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Pharmacology in Emergency Medicine

First-Dose Efficacy of Methylnaltrexone in Patients with Severe Medical Illness and Opioid-Induced Constipation: A Pooled Analysis

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□ **Abstract—Background: Opioid-induced constipation (OIC) is a frequent consequence of opioid analgesia that may increase patient risk for emergency department visits and hospitalization. Methylnaltrexone is a peripherally acting μ-opioid receptor antagonist indicated for the treatment of OIC. Objective: To assess the safety and efficacy of a single methylnaltrexone dose. Methods: Results were pooled from three randomized, placebo-controlled methylnaltrexone (MNTX) studies in opioid-treated patients with advanced illness and OIC, despite treatment with conventional laxatives. Baseline assessments included demographics, disease/treatment characteristics, and functional levels. Efficacy endpoints included rescue-free laxation (RFL) rates within 4 and 24 h, time to first RFL, pain score change, and adverse events (AEs) after a single MNTX dose or placebo. Results: The analysis included 281 patients receiving MNTX and 237 receiving placebo. Mean age was 66.2 years for MNTX and 65.8 for placebo; ∼50% were men. The most frequent primary diagnosis was cancer (MNTX = 70.5%; placebo = 66.2%) and most (∼98%) were receiving at least one laxative at baseline. RFL occurred in 61.4% vs. 16.0%, and 72.1% vs. 40.1% MNTX vs. placebo patients, within 4 and 24 h of the initial dose, respectively. Relative to placebo, MNTX use reduced the time to first RFL, with most MNTX-treated patients achieving RFL within 2 h. Baseline and posttreatment pain scores were similar ($p = 0.9556$ vs. placebo for current and worst pain change from baseline), demonstrating that MNTX did not negatively affect opioid analgesia. Most AEs were gastrointestinal related and dissipated by the second dose. Conclusions: Methylnaltrexone provides early RFL without compromising analgesia in patients receiving chronic opioid therapy. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)**

□ **Keywords—methylnaltrexone; opioid-induced constipation; chronic pain; narcotic antagonists; pain management**

Introduction

Among patients treated with opioid analgesics for pain, opioid-induced constipation (OIC) is a frequent side effect. It is considered by many to be the most bothersome symptom associated with opioid therapy, and is often responsible for significant declines in health-related quality of life (1–3). One hallmark feature of OIC is its tendency to persist unabated (despite use of conventional laxatives) during extended opioid use, even as other opioid-associated adverse events (AEs) (eg, nausea and vomiting) have long since dissipated (2,4,5).

Although the prevalence of OIC that presents in the emergency department (ED) is unknown, an analysis from the National Emergency Department Sample database showed that the frequency of ED visits for constipation increased by 42%, and the per-patient costs for consti-

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pation in the ED rose by 56% between 2006 and 2011, a time period during which a steep increase in opioid prescribing also occurred (6,7). Health resource utilization studies have shown that patients receiving opioids who experience constipation have significantly increased risk of ED visits, as well as increased hospitalization rates, overall length of hospital stay, treatment costs, pharmacy costs, and total medical costs (8–11). Of particular concern in the ED setting is the presentation of fecal impaction and stercoral perforation (12–14). Significant increases in morbidity and mortality have been observed in patients presenting to the ED with fecal impaction (12).

Patients presenting to the ED with OIC-related symptoms may have failed traditional first-line treatments (e.g., traditional laxatives and stool softeners), as these often have limited effectiveness to adequately control OIC symptoms in most patients (1,15). This is because laxatives fail to target the underlying mechanism of OIC, the agonism of peripheral μ-opioid receptors throughout the gastrointestinal (GI) tract by exogenous opioids. Opioid effects on the bowel include reduced propulsive contractions, increased nonpropulsive (local) contractions, and increased water absorption during stool formation (2,5,16). In the ED, laxatives are generally not a first-line treatment due to their unpredictable and slow effect. More commonly, refractory constipation or constipation is treated with disimpaction or enemas, but little is known about the outcomes of such procedures for OIC.

Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ) is a selective, peripherally acting μ-opioid receptor antagonist that decreases the constipating effect of opioid therapy without attenuating systemic opioid analgesia (17–20). MNTX tablets and subcutaneous (SC) injections are approved by the U. S. Food and Drug Administration for the treatment of OIC in adults with chronic noncancer pain. MNTX injection is the only peripherally acting μ-opioid receptor antagonist indicated for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care (17).

