Efficacy and Tolerability of Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: A Responder Analysis of 2 Randomized, Placebo-Controlled Trials

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Abstract

Background: Subcutaneous methylnaltrexone is efficacious and well tolerated in inducing bowel movements in patients with advanced illness and opioid-induced constipation (OIC); factors determining optimal responsiveness to OIC treatment, however, have not been elucidated. This post hoc responder analysis examined the influence of demographic and baseline characteristics on methylnaltrexone efficacy and tolerability in this population.

Methods: Data were pooled from 2 randomized, double-blind, placebo-controlled, phase 3 studies of subcutaneous methylnaltrexone (0.15 and 0.30 mg/kg) [ClinicalTrials.gov identifiers: Study 301 – NCT00401362; Study 302 – NCT00402038]. Subgroup analyses of the primary outcome, percentage of patients with rescue medication-free bowel movements (RFBM) within 4 hours of first dose, were conducted for age, sex, primary diagnosis, baseline constipation-related distress score, and baseline oral morphine equivalent dose.

Results: More than 50% of 165 patients treated with either methylnaltrexone dose experienced a RFBM within 4 hours vs. 14.6% of 123 placebo-treated patients (P < 0.0001 for both methylnaltrexone doses vs. placebo). Methylnaltrexone response was significantly greater than placebo response in all subgroups (P < 0.01). The largest
INTRODUCTION

Opioids are frequently prescribed to treat moderate to severe pain and dyspnea in patients with advanced illness. Despite its proven analgesic efficacy, opioid therapy is frequently complicated by adverse effects, such as constipation, nausea, and vomiting. Opioid-induced constipation (OIC) is a distressing adverse effect of chronic opioid therapy, evidenced in up to 90% of patients with advanced illness taking opioids. Unlike other adverse effects of opioid use (eg, nausea and vomiting), patients either do not develop tolerance for OIC or develop tolerance very slowly. Severe OIC may result in opioid dose reduction or may limit upward dose titration, leading to inadequate pain control.

Typically, OIC is treated nonspecifically with stool softeners, osmotic agents, and stimulant laxatives as first-line therapy; however, these treatments are often ineffective or only partially effective and burdensome, and evidence of their efficacy in controlled clinical trials is lacking in patients with OIC. Furthermore, these strategies do not target the underlying cause of OIC, which is mediated by \( \mu \)-opioid receptors in the gastrointestinal tract. Blocking \( \mu \)-opioid receptors with centrally acting nonselective antagonists such as naloxone can reverse OIC, but it can also compromise the central analgesic effect of opioids and precipitate opioid withdrawal. Therefore, peripherally restricted selective antagonists of \( \mu \)-opioid receptors, which have limited or no access to the central nervous system, might relieve OIC without compromising centrally mediated effects of opioid analgesia.

Methylnaltrexone, a derivative of naltrexone, is a selective, peripherally acting \( \mu \)-opioid receptor antagonist that has restricted ability to cross the blood–brain barrier. Methylnaltrexone antagonizes the negative opioid-induced effects on the gut, such as delayed gastric emptying and prolongation of oral-cecal transit time.

Methylnaltrexone, administered subcutaneously, is currently approved for the treatment of OIC in patients with advanced illness who are receiving palliative care and who have had an insufficient response to laxatives. Safety and efficacy of subcutaneous methylnaltrexone in inducing a bowel movement in patients who have advanced illness with OIC were demonstrated in 2 multicenter, randomized, double-blind, placebo-controlled clinical studies; demographic and baseline factors that predict optimal responsiveness to methylnaltrexone treatment, however, have not been elucidated. Responsiveness to opioid therapy for pain management is known to be influenced by several factors, including age, sex, ethnicity, genetic factors, and comorbidities. Therefore, a post hoc analysis of data from 2 previously published double-blind studies was conducted to examine the influence of demographic and baseline characteristics on the efficacy and tolerability of methylnaltrexone in patients with advanced illness and OIC.

