Mechanisms and Treatment of Postoperative Ileus

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Objective: To review the pathogenesis and treatment of postoperative ileus.

Data Sources: Data collected for this review were identified from a MEDLINE database search of the English-language literature. The exact indexing terms were “postoperative ileus,” “treatment,” “etiology,” and “pathophysiology.” Previous review articles and pertinent references from those articles were also used.

Study Selection: All relevant studies were included. Only articles that were case presentations or that mentioned postoperative ileus in passing were excluded.

Data Synthesis: The pathogenesis of postoperative ileus is complex, with multiple factors contributing either simultaneously or at various times during the development of this entity. These factors include inhibitory effects of sympathetic input; release of hormones, neurotransmitters, and other mediators; an inflammatory reaction; and the effects of anesthetics and analgesics. Numerous treatments have been used to alleviate postoperative ileus without much success.

Conclusions: The etiology of postoperative ileus can best be described as multifactorial. A multimodality treatment approach should include limiting the administration of agents known to contribute to postoperative ileus (narcotics), using thoracic epidurals with local anesthetics when possible, and selectively applying nasogastric decompression.

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ILEUS IS DEFINED in Dorland’s Illustrated Medical Dictionary simply as “obstruction of the intestines.” However, the definition of postoperative ileus, the topic of this review, is a bit less clear. In 1990, Livingston and Passaro defined ileus as “the functional inhibition of propulsive bowel activity, irrespective of pathogenetic mechanisms.” They further defined postoperative ileus as the “uncomplicated ileus occurring following surgery, resolving spontaneously within 2 to 3 days.” Finally, the term paralytic postoperative ileus was defined as that form of ileus lasting more than 3 days after surgery. Such a distinction was necessary because different mechanisms are probably responsible for the 2 types of postoperative ileus. It may be more correct to call postoperative ileus a primary ileus in that it is most likely an inevitable response to surgical trauma. In postoperative ileus, inhibition of small-bowel motility is transient, and the stomach recovers within 24 to 48 hours, whereas colonic function takes 48 to 72 hours to return. Determination of the end of postoperative ileus is somewhat controversial. The studies in the literature have used varying end points, and each has its own weakness. Bowel sounds are sometimes used as an end point, but they require frequent auscultation, their presence does not necessarily indicate propulsive activity, and they can be the result of small-bowel activity and not colonic function. Flatus also is not the ideal end point. It requires a conscious patient who is comfortable reporting its occurrence to the investigator. Also, there is some question as to the correlation between flatus and bowel movements. Bowel movements are seemingly the most reliable end point, although they too may be nonspecific, representing distal bowel evacuation as opposed to global gastrointestinal tract function. In the end, the health care provider should assess the patient as a whole to determine the resolution of postoperative ileus.

HISTORY

The reduction in bowel motility after surgery has been described since the late 1800s. A multiplicity of studies have been published on postoperative ileus, but the pathogenesis remains an enigma. Little advancement in effective treatment regi-
mens has taken place since the introduction of nasogastric decompression. Ileus is a significant medical problem and constitutes the most common reason for delayed discharge from the hospital after abdominal surgery. The economic impact of ileus has been estimated to be $750 million to $1 billion in the United States. More important than health care costs is patient discomfort. The symptoms of postoperative ileus range from cramping and abdominal pain to nausea and vomiting.

The presence of inhibitory spinal reflexes acting on the bowel was first demonstrated in 1872 by Goltz. In 1899, Bayliss and Starling determined that the ablation of splanchnic nerves would improve bowel motility after laparotomy. They discovered this by using a device termed the enterograph, which allowed them to study intact small-intestinal activity in the unanesthetized dog. During the past few decades, numerous reports have been published reaffirming the implication of sympathetic pathways in postoperative ileus. Over the years, experimental models of postoperative ileus have been developed to assess propulsive bowel motor function. Some of these models include gastric emptying, small- and large-bowel transit time, and stool pellet output as well as recording changes in bowel motility. An experimental model using strain gauge transducers in awake rats has been reported as a method of measuring gastrointestinal motility. Many new theories have been hypothesized to explain the pathogenesis of postoperative ileus.

