VALUE IN HEALTH 14 (2011) 177–183

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/jval

Effect of subcutaneous methylnaltrexone on patient-reported constipation symptoms

Shrividya S. Iyer, PhD, Bruce P. Randazzo, MD, PhD, Evan L. Tzanis, MA, Seth L. Schulman, MD, Haiying Zhang, PhD, Wenjin Wang, PhD, Amy L. Manley, BS*

Pfizer Inc, Collegeville, PA, USA

Keywords:
Chronic nonmalignant pain
Constipation symptoms
Methylnaltrexone
Opioid-induced constipation
Pain scores
Patient-reported outcomes

A B S T R A C T

Background: Methylnaltrexone, a selective peripheral acting mu-opioid receptor antagonist, alleviates the constipating effects of opioids without affecting centrally mediated analgesia.

Objectives: To assess the effect of subcutaneous (SC) methylnaltrexone injection on patient-reported constipation symptoms and pain scores.

Methods: A total of 469 subjects on opioids for chronic non-malignant pain with opioid-induced constipation were randomized to methylnaltrexone SC with once daily (QD) or every other day (QOD) dosing or placebo for 4 weeks. Constipation symptoms and pain were assessed using the patient assessment of constipation–symptoms (PAC-SYM) questionnaire and a 11-point scale, respectively, at baseline, Day 14 and Day 28. Change from baseline in PAC-SYM and pain scores were compared between methylnaltrexone and placebo arms at Day 28 using analysis of covariance, with treatment group as factor and baseline score as covariate.

Results: A majority of patients were women (60%), average age was 49 years old, and back pain (60%) was the primary pain condition. At Day 28, the methylnaltrexone SC QD group showed a significant improvement over placebo for rectal symptoms (−0.56 vs. −0.30; $P < 0.05$), stool symptoms (−0.76 vs. −0.43; $P < 0.001$) and global scores (−0.62 vs. −0.37; $P < 0.001$). Improvement in stool symptoms (−0.69 vs.−0.43; $P < 0.05$) and the global scores (−0.52 vs. −0.37; $P < 0.05$) were significantly greater than placebo in the methylnaltrexone QOD group. Differences in change from baseline in abdominal symptoms and pain scores between the methylnaltrexone SC QD or QOD dosing arms and placebo were not significant.

Conclusion: The results of our study indicate significant improvement in constipation symptoms with methylnaltrexone QD or QOD dosing compared to placebo without a significant effect on pain scores.

Funding: This study was supported by Wyeth Research, Collegeville, PA, USA, which was acquired by Pfizer Inc in October 2009.

* *Address correspondence to:* Shrividya Iyer, 500 Arcola Road, E-4269, Collegeville, PA 19426 USA.
E-mail: shrividya.iyer@pfizer.com.

1098-3015/$36.00 – see front matter

doi:10.1016/j.jval.2010.11.003

Introduction

Opioid therapy plays a key role in the management of chronic pain. Opioids have been widely used to treat malignant pain and their use to manage nonmalignant pain has also been increasing in recent years [1]. Despite proven analgesic efficacy in the management of pain, opioid therapy is frequently complicated by side effects [2]. Constipation is a common and unpleasant side effect associated with opioid therapy with approximately 40% of patients using opioids for non-malignant pain, reporting constipations symptoms [2]. Unlike most other common opioid side effects, opioid-induced constipation (OIC) is often persistent and can lead to serious medical consequences such as bowel obstruction or fecal impaction [1,3]. Severe and persistent constipation is one of the most common reasons for patient discontinuation of opioid analgesics, thus leading to a negative effect on pain management and quality of life [4]. Opioids impair normal bowel function primarily by binding to intestinal mu-opioid receptors and interrupting the coordinated rhythmic contractions required for intestinal motility [5]. Opioids can also alter intestinal fluid secretion by a direct effect on the enteric nervous system [6]. Selective blockade of the peripheral receptors might relieve constipation without compromising centrally mediated effects of opioid analgesia or precipitating withdrawal [7].