METHODS

Study Population

Data were pooled from 2 multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical studies (ClinicalTrials.gov identifiers: Study 301 – NCT00402038; Study 302 – NCT00402038) conducted in patients \( \geq 18 \) years of age with advanced illness and OIC. Both studies received institutional review board approval, and patients provided written informed consent prior to enrollment. Patients eligible for study 301 had a life expectancy of 1 to 6 months, OIC (no bowel movement in 48 hours), were receiving a stable opioid and laxative regimen, and were enrolled in hospice or palliative care programs. Eligible patients in study 302 had a life expectancy of \( \geq 1 \) month, OIC (\(< 3 \) laxations in the last week or no laxation in 48 hours), were receiving a stable opioid and laxative regimen, and were enrolled in hospice, nursing home, or palliative care programs. Patients with any history, signs and symptoms, or disease process suggestive of gastrointestinal...
tinal obstruction or patients with current peritoneal catheter for intraperitoneal chemotherapy or dialysis, clinically significant active diverticular disease, fecal impaction, acute surgical abdomen, or fecal ostomy were excluded in both studies. Further details of inclusion and exclusion criteria have been published previously.16,17

Study Design

Details on the study design of both trials have been previously published.16,17 Briefly, study 301 was a single-dose study followed by a 28-day open-label phase and a 3-month, open-label extension phase. In the double-blind phase, patients were randomly assigned to receive a single subcutaneous dose of methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.30 mg/kg, or placebo. Study 302 was a 2-week, multiple-dose study followed by a 3-month, open-label phase. In the double-blind phase, patients were randomly assigned to receive subcutaneous methylnaltrexone 0.15 mg/kg or placebo every other day. According to the study design for each trial, patients could continue their baseline laxative regimen throughout the studies and rescue laxatives were allowed as needed, although not within 4 hours before and after receiving a dose of study drug.

Efficacy

The primary efficacy measure in both studies was the percentage of patients with a rescue-free bowel movement (RFBM) within 4 hours after administration of a single (first and only) dose (study 301) or the first dose (study 302; which was a coprimary endpoint for this study).16,17 Patients needing rescue laxatives or disimpaction within 4 hours of dosing were considered nonresponders. All randomized patients who received at least 1 dose of the study drug in the double-blind phase of the studies were included in the efficacy analysis.16,17 In this study, the following subgroup analyses of the primary outcome measure were conducted: (1) age (<65 vs. ≥65 years); (2) sex (female vs. male); (3) primary diagnosis (cancer vs. noncancer); (4) baseline constipation-related distress score (≤3 vs. >3; [rated on a scale of 1 to 5: 1 = “none,” 2 = “a little bit,” 3 = “somewhat,” 4 = “quite a bit,” and 5 = “very much”]); and (5) baseline morphine equivalent dose (<150 mg/day vs. ≥150 mg/day).

Safety

Adverse events (AEs) occurring during the double-blind phases of the studies 301 and 302 were pooled for the methylnaltrexone groups (0.15 and 0.30 mg/kg groups) and the placebo groups. Data from study 301 included AEs occurring during single-dose administration of 0.15 or 0.30 mg/kg methylnaltrexone or placebo, whereas data from study 302 included AEs occurring during multiple-dose administration of 0.15 mg/kg methylnaltrexone or placebo every other day for 2 weeks. All patients who received at least 1 dose of the study drug in the double-blind phase of the studies were included in the safety analysis. AEs were also assessed across the same demographic and baseline characteristic subgroups used for analyses of the primary efficacy outcome in this study.

Statistical Analyses

Data were pooled from the double-blind portions of the single-dose study 301 and the first dose of the multiple-dose study 302. Demographic and baseline disease characteristics were summarized using descriptive statistics. To facilitate comparison among the different baseline opiates used in these 2 studies, oral morphine equivalents were derived by converting opioid doses utilizing standard equianalgesic conversion tables.19 Subgroup analyses of the primary outcome measure were performed using the chi-square test to explore the effects of methylnaltrexone vs. placebo treatment for each subgroup (based on selected demographic and baseline characteristics) on RFBM within 4 hours after the single (first)-dose (study 301) or the first dose (multiple-dose study 302). In addition, odds ratios and 95% confidence intervals were calculated.

