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Oliceridine as a Novel Selective mu-receptor G-protein Pathway Modulator: A Narrative review

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ABSTRACT

Objective: To review the literature on equianalgesic efficacy and better safety(less respiratory depression and gastrointestinal dysfunction) of oliceridine versus opioid analgesic in moderate to severe postoperative pain.

Methodology: A comprehensive literature search was conducted in PubMed (January 2021 to March 2021) using keywords as 'oliceridine', 'ligand biased mu receptor agonist', 'acute postoperative pain', 'conventional opioids' and 'morphine'. All English language full text pre-clinical and clinical research articles were searched. In addition, other data source was from ClinicalTrial. Gov.

Data Synthesis: Oliceridine is a novel selective μ (mu)-receptor G-protein pathway modulator. G protein biased mu receptor agonists are a new class of opioids exhibiting analgesic properties at par to morphine with less respiratory depressant properties. Oliceridine a first-in-class intravenous (IV) analgesic has received the US FDA approval in August 2020, for management of moderate to severe acute pain in adults. The drug can be administered in cases where the pain is severe enough to require an intravenous opioid and when alternative treatments become inadequate. Oliceridine is an opioid agonist with a rapid onset of action within two to five minutes, was administered via clinician-administered bolus dosing, patient-controlled analgesia (PCA), or a combination of the two. Bolus dosing was initiated at 1 to 2 mg, with supplemental doses of 1 to 3 mg every one to three hours, as needed, based on individual patient need and previous response to oliceridine in management of acute post-operative pain. If oliceridine was administered via PCA, the loading dose was 1.5 mg, the demand dose was 0.5 mg, and the lockout interval (repeat dose)was six minutes. The clinically relevant concentration range of 0 to 35 ng/ml. It is indicated for short-term use only & limited to hospitals or other controlled clinical settings. Oliceridine requires no dosage adjustments in patients with renal impairment as well as in patient with significant medical complications. Therefore, opioids that bias towards G-protein and away from β arrestin signaling should produce analgesia with reduced side effects.

KEYWORDS: Oliceridine, ligand biased mu receptor agonist, acute postoperative pain, conventional opioids, morphine.

INTRODUCTION [1–4]

Opioid analgesics are used for the treatment of moderate to severe pain, accompanied by gastrointestinal side effects, respiratory depression and addiction. Design and evaluation of analgesics with reduced side effect profiles is an important goal to overcome the opioid crisis. This led to development of a biased ligand to improve the benefit-risk profile of existing opioid analgesics.

Distinct pharmacological responses, such as specific beneficial or adverse effects, are often linked to different signaling pathways. Opioid receptors signal via a number of pathways including G-protein and beta arrest in pathways.

The mu opioid receptor (MOR) was one of the first G-protein coupled receptors (GPCRs) to demonstrate a potential for translating the advances in understanding GPCR pharmacology into the development of a biased ligand to improve the benefit-risk profile of existing analgesics. When activated by endorphins or opioids, the MOR triggers activation of two pathways inside the cell: G protein coupling, primarily associated with analgesic effects and β-arrestin coupling, primarily associated with respiratory and GI effects. Therefore, opioids that bias towards G-protein and away from β -arrestin signalling should produce analgesia with reduced side effects. "Biased" ligands could selectively engage some signaling pathways while avoiding, or even inactivating, other signaling pathways mediated by the same receptor developing new GPCR-targeted medicines that could offer improved benefit-risk profiles over existing therapies. The aim of this study was to review the literature on equianalgesic efficacy and better safety(less respiratory

depression and gastrointestinal dysfunction) of oliceridine versus opioid analgesic in moderate to severe postoperative pain.

METHODOLOGY

A comprehensive literature search was conducted in Pub Med(January 2021 to March 2021) using keywords as 'oliceridine', 'ligand biased mu receptor agonist', 'acute postoperative pain', 'conventional opioids' and 'morphine'. All English language full text pre-clinical and clinical research articles were searched. In addition, other data source was from ClinicalTrial.gov.

