

Dexmedetomidine provides a titratable form of hypnotic sedation. Its usual dose for procedural sedation is 1 mcg kg^{-1}, followed by an infusion of 0.2 mcg kg^{-1} h^{-1}. Its onset of action is less than 5 min, and the peak effect occurs within 15 min. It can also be easily reversed by an α2-AR antagonist atipamezole. [7].

Ketamine

Mechanism of Action

Ketamine, which was introduced into clinical practice in the 1960s, is seeing a resurgence. Even after 50 years of clinical use in anesthesia, its precise mechanism of action remains a mystery. Disruption of corticocortical information transfer in a frontal-to-parietal ("top down") distribution is the most likely path to general anesthesia [8].

Use in GI Endoscopy

Data are limited regarding the use of ketamine as either single agent or with midazolam in endoscopy anesthesia/sedation. Few enthusiastic anesthesia providers use it in combination with propofol (mixture) that they call "ketofol." It is supposed to provide better hemodynamic stability, less respiratory depression and limit the amount of propofol required. Like many anesthetic mixtures used by anesthesia providers (propofol–remifentanil, propofol–alfentanil), "ketofol" is also not approved by drug regulatory agencies. The stability of the mixture and their interaction are unknown [9].

In a prospective, randomized trial of patients undergoing advanced endoscopic procedures (ERCP or EUS), Varadarajulu et al. administered either ketamine or meperidine and diazepam, after administering meperidine 50 mg, midazolam 5 mg, and diazepam 5 mg. None of these patients were adequately sedated after initial drug administration. The ketamine group were found to be better sedated as assessed by qualitative physician rating ($p < 0.0001$) with shorter recovery times ($p < 0.0001$) than patients sedated using benzodiazepines and meperidine alone [10].

Another randomized, prospective, double-blind study compared three groups, namely propofol alone, propofol + ketamine, and propofol + dexmedetomidine. All the patients underwent upper gastrointestinal endoscopy. The authors concluded that dexmedetomidine with propofol reduced the incidence of gag reflex better than ketamine

when added to propofol (8% vs 20%), with less propofol consumption and lesser recovery time [11].

Ketamine sedation seems to be used more frequently in children. In a study involving the administration of ketamine either by intravenous route or intramuscular route, none of the patients developed apnea, bradycardia or arrest. In addition, no child developed emergence reactions, which was attributed to young age of the sample that ranged from 2 to 12 years. However, increased salivation (requiring preprocedure anticholinergic administration with associated tachycardia and postprocedural oral dryness), tachycardia are important side effects. Increased airway secretions can cause laryngospasm. Avoidance of emergence phenomenon requires co-administration of either diazepam or midazolam. Due to its analgesic properties, additional analgesia is not necessary when ketamine is used. Although ketamine causes tachycardia, this might be a useful side effect in some hemodynamically unstable patients. Wide margin of safety and absence of cardiopulmonary suppression seem to be the most important benefits of ketamine [12].

Conclusion

Ketamine is generally co-administered with propofol as a single dose of 0.5 mg kg^{-1} ketamine during endoscopic procedures like endoscopic ultrasound. It will reduce the dose of propofol. Propofol–ketamine combination in varying ratios of 2:1, 3:1, and 4:1 is also found to be safe and effective; 3:1 and 4:1 mixtures of ketofol were comparable to those for the combination of propofol with fentanyl 50 µg and propofol alone. With a 4:1 ratio (160 mg propofol and 40 mg ketamine), incidence of respiratory depression and postprocedural drowsiness will be lower [13].

Local Anesthetics

Mechanism of Action

Topicalization of upper airway prior to introduction of endoscope or bronchoscope is popular among anesthesia providers and bronchoscopists. Cocaine (4%), tetracaine (1%), benzocaine (20%) and most commonly lidocaine (1–10%) are employed for this purpose [14]. All local anesthetics act by blockade of sodium channels.

Use in GI Endoscopy

Use of topical pharyngeal anesthesia in sedated patients undergoing upper GI endoscopy is controversial. In a randomized clinical trial conducted on 130 patients undergoing upper gastrointestinal endoscopy, Khodadoostan et al. did not find any significant difference with regard to ease of procedure, patients' tolerance, and patients' satisfaction between those patients topicalized with viscous lidocaine solution and lidocaine spray. All of these procedures were performed with local anesthetic alone without any additional sedative medications. In both groups, ease of performance of more than half the procedures was rated as effortless or easy. Less than 10 percent were found to be difficult. These results clearly demonstrate the utility of local anesthetics in the performance of upper GI endoscopy [15]. Although topical anesthesia is effective in blunting sensory response to endoscope insertion, it will not alleviate patient anxiety, enhance patient cooperation, or mitigate patient's movement. These elements are undesirable during upper GI endoscopy and thus may necessitate the use of additional sedation, unless specific contraindications exist.

