

# PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

## Opioid-induced Constipation Case September 2018

### Patient Case

HK is an 81-year-old female who enrolled in hospice 2 weeks ago with a primary diagnosis of metastatic breast cancer. Additional diagnoses include hypothyroidism and hypertension. She has no drug allergies and lives with her daughter and son-in-law. When visiting HK today, she reports mild abdominal discomfort and bloating. Upon further questioning, she admits that her last bowel movement was over 5 days ago.

### Current medications:

- Fentanyl (Duragesic®) transdermal patch 50 mcg topically every 72 hours for pain
- Morphine (Roxanol®) 20mg/mL; 1ml (20mg) PO every 3 hours as needed for pain or SOB
- Hydrochlorothiazide 25mg; 1 tablet PO daily for blood pressure control
- Acetaminophen 325mg; 2 tablets (650mg) PO every 4-6 hours as needed for fever
- Calcium carbonate (Tums®) 500mg; Chew 1 tablet PO every 2 hours as needed for dyspepsia
- Multivitamin with iron; 1 tablet PO daily for supplementation
- Levothyroxine (Synthroid®) 100mcg; 1 tablet PO daily for the thyroid

HK's pain is controlled on her current regimen – she uses an average 1-2 doses of morphine for breakthrough pain each day and her pain rating is usually 3/10. Vital signs are within normal limits: BP 125/85, HR 80, RR 15, Temp 98.2°F. HK's abdomen is soft and non-tender with decreased bowel sounds. She admits to having a very small, pebble-like bowel movement after some considerable straining 4 days ago, but it did not relieve her discomfort. She is eating and drinking and denies nausea or vomiting. Based upon your patient history and assessment, your suspicion of a gastrointestinal obstruction is low.

### CONSTIPATION AT END OF LIFE

Constipation significantly increases burden on severely ill patients, their family, and the health care system. Symptoms and complications from constipation include discomfort, pain, distress, nausea and vomiting, hemorrhoids, anal fissures, spurious diarrhea, and fecal impaction. Severe constipation and its complications also result in ER visits and hospitalizations and poor quality of life. Constipation may increase healthcare costs, as well as overall system burdens and resource utilization.<sup>1</sup>

Risk factors for the development of constipation in patients with advanced illness include:<sup>2</sup>

- Medications: Opioids, anticholinergics (TCA antidepressants, antihistamines, antipsychotics), anti-diarrheals (Lomotil®, Imodium®), diuretics, anti-emetics (Zofran®), iron, calcium and aluminum-containing antacids
- Metabolic disturbances: Dehydration, electrolyte imbalances (i.e., hypokalemia, hypercalcemia), chronic kidney disease, depression diabetes, uremia, and hypothyroidism

# PALLIATIVE PEARLS

## BY ENCLARA PHARMACIA

- Neurologic disturbances: Brain tumors, spinal cord involvement, sacral nerve infiltration, autonomic dysfunction, multiple sclerosis, Parkinson's disease, and dementia
- Contributory issues: Anorexia, reduced food and fluid intake, low fiber, advanced age, inactivity, depression, and sedation

When constipation is confirmed, the intervention required is based on patient status and preference, disease trajectory and the amount of distress the constipation is causing. Non-pharmacological interventions can be tried initially, or to supplement medication therapy.

Non-pharmacological interventions include:

- Increasing oral intake of food, fiber, and fluid as tolerated
- Increasing mobility, if feasible
- Establishing a routine of timed toilet training  $\geq 2$  times/day (30 minutes after meals or waking, and for no more than 5 minutes)<sup>3</sup>
- Fecal disimpaction (pre-medicate with sedative and analgesic, if appropriate)

Increasing fiber either through supplements or diet may not be appropriate for severely debilitated patients, or for certain diagnoses, such as anorectal cancer. In addition, increasing fiber without adequate fluid intake or in patients with poor gut motility may lead to impaction. Opioid-induced constipation is refractory to non-pharmacological methods because opioids bind to receptors in the GI tract and reduce peristalsis.<sup>1</sup> For this reason, there is no definitive evidence that the above mentioned methods are effective in opioid-induced constipation.<sup>4</sup>

Whenever possible, medications that have constipating effects should be discontinued, replaced or reduced. Certain medications, like opioids, will need to be continued. When this is the case, we must take steps to medically manage the constipation. Unlike other common side effects of opioids (nausea, vomiting, sedation, and respiratory depression) that a patient eventually develops tolerance to, constipation does not resolve over time.