Currently, there is no approved drug indicated for the treatment of OIC in the population of patients receiving opioid therapy for chronic, non-malignant pain. Methylnaltrexone (N-methylnaltrexone bromide, RELISTOR [Progenics Pharmaceuticals, Tarrytown, NY, USA]), a quaternary derivative of naltrexone, has been approved as a subcutaneous (SC) injection for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient [8]. Unlike the uncharged systemic opioid antagonists naloxone and naltrexone, a charged antagonist like methylnaltrexone has restricted ability to cross the blood-brain barrier because of its polarity and low lipid solubility [9,10]. As a result, methylnaltrexone antagonizes the peripherally located opioid receptors in the gastrointestinal tract, thus reducing OIC without precipitating withdrawal symptoms or negatively affecting or reversing the analgesic effects of opioids [9,11–13].

A randomized, placebo-controlled, phase 3 study was designed to determine the efficacy and safety of SC methylnaltrexone compared with placebo in relieving OIC in patients receiving opioid therapy for chronic non-malignant pain. Two co-primary end points were defined during the double-blind period: 1) the proportion of subjects having a rescue-free bowel movement (RFBM) within 4 hours of the first dose, and 2) the percentage of active injections resulting in any RFBM within 4 hours [14]. In addition, data were collected on patient-reported pain scores, constipation symptoms, and quality of life using validated instruments.

Here we report the effect of methylnaltrexone SC on patient-reported constipation symptoms and pain intensity scores over a 4-week double-blind period in subjects experiencing constipation because they are receiving opioids for chronic non-malignant pain.

Methods

A double-blind, randomized, parallel-group, placebo-controlled, phase 3 study was conducted to evaluate the safety, efficacy and tolerability of SC methylnaltrexone versus placebo in subjects with chronic non-malignant pain who have OIC. Subjects were eligible if they had a history of chronic non-malignant pain for at least 2 months' duration, an opioid dose of equal to or greater than 50 mg oral morphine equivalents per day for at least 2 weeks, a history of constipation due to opioid use for at least 1 month, and fewer than 3 RFBMs per week before the screening visit. Eligible subjects who signed an informed consent form entered a 14-day (+ 2-day visit window) screening period, during which objective evidence of constipation was assessed. Constipation during the screening period was defined as fewer than 3 RFBMs per week (no laxative use within 24 hours prior to any bowel movement) that were associated with one or more of the following: a) a Bristol Stool Form Scale score [15] of 1 or 2 for at least 25% of the bowel movements; b) straining during at least 25% of the bowel movements; c) a sensation of incomplete evacuation after at least 25% of the bowel movements. Exclusion criteria included pregnant or breast feeding women, use of methylnaltrexone within 4 weeks of administration of the first dose of test article, non-compliance with subject diary completion, and use of rescue laxative. Subjects who remained eligible at the baseline visit were randomly assigned to receive daily injections containing placebo, methylnaltrexone 12 mg once daily (QD), or methylnaltrexone 12 mg every other day (QOD) in a 1:1:1 allocation ratio for 28 days. If subjects did not have a bowel movement for 3 consecutive days during the study, they were permitted to use bisacodyl tablets, which were provided by the investigator.

Beginning at the screening visit, eligible subjects reported the number of bowel movements per day including the time of each bowel movement by using an interactive voice response system (IVRS) via telephone. For each bowel movement, subjects assessed consistency, straining, and a sensation of complete evacuation. Also reported were rescue laxative use (including whether rescue medication was taken and the time of administration), doses of opioid medication, and pain intensity during the past 24 hours. At baseline and on Days 14 and 28, average pain intensity ratings were recorded on a scale of 0 (no pain) to 10 (worst possible pain) [16]. Safety evaluations included monitoring of adverse events from the screening visit through 14 days after the last dose of test article. Concomitant treatment including use of opioids and rescue laxatives from the screening visit through the follow-up period was recorded. At office visits, height, weight, and vital sign measurements were determined and physical examinations and laboratory evaluations were performed.

In addition, patient-reported constipation symptoms were assessed at baseline, Day 14, and Day 28 using the patient assessment of constipation symptoms (PAC-SYM) questionnaire. The PAC-SYM questionnaire is a 12-item survey that measures constipation symptoms and associated severity across three domains: stool symptoms, rectal symptoms, and abdominal symptoms with a recall period of "past 2 weeks"

Table 1 – Demographic and baseline clinical characteristics (mITT population).

