ORIGINAL ARTICLE

The Evaluation of Patient Outcomes with and without the Use of Alvimopan

Calvin Tucker, Gerard Woolyhand, John Baker

Clinical Manager, Pharmacy Services, St. Vincent's Medical Center Riverside, Jacksonville, FL, USA

ABSTRACT

Background: Alvimopan is a novel peripheral mu receptor antagonist that is indicated for preventing post-operative ileus in patients undergoing abdominal surgery or bowel resection. Alvimopan has specific administration requirements when given to patients to prevent post-operative ileus. **Methods:** A retrospective cohort of 80 patients was identified by a primary procedure of colon/rectal surgery. The primary outcome assessed was rate post-operative ileus. To control for acuity difference, the random sample of 80 patients were stratified by Charlson score using Optum One software. The patients were randomly selected reviewing patients who received or did not receive alvimopan. **Results:** The rate of post-operative ileus with alvimopan 33.3% compared to 32.5% without alvimopan was comparable (p=0.45). The 30-day readmission rate for patients receiving and not receiving alvimopan were 17.7% versus 18.5%, respectively (p=0.077). The evaluation of the random sample of 80 patients failed to demonstrate a difference post-operative length of stay (p=0.26) in time to tolerate a diet (p=0.76) and use of antiemetics (p=0.35). There was a significant difference in the use of laxatives (p=0.008) and time to first bowl movement by 1.2 days (p=0.033) outcomes were similar with regards to post-operative ileus (p=0.459) and 30-day readmission (p=0.0775) with each measure failing to achieve significance. **Conclusion:** The similar outcome profile between post-operative ileus and 30-day readmission rate do not support the use of alvimopan. Other alternatives to prevent post-operative ileus should be considered, and further explore the clinical effectiveness with alvimopan with other studies with regards to dose, administration, and surgery types.

Key words: Alvimopan, entereg, post-operative ileus, 30 day readmission, post-operative length of stay

Correspondence:
Calvin Tucker,
Clinical Manager, Pharmacy Services,
Shircliff Way Jacksonville, Florida, USA.
E-mail: Calvin.Tucker@jaxhealth.com

Access this article online

Website: www.jbclinpharm.org

Quick Response Code:

INTRODUCTION

Patients that undergo open abdominal surgery and/or bowel resection have a risk of developing post-operative ileus. A post-operative ileus is described as a transient cessation of bowel motility.[1] An ileus can present in various ways including abdominal pain, abdominal distention, nausea, vomiting, and collection of gas or fluids in the bowel. A change in bowel motility can have significant impact on patient outcomes causing discomfort, morbidity, and prolonged hospital length of stay.[1] Opioids play a role in management of post-operative patients, but they can exacerbate post-operative ileus due to their mu-opioid receptor action in the gut. The actions of opioid agents may lead to multiple effects on the gastrointestinal tract including decreased gastric motility, inhibition of small and large function, delayed oral-cecal transit time, inability to pass stool, and retention of fluids.[2]

In May 2008, the Food and Drug Administration (FDA) approved alvimopan (Entereg®) for the use to prevent post-operative ileus.[1,3] Alvimopan is only available through a program called Entereg Access Support and Education (E.A.S.E) ENTEREG Risk Evaluation and Mitigation Strategy (REMS) Program that restricts the use to enrolled hospitals. Patients being treated with alvimopan had more reports of myocardial infarctions when compared to placebo treated patients, leading to the FDA's decision to place alvimopan under REMS oversight.[1,3] Alvimopan is only available through the REMS program.

Alvimopan is a peripheral acting mu opioid receptor antagonist. The peripheral effects of alvimopan antagonize the effects of opioids on gastrointestinal motility and secretion by binding to mu opioid receptors.[3] The medication received accelerated approval by five phase III trials in North America and one phase III trial in Europe.[1,3] All the studies assessed the time to achieve resolution of post-operative ileus. Alvimopan is prescribed as a 12 mg oral dose where the first dose is to be given 30 minutes to 5 hours prior to surgery. After surgery, the maintenance dose is to begin the day after surgery as 12 mg every 12 hours for a maximum of 7 days or until discharged with the total number of 15 doses maximum.[1] The medication is not recommended in patients with severe hepatic impairment, end-stage renal disease, complete gastrointestinal obstruction, or patients who have surgery for correction of complete bowel obstruction.[3] Currently, alvimopan is to be used in the inpatient setting only to reduce post-operative ileus in patients undergoing abdominal or bowel resection. The side effect profile is comparable to placebo with regard to nausea, vomiting, gas pain, and abdominal distension except with a higher incidence of dyspepsia and acute myocardial infarction.[1,4]

Clinical trials that evaluated the use of alvimopan lead to its clinical use of preventing post-operative ileus. After its approval, various institutions have reported the effects of alvimopan with respect to return to bowel function, length of stay, and cost analysis.[5-7] We to completed a retrospective chart review stratified by Charlson score to evaluate the use of alvimopan at two of our institutions with respect to post-operative incidence of post-operative ileus.

