5-30-2020

Oliceridine and its potential to revolutionize GI endoscopy sedation

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Review Article

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ABSTRACT

Providing sedation to patients undergoing gastrointestinal (GI) endoscopy is a controversial and emotive issue. The mainstay of sedation is propofol, whose administration is within the sole jurisdiction of anesthesia providers, at least in the USA. Attempts have been made to seize the authority by the GI community. One of the first attempts was the use of the prodrug of propofol –fospropofol. However, as the drug has a similar adverse effect profile as propofol in terms of respiratory depression, the FDA did not approve its use by providers other than those trained in airway management. Sedasys® was the next attempt, which was a computer-assisted personalized sedation system. As a result of insufficient sedation that could be provided with the device, although very successful in research settings, it was not a commercial success. It seems that remimazolam is the next effort in this direction. It is likely to fail in this regard unless its respiratory depressant properties and failure rates could be addressed. G protein-biased μ-receptor agonists are a new class of opioids exhibiting analgesic properties similar to morphine without equivalent respiratory depressant properties. Oliceridine is the prototype. As a result, the drug can be additive to midazolam or remimazolam and allow screening colonoscopy to be comfortably completed without the need for propofol. For an anesthesia provider, the administration of oliceridine can eliminate the need for drugs such as fentanyl that add to the respiratory depressant properties of propofol. As a result, oliceridine has the potential to render the sedation for GI endoscopy procedures both safe and cost-effective.

Key words: Endoscopy; oliceridine; propofol; remimazolam; sedation

Introduction

Gastrointestinal (GI) endoscopy procedures are increasingly performed with sedation, both across the USA and worldwide.[1] Propofol is often considered as *Sine qua non* for both screening colonoscopy and more advanced procedures such as endoscopic retrograde cholangiopancreatography (ERCP). Short-acting potent opioids such as fentanyl and remifentanil are often administered with propofol, especially during esophagogastroduodenoscopy (EGD) and other procedures that involve significant patient discomfort. In addition to providing analgesia, opioids reduce the propofol requirements, thereby decreasing adverse events such as hypotension, although opioids themselves can cause hypotension. Propofol sedation, especially when administered by anesthesia providers, is seen to increase both the patient

Access this article online	
Website: www.saudija.org	Quick Response Code
DOI: 10.4103/sja.SJA_813_19	

How to cite this article: Goudra B, Singh PM. Oliceridine and its potential to revolutionize GI endoscopy sedation. Saudi J Anaesth 2020;14:349-54.

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Submitted: 26-Dec-2019, **Revised:** 13-Jan-2020, **Accepted:** 26-Jan-2020, **Publication:** 30-May-2020

and endoscopist satisfaction. In addition to increasing the throughput of the endoscopy units, propofol sedation provides near 100% success rates. None of the other drugs, such as midazolam or remimazolam (yet to be approved by the FDA), which provide moderate sedation, can match the success rates of propofol sedation.[2]

Hypoxemia is seen as the most troubling complication of propofol sedation, especially during EGD and ERCP.[3] It can lead to severe complications such as anoxic brain injury and death. Hypoventilation caused by sedatives is the most likely mechanism. As a result of significant pharmacokinetic and pharmacodynamic variability of both propofol and fentanyl, accurate titration of these agents is difficult, even for experienced clinicians.[4] Although coadministration of opioids such as fentanyl decreases the propofol requirements, it also increases the risk of hypoxemia. Advanced airway devices such as high-flow nasal cannula can reduce such hypoxemia events, although they are costly and have associated complications.[5] As a result, newer approaches that can reduce the incidence of hypoxemia without compromising the quality of sedation would be welcome.

The search for such an "ideal" drug for GI endoscopy sedation that has the properties of a sedative, an analgesic, and a hypnotic has ever eluded the investigators. Such a drug should not cause any respiratory depression, preserve airway protective reflexes, and yet allow the painless introduction of an endoscope. A fast onset and fast offset are necessary to allow rapid turnover. The absence of any hangover and nausea/vomiting is further desirable. Although such a drug is not available, we presume that oliceridine in combination with either propofol or remimazolam might come closer than ever. Oliceridine belongs to the group of G protein-biased μ-receptor agonists, which are a new class of drugs that can potentially make sedation in patients undergoing GI endoscopy significantly safer.

