PALLIATIVE CARE
CASE OF THE MONTH

"Opioid Induced Constipation and Opioid Antagonists"

by

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Case: The patient, CP, is a 65-year-old male with a history of prostate cancer with bony metastases. His cancer-related pain had been stable on methadone 30mg three times daily and hydromorphone 16mg every three hours as needed for breakthrough pain. To treat constipation from chronic opiate use, his outpatient bowel regimen consisted of polyethylene glycol 17gm twice a day, docusate 100mg twice a day and senna 2 tabs at bedtime.

CP was admitted for acute abdominal pain with nausea, vomiting and constipation. He reported no bowel movement for 14 days followed by the onset of severe sharp and stabbing mid-abdominal pain, nausea and vomiting for one day. He was placed on a hydromorphone PCA for abdominal pain and was administered polyethylene glycol 17gm three times a day, senna 17.2mg twice a day and multiple enemas for suspected Opioid-Induced Constipation (OIC) without bowel obstruction. Despite this, he did not move his bowels. A CT scan of his abdomen showed a moderate amount of retained stool in his ascending and transverse colon.

Discussion: OIC is a prevalent, often intolerable adverse-drug consequence of opioid therapy. It can occur in 15-90% of patients taking opioids on a regular basis. (Tuteja AK, 2010) The most commonly used opioids are μ-receptor agonists. When the μ-receptors are activated in the enteric nervous system, the transit of intestinal contents is decreased, water secretion is inhibited and the pyloric and internal anal sphincter tone is increased. This leads to constipation, harder stools, and incomplete evacuation of stool. Patients affected with OIC report lower quality of life due to these symptoms. (Panachal SJ, 2007) (Portenoy RK, 2016)

Typical interventions for OIC include lifestyle modifications such as increased dietary fiber, increased fluid intake, and increased physical activity. Laxative use with a stimulant, such as senna, is also common. (Panachal SJ, 2007) While most laxatives act on secondary mechanisms, such as increased intestinal osmotic load, to help relieve constipation, Peripherally-Acting Mu-Opioid Receptor Antagonists (PAMORAs) have been brought to market to address OIC directly by antagonizing peripheral μ-receptors. (Siemans W, 2015) The aim of this case of the month is to discuss two PAMORAs for OIC: methylnaltrexone (Relistor®), and naloxegol (Movantik®).

Methylnaltrexone was the first PAMORA. It was approved in the United States in 2008 for treatment of OIC in patients with advanced illness who are receiving palliative care for whom traditional laxatives have been ineffective. This medication only acts on the peripheral μ-opioid receptors; therefore, it doesn't inhibit pain control or induce opioid withdrawal.

Methylnaltrexone has been shown to increase the frequency of bowel movements to greater than three bowel movements per week and also to decrease the time to first bowel movement to four hours or less after administration when compared to placebo. (Siemans W, 2015) (Thomas J, 2008) (Portenoy RK, 2016) (Clemens KE, 2010) The number needed to treat to achieve this effect is 4. Methylnaltrexone is contraindicated in patients with suspected or confirmed mechanical gastrointestinal (GI) obstruction. (Siemans W, 2015) (Portenoy RK, 2016) It is administered subcutaneously (SQ) once every other day or every third day at a dose of 8mg SQ for patients weighing between 38-61 kg and 12 mg SQ for patients weighing between 62-114kg. The dose for patients outside of these weight ranges is 0.15mg/kg. Safety data regarding its use beyond 3 months is scarce and limited to case reports. (Dutka J, 2009) Abdominal pain and diarrhea are the most commonly reported adverse reactions with methylnaltrexone. As of April 2016, it costs $120 per dose.

Naloxegol was the first oral PAMORA, approved in 2014, for the treatment of OIC in adult patients with chronic non-cancer pain. It has not yet been studied in the palliative care population. Naloxegol is a pegylated form of naloxone and is unable to cross the blood brain barrier; therefore, it is able to act peripherally in the gut without producing opioid withdrawal. It has been shown to increase spontaneous bowel movements and to decrease the time to the patient's first bowel movement when compared to placebo. This medication should also be avoided in patients with known or suspected GI obstruction or patients at risk for developing GI obstruction. The dose is 25mg by mouth once daily. It is to be administered on an empty stomach either 1 hour before eating or 2 hours after the first meal of the day. Administration of naloxegol with moderate CYP 3A4 inhibitors (such as diltiazem, erythromycin, and verapamil) or strong CYP 3A4 inducers (such as rifampin) should be avoided, as concentrations of naloxegol can be significantly increased or decreased respectively. Significant adverse reactions include abdominal pain, diarrhea, flatulence and vomiting. (Siemans W, 2015) (Portenoy RK, 2016) (Chey WD, 2014) Currently, naloxegol costs $11.52/dose.

Resolution of Case: CP was administered two doses of methylnaltrexone 12mg SQ two days apart. He proceeded to have multiple bowel movements with improvement in his abdominal pain. The hydromorphone PCA was discontinued. His home methadone and hydromorphone medications were restarted at lower doses. With his abdominal pain resolved, CP was discharged to home with an increased home laxative schedule and plans for continued follow up in the outpatient palliative care clinic. He was advised to continue his opiates and laxatives as prescribed and to call the clinic with any questions or concerns.

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the *Palliative Care Program at PUH/MUH*, 647-7243, beeper 8511, *Shadyside Dept. of Medical Ethics and Palliative Care*, beeper 412-647-7243 pager # 8513, *Perioperative/ Trauma Pain* 647-7243, beeper 7246, *UPCI Cancer Pain Service*, beeper 644 –1724, *Interventional Pain* 784-4000, *Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore* and Children's page 958-3844. With comments about "Case of the Month" call Dr. Robert Arnold at (412) 692-4834.

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