PRELIMINARY COMMUNICATION

Methylnaltrexone for Reversal of Constipation Due to Chronic Methadone Use

A Randomized Controlled Trial

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Context Constipation is the most common chronic adverse effect of opioid pain medications in patients who require long-term opioid administration, such as patients with advanced cancer, but conventional measures for ameliorating constipation often are insufficient.

Objective To evaluate the efficacy of methylnaltrexone, the first peripheral opioid receptor antagonist, in treating chronic methadone-induced constipation.

Design Double-blind, randomized, placebo-controlled trial conducted between May 1997 and December 1998.

Setting Clinical research center of a university hospital.

Participants Twenty-two subjects (9 men and 13 women; mean [SD] age, 43.2 [5.5] years) enrolled in a methadone maintenance program and having methadone-induced constipation.

Main Outcome Measures Laxation response, oral-cecal transit time, and central opioid withdrawal symptoms were compared between the 2 groups.

Results The 11 subjects in the placebo group showed no laxation response, and all 11 subjects in the intervention group had laxation response after intravenous methylnaltrexone administration ($P<.001$). The oral-cecal transit times at baseline for subjects in the methylnaltrexone and placebo groups averaged 132.3 and 126.8 minutes, respectively. The average (SD) change in the methylnaltrexone-treated group was –77.7 (37.2) minutes, significantly greater than the average change in the placebo group (–1.4 [12.0] minutes; $P<.001$). No opioid withdrawal was observed in any subject, and no significant adverse effects were reported by the subjects during the study.

Conclusions Our data demonstrate that intravenous methylnaltrexone can induce laxation and reverse slowing of oral cecal-transit time in subjects taking high opioid dosages. Low-dosage methylnaltrexone may have clinical utility in managing opioid-induced constipation.

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OPIOIDS ARE WIDELY USED ANalgesics in patients with advanced cancer. Constipation is the most common long-term adverse effect of opioid pain medications in patients with metastatic malignancy[1,2] and can be severe enough to limit opioid use or dose.[3-5] This significant negative impact on the quality of life of these patients has received insufficient attention. Thus, there is a need to enhance palliative care in terminal cancer patients.[6]

Methylnaltrexone (*N*-methylnaltrexone bromide; Mallinckrodt Specialty Chemicals, St Louis, Mo) is the first quaternary ammonium opioid receptor antagonist that does not cross the blood-brain barrier in humans.[7,8] It offers the therapeutic potential to reverse adverse effects of opioid pain medications mediated by receptors peripherally located (eg, in the gastrointestinal tract), while sparing opioid effects mediated at receptors in the central nervous system, most importantly, analgesia. In healthy volunteers, intravenous methylnaltrexone, 0.45 mg/kg, effectively blocked acute morphine-induced delay in oral-cecal transit time without affecting analgesia.[9]

Recently, in a pilot study of 4 subjects with long-term methadone-induced constipation, we observed immediate laxation and a dramatic reduction in oral-cecal transit time after a low intravenous dose of methylnaltrexone, suggesting a clinical utility for the compound.[10] The present study is a double-blind, randomized,

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Financial Disclosure: Methylnaltrexone was originally formulated and subsequently modified by faculty at the University of Chicago. The University of Chicago and Drs Yuan, Foss, Moss, and Roizen hold patents and stand to benefit financially from the further development of methylnaltrexone.
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placebo-controlled trial, evaluating the effects of methylnaltrexone in treating long-term opioid-induced constipation. We conducted this trial with subjects in a methadone maintenance program, in which approximately 60% of the long-term methadone users have constipation.[11] These subjects served as a proxy group for patients with advanced cancer to evaluate the efficacy of methylnaltrexone on long-term opioid-induced constipation.

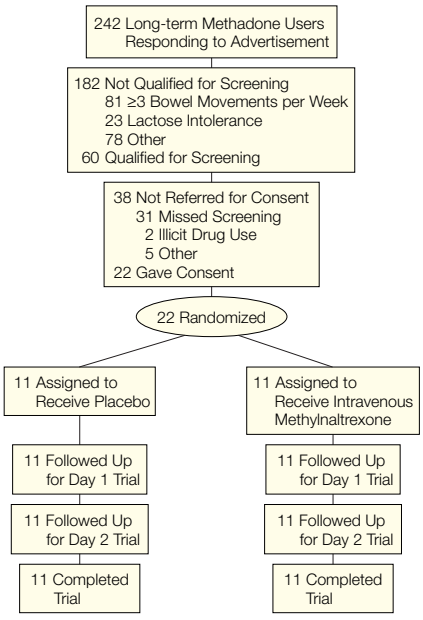
METHODS

Subjects

With approval from the University of Chicago Institutional Review Board, 9 men and 13 nonpregnant, nonbreastfeeding women were enrolled in the study (FIGURE 1). Mean (SD, range) age was 43.2 (5.5, 25-52) years.

