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Review Article

# Oliceridine from Pharmacology to Clinical Application

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## ABSTRACT

Pain is a common adverse event after surgery. The utilization of non-opioid analgesia and regional anesthesia techniques has reduced perioperative opioid usage considerably. In patients with uncontrolled pain, however, opioids remain the most frequently used rescue analgesic. It is well known that opioids are associated with risks of adverse events, such as nausea/vomiting, respiratory depression, sedation and addiction. Oliceridine is a novel opioid receptor agonist with dissimilar pharmacodynamics compared to conventional opioids, and is thought to be associated with a more favorable side effect profile. In this review, the authors discuss the pharmacology of oliceridine, the preclinical and clinical evidence for its use, as well as the potential role of oliceridine in the existing framework of perioperative pain management.

**Keywords:** Analgesia; Oliceridine; Opioid; Pain; Postoperative nausea; Vomiting

## INTRODUCTION

The management of postoperative pain represents a challenge for healthcare institutions. While opioid analgesics are frequently used for the management of moderate to severe pain, these medications are not without risks. Opioid related adverse events, such as sedation, respiratory depression and postoperative nausea and vomiting, occur in up to 10% of surgical patients. [1] Opioid use for postoperative pain is also thought to be a contributing factor to the global opioid pandemic. Minimizing the usage of opioid medications has thus become a focus for many healthcare providers. Strategies include the use of regional anesthesia and a multimodal regimen of non-opioid medications, such as NSAIDs, acetaminophen, gabapentinoids, and systemic local anesthetic. While effective, these approaches have not yet eliminated the need for opioids in postoperative pain management. Oliceridine is a novel opioid medication that has been shown to be associated with fewer adverse effects, and may possibly provide a safer opioid alternative for the management of postoperative pain.

## LITERATURE REVIEW

### Pharmacology

Oliceridine is a novel opioid receptor agonist. It is a ligand at the mu opioid receptor, a G protein coupled receptor associated with an inhibitory G protein that consists of Gα, β, and γ subunits. Upon binding to the ligand, the receptor undergoes a conformational change that causes dissociation of GDP from the Gα subunit [2]. The Gα subunit then binds GTP and dissociates from the βγ complex, leading to activation of downstream intracellular pathways and the resultant biological effects of the drug [3]. Mu opioid receptor activation is regulated in part by two known mechanisms, the binding of β-arrestin and Regulators of G protein signaling (RGS) proteins [4,5]. β-arrestin binds to phosphorylated G protein coupled receptors leading to deactivation. RGS protein binding promotes GTP hydrolysis by the Gα subunit, converting Gα-GTP to inactive Gα-GDP with subsequent inactivation of the βγ complex [6]. These regulatory pathways are thought to lead to the development of opioid tolerance, and the β-arrestin pathway may also contribute to opioid related adverse events [7]. One of the key differentiating factors between oliceridine and currently used opioids is that it causes 50% less mu opioid receptor phosphorylation than

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morphine and fentanyl [8]. This may explain the improved side effect profile of oliceridine compared to other commonly used opioids.

Oliceridine has been recently approved by the Food and Drug Administration (FDA) for inpatient use. It is available in intravenous formulation as a fumarate salt dissolved in a preservative free solution [9]. It is poorly soluble in water and highly plasma protein bound with an in vivo volume of distribution of between 90-120 L. It is primarily metabolized by hepatic enzymes cytochrome P450 3A4 and 2D6, and it has no known biologically active metabolites [10]. The half-life is estimated to be between 1.3 and 3 hours [11]. Despite being hepatically metabolized and renally cleared, oliceridine appears to be safe for use in patients with end stage renal disease and hepatic impairment. A recent study showed no significant difference in clearance between healthy volunteers and those with end stage renal disease or hepatic impairment after a single intravenous dose of the drug [12].

