979

Low Incidence of Opioid-Induced Respiratory Depression Observed with Oliceridine In High-Risk Elderly Obese Patients

Chen Joy B.A.[1,3], Kiana Nouri B.A.[1], Cathy Michalsky, M.S.[2], Linda Wase, M.D.[2], Jasleen Kukreja, M.D. Ph.D.[3], Marek Brzezinski M.D., Ph.D.[1]

[1]Department of Anesthesia, University of California at San Francisco Medical Center, San Francisco, CA, USA.; [2]Trevena Inc., Chesterbrook, PA, USA;
[3]Department of Surgery, University of California at San Francisco Medical Center, San Francisco, CA, USA.

ASRA 45th Annual Regional Anesthesiology & Acute Pain Medicine Meeting
April 23-25, 2020 | #ASRASPRING20
Hilton San Francisco Union Square | San Francisco, CA

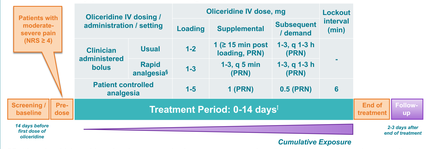
INTRODUCTION

- Opioids are considered an important therapy for potent analgesia, particularly for moderate to severe pain.[1]
- **Opioid-induced respiratory depression (OIRD)** is a potentially fatal complication associated with conventional opioids.[2]
- The reported incidence of OIRD ranges from:
  - 0.04 to 0.5% as defined by naloxone use.[3]
  - As high as 52.0%, using respiratory rate (RR) < 8 breaths/ min (bpm).[4]
  - As high as 77.4%, using oxygen saturation (SpO_2) < 90%.[5]
  - The reported mortality of patients with OIRD is 9.4% within the first 24 hours after surgery.[6]
- Advanced age and obesity are known risk factors for OIRD.[7]
- **Oliceridine**, a next generation investigational IV opioid not yet approved by FDA, is a G-protein selective agonist at the u-opioid receptor.[8]
- The G-protein selectivity results in analgesia with less recruitment of β-arrestin, a signaling pathway associated with adverse events such as OIRD.[8]
- In *Phase 3 controlled pivotal studies*, Oliceridine showed effective analgesia with improvements in safety/tolerability profile compared to morphine.[9,10]
- Recently, a *Phase 3 ATHENA open-label, multicenter study*, reported that Oliceridine IV in patients with moderate to severe acute pain, either in a broad range of surgical procedures or having painful medical conditions, is generally safe and well tolerated.[11]
- In this secondary analysis of data from the ATHENA trial, we report the incidence of OIRD among subsets of elderly patients (≥ 65 years) with BMI ≥ 30 kg/m², who underwent a broad range of surgical procedures.

METHODS

Figure 1: Study Design and Treatment Protocol

Men and women aged ≥ 18 years with a score ≥ 4 on an 11 – point numeric pain rating scale (NRS) treated as needed (PRN) with IV oliceridine via clinician-administered IV bolus dosing and / or by patient-controlled analgesia (PCA)



§Settings in which rapid analgesia was required, e.g., emergency department or post-anesthesia care unit
†As determined by the clinical need for parenteral opioid therapy
IV=intravenous; NRS=numeric rating scale; PRN, as needed

- Patients who underwent a surgical procedure were included:
  - **High-risk group:** ≥ 65 years with a BMI ≥ 30 kg/m².
  - **Low-risk group:** < 65 years with BMI < 30 kg/m².
- RR and SpO_2 were measured during the dosing period consistent with individual patient need and institutional standards of care.
- OIRD for this analysis was defined as
  - Administration of naloxone;
  - RR < 10bpm or SpO_2 < 90%
- Descriptive statistics were used to describe all events of OIRD up to 48 hours after the last dose of Oliceridine. Risk factors reported in the literature *to be associated with OIRD*[3] are listed in the descriptive analysis.

