PREVENTING PARALYTIC ILEUS: CAN THE ANESTHESIOLOGIST HELP

ELIZABETH A.M. FROST*

Introduction

Gastrointestinal (GI) function is readily altered by many factors including opioid administration. In the postoperative period and in patients who require long-term or terminal care narcotic usage, which essentially may have severe side effects and prolong hospital stay and increase patient discomfort.

Patients who are at greatest risk for developing postoperative ileus especially can be identified and practitioners can use newer management modalities that are designed to hasten recovery. While there are several current management strategies, they are associated with advantages and disadvantages.Pharmacoeconomic benefits to enhanced management of ileus may be considerable.

Definitions

Ileus is defined as the functional inhibition of propulsive bowel activity, irrespective of pathologic mechanisms. It is commonly associated with long-term opioid use and results often in debilitating constipation. Postoperative ileus (POI) is the transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake. It is termed primary in the absence of any precipitating complication and secondary if some predisposing complication exists. Paralytic ileus is a form of POI that lasts longer than 5 days after surgery.

Postoperative Ileus

The average time to resolution of POI after major abdominal surgery depends in part on the section of the GI tract affected by the surgery: For the small intestine, POI usually will last about 0-24 hours; for the stomach, it will last 24-48 hours; and for the colon, 48-72 hours. However, while the incidence of POI is greatest after bowel surgery (15-20%), it also occurs after hysterectomy (4%), cholecystectomy (8.5%), appendectomy (6%) and averages 9% for other procedures for an overall incidence of about 8.5% for all procedures.
Effects

The manifestation and consequences of POI are considerable. Passage of flatus and stool are delayed. Postoperative pain and cramping are increased, as are nausea and vomiting. If oral intake is sufficiently delayed, parenteral nutrition may have to be instituted. Wound healing is poor and postoperative mobilization is slowed. The risk of other complications such as pulmonary problems and nosocomial infections increases. Patient satisfaction is reduced as hospitalization is prolonged and healthcare costs rise.

Causes

The neural regulation of the digestive tract involves both intrinsic and extrinsic control systems. Intrinsic control is mediated via the enteric nervous system within the gut wall where neurons regulate both motility and secretion. Response to local and extrinsic events occurs. Extrinsic control is governed by the autonomic nervous system, which integrates gut function into the homeostatic balance of the body.

Alterations in other mechanisms contribute to the pathogenesis of POI as do several other pathways and mediators. In fact, the pathogenesis of POI is multifactorial. Minimizing any of the adverse effects could shorten the duration of POI and reduce morbidity (Fig. 1).

For example, gut manipulation results in the production of inflammatory mediators such as nitric oxide and vasoactive intestinal peptide. Macrophage and neutrophil infiltration can occur. Both endogenous opioids (produced by pain) and exogenous opioids (given to relieve pain) reduce propulsive activity. The autonomic nervous system stimulates sympathetic inhibitory pathways. The enteric nervous system releases substance P. General anesthesia may also inhibit gut function.

Opioids have a profound effect on the GI tract. Endogenous opioids are released as part of the stress response. Exogenous opioids are the most commonly used analgesics today. Both types of opioids activate the same receptor sites and decrease motility, secretion and the transport of fluids and electrolytes. As opioids inhibit peristaltic activity, gastric emptying and gut transit times are reduced and POI may be precipitated.

Management Strategies

Traditional strategies for management of POI have emphasized prevention and supportive care. Prevention revolves around anesthetic choice, surgical technique, use of opioid-sparing analgesia, early feeding and preoperative psychological preparation. Supportive care involves placement of a nasogastric tube, mobilization, fluid restriction and administration of prokinetic agents (Table 1).

Table 1

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<td>Epidural vs. general anesthesia</td>
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**Anesthetic Choice**

All agents used for induction and maintenance of general anesthesia may depress gastric motility. Reduced ileus is a significant benefit of epidural analgesia vs general anesthesia and opioid use\(^3\). Indeed, GI function may return 2-3 days earlier.

