

REVIEWS

Postoperative Ileus: Etiologies and Interventions

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This article will review the pathophysiology of postoperative ileus, with emphasis on potential therapeutic targets, and examine the efficacy of pharmacologic and nonpharmacologic interventions. Proposed mechanisms include actuation of spinal and local sympathetic neural reflexes, inflammatory mediation, and exacerbation by anesthetic or surgical procedures. Some procedures or agents have shown clinical benefit, and these include use of laparoscopic surgery, thoracic epidurals, nonsteroidal anti-inflammatory drugs, and opiate antagonists. Other procedures may be helpful with low risk of adverse effects. These include early feeding and ambulation, laxatives, and possibly neostigmine.

Postoperative ileus (POI) is a common and clinically important problem occurring after surgical procedures that may contribute to significant postoperative morbidity, including delaying enteral nutrition, causing patient discomfort, and prolonging hospitalization (Table 1). POI may be generally defined as a transient impairment in gastrointestinal (GI) motility in the postoperative setting; however, no standard nomenclature or grading system exists. Postoperative hypomotility may affect all parts of the GI tract but with differential recovery of normal function.^{1–4} Small intestine function generally normalizes first, often within several hours of surgery.^{2,5} Gastric motility usually returns to normal within 24–48 hours after surgery.^{3,6} The colon is usually the final portion of the GI tract to regain normal motility, which usually occurs within 48–72 hours after surgery.^{2,7} Motility normalizes in the proximal colon first and then progresses to the transverse and left colon.⁴ Most data support that colonic dysfunction is most frequently the factor that limits resolution of postoperative ileus.^{8,9}

Although some of the mechanisms underlying the abnormal intestinal motility found after surgery have been elucidated, an integrated understanding of the pathophysiology of POI remains elusive. Several factors may play a role, including spinal-intestinal neural reflexes, local and systemic inflammatory mediators, generalized sympathetic hyperactivity, and other exacerbat-

ing influences including exogenous and endogenous opiates and electrolyte abnormalities. Treatment of POI is currently largely supportive and historically has consisted of routine nasogastric intubation, intravenous hydration, and bowel rest. In the past, multiple pharmacologic agents have been used in the treatment of POI with little consistent success. Efforts aimed at minimizing POI by utilizing epidural anesthetic agents, providing pain control with opioid-sparing agents such as nonsteroidal anti-inflammatory medications, and utilizing less invasive surgical techniques have led to improved patient comfort, shorter duration of ileus, and earlier hospital discharge. New pharmacologic agents such as opiate antagonists show promise as emerging therapies.¹⁰

Pathophysiology

Motility of the GI tract is temporarily impaired after surgery and is characterized by disorganized electrical activity and lack of coordinated propulsion. In the stomach, studies have consistently demonstrated a postoperative period of gastric hypomotility associated with irregular and disorganized electrical activity.³ Gastric propulsion may be orad, and there may also be increased pyloric tone that contributes to abnormal gastric emptying.¹¹ Motor activity is similarly disorganized in the small bowel. The migrating motor complex (MMC) may be shortened and also produce retrograde contractions, leading to significant delays in small bowel transit.¹² Normal colonic motility is typically the last to return after surgery. Studies evaluating postoperative colonic motility frequently have found a period of relative hypomotility that is generally associated with random, disorganized bursts of electrical activity.^{7,13} Propagated

Abbreviations used in this paper: COX, cyclooxygenase; GI, gastrointestinal; MMC, migrating motor complex; NSAID, nonsteroidal anti-inflammatory drug; POI, postoperative ileus; VIP, vasoactive intestinal peptide.

