

Oliceridine - Breakthrough in the Management of Pain

Dhivya Elango, Divyashanthi Chellathambi Malathi, Priyadharsini Raman Palanisamy

Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, (JIPMER), Karaikal, Puducherry, India

Abstract

Oliceridine an intravenous opioid approved in 2020 by the Food and Drug Administration (FDA) to treat moderate-to-severe pain. Oliceridine developed with a novel mechanism that is biased agonism toward G-protein-coupled receptors pathway. Being biased agonist, it does not activate beta arrestin pathway responsible for opioid-related adverse events (ORAE), especially respiratory depression. Because of the novel mechanism, oliceridine has paved a pathway to decrease ORAE. Oliceridine has received breakthrough status by FDA. However, FDA denied oliceridine approval and withdrew breakthrough status by 2019. FDA made this decision because of the inadequacy of the safety data. Abuse potential and QT prolongation studies are conducted as per FDA recommendation in the year 2019; oliceridine was approved for moderate to severe pain in adults. This review will briefly summarize the pharmacological properties and study results of oliceridine in the management of pain. Thorough literature search was done for the efficacy and safety of oliceridine, search was done in electronic database of PubMed and Cochrane from inception till June 2021. Oliceridine was found to be effective in acute severe pain with less ORAE when compared to morphine. Oliceridine has many drawbacks than what is hypothesized earlier, but this approach has opened new options for patients suffering from severe pain. Long-term effect of oliceridine has to be monitored to assess the effects of biased agonism.

Keywords: Beta arrestin, Biased agonist, novel opioid, oliceridine, olivik, opioid-related adverse events

INTRODUCTION

Oliceridine (Olinvyk-Travena Inc., Chesterbrook, Pennsylvania) is a novel intravenous opioid agonist approved for acute severe pain in adults. Oliceridine is a small G protein-coupled receptor-selective agonist at μ opioid receptor (MOR). Opioids are the drug of choice for acute pain associated with surgery, trauma, and cancer. The major drawbacks of opioid medication are the adverse drug reactions and the potential for drug abuse. The most serious adverse drug reactions are respiratory depression and gastrointestinal side effects, which are mediated through the β -arrestin signaling pathway. β -arrestin recruitment is also related to MOR desensitization and internalization, leading to opioid tolerance.^[1,2] To counter the opioids-related adverse reactions, next-generation opioid which selectively produces analgesia with minimal Adverse drug Reactions (ADRs) are developed.^[3] Oliceridine is the first drug to be approved with biased agonism at MOR. This review will briefly summarize the pharmacological properties and study results of oliceridine in the management of pain.

METHODS

Oliceridine (Chemical name: 3-methoxythiophen-2-yl)methyl-2-[(9R)-9-pyridin-2-yl-6-oxaspiro [4.5] decan-9-yl] (3) ethanamine) is used for the treatment of moderate-to-severe acute pain in adults. A molecule preferentially activates one of the several signaling pathway” is known as biased agonism/functional dissociation/stimulus trafficking.^[4] Ligands that act through G-protein-coupled receptors (GPCR) can interact with a different type of G protein as well as other signaling pathways such as arrestin. By restricting the interaction with other signaling pathways, more selective/biased ligands are produced so that ADRS can be minimized. The above principle is utilized in the development of oliceridine. Oliceridine activates more

Address for correspondence: Dhivya Elango,

Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, (JIPMER), Karaikal, Puducherry - 609 602, India.

E-mail: dhivya.tvmc2008@gmail.com

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selectively GPCR pathway with less activation of the β arrestin pathway.^[5]

Thorough literature search was done for the efficacy, safety, and Food and Drug Administration (FDA) recommendations of oliceridine, search was done in electronic database of PubMed and Cochrane from inception till June 2021. Keywords used for searching are “Oliceridine,” “Olinvyk,” “biased agonist” AND “efficacy,” “safety,” “Pharmacokinetics,” “clinical trials.”

PRECLINICAL STUDIES

Beta1 arrestin knockout mice have shown less opioid-mediated adverse reactions, mainly respiratory depression and gastrointestinal effects, when treated with morphine.^[1,2] This discovery generated a hypothesis that anti-nociception and adverse drug reactions of opioids are mediated through the G protein and β arrestin pathway, respectively. Hence, the journey of the development of biased agonist like TRV 130 has started with a hope to produce potent analgesic agents without opioid-related ADRs.