Subjects met the following inclusion criteria: (1) enrollment in a methadone maintenance program for 1 month or longer; (2) methadone-induced constipation, ie, no or 1 bowel movement in the previous 3 days, or 2 or fewer bowel movements in the previous week[12,13] and (3) no laxative use 2 days before the study or during the study. Exclusion criteria were (1) history or current evidence of significant cardiovascular, respiratory, endocrine, renal, hepatic, hematological, or psychiatric disease; (2) any laboratory findings indicating hepatic or renal impairment, or abnormal physical examination findings; (3) current use of other medications, including street drugs; (4) known hypersensitivity to lactose or lactulose; and (5) participation in any investigational new drug study in the previous 30 days.

Figure 1. Flow Diagram of Participant Screening, Randomization, and Follow-up



Protocol

An investigator explained the study procedures and obtained written, informed consent from 22 paid subjects. These subjects, who continued to receive their usual dosage of methadone during the study, were admitted to the Clinical Research Center at the University of Chicago Medical Center for 2 days. An intravenous catheter was placed in each arm, one for test drug administration (placebo or methylnaltrexone) and the other for blood drawing.

On day 1, at 9 AM, after a restricted supper with no fiber the night before (required for the oral-cecal transit time measurement) and overnight fasting, subjects were instructed to ingest 10 g of lactulose (Solvay Pharmaceuticals, Marietta, Ga) in 100 mL of tap water. Subjects were also given placebo (normal saline) in 4 syringes (35 mL each) for intravenous injection (single-blinded to the subject).

At 5 PM, subjects were given placebo or methylnaltrexone up to 0.365 mg/kg in 4 syringes. Each syringe contained placebo or methylnaltrexone in 35 mL of normal saline and was administered intravenously over 9 minutes. For the methylnaltrexone group, syringes 1, 2, 3, and 4 contained 0.015, 0.05, 0.1, and 0.2 mg/kg of the study drug, respectively. The interval between administration of each syringe in both groups was 1 minute. The continued administration of each syringe depended on the absence of a clinical laxation response (ie, elimination of any stool) and/or potential adverse effects. Immediate laxation was defined as defecation either during or within 1 minute after cessation of the infusion. The injection was discontinued if the subject had a bowel movement.

After a fiber-free supper and overnight fasting, on day 2 at 9 AM, subjects were again given the test drug intravenously. Subjects were also given 10 g of lactulose at this time. Day 2 studies were performed to test the constancy of effect and measure the oral-cecal transit time; this study did not have a crossover design.

Injection assignment was prepared using a table of random numbers from which sealed envelopes were prepared and opened sequentially as subjects were enrolled in the study. No stratification or blocking factors were used, except to ensure that equal numbers of subjects were assigned to each treatment group after enrollment of the last (22nd) subject. Randomization and test drug preparation was done by a biostatistician and a physician, respectively, who did not participate in data acquisition and evaluation.

Vital signs were obtained 0, 5, 10, 30, 60, 90, and 120 minutes after each test drug administration. Illicit drug use was monitored by random urine drug screenings.

Blood and Urine Sampling and Analysis

Seven 5-mL blood samples were obtained 0, 5, and 30 minutes and 1, 2, 4, and 8 hours after each test drug administration. Three urine samples were collected 0, 2, and 4 hours after drug administration. Plasma and urine methylnaltrexone levels were determined by high-performance liquid chromatography,[9,14] with a detection limit of 2 ng/mL.

Bowel Function Assessment

Subjects were asked to record frequency and consistency of stools during the study period. Subjects' bowel movements were confirmed and recorded by a research nurse blinded to the group assignment. At the end of the study, the subjective opinion of the participants was gathered to rate subjects' satisfaction with respect to bowel movement.

Oral-Cecal Transit Time Measurement

Oral-cecal transit time was assessed by measuring pulmonary hydrogen produced when unabsorbed lactulose is fermented by colonic bacteria and excreted in the breath. The time between ingestion and the earliest detectable and sustained rise in pulmonary hydrogen excretion, ie, a sudden rise to the peak (>25 ppm) or an increase of at least 2 ppm above the baseline, maintained and increased in 3 consecutive samples, indicates that lactulose has reached the cecum.[9,15-17] Hydrogen breath tests were conducted every 15 minutes until oral-cecal transit time was determined.

