Reduced Incidence of Postoperative Vomiting with Oliceridine than with Morphine at Equianalgesic Conditions

A4284

Timothy L Beard[1], Cathy Michalsky[2], Keith A Candiotti[3], Paul Rider[4], Linda Wase[2], Ashraf S Habib[5], Mark A Demitrack[2], Michael J Fossler[2], Eugene R Viscusi[6]

[1]Department of Surgery and Clinical Research, Summit Medical Group/Bend Memorial Clinic, Bend, OR, USA; [2]Trevena, Inc. Chesterbrook, PA, USA; [3]Department of Anesthesiology, University of Miami/Jackson Health System, FL, USA; [4]Department of Surgery, University of South Alabama Medical Center, Mobile, AL, USA; [5]Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA; [6]Department of Anesthesiology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

BACKGROUND

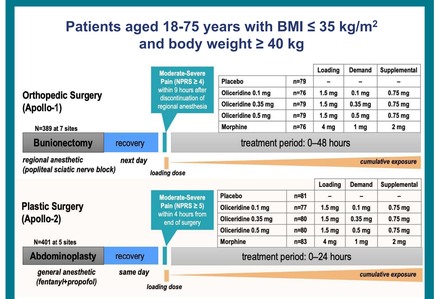
- Postoperative nausea and vomiting (PONV) is a frequent complication following surgery, with a reported 30% incidence among all post-surgical patients and up to 80% among high-risk patients; and use of conventional opioids increases the risk[1]
- Although postoperative vomiting often accompanies nausea, they are distinct, physiologic phenomena, where nausea is a subjective unpleasant sensation and vomiting is a forceful expulsion of stomach contents[2]
- Postoperative nausea alone poses limited health risks; while postoperative vomiting can potentially result in significant health risks, including dehydration, electrolyte imbalance, and, in extreme cases, esophageal rupture or aspiration[3]
- The cost associated with the treatment of a vomiting episode is significantly higher (3X as high) than that associated with nausea alone[4]
- At the cellular level, conventional opioid agonists bind to the μ opioid receptor (MOR) and stimulate the G protein post-receptor signaling leading to analgesia, and activation of the β-arrestin pathway leading to unwanted effects including respiratory and GI related side effects[5]
- Oliceridine, a next-generation IV opioid, is a G-protein selective agonist at the MOR with limited recruitment of β-arrestin[6,7]
- In two randomized, double-blind, placebo- and morphine-controlled phase 3 pivotal studies in patients with moderate to severe acute pain following either orthopedic surgery-bunionectomy, or plastic surgery-abdominoplasty, oliceridine at demand doses of 0.1 mg, 0.35 mg and 0.5 mg provided rapid and effective analgesia compared to placebo[8,9]
- In a retrospective analysis of the pooled data from the two pivotal trials, the rate of nausea and vomiting with oliceridine demand doses was lower compared to morphine[10]
  - Nausea: oliceridine 0.1 mg (40%), 0.35 mg (60%), 0.5 mg (69%), morphine (70%)
  - Vomiting: oliceridine 0.1 mg (20%), 0.35 mg (30%), 0.5 mg (42%), morphine (52%)

OBJECTIVES

- To characterize the GI adverse event profile of oliceridine vs morphine from these studies, we used the endpoint of "Complete GI Response" defined as the proportion of patients with no vomiting and no use of rescue antiemetic
- We also evaluated the Complete GI Response endpoint under equianalgesic conditions, where analgesia, as measured by Sum of Pain Intensity Difference (SPID), was held constant

METHODS

Figure 1: Study Designs of the Phase 3 Pivotal Trials



In this exploratory analysis, two outcomes were determined:

1. Complete GI Response, examined for each treatment arm by study and for the pooled data

- Logistic regression model was used with the main effects of treatment and baseline pain score as covariates

2. Complete GI Response between oliceridine and morphine when adjusted for analgesia (SPID 48/24)

- Analgesic effect was quantified using SPID 48/24 (for bunionectomy/ abdominoplasty respectively)
  - Pre-rescue SPID scores carried forward for 6 hours for those patients who received protocol-specified rescue analgesic medication
  - Patients receiving placebo were excluded from this analysis
- This model included the effects of treatment (pooled oliceridine demand dose regimens of 0.1, 0.35, and 0.5 mg as zero and morphine as one), baseline pain score, and SPID 48/24; with the final model selected by backward elimination with the p ≤ 0.1 criterion

