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Attenuation of Adverse Events Over 7 Doses in Methylnaltrexone-Treated Patients With Opioid-Induced Constipation and Severe Medical Illness

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INTRODUCTION

- Patients with chronic pain from cancer or noncancer-related illness often are prescribed opioids for analgesia when nonopioid methods are ineffective
- Opioid analgesia is often limited by opioid-induced constipation (OIC), which occurs in 40 to 80% of opioid users[1]
- OIC results from stimulation of μ-opioid receptors in the gastrointestinal (GI) tract, which slows motility and decreases mucosal secretions,[1]
- Consequences of OIC include longer length of hospital stay, greater hospital costs, and increased risk of readmission[2,3]
- Methylnaltrexone (MNTX) is an FDA approved peripherally acting μ-opioid receptor antagonist[4]
- MNTX blocks μ-opioid receptors in the GI tract but exhibits a limited ability to cross the blood-brain barrier, resulting in relief from OIC while permitting opioid-mediated analgesia[5]
- In 2 double-blind, placebo (PBO)-controlled clinical trials in patients with advanced illness[6-8]:
  - MNTX achieved significantly more rescue-free laxation (RFL) responses than PBO within 4 and 24 hours after the first dose, and within 4 hours after ≥ 2 of the first 4 doses
  - GI events were the most common treatment-emergent adverse events (TEAEs)
  - GI TEAEs such as abdominal pain appeared to be associated with RFL response from MNTX[9]
- We analyzed MNTX clinical trial data across 7 doses of MNTX versus PBO for possible associations between effective laxation response and TEAEs over time

METHODS

- MNTX is indicated for the treatment of OIC in the following patient populations:
  - Adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who not require frequent (ie, weekly) opioid escalation
  - Adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care

Study Design

- This post hoc analysis assessed the incidence of TEAEs across 7 doses of subcutaneous MNTX versus PBO for the treatment of OIC in patients with and without cancer
- Data were pooled from 2 multicenter, double-blind, randomized, PBO-controlled clinical trials
  - Study 302 (NCT00402038)[6]
    - MNTX 0.15 mg/kg (adjustable to 0.30 mg/kg beginning on day 9) versus PBO every other day for 14 days
  - Study 4000 (NCT00672477)[7]
    - MNTX (8 mg for patients ≥ 38 to < 62 kg; 12 mg for patients ≥ 62 kg) versus PBO every other day for 14 days

Eligibility Criteria

- Detailed inclusion and exclusion criteria for study 302 and study 4000 have been published[6,7]
- Briefly, eligible patients had the following characteristics:
  - Aged ≥ 18 years
  - Advanced illness with life expectancy ≥ 1 month
  - Received opioids for analgesia for ≥ 2 weeks before study entry
  - Stable regimen of opioids and laxatives for ≥ 3 days before study entry
  - OIC, defined as < 3 bowel movements during the preceding week and no clinically meaningful laxation within 24 hours before the first dose of study drug or no laxation within 48 hours before the first dose of study drug

Assessments

- TEAEs occurring within 24 hours following each dose were reported
- Events occurring within 24 hours following each dose were evaluated in patients with and without RFL responses to treatment within 4 hours to assess the influence of effective RFL response on the incidence of TEAEs, GI TEAEs, and abdominal pain

Statistical Analysis

- TEAEs were described for each treatment group using summary statistics
- Cohorts analyzed were the full pooled safety analysis cohort, the cancer cohort, and the noncancer cohort

RESULTS

Patient Disposition & Baseline Characteristics

- In the full pooled safety analysis cohort, 179 patients received MNTX (cancer patients, n = 116; noncancer patients, n = 63), and 185 patients received PBO (cancer patients, n = 114; noncancer patients, n = 71) (Table 1)