NORMAL PHYSIOLOGY OF GASTROINTESTINAL MOTILITY

Normal bowel motility results from complex interactions among the enteric nervous system, central nervous system, hormones, and local factors affecting smooth-muscle activity. Motility in the stomach and small intestine varies based on whether one is in the fasting or fed state. Compared with fasting, the fed pattern consists of continuous low varying-amplitude, ungrouped contractions whose number, intensity, and duration depend on the food ingested (amount and physical and chemical composition). However, between meals, the migrating motor complex (MMC) dictates the contractile pattern of the bowel. The MMC, first described by Szurszewski, is believed to serve a “housekeeper” function by propelling intraluminal contents distally during the fasting state. In humans, these contractions occur approximately once every 1 to 2 hours.

Four phases are involved in the MMC in the fasted state. The first phase includes oscillating smooth-muscle membrane potentials without actual muscle contractions. The occurrence of intermittent muscle contractions marks the transition to phase II. During phase III, the contractions increase to the maximal contractile frequency allowed by the slow wave (approximately 3 contractions per minute in the stomach and 11 contractions per minute in the duodenum). Phase IV is marked by cessation of contractions, and the bowel becomes quiescent. Feeding is followed by interruption of the MMC and the appearance of a different pattern consisting of sustained irregular phasic contractile activity.

Table 1. Possible Mechanisms of Postoperative Ileus

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Factors Involved</th>
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<tbody>
<tr>
<td>Autonomic nervous</td>
<td>Sympathetic inhibitory pathways</td>
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<tr>
<td>Enteric nervous</td>
<td>Substance P, nitric oxide</td>
</tr>
<tr>
<td>Hormones and</td>
<td>Vasoactive intestinal peptide; corticotropin-releasing factor ligands; calcitonin gene-related peptide ligands</td>
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<td>neuropeptides</td>
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<tr>
<td>Inflammation</td>
<td>Macrophage and neutrophil infiltration; cytokines, other inflammatory mediators</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>General anesthetics</td>
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<tr>
<td>Narcotics</td>
<td>Opiates</td>
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</table>

The musculature of the stomach is made of cells that are intimately associated, allowing them to conduct electrophysiologic functions. There are 3 distinctive electrical potentials: resting potential; slow-wave or pacemaker potential; and spike potential that trigger contractions. However, these potentials can only occur during the slow-wave frequency and thus are determined by the pacemaker. Numerous gastrointestinal hormones affecting gastrointestinal motility have been reviewed recently, and a detailed discussion of this topic is beyond the scope of this review. Gastric motility is thus determined by complex interactions among the electrophysiologic characteristics, neural input, and gastrointestinal hormones.

The colon, whose main purpose is to absorb water and store feces, differs in structure and function from the remainder of the bowel. Measured electrical activity in the colon reveals irregular oscillations with varying amplitude. Colonic smooth muscle does not contain gap junctions and therefore does not act as a single unit. In humans, 3 electrical activities of colonic motility can be distinguished: electrical control activity represents smooth-muscle membrane potential oscillations, discrete electrical response activity consists of spike-wave potentials superimposed on the oscillations, and continuous electrical response activity is not related to oscillations but is involved with contractions that sweep luminal contents distally.

PATHOGENESIS

Altered Gastrointestinal Motility in Postoperative Ileus

In the stomach and the small intestines, normal basal electrical activity is impaired after surgical procedures. Specifically, in the stomach there is an irregular pattern of gastric spike and slow-wave activity. In addition, after surgery, if patients are not being fed, MMC activity is thought to be the “only impetus to bowel contraction.” Therefore, patients who are restricted from taking anything by mouth after surgery are also thought to have minimally propulsive bowel motility. Various anesthetic agents can affect MMC activity. For example, ether and halothane are inhibitory, whereas enflurane is excitatory. Incising the peritoneum likewise inhibits MMC activity.
activity, and prolonged inhibition is observed after bowel manipulation.2

The colon’s electrical activity is also disturbed as a result of surgical procedures. After surgery in monkeys and humans, there is disruption of the 3 electrical activities described in the previous section.24,25 Continuous electrical response activity is the last to return to normal (approximately 72 hours after surgery) and is associated with the onset of flatus. Although the electrical activity of the gastrointestinal tract is disturbed in patients with paralytic postoperative ileus, the return of normal electrical activity does not always coincide with resolution of the ileus.