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Table 1. Potential Adverse Impact of POI

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| Increased postoperative pain |
| Increased nausea and vomiting |
| Delay in resuming oral intake |
| Poor wound healing |
| Delay in postoperative mobilization |
| Increased risk of other postoperative complications |
| Deconditioning |
| Pulmonary complications (pneumonia, pulmonary embolism, atelectasis) |
| Other nosocomial infections |
| Prolonged hospitalization |
| Decreased patient satisfaction |
| Increased health care costs |

colonic contractions typically return 72 hours after surgery and often mark the clinical recovery from ileus.¹³

Several mechanisms are thought to play a role in postoperative ileus (Table 2). One hypothesis is that sympathetic hyperactivity in the postoperative period generates high levels of circulating catecholamines, leading to POI. Plasma catecholamines have been demonstrated to be elevated after surgery,¹⁴ and high levels of catecholamines in nonsurgical settings have been associated with inhibited GI motility.¹⁵ Alpha- and beta-adrenergic blocking agents have been found to improve bowel motility in animal studies evaluating POI^{16,17} but have not consistently demonstrated beneficial effects in humans.^{18,19} In addition, data from subsequent animal studies suggest that elevated circulating catecholamines may not play as significant a role in POI as previously thought. In an animal model with rats that underwent adrenal demedullation, postoperative animals had lower than normal circulating catecholamines, yet they did not have a shorter duration of ileus.²⁰

Neural reflexes involving the sympathetic nervous system are thought to play an important role in POI by inhibiting intestinal motility. Several early studies found that intestinal motility in animals could be improved after abdominal surgery by blocking nerve conduction by transecting the spinal cord or splanchnic nerves.^{21,22} Early work with a rabbit model demonstrated that laparotomy did not inhibit intestinal contraction if the spinal cord had previously been severed.²¹ Abdominal sympathectomy in dogs has been shown to lead to a decreased incidence of ileus after laparotomy,²² and selective degradation of splanchnic afferent neurons with capsaicin has been found to decrease ileus in rats.²³ In addition, anesthetic agents administered via an epidural catheter have been found to decrease the duration of POI in several studies, possibly as a result of blockade of inhibitory sympathetic reflexes at the cord level.²⁴

The inflammatory response to surgery is another potential factor in the pathogenesis of POI. Animal models

have shown that surgical manipulation of the intestines resulted in a local inflammatory response, with the subsequent accumulation of inflammatory cells, principally polymorphonuclear neutrophils, in the muscularis and associated with significant jejunal muscle dysfunction.²⁵ A similar process also occurs after colonic manipulation.²⁶ Systemic cytokines, including interleukin-1 and interleukin-6, are elevated in the postoperative setting and may inhibit GI motility through undefined mechanisms.^{27,28}

Various neural and hormonal factors participate in normal GI motility as well as POI. However, the relative roles and interactions between individual mediators during POI remain poorly characterized. Several agents, including nitric oxide, vasoactive intestinal peptide (VIP), and substance P, appear to be inhibitory neurotransmitters in the enteric nervous system and may play a role in prolonging ileus after abdominal surgery.^{29–31} Investigations evaluating VIP and substance P antagonists,^{29,30} as well as inhibitors of nitric oxide synthesis,³¹ have shown improved postoperative bowel motility in animal studies. The stimulatory transmitter motilin, which initiates the MMC during fasting, has been found to be depressed at the end of abdominal surgery but elevated as ileus resolves.³² Another stimulatory peptide, ghrelin, appears to be a strong prokinetic agent and is capable of reversing postoperative gastric ileus in rats.³³

Other factors also clearly play a role in the duration and severity of POI. For example, opiates are widely used for analgesia in the postoperative setting. Peripheral opiate receptors are located throughout the GI tract and when stimulated by exogenous or endogenous opioids may have profound effects on gastrointestinal motility.³⁴ Opiates cause a delay in gastric emptying and have an overall inhibitory effect on the small bowel and colon.^{35–37} In the colon, morphine has been shown to decrease peristaltic waves and increase colonic tone, which delays stool transit and increases water absorption from the lumen,^{34,38} resulting in harder, drier stool. As discussed below, limiting narcotic use in the postoperative setting has been associated with a significant decrease in the duration of postoperative ileus.³⁹

Table 2. Pathophysiology of POI: Proposed Mechanisms

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|--|
| Spinal and local sympathetic neural reflexes |
| Local and systemic inflammatory mediators |
| Exacerbating factors |
| Opioid analgesics |
| Intraperitoneal surgery |
| Degree of bowel manipulation |
| Open surgical procedures |
| Hypokalemia |

Electrolyte abnormalities have been implicated in prolonged POI as well. Reports of patients presenting with prolonged POI associated with hypokalemia found that repleting potassium led to resolution of ileus.⁴⁰ It has been suggested by some authors that other electrolyte abnormalities including hyponatremia and hypomagnesemia play a role in POI, but this has not been confirmed by published data.