Table 1. Patient Demographics and Baseline Characteristics

	PBO (n = 185)	MNTX (n = 179)	Total (N = 363)
Age, mean (SD), years	66.1 (13.9)	66.5 (13.4)	66.3 (13.7)
Age category, n (%)			
< 65 years	89	83	172
≥ 65 years	96	95	191
Sex, n (%)			
Male	89 (48.1)	87 (48.9)	176 (48.5)
Female	96 (51.9)	91 (51.1)	187 (51.5)
Race, n (%)			
Black or African American	8 (4.3)	6 (3.4)	14 (3.9)
White	173 (93.5)	168 (94.4)	341 (93.9)
Other	4 (2.2%)	4 (2.2%)	8 (2.2%)
Ethnicity, n (%)			
Hispanic or Latino	11 (5.9)	11 (6.2)	22 (6.1)
Not Hispanic or Latino	174 (94.1)	167 (93.8)	341 (93.9)
Weight, mean (SD), kg	72.6 (24.0)	71.2 (19.7)	71.9 (22.0)
Primary diagnosis, n (%)			
Cancer	114 (61.6)	116 (65.2)	230 (63.4)
Cardiovascular disease	20 (10.8)	21 (11.8)	41 (11.3)
Neurologic disease	10 (5.4)	10 (5.6)	20 (5.5)
Pulmonary disease	18 (9.7)	23 (12.9)	41 (11.3)
Other	23 (12.4)	8 (4.5)	31 (8.5)
ECOG Score, n (%)			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	21 (11.4)	21 (11.8)	42 (11.6)
2	57 (30.8)	54 (30.3)	111 (30.6)
3	78 (42.2)	73 (41.0)	151 (41.6)
4	27 (14.6)	27 (15.2)	54 (14.9)
OME, mg/d			
Mean (SD)	372.8 (1016.9)	376.3 (699.9)	374.5 (874.7)
Median (range)	130 (0–10160)	156 (0–4427)	146 (0–10160)
OME categories, n (%)			
< 80 mg/d	57 (30.8)	42 (23.5)	99 (27.3)
80 to < 150 mg/d	42 (22.7)	39 (21.8)	81 (22.3)
≥ 150 mg/d	86 (46.5)	97 (54.2)	183 (50.4)
Laxatives used at baseline, n (%)			
Number of laxatives			
0	2 (1.1)	3 (1.7)	5 (1)
1	48 (25.9)	56 (31.5)	104 (29)
2	69 (37.3)	65 (36.5)	134 (37)
3	40 (21.6)	27 (15.2)	67 (18)
≥ 4	26 (14.1)	27 (15.2)	53 (14.6)
Type of laxative			
Osmotic agent	82	85	167
Stimulant	149	136	285
Stool softener	98	92	190

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; OME = oral morphine equivalent; PBO = placebo.

Incidence of TEAEs

- The majority of patients in either treatment group experienced at least 1 TEAE (MNTX, 81.6%; PBO, 76.2%), which were mostly GI in nature (ie, abdominal pain, nausea, and flatulence) and mild to moderate in severity (Table 2)
- The proportion of MNTX-treated patients with a TEAE in the full, cancer, and noncancer cohorts decreased from dose 1 (26.3%, 30.2%, 19.0%, respectively) to dose 7 (10.2%, 10.4%, 9.8%, respectively)
- Slight reductions in the incidence of TEAEs were also observed in the PBO group in the full, cancer, and noncancer cohorts from dose 1 (14.6%, 14.9%, 14.1%, respectively) to dose 7 (12.2%, 12.3%, 12.0%, respectively)
- GI TEAEs were reduced in the full, cancer, and noncancer cohorts in the MNTX-treated patients from dose 1 (20.7%, 25.0%, 12.7%) to dose 7 (7.4%, 7.5%, 7.3%) and in PBO-treated patients from dose 1 (8.1%, 8.8%, 7.0%) to dose 7 (4.1%, 5.5%, 2.0%)

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients

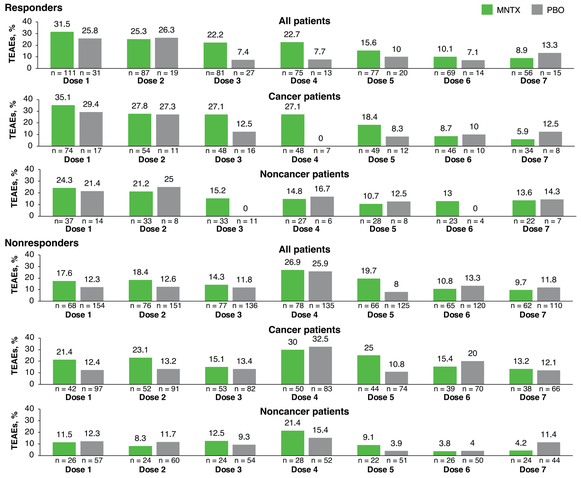
	PBO (n = 185)	MNTX (n = 179)
Patients with ≥ 1 TEAE	141 (76.2)	146 (81.6)
Abdominal pain	19 (10.3)	39 (21.8)
Nausea	23 (12.4)	20 (11.2)
Flatulence	10 (5.4)	16 (8.9)
Back pain	3 (1.6)	12 (6.7)
Peripheral edema	12 (6.5)	12 (6.7)
Abdominal pain NOS	9 (4.9)	11 (6.1)
Disease progression	17 (9.2)	10 (5.6)
Fall	11 (5.9)	10 (5.6)
Diarrhea	15 (8.1)	9 (5.0)
Confusional state	11 (5.9)	9 (5.0)
Asthenia	10 (5.4)	7 (3.9)
Malignant neoplasm progression	13 (7.0)	7 (3.9)
Abdominal distension	11 (5.9)	6 (3.4)
Vomiting	10 (5.4)	5 (2.8)

AE = adverse event; MNTX = methylnaltrexone; NOS = not otherwise specified; PBO = placebo; TEAE = treatment-emergent adverse event.

