Original Article

Subcutaneous Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Patients with Advanced Illness: A Double-Blind, Randomized, Parallel Group, Dose-Ranging Study

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Abstract

Methylnaltrexone, a peripherally-acting quaternary opioid antagonist, is an investigational treatment for opioid-induced constipation in patients with advanced illness. This randomized, parallel-group, repeated dose, dose-ranging trial included a double-blind phase for one week followed by an open-label phase for a maximum of three weeks. Opioid-treated patients with advanced illness who met criteria for opioid-induced constipation despite laxative therapy were potentially eligible. Double-blind treatment occurred on Days 1, 3, and 5; open-label therapy could be administered as often as every other day. The initial dose range of 1 mg, 5 mg, or 12.5 mg was extended by adding a 20 mg group during the study while still maintaining the double blind; the initial open-label dose of 5 mg could be titrated. The primary outcome was a laxation response within four hours after the first dose. Thirty-three patients received at least one dose of methylnaltrexone. Only one of 10 patients (10%) who received the 1 mg dose experienced laxation within four hours of dosing. The median time to laxation was > 48 hours for the 1 mg dose group, compared to 1.26 hours for all patients receiving ≥5 mg (P = 0.0003). There was no apparent dose-response above 5 mg. Most adverse events were related to the gastrointestinal system, were mild, and did not lead to discontinuation. In conclusion, methylnaltrexone relieved opioid-induced constipation at doses ≥5 mg in patients with advanced illness, and did not reduce analgesia or cause opioid withdrawal symptoms. J Pain Symptom Manage 2008;35:458–468. © 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.
Key Words
Constipation, opioid-induced, methylnaltrexone, peripheral opioid antagonist, subcutaneous, gastrointestinal side effects, advanced illness, clinical trial, dose-ranging

Introduction

Long-term opioid therapy is the mainstay treatment for pain associated with serious illnesses, such as cancer or AIDS,¹ and is slowly expanding to selected patients with chronic pain of other types.² Although side effects are common, treatment is usually well tolerated, particularly if adverse effects are carefully assessed and managed.³

Constipation is among the most common and persistent of the opioid-related side effects. Depending on the population surveyed, prevalence rates for constipation range between 20% and 80%.⁴—⁶ In seriously ill populations, the problem is so significant that prophylactic laxative therapy is usually recommended. Commonly used laxatives, such as senna, are helpful in many cases but burdensome or poorly effective in others.⁷

Opioid antagonist therapy may hold the promise of better outcomes in the management of opioid-related constipation. The potential efficacy of oral naloxone has been recognized for many years,⁸ and oral administration of the injectable compound is used occasionally in clinical practice. Use of naloxone can be problematic, however, because systemic absorption occurs and can lead to symptoms of opioid abstinence or worsening pain. These concerns, together with unpredictable dose requirements and cost, limit the utility of this approach.

A peripheral opioid antagonist, methylnaltrexone bromide, is used as a novel therapy for opioid-induced constipation.⁹ Methylnaltrexone (molecular weight, 436.3 g/mol) is a water-soluble quaternary ammonium derivative of naltrexone. The addition of a methyl group at the nitrogen ring increases polarity, reduces lipid solubility, and diminishes the ability of methylnaltrexone to cross the blood—brain barrier.⁹,¹⁰ With these characteristics, methylnaltrexone has the potential to block opioid actions mediated by peripheral opioid receptors while sparing actions mediated by centrally-located receptors.¹¹,¹²

Although opioid-induced constipation may be mediated by both peripheral and central mechanisms, early studies confirmed that peripherally-acting methylnaltrexone can induce sufficient bowel motility to have a therapeutic benefit. In human volunteer trials with intravenous methylnaltrexone, morphine-induced gastrointestinal dysmotility and prolonged transit time were reversed without affecting analgesia.¹³ A controlled clinical trial in 22 patients receiving methadone maintenance therapy for opioid addiction demonstrated immediate laxation in all patients at a methylnaltrexone dose of approximately 0.10 mg/kg.¹⁴ There was no evidence of opioid withdrawal or other significant adverse effects. Another human volunteer study showed methylnaltrexone to be active in relieving the peripheral side effects of opioids and well tolerated when given subcutaneously.¹⁵

The present study was designed to assess the efficacy and safety of subcutaneous methylnaltrexone in a population of patients with advanced illness and opioid-induced constipation, and to clarify whether a dose—response relationship could be identified for the purpose of dose selection in further clinical evaluations. The study included a one-week double-blind phase followed by a three-week open-label extension phase to explore the persistence of any benefit.