In another study, Davis et al. randomized 95 patients undergoing diagnostic upper endoscopy with conscious sedation to receive either topical pharyngeal anesthesia with 2% tetracaine/14% benzocaine spray or no pharyngeal anesthesia. All of them received intravenous midazolam and meperidine. The use of topical pharyngeal anesthesia in their patients did not improve patient tolerance or procedure performance. They concluded that elimination of local anesthetics in the performance of diagnostic upper endoscopy will save time and money without adversely affecting patient care or outcome [16].

Similarly, sun et al. found that lidocaine topical pharyngeal anesthesia in propofol-sedated esophagogastroduodenoscopy did not further reduce the pharyngeal discomfort or improve the satisfaction. However, they did not evaluate whether lidocaine topical pharyngeal anesthesia reduced the propofol dosing requirements [17]. Reduction in the dose of propofol will be a significant advantage as it is also likely to result in decreased incidence of apnea/hypopnea and desaturation. Cardiovascular side effects will be decreased especially in patients with significant cardiovascular disease.

Conclusion

Presently, it is not clear whether local anesthetic spray reduces the sedation requirements. Certainly, in selected patients, upper endoscopic procedures can be done with local anesthetic spray alone. Caution is advised while using benzocaine and tetracaine as reports of methemoglobinemia exist when higher doses were used [18]. It is unlikely that such doses will be used or needed to perform upper GI endoscopy. Absorption of local anesthetics could be extremely rapid, and as a result, adherence to the dosing recommendations is necessary. Those who receive pharyngeal anesthesia are also at greater risk of aspiration and postprocedure pneumonia [19].

Remifentanil

Mechanism of Action

Remifentanil is an ultrashort acting opioid with unique pharmacokinetic properties. Like other opioids, it acts on μ opioid receptors, which is responsible for analgesia. Unlike every other opioid known, it gets metabolized by tissues esterases including those present in plasma and red blood cells. As a result, it is eliminated rapidly and displays a fixed short elimination half-life, independent of duration of infusion, otherwise known as context-sensitive half-life [9].

Use in GI Endoscopy

Respiratory depression is a major adverse effect of remifentanil. The margin of safety is extremely small, and the dose needs to be tightly regulated. In a study comparing the infusion rates of remifentanil with additional patient-controlled boluses, investigators found that both 0.5 μg kg^{-1} and 0.8 μg kg^{-1} infusions were equally acceptable [20]. Addition of midazolam 0.03 mg kg^{-1} intravenously for premedication along with a remifentanil bolus and patient-controlled analgesia to provide further bolus doses with no "lockout" time is another effective approach [21]. The sedation provided by short acting opioids such as remifentanil and alfentanil along with intense analgesia suffices for most colonoscopies. Rapid onset and offset of action, analgesic and anxiolytic effects, ease of titration to desired level, rapid recovery, and an excellent safety profile are their major attractions [22].

Another interesting cocktail is combining remifentanil with ketamine. Karacaer et al. compared the two in 70 patients, between 2 and 16 years of age, scheduled for diagnostic colonoscopy. In this study, remifentanil–ketamine group received intravenous ketamine 2 mg kg^{-1} and remifentanil 0.25 μg kg^{-1} bolus, followed by 0.1 μg kg^{-1} min^{-1} remifentanil infusion. The propofol–ketamine group received intravenous propofol 1 and 2 mg kg^{-1} ketamine combination, followed by 1 mg kg^{-1} h^{-1} propofol infusion. It was found that both safely provided sedation and analgesia. At least in theory, remifentanil–ketamine group should produce less respiratory depression. They also found that sedation scores were significantly better in remifentanil–ketamine group ($p = 0.02$) than in propofol–ketamine group [23]. There was no difference in terms of bradycardia and salivary secretions.

Conclusions

Remifentanil is a potent opioid with significant respiratory depressant properties and low margin of safety. As a result, it should be used cautiously in small titrated doses along with propofol or ketamine. It can also be added to propofol at a concentration of 2.5–5.0 μg per ml of propofol and infused at a rate of 40–60 μg of propofol kg^{-1} min^{-1} (ignoring the remifentanil part of the mixture). It provides excellent hemodynamic stability with a reduction in coughing.

Remimazolam

Mechanism of Action

After more than a decade of development and clinical trials, remimazolam may be available to the clinicians. At the time of writing this review, Cosmo Pharmaceuticals N.V. (SIX: COPN) were notified by the Food and Drug Administration (FDA) of their acceptance of new drug application for review. However, this would mean that the drug is still many months away from a possible approval [24].

