

Original Article

Methylnaltrexone Treatment of Opioid-Induced Constipation in Patients with Advanced Illness

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Abstract

Methylnaltrexone, a peripherally acting mu-opioid receptor antagonist with restricted ability to cross the blood-brain barrier, reverses opioid-induced constipation (OIC) without affecting analgesia. A double-blind study in patients with advanced illness and OIC demonstrated that methylnaltrexone significantly induced laxation within four hours after the first dose compared with placebo. In this study, patients with advanced illness and OIC on stable doses of opioids and laxatives were randomized to methylnaltrexone 0.15 mg/kg (n = 62) or placebo (n = 71) subcutaneously every other day for two weeks. Laxation was assessed daily. Constipation distress, bowel status change, pain, laxative use, and opioid withdrawal symptoms were assessed weekly using standardized scales. Additional analyses to further characterize response to methylnaltrexone revealed that among patients with a bowel movement within four hours following the first dose, the median time to response was 0.5 hours for methylnaltrexone. Response rates among methylnaltrexone-treated patients who had responded to all previous doses were 57%–100% for doses two to seven. Among methylnaltrexone-treated patients who did not respond to the first or to the first two consecutive doses, 35% and 26% responded to the second and third dose, respectively. Higher percentages of patients and clinicians rated bowel status as improved in the methylnaltrexone than the placebo group. Fewer methylnaltrexone than placebo patients reported use of common laxative types, particularly enemas, during the study. Subcutaneous methylnaltrexone promptly and predictably induced laxation, improved constipation distress, and was associated with less laxative use in patients with advanced illness and OIC. J Pain Symptom Manage 2009;38:683–690. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

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Key Words

Methylnaltrexone, opioids, constipation, opioid receptor antagonist, palliative care

Introduction

Pain is a common and distressing symptom among patients with advanced illness. Effective management of pain often requires the use of opioids. However, opioids are associated with well-recognized and often distressing adverse effects, including sedation, nausea, and constipation.¹ Although tolerance develops to most of these unwanted effects with chronic use, constipation, which occurs in as many as 90% of patients treated with opioids,² is the exception, typically persisting as long as the opioids are in use.^{1,3} Laxatives are routinely used to manage opioid-induced constipation (OIC), and additional measures, such as enemas, are still frequently necessary.⁴ Unfortunately, aggressive management is often burdensome and sometimes ineffective in these patients.^{4,5}

OIC is largely mediated by mu-opioid receptors located in the gastrointestinal tract. Opioid agonist activity causes a decrease in motility via a decrease in peristalsis, with a secondary increase in intestinal fluid absorption.^{6,7} These effects can be reversed by the mu-opioid receptor antagonists naloxone and naltrexone, but these agents also reverse the central effects of opioids, resulting in loss of analgesia.^{8,9} Methylnaltrexone, a quaternary ammonium derivative of naltrexone, has limited ability to cross the blood-brain barrier and, therefore, reverses the peripheral effects of opioids without affecting analgesia.^{10,11} Subcutaneous methylnaltrexone has been demonstrated in clinical trials to be generally well tolerated and active in inducing a bowel movement in patients with advanced illness and OIC.^{12–14}

One of these studies, a two-week, double-blind, placebo-controlled clinical trial in 133 patients with OIC and advanced illness, evaluated the safety and efficacy of methylnaltrexone 0.15 mg/kg subcutaneously every other day for two weeks. Based on the primary endpoints of the study, significantly more patients treated with methylnaltrexone than placebo had rescue-free laxation within four hours after the first dose (48.4% vs. 15.5%) and within four hours after at least two of the first four

doses (51.6% vs. 8.5%).¹³ We report the results of post hoc analyses to further characterize the timing and predictability of laxation in response to methylnaltrexone. We also report the results of exploratory analyses to elucidate patients' subjective responses to methylnaltrexone therapy.

Methods

The study was conducted at 27 nursing homes, hospice sites, and palliative care medical centers in the United States and Canada. It was approved by central and/or local institutional review boards and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Each patient provided signed and dated informed consent before enrollment.

Patients

Patients 18 years or older had advanced illness, defined as a terminal disease such as incurable cancer or other end-stage disease, with a life expectancy of ≥ 1 month. Patients were required to have received opioids for pain control for ≥ 2 weeks with a stable dose for ≥ 3 days and were required to have been maintained on a stable laxative regimen for ≥ 3 days before the study. In addition, inclusion criteria required constipation defined as either less than three bowel movements during the preceding week, and no clinically significant bowel movement (investigator determined) within 24 hours before the first study drug dose, or no clinically significant bowel movement within 48 hours before the first study drug dose. Exclusion criteria included constipation not primarily caused by opioids (as determined by the investigator), fecal ostomy, or clinically significant active diverticular disease.

