American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 12, No 5 (May), 2011: pp 554-562
Available online at www.sciencedirect.com

Subcutaneous Methylnaltrexone for Treatment of Opioid-Induced Constipation in Patients With Chronic, Nonmalignant Pain: A Randomized Controlled Study

Edward Michna,* E. Richard Blonsky,[†,§] Seth Schulman,[‡] Evan Tzanis,[‡] Amy Manley,[‡] Haiying Zhang,[‡] Shrividya Iyer,[‡] and Bruce Randazzo[‡]

*Brigham and Women's Hospital, Boston, Massachusetts.
[†]Pain & Rehabilitation Clinic of Chicago, Chicago, Illinois.
[‡]Pfizer Inc, Collegeville, Pennsylvania.
[§]Deceased.

Abstract: **Methylnaltrexone is effective for opioid-induced constipation (OIC) in advanced illness patients. This 4-week, double-blind, randomized, placebo-controlled study investigated the effect of subcutaneous methylnaltrexone on OIC in patients receiving opioids for chronic, nonmalignant pain. Patients (N = 460) received subcutaneous methylnaltrexone 12 mg once daily (QD) or every other day (alternating with placebo) compared with placebo. Assessments included bowel movement count, time of bowel movement, straining, sense of complete evacuation, Bristol Stool Form Scales, and quality of life. Within 4 hours of first dose, 34.2% of patients in both methylnaltrexone groups had rescue-free bowel movements (RFBMs) versus 9.9% on placebo ($P < .001$). The estimated number needed to treat was about 4. On average, 28.9% of methylnaltrexone QD and 30.2% of methylnaltrexone alternate-day dosing resulted in RFBMs within 4 hours versus 9.4% QD and 9.3% alternate-day placebo injections (both $P < .001$). Both methylnaltrexone groups had significantly shorter time to first RFBM ($P < .001$) and greater increase in number of weekly RFBMs ($P < .05$) versus placebo. Adverse events included abdominal pain, diarrhea, nausea, and hyperhidrosis. Bristol Stool Form Scale scores ($P = .002$) and sensation of complete evacuation ($P < .04$) were significantly superior with methylnaltrexone QD; both methylnaltrexone groups reported no or mild straining during RFBMs in the first 2 weeks ($P < .02$). At 4 weeks, a significantly greater improvement in patient-reported, constipation-specific quality of life was seen in the alternate-day dosing ($P < .05$) and QD ($P < .001$) groups.**

Perspective: ***We present data demonstrating that subcutaneous methylnaltrexone 12 mg given once daily (QD) or every other day provides significant relief of OIC and was generally well tolerated in patients with chronic, nonmalignant pain. These results expand on prior effectiveness observed for the treatment of OIC in advanced illness patients to a broader population.***

Key words: *Methylnaltrexone, palliative care, constipation, abdominal pain, opioids, mu-opioid receptor antagonist, opioid-related disorders, chronic disease.*

Received May 11, 2010; Revised September 2, 2010; Accepted November 8, 2010.

This research was funded by Wyeth Research, which was acquired by Pfizer Inc in October 2009. Pfizer Inc provided funding for writing support, provided by On Assignment Clinical Research, a paid consultant to Pfizer in connection with the development of this manuscript, and for editorial support, provided by Peloton Advantage, LLC. Drs. Schulman, Zhang, Randazzo, and Iyer, Mr. Tzanis, and Ms. Manley are employees of Pfizer Inc. At the time of this study, they were employees of and stockholders in Wyeth.

No author received an honorarium or other form of financial support related to the development of this manuscript.

Address reprint requests to Edward Michna, MD, Brigham and Women's Hospital, 75 Francis Street, Department of Anesthesia, Boston, MA 02115. E-mail: emichna@partners.org

1526-5900/$36.00

doi:10.1016/j.jpain.2010.11.008

Opioid analgesics are increasingly used to treat chronic, nonmalignant pain in patients with a wide variety of conditions.[8] While the long-term utility of opioids for pain management in these patients has been questioned, Noble et al[15] recently examined 17 studies of long-term (6- to 48-week) opioid use in patients with chronic, noncancer-related pain and found that pain scores improved in patients remaining on treatment for at least 6 months. However, a substantial number of patients withdrew prior to 6 months because of adverse events. Analysis of these adverse events revealed that 32.5% of patients taking oral opioids and 17.5% of those using transdermal opioids

withdrew from the study, with opioid-induced constipation (OIC) among the most common side effects leading to discontinuation.[15]