Patients who present to the ED may have received opioid therapy for treatment of pain arising from diverse etiologies, including cancer and noncancer pain. Therefore, it may be useful to describe the early safety, efficacy, and onset of actions of MNTX across a wide spectrum of patients with varying baseline disease characteristics and varying degrees of pain severity and functional status. Our objective was to assess the early efficacy and safety of MTNX used to treat OIC in a population of laxative refractory, opioid-treated patients likely to present to the ED.

Materials and Methods

Study Design

This was a post hoc analysis of pooled data from three multicenter, double-blind, randomized, placebo-controlled clinical trials conducted in adult patients with OIC and advanced illness (study 301, NCT00401362; study 302, NCT00402038; and study 4000, NCT00672477) (18–21). All studies received institutional review board approval, and written informed consent was obtained from all patients. Whereas all the studies reported longer-term follow-up, only the first 24-h efficacy data are included in this analysis. In study 301, patients were randomized in a 1:1:1 ratio to receive a single SC injection of MNTX 0.15 mg/kg, MNTX 0.30 mg/kg, or placebo. In study 302, patients were randomized to receive SC injections of MNTX 0.15 mg/kg or placebo. In study 4000, study medication dose was determined on the basis of body weight; patients weighing $\geq$ 38 to $<$ 62 kg were randomized to receive SC MNTX 8 mg or placebo and patients weighing $\geq$ 62 kg were randomized to receive SC MNTX 12 mg or placebo.

Study Population

Patients eligible for study inclusion were men and women aged $\geq$ 18 years with OIC and a diagnosis of advanced illness (e.g., advanced diseases such as incurable cancer, acquired immunodeficiency syndrome, congestive heart failure) with a life expectancy of $\geq$ 1 month (studies 302 and 4000) or 1 to 6 months (study 301). OIC was defined as fewer than three bowel movements during the previous week and no clinically significant laxation during either the 24 h preceding the first dose of study drug (studies 302 and 4000) or the 48 h preceding the first dose of study drug (study 301). Patients must have been receiving opioid therapy chronically for discomfort or pain management for $\geq$ 3 days (study 301) or $\geq$ 2 weeks (studies 302 and 4000), excluding as-needed or rescue doses, and taking a stable regimen (defined as no dose reduction $\geq$ 50%) for $\geq$ 3 days prior to initiation of study medication. Patients taking laxatives (consisting of stool softener and senna or equivalent) must have been on a stable regimen for $\geq$ 3 days prior to study drug initiation. Patients were excluded if they had a history of MNTX treatment (except in study 4000, where MNTX was allowed after a 7-day washout period), any disease process suggesting the presence of a GI obstruction, evidence of fecal impaction, a history of fecal ostomy, or any potential nonopioid cause of bowel dysfunction that, in the opinion of the investigator, might have been primarily responsible

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Table 1. Mapping of World Health Organization (WHO) Performance Status to Eastern Cooperative Oncology Group (ECOG) Performance Status

Scale Rating	WHO Performance Scale	ECOG Performance Scale (22)
0	Able to carry out all normal activity without restriction	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work, with < 50% of waking hours in bed or chair	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care and confined to bed or chair more than 50% of waking hours	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled, not capable of any self-care, and confined to bed or chair	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

for constipation. Full study inclusion and exclusion criteria have been previously published (18,19,21).

Study Assessments

At baseline, enrolled patients were assessed with respect to demographics (e.g., age, gender, race/ethnicity, body weight) and disease/treatment characteristics (e.g., primary diagnosis, functional status, and opioid dosage [oral morphine equivalents]). Baseline functional status was assessed using scales from the World Health Organization (WHO) performance status (studies 301 and 302) and Eastern Cooperative Oncology Group (ECOG) status (study 4000) (22). For the current analysis, the WHO analysis results were mapped to their equivalent ECOG performance status categories (Table 1) (22).