Characteristic	Methylnaltrexone 12 mg QD treatment (n=150)	Methylnaltrexone 12 mg QOD treatment (n=148)	Placebo (n=162)
Age, mean (SD)	47.99 (10.74)	48.64 (11.05)	49.69 (10.77)
Female gender, N (%)	93 (62.0)	85 (57.4)	99 (61.1)
Weight, kg mean (SD)	87.5 (25.0)	85.1 (21.9)	87.2 (26.3)
Race N (%)			
White	139 (92.7)	133 (89.9)	141 (87.0)
Black	7 (4.7)	10 (6.8)	15 (9.3)
Asian	2 (1.3)	1 (0.7)	1 (0.6)
Other	2 (1.3)	4 (2.7)	5 (3.1)
Primary pain condition N (%)			
Back	96 (64.0)	83 (56.1)	99 (61.1)
Morphine equivalent dose (mg)			
Mean (SD)	214 (157)	225 (205)	225 (216)

All values are means (SD), unless otherwise noted, for all patients.
mITT, modified intent-to-treat; QD, once daily; QOD, every other day; SD, standard deviation.

[17]. Score changes on the PAC-SYM global score of approximately half a point have been reported to correspond to minimal clinical improvement, and changes of about 1 point correspond to moderate clinical improvement [17].

The PAC-SYM has been demonstrated and documented to be a sensitive, reliable, valid, and responsive measure for monitoring the symptoms of OIC [18]. Symptom items are rated on a 5-point Likert severity scale. Item values are scored from 0 to 4, with 0 indicating absence of symptom, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe indicating the worst severity of that symptom.

For each of the subscales, scores for the nonmissing items within the subscale are summed and divided by the total number of nonmissing items for that subscale (range, 0–4). For total instrument (Global) score, the scores of nonmissing items within the instrument are summed and divided by the total number of nonmissing items (total score range, 0–4). Change from baseline at Day 14 and Day 28 (end of the double-blind period) in pain, subscale, and total PAC-SYM scores were analyzed using analysis of covariance (ANCOVA) with treatment as a factor and baseline score as a covariate based on the last observation carry-forward (LOCF) data. As part of sensitivity analyses, the change from baseline analyses were rerun with the observed cases data. The proportion of patients showing minimal and moderate clinical improvement based on the PAC-SYM total score was calculated.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the guidelines for Good Clinical Practice. The institutional review boards or independent ethics committees of the participating medical centers approved the study protocol and informed consent document. All patients gave written informed consent before any study-related tests were performed.

Results

Patients: A total of 469 patients with chronic nonmalignant pain and OIC were randomized, of which 460 received at least one dose of study treatment. The modified intent-to-treat (mITT) population of 460 patients was analyzed for constipation symptoms. There were 388 subjects (84%) who completed the double-blind portion of the trial. Demographic and baseline disease characteristics of the study participants are shown in Table 1.

A majority of the patients in the study were women (60%) and white (90%); the average age was 49 years old and back pain (60%) was reported as the primary pain condition. The mean daily baseline oral morphine-equivalent opioid dose was 222 mg.

Descriptive statistics for the PAC-SYM and pain intensity scores at baseline are presented in Table 2. At baseline, the average scores for abdominal symptoms, rectal symptoms, and the PAC-SYM global score were in the mild to moderate severity range, whereas the average scores for stool symptoms were in the moderate to severe range across all treatment groups.

PAC-SYM global score and pain intensity score mean values at baseline were similar for the three treatment arms. On Day 14, data were missing for approximately 12% of cases in treatment groups and 5% of cases in the placebo group. For PAC-SYM global score on Day 14, the methylnaltrexone 12 mg QD group showed an improvement of 0.56 (29.5%) from baseline, compared with an improvement of 0.32 (17.8%) for placebo (between-group difference $P < 0.001$). At Day 14, the methylnaltrexone 12 mg QOD group showed an improvement of 0.42 (22.7%) from baseline in the PAC-SYM global score, which was not statistically significant compared with placebo (Table 3).

On Day 14, rectal symptoms showed statistically significant improvements compared with placebo in the methylnaltrexone QD group ($P < 0.001$) and the methylnaltrexone QOD group ($P < 0.05$). Similarly, for stool symptoms, statistically significant improvements compared with placebo were detected in the methylnaltrexone QD group ($P < 0.001$) and the methylnaltrexone QOD group ($P < 0.05$). For abdominal symptoms, no statistically significant differences were found in the change from baseline scores between the methylnaltrexone QD and QOD dosing arms and placebo (Table 3). Similarly, for pain intensity scores no statistically significant differences were found in the change from baseline scores between the methyl-

Table 2 – PAC-SYM and pain scores at baseline.