Methods

The study was a multicenter, randomized, parallel-group, repeated dose, dose-ranging trial with a double-blind phase during the first week and an open-label phase for three additional weeks. The Institutional Review Boards of the participating institutions approved the study and all patients provided signed informed consent prior to participation.

Study Population

The study population consisted of adult men and women with advanced illnesses
(defined as terminal or end-stage diseases, such as advanced metastatic cancer and AIDS) for which they were receiving palliative care and were receiving chronic opioid therapy for pain. Patients were eligible for the study if (1) they were receiving any opioid drug on a daily basis at a dose that had been stable for at least two weeks and was expected to remain stable for an additional four weeks or more, and (2) despite no or conventional laxative therapy (stable for more than four days), they had no bowel movements for two days and reported ongoing constipation, defined as more than two days with no bowel movement and a score of ≥3 on a five-point scale assessing constipation-related distress (see Assessments section below). After entry into the study, patients could receive the study medication only if they reported no bowel movement for at least two days, and had a score of ≥3 on a five-point scale assessing constipation-related distress (see Assessments section below). Inclusion criteria also included having a life expectancy of at least four weeks and stable vital signs with normal temperature.

Patients were excluded from the study if they had (1) fever or otherwise unstable vital signs; (2) a laboratory evaluation (required within seven days of study entry) with liver function tests >3 times the upper limit of normal, a serum creatinine level >2 times the upper limit of normal, or a platelet count <50,000/mm^3; (3) a new regimen or dose change of concurrent gastrointestinal-motility altering medications (e.g., cholinomimetic agents, antimuscarinic drugs, or chemotherapy) during the three weeks prior to study enrollment; (4) a history of gastrointestinal obstruction or other condition that could compromise drug action (e.g., acute abdomen, ostomy, active diverticulitis, ischemic bowel, postsurgical adhesions, rectocele, intussusception); (5) a diagnosis of active peritoneal cancer (e.g., ovarian cancer) that may have interfered with bowel function; or (6) a history of peritoneal catheter placement for chemotherapy or dialysis. Patients also were excluded if there was a known hypersensitivity to methylnaltrexone, naltrexone, or naloxone, or if any investigational drug or experimental product had been administered within the previous 30 days. Women of childbearing potential were allowed to enroll if a pregnancy test was negative at the time of enrollment.

**Study Procedures**

After providing consent, patients were initially randomized in a ratio of 1:1:1 to receive 1 mg, 5 mg, or 12.5 mg of methylnaltrexone. Following preliminary blinded assessment of the first 22 patients, the dose range was extended to 20 mg by protocol amendment. The 20 mg dose group was added by continuing double-blind randomization to the 1 mg, 12.5 mg, or 20 mg dose groups in a ratio of 1:1:3, to a total enrollment of 33 patients.

During the first week of the study, each patient received subcutaneous injections on Days 1, 3, and 5. The volume of injectate was identical across doses, except that the volume increased from 0.5 to 1.0 ml for all dosages after the 20 mg dose group was added.

The protocol required discontinuation of treatment during the double-blind phase if a patient experienced an adverse event with a severity Grade 4 (see Assessments section below), which was assessed by the investigator as possibly, probably, or definitely related to the study drug. If a patient experienced a Grade 3 adverse event in some degree related to study drug, the patient could remain in the study and undergo a 50% dose reduction in the study drug on the next scheduled treatment day. Double-blind treatment was maintained during dose modification.

Patients who were receiving laxatives were required to be on a stable laxative regimen for four days prior to the first dose of study drug and to continue on this regimen during the study. The use of a rescue laxative was permitted during the double-blind phase, with the exception that rescue laxatives could not be administered for 24 hours prior to Day 1 study treatment and for four hours after each double-blind dose.

Following the week of double-blind drug administration, patients were given the option to continue open-label therapy. Doses during this period could be administered as often as every other day. The initial dose was 5 mg and the dose could be increased or decreased by the investigator based on patient response. The maximum allowable dose was 15 mg every other day for the first 22 patients enrolled, and 20 mg every other day for the additional
11 patients. The duration of this open-label extension was a maximum of three weeks.

