Alvimopan provides rapid gastrointestinal recovery without nasogastric tube decompression after radical cystectomy and urinary diversion

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Introduction: Radical cystectomy is associated with significant morbidity, with rates of gastrointestinal complications as high as 30%. Alvimopan is a mu opioid receptor antagonist that has been shown in randomized control trials to accelerate gastrointestinal recovery in patients undergoing bowel resection with primary anastamosis. We report our experience with gastrointestinal recovery for patients undergoing cystectomy with urinary diversion treated with alvimopan. Materials and methods: Between January 2008 and August 2011, 50 consecutive patients underwent radical cystectomy with urinary diversion at our institution. The first 27 patients in our study did not receive alvimopan preoperatively. The latter 23 patients received perioperative alvimopan and were without postoperative nasogastric

decompression. Return of bowel function, initiation of diet, and gastrointestinal complications were evaluated. **Results:** Times to first flatus (3.1 versus 5.6 days, p < 0.001,95% CI 1.66-3.26) and bowel movement (3.8 versus 6.0 *days*, p < 0.001, 95% CI 1.35-2.99) were significantly shorter in those patients who received alvimopan. Additionally, the initiation of clear liquid diet (4.1 versus 6.3 days, p < 0.001, 95% CI 1.20-3.12), regular diet (5.7 versus 7.3 days, p = 0.023, 95% CI 0.57-2.63) and hospital *discharge* (7.4 *versus* 9.5 *days*, *p* = 0.04, 95% CI 0.03-4.21) were accelerated in the alvimopan cohort. There were no incidences of prolonged ileus in patients who received perioperative alvimopan (0% versus 25.9%, p = 0.012). Conclusion: In our experience, the use of alvimopan perioperatively significantly accelerates the rate of gastrointestinal recovery and hospital discharge, eliminates the need for nasogastric tube decompression, and reduces the incidence of postoperative ileus in patients following radical cystectomy and urinary diversion.

Key Words: cystectomy, ileus, alvimopan, morbidity, complications

Introduction

Radical cystectomy, while being the gold standard treatment for muscle invasive bladder cancer, is associated with significant morbidity and mortality. Gastrointestinal complications are the most common cause of postoperative morbidity and lead to extended length of hospitalization. They account for significant

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Address correspondence to Dr. Anup A. Vora, Department of Urology, Washington Hospital Center/Georgetown University, 3401 38th St NW, Suite 915, Washington, DC 20016 USA clinical and economic burden with a reported annual hospital cost of \$1.46 billion.¹ Although overall complication rates with this surgery have decreased over the past 20 years, the rates of gastrointestinal complications remain as high as 30%.²⁻⁴

Numerous prospective trials, in both general surgery and urologic literature, have shown benefits from decreased nasogastric decompression and the utilization of accelerated postoperative pathways.¹ However, even with these interventions, rates of gastrointestinal morbidity are reported as high as 25%.⁵⁹ This can be largely attributable to opioids, the current standard for postoperative pain management, which bind to mu opioid receptors of the gut and

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delay recovery of the gastrointestinal tract. Opioid receptors (mu, delta, kappa) are present in both the central and the enteric nervous system, and its effect to slow intestinal transit comes from stimulation in the myenteric and submucosal bowel plexus.^{10,11}

Over the past decade, extensive research has been performed to identify an agent to inhibit the gastrointestinal effect of opioids while not affecting analgesia, leading to the development of alvimopan.^{12,13} Several randomized control trials in general surgery have shown that alvimopan accelerates gastrointestinal recovery in patients undergoing bowel resection with primary anastamosis.¹⁴⁻¹⁶ With a lack of urologic literature regarding the utilization of this medication, we report the first experience with patients undergoing cystectomy and urinary diversion treated with alvimopan, and our rates of gastrointestinal morbidity.

Materials and methods

Between January 2008 and August 2011, 50 consecutive patients underwent radical cystectomy with urinary diversion at The Washington Hospital Center performed by a single surgeon. Thirty nine patients received neoadjuvant chemotherapy. All patients were seen by a multidisciplinary team composed of urology, medical and radiation oncology, stoma and palliative care services. Patients were counselled on both continent and conduit urinary diversions regarding quality of life, technical feasibility, and potential oncologic outcomes with the ultimate decision based on patient wishes.