Study Design

A detailed description of study design has been previously reported.¹³ This was a two-week, double-blind, randomized, placebo-controlled study. Patients were randomly assigned in a 1:1 ratio to receive either methylnaltrexone

0.15 mg/kg or placebo subcutaneously every other day for two weeks. Patients could continue their baseline laxatives throughout the study. Rescue laxatives could be used as needed but not within four hours before or after study drug dosing. The first dose of study drug was administered by study staff; subsequent doses were administered by caregivers. The dose could be doubled if by Day 8, patients had had less than three rescue-free bowel movements (defined as no rescue laxative such as enema or suppository taken between study drug administration and bowel movement). Patients who completed the double-blind study were eligible to enter an open-label extension phase; details of this phase are reported elsewhere.¹³

Assessments

Bowel movements were assessed and concomitant medications were recorded daily. Constipation distress (on a five-point scale, 1 = none to 5 = very much) was assessed at baseline and on Days 1, 7, and 14. Change in bowel status also was evaluated on Days 7 and 14 using patient- and clinician-reported Global Clinical Impression of Change (GCIC) on a seven-point balanced scale (1 = much worse to 7 = much better).^{15,16}

Adverse events (AEs) were evaluated daily; severity was assessed using National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0. A complete blood count and comprehensive metabolic panel were obtained at screening, Day 7, and Day 14. Vital signs were monitored before and after dose administration on Day 1 and for patients with dose escalation on Day 9.

Patients rated their current and worst pain level in the preceding 24 hours (0 = no pain, 10 = worst pain possible) at baseline and on Days 1 (four hours postdose), 7, and 14. Patients also rated the severity (1 = none, 4 = severe) of seven symptoms associated with central opioid withdrawal: yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, and restlessness; the withdrawal score was the sum of the ratings (modified Himmelsbach Withdrawal Scale).¹⁷

Statistical Analyses

Additional efficacy analyses were performed for the intent-to-treat (ITT) population, defined as all randomized patients who received

greater than or equal to one dose of study drug. The number and percentage of patients who had rescue-free laxation after dosing were reported by treatment group and time interval defined by the time to rescue-free bowel movement. For patients having rescue-free bowel movement within four hours after the initial dose, the time to rescue-free bowel movement was compared between treatment groups using a two-sided Wilcoxon rank sum test and *P* values were reported.

Descriptive statistics also were used to summarize laxative use at baseline and during the study. Laxative use during the study included both concomitant laxatives and rescue laxatives.

For efficacy analyses stratified by response to prior doses, only the ITT patient population who had all doses up to the dose being analyzed were included. Patients were classified into subgroups by previous response, and descriptive statistics were used to describe clinical response to current doses by subgroups. Fisher's exact test was used to compare laxation response between treatment groups by subgroup; *P* values from two-sided tests were reported.

Patient- and clinician-reported GCIC scores were compared between methylnaltrexone and placebo using analysis of variance. Correlation coefficients were estimated for GCIC scores (patient and clinician) and the change in constipation distress scores.

All safety data were presented using summary statistics and frequency distributions. Baseline values were determined before the first dose of study drug. AEs, laboratory data, and vital signs were summarized by treatment group.

Results

Patient Disposition

A total of 134 patients completed screening and received study drug. One patient received unblinded methylnaltrexone and was included only in the safety analysis. The efficacy analysis, therefore, included 133 patients, 62 in the methylnaltrexone and 71 in the placebo groups. There were no major between-group differences in baseline demographics or clinical characteristics (Table 1). The median oral morphine-equivalent opioid dose at baseline was 100 mg/day in the placebo group and 150 mg/day in the methylnaltrexone group.

Table 1
Baseline Patient Clinical Characteristics^a

	Placebo (n = 71)	Methylnaltrexone (n = 63)
Primary diagnosis, n (%)		
Cancer	41 (57.7)	37 (58.7)
Cardiovascular disease	7 (9.9)	8 (12.7)
COPD/emphysema	5 (7.0)	9 (14.3)
Alzheimer/dementia	4 (5.6)	4 (6.3)
Other ^b	14 (19.7)	5 (7.9)
Number of laxatives taken, median (range)		
By drug classes	2 (1–5)	2 (1–4)
By generic terms	3 (1–6)	2 (1–5)
Constipation distress, n (%)		
None	8 (11.3)	7 (11.1)
A little bit	6 (8.5)	6 (9.5)
Somewhat	11 (15.5)	9 (14.3)
Quite a bit	18 (25.4)	16 (25.4)
Very much	27 (38.0)	22 (34.9)
Not reported	1 (1.4)	3 (4.8)
WHO Performance Status, n (%)		
1	6 (8.5)	3 (4.8)
2	16 (22.5)	14 (22.2)
3	36 (50.7)	28 (44.4)
4	13 (18.3)	18 (28.6)

COPD = chronic obstructive pulmonary disease; WHO = World Health Organization.