Thoracic analgesia has been advocated as a means to reduce postoperative pain over intravenous opioid use\(^3\). Mechanisms by which this technique may promote GI activity include blockade of nociceptive afferent nerves and thoracolumbar sympathetic efferent nerve, unopposed parasympathetic efferent nerves, a reduced need for parenteral narcotics, increased GI blood flow and a systemic absorption of local anesthetic\(^4\). However, not all procedures and/or patients are amenable to regional techniques, whether for the surgical procedure or for postoperative pain management.

**Surgical Technique**

A meta-analysis of randomized clinical trials up to 2002, reviewed 2,512 cases in 12 trials. Relative improvements with laparoscopic techniques over open procedures for colorectal resection showed significant decrease in time to passage of flatus (34%), pain at 6 hours and 3 days (35% and 63%) and narcotic use (37%) as well as earlier toleration of diet (24%)\(^5\).

A less invasive surgical technique reduces the activation of inhibitory reflexes and local inflammation\(^6\). As bowel manipulation is minimized, the histogram count of infiltrating polymorphonuclear lymphocytes is significantly reduced.

**Opioid-Sparing Analgesia**

The use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief may improve POI by reducing the need for opioids by 20-30%\(^7\).

An additional positive effect may be related to an anti-inflammatory effect on bowel motility. In several studies, administration of ketorolac has been shown to allow faster resolution of POI and decreased nausea and vomiting and improved GI transit\(^8\). Potential side effects related to coagulation problems may make these agents relatively contraindicated in some surgeries. Ketorolac 30 mg is equivalent to morphine 10 mg or Demerol 100 mg.

**Early Feeding**

Several randomized clinical trials indicated that early feeding is beneficial, putting into question the common practice of withholding any intake until the resolution of POI\(^10\). However, some studies show equivocal results. Nevertheless, many surgeons recommend that chewing gum during the perioperative period will decrease the duration of POI. In theory, early feeding should stimulate GI motility by eliciting a reflex response and stimulation of hormonal factors. The technique appears safe and is generally well tolerated except in patients who are actively vomiting.

**Preoperative Psychological Preparation**

Many surgeons have claimed that POI may be reduced or eliminated by advising patients that they will not have any difficulties. The mechanism by which suggestion would work is unknown. One study found positive benefit in decreasing time to flatus and hospital discharge\(^11\). However, results are not reliable.

**Placement of a Nasogastric Tube**

Placement of a nasogastric (NG) tube should decompress the stomach and small bowel. While this may relieve the symptoms of POI, there is no evidence that it will decrease the duration.

A meta-analysis of 33 randomized trials (5240 patients) compared routine NG tube use at the end of surgery (2628 patients) with selective or no NG tube use (2612 patients). Patients who had no NG tube placement had an earlier return of bowel function (p<0.00001), and a decrease in pulmonary complications (p = 0.1)\(^12\). Vomiting favored NG tube placement which improved patient comfort. The study concluded that routine NG tube placement achieved none of the intended goals and should be replaced by selective use, such as when a patient is actively vomiting.

**Early Mobilization**

Early mobilization – getting patients out of bed and walking – may exert a mechanical stimulation of intestinal function. However, the evidence does
Fluid Restriction

Several studies have shown that restricting intravenous fluids may be beneficial. Lobo et al compared the standard administration of >31 water with 154 mmol sodium per day and restricted, <21 water and 77 mmol sodium intake, after hemicolecctomy. There were significantly more complications in the standard group. Both solid and liquid phase emptying times were significantly reduced in the study group. A recent review emphasizes the need for fluid restriction noting that failure to do so intraoperatively is associated with pneumonia, cardiac complications, postoperative blindness, coagulopathies, and increased cutaneous edema among many other problems.

Intravenous crystalloids remain in the intravascular space for very short periods, redistributing quickly to soft and damaged tissue and dependent areas such as the gut. Edema in the gut wall increases the inflammatory response and retards forward movement.