RESULTS

- In the ATHENA trial a total of 724 patients who underwent a broad range of surgical procedures (mean age 54.5 ± 15.9 years; mean BMI 30.6 ± 7.4 kg/m²), received Oliceridine IV.
  - Nearly half of the patients had a BMI ≥ 30 kg/m² (46.3%), and nearly one third (33.3%) were aged ≥ 65 years.
  - 120 patients were ≥ 65 years of age with BMI ≥ 30 kg/m² (high-risk group).
  - 268 patients were < 65 years of age with BMI < 30 kg/m² (low-risk group).

Table 1: Demographics and Clinical Characteristics in the High-Risk and Low-Risk Patients

	High-Risk Group	Low-Risk Group
N	120	268
Age, years, mean ± SD	70.3 ± 4.5	44.5 ± 13.7
BMI, kg/m², mean ± SD	35.6 ± 4.8	25.1 ± 3.4
Female, n (%) / Male, n (%)	72 (60.0) /48 (40.0)	189 (70.5)/ 79 (29.5)
Key Medical Comorbidities¶		
Asthma	13 (10.8)	20 (7.5)
Sleep Apnea	29 (24.2)	12 (4.5)
Chronic Obstructive Pulmonary Disease	14 (11.7)	7 (2.6)
Diabetes Mellitus	26 (21.7)	12 (4.5)
Hypertension	97 (80.8)	54 (20.1)
Key Prior Medications¶		
Other sedatives*	0	1 (0.4)
Benzodiazepines	102 (85.0)	237 (88.4)
Opioid anesthetics**	102 (85.0)	246 (91.8)
Gabapentinoids	78 (65.0)	38 (14.2)
Key Concomitant Medications¶		
Other sedatives*	0	0
Benzodiazepines	31 (25.8)	44 (16.0)
Opioid anesthetics**	1 (0.8)	16 (6.0)
Gabapentinoids	44 (36.7)	27 (10.1)

High-Risk Group: Age ≥ 65 years with BMI ≥ 30 kg/m²; Low-Risk Group: Age < 65 years with BMI < 30 kg/m², BMI=body mass index, SD=standard deviation
¶ Medical comorbidities and medications known to be associated with increased risk of OIRD[3]
**Other sedatives include dexmedetomidine and diphenhydramine*
***Fentanyl (used in most patients), sufentanil, remifentanil*

- **Table 1** shows the demographic and clinical characteristics in these subgroups.

Risk factors of OIRD

- The high-risk group had an overall higher incidence of medical comorbidities known to be associated with increased risk of OIRD[3] (**Table 1**).
- Use of medications known to be assoicated with increased risk of OIRD[3], eg, gabapentinoids, benzodiazepines and other sedatives, were higher in the high-risk group (**Table 1**).

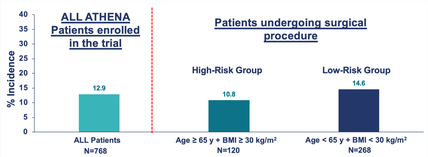
Exposure to Oliceridine (Table 2)

Table 2: Exposure to Oliceridine in the High-Risk and Low-Risk Patients

	High-Risk group	Low-Risk group
Administration		
PCA	72.5%	34.7%
Bolus IV	27.5%	65.3%
Mean cumulative dose, mg	37.1	30.0
Mean duration of expsoure, hours	39.8	28.1

High-Risk Group: Age ≥65 years with BMI ≥30 kg/m²; Low-Risk Group: Age <65 years with BMI <30 kg/m²

Figure 2: Incidence Of any OIRD in Patients Receiving Oliceridine



OIRD defined as any of the following: Respiratory rate (RR)< 10 bpm (including RR< 8 bpm), Oxygen saturation (SpO_2)< 90% (including SPO_2< 85%)

Table 3: Incidence of OIRD in the High-Risk and Low-Risk Patients

	High-Risk Group	Low-Risk Group
Oliceridine mean dose* (mg)	37.1	30.0
Naloxone Use, n	0	0
Any OIRD, n (%)	13 (10.8)	39 (14.6)
RR < 10 bpm, n (%)	6 (5.0)	31 (11.6)
SpO_2 < 90%, n (%)	8 (6.7)	11 (4.1)
RR < 10bpm and SpO_2 < 90%, n	0	0