^aAll patients enrolled in the double-blind study; one patient was enrolled but received unblinded study drug and was excluded from the ITT analysis.

^bOther diagnoses included failure to thrive, amyotrophic lateral sclerosis, end-stage multiple sclerosis, malabsorption syndrome, pernicious anemia, rheumatoid arthritis, Buerger's disease, cerebral vascular accident, idiopathic pulmonary fibrosis, peripheral vascular disease, diabetes mellitus, hypoxic brain injury, multiple systems failure, chronic pain or multiple fractures, and end-stage Parkinson's disease.

Fifty-two patients in the methylnaltrexone group and 54 patients in the placebo group completed the two-week study. The most common reason for study discontinuation was death (four patients taking placebo and five patients taking methylnaltrexone). All deaths were considered to be related to progression of the underlying illness.

Efficacy

Timing and Predictability of Bowel Movement Response. Among patients who had a bowel movement within four hours following the initial dose ($n = 30$ and 11 , methylnaltrexone and placebo, respectively), the median time to bowel movement response was 0.5 hours in the methylnaltrexone group and 2.0 hours in the placebo group ($P = 0.013$). Among these responders, 17 (56.7%) of methylnaltrexone vs.

two (18.2%) of placebo patients responded within the first half hour and 22 (73.3%) of methylnaltrexone vs. five (45.5%) of placebo patients responded within the first hour after dosing. A higher percentage of patients in the methylnaltrexone than the placebo group responded within the first half hour for all subsequent doses.

Response rates to methylnaltrexone were generally greater than placebo regardless of response to a previous dose of methylnaltrexone. Response rates tended to be consistent and predictable for individual patients across the seven doses. Among methylnaltrexone-treated patients who had responded to all their previous doses, response rates to the next methylnaltrexone dose (doses two through seven) ranged from 57% to 100% (Fig. 1a).

Among methylnaltrexone-treated patients who did not respond to the first dose, 34% had a response to the second dose. In contrast, only 9% of placebo-treated patients who failed to respond to the first dose subsequently responded to the second ($P = 0.006$) (Fig. 1b). Among patients who failed to respond to both Doses 1 and 2, the response rate to the third dose was numerically greater in the methylnaltrexone group (26%) than in the placebo group (12%), although the difference did not reach statistical significance ($P = 0.16$). When the cumulative response rate for patients who received all the first three study doses was considered, significantly more methylnaltrexone- than placebo-treated patients had laxation response to at least one of the three doses (methylnaltrexone 75% vs. placebo 29%, $P < 0.0001$). Similarly, more patients in the methylnaltrexone than the placebo group had laxation response to at least two of the first three doses (methylnaltrexone 43% vs. placebo 3%, $P < 0.0001$).

Change in Bowel Status and Constipation Distress.

As previously reported, 73.5% and 67.9% of methylnaltrexone-treated patients rated their bowel status as better compared with baseline on Days 7 and 14, respectively, on the GCIC scale; clinician ratings were similar or identical to patient ratings.¹³ In contrast, 63.1% and 51.8% of patients in the placebo group considered their bowel status unchanged from or worse than baseline on Days 7 and 14, respectively.

Higher percentages of patients in the methylnaltrexone than the placebo group reported

