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Improved Tolerability with Oliceridine Compared to Morphine at Equianalgesic Conditions

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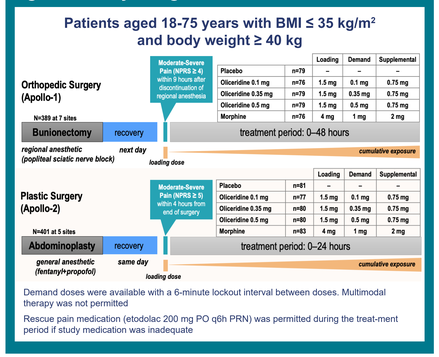
BACKGROUND

- Opioids remain important pharmacotherapeutic agents in the management of postsurgical pain.[1] The Centers for Disease Control and Prevention (CDC) states that in certain situations of postsurgical pain, the benefits of a limited course of opioids may outweigh the risks if pain management is inadequate with nonopioid therapies.[2]
- Conventional opioids have a narrow therapeutic index and are associated with dose-limiting opioid-related adverse events (ORAEs), including nausea, vomiting, and respiratory depression.[3]
- Oliceridine, a next generation IV opioid, is a G-protein selective agonist at the μ-opioid receptor.[4]
  - This G-protein selectivity results in analgesia with limited recruitment of β arrestin, a signaling pathway associated with ORAEs.[4]
- In two randomized, double-blind, placebo- and morphine-controlled studies in patients with moderate-to-severe acute pain following either orthopedic surgery (bunionectomy) or plastic surgery (abdominoplasty), oliceridine administered using patient-controlled analgesia (PCA) at demand doses of 0.1, 0.35, and 0.5 mg was highly effective compared to placebo and had a favorable safety profile.[5,6]
- We performed an exploratory analysis to determine the safety of oliceridine when adjusted for equal levels of analgesia compared to morphine.

METHODS

Figure 1: Study Designs of the Phase 3 Pivotal Trials



		Loading	Demand	Supplemental
Placebo	n=79	–	–	–
Oliceridine 0.1 mg	n=76	1.5 mg	0.1 mg	0.75 mg
Oliceridine 0.35 mg	n=79	1.5 mg	0.35 mg	0.75 mg
Oliceridine 0.5 mg	n=79	1.5 mg	0.5 mg	0.75 mg
Morphine	n=76	4 mg	1 mg	2 mg

		Loading	Demand	Supplemental
Placebo	n=81	–	–	–
Oliceridine 0.1 mg	n=77	1.5 mg	0.1 mg	0.75 mg
Oliceridine 0.35 mg	n=80	1.5 mg	0.35 mg	0.75 mg
Oliceridine 0.5 mg	n=80	1.5 mg	0.5 mg	0.75 mg
Morphine	n=83	4 mg	1 mg	2 mg

Demand doses were available with a 6-minute lockout interval between doses. Multimodal therapy was not permitted

Rescue pain medication (etodolac 200 mg PO q6h PRN) was permitted during the treat-ment period if study medication was inadequate

For this analysis:

- The adverse events (AEs) of oliceridine and morphine, adjusted for therapeutic effectiveness, were compared by logistic regression, with the final model selected by backward elimination with the p ≤ 0.15 criterion.
- AEs selected were events that occurred in ≥ 10% of patients in any treatment group. Patients receiving placebo were excluded from the analysis.
  - In both studies, spontaneously reported AEs were assessed during the randomized treatment and 7-day follow-up period, coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0.
- MedDRA events of nausea, vomiting, sedation, dizziness, pruritus, and hypoxia, with at least one treatment-emergent adverse event, was used as the composite safety endpoint.
- Analgesia was determined utilizing the weighted Sum of Pain Intensity Differences, SPID 48/24 (bunionectomy/ abdominoplasty).
- For patients who received rescue analgesics (etodolac 200 mg q 6h as needed), the pre-rescue pain score was used instead of the pain scores measured after rescue medication usage for 6 hours. This imputation was utilized in the calculation of the SPID score.
- The logistic model included effects of treatment, baseline pain score, and SPID 48/24. This analysis was done for both individual studies as well as the pooled data.

RESULTS

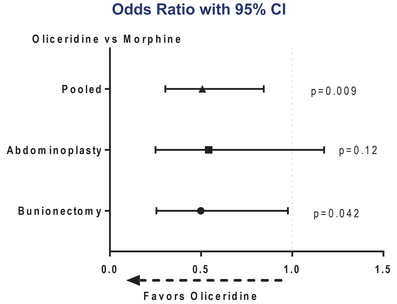
- The incidence of spontaneously reported MedDRA events used in the composite endpoint in any treatment group by study is shown in **Table 1**.
- At a given level of SPID 48/24, the odds ratio for the composite safety endpoint with oliceridine was approximately half of that observed with morphine (**Figure 2**). The findings were consistent across both the bunionectomy and abdominoplasty studies.