**Assessments**

A “laxation response,” which was defined as a bowel movement within four hours of the initial dose, was the primary efficacy endpoint for the double-blind phase of the study. Other efficacy endpoints included laxation within four hours of subsequent doses, during the 24-hour period after each dose, time to laxation, the use of rescue laxatives, and subjective outcomes. Subjective outcomes, including constipation-associated symptoms, pain intensity, symptoms potentially due to opioid withdrawal or opioid side effects, and patient satisfaction, were assessed with questionnaires that were administered prior to each dose of study medication and again at approximately three hours post-dose. After each dose, patients were evaluated for side effects and the injection site inspected for any adverse reaction. Vital signs were determined before and at 20, 30, 60, and 180 minutes after each dose.

Laboratory assessments were performed during screening and at the end of the double-blind treatment period. The assessments included serum chemistries and hematological profile. During the open-label period, vital signs, rescue laxative and concomitant medication use, and the occurrence of any adverse events were assessed daily. Questionnaires to assess constipation-associated symptoms, pain intensity, symptoms potentially due to opioid withdrawal or opioid side effects, and patient satisfaction with study medication were completed at the start and at the end of the open-label period. A laboratory evaluation and a physical examination were again performed at the completion of the open-label period. An attempt was made to contact the patient 30 days after the last dose of study drug to further assess safety and survival.

**Constipation Assessment.** Constipation severity and distress were each graded on five-point categorical scales. Severity was described as none, mild, moderate, severe, or very severe; distress was described as none, a little bit, somewhat, quite a bit, or very much. Whenever a bowel movement occurred during the study period, the patient was asked to characterize it in terms of consistency (diarrhea, soft-formed, firm, slightly hard, hard, very hard) and difficulty passing stool (no difficulty, slight, moderate, considerable, great).

**Pain Intensity.** Pain “right now” was graded using a five-point categorical scale (none, mild, moderate, severe, or excruciating).

**Opioid Withdrawal Scale.** Opioid withdrawal was assessed using a modified Himmelsbach scale. Patients were asked to grade each of a series of symptoms—yawning, tearing, runny nose, sweating, tremor, gooseflesh, and restlessness—on a four-point numeric scale (1 = none, 2 = mild, 3 = moderate, or 4 = severe).

**Patient Satisfaction.** Patients were asked to report their satisfaction with the study medication on a seven-point scale: 1 (very satisfied), 2 (satisfied), 3 (slightly satisfied), 4 (neither satisfied nor dissatisfied), 5 (slightly dissatisfied), 6 (dissatisfied), or 7 (very dissatisfied).

**Opioid Adverse Events.** All adverse events were graded in terms of severity on a four-point categorical scale (none, mild, moderate, or severe). Specific adverse events were designated by the investigator as likely or not to be opioid related. These included nausea, vomiting, sedation, myoclonus, urinary retention, and pruritus.

**Other Adverse Events.** A treatment-emergent adverse event was defined as any adverse event that occurred after administration of the first dose of study drug up through 30 days after the last dose of study drug, or an adverse event present at baseline but which worsened in severity during the study period. These adverse events were graded on a four-point severity scale and assigned a relationship to study drug by the investigator as follows: not related, unlikely related, possibly related, probably related, or definitely related.

**Statistical Analyses**

All analyses were performed using SAS® Version 8.2 or JMP Version 5.0. The initial sample size estimate of 10 patients per group was based on a two-sample Fisher’s Exact Test and expected four-hour laxation response rate of 10%–20% in the 1 mg group and 80%–90% in the 12.5 mg group. After the upper dose limit was raised by protocol amendment from 12.5 to 20 mg, the sample size was increased to 33 to permit adequate patient accrual to the 20 mg dose group; no additional enrollment into the 5 mg dose group occurred.
Comparability among treatment groups was evaluated for demographic and other baseline variables. Continuous variables (e.g., age) were analyzed using a one-way analysis of variance. Categorical measurements (e.g., race) were analyzed by Pearson’s Chi-square test for contingency tables.

The intent-to-treat and safety data set included all randomized patients who received at least one dose of study medication. An evaluable patient for the primary endpoint was defined as any patient who met all inclusion/exclusion criteria and received study drug and all assessments on Day 1. No imputations were made to account for missing data.

The primary efficacy outcome was laxation response, or laxation during the four hours after a dose of study medication. Because of the smaller sample size in the 20 mg dose group \( (n = 6) \), a planned step down procedure to determine a dose–response trend was not performed. Instead, the laxation response for each dose group was described statistically, and a comparison made between the laxation response of the higher dose groups combined (5 mg, 12.5 mg, and 20 mg) and the laxation response of the low dose group (1 mg).