Anesthetic agents may have a minor effect on GI motility in the postoperative setting. GI function is depressed to some degree by all agents used in the induction and maintenance phases of general anesthesia. However, it is doubtful these agents play a large role in the pathogenesis of POI, as evidenced by the large number of prolonged nonabdominal operations that occur under general anesthesia without a significant degree of POI.⁴¹ One of the most frequently evaluated agents in the literature is nitrous oxide, commonly used as an adjuvant induction and maintenance agent in patients undergoing general anesthesia. Theoretically, nitrous oxide, being more soluble than nitrogen, can accumulate in the intestinal lumen, causing distention and the need for prolonged intravenous hydration.⁴²⁻⁴⁴ Three prospective studies evaluating the role of nitrous oxide in causing postoperative bowel dysfunction have reported conflicting results.⁴³⁻⁴⁵ Halothane and enflurane have been studied in monkeys, and despite colonic smooth muscle depression initially, colonic contractile activity returned to normal within 15-30 minutes after the discontinuation of each medication.⁴⁶ The role of neuromuscular blocking agents used during general anesthesia has not been fully evaluated. The use of epidural infusions of local anesthetic will be discussed below.

Several studies suggest that the human stress response to noxious stimuli can lead to significant changes in normal bowel motility.⁴⁷⁻⁴⁹ Various types of centrally acting noxious stimuli, including cold pain and labyrinthine stimulation, have been found to depress intestinal motility.^{47,48} In contrast, a study evaluating gastric emptying found no differences between groups of patients undergoing elective and emergent surgeries, suggesting that stress associated with the emergent surgery did not play a significant role in postoperative bowel motility.⁵⁰

The type of surgical procedure performed can have significant effects on postoperative GI motility. Skin incision has no effect on bowel MMC activity, whereas opening the peritoneum will completely inhibit the MMC.⁵¹ For years, it was believed that the length of an operation played an important role in the duration of ileus^{52,53}; subsequent studies have cast doubt on the validity of this assumption, however.⁵⁴ Indeed, one study

suggested there might be an inverse relationship between the duration of the surgical procedure and the duration of POI.⁵⁵ In addition, studies comparing laparoscopic to open surgical procedures consistently find decreased duration of POI in the laparoscopic group, despite the longer duration of surgery in this population.⁵⁶⁻⁵⁸ However, there may be some bias in these studies in how aggressively patients are initially fed, leading to earlier oral intake in the laparoscopic group. Also, patients undergoing laparoscopic procedures may have decreased postoperative pain and decreased narcotic requirements, which may then lead to improved bowel motility.⁵⁹

Manipulation of the bowel during surgery has been implicated as a possible factor in prolonging POI. Early experiments found that simple exposure of abdominal contents had no effect on motility postoperatively, but manual handling of the intestines led to a delay in gastric and intestinal motility.⁶⁰ More recent research suggests that simply handling the bowel leads to transient increases in mucosal permeability, allowing translocation of bacteria and other toxins through the gut mucosa. This leads to a significant inflammatory response in the bowel wall.⁶¹ The degree of manipulation appears to be directly proportional to both the postoperative inflammatory response in the intestinal muscularis and the duration of POI.²⁵

Epidural anesthesia may play an important role in decreasing POI by blocking inhibitory reflexes originating from the spinal cord. In 10 studies comparing epidural anesthesia with systemic opiates, 7 showed a faster return of bowel function in the epidural groups.^{24,62-70} In the 3 studies that showed no positive effect of epidural anesthesia, 2 removed the epidural catheter within 24 hours.^{63,64} In the remaining study the medication in the epidural infusion was changed to a narcotic agent after 24 hours.⁶⁸ The location of the epidural catheter is important, because successful blockade of inhibitory spinal reflexes is accomplished only with thoracic administration of the anesthetic agent. Although epidurals placed at the thoracic level generally show benefit in shortening POI, lumbar or low thoracic epidurals have been ineffective in reducing ileus in several trials.^{64,71,72}