Evaluation of Central Opioid Withdrawal

To evaluate possible opioid withdrawal with methylnaltrexone, before and 10 minutes after the completion of test drug administration, subjects were asked to complete an adjective checklist of withdrawal symptoms modified from Fraser et al[18] and Jasinski.[19] Items rated (none, mild, moderate, severe) were yawning, lacrimation (excessive tearing), rhinorrhea, perspiration, tremor, piloerection (goosebumps), and restlessness. The ratings for individual items were translated to a 0-to-3 scale and summed to give a total symptom score. The total scores before and after test drug administration were compared between groups. Potential opioid withdrawal symptoms were also monitored by an investigator throughout the study.

Statistical Analysis

Laxation responses were compared between groups with the Fisher exact test. The Mann-Whitney *U* test was used to compare change from baseline in oral-cecal transit time between the 2 groups and evaluate statistical differences between sexes in oral-cecal transit times with $P<.05$ considered statistically significant. Changes in opioid withdrawal symptoms were analyzed similarly.

RESULTS

Mean (SD) stool frequency per week of the 22 subjects before the study was 1.5 (0.7). All 22 subjects showed no response to placebo on the morning of day 1.

Eleven subjects were randomly allocated to each treatment group. Those in the placebo group received all 4 syringes in the day 1 afternoon and day 2 morning sessions. As shown in the TABLE, subjects showed no laxation response after placebo and reported no abdominal cramping. At the end of the trial, 7 of the subjects who received placebo reported that they were disappointed when asked about bowel movement satisfaction. There were no significant frequency changes in bowel movement before and during the study, no opioid withdrawal, and no significant adverse effects in these subjects.

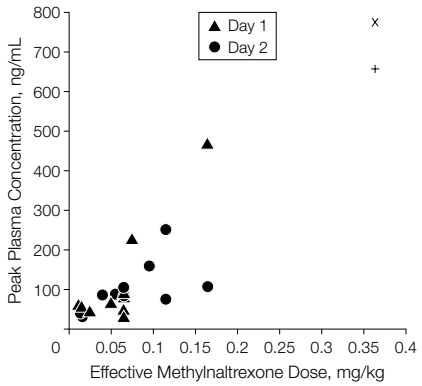
Ten subjects in the methylnaltrexone group had immediate laxation response in the day 1 afternoon session, and all 11 subjects had immediate laxa-

Table. Laxation Response in Subjects With Chronic Opioid Constipation*

Subject No.	Oral Methadone, mg/d	Day 1		Day 2		Bowel Movement Satisfaction
		Test Drug, mg/kg	Laxation Response	Test Drug, mg/kg	Laxation Response	
			Placebo Group			
1	50	Placebo	No	Placebo	No	Disappointed
2	65	Placebo	No	Placebo	No	Disappointed
4	85	Placebo	No	Placebo	No	Disappointed
5	61	Placebo	No	Placebo	No	Disappointed
8	42	Placebo	No	Placebo	No	Disappointed
11	89	Placebo	No	Placebo	No	Not available
14	85	Placebo	No	Placebo	No	Disappointed
16	50	Placebo	No	Placebo	No	Satisfied
18	50	Placebo	No	Placebo	No	Disappointed
19	75	Placebo	No	Placebo	No	Not available
22	50	Placebo	No	Placebo	No	Somewhat satisfied
			Methylnaltrexone Group			
3	55	0.015	Immediate	0.015	Immediate	Very satisfied
6	59	0.065	Immediate	0.065	Immediate	Very satisfied
7	68	0.165	Immediate	0.165	Immediate	Very satisfied
9	65	0.065	Immediate	0.115	Immediate	Satisfied
10	30	0.065	Immediate	0.065	Immediate	Very satisfied
12	45	0.075	Immediate	0.115	Immediate	Very satisfied
13	100	0.365	No	0.365	Immediate	Somewhat satisfied
15	40	0.065	Immediate	0.055	Immediate	Very satisfied
17	50	0.050	Immediate	0.095	Immediate	Somewhat satisfied
20	85	0.025	Immediate	0.040	Immediate	Very satisfied
21	75	0.011	Immediate	0.013	Immediate	Very satisfied

tion in the day 2 morning session (Fisher exact $P<.001$ vs placebo group response for both days 1 and 2). The stool of most subjects (>90%) was soft to loose and in large quantity. The mean (SD, range) methylnaltrexone dose received was 0.09 (0.10, 0.01-0.37) mg/kg and 0.10 (0.10, 0.01-0.37) mg/kg for day 1 and day 2, respectively. FIGURE 2 shows the relationship between effective methylnaltrexone dose and peak plasma concentration.

