Drug Monograph

Brand Name: Olinvyk

Generic Name: oliceridine

Manufacturer: Trevena

Drug Class: Analgesic / Central Nervous System Agent

Uses:

Labeled: Indicated for use in adults for the management of acute pain; severe enough to require an intravenous opioid and for whom alternative treatments are inadequate
Unlabeled: No unlabeled uses reported

Mechanism of Action:

Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The full mechanism of oliceridine is unknown, however, CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effect of this drug.

Pharmacokinetics:

Absorption:

T_{max}	Not reported
V_d	90 – 126 L
$t_{1/2}$	2.1 hours
Clearance	Metabolic
Protein binding	77%
Bioavailability	Not reported

Metabolism: Major route of metabolism for olinvyk is primarily by the liver. The main contributing CYP 450 enzymes include CYP3A4 and CYP2D6, but also involvement from CYP2C9 and CYP2C19 have been noted.

Elimination: Major routes of excretion for olinvyk include renal and feces. 70% or metabolites are eliminated changed in the urine and between 0.97 to 6.75% remain unchanged eliminated in the urine. 30% is found eliminated changed through the feces.

Efficacy:

Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, Singla N. Apollo-1: a randomized placebo and active-controlled phase III study investigating oliceridine (trv130), a g protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. *Journal of pain research*. 2019;12:927-943.

Study Design: Phase III, randomized, double-blind, placebo- and active-controlled study

Description of Study: *Methods:* 418 patients were randomized to receive either the study drug oliceridine at 3 different doses (0.1 mg, 0.35 mg, 0.5 mg), the active-control morphine, or placebo in patients undergoing surgery. Treatment duration lasted 48-hours where a clinician-administered fixed IV loading dose of either oliceridine 1.5 mg, morphine 4 mg, or volume matched placebo, followed by demand doses administered PRN via a patient-controlled analgesia (PCA) device. PCA doses were allowed from 10 minutes after loading dose and were limited by a 6-minute lockout interval. *Outcome Results:* 90.6% of patients receiving oliceridine completed treatment, compared to 63.3% of those receiving placebo, and 84.2% of those receiving morphine. Patients in the oliceridine group had a significant response in pain control compared to those receiving placebo; p-value <0.0001. Oliceridine 0.35 mg and 0. 5 mg regimens were non-inferior to morphine. Those in the oliceridine and morphine groups reported similar time of 6 minutes to perceptible pain relief and 12 minutes compared to 30 minutes in meaningful pain relief respectively. There was no significant difference with the composite outcome measure of respiratory safety burden (RSB) for any of the oliceridine group compared to morphine. Patients experiencing one or more gastrointestinal-related AEs, increased in a dose-dependent manner across all three oliceridine regimens compared to placebo, but the use of rescue antiemetic was significantly lower in all oliceridine regimens compared to morphine.

Limitations: This study was sponsored by Trevena Inc., the manufacture of oliceridine. Four authors of the study were full-time employers and stockholders of Trevena Inc. at the time the research was conducted, which may introduce a potential conflict of interest. Baseline characteristics were similar expect for mostly females being randomized to each group (>80%). Study duration was rather short and only focused on one specific surgery for post-op pain management.

Conclusion: The study showed that oliceridine has significant pain management response in post-op patients when compared to placebo and also non-inferior to morphine. It did not show that oliceridine had any significant difference in the composite of RSB compared to morphine. Although the study did show that dose of oliceridine 0.1 mg and 0.35 mg had significantly lower risk of experiencing a respiratory safety event compared to morphine. This supports the effectiveness of oliceridine in post-op pain management as well as the possible benefit of reduced adverse event associated with opioid analgesics. However, more studies will be needed in order to determine how the adverse events of oliceridine compare to other opioid analgesics used in the post-op setting and how well oliceridine can manage other situations in which an analgesic may be warranted.

Singla NK, Skobieranda F, Soergel DG, et al. Apollo-2: a randomized, placebo and active-controlled phase iii study investigating oliceridine (trv130), a g protein-biased ligand at the μ-opioid receptor, for management of moderate to severe acute pain following abdominoplasty. *Pain practice*. 2019;19(7):715-731.

