Review Article

Oliceridine- Opioid of the 21st Century

ABSTRACT

Oliceridine (Olinvyk® Trevena, PA, USA) was approved by the United States Food and Drug Administration for clinical use on Aug 8, 2020. Even though, the indication of its approval is very restrictive (to manage moderate-to-severe acute pain in adults when the pain is severe enough), for such an innovative opioid, off-label indications are bound to abound. What could be described as the "opioid of the century," it aims to overcome some of the stubbornest barriers to opioid prescribing, namely addiction liability, respiratory depression, and gastrointestinal (GI) side effects, just to name a few. The novel opioid accomplishes this by a unique mechanism of action. By selectively acting on the G-protein sub-pathway in preference to the beta-arrestin, it aims to mitigate these unwanted μ-opioid receptors-associated opioid side effects, while preserving its analgesic activity. What remains to be seen, however, is if these observations seen in phases 2 and 3 trials will be borne in actual large-scale clinical use, both inside and outside the USA. Unfortunately, the field of anesthesia is rife with innovations that have shown enormous promise at the research stage, only to end up as damp squibs when released to the clinicians for general use. Rapcuronium and althesin are some such examples. We aim to present some of the contentious and emerging issues associated with this drug and some of the potential pitfalls of this new opioid.

Key words: Biased agonist, G-protein, oliceridine

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Oliceridine belongs to a new class of opioids that target G-protein-coupled receptor. The credit for the discovery of this new family of G-protein-coupled receptor belongs to Robert Joseph Lefkowitz, an American physician, internist, cardiologist, and biochemist.[1] He was awarded the Nobel Prize in Chemistry for this discovery in 2012 along with Brian Kent Kobilka, an American physiologist.[2] It is now understood that the μ-opioid receptor is a G-protein-coupled receptor. The binding of the opioids to these receptors also activates a second downstream pathway labeled as the beta-arrestin pathway.[3] the Activation of the G-protein pathway is responsible for analgesia, while the activation of the beta-arrestin pathway contributes to unwanted effects of μ-opioid receptor activation such as respiratory depression and GI dysfunction.

Brief Review of the Published and Unpublished Scientific Studies

The active ingredient in Olinvyk is oliceridine, an opioid agonist. Oliceridine fumarate is a white- to lightly-colored solid that is sparingly soluble in water. The chemical name

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for oliceridine fumarate is [(3-methoxythiophen-2-yl) methyl]({2-[(9R)-9-(pyridin-2-yl)-6- oxaspiro[4.5]decan-9-yl] ethyl}) amine fumarate, and the molecular formula is C22H30N2O2S·C4H4O4. The theoretical average molecular mass is 502.62 (fumarate salt) and 386.55 (free base). The structural formula of oliceridine fumarate is found in Figure 1.

Olinvyk (oliceridine) injection is a clear, colorless, sterile, preservative-free solution, pH 6.4–7.4, in a glass vial for intravenous use. Each milliliter of the solution contains 1.0 mg of oliceridine-free base (1.3 mg of oliceridine fumarate salt), as well as l-histidine and mannitol in water for injection.

Trevena (the company making Olinvyk) conducted at least five studies involving a minimum of 2,091 patients prior to market approval. The drug was discussed for potential approval at the meeting of the anesthetic and analgesic drug products, FDA, on October 11, 2018.[4] These involved both the dose-finding and safety/efficacy studies. Similar to the established opioids, oliceridine is demonstrated to exhibit dose-dependent reductions in the pain scores. In terms of potency, it is approximately five times more potent than morphine. Of significance is that its therapeutic window is wider than morphine. It produces effective and rapid analgesia within 3–4 min.[4]

What differentiates oliceridine from traditional opioids is the safety profile which in turn is related to its unique mechanism of action. It is perceived to exhibit a low incidence of opioid-induced respiratory depression and decreased frequency of observed rates of postoperative nausea and vomiting. The important details of these studies are summarized in Table 1.[5–9]

Approved Indication

Patient-controlled analgesia (PCA), IV infusion, or bolus in Post-Anesthesia Care Unit (PACU) and postoperative phase for pain relief

