Management of Postoperative Ileus

Melissa Thompson, PharmD, BS; Barbara Magnuson, PharmD, BCNSP

Abstract: Postoperative ileus, a temporary cessation in bowel motility, is a common and significant complication of major surgery. Consequences of postoperative ileus include increased patient discomfort, delayed time to adequate nutrition, prolonged length of stay, and increased cost to the patient and healthcare system. The traditional, multi-modal approach to the resolution of postoperative ileus includes opioid minimization, early ambulation, and early feeding. Newer medications, such as methylnaltrexone and alvimopan (which are peripherally acting mu opioid receptor antagonists), have become available and have proven beneficial for use with postoperative ileus.

Postoperative ileus is a common complication of many surgical procedures. Although it is most commonly associated with abdominal surgery, it can be a complication of any major surgical procedure, including orthopedic surgery. Postoperative ileus is generally defined as a cessation of bowel motility. The clinical characteristics include delayed passage of flatus stool and abdominal distension. Although postoperative ileus is not considered a life-threatening condition, it can be associated with an increased length of hospital stay, increased patient discomfort, delayed time to proper nutrition postoperatively, and increased postoperative morbidity.

Intra-abdominal surgery can result in postoperative ileus due to opening of the peritoneal cavity or to resection or manipulation of the intestines. Nonintra-abdominal surgical procedures, including orthopedic procedures, can also cause postoperative ileus through different mechanisms but will ultimately result in the same clinical syndrome.

Complications of postoperative ileus include increased pain, poor nutritional intake, delayed wound healing, pulmonary complications and infections, prolonged hospital stay, and increased cost to the patient and healthcare system. The key to minimizing the consequences of postoperative ileus focuses on a multi-faceted approach to nutrition, hydration, pain management, postoperative ambulation, and pharmacologic prophylaxis or treatments in some patient populations.

The amount of time a patient has postoperative ileus has a direct correlation with the length and cost of the hospital stay. The economic burden has been previously reported to be >$1 billion per year. Treatment is focused on supportive care, the goals of which are to accelerate postoperative gastrointestinal recovery and minimize the potential complications of postoperative ileus.

This article describes the management of postoperative ileus in orthopedic patients, highlights the pathophysiology of the disease process, and reviews historical and current treatment options. Although the following data may be extrapolated to the pediatric patient population, this article focuses on the management of adult surgical patients with postoperative ileus.

Pathophysiology

Postoperative ileus has a multifactorial etiology. It is associated with the body's stress response to surgery, an activation of the sympathetic nervous system that creates an inhibi-
tory reflex in the bowel. Acute inflammation from the manipulation of the bowel and surgical site are also involved in postoperative ileus pathology.

Endogenous production of opioids (dynorphin and enkephalin) and exogenous opioids given as analgesic agents can contribute to postoperative ileus formation by stimulating mu opioid receptors in the gastrointestinal tract. The gastrointestinal tract is widely innervated by neural pathways that are responsible for peristalsis independent of the central nervous system. The interactions of these pathways help us understand the pathophysiology of postoperative ileus.

Three main types of neurons control the activities of the gastrointestinal tract: sensory neurons, interneurons, and inhibitory and excitatory motor neurons. Sensory neurons receive information from the intestinal epithelium, muscles, and mucosa. Interneurons create a bridge between sensory neuron input and the effects of the motor neurons, which are the primary effectors of peristalsis. Inhibitory and excitatory motor neurons work together to cause peristalsis through the control of smooth muscle tissue, epithelial cells, blood vessels, and glands. The inflammatory response to the stress of surgery can cause immune cells to infiltrate the intestines, releasing cytokines that will decrease smooth muscle contractility and can cause dysmotility.

Interactions with the intestinal opioid receptors—mu, delta, and kappa—play a major role in the development of postoperative ileus. Opioid-derived analgesics stimulate the central nervous system mu opioid receptors to derive its analgesic effects. Unfortunately, interactions with the same receptors outside of the central nervous system can have deleterious effects on gastrointestinal motility. The delicate balance between adequate analgesia in the postoperative surgical patient and avoidance of the gastrointestinal side effects creates a challenge for the surgeon.

Because the opioid medication class results in effective analgesia, these drugs are commonly prescribed as a first-line agent. High doses and prolonged opioid therapy predispose patients to developing opioid-induced bowel dysfunction, which is characterized by delayed gastric emptying, dysmotility, inhibition of small and large bowel propulsion, increased nonpropulsive contractions, and increased anorectal tone.

The clinical effects of this interaction can lead to increased gastrointestinal reflux, incomplete evacuation, abdominal distension, cramps, and constipation. The clinical symptoms, although nonspecific, are often found during the diagnosis of postoperative ileus.

Opioid receptors have been a target of pharmacotherapy development to decrease the incidence of postoperative ileus and dysmotility from opioid-derived analgesics, which is 1 of the main causes of postoperative ileus in the orthopedic surgery population.