Altarifi *et al.* tested TRV 130 (oliceridine) for tolerance to anti-nociceptive property, constipation, and abuse potential in, *in vitro* and *in vivo* experiments with rodents. The study revealed that anti-nociception through biased agonism does not show tolerance on single repeated administration of TRV 130. Gastrointestinal motility inhibition tested through fecal output measurement and colonic propulsion method in mice and abuse potential tested through intracranial self-stimulation procedure in rats showed similar results for morphine and oliceridine. This study supports the theory that opioid-induced tolerance can be mediated through the β arrestin pathway however, constipation and abuse liability are mediated through G protein agonism.^[6]

Another study was done by Liang *et al.* in the tibial fracture/ postsurgical model also revealed that oliceridine has a potent analgesic property with no tolerance and less hyperalgesia. However, this study also revealed that oliceridine has a dependence property. Oliceridine showed four-fold rise in analgesic activity in rat tail-flick assay in comparison with morphine. Conditioned place preference (CPP) in rodents used in this study to test the drug's rewarding property. At 10 mg/kg dose, oliceridine produced the same CPP as to that of morphine (5 mg/kg dose).^[7]

As per FDA guidance, Travena conducted a thorough QT prolongation study in animals as well as in healthy volunteers.

Nonclinical study was conducted using eight cynomolgus monkeys. Oliceridine was administered as IV infusion at the dose of 0.05 mg, 0.2 mg, and 1 mg/kg/h for 10 h. Animals were monitored for electrocardiography (ECG) changes and arrhythmias. The no observed adverse effect level dose for oliceridine was 0.2 mg/kg/h, which gives the plasma concentration of 143 ng/mL. The values are 2.3 times higher than the median human plasma concentration (61 ng/mL).^[8]

Another biased agonist, PZM21 is found through structure-based discovery, showed more potent activation of the G_i pathway with very minimal recruitment of β arrestin. It showed potent analgesia similar to morphine but devoid of respiratory depression.^[9] However, it has produced tolerance and augmented the rewarding effect by morphine in contrast to oliceridine. A recent study stated that the reduced side effect profile of biased agonists is due to lower intrinsic efficacy.^[10,11]

Preclinical studies conducted so far showed that beta arrestin recruitment is very low for oliceridine. However, GI side effects such as constipation and abuse liability are also mediated by G protein agonism. Thus, oliceridine can be an analgesic agent with possible ADRs of constipation, abuse liability similar to morphine. It did not cause QT prolongation in the cynomolgus monkey model but produced QT prolongation in some animal models.^[12] We need to go a long way to understand the biased activity of oliceridine completely.

PHASE 1 CLINICAL TRIAL

A single site Phase 1 trial was conducted in 74 healthy males to assess the pharmacokinetic and pharmacodynamic properties of oliceridine (TRV130). Single ascending doses of 0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg. were given to the study subjects as an intravenous infusion for 1 h in this study. Half-life is calculated as 1.6–2.7 h, and clearance is 34.0 L/h when given as IV infusion over 1 min to an hour. TRV130 is metabolized by CYP2D6 and CYP3A4 enzymes in, *in vitro* studies. As part of the study, C_{max} and area under curve of TRV 130 was assessed in CYP2D6 poor metabolizers. The results further supported that TRV130 is metabolized by CYP2D6 enzyme.

CNS effect of TRV130 was evaluated by measuring pupillary diameter. TRV130 produced dose-dependent miosis in the study subjects. Dose response curve was similar to that of morphine, so TRV 130 can also be given as a bolus or IV infusion.

