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Subcutaneous Methylnaltrexone Treatment of Opioid-Induced Constipation in Adults With Rheumatic Conditions

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ABSTRACT

Background/Purpose: In patients taking opioid analgesics, opioid-induced constipation (OIC) is estimated to affect up to 81% of patients and is caused by peripheral mu-opioid receptor activation in the gastrointestinal (GI) tract. Methylnaltrexone is a peripherally-acting mu-opioid receptor antagonist that reverses opioid-related constipating effects in the GI tract without affecting centrally-mediated analgesia. Patients with a rheumatic disease may take opioid analgesics for chronic pain and develop OIC. The aim of this subgroup analysis was to assess the efficacy/safety of methylnaltrexone for OIC in patients who participated in a phase 3 trial and had ankylosing spondylitis (AS), fibromyalgia, rheumatoid arthritis (RA), or osteoarthritis (OA).

Methods: A phase 3, randomized, double-blind, placebo-controlled trial enrolled adults with chronic (≥2 months) noncancer pain taking ≥50 mg oral morphine equivalent dose (MED) for ≥2 weeks who had a mean of <3 bowel movements/week. Enrolled patients with a medical history of AS, fibromyalgia, RA, or OA who received subcutaneous (SC) methylnaltrexone 12 mg every other day or placebo for 4 weeks were included in the current analysis. The original trial coprimary endpoints were the percentage of patients with a rescue-free (RF) bowel movement (ie, bowel movement occurring without any laxative use within previous 24 hours) within 4 hours after the first treatment was administered and the percentage of treatments (injections) resulting in an RF bowel movement within 4 hours during the 4-week treatment period.

Results: A total of 23 and 24 patients were included in the methylnaltrexone and placebo groups, respectively: the mean (SD) age was 50.6 (8.8) y vs 54.0 (11.8) y; the majority was female (82.6% vs 75.0%); the baseline mean (SD) weekly number of RF bowel movement was 0.8 (0.6) vs 1.1 (0.7); osteoarthritis (43.5% vs 58.3%) and fibromyalgia (39.1% vs 33.3%) were the most common conditions. The percentage of patients taking a morphine equivalent ≥100 mg at baseline was 56.5% and 45.8% in the methylnaltrexone and placebo groups, respectively. Overall, significantly more patients treated with SC methylnaltrexone 12 mg QOD had an RF bowel movement within 4 hours of the first dose compared with placebo (43.5% vs 4.2%; *P*=0.002), with a rapid onset of action. In addition, a significantly higher percentage of treatments (injections) during the 4-week period resulted in an RF bowel movement within 4 hours with methylnaltrexone vs placebo (28.7% vs 13.5%, respectively; *P*=0.01). One patient treated with methylnaltrexone discontinued from the study due to an adverse event (AE). Common AEs were mostly GI-related, possibly due to symptoms of OIC and/or mechanism of induction of an RF bowel movement. The most common AEs in the methylnaltrexone group (n=23) vs placebo (n=24) were: diarrhea (17.4% vs 8.3%), abdominal pain (13.0% vs 16.7%), headache (8.7% vs 4.2%), hot flush (8.7% vs 8.3%), nausea (8.7% vs 4.2%), upper abdominal pain (8.7% vs 0%), urinary tract infection (8.7% vs 4.2%), and flatulence (4.3% vs 8.3%).

Conclusion: Subcutaneous methylnaltrexone QOD was efficacious, with a rapid onset of action, and generally well tolerated for the treatment of OIC in adults with rheumatic disease.