Therapy

A variety of treatments have been used in an attempt to decrease the duration of POI (Table 3). Many of the studies evaluating different treatment modalities are small, retrospective, and/or have end points that make comparisons to other trials difficult. Resolution of POI is difficult to define given the lack of uniform

Table 3. Treatment Options for POI

| Treatment | Potential mechanism | Comments |
|--|---|---|
| Nonpharmacologic treatment options | | |
| NG tube | Gastric/small bowel decompression | No evidence NG tubes reduce duration of POI. May increase pulmonary postoperative complications ^{118–120} |
| Early enteral nutrition | Stimulates GI motility by eliciting reflex response and stimulating release of several hormonal factors | Appears safe, well tolerated. Some, but not all, studies suggest decrease in POI ^{95–102} |
| Sham feeding | Cephalic-vagal reflex | Small clinical trials suggest some benefit ^{101–103} |
| Early mobilization | Possible mechanical stimulation | No significant change in duration of POI, but may decrease other postoperative complications ¹⁰⁴ |
| Laparoscopic surgery | Decreased opiate requirements, decreased pain, less abdominal wall trauma | Most studies find decreased duration of POI with laparoscopy ^{56–58} |
| Psychological preoperative preparation | Improves bowel motility through visceral learning | One study found positive benefit in decreasing time to flatus and hospital discharge ¹⁰⁷ |
| Pharmacologic treatment options | | |
| Metoclopramide | Dopamine antagonist, cholinergic agent | Majority of RCTs suggest no benefit ^{122–127} |
| Cisapride | Dopamine antagonist, cholinergic agonist, serotonin receptor agonist | Possibly effective, ^{128–136} withdrawn from U.S. market due to cardiovascular side effects |
| Erythromycin | Motilin agonist | 2 RCTs suggest no benefit ^{138,139} |
| Opiate antagonists | Block peripheral opiate receptors | One RCT shows ADL8-2698 decreases time to flatus, bowel movement, and hospital discharge, ¹⁰ but not currently available outside of clinical trials. Other agents have not been evaluated in POI |
| Epidural anesthesia | Inhibits sympathetic reflex at cord level, opioid-sparing analgesia | Several RCTs suggest benefit in decreasing POI, ^{24,62–70} most effective when inserted at thoracic level |
| NSAIDs | Opiate-sparing analgesia, inhibits COX-mediated prostaglandin synthesis | Probable benefit. ^{39,74,75,78} COX-2 selective medications need further evaluation |
| Laxatives | Stimulant, prokinetic effects | No RCTs. One nonrandomized, unblinded study suggests possible benefit ¹⁰⁸ |
| Antiadrenergic agents | Blocks sympathetic neural reflex | Little practical benefit in POI drugs often limited by cardiovascular side effects ^{14,18,113} |
| Cholinergic agents | Acetylcholine modulation | Frequent systemic side effects. Neostigmine has possible benefit ^{115,116} |
| Multimodality therapy | Combination therapy may work via multiple mechanisms | Possible benefit in reducing POI. ^{41,88–91} No RCTs have been reported |

COX, cyclooxygenase; POI, postoperative ileus; RCTs, randomized controlled trials.

nomenclature or standardized grading systems. Despite this, some conclusions may be reasonably drawn.

Agents with Probable Therapeutic Benefit

Laparoscopic surgery. Laparoscopic surgery has consistently been found to decrease the duration of POI compared with conventional open procedures.^{56–58,73} Several studies have found that using a laparoscopic approach reduces the duration of ileus by 27%–40%.^{56,58,73} Some of this reduction may be due to decreased postoperative pain and narcotic requirements⁵⁹ as well as decreased intestinal manipulation and procedure-related inflammation.^{60,61}

Thoracic epidural anesthetic agents. Epidural anesthetics are additional therapeutic agents that appear to significantly reduce the duration of POI.^{24,62–70} As

discussed above, the location of the epidural catheter influences the anesthetic's effect on GI motility. Thoracic, but not lumbar or low thoracic, epidural catheters block the spinal reflexes thought to play an important role in the pathogenesis of POI.⁷²