The only approved indication for Olinvyk is for the postoperative phase for pain relief by patient-controlled analgesia (PCA), IV infusion, or bolus. It is available at 1 mg/mL concentration in 30 mg vials. Currently, the vial is intended for PCA use only. It is also available in 1 and 2 mL vials (1 mg/mL and 2 mg/2 mL). Figure 2 provides information on the marketed product. The total daily dose should not exceed 27 mg and the duration should be limited to less than 48 h. An initial dose of 1.5 mg can be administered by a healthcare provider followed by access to the patient demand doses with a 6-min lock-out. The recommended demand dose is 0.35 mg that may be increased to 0.5 mg in selected patients. Additionally, supplemental doses of 0.75 mg can be administered by the healthcare providers, beginning 1 h after the initial dose, and hourly thereafter as needed. The patient is expected to gain pain relief in 2–5 min, much like fentanyl. It is stated that a 1 mg dose of Olinvyk is approximately equipotent to morphine 5 mg.

In the absence of any significant advantages and given the many additional drawbacks such as prolonged QT interval, it is hard to imagine a PCA world free of fentanyl, morphine, or hydromorphone.[10] There is extensive experience among physicians and other healthcare providers with regards to these three popular opioids. One can recommend oliceridine over these established opioids if additional randomized-controlled trials are performed to establish a clear superiority over these established opioids.

the reduced incidence of GI side effects and opioid-induced respiratory depression are clear benefits in the postoperative period. However, one should remember that the true benefits of oliceridine in terms of reduced GI side effects, lack of significant respiratory depression, and less dependence and abuse liability are demonstrated only at lower doses.[4] These benefits tend to disappear at higher doses. As a result, it would be prudent to reduce the oliceridine dose by employing additional

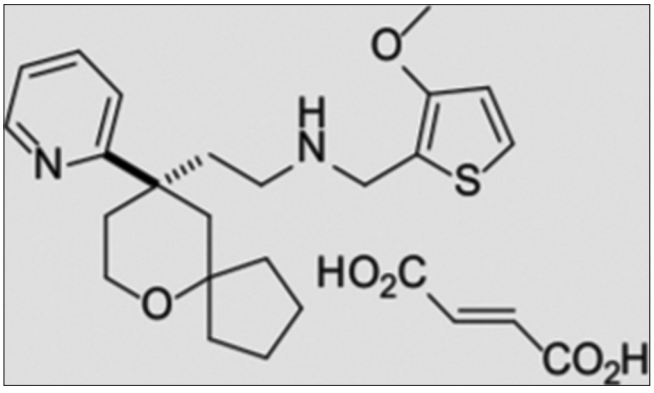

Figure 1:Chemical structure of Oliceridine

Figure 2: Clear sterile liquid in Olinvyk vials

Table 1: A brief description and results of oliceridine studies performed prior to FDA approval

Design	Study phase	Patients/dosing	Results
Fixed-dose Bunionectomy Study (multicenter, double-blind, randomized, placebo-controlled study)	2a	Stage A (pilot phase, 141 patients)- placebo, oliceridine 1, 2 , 3, or 4 mg q4h; morphine 4 mg q4h Treatment period: 48 h	Oliceridine produced dose-dependent reductions in pain scores Oliceridine was approximately five times more potent than morphine
		Stage B (primary phase, 192 patients)- placebo, oliceridine 0.5, 1, 2, or 3 mg q3h, morphine 4 mg q4h	Similar analgesic efficacy with oliceridine and morphine statistically significant, regimen- dependent reductions in the incidence of hypoventilation on events, nausea, and vomiting compared with the morphine regimen
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	2b	200 (n=39, 39, 83, and n=39) (loading/ patient-controlled demand doses [mg/mg] in the oliceridine regimen A-1.5/0.10, oliceridine regimen B-1.5/0.35, morphine-4.0/1.0, and placebo groups, respectively)	Effective and rapid analgesia; acceptable safety/ tolerability profile; potentially wider therapeutic window than morphine
Multicenter, various surgeries (ATHENA)	3	768 patients got oliceridine either as PCA regimen, both clinician-administered bolus and PCA, and clinician-administered bolus and PRN "pro re nata," bolus; duration as determined by the need for opioid therapy	Low incidence of opioid-induced respiratory depression observed with oliceridine regardless of age or body mass index
APOLLO 1 trial (analgesia in patients undergoing bunionectomy)	3	389 patients got oliceridine 1.5 mg loading dose and 0.1, 0.35, or 0.5 mg demand doses/compared to morphine	Superior analgesic efficacy to placebo morphine 1 mg>oliceridine 0.1 mg regimen=oliceridine 0.35 mg and 0.5 mg regimens. No clinically meaningful difference in efficacy was observed between the 0.35 and 0.5 mg regimens. Decreased incidence of respiratory safety events lower observed rates of postoperative nausea and vomiting
APOLLO 2 trial (for acute pain in patients following abdominoplasty)	3	401 patients (Oliceridine PCA a loading dose (LD) of 1.5 mg followed by demand doses of either 0.1, 0.35 or 0.5 mg/compared to morphine	