Study design: Phase III, multicentered, randomized, double-blind, placebo- and active-controlled study

Description of Study: *Methods:* 407 patients who were undergoing an abdominoplasty procedure were randomized to receive either the study drug oliceridine at doses of 0.1 mg, 0.35 mg, or 0.5 mg, active-control morphine, or placebo, but only 401 patients were treated with the study medications. Treatment duration lasted for 24 hours where a clinician administered IV fixed loading dose of either oliceridine 1.5 mg, morphine 4 mg, or volume matched placebo, followed by demand dose administered via a patient-controlled analgesia (PCA) device. PCA doses were allowed from 10 minutes after the loading dose and limited by a 6-minuted lockout interval. *Outcome results*: Treatment responders at the 24-hour pain numeric rating scale (NRS) assessment were significantly higher in all oliceridine patients compared to placebo; p-value = 0.029, p-value <0.0001, p-value = 0.0004 for oliceridine 0.1, 0.35, and 0.5 mg respectively. The 0.35 mg and 0.5 mg groups were also non-inferior to morphine. Outcome of RSB showed a dose-dependent increase across oliceridine regimens, but all being not statistically different from placebo. There was no significant difference in outcome of RSB for the higher demand doses of oliceridine 0.35 and 0.5 mg compared to morphine. Proportion of early responders over the first hour of treatment was greater in the oliceridine groups dosed at 0.35 mg and 0.5 mg at 10 and 15 minutes than for morphine. Serious adverse events were reported in 5 patients from the oliceridine group and 1 patient from the morphine group. Patients experiencing at least 1 adverse event increased in a dose-dependent manner for oliceridine 0.1, 0.35, and 0.5 mg dose regimens (89.6%, 93.7%, and 95% respectively) and occurred with 97.6% of patients receiving morphine.

Limitations: This study was sponsored by Trevena Inc., the manufacture of oliceridine, and also played a role in the design, conduct, analysis of data, and decision to publish the study. Five authors of the study were full-time employers and stockholders of Trevena Inc. at the time the research was conducted, which may introduce a potential conflict of interest. This study also enrolled patients that would need post-op pain management after one certain surgical procedure. Of the patients enrolled to the study, greater than 97% were female, limiting the generalizability of the findings to males. It only looked at the efficacy of oliceridine for the first 24 hours of treatment.

Conclusion: The study showed that oliceridine has significant pain management response in post-op patients when compared to placebo and is non-inferior to morphine over the first 24-hours of treatment. The study also demonstrated that oliceridine may be associated with a lower incidence of AEs when compared to morphine as an opioid analgesic. However, further studies that include a larger sample size and a more equal representation of genders is still needed in order to test the generalizability of oliceridine findings in this study to the entire population of post-op pain management patients.

Bergese SD, Brzezinski M, Hammer GB, et al. Athena: a phase 3, open-label study of the safety and effectiveness of oliceridine (trv130), a g-protein selective agonist at the μ-opioid receptor, in patients with moderate to severe acute pain requiring parenteral opioid therapy. *Journal of pain research*. 2019;12:3113-3126.

Study design: Phase III, multicenter, open-label clinical study

Description of Study: *Methods:* 1038 patients were enrolled in the ATHENA study, of which 768 patients were treated with the study drug oliceridine and were included in the safety and efficacy analysis population. Enrolled patients were treated with IV oliceridine via clinician-administered bolus dosing and/or patient-controlled analgesia (PCA). IV bolus dosing was a loading dose of 1 to 2 mg and a supplemental dose of 1 mg was given within 15 minutes if needed. Subsequent doses of 1 to 3 mg could be administered as needed every 1 to 3 hours. For the PCA dosing, a loading dose of 1.5 mg and then a demand dose of 0.5 mg were administered using a 6-minute lockout interval. The safety and tolerability of oliceridine were assessed by incidence of observed or self-reported AEs. The analgesic efficacy of oliceridine was assessed by use of change from baseline in the 11-point NRS for pain intensity. *Outcome results*: During this study 64% of patients reported at least one AE, most of which were mild (37%) or moderate (25%) intensity. The most frequent AEs reported were nausea (31%), constipation (11%), and vomiting (10%). Serious adverse events were observed in 26 (3%) patients but were stated to be mostly due to complications of surgery, underlying medical conditions, or opioid therapy. The mean NRS pain score at baseline was 6.3 +/- 2.1, with a mean change in baseline NRS pain score of -2.2 +/-2.3 at 30 minutes after the first dose.