Safety: One of the participants developed a vasovagal attack, considered as a serious adverse event and discontinued from the study. Another participant developed an increase in lipase, amylase and bilirubin levels but returned to normal range within the same day. Other observed ADRs are nausea, vomiting, dizziness, feeling relaxed, and somnolence at higher doses. These side effects are dose-related and none were off-target side effects.^[13]

Oliceridine in hepatic and renal impairment patients

Pharmacokinetic study was conducted in nine end-stage renal disease patients (ESRD) who were on hemodialysis and compared with eight healthy male controls. All the routine medicines were withheld 2 h before and after dosing. Oliceridine 0.5 mg was given as a single intravenous infusion over 2 min. Controls received 1 mg of oliceridine intravenous infusion over 2 min. Blood samples were collected in the appropriate interval and totally 15 samples were collected over 36 h. Oliceridine is metabolized in the liver by CYP 2D6

and CYP 3A4 and produces inactive metabolite TRV0109662. As part of the study, PK and safety analysis was done in mild, moderate, and severe hepatic impairment patients with the same dose of oliceridine used in ESRD patients. Blood samples were collected over 46 h and compared with healthy volunteers.

Oliceridine clearance (ESRD 49.2 L/h vs. Controls 55.3 L/h) and other PK parameters were not altered significantly in ESRD patients. Therefore, dose adjustment of oliceridine is not required in renal impairment patients in contrast to morphine. In the severe hepatic impairment group, dose-normalized C_{max} was significantly higher than healthy individuals. Half-life and volume of distribution were increased according to the severity of hepatic impairment. Half-life and volume of distribution of oliceridine in the severe hepatic impairment group was 6.3 h and 370.4 L when compared to 2.1 h and 129.3 L in healthy controls, respectively. Initial dose reduction will be required in hepatic impairment patients.^[14]

Thorough QT studies in humans

A randomized cross-over tQT study was conducted in 58 healthy adults. The effect of oliceridine on ECG was studied in comparison with placebo and moxifloxacin (300 mg). All the drugs are administered as a single IV bolus. Oliceridine was administered in therapeutic (3 mg over 5 min) and supratherapeutic doses (6 mg over 5 min) and patients were observed for 24 h. At 3 mg, no patient showed changes in ECG; at 6 mg one patient showed a transient increase in QT interval. Both the groups of oliceridine showed an increase in heart rate in the initial 5 min, which is resolved within 15 min of postdose. Clinically relevant changes in QT or PRS complex were not present in both oliceridine groups.^[15,16]

PHASE 2 CLINICAL TRIALS

Phase IIb single-centered study was conducted to evaluate the safety and efficacy of oliceridine in comparison with morphine and placebo in moderate to severe postoperative pain in patients who underwent an abdominoplasty. Patients were randomized to receive morphine, oliceridine, or placebo through patient-controlled analgesia. The pain was analyzed using Numeric Pain Rating Scale with 11 points at following time interval 0, 5, 10, 15, 30, and 45 min and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 18, 20, and 24 h following the oliceridine first dose.

Oliceridine was used in two different regimens, regime A 1.5/0.10, regime B 1.5/0.35, and for morphine 4/1 (loading dose/PCA demand dose in mg). Reduction in pain was statistically significant with placebo and equal to that of morphine for both regimes. When compared to placebo, oliceridine regimes A and B reduced pain by 2.3 and 2.1 points, respectively.

The most common adverse effects were nausea, vomiting, headache, and dizziness among the oliceridine and morphine groups. The morphine group had significantly high number of treatment-emergent adverse events when compared to

the oliceridine group. However, there was no difference in the incidence of common TEAE between two regimens of oliceridine.

Sedation (5%), hypotension (5%), and hypoventilation (31%) incidence was high among regime B and patients in regime A did not report sedation or hypotension. Three patients in regime A developed respiratory depression and one withdrew from the study. Nine patients in the morphine group developed respiratory depression and two withdrew from the study. Five patients discontinued from the study due to lack of therapeutic effect in the oliceridine regime A and B group.^[17]

Another Phase 2 study was conducted in post bunionectomy patients with moderate-to-severe acute pain to assess efficacy and tolerability of oliceridine (1, 2, 3 mg tid) in comparison with morphine (4 mg qid) and placebo. Efficacy was found to be equal to that of morphine in reducing pain intensity assessed by numeric rating scale (NRS) score over 48 h, oliceridine 3 mg produced meaningful pain relief that is subjective pain relief significantly than morphine. The most common ADRs seen in all groups are nausea, vomiting, headache, somnolence, and constipation. Respiratory depression is not reported in any of the groups. Overall severe ADRs are high in the oliceridine 3 mg group, 25.8% versus 12.8% in the morphine group. Four patients discontinued in the oliceridine group due to hypotension and one patient due to tachycardia.^[18]