Efficacy assessments, based on pooled data collected after the initial dose of study medication during the three trials, included the proportions of patients who achieved a rescue-free laxation (RFL; defined as laxation that occurs within the prespecified timeframes of 4 and 24 h after study drug administration, without the use of rescue laxatives), the proportions achieving RFL within 4 h and 24 h stratified by baseline functional level as measured by WHO/ECOG performance status, and time to RFL. Pain scores (including both current pain and worst pain) were assessed at baseline and 4 h after study drug administration, and changes from baseline pain score were assessed using an 11-point numerical rating scale of 0 (no pain) to 10 (worst pain imaginable).

Safety evaluation for this post hoc analysis was based on an evaluation of treatment-emergent adverse events (TEAEs). AEs were calculated for those who received treatment on treatment day 1 and on treatment day 2.

Statistical Analysis

Analyses of MNTX efficacy and pain scores were conducted on the intent-to-treat population, defined as all subjects who received at least one dose of study medication; this was identical to the safety population.

Response rates for patients achieving an RFL within 4 and 24 h were compared by treatment group and by baseline WHO/ECOG performance status scores, using the Cochran-Mantel-Haenszel test; p-values were generated based on chi-square tests. Time to RFL was analyzed and plotted using Kaplan–Meier methods. Change from baseline in pain scores was analyzed using t-test. Summary statistics were used to describe TEAEs by treatment group. For all comparisons, nominal levels of significance were set at $p < 0.05$, with no adjustments for multiplicity. All analyses were conducted using SAS® Version 9.4 (SAS Institute, Cary, NC).

Results

Study Population

A total of 518 patients received at least one dose of study medication (MNTX, n = 281; placebo, n = 237) and are included in the pooled analyses. Patient demograph-

Table 2. Pooled Study Population: Baseline Demographics and Characteristics

Characteristic	MNTXn = 281	Placebon = 237
Mean (SD) age, y	66.21 (13.8)	65.78 (14.4)
Range	26.0–101.0	21.0–100.0
Male, n (%)	143 (50.9)	117 (49.4)
Race/ethnicity, n (%)		
White	253 (90.0)	216 (91.1)
Black or African American	15 (5.3)	11 (4.6)
Hispanic	7 (2.5)	5 (2.1)
Other	3 (1.1)	3 (1.3)
Asian	2 (0.7)	1 (0.4)
American Indian or Alaskan Native	1 (0.4)	1 (0.4)
Mean (SD) weight, kg	69.86 (19.4)	71.39 (23.1)
Range	30.9–158.8	29.0–225.9*
Median (SD) daily dose of opioid morphine	170.0 (7607.8)	130.0 (1158.6)
equivalent, mg/day	0–122,560.0	0–10,160.0
Range		
Primary diagnosis		
Cancer	198 (70.5)	157 (66.2)
Cardiovascular	27 (9.6)	20 (8.4)
Neurologic disease	9 (3.2)	8 (3.4)
Pulmonary disease (other than malignancy)	31 (11.0)	23 (9.7)
Other	16 (5.7)	29 (12.2)
ECOG/WHO performance status, n (%)		
≤ 2	110 (39.3)†	99 (41.8)
> 2	170 (60.7)†	138 (58.2)
Mean (SD) current pain	3.6 (2.70)	3.6 (2.74)
Mean (SD) worst pain	5.4 (2.78)	5.3 (2.85)

* n = 236.
† n = 280.MNTX = methylnaltrexone; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization.

ics and baseline characteristics in the MNTX and placebo treatment groups are presented in Table 2. Cancer was the most common primary diagnosis in both treatment cohorts, affecting about two-thirds of each subset. Nearly all patients in both treatment cohorts were using at least one laxative (range: 1–7 laxatives) at baseline (MNTX: 272/280, 97.1%; placebo: 234/237, 98.7%). Median daily opioid consumption (morphine equivalents) was somewhat higher in the MNTX group than in the placebo population (170.0 vs. 130.0 mg, respectively).