The Role of the Autonomic Nervous System

A balance exists between excitatory and inhibitory input in the regulation of bowel motility. Parasympathetic stimulation increases gastrointestinal motility, whereas sympathetic stimulation is inhibitory. Sympathetic input serves as the predominant inhibitory impetus to the bowel and provides the efferent limb of numerous reflex pathways. Supporting evidence for this concept is based on animal experiments30 that demonstrated the predominance of sympathetic inhibition following division of the parasympathetic (vagal) and sympathetic (splanchnic) neural input. Previous studies have demonstrated sympathetic output as a factor in the pathogenesis of postoperative ileus. The mechanism of sympathetic inhibition involves preventing the release of acetylcholine from excitatory fibers located in the myenteric plexus. Small-bowel postoperative ileus and delayed gastric emptying are ablated using chemical sympathectomy with 6-hydroxydopamine.27,28 In addition, intestinal catecholamine stores are depleted more rapidly after laparotomy vs no laparotomy.29

However, sympathetic blockade is not always successful in reversing the inhibition of gastrointestinal motility induced by abdominal surgical procedures.30 Thus, other mechanisms, such as nonadrenergic noncholinergic nerves, are believed to play a role in inhibiting gut motility after surgery.

The Role of Neurotransmitters, Local Factors, and Hormones

A variety of neurotransmitters, local factors, and hormones has been proposed to contribute to postoperative ileus, although no single factor has been clearly proven to be responsible. Vasoactive intestinal peptide causes an increase in inhibitory input to the gastric cholinergic neurons, creating a decrease in antral and pyloric activity.31 Substance P, which is a neurotransmitter involved in pain, has also been hypothesized to have a role in postoperative ileus.32 Nitric oxide (NO) is believed to be the predominant inhibitory nonadrenergic noncholinergic neurotransmitter of the gastrointestinal tract. It is thought to act through its constitutive form of NO synthetase within enteric neurons.33 Researchers30,34 have examined the role of NO in a rat model of postoperative ileus. Rats were assigned to undergo a skin incision, laparotomy only, or laparotomy, evisceration, and manipulation. Of the cecum and small intestine, reserpine, an inhibitor of adrenergic neurotransmission, and Nω-nitro-L-arginine, an NO synthase inhibitor, were given alone and in combination. When given alone, reserpine significantly increased gastrointestinal transit in rats that underwent a skin incision, completely reversed the inhibition caused by laparotomy alone, but only partially reversed the inhibition of transit induced by laparotomy, evisceration, and manipulation. In contrast, Nω-nitro-L-arginine administration had no effect on gastrointestinal transit altered by the skin incision or by laparotomy only and partially reversed the negative effects on motility caused by laparotomy, evisceration, and manipulation. Given in combination, these drugs showed no additional effects over reserpine therapy alone in the skin incision and laparotomy-only groups; however, administration of these drugs resulted in a complete reversal of the inhibition of gastrointestinal motility induced by laparotomy, evisceration, and manipulation. These results support the involvement of NO release in postoperative ileus. The role of NO in the pathogenesis of postoperative ileus in humans remains unclear. Experimental evidence35,36 has shown that antagonists to vasoactive intestinal peptide, substance P, and inhibitors of NO synthesis improve postoperative bowel motility.

Calcitonin gene–related peptide (CGRP) is present in visceral afferent neurons in the gastrointestinal tract and acts on peripheral receptors to delay gastric emptying and gastrointestinal motility in rats.14,36 It is possible that abdominal surgical procedures stimulate the release of CGRP from these neurons, causing inhibition of bowel motility. The administration of CGRP receptor antagonists or monoclonal antibodies to CGRP has been shown36 to partially prevent postoperative gastric ileus in rats.

