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Low Incidence of Events with Oliceridine In Patients Predicted At High-Risk For Developing Opioid-Induced Respiratory Depression

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Introduction

In the management of acute postoperative pain, IV opioids remain an important pharmacotherapy, however, the benefits of analgesic effects are limited by opioid-related adverse events (ORAEs) (Small and Laycock 2020). Opioid-induced respiratory depression (OIRD) is among the most serious of the ORAEs that increases perioperative cost and hospital length of stay (LOS) and may result in permanent morbidity and mortality (Gupta et al. 2018). Oliceridine is a new biased IV opioid analgesic at μ-opioid receptors (DeWire et al. 2013), indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Preclinical studies report that oliceridine elicits robust G-protein signaling (analgesic effect) with less recruitment of β-arrestin (associated with ORAEs) (DeWire et al. 2013). Findings from an exploratory analysis of a Phase 3 open-label, multicenter safety study, ATHENA, reported that the postoperative use of IV oliceridine in patients with advanced age and/or increased body mass index (≥ 30kg/m2) experiencing moderate-to-severe pain was not associated with increased risk of OIRD [defined by a) use of naloxone; b) respiratory rate < 10 bpm c) oxygen saturation (SpO2 < 90%) within 48 hours of last dose of oliceridine (Brzezinski et al. 2021)].

The prospective, observational trial of blinded continuous capnography and oximetry, PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial that investigated the incidence and risk factors associated with OIRD episodes in hospitalized patients receiving parenteral opioids, reported a 46% incidence of respiratory depression (Khanna et al. 2020). A respiratory depression episode in PRODIGY was defined as respiratory rate ≤5 breaths/min (bpm), oxygen saturation ≤85%, or end-tidal carbon dioxide ≤15 or ≥60 mm Hg for ≥3 minutes; apnea episode lasting >30 seconds; or any respiratory opioid-related adverse event. This trial aided in creating a validated novel respiratory depression risk prediction tool, including 5 easy-to-assess variables: age ≥60 years by decade, sex, opioid naivety, sleep disorders, and chronic heart failure.

The ATHENA trial did not use continuous capnography and oximetry to monitor patients for OIRD. Thus, in this exploratory analysis from the ATHENA trial, we applied the PRODIGY risk scoring tool in patients with pre-existing comorbidities of sleep apnea and/or chronic heart failure to categorize them into low, intermediate, or high-risk; and we report the incidence of OIRD in these patients.

Materials and Methods

In the ATHENA trial, men and women aged ≥ 18 yrs with a score ≥ 4 on an 11-point numeric pain rating scale (NPRS) following a surgical procedure or a painful medical condition received IV oliceridine as needed via bolus dosing (1 to 3 mg q1−3h) and/or patient-controlled analgesia (PCA loading dose: 1.5 mg; demand dose: 0.5 mg; 6-min lockout interval).

For this exploratory analysis of the ATHENA trial, we utilized the PRODIGY risk scoring tool using the variables age ≥60 years by decade, sex, opioid naivety based on whether the patient had any prior medication within the opioid class in the WHO dictionary coding and applied in patients who had a medical history of sleep apnea and/or chronic heart failure (including congestive heart failure). The sum of points categorized patients to low (< 8 points)-, intermediate (≥8 and <15 points)-, and high-risk (≥ 15 points). We then assessed the incidence of OIRD in these 3 categories of patients using the definition of OIRD as reported in the previous analysis from ATHENA.

At the time of conduct of the ATHENA study, it was approved by the Institutional Review Board or Independent Ethics Committee at each investigational site and was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided written informed consent before participating in the study.

Results/Case Report

A total of 768 patients (mean age 54.1 ± 16.1 y; 65% females) were treated with oliceridine (up to 6 days). Among these, 103 patients had a medical history of sleep apnea and/or chronic heart failure. Utilizing the PRODIGY risk scoring tool, 13 patients (12.6%) were categorized as low-risk, 46 patients (44.7%) as intermediate-risk and 44 patients (42.7%) were categorized as high-risk patients. The overall incidence of OIRD in patients in all 3 risk categories was low. None of the patients required naloxone during treatment with oliceridine. No patient experienced SpO2 < 90% and RR < 10 bpm at the same time. As can be seen in the table, patients categorized as high-risk based on the PRODIGY score had a similar incidence of OIRD as patients with low- or intermediate risk (Table).

Discussion

Limitations: The metrics used to measure OIRD in the PRODIGY trial were different from the one used in the ATHENA study. The PRODIGY study collected continuous data whereas the ATHENA study only collected the oxygen saturation and respiration rate data at prespecified assessment timepoints throughout the course of the study. To conform with the PRODIGY metrics, we only included in the analysis patients with comorbidities of sleep apnea and/or chronic heart failure that resulted in a sample size of 103 patients.

Findings from this exploratory analysis suggest that oliceridine does not increase the incidence of opioid-induced respiratory depression in patients predicted to be at high-risk for development of respiratory depression using the PRODIGY scoring tool.

References

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Disclosures

Yes

Tables / Images

Table: Incidence of OIRD in patients with a medical history of sleep apnea and/or chronic heart failure

Prediction based on PRODIGY scoring system	Low risk < 8 points	Intermediate risk ≥8 and <15 points	High risk ≥15 points
N (%)	13/103 (12.6)	46/103 (44.7)	44/103 (42.7%)
At least one OIRD*, n (%)	2 (15.4)	0	1 (2.3)
OIRD measures			
SpO_2 < 90%, n (%)	0	2 (4.3)	4 (9.1)
RR < 10 bpm, n (%)	2 (15.4)	2 (4.3)	2 (4.5)

**defined by a) use of naloxone; b) respiratory rate < 10 bpm c) oxygen saturation (SpO2 < 90%) within 48 hours of last dose of oliceridine. No patients required naloxone during treatment with oliceridine. No patient experienced SpO2 < 90% and RR < 10 bpm at the same time. OIRD = opioid induced respiratory depression SpO2 = oxygen saturation, RR= respiratory rate*