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Subcutaneous Methylnaltrexone in Patients With Advanced Illness and Opioid-Induced Constipation: The Impact of Baseline Laxative Use

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INTRODUCTION

- Opioid-induced constipation (OIC) has a significant impact on patients in hospital and long-term care settings and is associated with longer hospitalization length of stay, greater total hospital costs, greater risks of intensive care admissions, and increased risk of hospital readmissions and emergency department visits[1,2]
- OIC is often difficult to treat, with the majority of inpatients using multiple types of laxatives often with little relief[3,4]
  - In a study of inpatients receiving oxycodone for pain, three quarters were receiving at least 1 laxative for OIC[5]
- Methylnaltrexone (MNTX) is a peripherally acting μ-opioid receptor antagonist indicated for OIC
- MNTX is approved for
  - The treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid dosage escalation[6]
  - The treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[6]
- It is unknow if rescue-free laxation (RFL) improvement observed in the double-blind, placebo-controlled, efficacy trials of MNTX varied based on the type of baseline laxative used
- We evaluated whether baseline osmotic agent (eg, milk of magnesia, polyethylene glycol, lactulose, sorbitol), stimulant (eg, senna, bisacodyl), or stool softener (eg, docusate sodium) use affected the efficacy and safety of MNTX in a subgroup of OIC patients with advanced illness

METHODS

Key Inclusion Criteria

- Aged ≥18 years
- Diagnosis of advanced illness with a life expectancy of ≥1 month
- Receiving opioids for discomfort or pain management for ≥2 weeks and taking a stable regimen for at least 3 days before the first dose
- OIC definition
  - <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before first dose of study drug
  - No clinically significant laxation within 48 hours before first dose of study drug
  - For patients taking laxatives, the regimen was to be stable for ≥3 days before the first dose of study drug and was permitted to continue throughout the study

Key Exclusion Criteria

- History of MNTX treatment (for study 4000, MNTX during the 7 days before the study dose)
- Mechanical bowel obstruction, fecal impaction, or history of fecal ostomy
- Any potential nonopioid cause of bowel dysfunction, in the opinion of the investigator, that might have been primarily responsible for constipation

Study Design

- Two multicenter, randomized, double-blind, placebo-controlled, institutional review board–approved clinical studies in adult patients with OIC and advanced illness were pooled (study 302, NCT00402038[7]; study 4000, NCT00672477[8])
  - Study 302 compared subcutaneous MNTX 0.15 mg/kg versus placebo every other day for 2 weeks
  - Study 4000 compared body weight–based subcutaneous MNTX 8 mg (38–<62 kg) or 12 mg (≥62 kg) versus placebo every other day for 2 weeks
- The number of patients who received baseline osmotic agents, stimulants, and/or stool softeners, which were permitted to continue during the studies, were identified

Assessments

- Efficacy endpoints
  - RFL within 4 or 24 hours after the first dose (ie, a spontaneous bowel movement without requiring rescue laxatives)
  - Pain intensity (evaluated using an 11-point scale)
- Safety endpoints included treatment-emergent adverse events

Statistical Analysis

- Efficacy analyses were performed on the intent-to-treat analysis, defined as patients who received at least 1 dose of study medication
- In both studies, RFL response data were analyzed by chi-square tests
- The nominal significance level was 0.05, with no multiplicity adjustment

RESULTS

Patient Disposition

- Pooling the studies yielded 363 patients with advanced illness (placebo = 185; MNTX = 178)
  - Of those, 286, 167, or 190 patients were using a laxative regimen at baseline that contained a stimulant, osmotic agent, or stool softener, respectively; patients were permitted to use more than 1 type of laxative (Table 1)
- A comparable number of patients discontinued the study whether they used an osmotic agent (28.2%–29.3%) a stimulant (23.4%–24.2%) or a stool softener (20.7%–23.5%) at baseline

Table 1. Patient Disposition by Baseline Laxative Type (Pooled ITT Analysis)

	Osmotic Agent		Stimulant		Stool Softener	
	Placebo (n = 82)	MNTX (n = 85)	Placebo (n = 149)	MNTX (n = 137)	Placebo (n = 98)	MNTX (n = 92)
Patients treated[a]	82 (100)	85 (100)	149 (100)	137 (100)	98 (100)	92 (100)
Patients completed	58 (70.7)	61 (71.8)	113 (75.8)	105 (76.6)	75 (76.5)	73 (79.3)
Patients discontinued	24 (29.3)	24 (28.2)	36 (24.2)	32 (23.4)	23 (23.5)	19 (20.7)
Administrative/ investigator decision	0	1 (1.2)	2 (1.3)	1 (0.7)	1 (1.0)	2 (2.2)
Adverse event	6 (7.3)	6 (7.1)	9 (6.0)	11 (8.0)	4 (4.1)	6 (6.5)
Death	9 (11.0)	9 (10.6)	12 (8.1)	11 (8.0)	10 (10.2)	6 (6.5)
Lack of efficacy	1 (1.2)	2 (2.4)	1 (0.7)	2 (1.5)	1 (1.0)	0
Missing/lost to follow-up	0	1 (1.2)	1 (0.7)	0	0	0
Withdrawal by patient	4 (4.9)	3 (3.5)	8 (5.4)	4 (2.9)	5 (5.1)	4 (4.3)
Protocol violation	2 (2.4)	0	1 (0.7)	1 (0.7)	0	1 (1.1)
Other	2 (2.4)	2 (2.4)	2 (1.3)	2 (1.5)	2 (2.0)	0

[a]Patients were permitted to use more than 1 laxative type at baseline.
All values are n (%).
ITT = intent to treat; MNTX = methylnaltrexone.