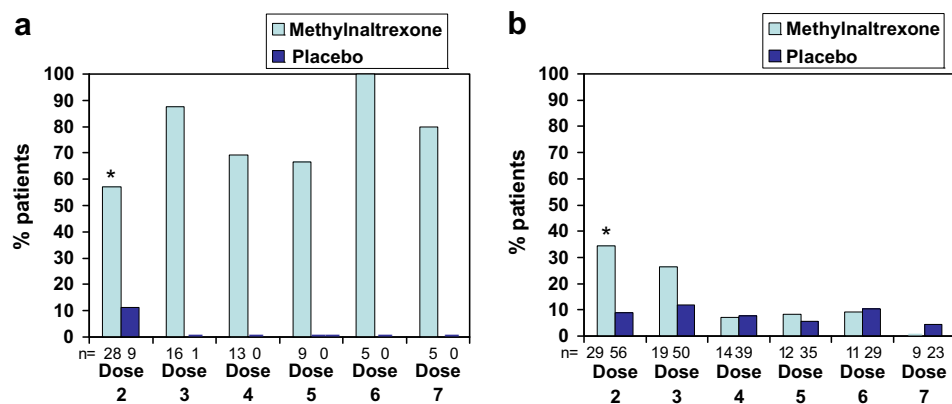


Fig. 1. a) Rescue-free laxation response rates within four hours post-dosing among responders to all previous doses, ITT patients who had doses up to current dose being analyzed. $*P=0.023$ vs. placebo. b) Rescue-free laxation response rates within four hours post-dosing among nonresponders to all previous doses, ITT patients who had doses up to current dose being analyzed. $*P=0.006$ vs. placebo.

that their constipation distress was improved from baseline on Days 1, 7, and 14 (Table 2). Conversely, higher percentages of patients treated with placebo than methylnaltrexone reported that their constipation distress was unchanged or worse at those assessments. A significant inverse correlation ($P < 0.05$) was found between the change in constipation distress and the clinician GCIC scores in the methylnaltrexone ($r = -0.55$) and placebo groups ($r = -0.36$) on Day 14. Similarly, a significant inverse correlation existed between the change in constipation distress and patient GCIC scores in the methylnaltrexone ($r = -0.62$) and placebo groups ($r = -0.32$) on Day 14.

Laxative Use. Baseline laxative use was similar between treatment groups. During the study, numerically fewer patients in the methylnaltrexone than the placebo group reported use of some major classes of laxatives. In addition, fewer methylnaltrexone patients who were responders, defined as laxation within four hours of greater than or equal to four of the seven doses, reported use of major categories of laxatives during the study than nonresponders (Table 3). In particular, the use of enemas was greatly reduced among those who responded to methylnaltrexone compared with placebo (5.3% vs. 35.2%).

Safety

The results of the safety assessments, which have been previously reported,¹³ are summarized in this study. The most common AEs

among patients taking methylnaltrexone were abdominal pain, flatulence, and vomiting. Among AEs occurring in $\geq 5\%$ of patients in either treatment group, abdominal pain, flatulence, nausea, increased body temperature, and dizziness occurred more frequently with methylnaltrexone than placebo. Most AEs were considered not or unlikely to be related to study drug with the exception of those related to the gastrointestinal system.

Most AEs were Grade 1 or Grade 2 according to CTC (mild or moderate). Grade 4 (life threatening) AEs occurred in both treatment groups, but all were considered to be related to the patients' primary illness such as the progression of the underlying malignancy.

Opioid Withdrawal and Pain. Patient ratings of current pain and worst pain within the previous 24 hours were essentially unchanged from baseline on Days 1, 7, and 14; mean scores changed less than one point on the 10-point scale in a negative direction at all measurements. Mean total opioid withdrawal scores were similar between treatment groups and essentially unchanged from baseline at each assessment. For individual symptoms on the modified Himmelsbach Withdrawal Scale, changes from ratings of none or mild at baseline to moderate at a subsequent evaluation occurred in $\leq 4\%$ of patients in either treatment group. One patient in the methylnaltrexone group had a change of rating from none at baseline to severe on Day 14. This patient

Table 2
Patients With Change From Baseline in Constipation Distress

Day	Placebo (n = 71), n (%)				Methylnaltrexone (n = 62), n (%)			
	n ^a	Improved	No Change	Worse	n ^a	Improved	No Change	Worse
1	64	19 (29.7)	40 (62.5)	5 (7.8)	55	29 (52.7)	24 (43.6)	2 (3.6)
7	48	24 (52.1)	12 (25.0)	12 (25.0)	45	29 (64.4)	12 (26.7)	4 (8.9)
14	54	29 (53.7)	15 (27.8)	10 (18.5)	53	32 (60.4)	13 (24.5)	8 (15.1)

^aNumber of patients with evaluations at baseline and day indicated.

underwent screening on the same day as the first dose of study drug. Perspiration was rated as severe at screening evaluation (one hour before first study dose) and none at baseline evaluation (21 minutes before first study dose). This patient was also taking exemestane, which is commonly associated with increased sweating. Four patients in the placebo group also reported changes from ratings of none, mild, or moderate at baseline to severe for single individual symptoms (on Days 1 and 7 for restlessness, on Day 1 for perspiration, and on Day 14 for yawning).