Preoperative care

All patients received a clear liquid diet and a mechanical bowel prep with polyethylene glycol (Go-Lytely, Braintree, MA, USA) the day before surgery. The first 27 patients in our study did not receive alvimopan preoperatively, while the latter 23 patients received their first dose of alvimopan (12 mg PO) at least 1 hour prior to the induction of anesthesia. Patients were excluded from receiving alvimopan if they had received opioids within 1 week of surgery or had a previous history of multiple bowel resections.

Surgical procedure

Following induction of anesthesia, all patients received nasogastric tube decompression. Standard radical cystectomy and bilateral pelvic lymphadenectomy was performed. Terminal ileum was used in all patients for both continent and non-continent diversions. After isolating the chosen segment of ileum, bowel continuity was restored using gastrointestinal stapling devices.

Postoperative management

In patients who received alvimopan, the nasogastric tube was removed at time of extubation. They were then started on postoperative alvimopan dosing of 12 mg PO bid until the initiation of a diet or a maximum of 15 doses was achieved. Patients who did not receive alvimopan had selective removal of their nasogastric tube based on bowel sounds, flatus and clinical status. Opioid patient-controlled anesthesia pumps or an epidural infusion with fentanyl was used for postoperative pain management. Transition to oral opioids was performed after successful initiation of diet.

Clear liquid diet was initiated after first flatus and was advanced to a regular diet typically within 24 hours after toleration of clear liquids (no nausea or emesis). A nasogastric tube was reinserted in patients with prolonged ileus or bowel obstruction, and total parenteral nutrition was initiated on postoperative day 7 if bowel complications persisted. Postoperative ileus was defined as the persistent absence of flatus and bowel movement on postoperative day 7 with associated radiographic findings on abdominal x-ray.

Statistical analysis

Data was collected retrospectively into an institutional review board approved database. Preoperative variables, including age, gender, body mass index, were compared between the two groups. Return of bowel function, advancement of diet, length of nasogastric decompression, duration of hospital stay, and gastrointestinal complications were used as study endpoints. All statistical analyses were performed using SPSS statistical software (IBM, Armonk, NY, USA) and groups were compared using a two-tailed paired t-test and a multivariate analysis of variation.

Results

The two groups had comparable preoperative demographics (age, sex, smoking status and body mass index) and comorbidities with no variable of statistical significance on multivariate analysis, Table 1. In the group receiving alvimopan, times to first flatus (3.1 versus 5.6 days, p < 0.001, 95% CI 1.66-3.26) and bowel movement (3.8 versus 6.0 days, p < 0.001, 95% CI 1.35-2.99) were significantly shorter than those who did not receive it. Additionally, the initiation of clear liquid diet (4.1 versus 6.3 days, p < 0.001, 95% CI 1.20 - 3.12), regular diet (5.7 vs 7.3 days, p=0.023, 95% CI 0.57 - 2.63) and hospital discharge (7.4 vs 9.5 days, p = 0.04, 95% CI 0.03-4.21) were accelerated in the alvimopan cohort. Patients who were not given alvimopan were maintained with nasogastric tube

	Alvimopan	Control	p value
Age	68.4	69.6	0.669
% Male	65.2 (15/23)	81.4 (22/27)	0.198
% Smoking history	86.9 (20/23)	88.9 (24/27)	0.838
Body mass index	28.4	29.8	0.682
% Hypertension	69.5 (16/23)	66.7 (18/27)	0.831
% Diabetes mellitus	30.4 (7/23)	33.3 (9/27)	0.830
% Coronary artery disease	39.1 (9/23)	33.3 (9/27)	0.678
% Hyperlipidemia	56.5 (13/23)	48.1 (13/27)	0.564
% Gastroesophageal reflux disease	17.3 (4/23)	11.1 (3/27)	0.533
% Ethanol abuse	08.7 (2/23)	0.0 (0/27)	0.123
% Atrial fibrillation	04.3 (1/23)	0.0 (0/27)	0.283
% Neoadjuvant chemotherapy	78.3 (18/23)	77.8 (21/27)	0.96

TABLE 1. Perioperative patient demographics

decompression for a mean of 3.9 days while those who received it were without a nasogastric tube for their entire postoperative course, Table 2.

