Opioid-induced constipation (OIC) remains one of the most difficult to manage adverse effects of chronic pain management in children and adults. The incidence of OIC has been reported to be as high as 57% of adults receiving opioids for chronic pain and 94% of patient receiving palliative care. Activity of opioid analgesics at mu-opioid receptors in the gastrointestinal tract lead to a number of physiologic changes, including decreased gut motility, increased fluid absorption from the gut along with decreased intestinal secretions, increased sphincter tone, and a reduced sensitivity to colonic distension. This combination of changes in GI function can produce constipation that often fails to improve with administration of standard laxatives.1-3

For many years, clinicians caring for patients with OIC have utilized low doses of naloxone, an opioid antagonist, given orally to counteract the effects of opioids on the GI tract.4 While often effective, the lack of an oral dosage form and the short duration of effect makes this therapy less than ideal. In 2008, the Food and Drug Administration approved subcutaneous methylnaltrexone for the treatment of OIC in adults with advanced illness who are receiving palliative care and have not responded to laxative therapy.2 Although not yet approved for use in children, several recent reports suggest a potential role for methylnaltrexone in pediatric OIC associated with opioid use for cancer or postoperative pain.

Mechanism of Action
Methylnaltrexone is a peripherally-acting selective mu-opioid antagonist. Unlike other opioids, it is a quaternary amine with a positive charge in solution and low lipid solubility which limit its ability to cross the blood brain barrier. This allows for reversal of the effects of opioids in the periphery without negatively affecting analgesia or producing opioid withdrawal.1,3

Pharmacokinetics
The pharmacokinetic profile of methylnaltrexone has been studied in adults, but not children. After subcutaneous administration, methylnaltrexone reaches peak concentrations of 117-140 ng/mL in 0.25-0.5 hrs. It is widely distributed to the tissues, with an estimated volume of distribution of 1 L/kg. Area under the concentration-time curve (AUC) ranges from 175 to 223 ng•hr/mL over the recommended dosing range in adults. Approximately 50% of a dose is cleared by the kidneys as unchanged drug. The remainder undergoes metabolism, primarily through N-methylation and conjugation via sulfotransferases SULT1E1 and SULT2A1. The elimination half-life of methylnaltrexone in healthy adults enrolled in clinical trials has ranged from 7.8 to 13.4 hrs. Clearance is significantly prolonged in patients with renal dysfunction. In a study of 32 adults, mean half-life increased 13.4 ± 4.8 hrs in the healthy controls to 17.5 ± 2 hrs in the patients with mild renal impairment, 18.7 ± 3.9 hrs in those with moderate renal impairment, and 19.6 ± 2.8 hrs in those with severe renal impairment. Hepatic impairment has little effect on half-life or total drug exposure.1,3

Clinical Experience
In 2011, Garten and colleagues at the Charité University Medical Center in Berlin reported the first use of methylnaltrexone in a pediatric patient.5 The patient was a newborn with hypoplasia of the aortic arch that subsequently developed neonatal necrotizing enterocolitis. Surgical resection of the bowel was successful, but resulted in a prolonged recovery. A second surgery included a colectomy and a primary ileosigmoid anastomosis. Postoperative management included a fentanyl infusion for analgesia, titrated to 2 mcg/kg/hr. After a week of minimal signs of bowel function, on postoperative day 8 the decision was made to administer methylnaltrexone for presumed opioid-induced ileus. A dose of 0.15 mg/kg was given IV (an approved route of administration in Germany). Within 15 minutes there was evidence of bowel motility. The patient was placed on a regimen of methylnaltrexone once daily while receiving fentanyl. Her bowel function continued to improve, with bowel
movements up to 4 times per day and increasing tolerance of enteral feeds. She received a total of five doses. There were no changes in her pain scores, as assessed by the Neonatal Pain, Agitation, and Sedation Scale (N-PASS), and no signs of opioid withdrawal. No adverse effects were noted.

Three additional case reports published within the last two years describe the use of methylnaltrexone in children. Lee and Mooney describe oral methylnaltrexone use in a 4-year-old boy receiving chronic opioid therapy for pain associated with epidermolysis bullosa (EB). The patient had been receiving oral naloxone for 3 years for OIC. While there was initial improvement with naloxone, the benefit had decreased over time and his opioid requirements began to increase. The authors elected to try methylnaltrexone in an effort to control the OIC without altering the patient’s analgesia. Due to the severity of his EB and the potential traumatic effects of repeated injections, the drug was administered via gastrostomy tube. Therapy was initiated with a 2 mg (0.16 mg/kg) dose given daily. The naloxone was tapered off over two days. Bowel function improved slowly, with improved tolerance of enteral feedings and resolution of the patient’s abdominal distention. Subsequent increases in the methylnaltrexone dose were well tolerated, but produced less benefit over time suggesting the development of tachyphylaxis or tolerance.