Figure 2. Relationship Between Effective Methylnaltrexone Dose and Peak Plasma Concentration in Subjects Receiving Long-term Methadone Treatment



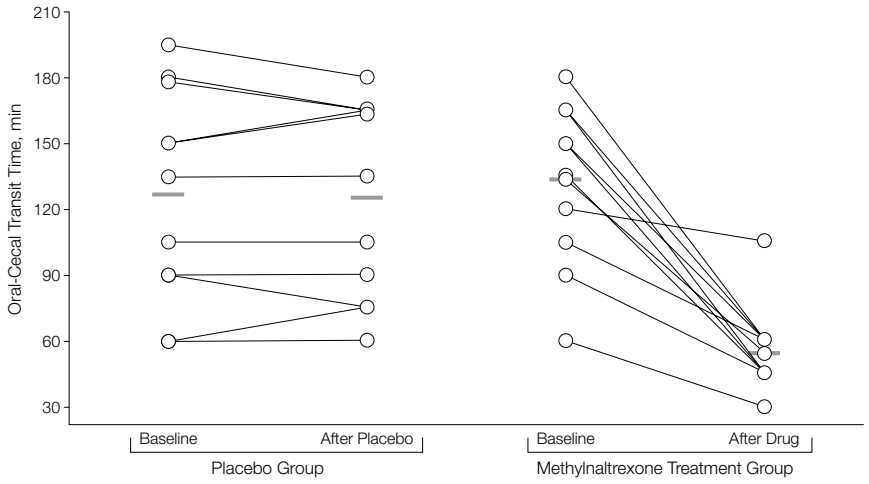
Peak plasma concentration is expressed as a function of methylnaltrexone dose that induced laxation response on first and second day of administration. Subject 13 failed to defecate at the maximum dose (0.365 mg/kg) on day 1 (x) but did respond to the same dose on day 2 (+). The r^2 value for the linear regression of concentration on effective dose is 0.77.

During and immediately after each study drug injection, all subjects reported mild to moderate abdominal cramping, which they described as being similar to a defecation sensation, without discomfort. No opioid withdrawal symptoms were observed in any of these subjects during the study. No significant adverse effects were reported by the subjects. Subject 13 reported mild light-headedness that resolved spontaneously. No subject showed any clinically significant change in blood pressure or heart rate from baseline with either the placebo or study drug infusions. Subjects did not have additional bowel movements after drug-induced immediate laxation, except subject number 15, who reported mild diarrhea. At the end of the study, all 11 subjects who received methylnaltrexone were satisfied with their bowel movement activity (Table 1).

Oral-cecal transit time data are presented in FIGURE 3. The mean (SD, range) transit times for subjects in the placebo group (n = 11) at baseline and after placebo injection were 126.8 (48.3, 60-195) minutes and 125.3 (45.0, 60-180) minutes, respectively. The transit times for subjects in the methylnaltrexone group (n = 11) showed that the study drug reduced the mean (SD, range) transit time from the baseline level of 132.3 (36.0, 60-180) minutes to 54.5 (19.3, 30-105) minutes. The average (SD) change in the methylnaltrexone group (–77.7 [37.2] minutes) was significantly greater than the average change in the placebo group (–1.4 [12.0] minutes) ($P<.001$). There were no statistical differences in oral-cecal transit times between sexes.

Mean (SD, range) peak plasma levels of the 11 subjects in the methylnaltrexone group for day 1 and day 2 were 162 (237, 30-774) ng/mL and 166 (177, 33-658) ng/mL, respectively. The percentage (SD, range) of the intravenous dose excreted unchanged in urine from 0 to 4 hours for day 1 and day 2 was 23.7% (10.5%, 9.6%-39.9%) and 37.6% (17.8%, 13.2%-73.6%), respectively.

Figure 3. Changes in Individual Oral-Cecal Transit Time of Subjects Receiving Long-term Methadone Treatment



Left, The transit time (ordinate) of 11 subjects in the placebo group from baseline to after placebo injection (abscissa). Right, The transit time (ordinate) of the 11 subjects in the methylnaltrexone group from baseline to after study drug administration (abscissa). Gray bars represent mean values. The average change in the methylnaltrexone group was significantly greater than the average change in the placebo group ($P<.001$).