There were no incidences of prolonged ileus and no requirements for total parenteral nutrition in patients pretreated with alvimopan. However, one quarter of the patients in the group not receiving alvimopan required nasogastric tube decompression and initiaton of parenteral nutrition for prolonged ileus (0% versus 25.9%, p = 0.012). The rate of non-gastrointestinal complication 26.1% versus 25.9%, p = 0.989) was also not statistically significant between the two groups, Table 3.

TABLE 2. Perioperative patient outcomes. All lengths are in days

	Alvimopan	Control	p value
Estimated blood loss (cc)	585.2	576.7	0.839
Operative time (min)	351.5	347.5	0.701
% Epidural PCA	26.1 (6/23)	25.9 (7/27)	0.701
% Ileal conduit urinary diversion	86.9 (20/23)	92.6 (25/27)	0.518
% Ileal neobladder	13.1 (3/23)	7.4 (2/27)	0.518
Duration of NGT	0	3.9	< 0.001
Time to flatus	3.1	5.6	< 0.001
Time to first bowel movement	3.8	6.0	< 0.001
Initiation of sips	3.3	4.8	0.014
Initiation of clear liquids	4.1	6.3	< 0.001
Initiation of regular diet	5.7	7.3	0.024
Length of hospital stay	7.4	9.5	0.047
% Requiring TPN	0	22.2 (6/27)	0.015
PCA = patient control analgesia NGT = nasogastric tube TPN = total parenteral nutrition			

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TABLE 3. Perioperative complications (%)					
	Alvimopan (n = 23)	Control (n = 27)	Clavian grade ²⁵		
Prolonged ileus/SBO (requiring NGT insertion)	0	7 (25.9)	IIIa		
Wound infection	3 (13.0)	4 (14.8)	II		
Deep vein thrombosis	0	1 (3.7)	II		
Acute alcohol withrdawal	1 (4.3)	0	II		
Wound deshiscence	1 (4.3)	1 (3.7)	IIIb		
Cardiac arrythmia	1 (4.3)	1 (3.7)	П		

Discussion

Radical cystectomy and urinary diversion are associated with serious postoperative complications with the 90 day morbidity rate reported as high as 64%. The majority of these complications usually develop early, and gastrointestinal complications are the most frequent in the postoperative period.³ The etiology of prolonged ileus after bowel reconstruction is multifactorial, and while it is inevitable that some degree of ileus will accompany any bowel resection, the duration is often exacerbated by intraoperative and postoperative narcotics used for induction and pain control.

Other agents such as metoclopramide,¹⁷ erythromycin,^{18,19} neostigmine²⁰ and propranol²¹ have also been extensively researched in the past to improve gastrointestinal outcomes after bowel reconstruction, but no single agent has shown consistent benefits. Even the use of chewing gum has been evaluated. Pruthi et al found that chewing gum was related to a shorter time to flatus and bowel movements, but patients had an identical gastrontestinal complication rate when compared to controls.²² Multimodal perioperative algorithms for patients undergoing cystectomy have also been investigated with the goal of improving the rate of gastrointestinal recovery. Strategies include the use of non-opioid analgesia, early ambulation and early nasogastric tube removal.8 Maffezzini et al reported on 71 patients who underwent a multimodal perioperative plan after radical cystectomy and found improved time to institution of a normal diet. However, when compared to their historical control group, the intolerance to oral feeding and postoperative ileus rates were similar.9

The issue of nasogastric tube decompression after urinary diversion itself has been a matter of debate and controversy. Recent perioperative tactics challenge surgical tradition with reports of consistent or improved

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gastrointestinal outcomes with early nasogastric tube removal. Park et al examined 101 patients after urinary diversion and found that early nasogastric tube removal was not correlated with increased rates of ileus.⁵ Adamakis et al recently published the first randomized prospective study to assess early nasogastric tube removal after urinary diversion. These results showed that early tube removal did not lead to ileus and was beneficial in terms of patient comfort and earlier ambulation.⁶ In addition, a meta-analysis by Cheatam et al showed that the practice of early nasogastric tube removal is associated with a significantly lower risk of pneumonia, atelectasis, and fever (n = 3964).²³

