Elevated Body Mass Index Does Not Affect Adverse Events Associated with Oliceridine, An Intravenous Opioid Agonist

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BACKGROUND

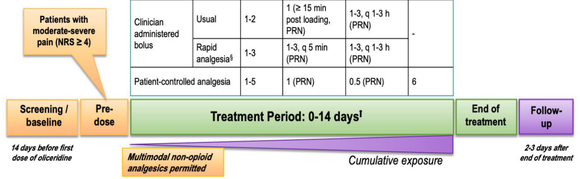
- In the postoperative setting, obesity has been shown to increase the likelihood of opioid-related adverse events (ORAEs), including respiratory and gastrointestinal events by 11% (1).
- This has a negative impact on patient health outcomes and can compromise optimal pain management.
- Oliceridine, a new class of IV opioid, that is a G protein-selective agonist at the mμ-opioid receptor, was recently approved for use in adults for the management of acute pain severe enough to require an IV opioid analgesic and for whom alternative treatments are inadequate (2).
- Preclinical findings showed that oliceridine is selective for G-protein signaling (achieving analgesia) with limited recruitment of β-arrestin (associated with ORAEs) (3). The translation of these findings in humans has not been fully established.
- Previously, in an exploratory analysis of a subgroup of patients undergoing a broad range of surgical procedures from the Phase 3 ATHENA open-label, multicenter study, we reported that the incidence of respiratory events associated with oliceridine was not affected by elevated body mass index (BMI) (4).
  - Incidence of opioid-induced respiratory depression (OIRD) defined as oxygen saturation (SpO_2) < 90% or respiratory rate < 10 bpm was 13.4% in patients with BMI 25-30 kg/m^2, 14.9% in patients with BMI > 30 to 40 kg/m^2 and 10.8% in morbidly obese patients (BMI > 40 kg/m^2) (4).
- Here we report the overall ORAEs from the ATHENA study by BMI categories (<30 kg/m^2, 30-40 kg/m^2 and >40 kg/m^2).

METHODS

Figure 1: ATHENA Study Design and Treatment Protocol

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

Oliceridine IV dosing / administration / setting		Oliceridine IV dose, mg			Lockout interval (min)
		Loading	Supplemental	Subsequent / demand	
Clinician administered bolus	Usual	1-2	1 (≥ 15 min post loading, PRN)	1-3, q 1-3 h (PRN)	-
	Rapid analgesia[§]	1-3	1-3, q 5 min (PRN)	1-3, q 1-3 h (PRN)	
Patient-controlled analgesia		1-5	1 (PRN)	0.5 (PRN)	6



[§]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

For this exploratory analysis:

- Safety and tolerability of oliceridine assessed by the incidence of observed or self-reported AEs, coded based on verbatim reported terms, using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0) are reported by BMI categories (<30 kg/m^2, 30-40 kg/m^2 and >40 kg/m^2).

RESULTS

- In the ATHENA study, 46% (352/768) of patients had BMI ≥ 30 kg/m^2, including 73 patients (10%) who were morbidly obese (BMI >40 kg/m^2).
- The patient demographics and clinical characteristics are shown in **Table 1**.

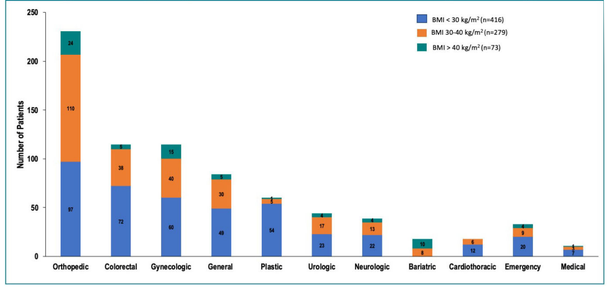
Table 1: Demographics and Clinical Characteristics