Remimazolam (CNS 7056) combines unique properties of two of the most popular drugs used in anesthesia, namely midazolam and remifentanil. While pharmacodynamically it is a short acting benzodiazepine (a GABA agonist) similar to midazolam, pharmacokinetically it behaves like remifentanil as it is metabolized by non-specific tissue esterases in the blood. The latter is possible as remimazolam contains a deliberately introduced carboxylic ester linkage. The metabolism is likely to be dose independent, where it follows first-order kinetics and is unlikely to change to zero order in the recommended doses. This property allows for use in patients with hepatic or renal impairment-either age related or caused by diseases, without fear of prolonged duration of action. It has a mean clearance of 70.3 ± 13.9 L h^{-1} and a mean steady-state volume of distribution of 34.8 ± 9.4 L and is associated with a context-sensitive half-time of 7–8 min after a 2-h infusion [25]. In terms of pharmacodynamics, it acts on the GABA receptor, specifically GABA-alpha [26].

Use in GI Endoscopy

Earlier studies of its use in GI endoscopy were less encouraging. In a phase IIa clinical trial providing procedural sedation to patients undergoing upper gastrointestinal endoscopy, the time to recovery was found to be shorter than midazolam [27]. The onset of clinical effect was not different from midazolam, which is to be expected. However, a failure rate of 56 percent even with high dose (0.2 mg per Kg of body weight) was a major drawback. Moreover, in these patients undergoing colonoscopy, hypotension and low oxygen saturation were observed to be a significant issue and the procedure could not be completed in 11/44 subjects mainly due to failed sedation [28].

In a randomized double-blind comparison of remimazolam to placebo for outpatient colonoscopy, Rex et al. could demonstrate faster recovery of neuropsychiatric function compared with placebo (with midazolam rescue) and midazolam alone. In this large multicentric study, 461 randomized patients in 12 US sites were recruited. The primary endpoint was an amalgamation of the following three criteria: completion of the colonoscopy, avoidance of rescue medication, and ≤ 5 doses of remimazolam or placebo in any 15-minute interval (≤ 3 doses of midazolam in any 12-minute interval in the open-label midazolam arm). Only 25.2% of patients met these criteria in the midazolam group, while 91.3% similarly met in the remimazolam group [29]. Nonetheless, procedures were completed with further intervention that included additional doses of midazolam and fentanyl. A small failure of 2% for procedure completion might be attributable to the absence of an anesthesia provider to either escalate the dose or supplement with propofol. In a practice environment where anesthesia providers may not interfere to complete an elective procedure leading to inevitable mid-procedure abortment and cancelation, such failures can contribute to a degree of patient dissatisfaction and inconvenience. A failure rate of nearly 75% with midazolam is also in sharp contrast to experience of other investigators in patients undergoing GI endoscopy [30–32]. This could be related to relatively lower doses of midazolam employed in this study.

Prolonged postendoscopy recovery times has been a consistent problem with all benzodiazepines including midazolam. Although time from completion to full alertness was shorter with remimazolam (to be expected given its unique metabolism), they did not result in significantly better discharge times. Moreover, facility discharge times often depend on many other factors than ready to discharge alone from the sedation standpoint.

High patient satisfaction with minimal recall has been the main reason for popularity of propofol in endoscopy sedation. Ability to recall (as tested with Brice questionnaire) is similar between midazolam and remimazolam. Patient satisfaction was also similar between midazolam and remimazolam.

Respiratory side effects like apnea and laryngospasm that result in hypoxemia are the most feared complications of administering any sedation. Remimazolam is probably no different to midazolam in this regard among patients undergoing colonoscopy when used in equipotent doses.

Conclusion

At best remimazolam provides similar degree of sedation, with similar patient satisfaction with earlier "readiness to discharge" times [33]. It is unlikely to replace propofol in patients undergoing colonoscopy; however, enthusiastic endoscopists will be able to perform majority of these procedures with remimazolam alone without the fear of delayed discharge. It could be valuable addition to propofol in advanced endoscopic procedures as it does not delay discharge.

Oliceridine

Mechanism of Action

Opioids such as morphine bind to μ-opioid receptors and activate two downstream signaling pathways. The first is G-protein coupling which is linked to analgesia, and the second is β-arrestin recruitment, linked to opioid-related adverse effects. The second property is the main factor which limits their efficacy [34].

Oliceridine (formerly known as TRV 130) is a G-protein-biased opioid agonist. On binding to the μ-opioid receptor (MOR), it selectively activates guanosine triphosphates (GTAase) and this action is responsible for analgesia. The second pathway results from activation of β-arrestin, which is responsible for many adverse effects such as respiratory depression, GI side effects, hyperalgesia, tolerance and addiction which is relatively spared by these G-protein-biased opioid agonists [34]. In other words, it differentially activates G-protein coupling while mitigating β-arrestin recruitment. However, the selectivity is not absolute and is less obvious in higher doses. By using a tail flick assay in mice, Liang et al. demonstrated that oliceridine has a fourfold more potent analgesic activity than morphine ($p < 0.001$). In addition, it caused less tolerance ($p < 0.001$) and opioid-induced hyperalgesia than morphine after 4 days of ascending-dose administration [35].

