

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

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Opioids are the mainstay of therapy for moderate-to-severe pain in patients with serious illness. Among those with advanced illness, the prevalence of opioid-induced constipation (OIC) approaches 90%.^{1,2} The symptoms associated with constipation, including abdominal pain and distention, nausea and vomiting, and anorexia, can become a significant source of distress, and more serious complications associated with fecal impaction, such as incontinence and confusion, may occur.³ Unlike other opioid side effects, such as sedation and nausea, tolerance to constipation develops slowly, if at all.

OIC is currently managed with a variety of commercially available laxatives, a practice that lacks a solid evidence base. Although the combination of a stimulant cathartic and a stool

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Abstract Methylnaltrexone, a peripheral mu-opioid receptor antagonist with restricted ability to cross the blood-brain barrier, may relieve opioid-induced constipation (OIC) without reversing analgesia. A total of 154 patients with advanced illness and OIC enrolled in a double-blind, randomized, placebo-controlled trial, with optional open-label phases (up to 4 months) in hospice and palliative care centers during 2003–2005. They received a single subcutaneous injection of methylnaltrexone (0.15 mg/kg or 0.3 mg/kg) or placebo. Laxation response within 4 hours was 62% and 58% for methylnaltrexone 0.15 mg/kg and 0.3 mg/kg, respectively, compared with 14% for placebo ($P < 0.0001$; each dose vs placebo). Approximately half of the methylnaltrexone responders defecated within 30 minutes of dosing. Open-label phase response rates mirrored those for methylnaltrexone during the double-blind phase. There was no change in pain scores or evidence of central opioid withdrawal. The most common adverse events (AEs) were abdominal pain and flatulence. Three patients had serious AEs attributed to methylnaltrexone. Subcutaneous methylnaltrexone was efficacious in rapidly inducing laxation and was generally well tolerated in patients with advanced illness and OIC. Trial Registration ClinicalTrials.gov Identifier: NCT00401362

softener was found to be more favorable than either agent alone in a human volunteer model of OIC,⁴ clinical studies of these and other drugs are largely lacking. Clinical experience suggests that existing therapies may be compromised by poor response, side effects such as bloating or cramping, or other outcomes that may impair quality of life, such as pill burden or unpredictable timing of laxation. Suppositories or enemas may be used but generally are not preferred because of discomfort or caregiver burden. Given the potential adverse consequences of poorly managed OIC, new therapies that are effective and safe are needed.

Mu-opioid receptor antagonists that have limited access to the central nervous system (CNS) are now undergoing evaluation as a potential novel targeted therapy for OIC. Although preclinical

Table 1**Inclusion/Exclusion Criteria**

Inclusion Criteria
Signed informed consent form
Advanced illness with a life expectancy of 1–6 months
Stable opioid regimen for the control of pain/discomfort for ≥ 3 days before randomization ^a
Stable scheduled laxative regimen for ≥ 3 days prior to treatment
No clinically significant laxation within 48 hours prior to the first study drug dose
Stable vital signs (systolic blood pressure ≥ 85 mm Hg and diastolic blood pressure ≥ 45 mm Hg, supine or sitting)
Age ≥ 18 years
Negative pregnancy test if of childbearing potential and using an effective method of birth control during the course of the study
Exclusion Criteria
Previous treatment with methylnaltrexone
Prior treatment with naltrexone or naloxone for treatment of opioid-induced constipation
Participation in any other studies involving investigational products within 30 days before screening
Any disease process suggestive of gastrointestinal obstruction
Any potential nonopioid cause of bowel dysfunction that in the opinion of the investigator may have been primarily responsible for constipation
History of current peritoneal catheter for intraperitoneal chemotherapy or dialysis
Clinically significant active diverticular disease
Evidence of fecal impaction by physical examination or x-ray
Surgically acute abdomen
Fecal ostomy
Pregnancy or nursing

^a A stable opioid regimen was defined as no reduction in opioid dose of ≥ 50% within 3 days before administration of the study drug. However, changes to the opioid regimen, such as an increase in dosage, addition of another opioid to the regimen, or as-needed dosing, were permitted within 3 days of randomization, if warranted.

data suggest that mu-opioid receptors in the CNS may mediate changes in bowel function, most evidence indicates that receptors located on enteric nervous system neurons are primarily responsible for OIC.⁵ Opioids applied to isolated bowel preparations induce changes linked to constipation, including disruption of peristalsis and decreased secretions,^{5,6} and the peripherally acting mu-opioid agonist loperamide induces constipation in humans.⁴