Alvimopan is a quaternary mu opioid receptor antagonist that inhibits enteric receptors while preserving central analgesia. Its chemical structure is similar to naloxone, a competitive antagonist of mu receptors and known opioid antidote, however, alvimopan does not penetrate the blood-brain barrier; thus preventing antagonism of the central receptor.¹² The drug was approved by the Federal Drug Administration in 2008 for acceleration of gastrointestinal recovery after primary bowel resection. This approval was primarily based upon three North American randomized, double-blind, placebocontrolled, parallel-group, phase III trials and a single European phase III trial which have shown alvimopan to shorten gastrointestinal convalescence and decrease incidence of postoperaive ileus after bowel resection. Delaney et al reported a pooled analysis of the phase III trials comparing 810 patients receiving alvimopan to 402 control patients with a gastrointestinal recovery endpoint (time to first toleration of solid food, time to first flatus and time to first bowel movement). Patients in the alvimopan group had significantly accelerated gastrointestinal recovery than controls (HR 1.51, p < 0.001) and a lower incidence of prolonged postoperative ileus and length of hospital stay (p < 0.001).^{15,24}

Our study represents the first of its kind applying the use of alvimopan and its anticipated clinical benefit to a cohort of urologic patients. While the etiology of postoperative ileus is complex and multifactorial (surgical manipulation, inflammatory response, release of endogenous opioid, etc.) we feel that an important contributing factor to prolonged ileus is the use of exogenous opioids given during the induction of anaesthesia and for pain control in the postoperative period. As a mu opioid receptor antagonist, alvimopan mitigates the adverse effects of opioid without compromising central based analgesia. In our review, the use of alvimopan significantly improved gastrointestinal convalescence in patients undergoing urinary diversion and radical cystectomy. The return of flatus and bowel movements (p < 0.001) and time to hospital discharge were accelerated (p = 0.047). Patients who received alvimopan were free from prolonged ileus and were able to start on a diet earlier than those who did not receive the drug.

Regarding nasogastric decompression, we feel that the absence of a postoperative nasogastric tube (alvimopan cohort) allows those patients to have a significant clinical advantage in terms of faster gastrointestinal recovery and overall comfort. While we acknowledge that in many centers postoperative nasogastric tubes are not utilized routinely, we still encourage the use of alvimopan. No patient in our study who received alvimopan postoperatively has required re-insertion of a nasogastric tube nor parenteral nutrition, while the rate of reinsertion in patients managed without nasogastric tube decompression and alvimopan has been reported to be as high as 20%.⁵⁻⁷

It is of importance to note that although patients treated with alvimopan had no gastrointestinal complications, the overall complication rate was similar to our control, Table 3. Socioeconomic factors (placement, home care, etc) of our urban population delayed hospital discharge for patients in both cohorts. We feel that these factors (non-gastrointestinal complications and placement issues) lead to the extended hospitalizations for our patients in the study when compared to milestones from other studies in the contemporary literature. Despite these limitations, we believe our study is of clinical significance to urologists who encounter and manage patients post urinary diversion with regard to gastrointestinal morbidity.

Conclusion

Urinary diversion status post radical cystectomy is associated with significant gastrointestinal morbidity. Our initial experience with alvimopan in patients undergoing radical cystectomy and urinary diversion demonstrates accelerated rates of gastrointestinal recovery and hospital discharge, elimination of the need for nasogastric tube decompression, and reduced incidence of post-operative ileus.

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EDITORIAL COMMENT

Much of the morbidity associated with radical cystectomy is related to gastrointestinal complications. Given the current need to perform a urinary diversion utilizing a segment of bowel, nearly all patients undergoing radical cystectomy require a form of bowel resection along with a primary anastomosis.

Over time, efforts have been made to shorten the time to recovery of bowel function. These include the use of streamlined postoperative pathways, avoidance of NG tube decompression, early ambulation, use of promotility agents and the conservative use of narcotics. Despite such efforts, bowel related issues continue to be a major component of prolonged hospitalizations and delayed recovery following surgery.

The investigators in this study examined the impact of alvimopan (a mu opioid receptor antagonist) on recovery of GI function following 50 consecutive radical cystectomies (the 1st 27 patients did not receive alvimopan, the final 23 patients did). This study appears to be the 1st report of utilizing alvimopan in the urologic literature. The results from this study are encouraging with an improvement in postoperative outcomes such as a reduction in the duration of hospitalization, avoidance of NGT decompression, reduction in the time to flatus and 1st BM, and earlier initiation of liquids. Furthermore, no patients receiving alvimopan required TPN or suffered GI related complications. We await the results of a recently completed a phase IV randomized trial (NCT00708201) to confirm these findings.

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