PHASE 3 CLINICAL TRIALS

Apollo I

Is a multicenter Phase III randomized controlled trial comparing oliceridine, placebo, and morphine (active control) in postoperative bunionectomy patients for moderate to severe pain. Totally, 389 patients have participated in the study. Drugs are given through patient-controlled analgesia, morphine 4/1 mg and oliceridine 1.5 mg/0.1, 0.35, 0.5 mg as loading/demand dose. Drug interval was 10 min after loading dose and lockout interval was 6 min. The maximum allowed oliceridine dose was 60 mg in 12 h after that, patients were managed with conventional protocols. Oral etodolac was kept as rescue medication.

The major primary endpoint was a composite outcome including, a time-weighted (sum of pain intensity difference-48) from baseline should improve by at least 30% at 24 h, no use of rescue medication, should not reach study medication dosing limit and should not discontinue study medication early for any reason. Respiratory safety burden (RSB) is kept as a secondary outcome. In the oliceridine (0.1, 0.35, 0.5 mg) and morphine (1 mg) group, 8, 4, 11, and 12 patients discontinued the study. Results showed oliceridine was superior in efficacy when compared to placebo. They did not conduct a noninferiority analysis between morphine and oliceridine. However, responders at 48 h in the morphine 1 mg and oliceridine groups 0.5 mg, 0.35 mg, 0.1 mg are, 71.7%, 65.8%, 62%, and 50% respectively.

RSB comprises, oxygen saturation <90%, respiratory rate $\leq$ eight, and sedation assessed by Moline-Roberts Pharmacologic Sedation Scale was the key safety outcome in this trial. However, the oliceridine regime failed to show any statistical difference from morphine-induced RSB. The events were similar across the oliceridine and morphine groups. Sedation was reported higher in the oliceridine 0.35 mg group (16 in 0.35 mg group vs. 15 in morphine 1 mg group). Gastro side effects were increased in the oliceridine group in dose-dependent manner, 0.1 mg-40.8%, 0.35 mg-59.5%, 0.5 mg-70.9% and in morphine 1 mg group-72.4%. Common ADRs are nausea, vomiting, constipation, sedation, and dry mouth similar to both oliceridine and morphine groups. Death was not reported in any of the groups.^[19]

Apollo II

Phase III study investigating oliceridine in post abdominoplasty patients with moderate-to-severe pain in comparison with placebo and morphine. Doses and administration of morphine and oliceridine were the same as APOLLO I trial. The primary endpoint was percentage response to study medication in 24 h period, and response was defined as given in APOLLO I trial and the secondary outcome was RSB in hours.

Proportion of responders in the oliceridine group (0.1 mg-61%, 0.35 mg – 76.3%, 0.5 mg-70%) was significantly higher than placebo, comparison with morphine (1 mg-78.3%) was not done. RSB increased in oliceridine group in dose-dependent manner. RSB in oliceridine 0.35 and 0.5 mg was not statistically different from morphine 1 mg group.

No death was reported in trial; however, five serious adverse events were reported. One from the morphine group (respiratory failure and pulmonary embolism) and 4 from the oliceridine group, namely postprocedural hemorrhage, syncope, lethargy (0.5 mg group) and abdominal wall hematoma (0.35 mg group). Except syncope and lethargy, all other SAEs are declared not directly related to the treatment.

Common ADRs are nausea, vomiting, headache, and hypoxia, which were similar across morphine and oliceridine groups.^[20]

ATHENA

Phase III, multi-centric, open-label study was done in moderate to severe acute pain in real-world surgical and nonsurgical patients. Among 1038 patients, 768 patients were enrolled in the study with a pain score of ≥ 4 according to the pain NRS. The major percentage of patients had postsurgical pain (90%).

Oliceridine was administered either as an intravenous bolus dose 55% (loading dose 1–2 mg followed by 1–3 mg every 1–3 h as-needed dose) or through patient-controlled analgesia 45% (loading dose 1.5 mg, subsequent dose 0.5 mg with lockout interval 6 min). The use of other oral or parenteral opioids during the study was not allowed.

