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Fixed-Dose Subcutaneous Methylnaltrexone in Patients With Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension

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INTRODUCTION

- Constipation is a common and often distressing adverse effect of chronic opioid therapy[1]
- Opioid-induced constipation (OIC) negatively affects patient health-related quality of life and is associated with increased healthcare costs[2,3]
- OIC may be managed nonspecifically with stool softeners, osmotic agents, and stimulant laxatives[4]; however, these treatments are often insufficient and do not target the underlying OIC pathophysiology[4-6]
- Methylnaltrexone (MNTX), a peripherally restricted μ-opioid receptor antagonist, has restricted ability to cross the blood-brain barrier and antagonizes the undesirable opioid effects on the gastrointestinal tract, such as delayed gastric emptying[7] and prolonged oral-cecal transit time[8]
  - Phase 3, double-blind, placebo-controlled studies have demonstrated that subcutaneous MNTX, using weight-based dosing, is efficacious and well tolerated for the treatment of OIC in patients with advanced illness receiving palliative care[9,10]
  - Compared with weight-based dosing, fixed-dose administration of subcutaneous MNTX can simplify and improve ease of administration for patients and caregivers

OBJECTIVE

- To determine the efficacy and safety of fixed-dose subcutaneous MNTX in patients with advanced illness and OIC

METHODS

- Adults with advanced illness and OIC (<3 bowel movements in the past week and no bowel movement in 24 hours, or no bowel movement in 48 hours) and who were receiving stable doses of laxatives and opioid analgesics were enrolled in a double-blind, multicenter, randomized, placebo-controlled trial (RCT; clinicaltrials.gov identifier: NCT00672477)
  - Patients were randomly assigned (1:1) to receive subcutaneous MNTX (8 mg or 12 mg based on body weight 38 to <62 kg or ≥62 kg, respectively) or placebo administered every other day (QOD) for 2 weeks
  - The primary endpoint of the RCT was the percentage of patients with rescue-free bowel movement (RFBM) within 4 hours after ≥2 of the first 4 doses in the first week
- Patients completing the RCT could enroll in a 10-week open-label extension (OLE; clinicaltrials.gov identifier: NCT00672139) study of MNTX administered based on body weight (8 mg or 12 mg for 38 to <62 kg or ≥62, respectively) on an as needed (PRN) basis, but no more than 1 dose per day
- Prohibited medications in the RCT and OLE included tegaserod, lubiprostone, opioid antagonists or partial antagonists, and combination opioid and opioid antagonist products
- The protocol was approved by institutional review boards and independent ethics committees, and all patients provided written informed consent

RESULTS

- In the RCT, of 237 patients randomized, 230 patients received ≥1 dose of the study drug (116 and 114 patients in the MNTX and placebo groups, respectively); of 156 patients entering the OLE study from the RCT, 149 received ≥1 dose of MNTX

RESULTS

- Demographic and baseline characteristics were generally similar between treatment groups in the RCT (Table 1)