* The morphine milligram equivalent (MME) of oliceridine to morphine is approximately 5:1. High-Risk Group: Age ≥65 years with BMI ≥30 kg/m²; Low-Risk Group: Age <65 years with BMI<30 kg/m²
OIRD defined as any of the following: RR<10 bpm (including RR< 8 bpm), SpO_2 <90% (including SPO_2 < 85%)

Respiratory Events

- Incidence of any OIRD in the high-risk group was similar to that observed in the low-risk group (**Figure 2**).
- No patients required naloxone or had both RR< 10 bpm *and* SpO_2 < 90% (**Table 3**).

Figure 3: Respiratory Events in A) High-Risk and Low-Risk Patients Receiving Oliceridine for Postoperative Pain and B) Historical Rates Reported in Literature in Surgical Population Receiving Conventional Opioids

Figure 3A: Naloxone Use

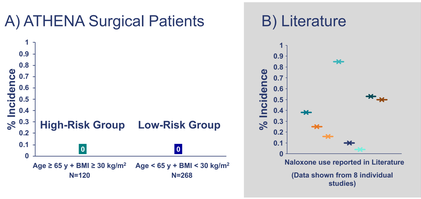


Figure 3B: RR < 10bpm

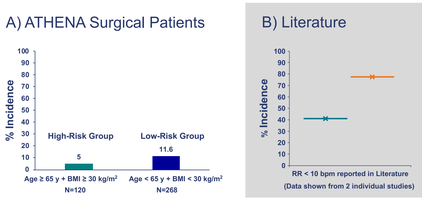
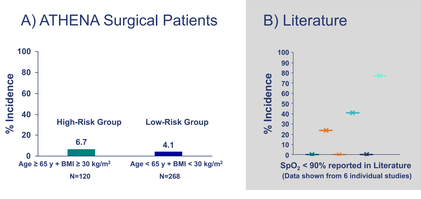


Figure 3C: SpO_2 < 90%



Data reported in the literature is based on a meta-analysis of published articles that included adult patients 18 years or older who were administered conventional opioids after surgery (general, orthopaedics, thoracic, urology, head and neck, transplant or neurosurgeries) and developed postoperative OIRD

CONCLUSION

- **The OIRD incidence in the high-risk group (elderly and obese) was similar to those observed in the low-risk group (younger and non-obese) despite higher age, BMI, comorbid burden, mean cumulative dose, mean duration of exposure, as well as higher PCA preference in the high-risk group.**
- **Findings suggest that elderly patients with high BMI receiving Oliceridine may not be at increased risk for OIRD.**
- **The use of Oliceridine may be clinically appropriate in patients at high risk for OIRD.**

References:

1. Kharasch ED, et al. Anesthesiology. 2016;124(4):960-965.
2. Overdyk F, et al. Pain Manag. 2014;4(4):317-325.
3. Gupta K, et al. BMJ open. 2018;8(12):e024086.
4. Lee LA, et al. Anesthesiology. 2015;122(3):659-665.
5. Taylor S, et al. Am J Surg. 2005;190(5):752-756.
6. Ramachandran SK, et al. J Clin Anesth. 2011;23(3):207-213.
7. Dahan A, et al. Anesthesiology. 2010;112(1):226-238.
8. DeWire SM, et al. J Pharmacol Exp Ther. 2013;344(3):708-717.
9. Singla NK, et al. Pain practice : the official journal of World Institute of Pain. 2019;19(7):715-731.
10. Viscusi ER, et al. Journal of Pain Research. 2019;12:927-943.
11. Bergese SD, et al. Journal of Pain Research. 2019;12:3113-3126.

Disclosure and Acknowledgements:

Oliceridine is an investigational IV opioid not approved by the FDA. Funding for the ATHENA study (NCT02656875) was provided by Trevena, Inc. Design for the poster and medical writing assistance (with guidance from authors) was provided by Kanaka Sridharan, MS R.Ph, employee at Trevena, Inc. Layout of the poster provided by Jenna Burnip from LARK & CO. CREATIVE, and funded by Trevena, Inc.