Efficacy

Compared with placebo, the proportion of patients who experienced an RFL within 4 h (61.4%; 95% confidence interval [CI] 55.7–67.1% vs. 16.0%; 95% CI 11.4–20.7%, $p < 0.0001$) and 24 h (72.1%; 95% CI 66.9–77.4% vs. 40.1%; 95% CI 33.8–46.3%, $p < 0.0001$) of study drug administration was greater with MNTX. Results were similar when stratified by baseline WHO/ECOG performance status (Figure 1). Within 4 h of study drug administration, the percentage of patients with RFL response receiving MNTX or placebo with a WHO/ECOG score of ≤ 2 was 65.5% (95% CI 56.6–74.3%) vs. 20.2% (95% CI 12.3–28.1%, $p < 0.0001$), respectively, and among patients with a WHO/ECOG score of > 2 was 58.8% (95% CI 51.4–66.2%) vs. 13.0% (95% CI 7.4–18.7%, $p < 0.0001$), respectively. Within 24 h of study drug administration, the RFL response rates for patients receiving MNTX or placebo with a WHO/ECOG score of ≤ 2 was 75.5% (95% CI 67.4–83.5%) vs. 45.5% (95% CI 35.6–55.3%, $p < 0.0001$), respectively, and among pa-

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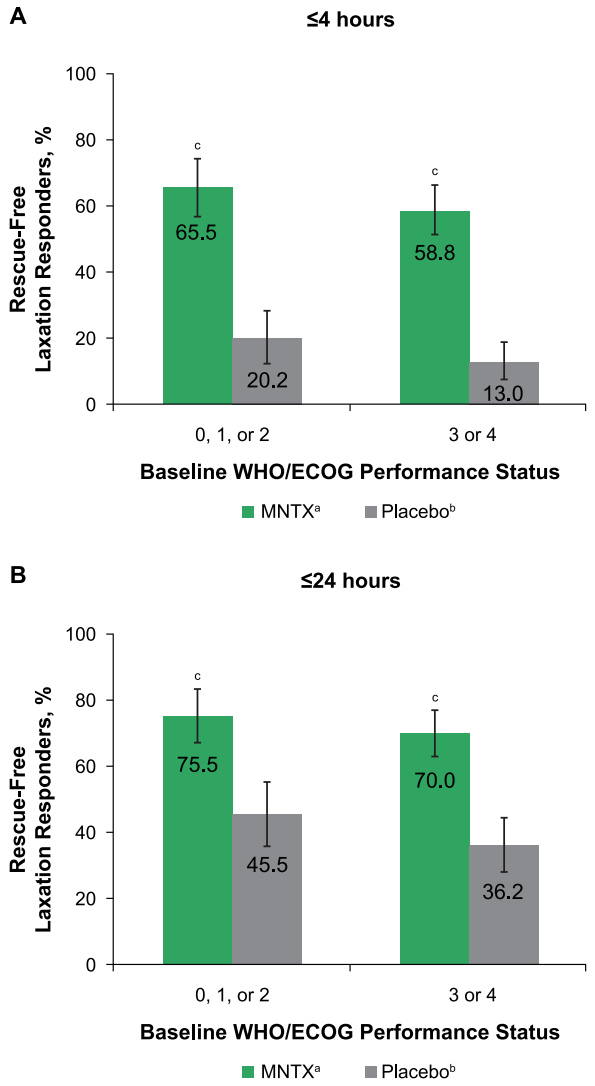

Figure 1. Proportion of responders, stratified by WHO/ECOG performance status, experiencing rescue-free laxation (A) within 4 h and (B) 24 h after treatment with MNTX or placebo (ITT population). Error bars indicate the 95% confidence interval for the proportion.
a. Baseline WHO/ECOG performance status 0, 1, or 2, n = 110; 3 or 4, n = 170.
b. Baseline WHO/ECOG Performance status 0, 1, or 2, n = 99; 3 or 4, n = 138.
c. $p < 0.0001$ vs. placebo.
WHO = World Health Organization; ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; ITT = intent to treat.

tients with a WHO/ECOG score of > 2 was 70.0% (95% CI 63.1–76.9%) vs. 36.2% (95% CI 28.2–44.3%, $p < 0.0001$), respectively.

Kaplan–Meier analysis showed the estimated median time to first RFL was much shorter with MNTX than placebo ($p < 0.0001$; Figure 2). More than 50% of MNTX-treated patients were likely to respond in < 2 h, and < 50% of placebo-treated patients were likely to respond within 24 h.

Safety

There was no evidence that MNTX treatment compromised opioid analgesia. At 4 h post dose, there were no between-group differences with respect to changes from baseline in mean current (mean [SD] = −0.4 [1.89] MNTX vs. −0.3 [1.82] placebo, $p = 0.9556$) and worst (mean [SD] = −0.6 [2.30] MNTX vs. −0.6 [2.17] placebo, $p = 0.9556$) pain scores, and mean pain scores declined slightly but were essentially unchanged given the variability in all patient groups.