COMMENT

The effect of opioids on gastrointestinal motility and transit is well appreciated as a clinical phenomenon. Opioids inhibit gastric emptying and propulsive motor activity of the intestine, thereby decreasing the rate of intestinal transit and producing constipation. Opioid receptors and endorphins are widely distributed in the central nervous system and throughout the gastrointestinal tract.[20] Based on data obtained from previous animal experiments, the site of opioid action (central vs peripheral) of exogenous opioid-induced gut motility change or constipation is still controversial.[21-25] Since the translation of animal experiment data in the literature to humans may be problematic because of differences in the physiology of the opioid systems, the action site for opioid-induced constipation in humans remains a matter of investigation. Methylnaltrexone, a peripheral opioid receptor antagonist, very effectively reversed chronic opi-

oid constipation in this clinical trial. Our data provide the first strong evidence that the methadone constipating effect in humans is predominantly mediated by receptors located in the peripheral gastrointestinal tract.

All 11 subjects who received intravenous methylnaltrexone had a laxation response immediately after administration of methylnaltrexone on day 1 or day 2, and all reported some degree (mild to moderate) of abdominal cramping prior to their bowel movement. We interpret their abdominal cramping as a physiological desire to defecate, because the cramping disappeared after bowel movement. Because the half-life of methylnaltrexone is approximately 2 hours,[9,26] one would expect the cramping caused by hyperactivity of the gut to be much more prolonged.

We used the lactulose hydrogen breath test in this study, the method most commonly used for gut transit time measurement.[27] Subjects received placebo the morning of day 1 to establish an oral-cecal transit time baseline. We observed a reduction in gut transit time in all subjects after methylnaltrexone treatment compared with baseline levels. This result is consistent with the methylnaltrexone-induced clinical laxation response in these individuals. Lactulose, a nonabsorbable osmotic agent that acts in the colon by increasing water content of the stool without directly stimulating gut peristaltic activity, may have laxative effects itself and could affect interpretation of our results. However, the dose used in this study (10 g) is one half to one third of a single dose and one sixth to one twelfth the daily dose recommended to produce soft stools. That this small dose of lactulose had no effect in our study is indicated by the absence of a laxation response and no change in oral-cecal transit time in the placebo group.

A relatively wide dose range of intravenous methylnaltrexone was used to achieve clinical laxation. However, the laxation doses for day 1 and day 2 for individuals were very similar, and no tachyphylaxis was noticed. The peak plasma concentrations of the compound and the percentage of the dose excreted unchanged in urine in our subjects were comparable to those reported in healthy volunteers who received similar doses.[9,26]

Tertiary opioid receptor antagonists, such as naloxone, naltrexone, and nalmephene, cross the blood-brain barrier and block both the beneficial pain-relieving effect and the adverse effects of morphine. Although oral naloxone may reverse opioid-induced constipation, the therapeutic index is very narrow; ie, reversal of the gut effects with naloxone occurred at doses near the reversal of analgesia.[28] Naloxone may also induce opioid withdrawal symptoms.[29-31] As a novel quaternary peripheral opioid receptor antagonist, methylnaltrexone, even at high doses, has not shown reversal of analgesic effect of morphine in rats[32] or humans.[9] In this study, no opioid withdrawal symptoms were observed in subjects receiving long-term methadone treatment, which further indicates that methylnaltrexone does not penetrate into the brain in humans.

Data from our previous studies in animals[33] and healthy human volunteers[34] suggest that oral methylnaltrexone is efficacious in preventing morphine-induced gut motility changes. The effects of the oral compound in long-term opioid users need to be investigated in future clinical trials. In this study, none of the 11 subjects in our methylnaltrexone group experienced significant adverse effects. However, the upper 95% confidence limit for the adverse event rate based on the rule of 3 is 25%.[35] Thus, the absence of significant adverse effects in this small group does not preclude the discovery of adverse effects in larger populations, especially those with terminal illnesses and additional comorbidities.

In the United States, approximately 500 000 patients die of cancer annually. Opioid pain medication is used in the terminal phase of care for more than 50% of these patients, and constipation, a significant clinical problem, affects 40% to 50% (approximately 125 000) of patients with metastatic malignancy who receive opioid pain medications.[36,37] A significant number of hospice patients receiving long-term opioid treatment for pain would rather endure their pain than face the severe, incapacitating constipation that opioids cause. Results from this clinical trial demonstrate that individuals receiving long-term methadone treatment are very sensitive to intravenous methylnaltrexone compared with healthy, opioid-naive subjects in our previous trial, who received 0.45 mg/kg of methylnaltrexone without any laxation response.[9] Our data suggest that cancer patients receiving long-term opioid treatment also may have increased sensitivity to methylnaltrexone and that low-dose methylnaltrexone administration may have clinical utility in managing opioid-induced constipation, thus potentially improving the quality of life in these patients.

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Do not become archivists of facts. Try to penetrate to the secret of their occurrence, persistently search for the laws which govern them.
—Ivan Pavlov (1849-1936)