Review Article

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Over View of Oliceridine Newer Opioid Analgesic

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Abstract

Pain relief requires a balance between adequate analgesia and risk of adverse effects. Opioids remain the cornerstone for managing moderate to severe pain, but are associated with opioid-induced respiratory depression (OIRD) and gastrointestinal complications. Opioids exert their analgesic effects predominantly via G-protein signaling, however, adverse effects including OIRD are mediated by the β-arrestin pathway. Oliceridine is the first of a new class of biased opioid agonists that preferentially activate G-protein signaling over β-arrestin, which would theoretically improve analgesia and reduce the risk of adverse effects. Oliceridine is approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe acute pain. The efficacy of Oliceridine was mainly established in two randomized controlled Phase III clinical trials of patients experiencing moderate to severe pain after bunionectomy (APOLLO-1) and abdominoplasty (APOLLO-2). The results of the APOLLO studies demonstrate that Oliceridine, when administered via patient-controlled analgesia (PCA) demand boluses of 0.35mg and 0.5mg, provides superior analgesia compared to placebo, and is equianalgesic to PCA morphine 1mg demand boluses, without significant difference in the incidence of respiratory complications. However, these studies were designed to evaluate analgesic efficacy, and it is still uncertain if Oliceridine has a better safety profile than conventional opioids. Although several post hoc analyses of pooled data from the trials reported that Oliceridine was associated with lower OIRD and gastrointestinal complications compared to morphine, prospective studies are needed to elucidate if biased agonists such as Oliceridine reduce the risk of adverse effects compared to conventional opioids.

Keywords: TRV130; Biased ligand; Opioid agonist; Mu-opioid receptor.

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Introduction

Opioids remain the cornerstone for analgesic management of moderate to severe acute pain, which affects approximately 75% of postoperative patients. Optimal pain relief requires a balance between providing adequate analgesia versus the risk of analgesia-related adverse effects. On one hand, inadequate analgesia has been associated with prolonged hospitalization, impaired recovery, and increased risk of developing chronic pain.[2]

Conversely, excessive opioid use is associated with nausea, vomiting, sedation, constipation, and opioid-induced respiratory depression (OIRD).[3–5] In particular, OIRD results from a combination of central respiratory depression, sedation, and airway obstruction, potentially leading to hypoxemia, hypercapnia, and cardiorespiratory arrest.[6,7]

The incidence of OIRD ranges from 0.04% to 41%, depending on the diagnostic criteria,8 and places a significant population at risk of morbidity or mortality.[9] In the last decade, opioid utilization has risen dramatically with concomitant increase in related mortality and adverse effects, which has prompted the search for novel drugs with improved analgesic efficacy and adverse effect profiles.

Severe acute pain occurs through nociceptive signalling involving both ascending and descending spinal pathways, in which nerve conductance is mediated in part by the action of opioid receptors. Opioid receptors are seven-transmembrane G-protein-coupled receptors (GPCRs), of which the μ-opioid receptor subtype is predominantly targeted by and is responsible for the effects of opioid agonists. However, due to the ability of some opioid agonists to bind to other targets, as well as activation of additional downstream pathways from opioid receptors such as those involving β-arrestin, the beneficial analgesic effects of opioids are coupled with severe adverse effects such as constipation and respiratory depression.

Oliceridine (formerly known as TRV130) is a "biased agonist" at the μ-opioid receptor by preferentially activating the G-protein pathway with minimal receptor phosphorylation and recruitment of β-arrestin. By acting as a biased agonist, oliceridine provides comparable analgesia compared with traditional opioids such as [morphine] at a comparable or decreased risk of opioid-related adverse effects such as constipation and respiratory depression.