Table 1: Incidence of Spontaneously Reported MedDRA Events Used in the Composite Endpoint

Orthopedic Surgery-Bunionectomy					
Adverse Drug Reaction	Placebo (n=79)	Oliceridine demand dose regimen 0.1 mg (n=76)	0.35 mg (n=79)	0.5 mg (n=79)	Morphine 1 mg (n=76)
Nausea	19 (24.1)	27 (35.5)	44 (55.7)	50 (63.3)	49 (64.5)
Vomiting	5 (6.3)	13 (17.1)	31 (39.2)	32 (40.5)	38 (50.0)
Sedation	6 (7.6)	6 (7.9)	19 (24.1)	12 (15.2)	12 (15.8)
Dizziness	8 (10.1)	21 (27.6)	25 (31.6)	28 (35.4)	26 (34.2)
Pruritus	6 (7.6)	2 (2.6)	13 (16.5)	5 (6.3)	24 (31.6)
Hypoxia	0	0	4 (5.1)	7 (8.9)	7 (9.2)
Plastic Surgery-Abdominoplasty					
Adverse Drug Reaction	Placebo (n=83)	Oliceridine demand dose regimen 0.1 mg (n=77)	0.35 mg (n=79)	0.5 mg (n=80)	Morphine 1 mg (n=82)
Nausea	38 (45.8)	34 (44.2)	49 (62.0)	60 (75.0)	61 (74.4)
Vomiting	11 (13.3)	18 (23.4)	17 (21.5)	34 (42.5)	44 (53.7)
Sedation	8 (9.6)	7 (9.1)	11 (13.9)	11 (13.8)	25 (30.5)
Dizziness	9 (10.8)	11 (14.3)	7 (8.9)	7 (8.8)	13 (15.9)
Pruritus	5 (6.0)	11 (14.3)	14 (17.7)	14 (17.5)	19 (23.2)
Hypoxia	4 (4.8)	6 (7.8)	16 (20.3)	14 (17.5)	19 (23.2)

AEs were spontaneously reported with onset at the time of or following the initiation of the loading dose with study medication until 7 days after the last dose of study medication

Figure 2: Odds Ratio for the Composite Safety Endpoint at Constant SPID levels

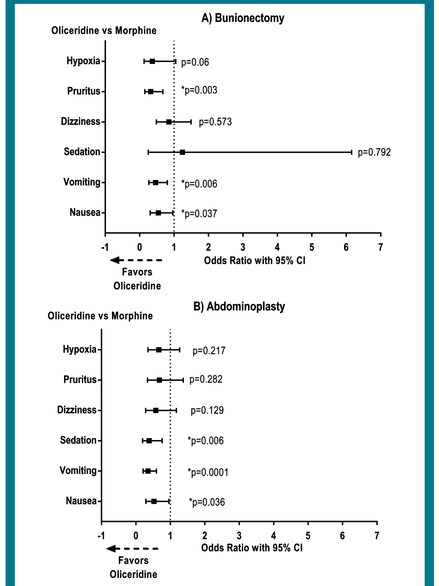


Pooled oliceridine demand dose regimens of 0.1 mg, 0.35 mg, and 0.5 mg was set as zero and morphine as one in the model

SPID = sum of pain intensity difference from baseline. The duration in the bunionectomy study was 48 h and in the abdominoplasty study was 24 h

- The odds ratio for the individual adverse events of nausea, vomiting, sedation, dizziness, pruritus, and hypoxia at a constant level of SPID for the bunionectomy and abdominoplasty study is shown in **Figure 3**.
  - In the bunionectomy study, at a constant level of SPID 48, the odds ratio was lower (odds ratio < 1) for 5/6 individual AEs with oliceridine vs. morphine, with statistically significant (p < 0.05) differences for nausea, vomiting and pruritus.
  - In the abdominoplasty study, at a constant level of SPID 24, the odds ratio was lower for all individual AEs with oliceridine vs. morphine, with statistically significant (p < 0.05) differences for nausea, vomiting and sedation.

Figure 3: Odds Ratio for the Individual Adverse Events at Constant SPID Levels



Pooled oliceridine demand dose regimens of 0.1 mg, 0.35 mg, and 0.5 mg was set as zero and morphine as one in the model

SPID = sum of pain intensity difference from baseline

The duration in the bunionectomy study was 48 h and in the abdominoplasty study was 24 h

CONCLUSIONS

- These findings suggest that, when analgesia (as measured by SPID 48/24) is held constant across treatment groups, patients receiving oliceridine were less likely to experience adverse events compared to patients treated with morphine.
- In both studies, the odds ratio for the composite safety endpoint with oliceridine was approximately half of that observed with morphine.
- The results from the pooled data were consistent with those observed in the individual studies.
- Findings from the analysis show that under equianalgesic conditions, oliceridine has a favorable risk/benefit profile compared to morphine.

References:

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Disclosure:

Oliceridine was recently approved in adults for the management of acute pain severe enough to require an intravenous opioid analgesic for whom alternative treatments are inadequate. For patient-controlled analgesia (PCA), the recommended demand dose is 0.35 mg with a 6-minute lock-out. A demand dose of 0.5 mg may be considered.

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