Incidence of TEAEs According to RFL Response

- The incidence of TEAEs was similar among responding patients at each dose with MNTX and PBO in the full, cancer, and noncancer cohorts (Figure 1A)
- At most doses, responders were more likely to have TEAEs than nonresponders, regardless of treatment (Figure 1A and 1B)

Figure 1. Incidence of TEAEs According to Treatment Response at Each Dose

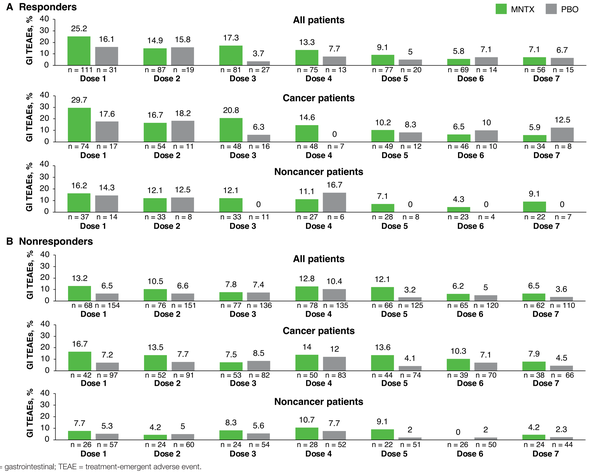


TEAE = treatment-emergent adverse event.

Incidence of GI AEs According to Treatment Response

- GI AEs were the most common TEAEs and decreased in MNTX responders from dose 1 (25.2%, 29.7%, 16.2%) to dose 7 (7.1%, 5.9%, 9.1%) and PBO responders from dose 1 (16.1%, 17.6%, 14.3%) to dose 7 (6.7%, 12.5%, 0%) in all patients, cancer patients, and noncancer patients, respectively (Figure 2A)
- At most doses, responders were more likely to have GI AEs than nonresponders, regardless of treatment (Figure 2A and 2B).

Figure 2. Incidence of GI TEAEs According to Treatment Response at Each Dose

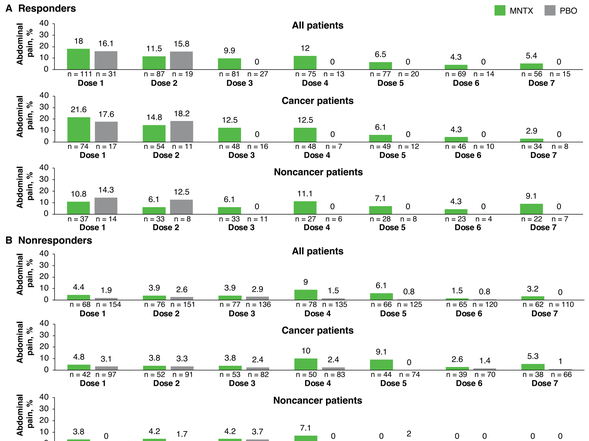


GI = gastrointestinal; TEAE = treatment-emergent adverse event.

Incidence of Abdominal Pain According to Treatment Response

- The incidence of abdominal pain decreased over time in responders (Figure 3A)
- Responders were more likely to have abdominal pain than nonresponders (Figure 3A and 3B)
- Among nonresponders, MNTX-treated patients had a significantly higher incidence of abdominal pain than PBO-treated patients with doses 4 and 5 in the full cohort and with dose 5 in the cancer cohort (Figure 3B)

Figure 3. Incidence of Abdominal Pain According to Treatment Response at Each Dose



CONCLUSION

- Consistent with previous observations, the most common TEAEs with MNTX treatment were GI in nature
- The association of observed TEAEs and treatment response suggests that laxation response is a factor driving AEs with MNTX
- The incidence of TEAEs with MNTX in patients with advanced illness and OIC improves with repeat dosing
  - This suggests that improvement of OIC with MNTX treatment reduces GI TEAEs

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DISCLOSURES

GS Sayuk is a consultant and speaker for Salix, Ironwood, Allergan, Alnylam, GI Health Foundation, and Rome Foundation. **ED Shah** has nothing to disclose. **QT Yu** has nothing to disclose. **NE Slatkin** is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US. **RB Brookfield** is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US. **N Stambler** is an employee of Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc. **RJ Israel** is an employee of Bausch Health US, LLC.

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