**DIAGNOSIS**

The diagnosis of postoperative ileus consists of clinical presentation and patient history. Generally, patients exhibit abdominal pain, abdominal distension, absent bowel sounds, lack of bowel movements or gas, and nausea or vomiting. Symptoms can include a persistent, dull, nonradiating pain. Postoperative ileus can affect all segments of the gastrointestinal tract, with resolution of different segments’ dysmotility occurring in different increments. Radiographic findings of the abdomen may reveal patterns of small and large bowel gas that are nonspecific, as well as scattered air or fluid levels.

**INEFFECTIVE TREATMENT OPTIONS**

The type of surgery has a direct correlation with the risk of developing postoperative ileus because laparoscopic procedures minimize direct intestinal manipulation. Minimization of opioid-derived analgesics, through use of nonsteroidal anti-inflammatory agents (NSAIDs) or patient-controlled epidural analgesia, can help reduce the intensity or duration of postoperative ileus.

Electrolyte abnormalities, such as hypokalemia, hypophosphatemia, and hypomagnesemia, have been strongly associated with the development of postoperative ileus. Postoperative electrolyte laboratory values should be proactively and routinely monitored; deficient electrolytes should be aggressively treated to establish normal values. Correction of electrolyte deficiencies, along with adequate hydration, may help prevent the development of or lessen postoperative ileus.
Although no gold standard treatment for postoperative ileus exists, clinicians generally recognize that early mobility, ambulation, initiation of liquid and solid diets, and removal of the nasogastric tube facilitate recovery of the upper and lower gastrointestinal track postoperatively.†

**Pharmacologic Treatment Options**

Currently, no standard treatment guidelines exist for the management of postoperative ileus because limited pharmacotherapy options are available. Drug therapy to treat postoperative ileus aims to bind with and block the activity of the gastrointestinal mu opioid receptors. Ideally, this agent would affect only the gastrointestinal tract receptors and not the central nervous system to avoid the reversal of the analgesia.

The Table summarizes the suggested drug treatment regimens, including adult doses, for postoperative ileus. Naloxone inhibits the mu opioid receptor in the gastrointestinal tract and in the central nervous system. However, naloxone is not indicated for patients with postoperative ileus because it can precipitate withdrawal symptoms due the central nervous system action.‡

Methylnaltrexone, a quaternary mu opioid receptor antagonist, elicits its main effects within the gastrointestinal tract, not the central nervous system. The methylation of naltrexone prevents the molecule from crossing the blood–brain barrier. When metabolized, it is not significantly demethylated, decreasing the risk of precipitating opioid withdrawal. Methylnaltrexone is administered by subcutaneous or intravenous injection. It has a relatively short half-life, approximately 2 to 3 hours, and is eliminated through renal clearance.‡ Common side effects include mild to moderate abdominal cramping and flatulence.

Thomas et al⁵ studied the use of methylnaltrexone for patients with opioid-induced constipation at 2 different doses: 0.15 and 0.3 mg/kg. The primary endpoint was laxation at 4 and 24 hours, respectively, and both doses were significantly more effective than the placebo at each time interval. The higher dose (0.3 mg/kg) produced laxation at 45 minutes, whereas the lower dose (0.15 mg/kg) produced laxation at 70 minutes.

Viscusi et al⁶ evaluated methylnaltrexone use in patients following segmental colectomy. Patients were randomly assigned to the methylnaltrexone or placebo group: 0.3 mg/kg was administered intravenously every 6 hours beginning within the first 90 minutes postoperatively and continued for up to 7 days. The methylnaltrexone group experienced a 24-hour reduction in the duration of time without a bowel movement (120 vs 97 hours, respectively). The methylnaltrexone group also experienced an average of a 24-hour length of stay reduction and tolerated a full liquid diet sooner than the placebo group (100 vs 125 hours, respectively), although this did not reach statistical significance. The length of stay decrease for patients receiving methylnaltrexone could represent a large cost savings for the institution and patient, despite the drug’s expense.

Hospital pharmacy and therapeutic committees may institute specific guidelines for prescribers on the proper use of methylnaltrexone. Because the drug was never specifically studied in the orthopedic surgery patient population, one must extrapolate from the available literature when making medication selections. When chosen for the appropriate patient, especially those at a high risk for ileus due to opioid use, methylnaltrexone may improve postoperative morbidity and decrease length of hospital stay.