Patient Demographics

- Table 2 describes the baseline and disease characteristics among the groups based on osmotic agent, stimulant, and/or stool softener use at baseline
- The study population was largely laxative refractory with 98.6% of patients using at least 1 laxative at baseline

Table 2. Baseline Demographics and Disease Characteristics by Laxative Type

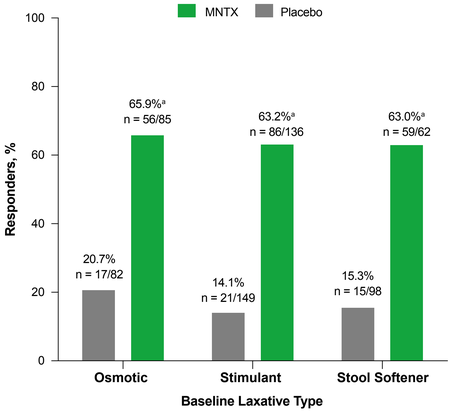
	Osmotic Agent		Stimulant		Stool Softener	
	Placebo (n = 82)	MNTX (n = 85)	Placebo (n = 149)	MNTX (n = 136)	Placebo (n = 98)	MNTX (n = 92)
Mean age, years (range)	63.4 (35–93)	64.6 (27–101)	66.7 (32–98)	66.7 (27–101)	68.3 (41–98)	67.4 (27–93)
Women, n (%)	41 (50.0)	46 (54.1)	80 (53.7)	66 (48.5)	54 (55.1)	50 (54.3)
Race, n (%)						
White	78 (95.1)	81 (95.3)	140 (94.0)	130 (95.6)	91 (92.9)	88 (95.7)
Black/African American	4 (4.9)	2 (2.4)	8 (5.4)	4 (2.9)	5 (5.1)	3 (3.3)
American Indian/Alaskan Native/Other	0	1 (1.2)	1 (0.7)	1 (0.7)	2 (2.0)	1 (1.1)
Asian	0	1 (1.2)	0	1 (0.7)	0	0
Baseline ECOG score, n (%)						
≤2	41 (50.0)	37 (43.5)	61 (40.9)	59 (43.4)	40 (40.8)	41 (44.6)
>2	41 (50.0)	48 (56.5)	88 (59.1)	77 (56.6)	58 (59.2)	51 (55.4)
Median daily dose opioid morphine equivalents (mg/d)	180.0	190.0	120.0	161.5	110.0	144.0
Primary diagnosis, n (%)						
Cancer	56 (68.3)	56 (65.9)	91 (61.1)	86 (63.2)	61 (62.2)	54 (58.7)
Pulmonary disease	9 (11.0)	10 (11.8)	18 (12.1)	21 (15.4)	9 (9.2)	14 (15.2)
Cardiovascular	7 (8.5)	8 (9.4)	14 (9.4)	17 (12.5)	12 (12.2)	16 (17.4)
Neurologic	3 (3.7)	5 (5.9)	9 (6.0)	7 (5.1)	5 (5.1)	5 (5.4)
Other	7 (8.5)	6 (7.1)	17 (11.4)	5 (3.7)	11 (11.2)	3 (3.3)

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone.

Efficacy

- A greater proportion of patients who received MNTX (63%–66%) had RFL within 4 hours compared with placebo (14%–21%) regardless of the type of laxative used at baseline ($P < 0.0001$, Figure 1)

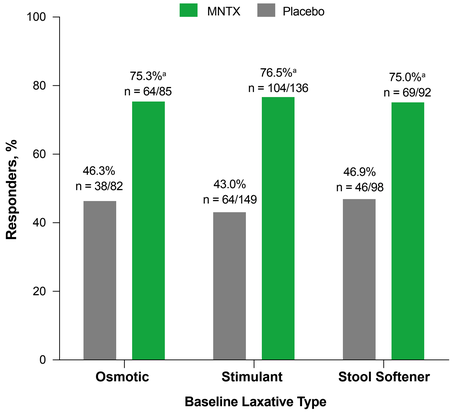
Figure 1. The Proportion of Patients With RFL Response (Responders) Within 4 Hours of Study Drug Administration



[a]$P < 0.0001$.
MNTX = methylnaltrexone; RFL = rescue-free laxation.