BACKGROUND

- In patients taking opioid analgesics, opioid-induced constipation (OIC) is estimated to affect up to 81% of patients[1-5]
  - Adults taking opioids who had OIC reported significantly worse health-related quality of life (Short-Form 8 Health Survey) compared with those who had not developed OIC (*P*<0.05; mental and physical components)[6]
  - In another study, more than half (57.0%) of 477 patients surveyed stated they had taken less opioid medication than prescribed due to adverse effects, and of those, 90.0% indicated this was mainly due to OIC[7]
- OIC is caused by opioid binding to peripheral mu-opioid receptors in the gastrointestinal (GI) tract, causing decreased GI motility and alterations in fluid secretion and absorption[8]
  - Although over-the-counter medications (eg, laxatives, stool softeners) may be tried as first-line therapy for OIC, they are often ineffective and do not address the underlying cause (ie, opioid–mu-opioid receptor binding)[8]
- Methylnaltrexone is a peripherally-acting mu-opioid receptor antagonist that reverses opioid-related constipating effects in the GI tract without affecting centrally mediated analgesia[9]
  - Oral and subcutaneous (SC) formulations are indicated for the treatment of OIC in adults with chronic noncancer pain
  - The SC formulation is also indicated for OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care
- Patients with a rheumatic disease may take opioid analgesics for chronic pain and develop OIC; therefore, safe and effective treatments are needed that target the underlying cause of OIC

PURPOSE

- To assess the efficacy and safety of SC methylnaltrexone for the treatment of OIC in patients with ankylosing spondylosis, fibromyalgia, rheumatoid arthritis (RA), or osteoarthritis (OA)

METHODS

Patient population

- Adults with chronic (≥2 months) noncancer pain taking ≥50 mg oral morphine equivalent dose (MED) for ≥2 weeks
  - History of constipation related to opioid use ≥1 month before screening, with constipation defined as mean of <3 bowel movements/week (rescue free [RF], defined as without laxative use within previous 24 hours) with ≥1 of the following:
    - Hard or lumpy stools
    - Sensation of incomplete evacuation after bowel movements
    - Straining during bowel movements
  - Exclusion criteria included history of inflammatory bowel disease within the previous 6 months, evidence of bowel obstruction or impaction, and history of chronic constipation before starting opioid therapy
- GI-targeted treatments that were not permitted during the study included bulking agents (eg, bran, psyllium), loperamide, lubiprostone, manual maneuvers, prokinetic agents (eg, metoclopramide), and stool softeners
- Current subgroup analysis included patients with a medical history of ankylosing spondylosis, fibromyalgia, RA, or OA who received ≥1 dose of study medication

Study design, treatment, and assessments

- Phase 3, randomized, double-blind, placebo-controlled trial
- Patients received SC methylnaltrexone 12 mg every other day (QOD) or placebo for 4 weeks*
- Information on the number of bowel movements, bowel movement consistency, straining, sensation of complete evacuation, and rescue laxative use was reported via a daily diary
- **Original trial coprimary endpoints:** percentage of patients with an RF bowel movement within 4 hours after the first treatment was administered and percentage of treatments (injections) resulting in an RF bowel movement within 4 hours during the 4-week treatment period

*SC methylnaltrexone 12 mg once daily treatment arm of the original trial was not included in the current analyses. Dosing of SC placebo was once daily and patients treated with SC methylnaltrexone 12 mg QOD received SC placebo on alternating days.

RESULTS

- A total of 23 and 24 patients were included in the methylnaltrexone and placebo groups, respectively (**Table 1**)
  - Majority of patients were female, baseline mean weekly number of RF bowel movements was approximately 1, and OA and fibromyalgia were the most common primary pain conditions in the 2 treatment groups
  - Percentage of patients taking a morphine equivalent ≥100 mg at baseline was 56.5% and 45.8% in the methylnaltrexone and placebo groups, respectively

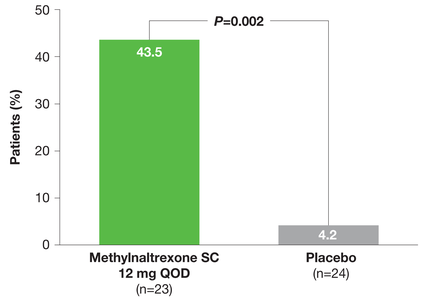
Table 1. Demographic and Baseline Characteristics