Chemical and nonclinical data [5]

Animal work indicates that β-arrestin gene (and hence protein) knock out facilitates opioid analgesia devoid of side effects. Ligand bias or functional selectivity is the principle that allows a drug to activate one pathway over another selectively, or to produce bias. Dr. Robert Lefkowitz, was awarded the Nobel Prize for Chemistry for his work in 2012. This profile is seen as beneficial in reducing its side effect profile. The scientific rationale for the discovery and development of oliceridine stemmed from findings that mice lacking β-arrestin-2 expression treated with morphine demonstrated enhanced analgesia and reduced respiratory and gastrointestinal (GI) dysfunction compared with wild-type animals. General toxicity, genotoxicity, developmental and reproductive toxicity studies did not identify any new toxicity other than conventional MOR agonists. Others are addiction, neonatal opioid withdrawal syndrome; reinforcing effects similar to morphine in animal abuse potential studies.

Pharmacodynamics [4–8]

Basic principle based of action is on modulation of G Protein-Coupled Receptors. Pre-clinical studies suggested that elimination of β-arrestin recruitment could reduce or attenuate, but not eliminate ORAEs such as respiratory depression and GI dysfunction. Oliceridine exerts its actions at both central and peripheral sites in a naloxone-reversible manner. These preclinical study results suggested that analgesia and opioid related adverse effects (ORAEs) are mediated by two distinct signaling pathways: G protein: responsible for analgesia; partial contribution to ORAEs. β-arrestin: contributes to ORAEs and attenuation of the analgesic response. Unlike conventional opioids that activate both the G protein and β-arrestin pathways, oliceridine stimulates G protein signaling with markedly reduced β-arrestin-2 recruitment [Figure 1]. Thus, it was hypothesized that oliceridine would be able to provide the rapid and systemic analgesia of an opioid, but with reduced incidence of ORAEs.

Pharmacokinetics [9, 10] : Oliceridine is an opioid agonist with a rapid onset of action within two to five minutes. Action lasts, over 2 minute to 1 hour. Oral bio availability of oliceridine is low (5.77%). So it is given intravenously (IV). Oliceridine preparation 1 mg/ml is a clear, colorless, sterile, preservative-free solution in a glass vial for IV use. Oliceridine exhibited a half-life ($t\frac{1}{2}$) of approximately 1.5 to 3 hours. Plasma protein binding in humans is 77%. When administered in CYP2D6 poor metabolizers tended to have a longer t1/2 than extensive metabolizers. Renal clearance of oliceridine is low (2.2 – 5.1% of total clearance). Renal impairment has no effect on the clearance of oliceridine; therefore, no dose adjustment of oliceridine is needed in patients with renal impairment and those with significant medical complications.

The dosing regimen for each patient should be initiated individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience and co-morbidities. The initial dose of oliceridine should be 1 to 2 mg. Onset of analgesic effect is expected within 5 minutes of the initial dose. As multiple doses may be needed, subsequent doses of 1 to 2 mg may be given 10 minutes after the previous dose based on individual patient need.

Maintenance of analgesia is achieved with oliceridine administered as doses of 1 to 2 mg every 1 to 3 hours as needed. Doses of 3 mg may be used in patients with more severe pain. For patient controlled administration, demand doses of 0.1 to 0.35 mg, with a 6-minute lockout, may be given as needed based upon patient response to initial bolus dose. IV oliceridine has a maximum recommended daily dose limit of 27 mg. Over the clinically relevant concentration range of 0 to 35 ng/ml, the oliceridine utility function was positive, indicating that the probability of analgesia exceeds the probability of respiratory depression

Phase III Clinical trials [11, 12]

The FDA approval of oliceridine was based on results from multiple phase 3 studies that evaluated oliceridine in more than 1,500 patients with moderate to severe acute pain. APOLLO 1 and APOLLO 2 Phase 3 Studies in bunionectomy and abdominoplasty.