Score	Methylnaltrexone 12 mg QD (n=150)	Methylnaltrexone 12 mg QOD (n=148)	Placebo (n=162)
PAC-SYM*			
Abdominal symptoms	1.77 (0.87)	1.73 (0.78)	1.60 (0.85)
Rectal symptoms	1.45 (1.01)	1.31 (0.90)	1.23 (0.89)
Stool symptoms	2.26 (0.95)	2.28 (0.93)	2.30 (0.88)
Global PAC-SYM score	1.90 (0.77)	1.85 (0.73)	1.80 (0.70)
Pain scores†	6.23 (1.93)	6.26 (1.93)	6.33 (1.72)

PAC-SYM, patient assessment of constipation–symptoms; QD, once daily; QOD, every other day.
* Reported values of raw scores across the 3 treatment groups ranged from 0 to 4 for each domain and global PAC-SYM score.
† Pain was rated on a scale of 0 (no pain) to 10 (worst possible pain).

naltrexone QD and QOD dosing arms and placebo (Table 3). On Day 14, proportion of patients meeting the minimal clinical improvement criteria of ≥ 0.5 point improvement from baseline on the global score was 48% of patients in the methylnaltrexone QD arm, 39% in the methylnaltrexone QOD arm, and 38% in the placebo arm. Similarly 25% of patients in the methylnaltrexone QD arm, 17% in the methylnaltrexone QOD arm, and 14% in the placebo demonstrated moderate clinical improvement with ≥1 point improvement on the global score.

On Day 28, data were missing for approximately 16% to 18% of cases in treatment groups and 11% of cases in the placebo group. At the end of the double-blind period (Day 28), the methylnaltrexone 12 mg QD group showed an improvement of 0.62 (32.6%) from baseline in PAC-SYM global mean scores, compared with an improvement of 0.37 (20.6%) for placebo (between-group difference $P < 0.001$). At Day 28, the methylnaltrexone 12 mg QOD group showed an improvement of 0.52 (28.1%) from baseline, which was significantly greater than that shown by the placebo group (between-group difference $P < 0.05$) (Table 4). For rectal symptoms and stool symptoms, statistically significant improvements compared with placebo were detected in the methylnaltrexone QD group ($P \leq 0.001$) and the methylnaltrexone QOD group ($P \leq 0.05$) (Table 4). Similar to Day 14, there were no statistically significant differences in the change from baseline scores between the methylnaltrexone QD and QOD dosing arms and placebo in abdominal symptom and pain intensity scores at the end of the double-blind period (Table 4). The analyses with the observed case data on Day 14 and Day 28 showed similar significant test results as reported above with the LOCF method except for the PAC-SYM global score on Day 14 in the methylnaltrexone QOD group, which showed a statistically significant ($P < 0.05$) greater improvement from baseline compared to placebo in the observed case analyses.

On Day 28, 53% of patients in the methylnaltrexone QD arm, 52% in the methylnaltrexone QOD arm, and 41% in the placebo arm demonstrated at least 0.5 point improvement from baseline on the global score, thus meeting the minimal

Table 3 – PAC-SYM and pain scores and change from baseline on day 14.