Nonsteroidal anti-inflammatory medications.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the duration of POI by their anti-inflammatory actions⁷⁴ as well as by decreasing the postoperative use of opiates for pain control. Administration of NSAIDs in most studies has resulted in improved bowel function in postoperative patients,^{39,74,75} but physicians must be wary of the antiplatelet effects and increased risk of GI bleeding with the use of these medications. Cyclooxygenase (COX)-2 has been implicated in the pathogenesis

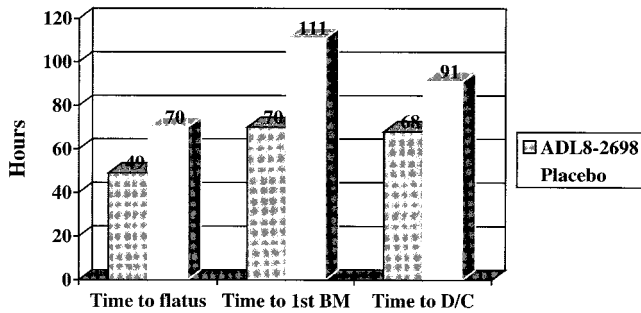


Figure 1. Comparison of time end points with opiate antagonist ADL8-2698 versus placebo for POI ($P < 0.05$ for all comparisons). BM, bowel movement; D/C, discharge. Data from Taguchi et al.¹⁰

of POI,^{76,77} and COX-2 selective inhibitors were reported to be effective in reducing POI in a recent small trial.⁷⁸

Opiate antagonists. Several opiate antagonists have been found to have a beneficial effect on GI motility in patients with chronic constipation and in surgical patients with POI. ADL8-2698 (Alvimopan; Adolor Corp, Exton, PA) is a selective mu-opiate antagonist that is absorbed poorly from the GI tract and does not readily cross the blood-brain barrier.⁷⁹ Thus, it provides reversal of opiate effects in the gut but does not appreciably interfere with pain control or precipitate opiate withdrawal.⁸⁰ A recent randomized, placebo-controlled trial investigating ADL8-2698 in patients undergoing partial colectomy ($n = 15$) or hysterectomy ($n = 63$) showed that patients receiving the study drug had a significant decrease in time to passage of flatus, bowel movement, and hospital discharge¹⁰ (Figure 1).

A second agent, methylnaltrexone, is another mu-opiate antagonist that does not readily cross the blood-brain barrier.⁸¹ When given intravenously, it appears to have effects limited mainly to the GI tract. Methylnaltrexone has been found to decrease the incidence of opioid-induced constipation without adversely affecting pain control or precipitating opiate withdrawal.⁸² However, methylnaltrexone has not yet been evaluated in the postoperative setting.

Naloxone, a competitive mu-opiate antagonist, readily crosses the blood-brain barrier when given intravenously and will reverse the centrally mediated effects of opiates, including analgesia, central nervous system depression, and respiratory depression.⁸³ Naloxone may also precipitate opiate withdrawal in susceptible persons.⁸³ However, when given orally, naloxone appears to have fewer central effects due to extensive first-pass hepatic metabolism⁸⁴ and thus may be a potential oral agent for the treatment of POI. Further, it has a long safety record and is widely available and relatively inexpensive. Oral naloxone has been found to decrease opioid-induced constipation in patients with chronic pain but in higher doses

led to increased symptoms of opiate withdrawal.^{85–87} The efficacy of oral naloxone in patients with POI is currently under investigation.

Multimodal therapy. Several authors have advocated a multimodal approach to the treatment of POI, combining several different therapeutic agents to reduce the duration of ileus. Several recent case series have shown significant improvement in the time to resolution of POI compared with standard postoperative care.^{88–91} Such treatment modalities include the avoidance of routine nasogastric tube placement, use of thoracic epidural anesthetic agents, early mobilization and oral intake, frequent use of laxative agents, and the use of additional opioid-sparing medications for pain control such as NSAIDs.^{41,88–91} Larger, randomized, placebo-controlled trials still need to be performed to confirm the validity of this approach, but multimodality therapy appears to be a promising and logical approach to a problem that has several mechanisms of pathogenesis and in which single-modality therapy is frequently ineffective.