Limitations: This study was sponsored by Trevena Inc., the manufacture of oliceridine. Seven authors of this study received research grant funding for the ATHENA study and have served as a consultant for Trevena Inc., which may introduce a potential conflict of interest. Patients may have received other analgesics at different points before or during the study including local anesthetics, NSAIDs, and oral opioids. All of which may have had effects on the outcomes of this study other than the study drug oliceridine. The study was not randomized, placebo-controlled, or double-blinded. Baseline characteristics of those enrolled favored females, and also significantly favored those aged less then 65 years old and Caucasian.

Conclusions: This study assessed the safety of oliceridine in a large group of adult patients experiencing moderate to severe pain following surgical procedures or non-surgical medical conditions. Since this was an open-label non-controlled study, no comparisons can be made with other treatment options. A large, powered, randomized, controlled study which enrolls patients with various pain ratings of moderate to severe, where use of concomitant medications is prohibited, is needed to truly assess the safety and efficacy of oliceridine.

Contraindications:

Olinvyk is contraindicated in use with asthma in an unmonitored setting or when in absence of resuscitative equipment, when a known hypersensitivity to oliceridine is indicated, with a known or suspected gastrointestinal obstruction including paralytic ileus, and with significant respiratory depression

Precautions:

Addiction: Addiction may occur at usual dosage and when appropriately prescribed. An increased risk is associated in patients with a personal history of substance use disorders. Counseling about risks and proper use and close monitoring is required.

Administration: Patient-controlled analgesia has resulted in adverse outcomes and cases of respiratory depression. Close patient monitoring is required.

Cardiovascular: QT prolongation may occur; Avoid total daily doses greater than 27 mg. Severe hypotension and orthostatic hypotension in ambulatory patients; Monitoring is recommended. May cause vasodilation that can further reduce cardiac output and blood pressure in patients with circulatory shock; Use should be avoided in this case.

Concomitant use: Avoid use of mixed agonist like pentazocine, nalbuphine, and butorphanol as well as partial agonist like buprenorphine as they can reduce analgesic effect and precipitate withdrawal.

Endocrine and metabolic: Adrenal insufficiency has been reported with opioid use usually with treatment duration longer than 1 month.

Gastrointestinal: May cause spasm within the sphincter of Oddi. May also cause elevations in serum amylase causing worsening symptoms in patients with biliary tract diseases.

Neurologic: Avoid use in patients with impaired consciousness or coma. Seizure frequency may increase in patients with seizure disorders. Respiratory drive may be reduced causing increased carbon dioxide retention that can also increase intracranial pressure; monitoring is required.

Respiratory: Carbon dioxide retention due to respiratory depression. Increased risk in elderly, cachetic or debilitated, and COPD patients. May cause dose-dependent sleep-related breathing disorders including sleep apnea and sleep-related hypoxemia; a dose reduction may be warranted.

Special population: Patients with decreased CYP2D6 function may experience increased plasma concentrations of oliceridine that can cause adverse reactions or exacerbate respiratory depression.

Withdrawal: Rapid tapering in those physically dependent to opioids may lead to withdrawal syndrome; a gradual taper in dosage is required and avoidance of abruptly discontinuing the dose.

Adverse effects:

Cardiovascular:

- Hypotension 1-5%
- Prolonged QT interval
- Tachycardia 1-5%

Dermatologic
- Injection site extravasation 1-5%
- Itching 4-17%
- Flushing 1-5%

Endocrine/Metabolic
- Hypokalemia 1-5%
- Hypomagnesemia 1-5%

Gastrointestinal
- Constipation 10-17%
- Nausea 29-75%
- Vomiting 9-43%

Hematologic
- Anemia 1-5%

Musculoskeletal
- Backache 6-13%

Neurologic
- Dizziness 9-35%
- Headache 4-26%
- Sedated 4-14%
- Somnolence 19%
- Fever 1-5%

Respiratory
- Hypoxia 5-20%

Drug interactions:

Inhibitors of CYP2D6 – Paroxetine, fluoxetine, quinidine, and bupropion
- Can cause an increase in the plasma concentration of oliceridine resulting in increased or prolonged opioid effects

Inhibitors of CYP3A4 – Macrolides, azole-antifungals, and protease inhibitors
- Can cause an increase in plasma concentration of oliceridine resulting in an increased or prolonged opioid adverse reaction

