Safety of Intravenous Oliceridine in Patients with Renal Impairment: Findings from a Phase 3 Open-label Study

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BACKGROUND

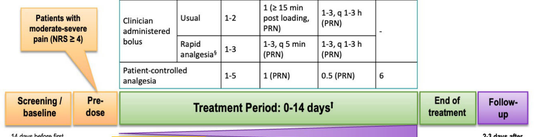
- Approximately 15% of the general population in the USA is estimated to have chronic kidney disease (CKD).[1]
- In the postoperative setting, patients with CKD are at a high risk of developing serious opioid related adverse events (ORAEs).[2]
- Furthermore, as most opioids or their metabolites are excreted by the kidneys, dosage adjustment is often required when estimated glomerular filtration rate (eGFR) falls below 50 mL/min.[3]
- Oliceridine, a new class of IV opioids, that is a G protein-selective agonist at the mu-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.[4]
- Preclinical findings showed that oliceridine is selective for G-protein signaling (achieving analgesia) with limited recruitment of β-arrestin (associated with ORAEs).[5] The translation of these findings in humans has not been fully established.
- Oliceridine has no active metabolites and findings from a Phase 1 pharmacokinetic study suggest no requirement for dosage adjustment in patients with renal impairment.[6]
- Here we report the safety of oliceridine in patients with renal impairment from the Phase 3 ATHENA open-label, multicenter study.
- The use of opioids for patients with moderate to severe renal insufficiency (stage 3 CKD or higher) poses one of the largest concerns for clinicians[7]
- Thus, for this report we combined the data for patients with stage 1 (eGFR ≥ 90 mL/min) or 2 CKD (eGFR 60 — < 90 mL/min) and compared them with those of patients with stage 3 CKD (eGFR 30 — < 60 mL/min).

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: Loading	Supplemental	Subsequent / demand	Lockout interval (min)
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

- ATHENA study included a total of 768 patients who received IV oliceridine for moderate to severe pain following a wide variety of surgeries or a medical condition. Based on calculated eGFR, the distribution of patients with CKD is shown in **Table 1**.

Table 1: Patients with CKD in the ATHENA trial

Stage of CKD	N = 768, n (%)
1	226 (29.4)
2	400 (52.1)
3	135 (17.6)
4	1 (0.1)
5	1 (0.1)
Total	**763**

Stage could not be calculated in 2 patients. Lab data was missing in 3 patients

For this analysis:

- A total of 761 patients was included in the overall analysis (*for the two patients with stage 4 or 5 CKD, the adverse events are reported separately*).
- The incidence of observed or self-reported adverse events (AEs), coded based on verbatim reported terms, using Medical Dictionary for Regulatory Activities (MedDRA, V19.0) is reported for patients with renal impairment at baseline.
  - We also report opioid-induced respiratory depression (OIRD) defined by oxygen saturation (SpO_2) < 90% or respiratory rate (RR) < 10 bpm.

RESULTS

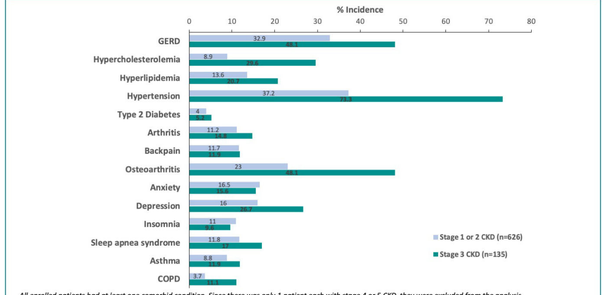
Table 2: Demographics and Clinical Characteristics

	Stage 1 or 2 CKD N = 626	Stage 3 CKD N = 135
Female, n (%)	404 (64.5)	90 (66.7)
Age, mean ± SD, years ≥ 65 to < 75 years, n (%) ≥ 75 years, n (%)	51.4 ± 15.8 125 (20.0) 35 (5.6)	66.3 ± 10.8 59 (43.7) 26 (19.3)
Race White, n (%) African American, n (%) Asian, n (%) Other, n (%)	 470 (75.1) 127 (20.3) 13 (2.1) 16 (2.6)	 123 (91.1) 10 (7.4) 0 2 (1.5)
BMI, mean ± SD, kg/m^2	30.3 ± 7.6	31.6 ± 6.4
BMI > 30 kg/m^2	266 (42.5)	78 (57.8)
Baseline NRS pain score, mean ± SD	6.3 ± 2.1	6.1 ± 2.1

BMI= body mass index, CKD= chronic kidney disease. There were 226 (29.6%) with stage 1 and 400 (52.1%) with stage 2 CKD.
Since there was only 1 patient each with stage 4 or 5 CKD, they were excluded from the analysis.

- The most common medical comorbidities are shown in **Figure 2.** The incidence of most comorbidities was numerically higher for the patients with stage 3 CKD.

Figure 2: Key Comorbidities in Patients with Chronic Kidney Disease



All enrolled patients had at least one comorbid condition. Since there was only 1 patient each with stage 4 or 5 CKD, they were excluded from the analysis.
GERD= Gastroesophageal reflux disease; COPD= Chronic obstructive pulmonary disease

- Almost half of all patients received oliceridine as a bolus injection; 57% of patients with stage 1 or 2 CKD and 43% of patients with stage 3 CKD (**Table 3**).

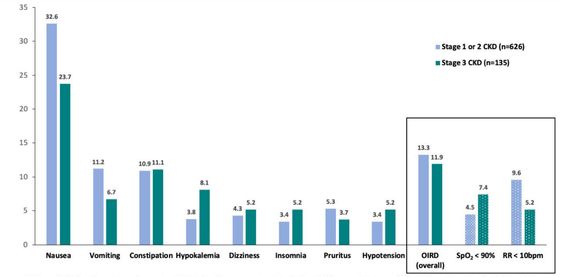
Table 3: Exposure to Oliceridine

	Stage 1 or 2 CKD N = 626	Stage 3 CKD N = 135
Bolus, n (%)	359 (57.3)	58 (43.0)
PCA, n (%)	267 (42.7)	77 (57.0)
Cumulative dose of oliceridine, mg Median (min, max)	8.0 (0.9, 223.5)	25.0 (1.0, 165.0)
Duration of exposure (h) Median (min, max)	19.3 (0, 141.1)	37.2 (0, 142.7)

PCA= Patient controlled analgesia. CKD= chronic kidney disease.
Duration of "0" h indicates use of a single dose of oliceridine. There were 226 (29.6%) with stage 1 and 400 (52.1%) with stage 2 CKD. Since there was only 1 patient each with stage 4 or 5 CKD, they were excluded from the analysis.

- The most common ORAEs were nausea, vomiting, constipation, hypokalemia, dizziness, insomnia, pruritus and hypotension. The incidence of ORAEs was comparable in the two CKD groups (**Figure 3**).
- The two patients with stage 4 or stage 5 CKD reported constipation, nausea or hypokalemia that were of mild intensity. Both of these patients did not experience OIRD.
- No patients received naloxone during treatment with oliceridine.

Figure 3: Most Common AEs in Patients with Chronic Kidney Disease



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. The 2 patients with stage 4 or 5 CKD did not experience OIRD.

CONCLUSIONS

- Use of IV oliceridine, did not increase the risk of ORAEs or OIRD in patients with stage 3 or higher CKD compared to those with stage 1 or 2 in this cohort.
- Use of IV oliceridine for moderate to severe acute pain may be clinically appropriate in patients with renal impairment.

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