Postoperative Ileus-Related Morbidity Profile in Patients Treated with Alvimopan after Bowel Resection

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BACKGROUND: Postoperative ileus (POI), an interruption of coordinated bowel motility after operation, is exacerbated by opioids used to manage pain. Alvimopan, a peripherally acting μ-opioid receptor antagonist, accelerated gastrointestinal (GI) recovery after bowel resection in randomized, double-blind, placebo-controlled, multicenter phase III POI trials. The effect of alvimopan on POI-related morbidity for patients who underwent bowel resection was evaluated in a post-hoc analysis.

STUDY DESIGN: Incidence of POI-related postoperative morbidity (postoperative nasogastric tube insertion or POI-related prolonged hospital stay or readmission) was analyzed in four North American trials for placebo or alvimopan 12 mg administered 30 minutes or more preoperatively and twice daily postoperatively until hospital discharge (7 or fewer postoperative days). GI-related adverse events and opioid consumption were summarized for each treatment. Estimations of odds ratios of alvimopan to placebo and number needed to treat (NNT) to prevent one patient from experiencing an event of POI-related morbidity were derived from the analysis.

RESULTS: Patients receiving alvimopan 12 mg were less likely to experience POI-related morbidity than patients receiving placebo (odds ratio = 0.44, $p < 0.001$). Fewer patients receiving alvimopan (alvimopan, 7.6%; placebo, 15.8%; NNT = 12) experienced POI-related morbidity. There was a lower incidence of postoperative nasogastric tube insertion, and other GI-related adverse events on postoperative days 3 to 6 in the alvimopan group than the placebo group. Opioid consumption was comparable between groups.

CONCLUSIONS: Alvimopan 12 mg was associated with reduced POI-related morbidity compared with placebo, without compromising opioid-based analgesia in patients undergoing bowel resection. Relatively low NNTs are clinically meaningful and reinforce the potential benefits of alvimopan for the patient and health care system. (J Am Coll Surg 2007;204:609–616. © 2007 by the American College of Surgeons)

All patients undergoing major abdominal operation are at risk for postoperative ileus (POI), a transient cessation of coordinated bowel motility after surgical intervention and most common after abdominal or pelvic operations.[1-3] Signs and symptoms associated with POI include inability to tolerate oral intake, delayed passage of flatus and stool, pain and abdominal distention, nausea, vomiting, lack of bowel sounds, and accumulation of gas and fluids in the bowel.[1,4] Although the cause of POI is complex, it is primarily associated with surgical trauma and manipulation of the bowel and opioids used for intra- and postoperative analgesia.[5-12] Opioid-based analgesics are widely used and are considered the standard of care for postoperative pain management.[8,13,14] Although opioids mediate analgesia by binding to receptors in the central nervous system, they also exacerbate POI.[8,14] Endogenous opioids are secreted

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Abbreviations and Acronyms

GI = gastrointestinal
LOS = length of stay
MSE = morphine sulfate equivalent
NGT = nasogastric tube
NNT = number needed to treat
POI = postoperative ileus

within the gastrointestinal (GI) tract in response to operations and can also contribute to the pathogenesis of POI by activating μ-opioid receptors within the enteric nervous system.[12,14,15]

POI can contribute to morbidity for patients recovering from operation and is associated with reduced patient satisfaction and increased risk of other postoperative complications, including pulmonary complications and nosocomial infections.[16-18] POI is one of the most common causes of delayed hospital discharge in patients undergoing laparotomy.[19,20] Because of POI-related increases in hospital length of stay (LOS), the economic cost of POI for hospitals, patients, and providers is estimated to approach $1 billion annually.[9,20,21] Indeed, in a retrospective chart review, prolonged POI was found to be associated with increased costs of $4,512 and $12,416 per patient undergoing hysterectomy and hemicolectomy, respectively.[22]

Although there are currently no pharmacologic treatments approved by the US Food and Drug Administration for the management of POI, peripherally acting μ-opioid receptor antagonists are under investigation.[23-27] Alvimopan, an oral peripherally acting μ-opioid receptor antagonist, accelerated GI recovery and reduced hospital LOS after laparotomy in randomized, multicenter, double-blind, placebo-controlled, phase III efficacy trials in North America.[23-26] Subsequent analysis revealed that the alvimopan benefit was greatest among patients who underwent bowel resection in these trials.[28,29] Analgesia was maintained, and alvimopan was well-tolerated and associated with a decreased rate of GI adverse events, including nausea, vomiting, abdominal distention, constipation, and POI.[23-25] Patients who received alvimopan had reduced rates of overall postoperative morbidity compared with patients who received placebo.[23-25] Postoperative morbidity related to POI was prospectively evaluated in only one of the North American phase III studies.[26] The objective of the current pooled, post-hoc analysis was to examine the POI-related postoperative morbidity of all patients who underwent bowel resection in North American phase III efficacy trials of alvimopan.

METHODS

Patients

Inclusion and exclusion criteria have been reported previously.[23-25] Briefly, eligible patients were 18 years of age or older, undergoing bowel resection with primary anastomosis, and scheduled for postoperative pain management with IV opioid-based patient-controlled analgesia. Patients with chronic opioid use within 1 week of operation were excluded. All patients provided written informed consent. All studies were approved by individual institutional review boards and followed the guidelines of the Declaration of Helsinki.

Study design and treatment

This was a pooled analysis of data from four randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase III efficacy trials (studies 14CL302, 14CL308, 14CL313, and 14CL314).[23-26] All patients were managed by a standardized, accelerated postoperative care pathway to facilitate GI recovery. This pathway included removal of the nasogastric tube (NGT), if used, by noon on postoperative day 1, encouragement of ambulation and offering liquids on postoperative day 1, and offering solid food on postoperative day 2. Alvimopan (6 mg or 12 mg) or placebo was administered 30 minutes to 5 hours before operation and then twice daily thereafter until hospital discharge or for a maximum of 7 postoperative days. Patients in studies 14CL302, 14CL308, and 14CL313 received a preoperative dose of the study drug (placebo, alvimopan 6 mg, or alvimopan 12 mg) 2 hours or less before operation, and patients in study 14CL314 received a preoperative dose of the study drug (placebo or alvimopan 12 mg) 30 to 90 minutes before operation.

Assessments

For the purpose of this pooled post-hoc analysis, overall POI-related morbidity, a composite end point, was defined as postoperative NGT insertion or experiencing complications of POI. Complications of POI included serious adverse events reports of POI, paralytic ileus, or small intestinal obstruction resulting in prolonged hospital stay or readmission 7 or fewer days after initial hospital discharge as determined by the