nonopioid analgesic options. These include and are not limited to dexmedetomidine, Non-steroidal anti-inflammatory drugs (NSAIDs), regional blocks, acetaminophen, and gabapentin.

There is increasing concern about the risk of both opioid dependence and abuse even in the setting of postoperative pain relief. Deaths from opioid abuse have become increasingly common. In the USA, in 2017, over 47,000 deaths were recorded due to prescription and nonprescription opioid overdose, and deaths are projected to reach nearly 82,000 by 2025.[11] Concerns have been raised about the dangers of introducing opioids perioperatively to an opioid-naive patient. One study in 2016 found that males and elderly patients (over 50 years of age) with histories of substance abuse had a greater risk of becoming opioid-dependent post-surgery where opioids were introduced.[12] As dependence and abuse seem to be a function of the beta-arrestin mediation, oliceridine might have a specific advantage in this area.

Potential Indications

Intravenous bolus administration during intraoperative period

Strangely, as per the drug insert, oliceridine is currently approved only for moderate-to-severe acute pain in adults. It does not specifically mention specific painful conditions such as dental pain or pain resulting from sprains; however, it is conceivable to be used in such situations. It is not approved for intraoperative use as an analgesic. If it lives up to its potential, it will be an ideal intraoperative analgesic either as a sole opioid or along with other opioid and nonopioid analgesics. Similar to PCA, the use of nonopioid analgesic supplements might reduce oliceridine requirements.

The anesthesia providers and researchers have spent significant time and resources to find ways of reducing opioid requirements during surgery. Multimodal analgesia and opioid-free surgery are some of the approaches that have gained momentum in recent years. By using preoperative measures such as "acetaminophen, pre-incisional bupivacaine skin infiltration, post-excision bupivacaine wound deposition, intraoperative ketorolac, providing instructions to use both acetaminophen and ibuprofen for postoperative analgesia, and finally appropriately counseling to set the expectation that opioids would not be required," Kang *et al*.[13] eliminated the need for postoperative opioids in 99% of the patients undergoing breast-conserving surgery. The main components of multimodal analgesia include some combination of regional anesthesia (including single-shot or continuous central neuraxial or peripheral nerve blocks and/or local infiltration analgesia), opioid analgesics, and nonopioid

systemic analgesics (acetaminophen and nonsteroidal anti-inflammatories).[14]

The benefits of avoiding or limiting opioid administration during intraoperative and immediate postoperative periods are many. The risk of respiratory depression, especially in susceptible patients, is evident. There are many documented cases of death and permanent brain damage as a result of respiratory arrest followed by subsequent cardiac arrest. In a systematic review and meta-analysis aimed to evaluate the risk factors associated with postoperative opioid-induced respiratory depression, Gupta *et al*.[15] noted that patients with postoperative opioid-induced respiratory depression received higher doses of morphine equivalent daily dose.

Certain groups of patients are especially prone to respiratory obstruction in the postoperative period. Subramani *et al*.,[16] reported 43 deaths or near-death events and 12 critical respiratory events, and five other life-threatening events in patients with obstructive sleep apnea undergoing surgery. A majority of these patients received a morphine equivalent daily dose of less than 10 mg. They concluded that morbid obesity, male sex, undiagnosed obstructive sleep apnea, partially treated/untreated OSA, opioids, sedatives, and a lack of monitoring are risk factors for death or near-death events. Nevertheless, the avoidance of opioids might have prevented some of these events. The use of biased agonists such as oliceridine in small doses that are known to produce little or no respiratory depression might have significant advantages in this category of patients.

Both intraoperative and postoperative administration of opioids is prospectively associated with opioid abuse. Euphoria caused even by a single dose of fentanyl is shown to be a strong inducement for future seeking and abuse. Its strong positive reinforcing properties (i.e. euphoria) translate into substantial abuse potential.[17] As a result, there is a definite need for an opioid with absent or limited euphoria properties which might further decrease addiction and abuse. We are not sure if oliceridine is capable of achieving this goal; however, it is a step in the right direction.

