

OBSERVATIONS

Selective Opioid Antagonist Improves Constipation in Terminally Ill Patients

The selective peripheral opioid-receptor antagonist methylnaltrexone significantly improves laxation compared with placebo in terminally ill patients with opioid-induced constipation. Because it does not cross the blood-brain barrier, it does not antagonize opioid central effects, Jay Thomas, MD, PhD, of San Diego Hospice & Palliative Care, said at the 41st Annual Meeting of the American Society of Clinical Oncology.

A single dose of methylnaltrexone significantly improved laxation at 4 and 24 hours after dosing. The drug was well tolerated, and serious adverse events were uncommon and equally distributed between treatment groups, Dr. Thomas reported.

In advanced medical illness, the incidence of opioid-induced constipation approaches 90%. The condition causes considerable suffering, including bloating, abdominal pain, nausea, vomiting, dyspnea, urinary retention, and fecal impaction.

“Unfortunately, as opposed to other opioid side effects, such as respiratory depression, to which we quickly become tolerant, tolerance never develops to opioid-induced constipation,” said Dr. Thomas.

He and his colleagues evaluated the

efficacy of subcutaneous methylnaltrexone to induce laxation in 154 hospice patients (123 of whom had cancer) with a life expectancy of no more than 6 months. Patients had no laxation for > 48 hours, had been on a stable opioid regimen for ≥ 3 days, and a stable laxative regimen for ≥ 3 days. Patients with non-opioid causes of bowel dysfunction, gastrointestinal obstruction, fecal impaction, surgically acute abdomen or fecal ostomy, or prior exposure to methylnaltrexone, naltrexone, or naloxone, were excluded.

Patients were randomized to a single subcutaneous dose of methylnaltrexone, 0.15 mg/kg or 0.3 mg/kg, or to placebo. The primary objective was to evaluate methylnaltrexone’s ability to induce laxation at 4 hours. Secondary objectives included changes in pain scores, opioid withdrawal symptoms, adverse events, and induction of laxation at 24 hours.

“To my knowledge this is the first multicenter, phase III, randomized, double-blind, placebo-controlled trial done in a hospice population,” said Dr. Thomas. “It is really gratifying to know that we can do evidence-based medicine in this very vulnerable and very needy population.”

For the primary endpoint of laxation

at 4 hours, more than 60% of patients in the 0.15 mg/kg group had achieved laxation, as had slightly less than 60% in the 0.3 mg/kg group, compared with slightly more than 10% in the placebo group ($P = 0.0004$). Laxation rates at 24 hours were slightly more than 30% in the placebo group compared with more than 60% in each of the methylnaltrexone groups ($P = 0.0004$ and $P = 0.0014$ for 0.15 mg/kg and 0.3 mg/kg, respectively). Median time to laxation was 70 minutes with 0.15 mg/kg methylnaltrexone, 45 minutes with 0.3 mg/kg, and more than 1,440 minutes with placebo ($P < 0.0001$).

The most common adverse events were abdominal cramping, flatulence, nausea, and dizziness, all of which were more common in the methylnaltrexone groups. However, serious adverse events were uncommon and equally distributed among placebo and methylnaltrexone groups.

“Methylnaltrexone may relieve the suffering from opioid-induced constipation in patients with advanced medical illness,” Dr. Thomas concluded. “A second multicenter, randomized, placebo-controlled phase III trial of repeated methylnaltrexone dosing versus placebo is ongoing.”