

Methylnaltrexone Rapidly Resolves Constipation

In a study of 288 frail hospice patients with opioid-induced constipation, 60% responded within 4 hours.

BY BRUCE JANCIN
Denver Bureau

DALLAS — Backed by two positive phase III randomized trials, methylnaltrexone is now under Food and Drug Administration review for treatment of opioid-induced constipation in patients with advanced illness.

The investigational drug, a quaternary derivative of naltrexone, offers significant advantages over conventional laxatives for this tough-to-treat condition, Dr. Jay Thomas said at the annual meeting of the Society of Hospital Medicine.



presented at the hospitalist meeting indicated that methylnaltrexone—this time given intravenously—accelerated GI recovery and hospital discharge eligibility without affecting opioid analgesia in patients who underwent bowel resection, reported Dr. James Rathmell of Harvard Medical School, Boston.

Dr. Thomas, principal investigator in the two phase III trials that included a total of 288 frail hospice patients with opioid-induced constipation, said about 60% of methylnaltrexone-treated patients responded to the drug with a bowel movement within 4 hours, compared with 13%-15% who received a placebo injection. All participants had continued on their baseline laxative regimen.

DR. THOMAS

In an interview, he said he sees two major advantages for methylnaltrexone: reduced pill burden, and the speed and smoothness of the drug's effect.

“Sometimes with these patients you have to titrate up the traditional laxatives such that the number of pills they're taking becomes a burden. And there can be an unpredictable response to them. For example, with an oral osmotic like magnesium citrate, sometimes the bowel movement can happen unpredictably—and in some cases explosively and uncontrollably,” he explained.

The response to subcutaneous methylnaltrexone is rapid, with most responders in the two double-blind, randomized, placebo-controlled phase III trials having a bowel movement within 1 hour of injection—and many within 30 minutes, Dr. Thomas said.

Moreover, as was shown in one of the phase III trials that included 134 patients, efficacy persists without tachyphylaxis when methylnaltrexone is administered every other day over a 2-week period, added Dr. Thomas, medical director of San Diego Hospice.

There is also interest in pursuing a second indication for methylnaltrexone in the future. The results of a phase II study

“The people in these studies who responded to methylnaltrexone did so within 30 minutes,” Dr. Thomas observed. “Let's say you want to go to the park with your grandkids. You can potentially do a subQ injection with methylnaltrexone and have a response within 30 minutes. If you need help from a caregiver, the caregiver can schedule [his or her] day. So it gives you some control back, especially for very sick advanced-illness patients, like hospice patients.”

“Whereas if you do an oral medication,” he continued, “it may be hours before you have a response, and you don't know when that response is going to happen. If you're in the park with your grandkids, you may have a hard time dealing with it. Sometimes patients lose control and soil themselves.”

Methylnaltrexone reverses the slowing of GI transit caused by opioids. Importantly, there was no sign of central opioid withdrawal or loss of analgesic effect in the 2-week study.

The most common methylnaltrexone-related side effect was mild to moderate abdominal pain, of a magnitude that could be associated with a normal physiologic bowel movement, in 29% of patients. There was also an increase in flatulence and nausea and vomiting. No patients dropped out because of these adverse events, Dr. Thomas said.

In a separate presentation, Dr. Rathmell reported on 65 patients who received opioids after undergoing segmental colectomy by laparotomy who were randomized in a double-blind manner to methylnaltrexone or placebo starting within 90 minutes after completion of the operation.

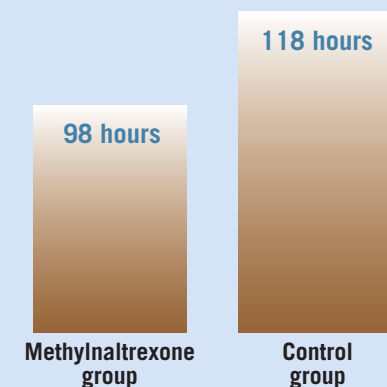
Mean time to first bowel movement was 98 hours in the methylnaltrexone group, 20 hours faster than in controls. The methylnaltrexone group was eligible for hospital discharge in a mean of 116 hours, which was 33 hours sooner than controls.