Construct	Treatment	N	Raw	Raw change	Adjusted change	Difference in adjusted change vs. placebo	
			Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	P value*
Abdominal symptoms	Methylnaltrexone 12 mg QD	150	1.39 (0.78)	−0.38 (0.74)	−0.35 (0.05)	0.02 (−0.13, 0.16)	0.825
	Methylnaltrexone 12 mg QOD	148	1.46 (0.75)	−0.27 (0.65)	−0.26 (0.05)	0.11 (−0.04, 0.25)	0.141
	Placebo	162	1.27 (0.86)	−0.32 (0.78)	−0.36 (0.05)		
Rectal symptoms	Methylnaltrexone 12 mg QD	150	0.90 (0.88)	−0.56 (0.88)	−0.51 (0.05)	−0.30 (−0.45, −0.15)	<0.001
	Methylnaltrexone 12 mg QOD	148	0.91 (0.90)	−0.40 (0.70)	−0.41 (0.05)	−0.20 (−0.35, −0.05)	0.009
	Placebo	162	1.06 (0.87)	−0.17 (0.68)	−0.21 (0.05)		
Stool symptoms	Methylnaltrexone 12 mg QD	150	1.52 (1.02)	−0.74 (0.98)	−0.75 (0.07)	−0.40 (−0.58, −0.21)	<0.001
	Methylnaltrexone 12 mg QOD	148	1.73 (0.99)	−0.56 (0.88)	−0.56 (0.07)	−0.20 (−0.38, −0.02)	0.030
	Placebo	162	1.94 (0.94)	−0.36 (0.81)	−0.36 (0.06)		
Global score	Methylnaltrexone 12 mg QD	150	1.32 (0.80)	−0.58 (0.70)	−0.56 (0.05)	−0.24 (−0.37, −0.11)	<0.001
	Methylnaltrexone 12 mg QOD	148	1.43 (0.76)	−0.42 (0.60)	−0.42 (0.05)	−0.10 (−0.23, 0.03)	0.134
	Placebo	162	1.50 (0.74)	−0.30 (0.61)	−0.32 (0.05)		
Pain scores	Methylnaltrexone 12 mg QD	149	6.23 (1.90)	−0.00 (1.59)	−0.02 (0.11)	0.07 (−0.24, 0.38)	0.665
	Methylnaltrexone 12 mg QOD	148	6.19 (1.99)	−0.07 (1.45)	−0.08 (0.11)	0.01 (−0.30, 0.32)	0.958
	Placebo	162	6.23 (1.93)	−0.10 (1.37)	−0.08 (0.11)		

A negative value in the difference in adjusted change from baseline in PAC-SYM domain and total scores between methylnaltrexone group and placebo indicates a greater improvement in patient-reported symptoms in the methylnaltrexone arm.
CI, confidence interval; PAC-SYM, patient assessment of constipation–symptoms; QD, once daily; QOD, every other day; SD, standard deviation; SE, standard error.
* *P* value of comparison of each methylnaltrexone dose group against placebo.

Table 4 – PAC-SYM and pain scores and change from baseline on day 28.

Construct	Treatment	N	Raw	Raw change	Adjusted change	Difference in adjusted change vs. placebo	
			Mean (SD)	Mean (SD)	Mean (SE)	Mean (95% CI)	P value*
Abdominal symptoms	Methylnaltrexone 12 mg QD	150	1.27 (0.82)	−0.50 (0.85)	−0.47 (0.06)	−0.12 (−0.27, 0.04)	0.135
	Methylnaltrexone 12 mg QOD	148	1.36 (0.83)	−0.36 (0.66)	−0.35 (0.06)	0.00 (−0.15, 0.15)	0.996
	Placebo	162	1.29 (0.85)	−0.31 (0.81)	−0.35 (0.05)		
Rectal symptoms	Methylnaltrexone 12 mg QD	150	0.83 (0.86)	−0.62 (0.98)	−0.56 (0.06)	−0.26 (−0.42, −0.11)	0.001
	Methylnaltrexone 12 mg QOD	148	0.86 (0.91)	−0.45 (0.68)	−0.46 (0.06)	−0.16 (−0.32, 0.00)	0.050
	Placebo	162	0.98 (0.84)	−0.25 (0.79)	−0.30 (0.06)		
Stool symptoms	Methylnaltrexone 12 mg QD	150	1.51 (1.04)	−0.75 (1.03)	−0.76 (0.07)	−0.33 (−0.51, −0.14)	<0.001
	Methylnaltrexone 12 mg QOD	148	1.59 (0.97)	−0.69 (0.85)	−0.69 (0.07)	−0.26 (−0.45, −0.07)	0.008
	Placebo	162	1.86 (0.98)	−0.44 (0.92)	−0.43 (0.07)		
Global score	Methylnaltrexone 12 mg QD	150	1.26 (0.81)	−0.63 (0.78)	−0.62 (0.05)	−0.25 (−0.39, −0.10)	<0.001
	Methylnaltrexone 12 mg QOD	148	1.33 (0.78)	−0.52 (0.61)	−0.52 (0.05)	−0.15 (−0.29, −0.01)	0.040
	Placebo	162	1.45 (0.75)	−0.35 (0.68)	−0.37 (0.05)		
Pain score	Methylnaltrexone 12 mg QD	149	6.09 (1.96)	−0.14 (1.62)	−0.16 (0.13)	−0.09 (−0.43, 0.25)	0.610
	Methylnaltrexone 12 mg QOD	148	5.96 (1.90)	−0.30 (1.55)	−0.30 (0.13)	−0.23 (−0.57, 0.11)	0.182
	Placebo	162	6.24 (2.04)	−0.09 (1.75)	−0.07 (0.12)		