Inducers of CYP3A4 – Rifampin, carbamazepine and phenytoin
- Can decrease the plasma concentration of oliceridine resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oliceridine

Benzodiazepines and other Central Nervous System Depressants
- Increases the risk of hypotension, respiratory depression, profound sedation, coma, and death

Serotonergic drugs – SSRI's, SNRI's, TCA's, triptans, 5-HT_3 receptor agonist, mirtazapine, trazodone, tramadol, cyclobenzaprine, metaxalone, and MAO inhibitors

Concomitant use of these drugs with oliceridine has resulted in serotonin syndrome

Muscle Relaxants

May enhance neuromuscular blocking agents and produce an increased degree of respiratory depression

Diuretics

Can reduce of the efficacy of diuretics by inducing the release of antidiuretic hormone

Anticholinergics

May increase risk of urinary retention and/or severe constipation which may lead to paralytic ileus

Dosing/Administration:

Adult dosing:

Initial dosage starts at 1.5 mg IV administered by a healthcare provider and then may be followed with supplemental doses of 0.75 mg IV administered by healthcare provider starting 1 hour after initial dose and continued hourly after if needed. Additionally if PCA is desired, a loading dose of 1.5 mg IV can be followed by PCA demand dose of 0.35 mg with a 6-minute lockout. A demand dose of 0.5 mg can be considered. The maximum single dose is 3 mg, and the maximum total daily dose is 27 mg. An initial 1 mg dose of oliceridine is approximately equipotent to morphine 5mg. Taper the dose gradually in patients who have been taking opioids regularly and may be physically dependent. Do not discontinue abruptly in physically dependent patients. If signs or symptoms of withdrawal occur during the taper, raise the dose to previous level and taper more slowly.

Geriatric dose:

Use caution when selecting a dosage for an elderly patient, start at the low end of the dosing range and reflect the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Pediatric dose:

Safety and effectiveness of oliceridine in pediatric patients has not been established

Renal impairment dose:

No dose adjustment necessary

Hepatic impairment dose:

Mild to moderate hepatic impairment require no dose adjustment but less frequent dosing may be considered. With severe hepatic impairment consider reducing the initial dose and administer subsequent doses only after a careful review of the patient's severity of pain and overall clinical status.

Use in special circumstances:

With known or suspected CYP2D6 poor metabolizers consider less frequent dosing and monitor patient closely. Fetal and infant risk cannot be ruled out for pregnant and breast-feeding mothers.

Conclusion:

Oliceridine appears to have promise as use as an alternative option for moderate to severe post-operative pain. There is some evidence that oliceridine is better tolerated regarding respiratory and GI adverse effects compared to morphine, but additional research is needed to confirm this benefit. There is limited information for the efficacy of oliceridine for pain management after surgeries other than bunionectomy and abdominoplasty and how much of a reduced adverse event profile it has when compared to opioids other then morphine. Large scale, randomized, blinded studies of oliceridine compared to other opioid analgesics need to be completed in the future in order to establish the place in therapy of oliceridine compared to other opioids when used for pain control. In addition, use of oliceridine to treat non-surgical acute pain has not been evaluated in clinical trials.

References:

1. Oliceridine. In: DRUGDEX System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 1, 2021.
2. Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, Singla N. Apollo-1: a randomized placebo and active-controlled phase iii study investigating oliceridine (trv130), a g protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. *Journal of pain research*. 2019;12:927-943. INSERT-MISSING-URL. Accessed April 2, 2021.
3. Singla NK, Skobieranda F, Soergel DG, et al. Apollo-2: a randomized, placebo and active-controlled phase iii study investigating oliceridine (trv130), a g protein-biased ligand at the μ-opioid receptor, for management of moderate to severe acute pain following abdominoplasty. *Pain practice*. 2019;19(7):715-731. doi:10.1111/papr.12801
4. Bergese SD, Brzezinski M, Hammer GB, et al. Athena: a phase 3, open-label study of the safety and effectiveness of oliceridine (trv130), a g-protein selective agonist at the μ-opioid receptor, in patients with moderate to severe acute pain requiring parenteral opioid therapy. *Journal of pain research*. 2019;12:3113-3126. INSERT-MISSING-URL. Accessed April 2, 2021

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