Endogenous opioids are released after surgery and have been suggested as a cause of postoperative ileus.37,38 Their effects on gastric emptying and intestinal smooth-muscle contraction are mediated by the μ-opioid receptor. Enkephalin is a potent δ-opioid receptor agonist that has been reported to inhibit gastric motility and increase pyloric tone in animal experiments.39,40 Corticotropin-releasing factor (CRF) is instrumental in orchestrating the stress response.41,42 A previous study by Taché et al43 has shown that the peripheral administration of CRF and CRF-related peptides induces a delay in gastric emptying and an inhibition of gastric motility similar to that seen in postoperative gastric ileus. Peripheral CRF decreases gastric emptying of a nonnutrient or nutrient meal in rats, mice, and dogs when administered intravenously. Similar effects are seen in rats and mice if the CRF or CRF-related peptides are injected intraperitoneally or subcutaneously.44,45 Furthermore, peripheral injection of a nonselective CRF receptor antagonist before laparotomy and cecal palpation completely alleviates postoperative gastric ileus assessed during the first 3 hours after surgery in rats.57,58 In humans, surgical stress has been associated with an elevation in circulating levels of CRF.32,33 The source of the CRF is unclear. The peptide is present in the adrenal medulla, and splanchnic nerves and hormonal stimulation can trigger its release.55-56 Specifically, arginine vasopressin that is released in response to surgical stress can trigger CRF release. Studies are ongoing to elucidate the mechanisms by which CRF inhibits gastric emptying.
The Role of Inflammation

In 1998, Kalff et al\textsuperscript{57} hypothesized that common surgical procedures performed on the intestine elicit activation of the macrophage network in the muscularis externa and generate leukocyte recruitment. He further proposed that this inflammatory reaction is responsible for a period of postoperative dysmotility.\textsuperscript{57} In this study, rats were exposed to varying degrees of “gentle” surgical manipulation, ranging from a midline laparotomy to “running” of the bowel. Rats that were not subjected to laparotomy or anesthesia served as age-matched controls. The results supported their hypothesis in that a progressive increase in neutrophil infiltration was seen with increasing degrees of bowel manipulation. The authors concluded that their data support the belief that an inflammatory event initiated by abdominal surgical procedures is associated with postoperative ileus. However, they also conceded that extra-abdominal, surgically induced postoperative ileus is caused by another mechanism.

Schwarz et al\textsuperscript{59} found an induction of cyclooxygenase 2 (COX-2) messenger RNA and protein in resident macrophages and a subpopulation of enteric neurons after laparotomy and intestinal manipulation in rats. The increase in COX-2 expression resulted in elevated levels of prostaglandins in the peritoneal cavity and the circulation. As a result, decreased jejunal circular muscle contractility was observed in vitro. This effect could be reversed with administration of COX-2 inhibitors. Clinicians should be cautious in applying this model to humans. Although in rats the small intestine is said to serve as a good model for postoperative ileus, the same does not hold true for humans. It would be worthwhile to investigate the effects of COX-2 inhibition on postoperative gastric and colonic motility.

ANESTHESIA

All types of anesthesia have an effect on bowel motility.\textsuperscript{59} Anesthetic agents exert their strongest effects on the region of the bowel that depends most on neural integration. Most notably, the large intestine is devoid of intercellular gap junctions, which makes the colon more susceptible to the inhibitory actions of anesthetics.\textsuperscript{2}

Delayed gastric emptying is observed after exposure to anesthesia. Atropine, halothane, and enflurane all decrease gastric emptying. The consequences of delayed gastric emptying are possible aspiration, increased risk of postoperative nausea and vomiting, and delayed absorption of medications.\textsuperscript{60-62}