A negative value in the difference in adjusted change from baseline in PAC-SYM domain and total scores indicates a greater improvement in constipation symptoms in the methylnaltrexone arm compared with placebo.
CI, confidence interval; PAC-SYM, patient assessment of constipation–symptoms; QD, once daily; QOD, every other day; SD, standard deviation; SE, standard error.
* *P* value of comparison of each methylnaltrexone dose group against placebo.

clinical improvement criteria. Similarly approximately 29% of patients in the methylnaltrexone QD arm, 18% in the methylnaltrexone QOD arm, and 17% in the placebo demonstrated moderate clinical improvement with at least a 1 point improvement from baseline on the global score.

Safety

The three most commonly reported adverse events (AEs) were abdominal pain, diarrhea, and nausea. In the methylnaltrexone 12 mg QD treatment group (N=150), the rates were 19.3% for abdominal pain, 6.0% for diarrhea, and 8.7% for nausea and were similar to those reported in the methylnaltrexone 12 mg QOD group (N=148): 15.5%, 11.5%, and 11.5%, respectively. These rates were higher than those reported in the placebo group (N=162): 3.7%, 3.7%, and 6.2%, respectively.

The most common AEs leading to withdrawal were abdominal pain and nausea. Eight patients withdrew due to abdominal pain (n = 3 in the 12 mg QD group; n = 5 in the 12 mg QOD group), 3 due to abdominal distension (n = 1 in the 12 mg QD group; n = 2 in the 12 mg QOD group), and 6 due to nausea (n = 2 in the 12 mg QD group; n = 4 in the 12 mg QOD group). Protocol violations accounted for 4.6% of the early withdrawals (n = 8 in the 12 mg QD group; n = 7 in the 12 mg QOD group, and n = 6 in placebo).

Discussion

Although recognized as the cornerstone of treatment for cancer-related pain, opioid therapy also represents an important therapeutic option for relief of moderate to severe non-malignant pain [19]. Successful pain management with opioids requires that adequate analgesia be achieved without excessive side effects like constipation. Current laxative therapy for OIC, even optimally titrated, may be burdensome or ineffective for some patients. A recent survey of patients taking oral opioids and laxatives found that opioid-induced bowel dysfunction (OBD) can compromise pain control: one-third of patients had missed, decreased, or stopped using opioids to ease having a bowel movement [20]. Furthermore, 92% of patients who had decreased or stopped using opioids due to OBD reported increased pain after doing so, resulting in negative effects on quality of life and activities of daily living. Opioid antagonists such as naloxone can cross the blood–brain barrier, resulting in pain and opioid withdrawal [7,21]. In contrast, methylnaltrexone belongs to a new drug class with selective antagonism of peripheral mu-opioid receptors and might help relieve OIC but maintain analgesia [7,22]. Thus, methylnaltrexone SC may address an unmet need in the management of chronic pain by treating OIC without diminishing analgesia.

Optimal pain management requires inclusion of the patient's perspective during treatment. Achieving optimal analgesia, while minimizing constipation, requires the accurate and standardized assessment of constipation symptoms with symptom evaluation and management over time [18]. One instrument used in this study to obtain patient's perspective was the PAC-SYM questionnaire, which has been demonstrated and documented to be a sensitive, reliable, valid, and responsive measure for assessing the symptoms of OIC [18]. Assessment with the PAC-SYM included symptoms of rectal bleeding, discomfort or bloating in the stomach, stool appearance, and whether the bowel movement felt "complete." The symptoms are among those that patients associate with OIC [5,23–25].