Constipation commonly occurs with the use of opioids.[21] Unlike other opioid-induced gastrointestinal (GI) side effects (eg, nausea or vomiting), wherein tolerance may develop and symptoms abate with continued use, constipation typically persists throughout treatment.[13] Information from the 2004 National Health and Wellness Survey performed in the United States, United Kingdom, France, and Germany demonstrated that during long-term opioid use, patients with OIC experience significantly more missed time from work, greater work and nonwork-related activity impairment, and greater health care resource utilization compared with patients without OIC ($P < .05$ for all comparisons).[1] Additionally, patients with OIC were noted to have significantly lower health-related quality of life (HRQOL) scores, indicating greater impairment, as measured by both the physical and mental component of the Short Form-8 Health Survey[24] questionnaire, compared with those without OIC ($P < .05$ for both comparisons).[1]

When opioids are prescribed over the long term, prophylactic measures used in an attempt to prevent OIC may include increasing fluid intake, increasing physical activity, and establishing a daily toileting schedule.[17] Unfortunately, these interventions only provide limited benefit in OIC,[17] especially in patients who require increasing opioid doses. Despite their frequent use, laxative treatments for OIC are unpredictable and are associated with side effects, such as bloating, increased gas production, and abdominal cramping.[16] A survey of patients receiving opioid therapy for noncancer-related pain found that only 46% of those requiring laxatives for constipation achieved the desired results more than 50% of the time compared with 84% of those with chronic noncancer-related pain not treated with opioids.[16] This finding is not unexpected given that laxatives do not address the underlying mechanism of OIC.

Opioid receptors have a wide distribution throughout the GI tract and the central nervous system (CNS).[11] While a centrally mediated effect of opioids has been postulated for the development of OIC, its predominant mechanism is thought to be peripherally mediated.[27] Opioid receptor agonists in the GI tract cause slowed bowel motility by decreasing effective peristaltic contractions and increasing sphincter tone. Additionally, opioids may also delay GI transit by reducing gut secretions and increasing the absorption of fluids from the gut,[10] thus providing a mechanism by which constipation could manifest.

Methylnaltrexone (Relistor; Pfizer Inc, Philadelphia, PA, and Progenics Pharmaceuticals, Tarrytown, NY), a selective, peripherally acting mu-opioid receptor antagonist available as a subcutaneous injection, is approved for the treatment of OIC in patients with advanced illness receiving palliative care whose response to laxative therapy has not been sufficient.[18,25] Owing to its high polarity and low lipid solubility, methylnaltrexone has restricted ability to cross the blood-brain barrier[28]; thus methylnaltrexone decreases the constipating effects of opioids without affecting centrally mediated analgesia.[26]

Studies have shown that methylnaltrexone decreases the adverse effects of opioids on the GI tract, including delayed gastric emptying[14] and delayed oral-cecal transit time.[30,32,33] Methylnaltrexone has demonstrated the ability to induce laxation in methadone maintenance patients with OIC.[29,31] Additionally, methylnaltrexone has demonstrated efficacy and safety in the treatment of OIC in advanced-illness patients, the majority of whom had cancer-related pain for which they were receiving opioids.[19,22] This study is the first to assess the effectiveness and safety of subcutaneous methylnaltrexone for the treatment of OIC in patients with chronic, nonmalignant pain.

Results from this study were presented in poster format at the 28th and 29th Annual Scientific Meetings of the American Pain Society, May 7-9, 2009 in San Diego, CA, and May 6-8, 2010, in Baltimore, MD, respectively, and at the International Society of Pharmacoeconomics and Outcomes Research 12th Annual European Congress, October 24-27, 2010, in Paris, France.[2,5,7]

Methods

Patients

Adults (aged 18 years and older) with OIC and chronic pain caused by a nonmalignant condition were screened to participate in this study. After providing informed consent, patients entered a 14-day screening period. Eligible patients had fewer than 3 rescue-free bowel movements (RFBMs; bowel movement[s] occurring without the use of any laxative in the prior 24 hours) per week that were associated with 1 or more of the following signs and symptoms: hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after a bowel movement. All patients had a history of chronic pain lasting at least 2 months prior to study enrollment and were taking opioid medications for at least 1 month, with an average daily dose greater than 50-mg oral morphine equivalents for at least 2 weeks. Patients were excluded from the study if they had a history of inflammatory bowel disease within the prior 6 months, evidence of bowel obstruction or impaction, history of rectal bleeding not due to hemorrhoids or fissures, history of malignancy within the previous 5 years, or a history of chronic constipation before starting opioid therapy. Patients were also excluded if they had a history of alcohol or drug abuse within the year prior to enrolling, if they were pregnant or breastfeeding, or if they had previously received subcutaneous methylnaltrexone.

The study was approved by independent ethics committees at each participating institution and was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki.

Study Design

This multicenter, double-blind, randomized, placebo-controlled phase 3 study was conducted from August