Table 1. RCT Demographic and Baseline Characteristics

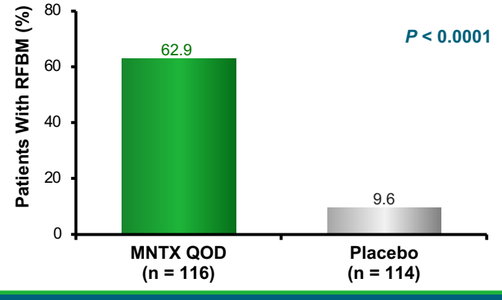
Characteristic		MNTX QOD (n = 116)	Placebo (n = 114)
Age, y, mean (SD)		65.3 (12.9)	65.7 (13.0)
Sex, n (%)	Male	60 (51.7)	58 (50.9)
	Female	56 (48.3)	56 (49.1)
Race, n (%)	White	108 (93.1)	108 (94.7)
	Black	5 (4.3)	3 (2.6)
	Other	3 (2.6)	3 (2.6)
Primary diagnosis, n (%)	Cancer	79 (68.1)	73 (64.0)
	Pulmonary disease	14 (12.1)	13 (11.4)
	Cardiovascular disease	13 (11.2)	11 (9.6)
	Other	10 (8.6)	17 (14.9)
Duration of underlying advanced illness, y, mean (SD)		4.2 (6.0)	5.0 (7.0)
Morphine equivalent, mg/d	Mean (SD)	369.5 (656.8)	404.6 (887.6)
	Median (range)	180.0 (4.5-4427.0)	160.8 (9.0-7228.6)
Weight category, n (%)	<62 kg	45 (38.8)	41 (36.0)
	≥62 kg	71 (61.2)	73 (64.0)
Duration of OIC, wk, mean (SD)		75.1 (152.9)	78.1 (227.4)
Number of BMs during the past 7 days before first dose, mean (SD)		1.7 (0.9)	1.7 (0.9)
Concomitant laxative use, n (%)		107 (92.2)	111 (97.4)

BM = bowel movement; SD = standard deviation.

Efficacy

- Patients treated with fixed-dose MNTX were significantly more likely to have a RFBM within 4 hours after ≥2 of the first 4 doses of study drug in the first week of treatment versus placebo in the RCT ($P < 0.0001$; Figure 1); patient baseline weight (<62 kg vs ≥62 kg) did not affect the primary endpoint response of MNTX treatment versus placebo ($P < 0.0001$; data not shown)

Figure 1. RFBM Within 4 Hours After ≥2 of the First 4 Doses of MNTX or Placebo During the First Week of Treatment (Primary Endpoint) in the RCT



RESULTS

- Significant differences favoring MNTX were also observed for secondary efficacy endpoints during the RCT (Table 2)

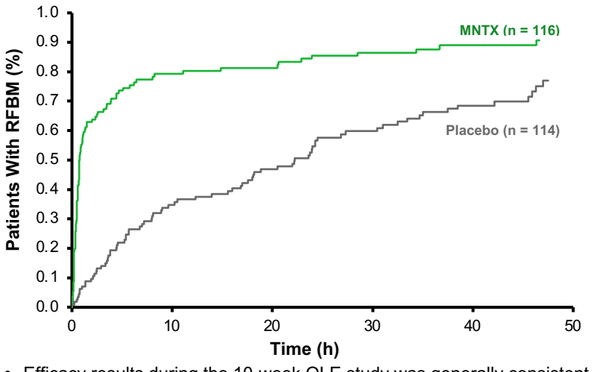
Table 2. RCT Secondary Efficacy Endpoints

Endpoints		MNTX QOD (n = 116)	Placebo (n = 114)	*P* value
Patients with first RFBM ≤4 h after the first dose, n/N (%)		81/116 (69.8)	20/114 (17.5)	<0.0001
Patients with RFBM ≤4 h after at least 4 of the maximum 7 doses, n/N (%)		56/90 (62.2)	4/82 (4.9)	<0.0001
Mean number of BM ≤24 h after dosing (95% CI)	Week 1	4.9 (4.3-5.6)	3.0 (2.3-3.7)	<0.0001
	Week 2	3.2 (2.7-3.7)	2.2 (1.7-2.8)	0.008
Mean number of RFBM ≤24 h after dosing (95% CI)	Week 1	4.9 (4.2-5.6)	2.7 (2.0-3.4)	<0.0001
	Week 2	3.2 (2.6-3.7)	2.0 (1.5-2.5)	0.002
Patients using rescue laxatives in the RCT, n/N (%)		31/116 (26.7)	46/114 (40.4)	0.002

CI = confidence interval.