Parameter	Methylnaltrexone SC 12 mg QOD (n=23)	Placebo (n=24)
Age, y		
Mean (SD)	50.6 (8.8)	54.0 (11.8)
Range	27-64	32-83
Female, n (%)	19 (82.6)	18 (75.0)
Race, n (%)		
White	20 (87.0)	18 (75.0)
Black	1 (4.3)	4 (16.7)
Other	2 (8.7)	2 (8.3)
Primary pain condition, n (%)		
Ankylosis spondylosis	1 (4.3)	0
Fibromyalgia	9 (39.1)	8 (33.3)
OA	10 (43.5)	14 (58.3)
RA	3 (13.0)	2 (8.3)
Baseline MED, n (%)		
≥50 to <60 mg	3 (13.0)	2 (8.3)
≥60 to <100 mg	7 (30.4)	11 (45.8)
≥100 to <400 mg	11 (47.8)	7 (29.2)
≥400 mg	2 (8.7)	4 (16.7)
Baseline weekly number of RF bowel movements, mean (SD)	0.8 (0.6)	1.1 (0.7)

MED = morphine equivalent dose; OA = osteoarthritis; QOD = every other day; RA = rheumatoid arthritis; RF = rescue-free; SC = subcutaneous.

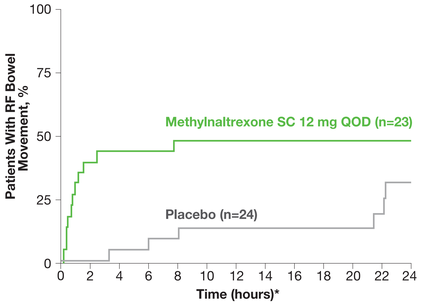
- Significantly more patients treated with methylnaltrexone 12 mg QOD had an RF bowel movement within 4 hours of the first dose compared with placebo (**Figure 1**; *P*=0.002), with a rapid onset of action (**Figure 2**)

Figure 1. Percentage of Patients With a RF Bowel Movement Within 4 Hours of the First Treatment Dose



QOD = every other day; RF = rescue-free; SC = subcutaneous.

Figure 2. Time to First RF Bowel Movement After First Dose



*Data censored at 24 hours.
QOD = every other day; RF = rescue-free; SC = subcutaneous.

- In addition, a significantly higher percentage of treatments (injections) during the 4-week period resulted in an RF bowel movement within 4 hours with methylnaltrexone vs placebo (28.7% vs 13.5%, respectively; *P*=0.01)
- Methylnaltrexone was well tolerated, and the most common treatment-emergent adverse events were mostly GI-related, possibly due to symptoms of OIC and/or mechanism of induction of an RF bowel movement (**Table 2**)

Table 2. Adverse Event Summary

Patients with an AE, n (%)	Methylnaltrexone SC 12 mg QOD (n=23)	Placebo (n=24)
Any AE	11 (47.8)	12 (50.0)
Discontinuations due to an AE	1 (4.3)	0
Serious AEs	0	0
Most common AEs*		
Diarrhea	4 (17.4)	2 (8.3)
Abdominal pain	3 (13.0)	4 (16.7)
Headache	2 (8.7)	1 (4.2)
Hot flush	2 (8.7)	2 (8.3)
Nausea	2 (8.7)	1 (4.2)
Upper abdominal pain	2 (8.7)	0
Urinary tract infection	2 (8.7)	1 (4.2)
Flatulence	1 (4.3)	2 (8.3)

*≥5.0% of patients in any treatment group (excluding primary pain conditions defined as an AE).
AE = adverse event; SC = subcutaneous.

CONCLUSIONS

- Subcutaneous methylnaltrexone QOD was efficacious, with a rapid onset of action, and generally well tolerated for the treatment of OIC in adults with rheumatic disease
- A high index of suspicion for OIC should be maintained for patients taking opioid analgesics for chronic noncancer pain, and a proactive approach in managing this opioid-related adverse effect may be warranted

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