Other efficacy endpoints included time-to-laxation, patient-recorded evaluation of bowel movement (consistency and difficulty), constipation (severity and distress), pain, opioid withdrawal effects, opioid side effects, patient satisfaction during the double-blind treatment week, and global satisfaction during the open-label treatment period. Chi-squared tests were used to analyze these secondary endpoints. Time to laxation following dosing during the double-blind and open-label periods was analyzed using a product-limit (Kaplan–Meier) method with a log-rank test.

Safety was evaluated throughout the double-blind and open-label dosing periods based on the incidence, severity, and type of adverse events, as well as changes in clinical laboratory results, physical examination findings, and vital signs relative to baseline.

**Results**

Thirty-nine patients were screened and 33 patients met eligibility criteria and received one or more doses of the study drug (intent-to-treat and safety populations). Eleven of the 33 patients (33%) discontinued the study during the double-blind phase. The most common reason for discontinuation during the double-blind phase was “patient request” \( (n = 7) \); only one patient discontinued in response to an intolerable adverse event (Fig. 1).

Study patients had a mean age of 61 years (range, 20–87), and a mean body weight of 64 kg (range, 32–113); slightly more patients were female (55%), most were Caucasian (79%), and most had a primary cancer diagnosis at baseline (85%) (Table 1). Most patients were using a laxative at baseline (88%); the specific treatments included contact laxatives (73%), softeners/emollients (33%) and osmotic agents (27%). Five patients were not receiving a laxative due to either failure of or intolerance to conventional laxative therapy, and had ongoing constipation as previously defined. Differences in demographic and baseline characteristics among the treatment groups were not statistically significant.

**Double-Blind Phase**

The proportion of patients who reported a laxation response within four hours, and within 24 hours of study medication during the double-blind phase is summarized in Table 2. Per protocol, no patient had reported a bowel movement within two days prior to the first dose of methylnaltrexone. Following the initial dose, only one of the 10 patients receiving the 1 mg dose had a response within four hours, but 11 of 23 patients (48%) who received either 5 mg, 12.5 mg, or 20 mg of methylnaltrexone responded \( (P = 0.05) \). There was no dose–response relationship across the three highest doses, and the statistical comparisons between the group receiving the 1 mg dose and each of the higher dose groups were as follows: 5 mg vs. 1 mg, \( P = 0.05 \); 12.5 mg vs. 1 mg, \( P = 0.06 \); and 20 mg vs. 1 mg, \( P = 0.52 \). Lack of a dose–response relationship over a certain threshold was also demonstrated if patients were grouped by weight-adjusted dose categories (Fig. 2).

Laxation responses within four hours of the dose on the second and third administration of study drug, and within 24 hours after each study drug administration, were considered secondary outcomes. Laxation responses for these secondary outcomes were not significantly different, but the positive trends were
similar to those observed in the first dose four-hour interval; the differences between the lowest dose and the higher doses considered as a single group were in the expected direction and no dose—response was evident with doses of 5 mg or higher.

The median time to laxation was >48 hours for the 1 mg dose group and 1.72, 0.48, and 6.75 hours in the 5, 12.5, and 20 mg dose groups, respectively, and can be visualized in plots of laxation response vs. time post-dosing (Fig. 3). The median time to laxation was 1.26 hrs for all patients dosed ≥5 mg, and was statistically significant compared to the 1 mg group (P=0.0003).

The number of bowel movements per week was essentially unchanged between the week prior to the study and first week of the study in the 1 mg dose group and was generally improved over the same time frame in patients who received methylnaltrexone at doses of ≥5 mg. The median (range) for those who received the 5 mg, 12.5 mg, and 20 mg doses rose from 2 (0–3) to 4 (1–18), from 1 (1–3)
to 6 (1–32) and from 2 (0–9) to 5 (0–13), in the three dose groups, respectively ($P = 0.19$).

A trend toward the use of less laxative rescue medication also was observed among those patients treated with higher methylnaltrexone doses. On Day 1, 22 (67%) patients overall took a rescue medication to induce laxation. By Days 3 and 5, fewer patients (14 [54%] and 13 [57%], respectively) required rescue medication. Patients in the 1 mg dose group required a rescue laxative approximately twice as often as those in the higher dose groups.