Prokinetic Agents

Use of dopamine antagonist and cholinergic agonist agents such as metoclopramide should theoretically improve gut function. However, most randomized clinical trials (RCT) suggest no prophylactic or therapeutic benefit. Indeed, side effects of metoclopramide occurred in 15-20% of patients and included drowsiness, dystonic reactions and agitation, especially in younger patients. Cisapride, a serotonin receptor agonist is possibly effective but has been withdrawn from the Unites States market because of cardiovascular side effects. Erythromycin is a motilin agonist and again, two RCTs suggest no significant change in the duration of POI.

Newer Approaches

The use of laparoscopic techniques, regional anesthesia and NSAIDS’s, selective NG placement, early ambulation and fluid restriction are referred to as “fast-tracking”.

While several RCTs have shown that fast-tracking reduces the length of hospital stay and the duration of bowel dysfunction compared to traditional care, the problem of POI remains indication that additional therapies might improve the quality of care and patient satisfaction.

Most surgical and terminal-care patients require opioids for pain management. Opioids inhibit propulsive motility and secretion, effects mediated primarily by μ opioid receptor sites in the bowel. Both naloxone and naltrexone reduce bowel dysfunction but reverse analgesia. Naloxone is a competitive μ-opioid receptor antagonist, which readily crosses the blood-brain barrier when given intravenously. It reverses the centrally mediated effects of opioids and may precipitate opioid withdrawal. There are no current data to show benefit in POI.

Ideally, POI therapy would be a peripheral receptor antagonist that reverses GI effects without compromising analgesia (Fig. 2).

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Fig. 2

Opioid receptors are in both the gut and the brain. Antagonists must not cross the blood brain barrier if pain relief is to be maintained.

The US Food and Drug Administration has recently approved two drugs that do this: methylnaltrexone and alvimopan (Table 2).

Both agents are peripherally acting μ opioid receptor antagonists. Neither crosses the blood-brain barrier, and both preserve pain relief. Time to recovery of GI function was shown to be significantly decreased with both drugs in multiple trials.

Need for reinsertion of an NG tube postoperatively
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Alvimopan Approved for Short-Term Use

Alvimopan (Entereg®, Adolor/GlaxoSmithKline) was approved by the FDA in May 2008 to accelerate restoration of normal bowel function after bowel-resection surgery. The recommended dose is one 12 mg capsule given 30 minutes to 5 hours prior to surgery, followed by a 12 mg capsule twice daily for up to 7 days but not to exceed 15 doses. The drug is available for hospital use only with a Risk Evaluation and Mitigation Strategy (REMS) and EASE program (Entereg® Access Support and Education). Hospitals must complete a registration process. The drug is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking alvimopan. The program is designed to maintain benefits associated with short-term use only.

was reduced by 50% with both alvimopan 6 mg and 12mg. Serious adverse events were reduced from 6.7% to 1.8%.

Prolonged hospital stay with alvimopan decreased from 13.7% to 7% and readmission was also reduced from 11.7% to 7.5%. The time to toleration of solid foods after methylnaltrexone was 100 hours against 125 hours in the placebo group. Similar figures were obtained for alvimopan. Reduction in time to first bowel movement averaged 25 hours with methylnaltrexone. In several trials using alvimopan, time reduction was about 50% from control.

In all the studies of both drugs, the time to discharge-eligibility was decreased by about 1 day over control. Pooled data of any morbidity for alvimopan showed a decrease from 16% to 8%.

However, based on one study, concerns were raised about cardiovascular adverse events with alvimopan. Reviewing 2610 patients in 8 trials the incidence of myocardial infarction was 0.5% which matched the control finding of 0.51%. But one study of 538 patients indicated 7 cases of myocardial infarction against 0 in the control group. After this data became available, the FDA reviewed a 12-month study of alvimopan in patients treated with opioids for chronic pain. In the study, there were more reports of myocardial infarction in patient treated with the low dose of alvimopam, and imbalance not observed in other studies of patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. The conclusion was that a causal relation between alvimopan and myocardial infarction has not been established.