Two patients in the methylnaltrexone group developed postoperative ileus, compared with five controls. These are clinically meaningful improvements, Dr. Rathmell noted.

Analgesic requirements and pain scores were similar in the two study arms. Nausea, vomiting, and abdominal pain were more frequent in the placebo arm.

All three clinical investigations were sponsored by Progenics Pharmaceuticals Inc. ■

Mean Time to Bowel Movement After GI Surgery



Note: Based on a study of 65 patients who received opioids after segmental colectomy by laparotomy.
Source: Dr. Rathmell

ELSEVIER GLOBAL MEDICAL NEWS

Behavioral Therapy of No Benefit in Constipated Children

BY PATRICE WENDLING
Chicago Bureau

MILWAUKEE — Intensive behavioral therapy with laxatives is no better than conventional therapy in the treatment of childhood constipation, data from a randomized controlled trial show.

Little is known about the effectiveness of behavioral therapy in the treatment of constipation, although it is thought that learned behavior plays a role in the development of constipation, Dr. Marc Benninga reported at an international symposium sponsored by the International Foundation for Functional Gastrointestinal Disorders.

Children may consciously or unconsciously contract their pelvic and gluteal muscles when they feel the urge to defecate. Physiologically, the rectum becomes increasingly distended, which disrupts rectal compliance and the urge to defecate.

Behaviorally, the child experiences repeated difficulty with defecation and pain due to large or hard stools, reinforcing the stool-withholding behavior. The combination creates a vicious cycle of learned behavior that, in theory, could be unlearned through intensive behavioral therapy, Dr. Benninga explained.

Dr. Benninga and associates tested the theory in 129 youths aged 4-18 years who visited a gastrointestinal outpatient clinic for functional constipation. For the study, functional constipation was defined as the presence of at least two of the following criteria: defecation less than

three times per week, fecal incontinence two or more times per week, and the presence of large amounts of stool or a palpable fecal mass.

Participants were randomized to 12 months of either conventional therapy—consisting of education, oral laxatives, toilet training, and dietary advice, or a five-element, age-based behavioral intervention program that was developed over a decade (Patient Educ. Couns. 2007 March 17 [Epub doi:10.1016/j.pec.2007.02.002]). Twelve sessions were held over the 12 months.

Children aged 4-8 received the following: education along with their parents that was designed to reinforce a nonaccusatory attitude regarding defecation; anxiety reduction through play therapy; laxatives and skill learning, including appropriate defecation straining; reinforcement using stickers; and establishment of a toileting routine.

The protocol for children older than 8 years did not include anxiety reduction, but instead focused on taking responsibility for their own bowel habits and keeping a bowel diary, said Dr. Benninga, of the department of pediatric gastroenterology and nutrition, Emma Children's Hospital/Academic Medical Center, University of Amsterdam.

Most participants were male, with an average age of 6.5 years in the conventional therapy (CT) group, compared with 7 years in the behavioral therapy (BT) group.

Data analysis was based on 58 patients in the BT group (9 treatment dropouts) and 56 in the CT group (2 treatment dropouts and 4 lost to follow-up).

Among the study's three primary outcomes, only defecation frequency per week showed a significant difference in favor of BT, but that difference was not sustained after 6 months of follow-up, said Dr. Benninga, who characterized the results as “not very convincing.”

Defecation frequency increased from 2.2/wk at baseline to 7.5/wk post treatment to 6.3/wk at follow-up in the BT group, compared with 2.2/wk, 5.5/wk, and 5.7/wk in the CT group, Dr. Benninga reported at the meeting, which was cosponsored by the University of Wisconsin.

Fecal incontinence frequency decreased significantly in both groups from 15 times per week to roughly 3 times per week at follow-up.

Treatment success was slightly higher at follow-up in the BT group (63%), compared with the CT group (54%), but again the difference was not significant. Success was defined as defecation frequency more than twice a week and fecal incontinence less than once every 2 weeks.

“The only striking finding of this study,” Dr. Benninga said, was that significantly fewer children treated by a psychologist had abnormal scores on the Child Behavior Checklist at follow-up, compared with those treated conventionally (38% vs. 82%).

Based on the findings of this investigation, Dr. Benninga recommended screening for behavioral problems in constipated children and referring those with problems to a pediatric psychologist or behavioral therapist. ■