### Table 1
Population Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methylnaltrexone Dose Level</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg ($n = 10$)</td>
<td>5 mg ($n = 7$)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male</td>
<td>6 (60)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian</td>
<td>7 (70)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>2 (20)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean</td>
<td>59.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>20–87</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean</td>
<td>63.0</td>
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<tr>
<td></td>
<td>SD</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>38.6–77.9</td>
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<tr>
<td>Opioid (morphine equivalent) dose at baseline, mg/day</td>
<td>Mean (SD)</td>
<td>266.5 (209.7)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>196.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>9–780</td>
</tr>
<tr>
<td>Primary diagnosis at baseline</td>
<td>Cancer</td>
<td>9 (90%)</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>AIDS</td>
<td>0</td>
</tr>
<tr>
<td>WHO Performance Status Rating at baseline</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (40%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 (30%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Number of bowel movements per week at start of study</td>
<td>Mean</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1–6</td>
</tr>
</tbody>
</table>

### Table 2
Patients (%) with Bowel Movements Within 4 or 24 Hours After Dosing During the Double-Blind Study Phase

<table>
<thead>
<tr>
<th>Methylnaltrexone Dose Level</th>
<th>Dosing Day</th>
<th>1 mg</th>
<th>5 mg</th>
<th>12.5 mg</th>
<th>20 mg</th>
<th>≥5 mg combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-hour response</td>
<td>1</td>
<td>1/10 (10%)</td>
<td>3/7 (43%)</td>
<td>6/10 (60%)</td>
<td>2/6 (33%)</td>
<td>11/23 (48%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2/9 (22%)</td>
<td>4/6 (67%)</td>
<td>5/7 (71%)</td>
<td>2/4 (50%)</td>
<td>11/17 (65%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0/7 (0%)</td>
<td>4/5 (80%)</td>
<td>4/7 (57%)</td>
<td>3/4 (75%)</td>
<td>11/16 (69%)</td>
</tr>
<tr>
<td>24-hour response</td>
<td>1</td>
<td>5/10 (50%)</td>
<td>5/7 (71%)</td>
<td>7/10 (70%)</td>
<td>2/6 (33%)</td>
<td>14/23 (61%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3/9 (33%)</td>
<td>4/6 (67%)</td>
<td>5/7 (71%)</td>
<td>3/4 (75%)</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1/7 (14%)</td>
<td>4/5 (80%)</td>
<td>4/7 (57%)</td>
<td>3/4 (75%)</td>
<td>11/16 (69%)</td>
</tr>
</tbody>
</table>
Although evaluation of other secondary outcomes was limited by the small sample size (and low response rate for some items), several trends were noted. Compared to patients who received the 1 mg dose during the double-blind phase, those treated with \( 5 \) mg reported an improvement in stool consistency and difficulty passing stool. The proportion of patients reporting relatively high baseline constipation severity (28 of 33 patients with moderate, severe, or very severe constipation) or distress (28 of 33 patients with somewhat, quite a bit, or very much distress) declined by the end of the double-blind period (to four of the 11 patients assessed for severity and distress). There were no differences in pain among the dose groups at baseline, on dosing Days 1, 5, or 5, or at the end of the double-blind treatment period (Day 7) and no trends suggestive of worsening pain control over time. There also was no evidence of methylnaltrexone-induced opioid withdrawal during the double-blind phase of the study. There were no trends in patient satisfaction scores.

**Open-Label Treatment Phase**

Data from the open-label phase was limited in that only 18 of 33 subjects who entered the double-blind phase continued into the open-label phase. A total of 100 doses were
administered during the open-label phase. The large majority of doses were in the 5–12.5 mg range, with only two doses administered at <5 mg, and four doses at 15 mg. Regardless of dose, laxation response to methylnaltrexone during the open-label period continued at a rate similar to that observed during the double-blind phase, namely between 49% and 63% for doses between 5 and 12.5 mg (Table 3). Secondary outcomes could not be meaningfully evaluated due to the small number of observations.

**Adverse Events**

All patients experienced at least one treatment-emergent adverse event during the double-blind phase (Table 4). Abdominal pain was the most common adverse event (15 patients, or 45%). Most adverse events (64%) were mild in intensity and there were no trends in relation to dose (Table 5).

One patient died during the double-blind treatment phase (5 mg dose); the event was unrelated to the study medication. One patient, an 84-year-old man, was withdrawn due to syncope (12.5 mg dose). The event, assessed by the investigator as related to study medication, was transient and resolved without sequelae. Five patients experienced non-death serious adverse events (SAEs): lymphadenectomy, febrile neutropenia, depressed level of consciousness, suicide attempt, and delirium; all were considered unrelated to study medication.