### CHOOSING THE BEST LAXATIVE<sup>4</sup>

Constipation is commonly treated with a **stimulant laxative** alone, on a scheduled basis (as opposed to "as needed") for prevention, and titrated to effect. Stimulant laxatives, such as **senna (Senokot®)** or **bisacodyl**, work by direct stimulation on the smooth muscle of the colon, resulting in peristaltic movement and improved GI motility. Common side effects include abdominal cramping and pain that may be avoided by dividing the total daily dose into smaller, more frequent doses.<sup>4</sup>

# PALLIATIVE PEARLS

## BY ENCLARA PHARMACIA

**Saline laxatives**, such as **magnesium citrate (Citroma®)**, **magnesium hydroxide (Milk of Magnesia®)** and **sodium phosphate (Fleet® enema or oral liquid)** work by exerting a hyperosmotic effect in the small intestine causing retention of water and stimulation of peristalsis. Use caution in patients with renal failure or those with hypermagnesemia.

**Osmotic laxatives** like **glycerin suppositories**, **polyethylene glycol (i.e., Miralax®)**, **sorbitol**, and **lactulose** work by binding water and retaining it within the stool. If cramping occurs with stimulant laxatives, and the patient is not dehydrated, an osmotic laxative may be substituted or added for persistent constipation.

**Bulk-forming laxatives**, such as **psyllium (Metamucil®)**, **calcium polycarbophil (FiberCon®)** and **methylcellulose (Citrucel®)**, absorb liquid in the GI tract, thereby altering intestinal fluid and electrolyte transport, causing expansion of the stool, and the resultant bulk facilitates peristalsis and bowel motility. These agents are not typically recommended for constipation in hospice patients because of intolerance to the volume of liquid necessary for administration.

**Mineral oil** is a **lubricant laxative** that can be used orally or as an enema. Mineral oil slows colonic absorption of fecal water and softens the stool. Rectally, mineral oil works locally to lubricate and soften the stool. The oral formulation should be used with caution in patients with dysphagia or bed-bound patients, since it can increase the risk of aspiration pneumonia.

- Frozen Vaseline® balls, which contain petrolatum, a product derived from oil, are anecdotally used in the hospice population. They are typically used for a high impaction, and made by rolling Vaseline® into pea-sized balls, coating with sugar, freezing the balls, and administering them orally 1-3 times per day, as needed. There is no published evidence to support this practice.

**Lubiprostone (Amitiza®)** is a unique gastrointestinal agent that increases intestinal fluid secretion by activating specific chloride channels in the luminal cells of the intestinal epithelium. Lubiprostone, available as an oral capsule, alters stool consistency and promotes regular bowel movements, without altering serum electrolyte concentrations or producing tolerance. Note that unlike other opioids, lubiprostone may not work for patients prescribed methadone, since methadone interacts with lubiprostone, reducing its effects.<sup>2,5,6</sup>

**Peripherally-acting  $\mu$ -opioid receptor antagonists** work by blocking the opioid receptors responsible for constipation without causing significant opioid withdrawal or loss of analgesia. Medications include oral **naloxegol (Movantik®)**, oral and subcutaneous **methylnaltrexone (Relistor®)** and oral **naldemedine (Symproic®)**. Only the parenteral form of methylnaltrexone is approved for the treatment of opiate agonist-induced constipation in patients with advanced illness who are receiving palliative care when there is an insufficient response to laxative therapy. Note that these agents are contraindicated in complete bowel obstruction. Also, naloxegol and naldemedine interact with numerous medications

# PALLIATIVE PEARLS

## BY ENCLARA PHARMACIA

metabolized by the liver's cytochrome P450 system – use of proton pump inhibitors, certain antibiotics, HIV medications, and –azole antifungals should be avoided, among other medications.<sup>2,10</sup> All are very costly and should be considered last line for those who have failed other therapies.

### WHAT TO AVOID

**Stool softeners (Docusate sodium (Colace®))** work by lowering the oil-water tension at the surface of the feces, allowing water and lipids to penetrate the stool, which hydrates and softens the fecal material, facilitating defecation. By mechanism, stool softeners should work on the stool that is about to be formed, with softening becoming apparent after 1-3 days of therapy, and will not work on hard stool that has already been formed. In addition, the effectiveness of stool softeners is not supported in the literature and experts now recommend not adding this to bowel regimens.<sup>4,5,7-9</sup>

### LAXATIVE SELECTION BY OUTCOME AND ONSET<sup>10</sup>

Watery evacuation (1-6 hours):

- Magnesium citrate (Citroma®)
- Magnesium hydroxide (Milk of Magnesia®)
- Sodium phosphates (Fleet® oral liquid, enema)
- Bisacodyl (rectally)
- Glycerin suppositories
- Polyethylene glycol-electrolyte preparations (i.e., Miralax®, Golytely®)

Soft or semifluid stool (6-12 hours):

- Bisacodyl (oral)
- Senna (Senokot®)

Softening of feces (1-3 days):

- Bulk forming agents (i.e., methylcellulose, polycarbophil)
- Lactulose
- Sorbitol
- Mineral Oil

### LAXATIVE AGENTS & PLACE IN THERAPY

A 2011 Cochrane systematic review of constipation management in palliative care patients did not identify a laxative and/or approaches considered superior than any other.<sup>11</sup> Select the medication and/or approach consistent with patient status and goals of care.<sup>1</sup>