Total Intravenous Anesthesia

Currently, short-acting opioids (such as sufentanil and alfentanil) and ultrashort acting (remifentanil) are essential components of total intravenous anesthesia (TIVA). Of these, remifentanil is the most popular. Sufficient evidence has accumulated to be concerned about hyperalgesia both during the surgery and in the postoperative period.[18] Selective activation of the G-protein pathway might be the way to avoid hyperalgesia.

At the doses required to produce immobility (an expectation from surgeons during any procedure), all currently employed opioids in TIVA produce significant respiratory depression. In fact, remifentanil, a popular companion to propofol during TIVA, frequently produces apnea which requires controlled mechanical ventilation. Other opiates such as alfentanil and sufentanil suffer from similar limitations. In addition, at the doses employed, severe hypotension often ensues requiring a continuous infusion of vasopressors such as phenylephrine. Biased μ-opioid receptor agonists might be the way to avoid such respiratory-depressant effects while preserving significant analgesia; however, we are not sure if oliceridine is the appropriate candidate for such a role. The preservation of spontaneous ventilation with a laryngeal mask airway will be achievable, thus, avoiding positive pressure ventilation.

Further, the pharmacokinetics of oliceridine is not ideal for intravenous infusion. A mean steady-state volume of distribution ranging between 90 and 120 L indicates extensive tissue distribution. It is metabolized primarily by CYP3A4 and CYP2D6 P450 hepatic enzymes, with minor contributions from CYP2C9 and CYP2C19 into the inactive metabolites. The result is likely to be a prolonged elimination time. Nevertheless, oliceridine is shown to display concentration-dependent pharmacodynamics with less respiratory depression and hypotension at lower doses. Moreover, the metabolites do not have any appreciable activity at the μ-opioid receptor. Renal impairment does not pose any major risk. However, moderate-to-severe hepatic impairment does. Both the half-life and estimated volume of distribution of oliceridine are significantly higher in patients with moderate or severe hepatic impairment. As a result, dose adjustment is needed in these patients. Finally, caution should be exercised in patients who are either on CYP2D6 inhibitors or receiving such medications in the perioperative period. Plasma clearance of oliceridine is significantly reduced in these patients (approximately 50%). Moreover, 3–10% of Whites, 2–7% of African-Americans, and <2% of Asians, generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers.

These factors are also relevant in patients receiving oliceridine as part of PCA or IV infusion or bolus in PACU and postoperative phase for pain relief.

Labor Analgesia

One of the most promising indications for biased μ-agonists would be labor pain relief. The absence of or minimal respiratory depression is a major advantage that can virtually eliminate the need for labor epidurals. However, oliceridine is unlikely to fill this void, and labor epidurals will be required

in a majority of laboring women looking for meaningful and reliable pain relief. A very small proportion of women become opioid-dependent following cesarean delivery.[19] Currently, there are very few dependable pain relief options in women reluctant to accept epidural analgesia. Among opioids, meperidine (pethidine) is popular. Remifentanil has been used in research settings; however, respiratory depression is a major drawback.[20,21] Case reports of maternal cardiac arrest are reported.[22]

There are no studies exploring the role of oliceridine in labor analgesia or with spinal anesthetics and it is not approved for use in pregnancy or labor. In fact, currently, morphine is the only medication approved by the US FDA for use via the intrathecal route.[23] Yet, one should be cognizant of the fact that fentanyl was never approved by the FDA for spinal use and is still routinely used for cesarean section analgesia via this route. It is quite likely that as experience is gained, clinicians might use oliceridine for labor analgesia via the intravenous route. Lower doses that display beneficial effects in terms of respiratory depression and GI side effects may be employed in combination with Entonox. It is known that the use of Entonox can reduce the need for pethidine (Meperidine), and as a result, the relevant fetal and maternal complications, thus facilitating painless labor.[24] Similar benefits are possible with oliceridine if it is demonstrated to be safe in pregnancy and labor.