G Protein-Biased μ-Receptor Agonists

G protein-coupled receptors are cell surface receptors which are potential pharmacological targets in new opioids development. They represent the largest family of membrane proteins in the human genome and also the richest source of targets for the pharmaceutical industry.[6] Opioids such as fentanyl and morphine bind to the μ-opioid receptor, which is a G protein-coupled receptor. However, these drugs also activate a second downstream pathway labeled as a beta-arrestin pathway. It is hypothesized that activation of the G protein pathway is responsible for analgesia, while activation of the beta-arrestin pathway contributes to unwanted effects of μ-opioid receptor activation such as respiratory and GI dysfunction. It is observed that mice that are genetically modified to knock out their beta-arrestins display enhanced and prolonged morphine-induced antinociception.[7] It is likely that the absence of beta-arrestins in these mice leads to selective amplification of the analgesic pathway. It is also likely that beta-arrestins cause acute desensitization thereby reducing the efficacy of morphine-like opioid agonists.[8] Consequently, a drug that can selectively activate the G protein pathway without acting on the beta-arrestins is likely to produce analgesia with limited traditional adverse effects of morphine-like opioids.

Oliceridine

Oliceridine (TRV130) is a μ-receptor agonist that selectively engages the G-protein-coupled signaling pathway while avoiding the beta-arrestin pathway. Such a drug is said to be a biased agonist. It is proposed to achieve adequate analgesia with limited opioid-related adverse events such as nausea, vomiting, sedation, constipation, reward/euphoria, dependence/withdrawal, and respiratory depression. Other G-protein-selective opioid receptor agonists, specific to the delta, and kappa, might be developed with beneficial effects or at least devoid of unwanted effects such as aversion/dysphoria, sedation, and diuresis (kappa-receptors), and convulsions and reward (delta-receptors).[9] It is proposed that G protein-biased kappa agonists can reduce pain and itch, and exhibit fewer side effects, such as anhedonia and psychosis.[10] Such drugs might be still many years away. Currently, oliceridine is the only drug in the class of biased agonists and it was recently denied FDA approval. It is likely that it is undergoing further studies and might become available to clinicians in the near future. The aim of the current review is to discuss general pharmacology, data from currently available studies, and its potential application in the field of GI endoscopy sedation.

Nevertheless, it is important to bear in mind that biased agonism may decrease the adverse effects of opioids, it will probably not eliminate them. Specifically, ligand bias is unlikely to reduce the danger of dependence, as both analgesia and dependence seem to be G protein-mediated. In fact, available data suggest that oliceridine has a potential for abuse similar to that of morphine.

Clinical pharmacology

Currently, an intravenous preparation of oliceridine is studied in research settings, both in animals and humans. The exposure to drug increases with an increase in the dose from 0.15 to 7 mg and such an increase is nonlinear by about

15%. In patients with cytochrome P450 2D6 polymorphism, there is a 50% decrease in the clearance that could be clinically significant. The enzyme CYP2D6 is thought to be involved in the metabolism of up to 25% of commonly used drugs.[11] *CYP2D6* polymorphism may be associated with poor opioid treatment outcomes.[12] Patients vary in their metabolism and among Caucasians, the frequency of occurrence of different groups are 5–10% (poor metabolizers), 10–15% (intermediate metabolizers), 65–80% (extensive metabolizers), and 5–10% (ultrarapid metabolizers), respectively.[12] Another study suggested that about 7% of Caucasians and only 1% of Orientals are poor metabolizers.[13] Such a degree of variation may be a factor in variability. The half-life of oliceridine is approximately 1.5–3 h when administered IV over 1 min to 1 h. While the poor metabolizers tend to have longer half-lives, it will be short in ultrarapid metabolizers. Nonetheless, clinicians typically titrate opioids to effect. As a result, when used as sedatives, dose adjustments are not necessary, although these would have to be studied in a controlled setting if oliceridine were to be developed for a sedation indication.[14]

Oliceridine has low renal clearance and renal dysfunction does not require dose adjustments. A phase 1, open-label, single-dose study found no difference in clearance at a dose of 0.5 mg administered intravenously in patients with end-stage renal disease.[15] These authors also studied the effect of hepatic impairment and found an increased volume of distribution, which corresponded with the degree of hepatic impairment; however, no effect on the clearance. They recommended no dose adjustment in patients with renal impairment or in patients with mild or moderate hepatic impairment. Its oral bioavailability is low.[16]

Oliceridine has no known active metabolites and the clinical effect in terms of analgesia is seen in about 5 min. Factors such as age, body weight, and gender have no significant impact in terms of pharmacokinetics. Simulation studies suggest that oliceridine doses of 1–3 mg *pro re nata* (PRN) are probably effective in reducing numeric pain-rating scale (NPRS) scores relative to placebo.[14] If required, the supplemental doses should be 1 mg and administered about 15 min after the loading dose. These studies also suggest that when oliceridine is administered on an as-needed basis, a longer interval between doses is observed in simulated CYP2D6 poor metabolizers, consistent with their reduced oliceridine clearance. However, it should be remembered that pharmacodynamic variability in general, among opiates and other sedatives, is worrying and can lead to a quick overdose in the elderly.