The two randomized, double-blind, placebo and morphine controlled studies enrolled 790 patients with moderate to severe acute pain (pain intensity of $\geq$4 on a 0-10 numerical rating scale) after bunionectomy or abdominoplasty. In each study, patients were randomized to one of three oliceridine treatment regimens: a placebo-controlled regimen, or a morphine-controlled regimen. To participate in APOLLO 1 or APOLLO 2, patients enrolled were having inclusion criteria as : age $\geq$ 18 and $\leq$ 75 years at screening, $\geq$ 40 kg in body weight or a body mass index (BMI) of $\leq$ 35 kg/m^2, and scheduled to undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation (hard tissue/ non visceral pain model; APOLLO 1) or an abdominoplasty procedure with no additional collateral procedures (soft tissue model/visceral pain; APOLLO 2). Key exclusion criteria included current diagnosis of sleep apnea or suspicion of sleep apnea. Additionally, patients must have rated their pain intensity (via the Numerical Rating Scale) as $\geq$ 4 within 9 hours after discontinuation of regional anes-

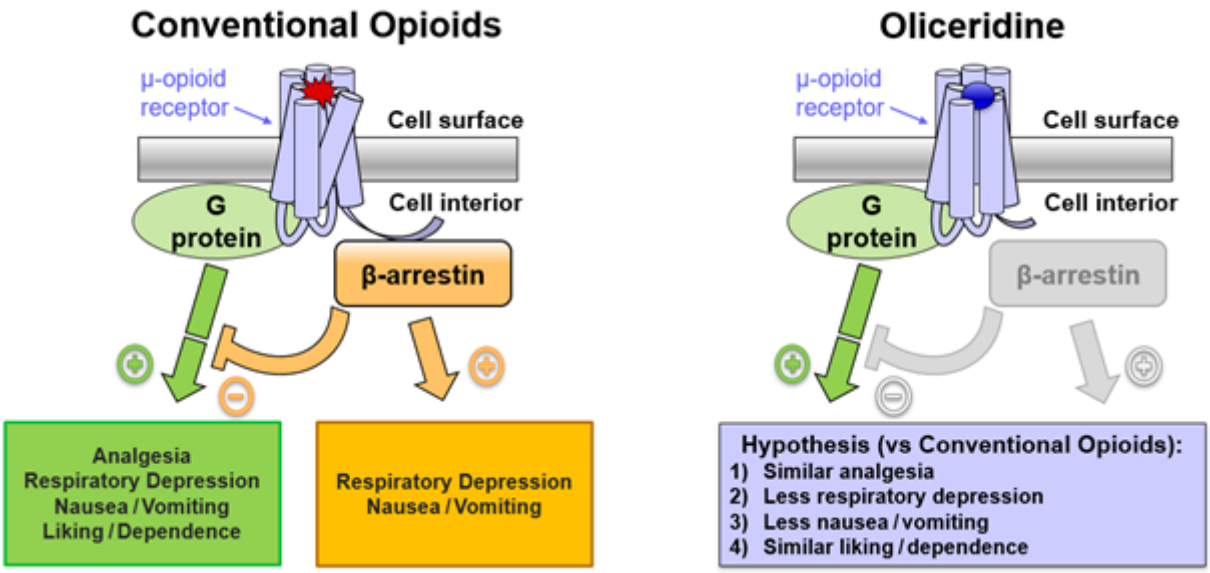

Figure 1: μ-Opioid Receptor Binding of Conventional Opioids and Oliceridine

thesia (APOLLO 1) or $\geq$ 5 within 4 hours after the end of surgery (APOLLO 2). The loading dose for all oliceridine treatment regimens was 1.5 mg and demand doses were 0.1, 0.35 or 0.5 mg, according to the assigned treatment group; supplemental doses were 0.75 mg. A lockout interval (re administration time) of six minutes was used for all patient-controlled analgesic (PCA) regimens. Patients who were administered oliceridine doses of 0.35 and 0.5 mg had a significantly greater summed pain intensity difference after 48 hrs in bunionectomy & 24 hrs in an abdominoplasty procedure (SPID-48/24) scores than patients who used a placebo. The time-weighted SPID from baseline was calculated by the sum of the time-weighted pain intensity difference (PID = difference between current pain and pain at baseline) multiplied by the interval between ratings. The patients who underwent bunionectomy or abdominoplasty reported rapid analgesic efficacy from oliceridine that was statistically significant over placebo.