In this study, patients in both the methylnaltrexone QD and QOD groups showed significant improvements in several PAC-SYM domains compared with placebo as early as the first assessment on treatment on Day 14, and these were maintained until Day 28. The changes from baseline in the global PAC-SYM score between the two dosing arms and placebo

were statistically significant at Day 28. Improvements in subscale scores for stool symptoms indicate favorable outcomes on one or more of the symptoms including straining, hard stools and a feeling of incomplete evacuation. Activation of the mu-opioid receptor within the bowel wall interferes with normal tone and contractility, delaying transit time of the fecal contents [26]. Increased contractions of circular muscles cause non-propulsive kneading and churning, increasing fluid absorption, which dries and hardens the stool. At the same time, longitudinal propulsive peristalsis is decreased, providing additional time for drying of the stool, ultimately resulting in reduced frequency of bowel movements, formation of hard stools, straining, incomplete evacuation of bowel, and sensation of anorectal bowel obstruction [5,27,28]. As a peripheral mu-opioid receptor antagonist, methylnaltrexone has the potential to block opioid actions mediated by peripheral opioid receptors and thus relieve the associated stool symptoms. The results of our study confirm that in addition to improving frequency of bowel movements, methylnaltrexone has a significant effect on the stool symptoms associated with opioid-induced constipation.

Significant improvements in rectal symptoms (including changes in painful defecation, rectal burning, and bleeding) were observed as early as Day 14 in patients treated daily with methylnaltrexone and persisted until Day 28. Activation of mu-opioid receptors increases anal sphincter tone; hence, reflexive relaxation in response to rectal distension is reduced and defecation becomes more difficult and painful [5,26,27]. Thus methylnaltrexone may be able to improve anorectal dysfunction associated with opioids and alleviate rectal symptoms as seen in the results of our study.

We observed no statistical differences in the change from baseline at Day 14 or Day 28 in abdominal symptoms scores between the methylnaltrexone QD and QOD dosing arms and placebo despite the fact that abdominal pain is the most commonly reported AE in this study population. We note that AEs experienced by both treatment groups were primarily gastrointestinal events, consistent with reports for other drugs administered for the treatment of chronic constipation [24,29]. Abdominal pain was also commonly reported as an adverse event in previous methylnaltrexone clinical studies of patients with advanced illness [7,22].

Overall, the response to treatment with methylnaltrexone SC of patients having OIC related to chronic non-malignant pain as assessed by the PAC-SYM questionnaire was consistent with the primary end point results of this study [14]. In contrast to the improvement demonstrated by the primary end points, which were based on daily assessments at 4 hours or at 24-hours post dose, the PAC-SYM responses reported here provide evidence of improvement over 28 days, which may better reflect long-term change in constipation symptoms for patients on chronic therapy of opioids. The short duration of treatment is a limitation of the study.

We observed no statistical differences in the change from baseline on Day 14 or Day 28 in pain intensity scores between the methylnaltrexone QD and QOD dosing arms and placebo thus suggesting that methylnaltrexone decreases the constipating effects of opioids without affecting centrally mediated analgesia. By adding an alkyl-substituent on the nitrogen atom of a tertiary opioid antagonist, quaternary opioid antagonists were designed with relatively greater polarity and less lipid solubility than the parent compound. Due to its quaternary ammonium structure, N-methylnaltrexone has very little permeability of the blood-brain barrier. This structure should have little effect on central opioid receptor binding [30].

Previous studies of methylnaltrexone therapy of patients with advanced illness and OIC showed a favorable impact on patient-reported constipation distress and Global Clinical Improvement of Change (GCIC) in bowel status scores [22,31]. Our study measured constipation symptoms from a broader perspective using the PAC-SYM, a validated multi-item instrument to assess constipation symptoms with a change of approximately half a point corresponding to minimal clinical improvement and changes of about 1 point corresponding to moderate clinical improvement [17]. Our study results showed that at the end of the double-blind period, approximately 53% of patients in each of the methylnaltrexone arms met the minimal improvement criteria compared to approximately 41% in the placebo group. About one-third of the patients (29%) in the methylnaltrexone QD arm met the criteria for moderate clinical improvement compared to 18% and 17% in the methylnaltrexone QOD arm and placebo groups, respectively.

It is important to acknowledge the potential limitations of the study. First, the trial's limited duration (4-week, double-blind period) does not reflect the nature of the management of OIC in chronic, non-malignant pain. The median duration of OIC in our patient population was more than 58 months, which speaks to the need for studies providing evidence of maintenance of the efficacy observed at 4 weeks over a longer time period. Second, patients enrolled were not expected to require further titration of their opioid dosage; however, in clinical practice, exacerbations of pain may necessitate upward opioid titration. In addition, the population studied was limited to North America and additional studies may be required in other regions.