Interest in using an opioid antagonist for the treatment of refractory OIC began with naloxone, which has low oral bioavailability. Oral naloxone can relieve OIC, but the relatively high doses required and variations in individual sensitivity to the drug may result in enough systemic absorption to reverse analgesia or induce CNS opioid withdrawal.^{7–9} To avoid these centrally mediated effects, new compounds that have little ability to cross the blood-brain barrier have been developed. Methylnaltrexone (*N*-methylnaltrexone bromide), a quaternary compound created by adding a methyl group to the opioid antagonist naltrexone, is one such agent.^{10,11}

Methylnaltrexone has been reported to reverse opioid-induced delays in gastric emptying¹² and oral-cecal transit^{13–15}

and to induce laxation in methadone-maintained patients with OIC.^{16,17} The efficacy of methylnaltrexone for treatment of OIC in patients with advanced illness has recently been reported in a placebo-controlled, multicenter trial.¹⁸ In that study, methylnaltrexone (0.15 mg/kg) or placebo was given every other day for 2 weeks. The current report describes the results of a dose-ranging, multicenter, randomized controlled trial that examined the safety and efficacy of a single subcutaneous (SC) injection of methylnaltrexone (0.15 mg/kg or 0.3 mg/kg) versus placebo followed by open-label active treatment for up to 4 months in patients with advanced illness and OIC.

Methods**STUDY DESIGN**

This was a multicenter, single-dose, double-blind, randomized, placebo-controlled study followed by a 28-day, open-label phase conducted in patients with advanced illness and OIC. After completing these phases, patients could elect to enter a 3-month, open-label extension study. The study drug was administered as needed (PRN) in both open-label phases.

A central or local institutional review board approved the study protocol for the 17 study sites, which were located

Table 2**Data Collection: Assessments Made at Baseline, 24 Hours, and Termination of Open-Label Phase**

Vital signs ^a
Physical examination
World Health Organization performance status
Prior and concomitant medications
Complete blood cell count
Comprehensive metabolic profile
Laxation response (occurrence of bowel movement frequency and difficulty) ^a
Stool consistency (1 = very hard; 2 = hard; 3 = slightly hard; 4 = firm; 5 = soft/formed; 6 = watery) ^a
Constipation distress (1 = none; 2 = a little bit; 3 = somewhat; 4 = quite a bit; 5 = very much) ^a
Pain evaluation (current and worst pain in the past 24 hours, ranked on a 0–10 scale, with 10 being the worst pain imaginable ^a)
Opioid withdrawal scale, derived from a modified Himmelsbach scale by summing the numeric value (1 = none; 2 = mild; 3 = moderate; 4 = severe) of each of seven opioid withdrawal symptoms—rhinorrhea, tremor, piloerection, yawning, perspiration, restlessness, and lacrimation—resulting in a minimum score of 7 and a maximum score of 28 ^a
Global clinical impression of change (GCIC; scored as much worse, somewhat worse, slightly worse, no change, slightly better, somewhat better, much better) ^b
Adverse events ^a

^a Also assessed at 4 hours

^b Assessed only at 24 hours following double-blind and last administered dose

Following each dose of study medication administered during the open-label and extension trials, a complete dosing log and log of laxation response, including stool consistency, were maintained. Prior and concomitant medications and adverse events also were recorded.

throughout the United States. All patients, accrued from February 2003 to February 2005, gave written informed consent before study entry.

SETTING AND PARTICIPANTS

Patients were recruited from hospices and palliative care settings (Table 1). Baseline laxative regimens, defined as laxatives being taken at the time of study entry, could be continued throughout the study. Rescue laxatives, defined as laxatives administered on a PRN basis, were allowed but not within 4 hours before or after the administration of the double-blind dose and the first open-label dose.

RANDOMIZATION AND INTERVENTION

The double-blind trial consisted of a single SC injection of methylnaltrexone (0.15 mg/kg or 0.3 mg/kg) or placebo. Eligible patients were randomly assigned in blocks of three to the three treatment groups in a 1:1:1 ratio. Identical-appearing vials containing 1.1 mL of methylnaltrexone in concentrations of 20 mg/mL or 40 mg/mL, or 1.1 mL of saline placebo, were prepared according to a computer-generated randomization scheme performed by a statistician external to the sponsor. A study pharmacist who knew the contents of each vial prepared a weight-based SC dose of methylnaltrexone or placebo, ensuring that each syringe had identical volume. Syringe contents were blinded to patients and staff administering injections. SC injection sites included the deltoid, abdomen, buttocks, and thighs.