Opiod Receptor Classification and Location

Receptor	CNS location	Response on activation
Mu	Brain (laminae III and IV of the cortex, thalamus, periaquadectal gray), spinal cord(substantia gelatinosa)	Mu1: Supraspinal analgesia, physical dependence. Mu2: Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, Physical dependence.
Kappa	Brain (hypothalamus, periaquadectal gray, claustrum), spinal cord(substantia gelatinosa)	Spinal analgesia, dieresis, dysphoria, sedation, miosis, depersonalization and derealization
Delta	Brain (pontine nucleus, amygdale, olfactory bulbs, deep cortex)	Analgesia may be associated with mood change.

Chemistry

Molecular structure: N-[(3-methoxythiophen-2-yl)methyl]-2-[(9R)-9-pyridin-2-yl-6-oxaspiro[4.5] decan-9-yl]ethanamine.

Molecular weight : 386.6g\mmol.

Mechanism of Action

Oliceridine acts as a "biased agonist" at the μ-opioid receptor by preferentially activating the G-protein pathway with minimal receptor phosphorylation and recruitment of β-arrestin.[A218026, A218031] Competetive binding assays and structural modelling suggest that the binding site for oliceridine on the μ-opioid receptor is the same as for classical opioids. [A218026, A216961] However, molecular modelling supports a model whereby oliceridine binding induces a different intracellular conformation of the μ-opioid receptor, specifically due to a lack of coupling with transmembrane helix six, which confers the specificity for G-protein over β-arrestin interaction. [A216961].

Numerous in vitro,in vivo and clinical studies support the view that this biased agonism results in comparable analgesia compared with traditional opioids at a comparable or decreased risk of opioid-related adverse effects such as constipation and respiratory depression. [A218026, A218031, A218051, A218056, A218061, A218066, A218071, L15516].

Oliceridine is a biased μ-opioid receptor agonist that acts through downstream signalling pathways to exert antinociceptive analgesia in patients experience severe acute pain. [A218026, A218031, A218036, A218041, A218046, L15516] Results from multiple clinical studies[A218051, A218056, A218061, A218066, A218071, L15516] and

simulation data [A218076, A218081] demonstrate that oliceridine exerts significant analgesic benefits within 5-20 minutes following administration but dissipates quickly with a half-life between one and three hours. [A218051, A218056, A218061, A218066, A218071, L15516] Despite an improved adverse effect profile over conventional opioids [A218051, A218056, A218061, A218066, A218071, L15516], oliceridine carries important clinical warnings.

Oliceridine has the potential to cause severe respiratory depression, especially in patients who are elderly, cachectic, debilitated, or who otherwise have chronically impaired pulmonary function.

Pain perception follows a complex pathway initiated in primary sensory neurons, subsequently transmitted to the spinal cord dorsal horn and through ascending axons to multiple regions within the thalamus, brainstem, and midbrain, and finally relayed through descending signals that either inhibit or facilitate the nociceptive signalling. [A218041, A218046].

Opioid receptors are seven-transmembrane G-protein-coupled receptors (GPCRs) that can be divided into μ, κ, δ, and opioid-like-1 (ORL1) subtypes,[A218031, A218046].

However, the μ-opioid receptor is predominantly targeted by and is responsible for the effects of traditional opioids. [A218046].

GPCRs in the inactive state are bound intracellularly by a complex consisting of a Gα, β, and γ subunit together with guanosine diphosphate (GDP). Activation of the GPCR through extracellular agonist binding catalyzes the replacement of GDP with guanosine triphosphate (GTP), dissociation of both Gα-GTP and a βγ heterodimer, and subsequent downstream effects.[A218046].

In the case of the μ-opioid receptor, the Gα-GTP directly interacts with the potassium channel Kir3 while the dissociated Gβγ subunit directly binds to and occludes the pore of P/Q-, N-, and L-type Ca2+ channels.

Furthermore, opioid receptor activation inhibits adenylyl cyclase, which in turn reduces Camp-dependent Ca^{2+} influx. By altering membrane ion conductivity, these effects modulate nociceptive signalling and produce an analgesic effect. [A218036, A218041, A218046] In addition to the G-protein pathway, μ-opioid receptor activation can also result in downstream signalling through β-arrestin, which results in receptor internalization and is associated with negative effects of opioid use including respiratory depression, gastrointestinal effects, and desensitization/tolerance.[A218026, A218031, A218036, A218041, A218046].