In theory, epidurals with local anesthetics can block afferent and efferent inhibitory reflexes, increase splanchnic blood flow, and have anti-inflammatory effects.\textsuperscript{56,69} Epidural anesthetics have the added benefit of blocking the afferent stimuli that trigger the endocrine metabolic stress response to surgery and thus inhibit the catabolic activity of hormones released during this process.\textsuperscript{69} In most studies,\textsuperscript{60-62} thoracic epidurals with bupivacaine hydrochloride significantly reduced ileus vs systemic opioid therapy in patients undergoing abdominal surgical procedures. In one of the statistically nonsignificant studies,\textsuperscript{59} an epidural anesthesia of 24-hours’ duration was used as opposed to that of 48 to 72 hours’ duration, as used in other studies. At least 4 studies\textsuperscript{67,72,74,75} have compared epidural bupivacaine with epidural opioid, and 3 of these studies demonstrated a significant reduction in the duration of postoperative ileus in the epidural bupivacaine group compared with the epidural opioid group. Of the few prospective studies\textsuperscript{72,74,76} comparing the effects of epidural bupivacaine and combined epidural bupivacaine and morphine on recovery from postoperative ileus, epidural bupivacaine alone seems to be superior without significantly adversely affecting pain relief. The location of the epidural is important; low-thoracic and lumbar epidural administration has not been shown\textsuperscript{64,72,73,77,78} to have beneficial effects on postoperative ileus.

POSTOPERATIVE NARCOTIC ANALGESIA

Opioids have an inhibitory effect on gastric motility and also increase tone in the antrum and the first portion of the duodenum in healthy individuals.\textsuperscript{79} The effects of opiates on the small intestine are slightly more complicated. Morphine sulfate has biphasic properties in humans: (1) initial effects on motility are stimulatory via activation of MMC phase III, and (2) this stimulation is followed by atony, which is responsible for the slowing of gastrointestinal transit.\textsuperscript{79,80} Morphine increases the tone and amplitude of nonpropulsive contractions and decreases propulsive waves in the colon. The additive effect of these actions is to decrease colonic motility.\textsuperscript{79}

However, treatment with the morphine receptor antagonist naloxone hydrochloride has proven ineffective in the treatment of postoperative ileus.\textsuperscript{2} New μ-opioid receptor antagonists are being developed and may have the potential to alleviate opiate-related adverse effects. Methylnaltrexone bromide, a quaternary derivative of naloxone, is one such drug. It is poorly lipid soluble and therefore does not cross the blood-brain barrier, but it can inhibit the negative effects of opioids on the gut. As a result, it does not antagonize the central analgesic effects of morphine or initiate opioid withdrawal.\textsuperscript{81} Another drug being investigated is the μ-opioid receptor antagonist ADL-8-2698. Administration of 6 mg of this drug shortened the median time to passage of first flatus, the median time to the first bowel movement, and the length of hospital stay in a study\textsuperscript{82} of 79 patients, of which 15 underwent partial colectomy and 63 underwent total abdominal hysterectomy. Other experimental studies\textsuperscript{37} indicate that opioid agonists working at the κ receptor may be beneficial by serving as an analgesic and decreasing postoperative ileus. Questions remain about the role of these agents in patients not treated with opioids for postoperative pain and about whether the beneficial effects of these agents are seen in patients undergoing other surgical procedures.

TREATMENTS

Nasogastric Intubation

For many years, the nasogastric tube has been the mainstay of treatment; however, recent studies have questioned its routine use. These randomized clinical stud-
ies\cite{63,64} conclude that nasogastric decompression does not shorten time to first bowel movement or decrease time to adequate oral intake. Furthermore, these studies\cite{63,64} report that inappropriate use may contribute to postoperative complications such as fever, pneumonia, and atelectasis. Although these studies do not recommend routine use of nasogastric intubation, the clinician may have selected cases in which the patient benefits from symptomatic relief.