RESULTS

Patient Disposition and Demographics

Although 154 and 134 patients received study drug (methylnaltrexone or placebo) in studies 301 and 302, respectively, 154 and 133 patients were randomized (Figure 1).16,17 One patient in the methylnaltrexone 0.15 mg/kg group in study 302 received methylnaltrexone in an unblinded manner; therefore, this patient was included only in the safety analysis and not in the efficacy analyses. After pooling data, there were 110, 55, and 123 patients in the methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.30 mg/kg, and placebo groups,
respectively, in the safety population. Demographic and baseline characteristics were generally similar among treatment groups (Table 1). More than 50% of the patients were ≥ 65 years of age and approximately 70% of the patients had a primary cancer diagnosis in this pooled dataset. Most of the patients (96.5%) were taking laxatives at baseline.\textsuperscript{16,17} Approximately 50% of the patients were prescribed a baseline morphine equivalent dose of ≥ 150 mg/day.

### Primary Outcome

In the pooled analysis, a significantly larger percentage of patients treated with methylnaltrexone 0.15 mg/kg or 0.30 mg/kg experienced a RFBM within 4 hours after the first dose vs. placebo (Figure 2). In the subgroup analyses involving selected demographic (age and sex) and baseline (primary diagnosis, constipation-related distress, and morphine equivalent dose) characteristics, responsiveness to both doses of methylnaltrexone (ie, patients experiencing a RFBM within 4 hours after administration) was significantly greater vs. placebo across all subgroups (Figure 3A,B). The range of methylnaltrexone responses was 40.0%-73.3%, and the range of placebo responses was 10.2%-18.8% (\(P < 0.01\) for all comparisons). The largest differences compared with placebo were observed in the 0.30 mg/kg methylnaltrexone group of patients with noncancer primary diagnosis and patients maintained on ≥ 150 mg/day baseline oral morphine equivalent doses. Among patients with noncancer primary diagnosis and taking 0.30 mg/kg methylnaltrexone or placebo, RFBM was 70.0% or 12.8%, respectively (\(P < 0.001\)), and for

### Table 1. Demographic and Baseline Characteristics

| Characteristic                              | Methylnaltrexone 0.15 mg/kg | Methylnaltrexone 0.30 mg/kg | Placebo |
|--------------------------------------------|-----------------------------|-----------------------------|---------|
|                                            | \(n = 110\)                 | \(n = 55\)                  | \(n = 123\) |
| Age group                                  |                             |                             |         |
| < 65 years                                 | 42 (38.2)                   | 24 (43.6)                   | 61 (49.6) |
| ≥ 65 years                                 | 68 (61.8)                   | 31 (56.4)                   | 62 (50.4) |
| Sex                                        |                             |                             |         |
| Male                                       | 52 (47.3)                   | 31 (56.4)                   | 59 (48.0) |
| Female                                     | 58 (52.7)                   | 24 (43.6)                   | 64 (52.0) |
| Race                                       |                             |                             |         |
| White                                      | 99 (90.0)                   | 46 (83.6)                   | 108 (87.8) |
| Black                                      | 6 (5.4)                     | 4 (7.3)                     | 8 (6.5) |
| Other                                      | 5 (4.5)                     | 5 (9.1)                     | 7 (5.7) |
| Primary diagnosis                          |                             |                             |         |
| Cancer                                     | 74 (67.3)                   | 45 (81.8)                   | 84 (68.3) |
| Noncancer                                  | 36 (32.7)                   | 10 (18.2)                   | 39 (31.7) |
| Any laxative use, \(n\) (%)                | 107 (97.3)                  | 51 (92.7)                   | 120 (97.6) |
| Constipation-related distress              |                             |                             |         |
| None                                       | 11 (10.0)                   | 4 (7.3)                     | 14 (11.4) |
| A little bit                                | 13 (11.8)                   | 7 (12.7)                    | 16 (13.0) |
| Somewhat                                   | 18 (16.4)                   | 12 (21.8)                   | 21 (17.1) |
| Quite a bit                                | 33 (30.0)                   | 19 (34.5)                   | 36 (29.3) |
| Very much                                   | 33 (30.0)                   | 13 (23.6)                   | 35 (28.5) |
| Not reported                                | 2 (1.8)                     | 0                           | 1 (0.8) |
| Oral morphine equivalents                   |                             |                             |         |
| < 150 mg/day                               | 47 (42.7)                   | 25 (45.5)                   | 69 (56.1) |
| ≥ 150 mg/day                               | 63 (57.3)                   | 30 (54.5)                   | 54 (43.9) |