## Clinical evidence

Several clinical trials have been performed to determine the analgesic efficacy and safety of oliceridine. One phase II trial by Viscusi compared a standard morphine Patient-Controlled Analgesia (PCA) regimen to various dosing regimens of oliceridine PCA in patients undergoing bunionectomy. Results of the study revealed that dosing with 1 mg oliceridine was equally as efficacious as morphine 4 mg, while dosing with 2 and 3 mg oliceridine proved more efficacious with statistically significantly lower pain scores [13]. Another phase II trial conducted by Singla et al compared three PCA regimens in postoperative abdominoplasty patients: 4 mg loading dose of morphine with 1 mg PCA bolus (4 mg/1 mg), oliceridine 1.5 mg/0.1 mg and oliceridine 1.5 mg/0.35 mg. The primary outcome measure was Time-Weighted Average (TWA) change in pain score. Secondary outcomes were rescue analgesia requirement and pain relief onset. Results showed that all regimens had comparable TWA and rescue analgesia requirement at 24 hours, and the oliceridine 1.5 mg/0.35 mg regimen had significantly shorter pain relief onset [14]. A multicenter clinical trial, the APOLLO-1 trial, was conducted by Viscusi. To compare various PCA regimens of morphine and oliceridine in patients undergoing bunionectomy. The primary outcome was percentage responders: patients who reported 30% improvement in pain with no rescue analgesia requirement. Secondary outcomes were time to analgesic effect and time to rescue analgesia. Results showed that the oliceridine 1.5 mg/ 0.35 mg and 1.5 mg/0.5 mg PCA regimens were similar to the morphine 4 mg/1 mg PCA regimen in terms of percentage responders and requirement of rescue analgesia. The oliceridine PCA 1.5 mg/0.1 mg regimen was less effective. Time to analgesic response was significantly longer for the morphine PCA regimens when compared to all doses of oliceridine PCA [15]. Similar results were found in the APOLLO-2 trial; another multicenter study conducted by Viscusi et al. Various PCA regimens of morphine and oliceridine were compared for management of postoperative pain after abdominoplasty. The oliceridine PCA 1.5 mg/0.35 mg and 1.5 mg/ 0.5 mg regimens were similar to the morphine PCA 4 mg/ 1 mg regimen, while the oliceridine 1.5 mg/ 0.1 mg regimen was less effective [16]. The safety and tolerability of olicerdine was also assessed in the ATHENA trial, a phase 3 multicenter trial that included 768 adult surgical or medical patients experiencing moderate to severe acute pain. Patients were treated with either oliceridine intravenous bolus (1-3 mg every 1-3 hours) or PCA (1.5 mg/0.5 mg) [17]. Findings revealed that oliceridine was both potent and rapid in reducing pain, with a 2.2 point mean reduction in NRS pain score at 30 minutes [17]. Overall, clinical data suggests that oliceridine is efficacious as an analgesic treatment for pain warranting use of parenteral opioids, comparable to morphine in both bolus and PCA regimens. A PCA regimen of 1.5mg loading dose of oliceridine followed by 0.35 mg and 0.5 mg PCA doses was equianalgesic with morphine 4mg/1mg PCA [16]. Further studies should be conducted to confirm these results. Secondary findings from the clinical trials described show oliceridine to be associated with a lower risk of nausea and vomiting compared to morphine. In fact, the use of oliceridine was found to be similar to the use of antiemetic prophylaxis [18]. The use of total intravenous anesthesia with propofol in reducing postoperative nausea and vomiting [19]. Additionally, an exploratory analysis of the data from the APOLLO-1 and APOLLO-2 trials found that patients treated with oliceridine versus those treated with morphine were significantly more likely to achieve "complete GI response," defined as not experiencing vomiting or requiring a rescue antiemetic [20]. Another exploratory analysis of the data from the APOLLO trials confirmed this conclusion, finding that patients receiving oliceridine were significantly less likely to experience vomiting than patients receiving morphine at equianalgesic levels [21]. The risk of adverse respiratory events with oliceridine compared to morphine, however, was variable among studies. The phase II trial by Viscusi. Comparing interval dosing of oliceridine to morphine and placebo in postoperative bunionectomy patients found a statistically lower risk of desaturation in the oliceridine group compared to morphine [13]. Similarly, a second study by Dahan. found that at therapeutic plasma concentrations, there was significantly less respiratory depression in patients treated with oliceridine [22]. The APOLLO-1 and APOLLO-2 trials, however, did not find any statistically significant difference in adverse respiratory events when comparing oliceridine PCA to morphine PCA at equianalgesic doses [15,16]. However, a reanalysis of the data from these two trials performed by Ayad et al. concluded that oliceridine has an improved respiratory safety profile when compared to morphine, with less desaturation ($SpO_2<90\%$) and less respiratory depression ($RR<8$) in patients using oliceridine PCA[23]. The data from another exploratory analysis of the APOLLO trials found no statistical difference in hypoxia events between patients receiving oliceridine and morphine at similar analgesic levels. The analysis showed, however, a lower incidence of sedation in the oliceridine treatment group in the APOLLO-2 study [21]. The ATHENA trial revealed an overall incidence of desaturation to be 5.5 and respiratory depression to be 0.1%, with no patient necessitating treatment with naloxone [17]. The authors subsequently performed a retrospective, observational chart review to compare the incidence of respiratory depression events associated with oliceridine administration to a control group treated with conventional opioids. They found a significantly