**Electrical Stimulation**

Given the previous descriptions of abnormal gastrointestinal electrical activity, efforts have been made to use electrical stimulation as a corrective measure. An attempt has been made to apply electrical stimulation directly to the bowel wall in dogs, but this procedure was not successful.\cite{65} Other studies show that using gastrointestinal pacing in humans is largely ineffective.\cite{2}

**Early Postoperative Feeding**

Early postoperative enteral feeding via oral or nasoenteric administration has been suggested as a way to decrease the duration of postoperative ileus. The logic behind early enteral feeding is that food intake can (1) stimulate a reflex that produces coordinated propulsive activity and (2) elicit the secretion of gastrointestinal hormones, causing an overall positive effect on bowel motility.\cite{66} The role of early postoperative enteral feeding remains unclear because some studies support and others refute its benefit on shortening postoperative ileus.\cite{87,91}

**Laparoscopic Procedures**

Laparoscopic procedures offer the theoretical advantage of decreased tissue trauma compared with open procedures. This decrease in tissue trauma may lead to faster recovery of postoperative bowel function. Recently, Leung et al\cite{97} found lower levels of cytokines (interleukin 1β and interleukin 6) and C-reactive protein in patients undergoing laparoscopic colon resection compared with those who had open procedures. Animal studies and clinical trials\cite{93-95,98} have found statistically significant decreases in the duration of postoperative ileus after laparoscopic vs open procedures for colon resection. The exact mechanism responsible for this improvement in postoperative bowel motility remains elusive. Ongoing research may answer this question and give insight into the etiology of paralytic ileus after open procedures.

**Pharmacologic Agents**

Nonsteroidal anti-inflammatory drug therapy may improve postoperative ileus by allowing the clinician to reduce the amount of opioid given by 20% to 30%.\cite{77} An additional benefit on bowel motility may be derived from the anti-inflammatory properties of nonsteroidal anti-inflammatory drugs.\cite{58} In most experimental and clinical studies,\cite{99-101} giving nonsteroidal anti-inflammatory drugs resulted in decreased nausea and vomiting and improved gastrointestinal transit.

Many clinicians use laxatives as a treatment for paralytic postoperative ileus. No randomized trials evaluating the role of these agents in paralytic postoperative ileus have been conducted, to our knowledge. Conducting a MEDLINE database search for the key words “laxatives” and “postoperative ileus,” only 1 nonrandomized, unblinded trial was found. This trial consisted of 20 patients who underwent radical hysterectomy and were postoperatively treated with 30 mL of milk of magnesia by mouth twice daily and biscolic suppositories every day.\cite{99} The median time to flatus and bowel movement was 3 days. The authors observed a 50% reduction in the length of hospital stay vs a group of patients from a previously reported prospective study\cite{100} of patients undergoing radical hysterectomy (4 vs 8 days). This study should be followed by a randomized, prospective, double-blind, controlled study to determine the benefit, if any, of using laxatives.

Prostaglandins are known to affect bowel motility. The mechanism of prostaglandin E\textsubscript{2} and prostaglandin F\textsubscript{2}, although not entirely clear, seems to be the stimulation of acetylcholine release from myenteric plexus neurons.\cite{104} In humans, oral prostaglandin E\textsubscript{2} is reported to increase small intestine and colonic transit.\cite{3} Further studies are needed to determine whether there is clinical benefit from prostaglandins.

Sympathetic inhibitory input is thought to play a role in the pathogenesis of postoperative ileus.\cite{27,28} Thus, based on existing experimental evidence, human studies attempting to induce adrenergic inhibition and cholinergic activation were conducted. These studies\cite{105} did not demonstrate resolution of postoperative ileus. Studies\cite{106-107} using edrophonium chloride and bethanechol chloride have reported improvement in postoperative ileus in humans, but the adverse effects of these agents limit their use.

Acetylcholine is released from the enteric nervous system and causes increased gut wall contractility.\cite{108} Acetylcholine is degraded in the synaptic cleft by acetylcholinesterase. Neostigmine is a reversible inhibitor of acetylcholinesterase and as such has been investigated as a potential treatment for postoperative ileus. Kreis et al\cite{109} recently found that neostigmine therapy significantly increased colonic motility in the early postoperative period in patients undergoing colorectal surgery. These results are encouraging, but the “early postoperative period” is most likely a physiologic ileus, and experiments to determine the effect of neostigmine use on paralytic ileus should be performed.