Discussion

Methylnaltrexone promptly and predictably induced laxation in patients with advanced illness and OIC. Our results further showed that methylnaltrexone therapy was associated with numerically reduced use of laxatives compared with placebo, particularly enemas, and improvement in subjective measures of constipation. Methylnaltrexone was generally well tolerated and did not reduce pain control or induce opioid withdrawal symptoms.

Methylnaltrexone was reported to induce rescue-free bowel movement within four hours of dosing in approximately 48.4% of patients

in the primary analysis of this study compared with 15.5% of placebo patients ($P < 0.001$).¹³ Findings are consistent with another study of double-blind single-dose methylnaltrexone ($n = 154$), which demonstrated rescue-free laxation response rates of 61.7% and 58.2% for methylnaltrexone 0.15 and 0.30 mg/kg, respectively.¹² In this present two-week study, laxation response was not correlated with age, performance status, and baseline opioid dose.¹³ A three-month open-label extension of this study demonstrated continued efficacy with open-label methylnaltrexone treatment for up to three months.^{13,18}

Identifying and reducing symptoms to improve constipation and constipation-associated well-being are the primary considerations when caring for the advanced illness population.^{19,20} The results of the additional analyses reported in this study show that methylnaltrexone improves patients' subjective experience of constipation. Greater proportions of patients reported improvement on both GCIC in bowel status and constipation distress measures in the methylnaltrexone group compared with the placebo group.^{15,16} This reduction of subjective constipation distress occurred without reducing pain control or inducing opioid withdrawal symptoms.

Table 3
Patients Reporting Laxative Use—n (%)

	Methylnaltrexone				Placebo			
	Baseline (n = 62)	During the Study			Baseline (n = 71)	During the Study		
		R ^a (n = 19)	NR (n = 43)	All (n = 62)		R ^a (n = 1)	NR (n = 70)	All (n = 71)
Contact laxatives	51 (82.3)	15 (78.9)	37 (86.0)	52 (83.9)	58 (81.7)	1 (100)	65 (92.9)	66 (93.0)
Stool softeners	26 (41.9)	7 (36.8)	19 (44.2)	26 (41.9)	29 (40.8)	0	30 (42.9)	30 (42.3)
Magnesium compounds	13 (20.9)	6 (31.6)	11 (25.6)	17 (27.4)	25 (35.2)	1 (100)	31 (44.2)	32 (45.1)
Osmotic agents	19 (30.6)	4 (21.1)	16 (37.2)	20 (32.3)	25 (35.2)	0	28 (40.0)	28 (39.4)
Enemas	10 (16.1)	1 (5.3)	14 (32.6)	15 (24.2)	11 (15.5)	0	25 (35.7)	25 (35.2)

R = responders; NR = nonresponders.

^aResponders had bowel movement within four hours after \geq four doses during the two-week study.

The promptness of the response to methylnaltrexone as well as the numerically decreased requirement for laxatives in the methylnaltrexone group than the placebo group are also important features for managing OIC in this advanced illness population. The more predictable bowel movement within a practical time frame (approximately 75% who responded within four hours of dosing did so within the first hour) may afford patients more control over their lives. In addition, fewer requirements for laxatives should decrease pill burden, which is likely to be large in this patient population.²¹ Furthermore, decreased need for enemas among those who respond to methylnaltrexone may decrease discomfort and loss of dignity for the patient as well as reducing requirements for nursing time. Of note, there was no requirement in the study protocol to taper laxatives. In clinical practice of managing OIC in palliative care patients, the laxative regimen is usually continued.

Although clinical and demographic parameters have not been shown to predict which patients will respond to methylnaltrexone,¹³ response or lack of response to previous doses of methylnaltrexone is a useful indicator of the probable benefit of additional doses. Patients who have responded to all previous doses are likely to continue to respond, with a response rate of 57%–100% for subsequent doses, suggesting sustainable response with multiple doses. Conversely, a lack of response to a first or both first and second dose decreases the likelihood of response to further doses. However, after nonresponse to the first dose, a response may still occur in approximately one-third of patients for a second dose, and after nonresponse to the first two doses, a response may still occur in approximately one-quarter of patients for a third dose, and both response rates remain greater than the placebo response. In patients who have not responded to any of the first three consecutive doses, reasons for constipation other than opioids should be entertained.

In conclusion, methylnaltrexone rapidly and predictably induces bowel movement in OIC in advanced illness patients while maintaining analgesia. The response to methylnaltrexone was sustained in this two-week multiple-dose study. The generally lower laxative requirements and improvement in subjective measures

of constipation in the methylnaltrexone-treated patients demonstrated in this study complement the demonstrated bowel movement response to methylnaltrexone and provide additional measures of comfort and well-being in patients with advanced illness and OIC.

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