The overall rate and intensity of adverse events during the open-label phase was similar to that observed during the double-blind phase. A 20-year-old man was withdrawn due to abdominal cramping, probably related to study medication, after having received three doses during the double-blind phase. A total of six SAEs, including pulmonary embolism, lobar pneumonia, dehydration, failure to thrive, neuropathic pain, and pneumonia, were experienced by four patients during the open-label phase. All of the SAEs were assessed as unrelated to study drug and consistent with known, underlying disease. There was one death during the open-label phase, which was attributed to an underlying medical condition. There were no significant changes in laboratory evaluations or vital signs.

**Discussion**

In patients with advanced illness and opioid-induced constipation, subcutaneously administered methylnaltrexone in doses between 5 and 20 mg (0.05–0.5 mg/kg) induced a laxation response (a bowel movement within four hours) significantly more often than a dose of 1 mg (<0.05 mg/kg). There was no dose–response relationship above 5 mg per day. Approximately 50% of patients responded to doses ≥5 mg within four hours of dosing and favorable effects on bowel movement

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### Table 3

**Open-Label Dosing and Laxation Responses to Methylnaltrexone**

<table>
<thead>
<tr>
<th>Methylnaltrexone Dose Level</th>
<th>2.5 mg</th>
<th>3.75 mg</th>
<th>5 mg</th>
<th>7.5 mg</th>
<th>10 mg</th>
<th>12.5 mg</th>
<th>15 mg</th>
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<tbody>
<tr>
<td>Number of doses</td>
<td>1</td>
<td>1</td>
<td>33</td>
<td>30</td>
<td>19</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Four-hour response, n (%)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>16 (49)</td>
<td>18 (60)</td>
<td>12 (63)</td>
<td>6 (50)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>24-hour response, n (%)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>17 (52)</td>
<td>18 (60)</td>
<td>12 (63)</td>
<td>7 (58)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>

### Table 4

**Overview of Adverse Events During Double-Blind Treatment**

<table>
<thead>
<tr>
<th>Category</th>
<th>1 mg (n = 10)</th>
<th>5 mg (n = 7)</th>
<th>12.5 mg (n = 10)</th>
<th>20 mg (n = 6)</th>
<th>All Patients (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>33 (100%)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>25 (76%)</td>
</tr>
<tr>
<td>All grade 3 or 4 AEs</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>20 (61%)</td>
</tr>
<tr>
<td>All SAEs</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Deaths (during treatment)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

AEs = adverse events.
frequency were maintained with repeated dosing. Although there were improving trends in the use of rescue laxatives, stool consistency, and difficulty passing stool, as well as in some subjective ratings of symptoms, these trends did not reach statistical significance due to the small number of patients participating in this exploratory study. There was no evidence that administration of methylnaltrexone produced systemic opioid withdrawal or changes in pain control, and although other treatment-emergent adverse effects occurred, these were generally mild and tolerable.

Given the limitations of this trial, including the small sample size, the severity of illness that characterized the patients, and the use of face valid measures of subjective effects, interpretation of these results is best limited to proof of principle. Although the lack of a placebo group might be considered a limitation of the study design, it was felt at the time of the study that inclusion of a placebo group would be impractical and pose an ethical dilemma in this study population with advanced illness and significant comorbidity. The data support the conclusion that methylnaltrexone at a dose of 5 mg or greater can reverse opioid-induced constipation in a medically ill population, but additional work is needed to confirm the results in a larger population, to clarify the optimal indications for treatment, and to assess the full range of potential outcomes.

These results provide broader evidence for the potential efficacy of systemically administered, peripherally-acting opioid antagonists as a new approach for the management of opioid-induced constipation. These agents presumably reverse opioid-induced changes in bowel motility through an action on opioid receptors in the gut. This conclusion gains support from a controlled trial of another opioid antagonist, alvimopan, and earlier experience with oral naloxone. In contrast to naloxone, these newer drugs have not been associated with opioid withdrawal or diminished pain control.

Constipation is an extremely prevalent problem in opioid-treated populations, particularly those with advanced illness. Numerous laxative therapies are now in use but the extent to which any particular population is refractory to these approaches, or which therapies may be themselves associated with ill effects, has not been adequately studied. Nonetheless, persistent constipation-associated distress is commonly encountered in this clinical setting and opioid antagonist therapy holds promise as a new therapeutic approach.

The present trial has demonstrated that subcutaneously administered methylnaltrexone can produce a rapid relief of constipation in opioid-treated patients with advanced illness, and that doses associated with this action do not cause opioid withdrawal or a flare of pain. Larger controlled studies are warranted to establish the effective dose range and clarify the nature of the clinical response.

References