\*One patient in study 302 in the methylnaltrexone 0.15 mg/kg group received methylnaltrexone in an unblinded manner and was not included in efficacy analysis. This patient was included only in the safety analysis and not in efficacy analyses.

![Figure 1. Patient disposition.](image)

![Figure 2. Rescue-free bowel movement within 4 hours of administration of the first dose of methylnaltrexone or placebo.](image)
patients maintained on ≥ 150 mg/day baseline oral morphine equivalent doses and taking 0.30 mg/kg methylnaltrexone or placebo, RFBM was 73.3% or 16.7%, respectively (P < 0.0001). The responsiveness to both doses of methylnaltrexone was supported by odds ratios and 95% confidence intervals favoring methylnaltrexone vs. placebo for all subgroups analyzed (Figure 3A, B).

Safety

Gastrointestinal-related AEs generally were the most commonly reported AEs during treatment, with abdominal pain (pooled methylnaltrexone: 27.9%, placebo: 9.8%), flatulence (13.3%, 5.7%), and nausea (10.9%, 4.9%) being the most frequent in the pooled methylnaltrexone group (Table 2). The majority (> 75%) of AEs were mild or moderate in intensity. Tolerability of methylnaltrexone treatment was generally comparable across the subgroups analyzed. Although the incidence of abdominal pain was reported more often in patients treated with methylnaltrexone vs. placebo, the percentage of patients with abdominal pain was consistent across all methylnaltrexone-treated subgroups (Table 3). Similarly, incidences of other frequently reported AEs were also consistent across all subgroups.

The most frequently reported serious AE (SAE) was malignant neoplasm progression, which reflected underlying disease progression in a population comprised largely of patients with cancer. These SAEs were not considered by the investigators to be drug related and were mostly reported in patients with cancer as their primary diagnosis (8.4% in pooled methylnaltrexone
group and 16.7% in placebo group in patients with cancer as primary diagnosis vs. 2.2% in pooled methylnaltrexone group and 0% in placebo group in patients with noncancer as primary diagnosis).

**DISCUSSION**

The findings from the 2 double-blind, placebo-controlled trials in patients with advanced illness and OIC showed that methylnaltrexone provided significant relief from OIC compared with placebo, with more than half of the pooled methylnaltrexone-treated patients having achieved a response after the first dose. A number of factors associated with patients who have advanced illness, such as the underlying disease process and concomitant medications, may impact their response to OIC treatment. Because most clinical trials are designed to evaluate the likelihood of a response over a large general population of patients, a responder analysis of the clinical trial data can be important in identifying the odds of a select patient population experiencing a clinically meaningful treatment effect. This post hoc responder analysis of pooled data from 2 double-blind, placebo-controlled trials of subcutaneous methylnaltrexone in patients with advanced illness and OIC was performed to analyze the potential influence of demographic and baseline characteristics on the efficacy and tolerability of methylnaltrexone. The results of this responder analysis support that, in patients with advanced illness and OIC, methylnaltrexone produces a rapid (within 4 hours) RFBM that is consistent across age (< 65 years vs. ≥ 65 years), sex (male vs. female), primary diagnosis for...
opioid use (cancer vs. noncancer), baseline constipation-related distress experienced by patients (mild distress with a score of \( \leq 3 \) vs. more distress with a score of \( \geq 3 \)), and baseline opioid use \( (< 150 \text{mg/day} \text{ vs. } \geq 150 \text{mg/day morphine equivalents}) \).