OUTCOMES AND FOLLOW-UP

At baseline, and at prespecified times thereafter, clinical assessments were performed for each study phase. Outcomes included measures of bowel function, pain, opioid withdrawal, global clinical impression of change (GCIC), and adverse events (AEs; Table 2). Concurrent medications were recorded throughout the double-blind and open-label phases of the study. To facilitate comparison, opioid doses were converted to oral morphine equivalents, using accepted equianalgesic conversion tables.^{19,20}

The primary outcome was the proportion of patients with laxation within 4 hours after administration of the double-blind dose. Patients needing rescue laxative or disimpaction within 4 hours of dosing were considered nonresponders. Secondary outcomes included the proportion of patients with rescue-free laxation within 24 hours post dosing, improvement in GCIC scale (defined as a rating of slightly better, somewhat better, or much better), improvement in constipation distress (defined as a change by at least one category toward none), and improvement in stool consistency. Additional secondary outcomes included changes in baseline pain, symptoms/signs of central opioid withdrawal, and AEs. All AEs were coded to preferred term and primary System Organ Class using the Medical Dictionary for Regulatory Activities, version 6.0, and assessed for severity and relationship to study drug. Intensity for each AE was determined using the National Cancer Institute—Common Tox-

icity Scale (version 2.0).

A serious adverse event (SAE) occurring at any dose and regardless of causality was defined as any AE that resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect; or was an important medical event that did not fulfill the above criteria. Such events were considered serious when, based on appropriate medical judgment, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

After completing the double-blind phase, patients could enter a 28-day open-label phase, during which they could receive one dose of methylnaltrexone as often as every 24 hours PRN. Family caregivers were trained to perform these injections. The initial methylnaltrexone dose during this open-label phase was 0.15 mg/kg, which could be reduced to 0.075 mg/kg or increased to 0.3 mg/kg based upon clinical response. At the end of the open-label phase, patients could enter a 3-month protocol extension with additional informed consent. During this extension, the initial dosing regimen remained identical to the last dose in the open-label phase, with subsequent doses adjusted to 0.075 mg/kg, 0.15 mg/kg, or 0.3 mg/kg at the investigators' discretion. Patients received 30-day follow-up after their last study dose.

STATISTICAL ANALYSIS

Sample size calculation used laxation response data from previous studies^{16,21} and was performed at the 0.025 type I level of statistical significance to adjust for multiple planned tests. This calculation indicated that 50 patients per group would detect a difference in the proportion of responders of at least 0.35.

Analyses were on an intent-to-treat basis and defined as all patients who received the study drug during the double-blind phase of the study. The primary endpoint analysis was performed using the Cochran-Mantel-Haenszel test to compare 4-hour rescue-free laxation response across methylnaltrexone at each dose and placebo. This analysis included a term for treatment-by-center interaction, which was created by pooling study sites with up to three patients per site to avoid the possibility of spurious *P* values due to dichotomous data. This treatment-by-center interaction was not significant ($P > 0.10$ on the Breslow-Day test), and, consequently, Chi-square tests were used to compare each methylnaltrexone dose against placebo at the type I error level of 0.0249 (selected to account for a planned interim analysis of efficacy). Logistic regression was used to assess the correlation between laxation response and baseline oral morphine equivalent dose categorized as < 80 mg/d, 80 to < 200 mg/d, and ≥ 200 mg/d. Time-to-first laxation was plotted on a Kaplan-Meier graph, and log-rank tests for time-to-first laxation were performed in a pair-wise manner to compare each methylnaltrexone dose with placebo. Secondary analyses were exploratory, and correction was not made for multiple tests.