RESULTS

Selected Patient Demographics

	Bunionectomy N=389		Abdominoplasty N=401	
	Oliceridine N=234	Morphine N=76	Oliceridine N=237	Morphine N=83
Mean Age (SD), years	46.0 (13.5)	43.3 (14.1)	41.4 (10.2)	40.4 (10.4)
Mean BMI (SD), kg/m²	26.5 (4.2)	26.5 (4.5)	27.5 (3.2)	26.8 (3.3)
Female, n (%)	195 (83.3)	65 (85.5)	236 (99.6)	81 (97.6)
Race, n (%)				
White	164 (70.1)	50 (65.8)	150 (63.3)	55 (66.3)
Black or African American	52 (22.2)	21 (27.6)	74 (31.2)	24 (28.9)
Baseline Pain Intensity-NRS score, Mean (SD)	6.6 (1.8)	6.7 (1.6)	7.4 (1.5)	7.3 (1.5)
Apfel Risk score, n (%)				
1	9 (3.8)	0	0	0
2	45 (19.2)	20 (26.3)	14 (5.9)	5 (6.0)
3	144 (61.5)	43 (56.6)	183 (77.2)	67 (80.7)
4	36 (15.4)	13 (17.1)	40 (16.9)	11 (13.3)

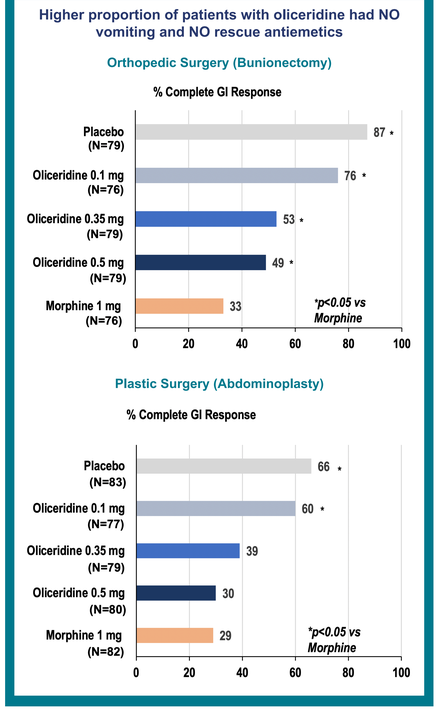
BMI = Body mass index, NRS = numeric rating scale, SD = standard deviation

- Majority of the patients enrolled across treatment arms in both studies had Apfel risk scores ≥ 3

Complete GI Response

- Complete GI Response by study is shown in **Figure 2**
- In the retrospective analysis of the pooled data from both studies, a statistically significantly greater proportion of patients in the placebo regimen (76.4%) and patients in two of the oliceridine treatment regimens, 0.1 mg: 68.0% and 0.35 mg: 46.2%achieved Complete GI Response compared to morphine (30.8%, p < 0.001 vs. morphine)

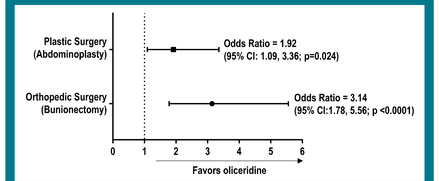
Figure 2: Complete GI Response by Study by Treatment Arm



Complete GI Response after adjusting for analgesic effect

The odds ratio for Complete GI Response with oliceridine (combined demand doses) vs morphine after adjusting for analgesic effect is shown in **Figure 3**

Figure 3: Odds Ratio to Experience Complete GI Response with Oliceridine vs Morphine after Adjustment of Analgesic Effect



CONCLUSIONS

- Findings from this exploratory analysis show that Complete GI Response (defined as no postoperative vomiting and no use of rescue antiemetics) was significantly higher with the lower doses of oliceridine than morphine
- When controlled for the analgesic effects (at constant SPID 48/24) the odds ratio for Complete GI Response was higher with oliceridine than morphine
- Oliceridine, a G-protein selective MOR agonist, may have improved gastrointestinal tolerability compared to morphine, and provides an important new option for the clinical management of postoperative pain. Future prospective studies are needed to confirm these findings

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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 and for whom alternative treatments are inadequate. For patient-controlled analgesia (PCA), 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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