- The time to RFBM after the first dose in the RCT was rapid in the MNTX group, with a median time of 0.8 hour versus 23.6 hours for the placebo group ($P < 0.0001$; Figure 2)

Figure 2. Time to Bowel Movement After First Dose MNTX or Placebo in the RCT



- Efficacy results during the 10-week OLE study was generally consistent with results from the 2-week RCT (Table 3)

Safety

- In both the RCT and OLE study, the most common adverse events (AEs) in the MNTX group were gastrointestinal-related or related to underlying disease progression (Table 4)

RESULTS

Table 3. OLE Study Exploratory Efficacy Endpoints

Endpoints		Overall MNTX PRN Population (n = 147)[a]
Number of BMs ≤24 h of dosing per patient per week, mean (SD)	Range per week	2.2 (1.6) to 3.1 (3.0)
	Overall (10 weeks)	13.9 (15.9)
Number of days with BMs ≤24 h of dosing per patient per week, mean (SD), d	Range per week	1.6 (1.2) to 2.0 (1.6)
	Overall (10 weeks)	9.6 (9.3)
Percentage of injections resulting in BM ≤4 h, mean (SD)		54.9 (33.4)

[a]2 patients in the MNTX 12-mg group did not have diary data and were not included in the efficacy analyses.

Table 4. Summary of Adverse Events

Adverse Event, n (%)		RCT: MNTX QOD (n = 116)	RCT: Placebo (n = 114)	OLE Study: MNTX PRN (n = 149)
Any AE		95 (81.9)	84 (73.7)	135 (90.6)
	Discontinuations due to AE	12 (10.3)	7 (6.1)	9 (6.0)
	Any drug-related AE	49 (42.2)	21 (18.4)	38 (25.5)
	Any serious AE	14 (12.1)	24 (21.1)	59 (39.6)
	Deaths	11 (9.5)[a]	14 (12.3)[b]	41 (27.5)[c]
Most common AEs[d]	Abdominal pain	39 (33.6)	19 (16.7)	40 (26.8)
	Nausea	13 (11.2)	18 (15.8)	21 (14.1)
	Disease progression	10 (8.6)	17 (14.9)	44 (29.5)
	Back pain	9 (7.8)	3 (2.6)	7 (4.7)
	Diarrhea	9 (7.8)	15 (13.2)	24 (16.1)
	Fall	9 (7.8)	4 (3.5)	21 (14.1)
	Flatulence	8 (6.9)	5 (4.4)	7 (4.7)
	Confusional state	7 (6.0)	9 (7.9)	23 (15.4)
	Peripheral edema	7 (6.0)	4 (3.5)	26 (17.4)
	Vomiting	5 (4.3)	10 (8.8)	10 (6.7)

[a]9 deaths were considered related to underlying disease progression. [b]13 deaths were considered related to underlying disease progression. [c]37 deaths were considered related to underlying disease progression. [d]>5% of patients in any group in the RCT; listed by most common AE during the RCT for MNTX group.

CONCLUSIONS

- **Fixed-dose MNTX demonstrated robust and durable efficacy in the treatment of OIC in patients with advanced illness**
- **Similar to weight-based dosing, fixed-dose MNTX was generally well tolerated for up to 12 weeks**

REFERENCES **1.** Bader S, et al. *Clin Med Insights Oncol.* 2011;5:201-211. **2.** Candrilli SD, et al. *J Pain Palliat Care Pharmacother.* 2009;23(3):231-241. **3.** Penning-van Beest FJ, et al. *J Med Econ.* 2010;13(1):129-135. **4.** Licup N, Baumrucker SJ. *Am J Hosp Palliat Care.* 2011;28(1):59-61. **5.** Panchal SJ, et al. *Int J Clin Pract.* 2007;61(7):1181-1187. **6.** Candy B, et al. *Cochrane Database Syst Rev.* 2011;(1):CD003448. **7.** Murphy DB, et al. *Anesthesiology.* 1997;87(4):765-770. **8.** Yuan CS, et al. *Clin Pharmacol Ther.* 1996;59(4):469-475. **9.** Slatkin N, et al. *J Support Oncol.* 2009;7(1):39-46. **10.** Thomas J, et al. *N Engl J Med.* 2008;358(22):2332-2343.

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