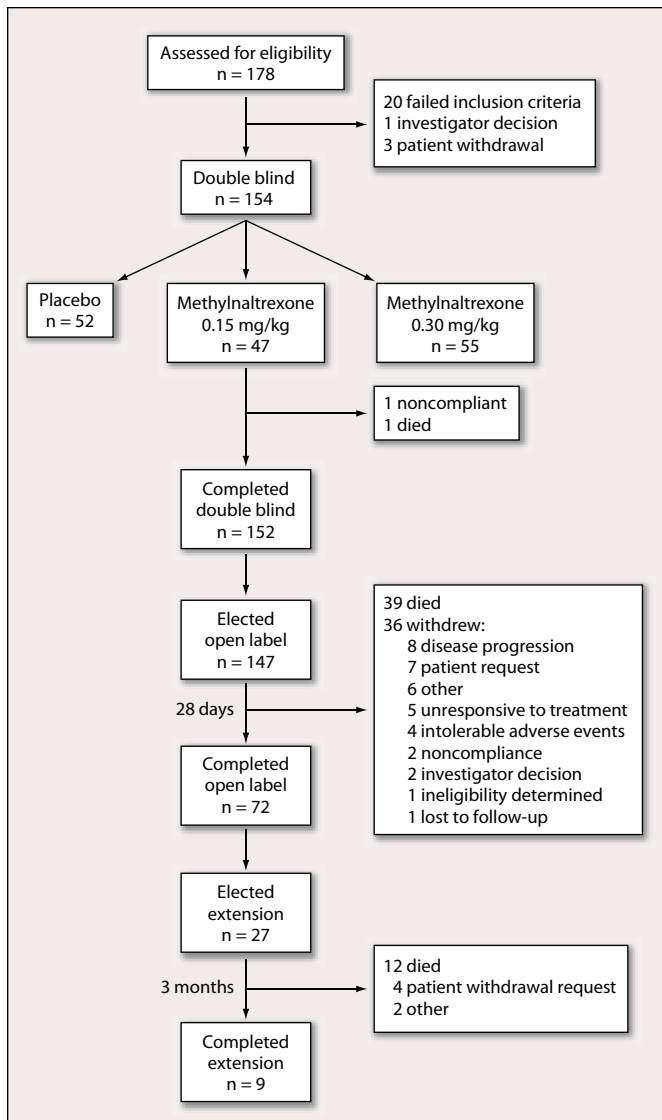


Figure 1 Patient Disposition

Results

A total of 154 patients were randomized and received the study drug (methylnaltrexone 0.15 mg/kg, n = 47; methylnaltrexone 0.3 mg/kg, n = 55; placebo, n = 52; Figure 1). One additional patient was randomized but developed bowel obstruction and was no longer considered eligible for the study and did not receive the study drug. Baseline characteristics were well balanced among the treatment groups (Table 3). The median age was more than 60 years, and approximately 80% had a primary cancer diagnosis. The median daily oral morphine equivalent doses were 207 mg/d, 188 mg/d, and 150 mg/d for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively. Baseline laxative use was similar among all arms.

EFFICACY

During the double-blind phase, the proportion of patients who defecated within 4 hours of receiving methylnaltrexone

0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo was 61.7% (95% confidence interval [CI], 47.8%–75.6%), 58.2% (95% CI, 45.1%–71.2%), and 13.5% (95% CI, 4.2%–22.7%), respectively ($P < 0.0001$ for each methylnaltrexone dose vs placebo; Figure 2). Corresponding 24-hour, rescue-free laxation response rates were 68.1% (95% CI, 54.8%–81.4%), 63.6% (95% CI, 50.9%–76.3%), and 26.9% (95% CI, 14.9%–39.0%) for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively ($P < 0.0001$ for each methylnaltrexone dose vs placebo; Figure 2). Laxation response to methylnaltrexone was not correlated with the baseline oral morphine-equivalent dose.

For all patients, the median time to rescue-free laxation was 1.10 hours in the methylnaltrexone 0.15 mg/kg group, 0.8 hours in the methylnaltrexone 0.3 mg/kg group, and > 24 hours in the placebo group. Comparisons between each methylnaltrexone group and the placebo group were significant ($P < 0.0001$). Among methylnaltrexone-treated patients who defecated within 4 hours, approximately half responded within 30 minutes (Figure 3).

Administration of methylnaltrexone did not change baseline pain. The mean current pain scores \pm standard deviation (SD) at baseline were 3.2 ± 2.82 , 3.1 ± 2.84 , and 3.2 ± 2.67 for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively. At the 4-hour evaluation, mean changes in current pain scores from baseline were -0.74 ± 1.98 , -0.23 ± 1.93 , and 0.02 ± 1.56 for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively. The median change in pain score was 0.

Similarly, use of methylnaltrexone did not result in opioid withdrawal. On the modified Himmelsbach opioid withdrawal scale, baseline mean \pm SD scores were 8.11 ± 1.74 , 7.91 ± 1.31 , and 7.71 ± 1.21 for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively; the mean \pm SD changes from baseline at 4 hours were -0.21 ± 1.55 ,