Although demographic characteristics are known to influence responsiveness to opioid agonists,\(^{18}\) age and sex did not appear to impact response to the \( \mu \)-opioid receptor antagonist methylnaltrexone in this study. Baseline disease characteristics, such as primary diagnosis for opioid use, constipation-related distress, and opioid use, also did not predict variations in responsiveness to methylnaltrexone in this analysis. However, 2 subgroups in the methylnaltrexone 0.30 mg/kg treatment group, patients with noncancer primary diagnosis and patients maintained on \( \geq 150 \text{mg/day} \) baseline morphine equivalent doses, elicited particularly favorable responses vs. the placebo group. Identifying whether a patient population might benefit from a higher or lower dose of methylnaltrexone or more or less frequent dose regimen (eg, once daily) with longer-term management may improve response rates and potentially improve the cost-effectiveness of methylnaltrexone therapy.

The larger difference in response with the higher dose of methylnaltrexone (0.30 mg/kg) vs. placebo observed for patients maintained on higher doses of morphine equivalents \( (\geq 150 \text{mg/day}) \) is intriguing and may suggest at least some methylnaltrexone-to-opioid dose response (antagonist-agonist ratio). Such a relationship might be expected based on the receptor pharmacology of methylnaltrexone, which functions as a competitive antagonist of \( \mu \)-opioid receptors.\(^{20}\) The results from the single-dose, double-blind, placebo-controlled study of methylnaltrexone in patients with advanced illness and OIC demonstrated no apparent dose–response relationship with 0.15 mg/kg vs. 0.30 mg/kg and no correlation between RFBM and baseline opioid use.\(^{16}\) The study did not specifically compare response rates, however, between the methylnaltrexone 0.30 mg/kg and placebo treatment groups in patients maintained on higher \( (\geq 150 \text{mg/day}) \) doses of oral morphine equivalent dose.

The tolerability profile of subcutaneous methylnaltrexone was generally comparable across all subgroups evaluated in this study. The AEs most frequently reported in the 2 studies included abdominal pain, flatulence, and nausea. The incidence of abdominal pain and flatulence is likely related to an intentional propulsive effect of the gut during the normal process of a bowel movement. Another post hoc analysis of these 2 trials that characterized the AE of abdominal pain indicated that abdominal pain was mostly mild to moderate in intensity and that the incidence decreased after the first dose while response to methylnaltrexone treatment was maintained.\(^{21}\)

The strengths of this post hoc analysis included that both studies enrolled patients with similar inclusion and exclusion criteria and that the patients were under the care of palliative care practitioners. The primary outcome was based on efficacy after the first dose of methylnaltrexone or placebo. Therefore, the differences in study design between the 2 studies (eg, single dose vs. multiple dose) should not have affected the primary endpoint. A limitation of the study was that the subgroup analyses provided only a short-term (single [first]-dose) assessment of the potential differences in response based on demographic and baseline characteristics. In addition, the post hoc nature of the subgroup analyses was another limitation of the study. Therefore, the results from this study are considered exploratory and need validation with analysis of multiple-dose data from a prospective study.

In conclusion, subcutaneous methylnaltrexone is a well-tolerated and effective treatment option for the management of OIC in patients with advanced illness receiving palliative care, with rapid and robust occurrence of a RFBM noted across various demographic and baseline characteristic subgroups. Further studies are warranted to help clarify the particularly favorable response observed with methylnaltrexone 0.30 mg/kg in patients receiving higher doses \( (\geq 150 \text{mg/day}) \) of baseline morphine equivalents and in patients with noncancer primary diagnosis, in addition to the relationship, if any, between methylnaltrexone dose and morphine equivalent dose.

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