In summary, the pharmacokinetics of oliceridine (administered intravenously) are predictable across age groups and independent of renal and hepatic function.

Clinical studies

There are a number of studies examining the analgesic effects of oliceridine, all in research settings. It should be remembered that often the results seen in such settings may not be reproducible in non-research clinical use. Sedasys, the computer-assisted personalized sedation system is a classic example, which worked extremely well in a research environment,[17,18] but failed badly after FDA approval in routine clinical use leading to its withdrawal from the market.

Respiratory depression and oliceridine

In a phase 1b, randomized, double-blind, placebo-controlled, five-period crossover study involving 30 healthy volunteers receiving placebo, morphine 10 mg, and oliceridine 1.5, 3, and 4.5 mg as 2-minute IV infusions, oliceridine displayed significantly lower impact on respiratory depression than morphine 10 mg in all doses.[16]

Similarly, both phases 2b and 2a/b studies involving respectively patients undergoing abdominoplasty and bunionectomy, the superiority of oliceridine in terms of respiratory safety was evident.[19,20] A more recent phase III, double-blind, randomized trial in patients with moderate-to-severe pain following bunionectomy, the respiratory safety burden that represents the cumulative duration of respiratory safety events was studied. These authors found it to have a favorable safety and tolerability profile with regard to respiratory and GI adverse effects compared to morphine.[21]

Recently, three abstracts addressing respiratory safety of oliceridine were presented at the American Society of Anesthesiology annual meeting in October 2019. While studying objective and precise assessments of the probability of analgesia relative to the probability of respiratory depression, Bergese *et al*. estimated the probability of analgesia of oliceridine exceeding the respiratory depression, over the entire dose range. They found a 2.5-fold greater respiratory depression with morphine compared to oliceridine while equipotency was observed for the analgesic efficacy of the two opioids.[22] Similarly, Brzezinski *et al*.[23] administered IV oliceridine as needed via bolus dosing (1–3 mg q1−3h) and/or patient-controlled analgesia (PCA loading dose: 1.5 mg; demand dose: 0.5 mg; 6-min lockout interval) to 768 men and women aged ≥18 years with a score ≥4 on an 11-point numeric pain rating scale. 30.5% of patients had respiratory comorbidities while 12.6% had sleep apnea. Among the respiratory variables

studied were respiration rate (RR) <10 bpm, SpO_2 <90%, and the need for naloxone administration. They found a reduced incidence of opioid-induced respiratory depression compared to rates reported in the literature using similar definitions. In yet another study, Ayad *et al*.[24] analyzed the data from phase 3 APOLLO studies. They demonstrated less opioid-induced respiratory depression with oliceridine than morphine as measured by the average cumulative duration of dosing interruption in patients being treated for acute postsurgical pain.

Analgesia and oliceridine

Oliceridine produces analgesia within 5 min of IV administration that has a clinical duration of 1–3 h after a single IV dose. It is titratable and the relative lack of respiratory effects might allow the clinician to administer higher doses. Until now, all the studies have addressed postoperative pain.

Viscusi *et al*. administered a placebo, oliceridine (1.5 mg), or morphine (4 mg), followed by demand doses via patient-controlled analgesia (0.1, 0.35, or 0.5 mg oliceridine, 1 mg morphine, or placebo) to treat moderate-to-severe pain following bunionectomy.[21] In comparison to the placebo, all doses of oliceridine produced effective analgesia and the analgesic efficacy was comparable to morphine. They found a favorable safety and tolerability profile with regard to respiratory and GI adverse effects compared to morphine at all doses.

Singla *et al*. demonstrated similar analgesic efficacy comparable to morphine when administered for postoperative pain relief of patients who underwent an abdominoplasty. The safety and tolerability profile regarding respiratory and GI adverse effects, when compared to morphine was favorable.[25]

Potential drawbacks

Although oliceridine has shown analgesic efficacy similar to morphine, there are a number of drawbacks. Equianalgesic doses of oliceridine and morphine are found to possess similar abuse potential, thereby questioning the very foundation of the selectivity hypothesis. Prolongation of QT interval is seen both in animals (monkeys) and healthy adults. However, in human studies, it was not associated with a clinically meaningful increase in risk for ventricular arrhythmia or other indices of cardiovascular safety under the proposed conditions for clinical use. Evidence of a clinically significant liver safety signal with oliceridine treatment is lacking. It possesses a similar risk of overdoses like other opioids that can cause injury or death. As the binding to the morphine receptor is reversible and competitive, an overdose can be quickly reversed by naloxone.