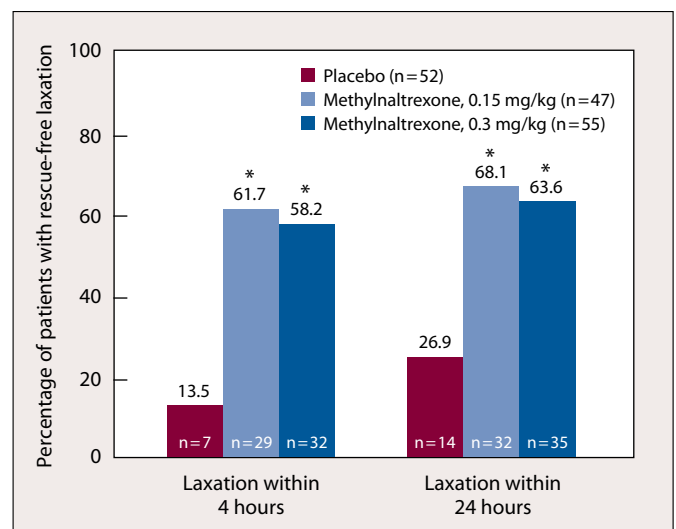


Figure 2 Rescue-free Laxation Within 4 Hours and 24 Hours of a Double-Blind Dose

* $P < 0.0001$ for methylnaltrexone vs placebo

Table 3**Demographic and Baseline Characteristics at Entry of the Double-Blind Study**

CHARACTERISTIC ^a	STATISTIC/CATEGORY	PLACEBO (n = 52)	METHYLNALTREXONE 0.15 mg/kg (n = 47)	METHYLNALTREXONE 0.3 mg/kg (n = 55)	TOTAL (n = 154)
Age, years	Mean (SD)	64.7 (16.20)	65.9 (15.51)	65.3 (13.43)	65.3 (14.96)
	Median	62.5	67.0	68.0	66.0
	Range	21–100	26–96	34–89	21–100
Sex, n (%)	Male	28 (53.8%)	25 (53.2%)	31 (56.4%)	84 (54.5%)
	Female	24 (46.2%)	22 (46.8%)	24 (43.6%)	70 (45.5%)
Race, n (%)	Caucasian	43 (82.7%)	38 (80.9%)	46 (83.6%)	127 (82.5%)
	Black	3 (5.8%)	5 (10.6%)	4 (7.3%)	12 (7.8%)
	Hispanic	5 (9.6%)	3 (6.4%)	4 (7.3%)	12 (7.8%)
	Asian	1 (1.9%)	1 (2.1%)	0	2 (1.3%)
	Other	0	0	1 (1.8%)	1 (0.6%)
Weight, kg	Number	51 ^b	47	55	153
	Mean (SD)	67.1 (19.12)	70.4 (21.08)	65.5 (16.03)	67.6 (18.71)
	Median	68.1	70.0	64.0	65.9
	Range	29–133	31–135	31–110	29–135
Primary diagnosis, n (%)	Cancer	43 (82.7%)	37 (78.7%)	45 (81.8%)	125 (81.2%)
	Cardiovascular	2 (3.8%)	4 (8.5%)	2 (3.6%)	8 (5.2%)
	HIV/AIDS	0	1 (2.1%)	0	1 (0.6%)
	Other	7 (13.5%)	5 (10.6%)	8 (14.5%)	20 (13.0%)
WHO Performance Status, ^c n (%)	0	0	1 (2.1%)	0	1 (0.6%)
	1	2 (3.8%)	2 (4.3%)	1 (1.8%)	5 (3.2%)
	2	17 (32.7%)	13 (27.7%)	15 (27.3%)	45 (29.2%)
	3	21 (40.4%)	19 (40.4%)	30 (54.5%)	70 (45.5%)
	4	12 (23.1%)	12 (25.5%)	9 (16.4%)	33 (21.4%)
Oral morphine equivalents, mg/d	Median	150.0	207.0	188.0	186.5
	Range	8–9,720	10–12,2560	12–33,120	8–12,2560
Current pain score ^d	N	49	45	54	148
	Mean (SD)	3.2 (2.67)	3.2 (2.82)	3.1 (2.84)	3.2 (2.76)
	Median	3.0	3.0	2.5	3.0
	Range	0–9	0–9	0–10	0–10
Worst pain score ^d	N	49	44	54	147
	Mean (SD)	5.6 (2.77)	6.4 (2.75)	5.3 (2.92)	5.7 (2.83)
	Median	6.0	7.0	6.0	6.0
	Range	0–10	0–10	0–10	0–10
Constipation distress	None	4 (8.2%)	4 (8.7%)	4 (7.4%)	12 (8.1%)
	A little bit	9 (18.4%)	7 (15.2%)	5 (9.3%)	21 (14.1%)
	Somewhat	10 (20.4%)	9 (19.6%)	13 (24.1%)	32 (21.5%)
	Quite a bit	18 (36.7%)	14 (30.4%)	21 (38.9%)	53 (35.6%)
	Very much	8 (16.3%)	12 (26.1%)	11 (20.4%)	31 (20.8%)
	Missing	3	1	1	5
Number of baseline laxatives taken per patient by drug class	Mean (SD)	1.8 (0.96)	1.7 (0.92)	1.7 (1.15)	1.7 (1.01)
	Median	2.0	2.0	2.0	2.0
	Range	0–4	0–4	0–5	0–5
Baseline laxative use	Patients using any laxative ^e	50 (96%)	45 (96%)	51 (93%)	146 (95%)
	Patients taking a stimulant ^{f,g}	46 (89%)	37 (79%)	45 (82%)	128 (83%)
	Patients taking an osmotic laxative ^{g,h}	30 (58%)	23 (49%)	33 (60%)	86 (56%)
	Patients taking a stool softener ^g	12 (23%)	18 (38%)	12 (22%)	42 (27%)