Kissling and colleagues described the use of methylnaltrexone in an 8-year-old girl receiving opioids for pain associated with relapsed Stage IV neuroblastoma. At the time of admission, the patient was receiving immediate-release morphine and had gone several days without a bowel movement. In the hospital, her pain management was transitioned to patient-controlled analgesia with morphine and transdermal fentanyl. Her pain scores, using the Face, Legs, Activity, Cry, Consolability (FLACC) Pain Assessment Tool, ranged from 0 to 8. Treatment with polyethylene glycol 3350, glycerin suppositories, and magnesium hydroxide did not improve her OIC. The patient refused docusate, sennosides, and magnesium hydroxide. The lack of bowel movements continued. During this period her oral intake also declined, in response to intractable nausea. Her analgesia regimen had escalated to 96 mg of morphine per day. On hospital day 25, a single 3 mg (0.15 mg/kg) methylnaltrexone dose was administered subcutaneously. The patient had a bowel movement within 10 minutes. A second bowel movement occurred 29 hours after the dose. The patient’s nausea and appetite improved over the remainder of her admission. She continued on her opioid regimen and maintained FLACC scores of 0 to 2. She required no additional methylnaltrexone doses.

Laubisch and Baker described a case involving a 17-month-old girl with OIC resulting from pain management for relapsed acute myelogenous leukemia post hematopoietic stem cell transplantation. She had been managed with enteral feedings via nasogastric tube and enteral laxatives, but as her condition worsened the nasogastric tube was removed because of the risk for aspiration. At this point, her analgesia regimen was changed to a hydromorphone infusion. Without enteral laxatives, the patient developed worsening abdominal distention and rectal prolapse. The authors elected to administer a 1 mg (0.12 mg/kg) dose of methylnaltrexone subcutaneously. The patient passed multiple stools within an hour of the dose, with subsequent resolution of her rectal prolapse and improvement in her abdominal distention. No additional doses were required.

In 2013, Rodrigues and colleagues at The Hospital for Sick Children published the results of a retrospective study of children with cancer treated with methylnaltrexone for OIC between May 2008 (the date when the drug became available in Canada) and September 2012. Fifteen patients (median age 14 years, range 4-17 years) were included. At the time they received methylnaltrexone, the patients were receiving Morphine, hydromorphone, or fentanyl at a median oral morphine dose equivalent of 5.7 mg/kg/day (range 1.5-29.2 mg/kg/day). The median time of opioid administration was 10 days (range 2 days-6 months). All of the children had previously been treated with multiple laxatives without improvement. Four patients had abdominal distention and one patient had fecal impaction.

Methylnaltrexone was administered at a mean dose of 0.15 ± 0.02 mg/kg (range 3-12 mg) by subcutaneous injection. Twelve patients received a single dose, while three were given multiple doses. The median time between doses was 17.5 days. A bowel movement occurred within 4 hrs after 14 of the 19 doses administered. In 10 cases, the bowel movement happened within 30 minutes. Two patients reported abdominal discomfort, and one patient reported nausea, flatulence, and dizziness. There were no cases of reduced pain control or opioid withdrawal.

A phase 4 randomized open-label study of methylnaltrexone is currently underway at the Shriners Hospitals for Children. The purpose of
this study is to assess the efficacy of methylnaltrexone prophylaxis in decreasing the incidence of OIC in patients 12 to 21 years of age requiring opioids after spinal fusion. All patients will receive a standard bowel regimen consisting of polyethylene glycol 3350, docusate, or senna starting postoperative day 1, with the addition of bisacodyl or magnesium hydroxide at 72 hours if needed. Patients randomized to the active study group will also receive methylnaltrexone (0.15 mg/kg given subcutaneously) on postoperative day 3 and again 24 hrs later if needed. The primary outcome for the study will be the incidence of OIC in the first week after surgery, with additional outcome measures of time to ambulation and time to oral intake. The estimated completion date for the study is June 2015.

While primarily administered for the treatment of OIC, methylnaltrexone may also have a role in reversing opioid-induced urinary retention. In a 2007 paper published in Clinical Pharmacology and Therapeutics, Rosow and colleagues reported the effects of methylnaltrexone on urodynamics in 13 healthy adults given an opioid. Based on the results from this study, Garten and Bührer used methylnaltrexone to treat a newborn male who developed opioid-induced urinary retention. The patient experienced severe birth asphyxia following placental abruption and was placed on therapeutic hypothermia at 2 hours of life. Morphine was administered by continuous infusion for sedation and analgesia during cooling, with titration to 15 mcg/kg/hr based on N-PASS scores. After 36 hours of therapeutic hypothermia, the patient developed urinary retention without constipation. Bladder volume increased, with impendence of venous return through the iliac veins producing engorgement and purple discoloration of the baby’s legs. Bladder catheterization was unsuccessful.