Similar to another schedule II full-morphine agonists used for the treatment of acute pain, oliceridine displays physical dependence potential. Although minimal, post-discontinuation adverse events associated with withdrawal are seen. GI side effects such as nausea, vomiting are seen similar to morphine, although to a lesser extent.

The loss of selectivity with higher doses of oliceridine is unexplained. It is possible that at higher doses it might also stimulate the beta-arrestin pathway, thereby contributing to the traditional opioid-related side effects. It is also possible that mechanisms other than beta-arrestin are involved in effects such as nausea and vomiting.

Potential application in GI endoscopy sedation

As discussed in the introduction, hypoxemia continues to be a major challenge in providing sedation to patients undergoing GI endoscopy, especially advanced upper GI procedures such as ERCP. Anesthesia providers have addressed this issue in multiple ways, none very satisfactorily.

Administration of propofol alone is known to be associated with a lesser incidence of hypoxemia. However, such an approach is not always feasible especially in advanced endoscopic procedures. Moreover, it increases the risk of hypotension. Potentially, it can delay the recovery due to an increase in context-sensitive half-life, especially during prolonged infusions.

The administration of fentanyl with propofol can decease the propofol requirements. Nonetheless, respiratory depression contributed by fentanyl is a major setback. There are no easy options to treat hypoventilation in a patient undergoing an EGD or ERCP. Unlike colonoscopy, the airway in these patients is not at the exclusive disposal of anesthesia providers. Many novel and innovative methods are available to address hypoventilation and hypoxemia. These include the use of a high-flow nasal cannula,[5] LMA Gastro Airway,[26] and modified nasopharyngeal airway.[27]

The administration of ketamine or dexmedetomidine is associated with a significantly lower incidence of hypoxemia and hypoventilation.[28] In addition, coadministration of ketamine maintains cardiovascular stability. Although the dexmedetomidine-propofol combination is associated with less respiratory depression, it has the potential to cause bradycardia and hypotension.

Recently, a novel benzodiazepine named remimazolam has undergone trials for providing sedation to patients undergoing colonoscopy.[2] Although older studies revealed

a very high degree of failure rates,[29] recent studies are encouraging. Yet, a failure rate of 2% for a screening colonoscopy would be deemed high. To cancel a screening colonoscopy for inadequate sedation would be unacceptable. In addition, it would be nearly impossible to perform EGD and ERCP with remimazolam alone. This drug has a similar pharmacodynamic profile to midazolam and structural similarity. The difference is in its pharmacokinetics, wherein it undergoes an organ independent ester hydrolysis. Consequently, wake-up times will be shorter and patients can be discharged sooner similar to propofol sedation.

A major benefit of oliceridine is its reduced propensity to cause respiratory depression, most definitively observed in lower doses. In lower doses, it also has a better GI side effects profile with lesser nausea and vomiting. Although the onset of clinical action is slower than fentanyl (about 5 min), this is less of a setback. If used with propofol, the clinician can reduce the propofol requirements without compromising the quality of sedation. As a result, both cardiovascular and respiratory depressant effects are minimized. Additionally, oliceridine can be administered with remimazolam (when it becomes available). It is likely that this combination can revolutionize the sedation for screening colonoscopy. Reduction of the dose of benzodiazepine can improve cardiovascular stability and respiratory depression. This is possible due to the potent analgesic properties of oliceridine. Lack of hepatobiliary effects would be beneficial in hepatobiliary procedures such as ERCP. A longer duration of the clinical effect of oliceridine would also mean better and longer postprocedural analgesia.

Conclusions

G protein-biased μ-receptor agonists are a new class of opioids that hold immense promise in the field of GI endoscopy sedation. They can revolutionize sedation for both screening colonoscopy and more advanced EGD and ERCP. The ability to provide analgesia equipotent with morphine without respiratory depressant properties has many dividends. It can reduce the propofol requirements with less risk of hypoventilation and hypoxemia. Coadministration with midazolam (or not yet approved remimazolam) might allow the effortless completion of a screening colonoscopy without the respiratory depressant properties of fentanyl.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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