Abbreviations: n = number of treated patients; SD = standard deviation; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; WHO = World Health Organization. Percentages are based on the number of patients with non-missing data.

^a Values at entry into the study

^b One patient in the placebo group was missing baseline weight measurements because of inability to bear weight; the patient's last measurement was used.

^c WHO Performance Status: 1 = restricted in physically strenuous activity but ambulatory and able to carry out work; 2 = ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours; 3 = capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4 = completely disabled; cannot carry on any self-care; totally confined to bed or chair

^d Current and worst pain assessed where pain was scored as 0 (none) to 10 (worst possible pain)

^e Patients may have been on more than one laxative; only the most common types of laxatives used are listed (stimulant, osmotic, and stool softeners).

^f Including bisacodyl, senna, or senna with docusate sodium

^g Patients may have been on more than one agent in that laxative class but were counted only once for that class.

^h Including magnesium compounds, lactulose, or polyethylene glycol

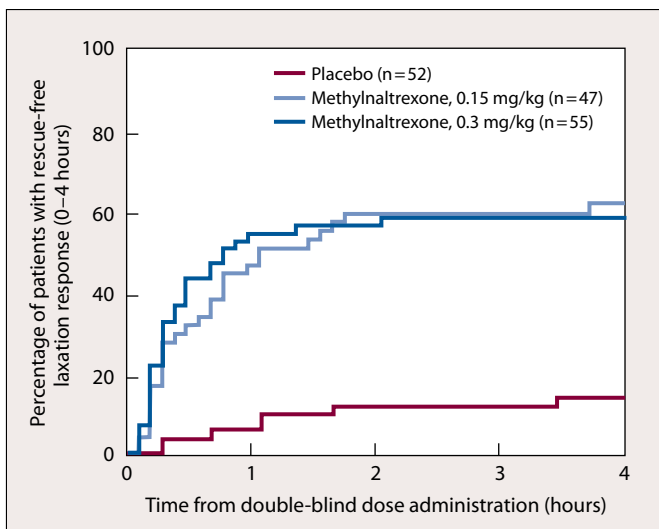


Figure 3 Kaplan-Meier Plots of Time to First Rescue-Free Laxation Within 4 Hours After the Double-Blind Dose

-0.17 ± 1.16 , and -0.16 ± 0.90 for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively. Corresponding mean changes from baseline on day 2 were -0.50 ± 1.6 , -0.25 ± 1.38 , and -0.10 ± 0.76 , respectively. The median change from baseline on days 1 and 2 was 0 in all treatment groups.

During the double-blind phase, approximately 50% of patients who defecated reported improvement in stool consistency, irrespective of treatment. Two patients who received methylnaltrexone 0.3 mg/kg reported their first laxation within 24 hours as watery, compared with none who received methylnaltrexone 0.15 mg/kg. Some patients had multiple laxations with subsequent watery stools. Focusing only on patients who laxated within 4 hours of double-blind dosing, 8 of 29 patients (27.6%) in the methylnaltrexone 0.15 mg/kg group and 12 of 32 patients (37.5%) in the methylnaltrexone 0.3 mg/kg group had at least one watery laxation, compared with 0 of 7 who received placebo.

Changes in constipation distress and GCIC generally paralleled laxation results. The proportion of patients who reported any improvement in constipation distress at the 4-hour assessment was 64.4%, 63.5%, and 34.0% for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively. Similarly, the proportion of patients who reported any improvement in their GCIC at the end of the double-blind phase was 58.7%, 58.8%, and 21.6% for methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.3 mg/kg, and placebo, respectively.