	BMI < 30 kg/m^2 N = 416	BMI 30-40 kg/m^2 N = 279	BMI > 40 kg/m^2 N = 73
Female, n (%)	267 (64.2)	173 (62.0)	58 (79.5)
Age, mean ± SD, years ≥ 65 to < 75 years, n (%) ≥ 75 years, n (%)	52.6 ± 17.5 85 (20.4) 39 (9.4)	56.9 ± 14.0 86 (30.8) 20 (7.2)	51.6 ± 13.4 14 (19.2) 3 (4.1)
*Race**			
White, n (%)	319 (76.7)	227 (81.4)	50 (68.5)
African American, n (%)	76 (18.3)	40 (14.3)	21 (28.8)
Asian, n (%)	10 (2.4)	3 (1.1)	0
Other, n (%)	9 (2.2)	9 (3.2)	2 (2.7)
Baseline NRS pain score, mean ± SD	6.2 ± 2.0	6.3 ± 2.2	6.6 ± 2.5

*Race not reported in 2 patients in the BMI category < 30 kg/m^2, BMI= Body mass index

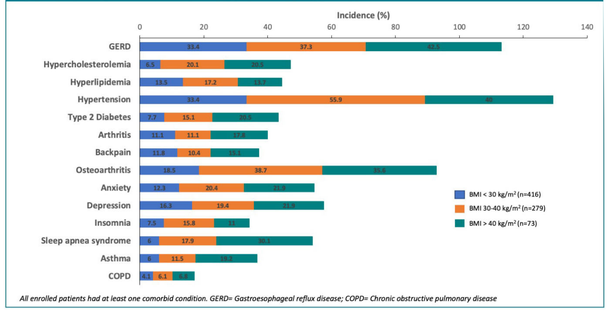
- The types of surgeries by BMI are shown in **Figure 2**. Obese patients (BMI > 30 kg/m^2) underwent comparable procedures to the non-obese patients, with the exception of plastic surgery.

Figure 2: Patients Receiving Oliceridine for Various Surgical Procedures or Nonsurgical Emergency or Medical Conditions Stratified by BMI Categories



- As seen in **Figure 3**, obese patients (BMI > 30 kg/m^2) had increased incidence of comorbidities.

Figure 3: Key Comorbidities by BMI Categories



All enrolled patients had at least one comorbid condition. GERD= Gastroesophageal reflux disease; COPD= Chronic obstructive pulmonary disease

- The distribution of patients receiving bolus or PCA dosing was similar for the three BMI categories. Likewise, the median dose and duration of exposure was also similar across the three BMI categories (**Table 2**).

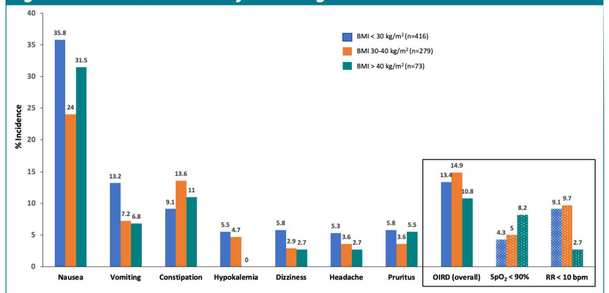
Table 2: Exposure to Oliceridine

	BMI < 30 kg/m^2 N = 416	BMI 30-40 kg/m^2 N = 279	BMI > 40 kg/m^2 N = 73
Bolus, n (%)	243 (58.4)	139 (49.8)	38 (52.1)
PCA, n (%)	173 (41.6)	140 (50.2)	35 (47.9)
Cumulative dose of oliceridine, mg Median (min, max)	17.0 (0.9, 223.5)	21.0 (1.0, 165.0)	20.0 (1.0, 158.9)
Duration of exposure (h) Median (min, max)	20.0 (0, 138.3)	21.3 (0, 142.7)	21.5 (0, 89.7)

PCA= Patient controlled analgesia. Duration of "0" hours refers to patients receiving only a single dose of oliceridine.

- Adverse events reported by at least 5% of patients in any BMI category are shown in **Figure 4**. Adverse events were comparable across the BMI categories.

Figure 4: Most Common AEs by BMI Categories



OIRD= opioid induced respiratory depression. OIRD defined by oxygen saturation (SpO_2 < 90%) or respiratory rate (RR) < 10 bpm. No patient had SpO_2 < 90% and RR < 10 bpm at the same time. No patient received naloxone during treatment with oliceridine.

CONCLUSIONS

- In patients treated with oliceridine, elevated BMI is not associated with increased risk of opioid-related adverse events.
- Oliceridine use in the postoperative setting for management of acute pain may be clinically appropriate in obese/morbidly obese individuals.

REFERENCES

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