Conclusions

G-protein-biased opioid agonists are likely to have many benefits in endoscopy sedation. Considering that respiratory depression is one of the commonest causes of desaturation that can possibly result in cardiac arrest, any effort at limiting such a possibility is a welcome move. Oliceridine is a breakthrough drug that produces similar analgesia compared with morphine but causes fewer adverse events. At least in short-term administration, it is known to have reduced desensitization, constipation, and respiratory depression [36, 37]. Since the majority of GI endoscopies are of short duration, these properties are ideally suited for sedation supplement. The intense analgesic properties are likely to reduce the propofol requirement, just enough to provide hypnotic effect. The degree of analgesia needed is low, and as a result, the loss of selectivity seen at higher doses is not a concern in providing sedation for endoscopy. In essence, G-protein-biased opioid agonists are likely to play a crucial role in

Table 1 Comparison of sedatives employed in GI endoscopy

Drug	Mechanism of action	Advantages/uses	Limitations
Dexmedetomidine	α_2-adrenoceptor agonist Sedative and analgesic	Less respiratory depression As a supplement with propofol	Increased incidence of Bradycardia and hypotension
Ketamine	Disruption of corticocortical information transfer in a frontal-to-parietal ("top down") distribution	Effective analgesic As a supplement with dexmedetomidine or propofol to reduce propofol requirements	Increased salivation Increased risk of laryngospasm Emergence phenomena such as hallucinations
Local anesthetics	Blockade of sodium channels	Procedures may be performed in selected patients with topicalization alone Might decrease the propofol requirement	Risk of methemoglobinemia Greater risk of aspiration and postprocedure pneumonia
Remifentanil	Ultrashort acting opioid acts on μ opioid receptors	Decreased incidence of coughing, better hemodynamic stability Used as a supplement with propofol or dexmedetomidine	Increased risk of apnea, hypoventilation and consequent hypoxemia
Remimazolam	A short acting benzodiazepine, agonist at GABA receptors	Due to its unique elimination, patients wake up faster; as a result, recovery time is reduced	Unlikely to provide sufficient depth of sedation without compromising respiration Not yet available
Oliceridine	G-protein-biased opioid agonist	First selective μ-opioid receptor agonist devoid of opioid-induced side effects such as respiratory depression, GI side effects, hyperalgesia and addiction liability	Loss of selectively at higher doses Not yet available

providing sedation to patients undergoing GI endoscopy and obviate the need for repeated ventilation interventions and allow for quick recovery and discharge.

Conclusions

Although new sedative drugs potentially useful in GI endoscopy sedation are on the cusp of approval, the existing drugs can be used more effectively with appropriate improvisations. The most prominent of these is dexmedetomidine. Prolonged onset and slow offset of its clinical effect are an obvious drawback. However, it is easy to overcome this handicap by administering propofol. A bolus of propofol can provide appropriate conditions for endoscope insertion, which can be followed by dexmedetomidine bolus and infusion. One can continue low-dose propofol infusion alongside. Respiratory depression is unlikely, and the technique is especially useful in prolonged procedures with significant risk of respiratory depression such as advanced upper endoscopic procedures.

Ketamine continues to enjoy popularity in pediatric GI endoscopic procedures. Minimal respiratory depression and cardiovascular stability are a major plus. Propofol–ketamine is a popular cocktail among anesthesia providers. An antisialagogue and a benzodiazepine can decrease secretions and eliminate emergence phenomenon, respectively.

If G-protein-biased opioid agonists live up to their promise, they can entirely revolutionize the practice of sedation and anesthesia. Ability to produce morphine degree of analgesia with negligible opioid side effects such as respiratory depression, tolerance, GI-related side effects and withdrawal will be a game changer.

Remimazolam alone is unlikely to make a significant dent in GI sedation practice. The drug is not much different to midazolam, and esterase elimination is hardly an advantage. It might have the benefit of faster offset, especially with prolonged procedures. In US practice, where patient satisfaction is paramount in medical practice, another benzodiazepine like remimazolam is unlikely to make a difference. However, when both oliceridine and remimazolam become available, we will be able to effectively replace propofol in GI endoscopy sedation without compromising the quality of sedation.

Topicalization of pharynx can reduce the propofol requirements. One should be aware of dosing limits and the risk of toxicity, especially methemoglobinemia. Table 1 provides a brief description of the drugs discussed in this review.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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