Of the 152 patients who completed the double-blind phase, 147 (96.7%) opted to continue into the open-label phase; 136 of these patients received at least one dose of methylnaltrexone. Within 4 hours of the initial open-label dose, laxation occurred in 54.2% (95% CI, 40.1%–68.3%) of the 48 patients originally randomized to receive placebo in the double-blind

period, 61.9% (95% CI, 47.2%–76.6%) of the 42 patients originally randomized to receive methylnaltrexone 0.15 mg/kg, and 52.2% (95% CI, 37.3%–66.6%) of the 46 patients originally randomized to receive methylnaltrexone 0.3 mg/kg.

A total of 1,160 doses were administered during the double-blind, open-label, and extension phases. Patients received a median of five doses of methylnaltrexone over a median duration of 28.5 days, with a median interval of 3 days between doses. The mean individual laxation response rates within 4 hours were 55.8% during weeks 1 and 2, 61.7% during weeks 3 and 4, 58.8% during weeks 5–8, and 63.7% beyond 8 weeks.

ADVERSE EVENTS

Table 4 lists AEs that occurred during the double-blind phase in $\geq 5\%$ of patients in any category. The most common AE in methylnaltrexone-treated patients was abdominal pain, which was mild to moderate, was dose dependent, and occurred with a higher incidence than in the placebo group. The incidence of flatulence, nausea, and dizziness also appeared to be related to the methylnaltrexone dose, albeit at lower rates.

During the double-blind and open-label treatment periods, 19 patients experienced severe AEs that were at least possibly related to methylnaltrexone, with some experiencing more than one event. There were 15 incidents of abdominal pain; 3 of increased sweating; 2 of increased pain; and 1 each of burning at the injection site, vomiting, diarrhea, asthenia, increased blood pressure, dehydration, muscular cramp, loss of consciousness, tremor, delirium, hallucination, dyspnea, and flushing.

SAEs related to methylnaltrexone did not occur during the double-blind phase but were reported in three patients during the open-label periods. One patient had flushing, and another had delirium possibly related to methylnaltrexone. A third patient had severe diarrhea and subsequent dehydration and cardiovascular collapse considered to be related to the drug. This was a 73-year-old woman with advanced metastatic breast cancer who initially received double-blind methylnaltrexone (0.3 mg/kg) without incident. Subsequently, she received 0.15 mg/kg of methylnaltrexone open label without response. When her dose was increased to 0.3 mg/kg, she passed a large amount of stool after 30 minutes. Over the next few days, she received two additional 0.3 mg/kg doses, and after the second she developed severe diarrhea, nausea and vomiting, and later syncope. After she regained consciousness, medical intervention was limited to comfort measures; no rehydration attempts were initiated. The patient died a day later. No diagnostic tests or autopsy was performed. The cause of death was reported as metastatic breast cancer, exacerbated by diarrhea, and subsequent dehydration and cardiovascular collapse.

Other SAEs were due to underlying disease progression rather than methylnaltrexone. There were 87 deaths, and all but the one previously described were attributed to the underlying disease. There were no observable changes from baseline in vital signs, physical examination findings, or laboratory values attributable to methylnaltrexone.

Discussion

This study indicates that SC methylnaltrexone is efficacious in treating OIC and generally well tolerated in patients with advanced illness. When enrolled in the study, patients were receiving a median oral morphine-equivalent dose ranging from 150 mg/d to 207 mg/d and a median of two classes of laxatives; approximately 90% were experiencing distress from constipation. Within 4 hours of receiving the study drug, 62% (0.15 mg/kg) and 58% (0.3 mg/kg) of methylnaltrexone-treated patients defecated, compared with 14% of patients in the placebo group. The study demonstrated no dose-response relationship in the dose range studied and no correlation between laxation response and baseline opioid doses. Therefore, the optimal dose appears to be 0.15 mg/kg. During the open-label phase, 54% of the patients who had received placebo in the double-blind phase defecated within 4 hours of receiving initial open-label methylnaltrexone (0.15 mg/kg), a response rate similar to the double-blind methylnaltrexone response. Over the entire study (double-blind, open-label, and extension phases), patients received a median of five methylnaltrexone doses and continued to respond to each dose at a comparable rate.

This study adds important experience to a previous report of methylnaltrexone for OIC in patients with advanced illness.¹⁸ Compared with the previous study, the current study included additional patients treated with methylnaltrexone in the double-blind phase, had a longer open-label phase (4 months vs 3 months), and provided dose-ranging efficacy as well as important additional safety information. A key finding in the current study is that the 0.3 mg/kg dose of methylnaltrexone did not provide better efficacy but was associated with more abdominal pain than the 0.15 mg/kg dose of methylnaltrexone, thus identifying the lower dose as the preferred dose for clinical use.