lower incidence of opioid-induced respiratory depression in the oliceridine group compared to the control group (8% *vs.* 30%) [24]. A recent exploratory analysis of the ATHENA trial data found that oliceridine use in patients 65 years or older and/or with BMI 30 kg/m2 was not associated with increased risk of respiratory depression [25]. The ATHENA trial also noted an increase in QTc interval on electrocardiogram (EKG) tracings in 22 of the 768 patients (2.9%) treated with oliceridine.

Half of these patients had confounding factors to potentially explain the EKG changes, such as electrolyte abnormalities or use of other drugs known to prolong QTc interval. Of note, none of these patients experienced ventricular arrhythmias [26].

### Preclinical evidence of tolerance, dependence, and hyperalgesia.

Long-term use of conventional opioids is associated with the development of tolerance, dependence, as well as opioid induced hyperalgesia. β-arrestin induced internalization of the opioid is a proposed mechanism for the development of tolerance. Bohn et al. and Raehal et al. studied the effects of morphine on β-arrestin knockout mice and both found that the loss of morphine sensitivity over time was not as significant in the knockout mice [27,28]. Looked at tolerance in morphine and oliceridine and found that the anti-nociceptive efficacy decreased after three days of morphine, but this was not seen with oliceridine [29]. Another study by Liang et al. evaluated the efficacy of morphine and oliceridine after multiple days of consistent administration. This study found that while the efficacy of morphine diminished after four days of regular administration, the analgesic efficacy of oliceridine remained constant[30]. Found that wild-type and β-arrestin knockout mice had no difference in physical symptoms of morphine dependence [28]. In their study, also reported that three days of conditioning with oliceridine resulted in no difference in physical dependence symptoms, but did result in significantly less reward behavior when compared with morphine [30].

Opioid-induced hyperalgesia is a state of nociceptive sensitization caused by chronic exposure to opioids. β-arrestin is thought to play a role in development of allodynia. In an animal model, the β-arrestin inhibitor Barbadin was reported to neutralize the development of allodynia by Aberoumandi [31]. When compared with morphine, oliceridine was associated with significantly less allodynia after four days, as reported [30].

## DISCUSSION

### Role of oliceridine in clinical practice

Pain is a very common adverse event after surgery. Improvements in regional anesthesia, and a concerted effort to apply multimodal, opioid-sparing analgesia has allowed many of today's procedures to be performed with minimal perioperative opioids. Despite these efforts, opioids remain the most common rescue analgesic option for moderate to severe pain. Opioid use is associated with many short and long-term adverse effects including Post-Operative Nausea/Vomiting (PONV), sedation, respiratory depression, misuse, and addiction. Opioid related adverse events responsible for a significant contribution to the potentially avoidable costs to the healthcaresystem. Oliceridine shows promise as a possible opioid analgesic.

with reduced risk of side effects. Current data shows that oliceridine has a lower risk of PONV and possibly a lower risk of respiratory depression. This may make oliceridine preferable to conventional opioids in patients who are at high risk of developing postoperative respiratory complications and in patients/procedures with increased risk of PONV.

While the evidence for oliceridine's use as an opioid analgesic with fewer side effects is promising, the clinical evidence on its use is limited. More studies are needed to fully elucidate the safety and efficacy of oliceridine. Most of the currently available studies are also underpowered to identify any significant differences in rarer adverse events such as respiratory depression. Lastly, most of the currently available evidence is based on healthy patients without histories of chronic opioid use. There are preclinical studies in animals suggesting that biased ligands may reduce the risk of opioid tolerance, however, clinical trials have yet to determine that biased ligands such as oliceridine pose less risk of tolerance [27-33].

## CONCLUSION

Oliceridine is a biased opioid receptor ligand that preferentially activates the G-protein coupled intracellular pathway, while limiting the activation of the β-arrestin pathway. It has shown to have similar efficacy as morphine when administered intravenously as an analgesic, yet is associated with significantly lower risk of PONV. Although more research must be done, there is evidence that oliceridine may be associated with less respiratory depression than conventional opioids and pre-clinical studies suggest that it may also have decreased risk of tolerance, dependence, and hyperalgesia.

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