- Similar findings were observed for those with RFL response within 24 hours of MNTX treatment (75%–77%) versus placebo (43%–47%, $P \leq 0.0001$, Figure 2)

Figure 2. The Proportion of Patients With RFL Response (Responders) Within 24 Hours of Study Drug Administration

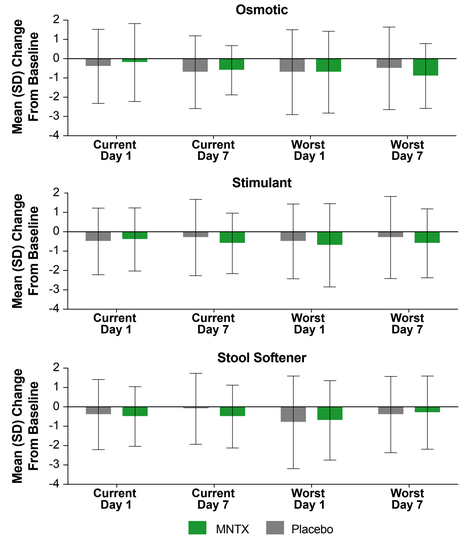


[a]$P \leq 0.0001$.
MNTX = methylnaltrexone; RFL = rescue-free laxation.

Safety

- There were no significant differences between MNTX or placebo in the change from baseline in current or worst pain scores after 1 day or 7 days regardless of the type of laxative used at baseline (Figure 3)

Figure 3. Mean (SD) Change From Baseline in Current and Worst Pain Scores at Day 1 and Day 7 Among Patients Using an Osmotic, Stimulant, or Stool Softener Laxative



- The most commonly reported treatment-emergent adverse event was abdominal pain (Table 3)

Table 3. Treatment-Emergent Adverse Events for Patients Who Used an Osmotic Agent, Stimulant, or Stool Softener Laxative at Baseline (>5%, Safety Population)

	Osmotic Agent		Stimulant Use		Stool Softener	
	Placebo (n = 82)	MNTX (n = 85)	Placebo (n = 149)	MNTX (n = 137)	Placebo (n = 98)	MNTX (n = 92)
Abdominal pain[a]	15 (18.3)	32 (37.6)	24 (16.1)	39 (28.5)	15 (15.3)	20 (21.7)
Nausea	13 (15.9)	13 (15.3)	16 (10.7)	12 (8.8)	13 (13.3)	9 (9.8)
Flatulence	3 (3.7)	11 (12.9)	8 (5.4)	11 (8.0)	7 (7.1)	8 (8.7)
Disease progression	10 (12.2)	8 (9.4)	15 (10.1)	9 (6.6)	11 (11.2)	7 (7.6)
Back pain	1 (1.2)	8 (9.4)	3 (2.0)	9 (6.6)	3 (3.1)	5 (5.4)
Abdominal distention	7 (8.5)	6 (7.1)	10 (6.7)	4 (2.9)	7 (7.1)	3 (3.3)
Asthenia	5 (6.1)	6 (7.1)	8 (5.4)	6 (4.4)	6 (6.1)	4 (4.3)
Peripheral edema	8 (9.8)	6 (7.1)	9 (6.0)	11 (8.0)	6 (6.1)	7 (7.6)
Fall	9 (11.0)	6 (7.1)	9 (6.0)	9 (6.6)	6 (6.1)	8 (8.7)
Diarrhea	7 (8.5)	5 (5.9)	14 (9.4)	7 (5.1)	10 (10.2)	7 (7.6)
Vomiting	6 (7.3)	5 (5.9)	8 (5.4)	3 (2.2)	7 (7.1)	2 (2.2)
Dizziness	3 (3.7)	5 (5.9)	7 (4.7)	6 (4.4)	4 (4.1)	2 (2.2)
Confusional state	8 (9.8)	5 (5.9)	10 (6.7)	7 (5.1)	6 (6.1)	7 (7.6)
Pyrexia	5 (6.1)	4 (4.7)	5 (3.4)	7 (5.1)	2 (2.0)	5 (5.4)
Malignant neoplasm progression	7 (8.5)	2 (2.4)	10 (6.7)	7 (5.1)	3 (3.1)	1 (1.1)
Fatigue	3 (3.7)	3 (3.5)	5 (3.4)	4 (2.9)	5 (5.1)	3 (3.3)

[a]Includes abdominal pain and abdominal pain not otherwise specified.
All values are n (%).

CONCLUSIONS

- **Among laxative-refractory patients with advanced illness and OIC, use of MNTX significantly increased the proportion of patients with RFL response within 4 and 24 hours of treatment independent of the type of laxative used**
- **MNTX did not reduce the analgesic effects of opioid treatment and did not induce unexpected adverse events within the cohorts**
- **MNTX may be particularly useful in the hospital or emergency department settings for the treatment of OIC in patients with serious or advanced illness who have failed to respond to laxative treatment**

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DISCLOSURES

Dr. Yu has nothing to disclose. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US, LLC. Dr. Stambler is an employee of Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc. Dr. Israel is an employee of Bausch Health US, LLC.

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