Alvimopan is also a quaternary mu opioid receptor antagonist similar to methylnaltrexone but with a higher receptor-site affinity. Like methylnaltrexone, alvimopan does not cross the blood–brain barrier; therefore, it is unlikely to precipitate an acute withdrawal in patients receiving chronic opioids. Alvimopan has a half-life of 2.5 to 6 hours and does not require dose adjustments for liver or kidney dysfunction.″

Paulson et al⁷ randomized chronic opioid users to receive a 0.5- or 1 mg oral dose of a
The prokinetic medications metoclopramide and erythromycin are not effective therapy and should not be used to treat postoperative ileus. Identifying and treating electrolyte abnormalities, such as hypokalemia and dehydration, will help prevent postoperative ileus. Newer mu opioid antagonist medications, such as methylnaltrexone and alvimopan, have been shown to reduce time to first bowel movement and reduce length of stay for patients with postoperative ileus.

The Bottom Line
- Development of postoperative ileus can contribute to significant morbidity and financial burden.
- The prokinetic medications metoclopramide and erythromycin are not effective therapy and should not be used to treat postoperative ileus.
- Identifying and treating electrolyte abnormalities, such as hypokalemia and dehydration, will help prevent postoperative ileus.
- Newer mu opioid antagonist medications, such as methylnaltrexone and alvimopan, have been shown to reduce time to first bowel movement and reduce length of stay for patients with postoperative ileus.

The time to first bowel movement was measured as the primary endpoint. Patients reached the endpoint within 8 hours after drug administration in 54% of patients taking 1 mg, 43% of patients taking 0.5 mg, and 29% of patients taking the placebo. A significant reduction in the time to first bowel movement was found for the patients taking 1 mg of alvimopan vs placebo (3 vs 21 hours, respectively).

In general, the current recommendation for treating opioid-induced bowel dysfunction is with the smaller daily oral doses of 0.5 to 1 mg of alvimopan. In trials evaluating postoperative ileus, alvimopan was given to high-risk patients preoperatively—12 mg orally and then 12 mg orally twice daily for up to 7 days or until the first bowel movement. High-risk patients include those undergoing small bowel resection, partial colectomy, or abdominal hysterectomy. Patients taking alvimopan experienced faster gastrointestinal recovery than those taking a placebo; time to first bowel movement or time to first oral solid food occurred faster for patients taking alvimopan than for those taking a placebo (96 vs 112 hours, respectively). Patients receiving alvimopan also had a shorter length of hospital stay, averaging a 24 hour shorter stay across all trials.

If the first 12-mg dose was not administered preoperatively, the treatment effect was not realized. Therefore, a 12-mg preoperative dose is crucial and should be followed by a 12-mg dose twice daily until laxation. Careful selection of the high-risk patients and proper administration of alvimopan can reduce the incidence of postoperative ileus and shorten the length of hospital stay.

Myocardial infarction was seen more often in the alvimopan treatment groups during the clinical trials, although the patients experiencing the myocardial infarction had more cardiovascular risk factors. The US Food and Drug Administration monitors these side effects through a Risk Evaluation and Mitigation Strategy program, and a warning exists for its use in patients with a history of coronary artery disease. Theoretically, NSAIDs such as ibuprofen and ketorolac relieve postoperative ileus by inhibiting inflammatory mediated cytokines, and they may decrease gastrointestinal inflammation, which can attenuate the inflammatory mediated bowel dysfunction seen postoperatively and in critical illness. The analgesic properties of NSAIDs can reduce the opioid doses, which can be advantageous in the treatment or minimization of postoperative ileus. In the absence of contraindications, NSAIDs offer an alternative, advantageous mechanism for pain relief without the risk of causing ileus.

Neostigmine is often prescribed for critical illness-related colonic ileus, a type of ileus primarily seen in hospitalized patients. The primary etiology for critical illness-related colonic ileus involves adrenergic gastrointestinal track stimulation via adrenergic agents or critical stress. Neostigmine, a cholinesterase inhibitor, inhibits the breakdown of acetylcholine at the neuromuscular junction and then stimulates the parasympathetic nervous system to increase gastrointestinal contractions.

Neostigmine is also used to treat an ileus with a dilated component, resembling Ogilvie’s syndrome; however, it is not indicated for patients with opioid-induced bowel dysfunction. White and Sandhu evaluated neostigmine in critical illness-related colonic ileus as a continuous infusion of 0.4 to 0.8 mg per hour over 24 hours vs placebo. The neostigmine patient group passed stool 79% more often compared with the placebo group, and when patients were switched from the placebo group to the treatment group, even more met the primary endpoint. A slow intravenous 2.5-mg bolus infusion of neostigmine has been shown to be effective. Because the half-life of neostigmine is approximately 1 hour, administering a lower dose over a longer period may optimize the pharmacokinetic properties of the drug.

Several studies report that patients respond better to a continuous infusion and not the intravenous bolus. The most common side effect of neostigmine is bradycardia; however, it is generally believed to be safe when used with close monitoring. Neostigmine is an attractive option for patients with an ileus who are in the intensive care unit. With close physician and nursing monitoring of side effects and treatment effects, it can cause laxation quickly and safely.

References
2. Viscusi ER, Gan TJ, Leslie JB, et al. Peripheral acting mu-opioid receptor antagonists and...