# PALLIATIVE PEARLS

## BY ENCLARA PHARMACIA

### General guidance:

- Avoid the use of docusate sodium in chronic constipation due to the lack of evidence to support its use alone or in combination with stimulant laxative therapy
- Use stimulant laxatives as first line therapy – they are effective in most patients, simple to use and readily available at a low cost
- When titration of a stimulant laxative fails to produce a bowel movement, consider adding an agent from a different laxative class (i.e., saline or osmotic laxative, depending on patient-related factors)
- For opioid-induced constipation refractory to agents above, consider the use of opioid receptor antagonist therapy or lubiprostone. Methylnaltrexone has the most evidence to support its usefulness in the palliative care population.<sup>1,6</sup>

### **Pharmacist Assessment:**

Constipating medications on HK's profile include fentanyl, morphine, calcium carbonate, multivitamin with iron and hydrochlorothiazide due its potential to dehydrate. These medications require evaluation and decisions on whether to discontinue and replace with less constipating agents.

### **Recommendations**

1. Continue fentanyl and morphine for pain management.
2. Start a stimulant laxative such as Senna and continue for as long as she is using chronic opioid therapy. Start with 1 tablet by mouth at bedtime and titrate to desired bowel movement frequency. Goal should be 1 non-forced bowel movement every 1-2 days<sup>12</sup>
3. Discontinue the multivitamin with iron.
4. Discontinue calcium carbonate. Do not replace with another agent until the results of senna administration are assessed. Patient's constipation likely lends itself to dyspepsia and may be relieved with regular bowel movements.
5. Continue hydrochlorothiazide for now. Assess HK's blood pressure during the next visit. If similarly stable (today's 125/85), considering cutting dose by one-half and assessing impact. Over time, this medication may be able to be discontinued due to progression of disease and resulting low blood pressure.

### **For additional information on this topic, please review these references:**

Enclara Pharmacia's On Demand Educational Webinar, "Gastrointestinal Complications in Hospice". Click [here](#) to log in.

1. Portenoy RK, Mehta Z, Ahmed E. Prevention and management of side effects in patients receiving opioids for chronic pain. UpToDate. Published Sept 7, 2018.
2. Clinical Resource, Treatment of Constipation in Adults. Pharmacist's Letter/Prescriber's Letter. April 2017.

# PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

3. Rao SSC. Constipation in the older adult. UpToDate. Published May 21, 2018.
4. Badke A, Rosielle DA. Fast Facts and Concepts #294: Opioid induced constipation part 1: Established management strategies. PCNOW. Published Apr 2015.
5. Article, Emphasize an Effective Bowel Regimen for Opioid-Induced Constipation, Pharmacist's Letter, December 2017.
6. Badke A, Rosielle DA. Fast Facts and Concepts #295: Opioid induced constipation part 2: Newer therapies. PCNOW. Published Apr 2015.
7. MacMillan TE, Kamali R, Cavalcanti RB. Missed opportunity to deprescribe: docusate for constipation in medical inpatients. *Am J Med* 2016 May 3. doi: 10.1016/j.amjmed.2016.04.008.
8. Professional Resource, Docusate. Pharmacist's Letter/Prescriber's Letter. September 2016.
9. Paauw DS. 11 Drugs You Should Seriously Consider Deprescribing. Medscape News & Perspective. Published Sept 5, 2017. <https://www.medscape.com/slideshow/deprescribing-6009041#1>. Accessed 2018 Sept.
10. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2018. Access 2018 Sept.
11. Candy B, Jones L, Goodman ML, et al. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev*. 2011; :CD003448.
12. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): Palliative Care. Version 1.2018. [www.NCCN.org](http://www.NCCN.org). Accessed 2018 Sept.
13. Gandell D, Straus SE, Bundookwala M, et al. Treatment of constipation in older people. *CMAJ*. 2013 May 14; 185(8): 663–670.
14. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med*. 2008;11(4):575-581.
15. Larkin PJ, Sykes NP, Centeno C, et al., The management of constipation in palliative care: Clinical practice recommendations. *Palliative Medicine*. 2008; 22: 796–807.
16. Lee TC, McDonald EG, Bonnici A. Less is more: Pattern of inpatient laxative use: Waste not, want not. *JAMA Intern Med*. 2016;176:1216-1217.
17. McKee TY, Widera E. Less is more: Habitual prescribing of laxatives – it's time to flush outdated protocols down the drain. *JAMA Intern Med*. 2016;176:1217-1219.
18. Tarumi Y, Wilson MP, Szafran O, et al., Randomized double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *J Pain Symptom Manage*. 2013 Jan; 45(1): 2-3.
19. Twycross R, Sykes N, Mihalyo M, Wilcock A. Stimulant laxatives and opioid-induced constipation. *J Pain Symptom Manage*. 2012;43:306-13.