The AEs reported by more than 2% of patients in any treatment group on treatment day 1 and treatment day 2 are listed in Table 3; the incidence of TEAEs numerically decreased from day 1 to day 2. The most common TEAEs were GI in nature, including abdominal pain, flatulence, nausea, and vomiting.

Discussion

In this post hoc analysis of pooled results from three randomized, placebo-controlled trials, a single dose of MNTX effectively produced RFL responses within 4 and 24 h in significantly greater proportions of severely ill patients with OIC compared with placebo. The proportion of responders and the magnitude of effect of MNTX was greater than placebo regardless of baseline functional status. Mean time to the first RFL was substantially shorter after a single dose of MNTX compared with placebo, with most MNTX-treated patients estimated to achieve RFL within 2 h.

There was no observable effect of MNTX treatment on the efficacy of opioid analgesia. Mean pain assessment scores from pre-dose to 4 h post-dose declined slightly and to a similar degree in both MNTX-treated and placebo-treated patients. These observations support the clinical importance of the inability of MNTX to cross the blood–brain barrier, which limits its ability to affect centrally mediated pain pathways (18,19,21).

Most TEAEs were gastrointestinal in nature, with incidence rates declining from treatment day 1 to day 2, and with MNTX and placebo groups aligning with one another on day 2. These results mirror another post hoc analysis showing that abdominal pain after MNTX treatment was mostly mild or moderate in severity, decreased with subsequent dosing, and was associated with an increased likelihood of an RFL within 4 h of dosing (23). This is important because GI TEAEs reported seem to be transient and may be associated with successful laxation.

This analysis is strengthened by its diverse patient population, which is typical of those most likely to seek

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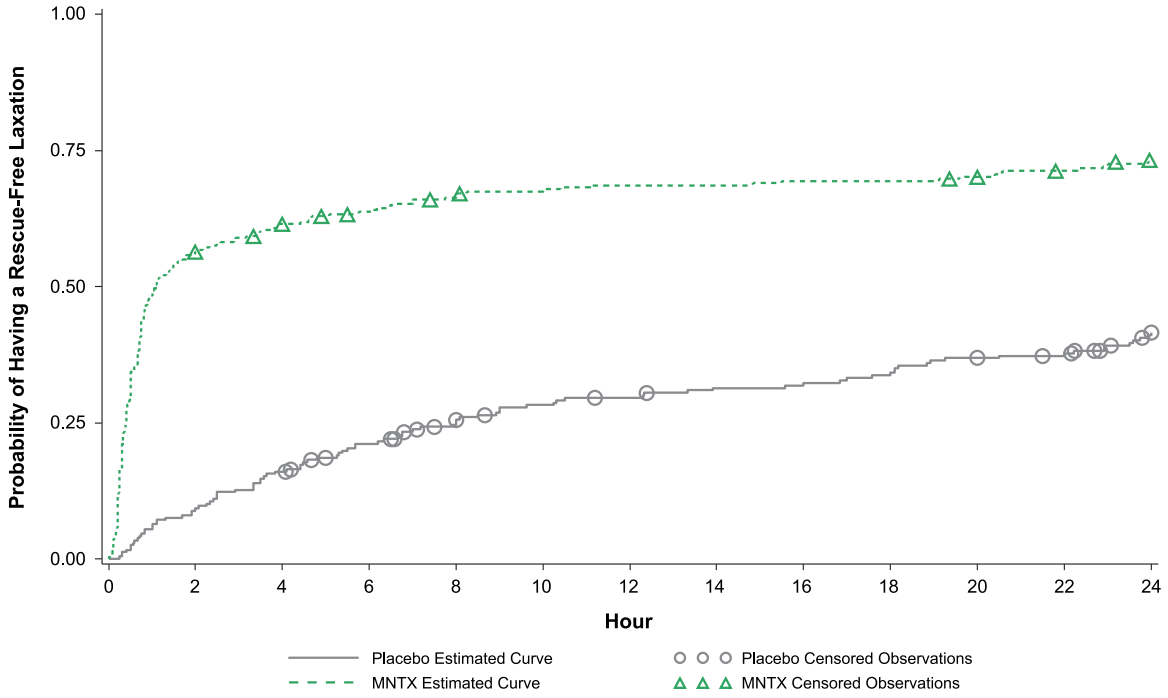

Figure 2. Kaplan–Meier estimates of time to first rescue-free laxation within 24 h after the first study treatment dose (ITT population).
ITT = intent to treat; MNTX = methylnaltrexone.

