

Over View of Oliceridine Newer Opioid Analgesic

Anurita Konnur¹, Yoganarasimha N², Kripa Anand³

Author's Affiliation: ¹Post Graduate, ²Professor, ³Senior Resident, Department of Anesthesiology, BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, 560060, India.

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.

How to cite this article:

Anurita Konnur, Yoganarasimha N, Kripa Anand/Over View of Oliceridine Newer Opioid Analgesic/Indian J Anesth Analg. 2022; 9(2): 87-92.

Corresponding Author: Anurita Konnur, Post Graduate, Department of Anesthesiology, BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, 560060, India.

E-mail: dranurita85@gmail.com, **Received on:** 02.01.2022, **Accepted on:** 20.02.2022

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.

Opioid Receptor Classification and Location

Receptor	CNS location	Response on activation
Mu	Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	Mu1: Supraspinal analgesia, physical dependence. Mu2: Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, Physical dependence.
Kappa	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, diuresis, dysphoria, sedation, miosis, depersonalization and derealization
Delta	Brain (pontine nucleus, amygdala, 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] Competitive 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 $G\alpha$, 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 $G\alpha$ -GTP and a $\beta\gamma$ heterodimer, and subsequent downstream effects. [A218046].

In the case of the μ -opioid receptor, the $G\alpha$ -GTP directly interacts with the potassium channel Kir3 while the dissociated $G\beta\gamma$ subunit directly binds to and occludes the pore of P/Q-, N-, and L-type Ca^{2+} channels.

Furthermore, opioid receptor activation inhibits adenylyl cyclase, which in turn reduces 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 C_{max} 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 C_{max} 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 Bioavailability

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 opioid receptor, used to treat severe acute pain with less adverse effects caused by morphine like respiratory depression and constipation.

References

1. DeWire SM, Yamashita DS, Rominger DH, Liu G, Cowan CL, Graczyk TM, Chen XT, Pitis PM, Gotchev D, Yuan C, Koblish M, Lark MW, Violin JD: A G protein-biased ligand at the mu-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J Pharmacol Exp Ther*. 2013 Mar;344(3):708-17. doi: 10.1124/jpet.112.201616. Epub 2013 Jan 8. [PMID:23300227].
2. Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, Levit A, Kling RC, Bernat V, Hubner H, Huang XP, Sassano MF, Giguere PM, Lober S, Da Duan, Scherrer G, Kobilka BK, Gmeiner P, Roth BL, Shoichet BK: Structure-based discovery of opioid analgesics with reduced side effects. *Nature*. 2016 Sep 8;537(7619):185-190. doi: 10.1038/nature19112. Epub 2016 Aug 17. [PMID:27533032].
3. Ok HG, Kim SY, Lee SJ, Kim TK, Huh BK, Kim KH: Can oliceridine (TRV130), an ideal novel micro receptor G protein pathway selective (micro-GPS) modulator, provide analgesia without opioid-related adverse reactions? *Korean J Pain*. 2018 Apr;31(2):73-79. doi: 10.3344/kjp.2018.31.2.73. Epub 2018 Apr 2. [PMID:29686804].
4. Azzam AAH, McDonald J, Lambert DG: Hot topics in opioid pharmacology: mixed and biased opioids. *Br J Anaesth*. 2019 Jun;122(6):e136-e145. doi: 10.1016/j.bja.2019.03.006. Epub 2019 Apr 19. [PMID:31010646].
5. Urits I, Viswanath O, Orhurhu V, Gress K, Charipova K, Kaye AD, Ngo A: The Utilization of Mu-Opioid Receptor Biased Agonists: Oliceridine, an Opioid Analgesic with Reduced Adverse Effects. *Curr Pain Headache Rep*. 2019 Mar 18;23(5):31. doi: 10.1007/s11916-019-0773-1. [PMID:30880365].
6. Soergel DG, Subach RA, Burnham N, Lark MW, James IE, Sadler BM, Skobieranda F, Violin JD, Webster LR: Biased agonism of the mu-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. *Pain*. 2014 Sep;155(9):1829-35. doi: 10.1016/j.pain.2014.06.011. Epub 2014 Jun 19. [PMID:24954166].
7. Viscusi ER, Webster L, Kuss M, Daniels S, Bolognese JA, Zuckerman S, Soergel DG, Subach RA, Cook E, Skobieranda F: A randomized, phase 2 study investigating TRV130, a biased ligand of the mu-opioid receptor, for the intravenous treatment of acute pain. *Pain*. 2016 Jan;157(1):264-72. doi: 10.1097/j.pain.0000000000000363. [PMID:26683109].
8. Singla N, Minkowitz HS, Soergel DG, Burt DA, Subach RA, Salamea MY, Fossler MJ, Skobieranda F: A randomized, Phase IIb study investigating oliceridine (TRV130), a novel micro-receptor G-protein pathway selective (mu-GPS) modulator, for the management of moderate to severe acute pain following abdominoplasty. *J Pain Res*. 2017 Oct 6;10:2413-2424. doi: 10.2147/JPR.S137952. eCollection 2017. [PMID:29062240].
9. Singla NK, Skobieranda F, Soergel DG, Salamea M, Burt DA, Demitrack MA, Viscusi ER: APOLLO-2: A Randomized, Placebo and Active-Controlled Phase III Study Investigating Oliceridine (TRV130), a G Protein-Biased Ligand at the mu-Opioid Receptor, for Management of Moderate to Severe Acute