Metoclopramide hydrochloride is a prokinetic agent that acts as a cholinergic agonist and a dopamine antagonist. It initiates MMC phase III activity via its antagonistic actions on dopamine. At least 6 controlled clinical trials\cite{105-111} have investigated the effect of metoclopramide therapy on patients undergoing abdominal surgical procedures. Although the end points used in the studies differed, none of them had a significant benefit in the treatment of postoperative ileus.\cite{110-116}

Erythromycin is a 13-carbon antibiotic belonging to the macrolide family. The gastrointestinal adverse effects induced by this antibiotic include abdominal cramping, nausea, vomiting, and diarrhea. Erythromycin is a motilin receptor agonist that binds to gastrointestinal
smooth-muscle membrane receptors, displacing the endogenous ligand motilin. Erythromycin therapy did not resolve postoperative ileus in patients who underwent abdominal surgery in the prospective, randomized clinical trials conducted.117,118

Cisapride is a serotonin agonist that facilitates acetylcholine release from the intrinsic plexus. At least 9 randomized clinical trials119-127 have been performed on patients treated with cisapride for postoperative ileus after undergoing various surgical procedures. However, comparison of these studies is difficult because various end points were used, patients underwent different surgical procedures, and the doses, durations, and routes were variable. In 4 studies,119-122 there was a statistically significant reduction in postoperative ileus. Although these results are encouraging, just as many studies123,126,127 reported no statistically significant effects. The questions regarding the effectiveness of cisapride will remain as it has been removed from the market for deleterious side effects.

Ceruletid is a synthetic peptide that may enhance gastrointestinal motility by acting as a cholecystokinin antagonist. A slight reduction in ileus was noted in 2 clinical placebo-controlled studies.128,129 Ceruletid therapy has the adverse effects of nausea and vomiting, which may limit its clinical effectiveness. Further investigation is needed before clinical use can be recommended.

Octreotide is an analogue of somatostatin that is known to inhibit the secretion of many gastrointestinal hormones. Cullen et al130 showed that octreotide therapy shortens the duration of ileus in the small intestine and colon of dogs. However, clinical studies are needed to prove its efficacy in humans.

Other Treatments

Gum chewing may be a simple but effective treatment for postoperative ileus. Asao et al131 conducted a randomized, prospective, controlled study on gum chewing as a method to stimulate bowel motility after laparoscopic colectomy for colorectal cancer. The patients chewed gum 3 times a day starting postoperative day 1 until oral intake. The passage of first flatus was on average 1.1 days earlier in the gum-chewing group than in controls (day 2.1 vs 3.2). The first defecation also was significantly earlier in the gum-chewing patients (postoperative day 3.1) than in controls (postoperative day 5.8). However, the length of hospital stay was not significantly different between the 2 groups (13.5 vs 14.5 days) and overall was somewhat longer than that reported in the literature. The authors hypothesized that the aid in recovery from postoperative ileus achieved by gum chewing may be related to the effects of sham feeding. Sham feeding causes vagal cholinergic stimulation of the gastrointestinal tract and elicits the release of gastrin, pancreatic polypeptide, and neurotensin, all of which affect gastrointestinal motility.132,133 Further prospective, randomized controlled studies on the effect of gum chewing on postoperative bowel motility are warranted.

Lobo et al134 wanted to determine the effects of water and salt balance on the recovery of gastrointestinal transit in patients undergoing colorectal resection for colon cancer. Their study design randomly assigned patients to receive a standard postoperative fluid regimen (3 L of water and 154 mmol of sodium per day) or a restricted fluid protocol (≤2 L of water and 77 mmol of sodium per day). The primary end points of the study included solid- and liquid-phase gastric emptying as measured by isotope radionuclide scintigraph on the fourth postoperative day, with first flatus and bowel movement serving as secondary end points. The results demonstrated significantly longer solid and liquid gastric emptying for the standard group vs the restricted fluid group (solid: 175 vs 72 minutes; liquid: 110 vs 73 minutes). Patients receiving restricted fluids passed first flatus 1 day earlier, had the first bowel movement 2.5 days earlier, and had a 3-day shorter median length of stay in the hospital than patients receiving standard fluid volumes (P=.001 for all). The authors concluded that a positive salt and water balance significant enough to add 3 kg of body weight after colonic resection delays gastrointestinal transit and prolongs hospital stay.