Agents With Possible Therapeutic Benefit and Low Risk of Harm

Early or sham feeding. Early enteral feeding has been promoted as a possible way to decrease duration of POI, in part by eliciting a contractile response in the GI tract.^{92,93} In the past, food was withheld after surgery until clinical evidence of ileus had resolved, with the gradual advancement of diet after the passage of flatus or stool. Unfortunately, this often resulted in days with minimal or no oral nutrition with a subsequent negative nitrogen balance and potentially poor wound healing, as well as decreased immune function.⁹⁴ Some, although not all, recent studies have suggested that early enteral feeding is safe and leads to decreased duration of POI and earlier hospital discharge.^{95–100} In addition, small studies evaluating sham feeding^{101,102} and chewing gum¹⁰³ in the postoperative setting have found that bowel motility is enhanced in these groups, possibly via direct vagal stimulation and indirectly by the release of stimulatory hormones and increased secretions. However, larger, randomized trials need to be performed before sham feeding becomes standard practice in the management of POI. Although early feeding has not been definitively proved to reduce POI, it appears generally safe and may confer benefits beyond influencing the duration of ileus.

Early ambulation. Early ambulation has not been shown to shorten the duration of postoperative ileus.¹⁰⁴ However, prolonged immobilization appears to increase the risk of other postoperative complications^{105,106} and so should generally be avoided for reasons other than solely recovery of GI function.

Preoperative psychological preparation. One study evaluating an alternative to pharmacologic and conventional supportive therapy used preoperative psychological preparation in an attempt to decrease the duration of POI.¹⁰⁷ In this study, patients in the experimental group received specific information regarding early return of bowel function after surgery, whereas the control group received nonspecific preoperative instructions. The authors found a significant decrease in time to flatus and time to hospital discharge in the experimental group, suggesting that psychological preparation can reduce the severity of POI.¹⁰⁷

Laxatives. Laxatives are a potential agent to be used in treating POI, but there are no randomized controlled trials that have assessed their utility in this setting. One nonrandomized study evaluated 20 consecutive patients given laxative agents postoperatively and reported a reduction in time to flatus and first bowel movement, as well as decreased length of hospitalization, compared to historical controls.¹⁰⁸ However, further evaluation with larger, placebo-controlled trials should be performed before the use of laxatives becomes a routine part of postoperative patient care. Laxatives have also been used with other therapies in multimodal rehabilitation studies after abdominal surgery with promising results, as discussed below.⁸⁸

Neostigmine. Studies evaluating cholinergic agonists in the setting of POI have often produced conflicting results and are frequently limited by systemic side effects.^{109–111} However, neostigmine is one agent that may hold promise in the treatment of POI. Neostigmine is an acetylcholinesterase inhibitor that increases contractility in the small and large intestine, resulting in improved GI motility.¹¹² Early studies evaluating neostigmine in combination with adrenergic blocking agents produced conflicting results^{19,113,114} in patients with POI. A more recent trial evaluating neostigmine in colonic pseudo-obstruction showed that this agent led to rapid resolution of pseudo-obstruction in most patients.¹¹⁵ Another small nonrandomized trial involving spinal surgery patients with POI and evidence of pseudo-obstruction showed a significant reduction in the duration of ileus after the administration of neostigmine,¹¹⁶ but larger, placebo-controlled trials need to be performed to clarify its role in the management of POI.

Agents With No Therapeutic Benefit or That Are Potentially Harmful

Nasogastric decompression. The use of a nasogastric (NG) tube is common after abdominal surgery.

Nasogastric suction has been a cornerstone of supportive treatment for POI for more than 50 years¹¹⁷ in an attempt to decrease gastric distention and to remove GI secretions. However, several more recent randomized controlled trials have concluded that NG tubes do not help and may actually impair postoperative recovery.^{118,119} Indeed, in a meta-analysis that evaluated selective versus routine NG tube placement,¹²⁰ patients with routine NG tube placement had higher incidences of fever, atelectasis, and pneumonia. Patients with selectively placed NG tubes did have a higher incidence of abdominal bloating, nausea, and vomiting, but this did not have any effect on the overall postoperative complication rate.¹²⁰ Thus, the routine use of NG tubes after abdominal surgery should be individualized.