Table 3. Treatment-Emergent Adverse Events (TEAEs) Reported in > 2% of Patients in Any Treatment Group (Safety Population)

	Treatment Day 1		Treatment Day 2	
System Organ Class Preferred Term, n (%)	MNTX(n = 281)	Placebo(n = 237)	MNTX(n = 160)	Placebo(n = 170)
Abdominal pain*	64 (22.8)	11 (4.6)	13 (8.1)	7 (4.2)
Flatulence	19 (6.8)	5 (2.1)	2 (1.3)	3 (1.8)
Nausea	14 (5.0)	5 (2.1)	3 (1.9)	3 (1.8)
Vomiting†	9 (3.2)	1 (0.4)	2 (1.3)	1 (0.6)
Dizziness	9 (3.2)	1 (0.4)	1 (0.6)	1 (0.6)
Restlessness	8 (2.8)	4 (1.7)	0	0
Sweating increased	8 (2.8)	4 (1.7)	2 (1.3)	0
Pain exacerbated	7 (2.5)	3 (1.3)	0	1 (0.6)
Rhinorrhea	7 (2.5)	1 (0.4)	1 (0.6)	0
Back pain	6 (2.1)	2 (0.8)	0	0

* Includes the following system organ class preferred terms: abdominal pain and abdominal pain not otherwise specified.
† Includes the following system organ class preferred terms: vomiting and vomiting not otherwise specified.MNTX = methylnaltrexone.

care in the ED. For example, we reported on patients with various types of advanced illnesses, including cancer, and stratified patients by varying degrees of baseline WHO/ECOG scores. Regardless of type of illness or functional status, MNTX remained efficacious and improved laxation response. Furthermore, most patients (> 98%) were laxative refractory at baseline, which is precisely the type of patient more apt to seek ED care for OIC. This

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suggests that MNTX may be suitable for a wide range of potential ED OIC patients presenting with various baseline etiologies.

Limitations

There are several limitations to this analysis. As a post hoc analysis, the pooled data were not powered by a shared primary endpoint. In study 301, the primary endpoint was the proportion of patients with laxation within 4 h after administration of the single double-blind dose (18). For study 302, there were two primary endpoints: the proportion of patients with RFL within 4 h after the first dose and the proportion of patients with RFL within 4 h after two or more of the first four doses (19). In study 4000, the primary endpoint was the percentage of patients with RFL within 4 h after two or more of the first four doses (21). In addition, the dosing regimen and some inclusion and exclusion criteria were not identical, which may have lent to some degree of heterogenicity. Of particular consideration is that this collective patient population included very sick patients, who were often receiving complex concomitant drug regimens. Although pharmacokinetic drug interactions with MNTX are not reported because MNTX is not metabolized by cytochrome P450 enzymes, co-administered drugs could confound the efficacy or safety profile or contribute to other causes of constipation besides opioid therapy (17). Finally, this study did not examine ED patients. As such, application to an ED cohort must consider the greater potential for underlying acute illness and the possibility for greater rates of adverse outcomes.

Conclusions

These results demonstrate that MNTX provides effective, safe, and rapid relief of OIC symptoms without compromising opioid analgesia in OIC patients with diverse forms of severe illnesses having varying degrees of disability. The rapid onset of MNTX effect might help reduce the need for hospitalization among patients with OIC seeking ED treatment.