Effectiveness was analyzed by the mean change in the baseline NRS scale (6.3 ± 2.1) after the first dose of oliceridine. The

mean change was -2.2 ± 2.3 at 30 min after the first dose and -3.1 ± 3.1 at the end of the treatment.

Common ADRs noted were nausea, vomiting, and constipation and their incidence were dose-dependent. SAE was reported in 26 patients. Among them, three were considered possibly related to oliceridine therapy namely postoperative ileus, respiratory depression, hepatic and renal failure. QT prolongation is not reported during any of the Phase III trials. Authors have mentioned that these SAEs can be due to surgical complications also. ADRs were higher in obese patients 61% when compared to the overall population 64%.^[21]

FOOD AND DRUG ADMINISTRATION APPROVAL

Oliceridine has received breakthrough status by FDA. However, FDA denied oliceridine approval and withdrew breakthrough status by 2019. This decision was made because of the inadequacy of the safety data.^[22]

Intravenous injection of oliceridine (olinvyk) is approved by FDA in August 7, 2020, for moderate to severe acute pain in adults in controlled settings. Oliceridine is the first opioid agonist approved with a novel mechanism-biased agonist.^[23]

PHARMACOKINETICS OF OLICERIDINE

Oliceridine has a very poor oral bioavailability (5.7%). The half-life of oliceridine was 1.5–3 h when administered intravenously. Oliceridine is 77% plasma protein bound.

Metabolism and excretion

Oliceridine is metabolized primarily in the liver by oxidation and glucuronidation. It has produced two inactive metabolites, M22 and M23. Metabolites are excreted majorly in urine (70%) and some in feces (18%). In contrast to morphine, oliceridine produces inactive metabolites. *In vitro* studies showed that oliceridine is a substrate for both CYP2D6 and 3A4, so drug interactions will be common. The half-life of oliceridine is more in CYP3A4 poor metabolizers.

Dose adjustment is not required in mild-to-moderate hepatic impairment and renal impairment. However, the initial dose should be reduced in severe hepatic impairment as well as the frequency of administration should be reduced in mild to moderate hepatic impairment.^[24]

Abuse liability

A double-blind, randomized cross-over study was conducted in 60 nondependent opioid users in comparison with morphine. The main objective of the study was to assess the abuse potential of oliceridine among opioid users. Abuse liability assessed using overall drug liking scores and drug liking scores after administering intravenous morphine (10,20 mg) or oliceridine (1, 2, 4 mg) for 1 min. Results showed that oliceridine 2 mg had similar effects as morphine 10 mg and oliceridine 4 mg had similar effects as morphine 20 mg; mean drug liking scores were less for oliceridine. Oliceridine is included in Schedule II drug along with other opioids.^[24]

ADMINISTRATION AND DOSING SCHEDULE

Oliceridine can be administered as intravenous injection or through patient-controlled analgesia. Individualizing the oliceridine according to the patient's need will yield optimal effect. According to the trial result, the initial dose of oliceridine is 1–2 mg, the onset of action is 5 min, maintenance dose 1–2 mg every 1–3 h as needed dose. The maximum allowable daily dose of oliceridine is 40 mg. The first maintenance dose can be administered as early as 10 min. For PCA, the demand dose is 0.1–0.35 mg.

ADVERSE DRUG REACTIONS

The most common ADRs reported during clinical trials are,

- Nausea, vomiting, constipation
- Sedation, drowsiness
- Headache
- Hypoxia, respiratory depression
- Elevated liver enzymes

However, authors have stated that these ADRs are dose dependent and have low incidence when compared to morphine.

CONCLUSION

Oliceridine is the first in class to get approved as a biased agonist for opioid receptors. Oliceridine was found to be effective in acute severe pain with less (opioid-related adverse events [ORAE]). However, oliceridine does produce adverse reactions similar to morphine. Respiratory events are reported for oliceridine. This may be because respiratory depression is partially mediated by GPCR signaling pathway. Oliceridine is categorized as Schedule II drug because of the drug abuse potential. Oliceridine has many drawbacks than what is hypothesized earlier, but this approach has opened new options for patients suffering from severe pain. Long-term effect of oliceridine has to be monitored to assess the effects of biased agonism.

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Conflicts of interest

There are no conflicts of interest.

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