- Pain Following Abdominoplasty. *Pain Pract.* 2019 Sep;19(7):715-731. doi: 10.1111/papr.12801. Epub 2019 Jun 24. [PMID:31162798].
10. 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 micro-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. *J Pain Res.* 2019 Mar 11;12:927-943. doi: 10.2147/JPR.S171013. eCollection 2019. [PMID:30881102].
 11. Fossler MJ, Sadler BM, Farrell C, Burt DA, Pitsiu M, Skobieranda F, Soergel DG: Oliceridine, a Novel G Protein-Biased Ligand at the mu-Opioid Receptor, Demonstrates a Predictable Relationship Between Plasma Concentrations and Pain Relief. II: Simulation of Potential Phase 3 Study Designs Using a Pharmacokinetic/Pharmacodynamic Model. *J Clin Pharmacol.* 2018 Jun;58(6):762-770. doi: 10.1002/jcph.1075. Epub 2018 Feb 2. [PMID:29393971].
 12. Fossler MJ, Sadler BM, Farrell C, Burt DA, Pitsiu M, Skobieranda F, Soergel DG: Oliceridine (TRV130), a Novel G Protein-Biased Ligand at the mu-Opioid Receptor, Demonstrates a Predictable Relationship Between Plasma Concentrations and Pain Relief. I: Development of a Pharmacokinetic/Pharmacodynamic Model. *J Clin Pharmacol.* 2018 Jun;58(6):750-761. doi: 10.1002/jcph.1076. Epub 2018 Feb 7. [PMID:29412458].
 13. Schneider S, Provasi D, Filizola M: How Oliceridine (TRV-130) Binds and Stabilizes a mu-Opioid Receptor Conformational State That Selectively Triggers G Protein Signaling Pathways. *Biochemistry.* 2016 Nov 22;55(46):6456-6466. doi: 10.1021/acs.biochem.6b00948. Epub 2016 Nov 7. [PMID:27778501].
 14. Chen XT, Pitis P, Liu G, Yuan C, Gotchev D, Cowan CL, Rominger DH, Koblish M, Dewire SM, Crombie AL, Violin JD, Yamashita DS: Structure-activity relationships and discovery of a G protein biased mu opioid receptor ligand, [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine (TRV130), for the treatment of acute severe pain. *J Med Chem.* 2013 Oct 24;56(20):8019-31. doi: 10.1021/jm4010829. Epub 2013 Oct 14. [PMID:24063433].
 15. FDA Approved Drug Products: Olinvyk (oliceridine) injection.
 16. FDA Briefing Document: Oliceridine.
 17. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL: Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin.* 2014;30(1):149-160. doi:10.1185/03007995.2013.860019 [PubMed] [CrossRef] [Google Scholar].
 18. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res.* 2017;10:2287-2298. doi:10.2147/JPR.S144066 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
 19. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain.* 2002;3(3):159-180. doi:10.1054/jpai.2002.123652 [PubMed] [CrossRef] [Google Scholar].
 20. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science.* 2018;361(6408):eaau1184. doi:10.1126/science.aau1184 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
 21. Bedene A, Lijfering WM, Niesters M, et al. Opioid prescription patterns and risk factors associated with opioid use in the Netherlands. *J Pain.* 2019;2(8):e1910223. doi:10.1001/jamanetworkopen.2019.10223 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
 22. Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth.* 2004;93(2):212-223. doi:10.1093/bja/aeh180 [PubMed] [CrossRef] [Google Scholar].
 23. Macintyre PE, Loadman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care.* 2011;39(4):545-558. doi:10.1177/0310057X1103900405 [PubMed] [CrossRef] [Google Scholar].
 24. Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. *BMJ Open.* 2018;8(12):e024086. doi:10.1136/bmjopen-2018-024086 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
 25. Kessler ER, Shah M, Gruschus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy.* 2013;33(4):383-391. doi:10.1002/phar.1223 [PubMed] [CrossRef] [Google Scholar].

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.