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References

1. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European patient survey (PROBE 1). Pain Med 2009;10:35–42.
2. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014;26:1386–95.
3. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007;61:1181–7.
4. Coyne KS, Margolis MK, Yeomans K, et al. Opioid-induced constipation among patients with chronic noncancer pain in the United States, Canada, Germany, and the United Kingdom: laxative use, response, and symptom burden over time. Pain Med 2015;16:1551–65.
5. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterol Res Pract 2014;2014.
6. Sommers T, Corban C, Sengupta N, et al. Emergency department burden of constipation in the United States from 2006 to 2011. Am J Gastroenterol 2015;110:572–9.
7. National Institute on Drug Abuse, National Institutes of Health. America's addiction to opioids: heroin and prescription drug abuse. 2014. Available at: https://archives.drugabuse.gov/testimonies/2014/americas-addiction-to-opioids-heroin-prescription-drug-abuse#_ftnref4. Accessed June 18, 2020.
8. Fine PG, Chen YW, Wittbrodt E, Datto C. Impact of opioid-induced constipation on healthcare resource utilization and costs for can-

cer pain patients receiving continuous opioid therapy. Support Care Cancer 2019;27:687–96.
9. Suh DC, Kim MS, Chow W, Jang EJ. Use of medications and resources for treatment of nausea, vomiting, or constipation in hospitalized patients treated with analgesics. Clin J Pain 2011;27:508–17.
10. Fernandes AW, Kern DM, Datto C, Chen YW, McLeskey C, Tunceli O. Increased burden of healthcare utilization and cost associated with opioid-related constipation among patients with noncancer pain. Am Health Drug Benefits 2016;9:160–70.
11. Wan Y, Corman S, Gao X, Liu S, Patel H, Mody R. Economic burden of opioid-induced constipation among long-term opioid users with noncancer pain. Am Health Drug Benefits 2015;8:93–102.
12. Sommers T, Petersen T, Singh P, et al. Significant morbidity and mortality associated with fecal impaction in patients who present to the emergency department. Dig Dis Sci 2019;64:1320–7.
13. Davies A, Webber K. Stercoral perforation of the colon: a potentially fatal complication of opioid-induced constipation. J Pain Symptom Manage 2015;50:260–2.
14. Poitras R, Warren D, Oyogoa S. Opioid drugs and stercoral perforation of the colon: case report and review of literature. Int J Surg Case Rep 2018;42:94–7.
15. Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. Aliment Pharmacol Ther 2008;27:1224–32.
16. Nelson AD, Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. Therap Adv Gastroenterol 2015;8:206–20.
17. . Relistor [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2018.
18. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol 2009;7:39–46.
19. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332–43.
20. Yuan CS, Foss JF, O'Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: a double-blind randomized placebo-controlled trial. Clin Pharmacol Ther 1996;59:469–475.
21. Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. J Palliat Med 2015;18:593–600.
22. ECOG-ACRIN Cancer Research Group. ECOG performance status. 2019. Available at: https://ecog-acrin.org/resources/ecog-performance-status. Accessed October 3, 2019.
23. Slatkin NE, Lynn R, Su C, Wang W, Israel RJ. Characterization of abdominal pain during methylnaltrexone treatment of opioid-induced constipation in advanced illness: a post hoc analysis of two clinical trials. J Pain Symptom Manage 2011;42:754–760.

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ARTICLE SUMMARY

1. Why is this topic important?

Constipation is prevalent among patients presenting to the emergency department (ED). In particular, patients receiving opioids who experience constipation have significantly increased risk of ED visits, hospitalization rates, treatment costs, and medical costs.

2. What does this study attempt to show?

The objective of this post hoc analysis was to assess the efficacy and safety of a single methylnaltrexone (MNTX) dose for opioid-induced constipation (OIC) patients with severe medical illness who had insufficient response to laxative therapy and who had varying degrees of baseline functional status.

3. What are the key findings?

In this post hoc analysis of pooled results from three randomized, placebo-controlled trials, a single dose of MNTX effectively produced responses within 4 and 24 h regardless of baseline functional status in significantly greater proportions of severely ill patients with OIC compared with placebo.

The time to first rescue-free laxation was substantially shorter after a single dose of MNTX than placebo with most MNTX-treated patients estimated to achieve a rescue-free laxation within 2 h.

MNTX treatment did not affect the efficacy of opioid analgesia; most treatment-emergent adverse events were gastrointestinal in nature.

4. How is patient care impacted?

MNTX provides effective, safe, and rapid relief of OIC symptoms without compromising opioid analgesia in patients with various forms of advanced illness and OIC.

The rapid onset of MNTX effect might help reduce the need for hospitalization among patients with OIC seeking treatment in the ED.

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