ATHENA an open-label phase 3 safety study [13]

Patients with moderate to severe acute pain in diverse clinical settings in a patient population with more co-morbidities following a surgical procedure or due to a medical condition or emergency department, a total of 768 patients received at least one dose of oliceridine. Oliceridine was administered via clinician administered bolus dosing, patient-controlled analgesia (PCA), or a combination of the two. Bolus dosing was initiated at 1 to 2 mg, with supplemental doses of 1 to 3 mg every one to three hours, as needed, based on individual patient need and previous response to oliceridine. If oliceridine was administered via PCA, the loading dose was 1.5 mg, the demand dose was 0.5 mg, and the lockout interval was six minutes. Supplemental doses of 1 mg were given as needed, considering the patient's use of PCA demand doses, the individual patient need and previous response to oliceridine. The most frequent condition treated in the open-label safety study was post surgical acute pain, and included orthopedic, gynecologic, colorectal, general, plastic, urologic, neurologic (including spinal), bariatric and cardiothoracic surgical procedures. Of the 768 patients treated with oliceridine, mean age 54.1(18-89 year) 32% were aged 65 years or older and mean BMI 30 kg/m^{2}and 13% of patient had a diagnosis of sleep apnea syndrome as co-morbidity. Oliceridine was administered as needed; 55% of patients received oliceridine via clinician bolus administration only, and 45% of patients received oliceridine via PCA self-administration or a combination of clinician bolus and PCA self-administration. Intravenous oliceridine showed statistically superior analgesia than placebo in patients with moderate or severe pain after surgery, with a favorable safety and tolerability profile regarding respiratory and gastrointestinal adverse effects, compared with morphine.

Adverse effects and contraindications [14, 15]

Common side effects of oliceridine were similar to other opioids like nausea, vomiting, dizziness, headache and constipation. Others are addiction, neonatal opioid withdrawal syndrome; reinforcing effects similar to morphine in animal abuse potential studies suggests that oliceridine is similar to conventional Schedule II opioids. Oliceridine should not be given to patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction; or known hypersensitivity to the drug. Risks from concomitant use with benzodiazepines or other central nervous system depressants.

Olecridine indication [8, 16–18]

The drug can be administered in adult patients where the pain is severe enough to require an IV opioid and when alternative treatments become inadequate. The use of oliceridine is limited to hospitals or other controlled clinical settings, noted the agency. It is indicated for short-term use only.

Application of oliceridine GI endoscopy sedation: Oliceridine has the potential to render the sedation for GI endoscopy procedures both safe and cost effective drug can be additive to midazolam or remimazolam and allow screening colonoscopy without the need for propofol. Oliceridine can eliminate the need for drugs such as fentanyl that add to the respiratory depressant properties of propofol.

CONCLUSION

G protein-biased μ-receptor agonists are a new class of opioids exhibiting analgesic properties similar to morphine without equivalent respiratory depressant properties. Oliceridine has the property of activating G-protein signaling while causing low β-arrestin recruitment to the μ-receptor. The analgesic capacity of oliceridine is at least comparable to that of morphine at clinically relevant dosages, with a rapid onset of action. Also, it may be associated with a lower incidence of adverse events at dosing regimens associated with comparable analgesia. These data suggest that oliceridine may provide an important new treatment option for the management of moderate to severe postoperative pain where an intravenous opioid is warranted. To review the pharmacological characteristics, clinical evidence, and place in the management of acute postoperative pain severe enough to require an intravenous opioid. Oliceridine has obvious analgesic effects in patients with moderate or severe pain after surgery; additionally, it has a favorable safety and tolerability profile.

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