Pharmacokinetic Properties

Oliceridine is primarily metabolized in liver by CYP3A4 and CYP2D6 in vitro, with minor contributions from CYP2C9 and CYP2C19. [L15516] None of oliceridine's metabolites are known to be active. [A218046, L15516] Metabolic pathways include N-dealkylation, glucuronidation, and dehydrogenation. [L15516]. Oliceridine has a half-life of 1.3-3 hours while its metabolites, none of which are known to be active, have a substantially longer half-life of 44 hours.[L15516].

Absorption

Oliceridine administered as a single intravenous injection of 1.5, 3, or 4.5 mg in healthy male volunteers had a corresponding Cmax of 47, 76, and 119 ng/mL and a corresponding AUC0-24 of 43, 82, and 122 ng*h/mL.[A218051] Simulations of single doses of oliceridine between 1-3 mg suggest that the expected median Cmax is between 43 and 130 ng/mL while the expected median AUC is between 22 and 70 ng*h/mL.[A218081]. Oliceridine has a mean steady-state volume of distribution of 90-120 L.[L15516].

Oral Bioavailibility

Distribution

Oliceridine is approximately 77% bound to plasma proteins. [L15516].

Elimination

Approximately 70% of oliceridine is eliminated via the renal route, of which only 0.97-6.75% of an initial dose is recovered unchanged. The remaining 30% is eliminated in faeces.[L15516].

Indications

Management of acute pain

Contraindications

- Acute or severe Bronchial Asthma in an unmonitored setting.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Known hypersensitivity to Oliceridine.

Dosage, Administration and Storage

Available as 30mg\30ml vial for Patient Controlled Analgesia.

Cumulative daily dose should not exceed 27mg.

Stored at controlled room temperature 20-25 degree celcius

Protect from freezing and light.

Toxicity

Symptoms of oliceridine overdose are variable but can include respiratory depression, airway obstruction, pulmonary edema, bradycardia, hypotension, muscle flaccidity, cold skin, and somnolence progressing to either stupor or coma. Miosis is commonly observed but in cases of severe hypoxia, mydriasis may be observed instead. Oliceridine overdose may be fatal. In case of overdose, the establishment of a protected airway followed by the institution of assisted or controlled ventilation is a high priority; in case of cardiac arrhythmias or arrest, additional supportive measures may be immediately required. Supportive treatment, including oxygen, vasopressors, and the administration of an opioid antagonist such as naloxone may be applied but should be tailored to the individual patient's condition. [L15516].

Addiction Liability None

Precautions

- Addiction, Abuse and misuse
- Life threatening respiratory depression
- Prolonged use of opioid analgesics during pregnancy-Neonatal opioid withdrawal syndrome
- Potential for QT prolongation with daily dose > 27mg
- Adrenal insufficiency
- Severe hypotension

Conclusion

Oliceridine is a biased agonist at mu opiod receptor, used to treat severe acute pain with less adverse effects caused by morphine like respiratory depression and constipation.

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Drug Bank

Studies

1. Evaluating the Incidence of Opioid-Induced Respiratory Depression Associated with Oliceridine and Morphine as Measured by the Frequency and Average Cumulative Duration of Dosing Interruption in Patients Treated for Acute Postoperative Pain.
2. The Utilization of Mu-Opioid Receptor Biased Agonists: Oliceridine, an Opioid Analgesic with Reduced Adverse Effects.
3. Oliceridine is Associated with Reduced Risk

of Vomiting and Need for Rescue Antiemetics Compared to Morphine: Exploratory Analysis from Two Phase 3 Randomized Placebo and Active Controlled Trials.

4. Low Incidence of Opioid-Induced Respiratory Depression Observed with Oliceridine Regardless of Age or Body Mass Index: Exploratory Analysis from a Phase 3 Open-Label Trial in Postsurgical Pain.