Regarding other potential side effects, patients with severe hepatic impairment may have a potential for 10-fold higher plasma levels, although no studies are available in this patient population. It is not recommended for patients with end-stage renal disease.

While teratogenic effects in humans are unknown, reproduction studies in pregnant rats and rabbits at many multiples of human dosages have not revealed any evidence of impaired fertility or fetal harm. However, alvimopan and its metabolite have been detected in the milk of lactating rats.

### Table 2

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<th>Alvimopan (Entereg)</th>
<th>Methylnaltrexone (Relistor)</th>
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<tr>
<td>Side effects</td>
<td>low blood-calcium levels, anemia and gastrointestinal problems, including constipation, dyspepsia (heartburn) and flatulence (excess bowel gas)</td>
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**Methylnaltrexone Approved for Palliative Care**

Methylnaltrexone (Relistor®, Wyeth/Progenics), the other peripherally acting µ opioid antagonism was approved by the FDA in April 2008 for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. It is administered as a subcutaneous injection. The recommended starting schedule is 0.15 mg/kg on alternate days, not to exceed 1 dose in a 24 hours period20. The drug is packaged in a vial as 12 mg/0.6 ml. It should not be given if there is any mechanical bowel obstruction and has not been studied in patients with peritoneal catheters or in the pediatric population. The most common side effects include abdominal pain, flatulence and nausea.

**Chronic Illness and Methylnaltrexone**

Thomas et al22 enrolled a total of 133 patients who had received opioids for 2 or more weeks and who had received stable doses of opioids and laxatives for 3 or more days without relief of opioid-induced constipation.

The patients were randomly assigned to receive subcutaneous methylnaltrexone (at a dose of 0.15 mg per kilogram of body weight) or placebo every other day for 2 weeks. Co-primary outcomes were laxation (defecation) within 4 hours after the first dose of the study drug and laxation within 4 hours after two or more of the first four doses. Patients who completed this phase were eligible to enter a 3-month, open-label extension trial.

They found in the methylnaltrexone group that 48% of patients had laxation within 4 hours after the first study dose, as compared with 15% in the placebo group, and 52% had laxation without the use of a rescue laxative within 4 hours after two or more of the first four doses, as compared with 8% in the placebo group (p < 0.001 for both comparisons).

The response rate remained consistent throughout the extension trial. The median time to laxation was significantly shorter in the methylnaltrexone group than in the placebo group. Evidence of withdrawal mediated by central nervous system opioid receptors or changes in pain scores was not observed. Abdominal pain and flatulence were the most common adverse events.

The authors concluded that subcutaneous methylnaltrexone rapidly induced laxation in patients with advanced illness and opioid-induced constipation. Treatment did not appear to affect central analgesia or precipitate opioid withdrawal.

**Economic Considerations with POI**

POI is the most common reason for delayed discharge after abdominal surgery. Increased health-care costs in the United States related to this complication are estimated to reach $1 billion annually because of increased need for supplies, nursing care and laboratory testing. The possible benefits of adding a peripherally acting µ opioid receptor antagonist such as alvimopan to a fast tracking model are shortened hospital stay, reduced use of resources, fewer complications, fewer readmissions and improved patient satisfaction18.

**Conclusion**

POI affects between 4-20% of abdominal surgical patients. Constipation is a major problem for the terminally ill who are maintained on opioids. In both situations there is a detrimental effect on clinical outcomes and cost of care. Accelerating recovery and even maintaining GI function enhances patient comfort and improves outcome. Treatment options include both pharmacologic and non pharmacologic approaches. The anesthesiologist can make an important contribution to improved care.
References

20. FDA Web site: www.FDA.gov/ohrms/dockets/ac/cder08.html#gdac