Metoclopramide. Numerous studies have evaluated the use of intestinal prokinetic agents in POI. Metoclopramide is an antiemetic agent that enhances motility by acting as a dopamine antagonist and cholinergic stimulant.¹²¹ Despite its theoretical promise, multiple randomized placebo-controlled trials have failed to demonstrate a consistent beneficial effect in patients with POI.^{122–127} Although some found earlier oral intake in patients receiving metoclopramide, this has been attributed by some authors to its antiemetic effects.

Cisapride. Cisapride, a serotonin receptor agonist that enhances acetylcholine release in the myenteric plexus,¹²¹ has also been evaluated in several randomized controlled trials in the postoperative setting. Cisapride administration led to a significant reduction in POI in 3 of 4 studies in which it was given intravenously; one study in which cisapride was given orally showed a significant reduction in POI, and only 1 of 4 studies showed a significant benefit when given rectally, suggesting that its route of administration has an impact on its overall efficacy in POI.^{128–136} Unfortunately, cisapride has been associated with prolongation of the QT interval and cardiac arrhythmias, leading to its withdrawal from the U.S. market.

Erythromycin. Erythromycin, a commonly used macrolide antibiotic that also acts as a motilin agonist and stimulates MMC activity in the GI tract, could theoretically improve bowel motility after abdominal surgery.¹³⁷ Two randomized controlled trials have been reported in humans that showed no significant change in the duration of POI.^{138,139}

Adrenergic inhibitors/parasympathomimetic agents. Despite the apparent importance of sympathetic neural reflexes in the pathogenesis of POI, trials evaluating beta-adrenergic blocking agents have reported generally negative results, even at doses leading to cardio-

vascular side effects.¹⁸ Blockade of both alpha- and beta-adrenergic receptors also fails to improve postoperative GI motility in animal models.¹⁴ Studies evaluating the combination of adrenergic inhibition with cholinergic activation in POI have given conflicting results in several studies.^{19,113,114} Cholinergic agents used alone also have not been definitively proven to shorten the duration of POI^{110,111,113} and may be limited by systemic side effects. Given the conflicting data and lack of consensus regarding the effectiveness of adrenergic blockers and cholinergic agonists in the setting of POI, neither class of drug is widely used in the postoperative setting.

Potential Therapies That Have Not Been Evaluated in Postoperative Ileus

Fedotozine. Agents with selectivity for the kappa-opioid receptor have been studied in animals. Fedotozine is a kappa-opioid receptor agonist that has shown promise by providing analgesia and also improving bowel function in rats^{140–142} but has not been evaluated in the postoperative setting in humans.

Somatostatin. Somatostatin inhibits the secretion of several hormones involved in bowel motility, and the somatostatin analogue octreotide has been found to enhance GI transit in animal models.¹⁴³ Further study of somatostatin or its analogues in the treatment of POI will be required to evaluate its effectiveness.

Domperidone. Domperidone is a prokinetic agent that blocks peripheral dopamine receptors and acts as a prokinetic agent. It is not currently available in the United States and has not been evaluated in the postoperative setting.

Conclusion

Postoperative ileus is a pervasive problem after major abdominal surgery and may lead to significant postoperative morbidity, prolonged hospitalization, and increased health care costs. Several mechanisms are thought to play a role in POI, including sympathetic neural reflexes, local and systemic inflammatory mediators, and changes in various neural and hormonal transmitters. Many potential treatment options exist for POI, but data regarding the efficacy of various therapies are generally limited. It appears that thoracic epidural anesthetic agents decrease the duration of POI, in part by blocking neural reflexes at the spinal cord and by decreasing post-procedure narcotic use by the patient. NSAIDs may also speed recovery of bowel function by inhibiting bowel inflammation and by decreasing opioid use. Prokinetic agents such as metoclopramide and erythromycin have not been conclusively shown to de-

crease the duration of POI. Early enteral feeding and early ambulation have also not been definitively shown to shorten the duration of POI, but each appears to have other beneficial effects and may decrease postoperative morbidity and thus should be encouraged. Most recently, opioid-receptor antagonists have shown promise in reducing postoperative ileus but still require further studies. Multimodality treatment approaches combining several therapies may represent a logical approach but require further evaluation in larger, randomized trials, as do novel emerging therapies such as VIP and substance P antagonists or nitric oxide synthesis inhibitors.

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