GI Endoscopy and Bronchoscopy

A recent review by the authors of this manuscript discussed in detail the potential of oliceridine to revolutionize gastrointestinal (GI) endoscopy sedation.[25] One of the biggest concerns of propofol-induced sedation in GI endoscopy is respiratory depression. Airway difficulties and hypoxia are common causes of cardiac arrest in patients undergoing GI endoscopy with deep sedation.[26,27] Short-acting opioids such as fentanyl are commonly used along with propofol for sedating these patients, especially for advanced endoscopic procedures.[28] the addition of any such opioid increases the risk of apnea and subsequent hypoxia. Oliceridine will be an ideal opioid in GI endoscopy alongside propofol. It can provide analgesia and reduce propofol requirements. However, these assumptions are made based on the pharmacokinetics of both these drugs. The quick onset of action is a clear pharmacodynamic advantage.

The use of anesthesia providers contributes to a major cost increase in GI endoscopy.[29] Avoiding reliance on anesthesia providers necessitates the provision of a similar degree of sedation, yet avoid propofol use. It is possible that the use of oliceridine in combination with remimazolam (a new benzodiazepine approved by the FDA in the last few months) might fill this void in the majority of non-advanced GI endoscopy procedures.[30]

Prescribing Information and Its Clinical Relevance

Regrettably, many of the details in the prescribing information are, at least partly, contrary to the conclusions made in phases 2 and 3 studies and reviews.[7,25,31-33] The label clearly states that "Olinvyk exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death."[34,35] It further mandates clinicians to evaluate each patient for the development of behaviors or conditions suggesting addiction, abuse, and misuse. The label also highlights the possibility of serious, life-threatening, or fatal respiratory depression and requires respiratory monitoring, especially during initiation or following a dose increase. Neonatal opioid withdrawal syndrome is a distinct and present danger in case of prolonged use in pregnant patients. The likelihood of neonatal opioid withdrawal syndrome should be kept in mind. Finally, there are dangers of profound sedation, respiratory depression, coma, and death if Olinvyk is administered along with benzodiazepines or other central nervous system (CNS) depressants.

As a result of these warnings, one can only conclude that Olinvyk is no better than the traditional opioids in any measures of safety. Consequently, the excitement of biased agonism needs to be tempered with an abundance of caution.

Unfortunately, there are additional warnings and precautions. In daily doses exceeding 27 mg, there is a heightened risk of QT prolongation. The perioperative period is inundated with drugs that cause QT prolongation.[36,37] The use of ondansetron is almost ubiquitous. Other drugs used in the perioperative period and capable of causing QT prolongation include diphenhydramine, nicardipine, granisetron, dolasetron, haloperidol, albuterol, salmeterol, famotidine, cocaine, methadone, oxytocin, droperidol, and ephedrine. Adrenal insufficiency is mentioned as a warning and it is not something to be expected with traditional opioids. As a result, administration with etomidate or in patients with sepsis will be an issue.[38,39] In fact, etomidate causes relative adrenal insufficiency in up to 90% of the patients after a single dose. Contrary to hemodynamic stability expected with opioids-dominant anesthesia, severe hypotension is mentioned as a warning and Olinvyk should be avoided in patients with circulatory shock.

Nevertheless, the frequency and severity of many of these warnings and adverse effects will only become apparent

in the months and years to come. It is quite likely that the manufacturers mentioned these rare incidents to gain FDA approval and may be statistical facts which are not clinically relevant. It is also possible that we might encounter adverse events hitherto unreported that might prompt swift withdrawal of the drug from the market altogether.

Conclusions

In this review, we have provided an insight into the emerging world of biased μ-opioid receptor agonists. By selectively acting on the G-protein sub-pathway after the μ-opioid receptor activation, these drugs are likely to reduce and potentially eliminate many adverse effects associated with the traditional opioid agonists such as morphine and fentanyl. Side effects such as respiratory depression, nausea/vomiting, hyperalgesia are common after the traditional opioids and are troubling for both the patients and the care providers. The addiction liability is the result of their euphoric properties and is responsible for abuse causing hundreds of thousands of deaths the world over each year. The unwanted effects of opioids are predominantly the result of beta-arrestin pathway activation. The traditional opioids are not selective and activate both the G-protein and beta-arrestin sub-pathways. By selectively acting on the G-protein pathway (at least at lower doses), oliceridine has an enormous potential to increase the safety of opioids on multiple fronts. However, one stumbling block seems to be the loss of such selectivity at higher doses. These doses are still clinically relevant and required for most indications. In short, the concept of biased opioid agonism is fascinating; the question is if oliceridine can truly deliver on that promise.

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Conflicts of interest
There are no conflicts of interest.

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