Conclusion

Despite these limitations, the results of our study indicate clinically meaningful improvement in constipation symptoms over 1 month of treatment without a significant effect on pain intensity scores. This improvement, based on patient assessment, is of relevance in the management of OIC in clinical practice and complements the efficacy based on bowel movement response rates [14]. In conclusion, a significant improvement in patient-reported constipation symptoms was demonstrated with methylnaltrexone SC therapy with QD or QOD dosing in patients with chronic non-malignant pain and OIC without affecting centrally mediated analgesia.

Acknowledgment

The authors would like to thank J. Maitland Young, PhD, for assistance with the preparation of the manuscript.

REFERENCES

[1] Staats PS, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: a comparative study. South Med J 2004;97:129–34.

[2] Pappagallo M. Incidence, prevalence and management of opioid bowel dysfunction. Am J Surg 2001;182(Suppl.):11S–18S.

[3] Schug SA, Garrett WR, Gillespie G. Opioid and non-opioid analgesics. Best Pract Res Clin Anaesthesiol 2003;17:91–110.

[4] Thorpe DW. Management of opioid induced constipation. Curr Pain Headache Rep 2001;5:237–40.

[5] Gutstein HB, Akil H. Opioid analgesics. in: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill Medical Publishing Division; 2001.

[6] De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. Pharmacol Ther 1996;69:103–15.

[7] Thomas J, Karver S, Cooney, GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332–43.

[8] RELISTOR (methylnaltrexone bromide) [prescribing information]. Progenics® Pharmaceuticals, Inc, Tarrytown, NY, USA. Available from: www.relistor.com and www.wyeth.com/hcp/relistor/prescribing-information. [Accessed January 22, 2010.]

[9] Foss JF. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. Am J Surg 2001;281(5A Suppl.): 19S–26S.

[10] Brown DR, Goldberg LI. The use of quaternary narcotic antagonists in opiate research. Neuropharmacology 1985;24: 181–91.

[11] Ho WZ, Guo CJ, Yuan CS, et al. Methylnaltrexone antagonizes opioid-mediated enhancement of HIV infection of human blood mononuclear phagocytes. J Pharmacol Exp Ther 2003:307(3);1158–62.

[12] Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 2003; 63:649–71.

[13] Shaiova L, Rim G, Friedman D, Jahdi M. A review of methylnaltrexone, a peripheral opioid receptor antagonist, and its role in opioid-induced constipation. Palliat Support Care 2007;5:161–6.

[14] Blonsky R, Michna E, Schulman S, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic non-malignant pain. J Pain 2009;10(Suppl.):S52.

[15] Lewis SJ, Heaton KW. Stool form as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4.

[16] Farrar JT, Young Jr. JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

[17] Frank L, Kleinman L, Farup C, et al. Psychometric validation of a constipation symptom assessment questionnaire. Scand J Gastroenterol 1999;34:870–7.

[18] Slappendel R, Simpson K, Dubois D, Keininger D. Validation of the PAC-SYM questionnaire for opioid induced constipation in patients with chronic low back pain. Eur J Pain 2006;10:209–17.

[19] Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996;11:203–17.

[20] Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European survey (PROBE 1). Pain Med 2008;10:35–42.

[21] Culpepper-Morgan JA, Inturrisi CE, Portenoy RK, et al. Treatment of opioid-induced constipation with oral naloxone: a pilot study. Clin Pharmacol Ther 1992;52: 90–5.

[22] Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage 2008;35: 458–68.

[23] Lembo A, Camilleri M. Chronic constipation. N Engl J Med 2003;349:1360–8.

[24] Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008;358:2344–54.

[25] McShane RE, McLane AM. Constipation: consensual and empirical validation. Nurs Clin North Am 1985;20:801–8.

[26] De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil 2004;16:383–94.

[27] McMillan SC. Assessing and managing opiate-induced constipation in adults with cancer. Cancer Control 2004;11(Suppl.):3S–9S.

[28] Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use. JAMA 2000;283:367–72.

[29] Di Palma JA, Cleveland MvB, McGowan J, Herrera JL. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. Am J Gastroenterol 2007;102:1964–71.

[30] Becker G, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. J Pain Symptom Manage 2007:34:547–65.

[31] Chamberlain B, Cross K, Winston J, et al. Methylnaltrexone treatment of opioid induced constipation in patients with advanced illness. J Pain Symptom Manage 2009. Available from: http://dx.doi.org/10.1016/j.jpainsymman.2009.02.234.