The Multimodal Approach to Postoperative Ileus

Of all the treatments available (Table 2), which is best? The best treatment currently available is a multimodal regimen. Basse et al135 examined a multimodal rehabilitation regimen for the treatment of postoperative ileus consisting of continuous epidural analgesia, early oral nutrition and mobilization, and cisapride and laxative treatment with magnesia. Using this regimen, the authors observed normalization of gastrointestinal transit time within 48 hours of colonic resection compared with matched controls. Gastrointestinal transit time was assessed by an indium In 111 pentetate scintigraphic method. The relative contribution of each modality is unknown. This particular approach is less than ideal, given that cisapride is no longer available. Also, ambulation has not been shown to improve postoperative bowel motility, although it is beneficial to patients for other reasons.136

Another study137 supporting the multimodal approach was conducted on patients undergoing segmental colectomy. The authors used a regimen that included thoracic epidural anesthesia for 48 hours, omission of a nasogastric tube, 1 L of fluid orally on the day of surgery, mobilization within 8 hours of surgery, use of milk of magnesia, and an alteration in the incision (curved or transverse) to minimize pain and pulmonary dysfunction. Ninety-five of 100 patients evaluated defecated in 48 to 72 hours.

SUMMARY

Paralytic postoperative ileus continues to be a significant clinical problem. The etiology of this process can best be described as multifactorial. These factors act simultaneously or at various times during the development of postoperative ileus. The mechanisms involved in paralytic postoperative ileus include inhibitory sympathetic input; release of hormones, neurotransmitters, and other mediators; an inflammatory reaction; and the effects of analgesics. Experimental studies continue to elucidate the roles and mechanisms of action of all of these factors. Numerous methods have been used in an attempt to alleviate postoperative ileus in the clinical setting, without much suc-
Table 2. Treatments for Postoperative Ileus

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Benefits</th>
<th>Drawbacks</th>
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<tbody>
<tr>
<td>Nasogastric tube</td>
<td>• Possible relief of vomiting and bloating</td>
<td>• Do not shorten duration of ileus</td>
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<tr>
<td>Early postoperative feeding</td>
<td>• Stimulates reflex for propulsive bowel motility</td>
<td>• May contribute to fever and atelectasis</td>
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<tr>
<td>Laparoscopic procedures</td>
<td>• Earlier hospital discharge</td>
<td>• Data not conclusive</td>
</tr>
<tr>
<td>Local epidural anesthetic/analgescs</td>
<td>• Earlier return of bowel function and earlier hospital discharge</td>
<td>• Patients may not tolerate feeding</td>
</tr>
<tr>
<td></td>
<td>• Reduced duration of ileus vs epidural and systemic morphine</td>
<td>• Not all surgical procedures are amenable to the laparoscopic approach</td>
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<tr>
<td></td>
<td>• Increases splanchnic blood flow</td>
<td>• Complications associated with epidural catheters</td>
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<td>Gum chewing</td>
<td>• Anti-inflammatory</td>
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<tr>
<td>Laxatives</td>
<td>• Only one small trial that was limited to laparoscopic colectomy</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>• May shorten the duration of ileus</td>
<td>• Clinical data proving effectiveness/lacking</td>
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<tr>
<td></td>
<td>• Simple and inexpensive</td>
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<tr>
<td></td>
<td>• Decreased amount of opioid needed for postoperative pain management</td>
<td>• Possible increased risk of postoperative bleeding</td>
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<tr>
<td></td>
<td>• May increase motility by acting as an anti-inflammatory</td>
<td>• Other adverse effects associated with these agents</td>
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32. Holzer P, Lippe IT. Inhibition of gastrointestinal transit due to surgical trauma or peritoneal irritation is reduced in capsaicin-treated rats. Gastroenterology. 1986;91:360-363.