A single dose of methylnaltrexone (0.15 mg/kg) given IV resulted in spontaneous urination within 20 minutes. Bladder volume was reduced and all signs of impaired venous drainage resolved. A second dose given 24 hrs later also resulted in urine production within 20 minutes. No adverse effects were noted, and there was no apparent change in the number of bowel movements during treatment. There were no changes in N-PASS scores and no evidence of opioid withdrawal. Morphine was discontinued after 72 hrs at the completion of the hypothermia protocol. The patient had no further complications and was discharged at 11 days of age.

Contraindications and Warnings
Methylnaltrexone is contraindicated in patients with known or suspected GI obstruction. Use of methylnaltrexone has been associated with perforation of the stomach, duodenum, and colon in adults with OIC. The risk for perforation may be greater in patients with obstruction or disease states associated with possible reduction in the integrity of the bowel wall, such as cancer or peptic ulcers. Families should also be aware that patients treated with methylnaltrexone are at risk for severe diarrhea. If severe abdominal pain, emesis, signs of gastric bleeding, or diarrhea occur, treatment should be discontinued and the patient’s healthcare provider should be notified immediately. Methylnaltrexone should be discontinued as soon as opioid therapy is stopped.

Adverse Effects
In clinical trials of adults with OIC, the most commonly reported adverse effects after methylnaltrexone administration included abdominal pain (in 29% of patients), flatulence (13%), nausea (12%), dizziness (7%), diarrhea (6%), and hyperhidrosis (7%). Similar adverse effects have been reported in some of the pediatric papers described earlier. Rates of discontinuation due to adverse effects in the adult methylnaltrexone studies were low (1.2% with treatment, compared to 2.4% of patients receiving placebo). Post-marketing surveillance has included reports of opioid withdrawal.

Drug Interactions
There have been no clinically significant drug interactions reported with methylnaltrexone. In a study of adults given methylnaltrexone and cimetidine, renal clearance of methylnaltrexone decreased by approximately 40%, but the resulting AUC increased by only 10%.

Availability
Methylnaltrexone (Relistor®) is available in single-use vials containing 12 mg/0.6 mL solution for subcutaneous injection, as well as pre-filled syringes containing either 8 mg/0.4 mL or 12 mg/0.6 mL solution. The syringes are available individually or in packages of seven per box. Detailed instructions for preparing the dose are included in the patient information provided with each vial or syringe package.

Dosing Recommendations
In adults, the dose of methylnaltrexone is based on patient weight, according to recommendations from the manufacturer (Table). Extrapolating from this information, the reports published to date in infants and children have used a dose of 0.15 mg/kg. This is also the dose for the phase 4
Methylnaltrexone is typically administered once every 48 hrs in adults, but some patients benefit from escalation to once daily. Methylnaltrexone should not be administered more than once in a 24-hr period. Patients with severe renal impairment (creatinine clearance < 30 mL/min) should receive half of the calculated dose to account for prolonged clearance. No adjustment is required for patients with mild to moderate renal impairment or hepatic impairment.

Summary

Methylnaltrexone may serve as a useful treatment option for children with OIC who have not responded to traditional laxative therapy. The risks of this agent, including potential GI perforation, must be taken into account when contemplating its use. More research, including the prospective study currently underway, is needed to provide guidance regarding optimal dosing and to clarify the benefits and risks of methylnaltrexone in pediatric OIC.

The editors would like to thank Dr. Stephen Borowitz for serving as our guest editor for this issue of the newsletter.

References


Formulary Update

The following actions by the Pharmacy and Therapeutics Committee on 2/28/14:

1. Liposomal bupivacaine (Exparel®) was added to the Formulary with restriction to postoperative analgesia and total knee arthroplasty for a 6-month trial period.

2. An anesthetic skin refrigerant, pentafluoropropane-tetrafluoroethane (Gebauer’s Pain Ease®) was added for pain management with IV insertion, lacerations, vaccinations, or minor surgical procedures. This product will replace ethyl chloride spray.

3. Verteporfin (Visudyne®) was added for the treatment of age-related macular degeneration, pathologic myopia, or ocular histoplasmosis.

4. Custodial® HTK solution was added for the preservation of donor organs during transport.