The response rate of greater than 50% in this study of patients with advanced illness is lower than that seen in a small trial of methylnaltrexone for OIC in chronic methadone-maintenance patients.¹⁶ In that trial, varying doses of intravenous methylnaltrexone induced immediate laxation in 100% of patients. The lower response rate in patients with advanced illness may be related to the existence of multiple nonopioid etiologies that potentially contributed to constipation, including immobility, decreased oral intake, a low-fiber diet, metabolic and endocrine imbalances, neurologic disorders, side effects of concomitant drugs, inadequate toileting arrangements, sedation, depression, and differences in the route of medication administration.

The most common AE related to methylnaltrexone was abdominal pain. Based on patient anecdotal reports, this symptom was perceived by many as related to the normal process of laxation.

Nineteen patients experienced severe AEs, and three patients experienced SAEs that were at least possibly related to methylnaltrexone. All patients had advanced illness, and approximately two-thirds were extremely frail, as indicated by

Table 4

Incidence of Adverse Events Occurring in \geq 5% of Patients per Category: Double-Blind Patients

ADVERSE EVENT, n (%)	PLACEBO (n = 52)	METHYLNALTREXONE	
		0.15 mg/kg (n = 47)	0.3 mg/kg (n = 55)
Patients with at least one adverse event	25 (48.1%)	34 (72.3%)	44 (80.0%)
Abdominal pain ^a	2 (3.8%)	13 (27.7%)	21 (38.2%)
Flatulence	2 (3.8%)	6 (12.8%)	8 (14.5%)
Sweating increased	4 (7.7%)	4 (8.5%)	4 (7.3%)
Restlessness	4 (7.7%)	4 (8.5%)	4 (7.3%)
Nausea	1 (1.9%)	2 (4.3%)	8 (14.5%)
Pain exacerbated	2 (3.8%)	3 (6.4%)	5 (9.1%)
Rhinorrhea	1 (1.9%)	4 (8.5%)	2 (3.6%)
Dizziness	0 (0.0%)	2 (4.3%)	5 (9.1%)
Vomiting ^a	0 (0.0%)	3 (6.4%)	3 (5.5%)
Upper abdominal pain	1 (1.9%)	2 (4.3%)	3 (5.5%)
Fatigue	1 (1.9%)	4 (8.5%)	0 (0.0%)
Anxiety	0 (0.0%)	1 (2.1%)	4 (7.3%)
Arthralgia	1 (1.9%)	3 (6.4%)	0 (0.0%)
Somnolence	0 (0.0%)	3 (6.4%)	1 (1.8%)
Asthenia	0 (0.0%)	0 (0.0%)	3 (5.5%)

^a Not otherwise specified

a World Health Organization performance status of 3 or 4. It was anticipated that risk of AEs would be relatively high in this population, and it was often difficult to determine the extent to which the advanced nature of the illness contributed to the occurrence of AEs, a challenge that generally applies to therapeutic studies in palliative care. Nonetheless, the study demonstrates that the rapid reversal of constipation in very ill patients can be associated with AEs, and this finding highlights the need for caution and therapeutic decision-making based upon a critical evaluation of potential benefits and possible risks. Overall, the prompt reversal of constipation was a favorable outcome, as revealed by the positive change in the GCIC, the low rate of discontinuation due to side effects, and the very high rate at which patients who participated in the double-blind phase opted to proceed with the open-label phases (147 of 152 patients).

Patients who responded to methylnaltrexone often defecated soon after the drug was administered, with approximately half responding within 30 minutes. This timing also was generally viewed as favorable in that it was rapid but allowed sufficient time for toileting. There were no anecdotal reports of difficulty with the administration of injections.

Consistent with the presumed peripheral mechanism of methylnaltrexone and a previous study of intravenous methylnaltrexone,¹⁶ there was no change in pain or symptoms/signs of opioid withdrawal at the 4 hours immediately following administration of methylnaltrexone. The abdominal pain and watery stools experienced by some patients may have represented localized "bowel withdrawal" similar to that seen in studies of oral naloxone for OIC but without the broader spectrum of systemic withdrawal effects reported with naloxone.^{7,8} Alternatively, these

events may be consistent with symptoms typically occurring after peristalsis is activated and hard, desiccated stool is expelled.

Conclusion

This study demonstrated that SC methylnaltrexone (0.15 mg/kg and 0.3 mg/kg) rapidly and consistently induced laxation in patients with advanced illness and OIC. Both doses of meth-

yl naltrexone appeared to be equally efficacious and were generally well tolerated.

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