MATERIALS AND METHODS

This study was conducted in compliance by St. Vincent's Medical Center the institutional review board. This study is a retrospective chart review of 80 patients identified. The patients were identified by isolating surgical procedures done by one colon/rectal surgeon during the period July 1, 2010 thru June 30, 2015. Data was further restricted to procedures that were done on at least five patients in the time period which at least one case received alvimopan and one case did not receive alvimopan. Optum One software was used to stratify patients based on Charlson Severity Score. Patients with Charlson scores greater than zero were excluded from further analysis. Information was reviewed through the electronic medical record (EMR) system where two groups, each with 40 patients, were evaluated; one group received no alvimopan doses compared to the other group that received at least one

Cite this article as: Tucker C, Woolyhand G, Baker J. The Evaluation of Patient Outcomes with and without the Use of Alvimopan. J Basic Clin Pharma 2017;8:259-261.

dose of alvimopan. The primary outcome was rate of post-operative ileus. Secondary outcomes consisted of 30-day readmission, length of stay, analgesic use, use of laxatives and anti-emetics, diet, and bowel movements. For patients that received alvimopan, the number of doses and duration of therapy were assessed. Exclusion criteria included pregnant and incarcerated patients.

DATA ANALYSIS

The student's t-test was used for continuous data. Mann Whitney U was utilized for ordinal and non-normally distributed continuous data. For categorical data, the chi-square test or Fisher's exact test was used as appropriate.

RESULTS

For baseline demographics of the 80 patient assessments [Table 1], there are no differences exhibited between the groups except elective surgeries. Patients that received alvimopan were more likely to have an elective surgery (95.7%) compared to patients that did not receive alvimopan (62.5%) (p<0.001). The uses of pain medications were similar between the two groups [Table 1]. The average duration of therapy for patients receiving alvimopan was 3.55 days, most patients did not receive more than 6 doses [Table 2]. The rate of post-operative ileus was seen in 33.3% of patients receiving alvimopan and 32.5% for not receiving alvimopan (p=0.45) [Table 3]. The rate 30-day readmission for patients receiving alvimopan was 7.5% compared to no readmissions for not receiving alvimopan (p=0.077). The length of stay was significantly shorter in patients that received alvimopan (5.92 days) compared to patients that didn't receive alvimopan (7.95 days) (p=0.036). The post-operative length of stay was not significantly different between the groups (5.85 vs 6.68 days, p=0.26). There was less use of laxatives in patients receiving alvimopan doses with only one patient requiring laxatives; 12 patients with no alvimopan doses required laxatives (p=0.0008) [Table 3]. Anti-emetics were used similar between both groups with 13 patients and 17 patients, respectively (p=0.356) [Table 3]. The time to first diet did not differ between the groups. Both groups received a diet approximately 2 days after surgery (p=0.767). Patients that received alvimopan had a bowel movement a day sooner compared to patients that did not receive alvimopan which showed significance (p=0.0331). Despite a shorter time for bowel movements, there was little difference in the average number of bowel movements [Table 4].

DISCUSSION

Table 1: Baseline characteristics

Baseline Characteristics	Group 1: No Alvimopan (mean, n=40)	Group 2: Alvimopan (mean, n=40)
Age (year)	65.3	62.6
Gender (n)		
Female	21	16
Male	19	24
Elective surgery (%)*	62.5	97.5
ICU stay (n)		
No	42	35
Yes	8	5
Use of opioids post-operative (n)		
Yes	34	34
No	6	6

There are multiple studies available in literature that assesses the use of alvimopan. Gaines *et al.* completed a retrospective and prospective study of elective bowel resection pateints.[5] Surgeons were assigned as alvimopan users (treatment group) and alvimopan non-users (control). The return to bowel function was 2.93 ± 1.22 days for the treatment group and 4.22 days ± 1.81 days in the control group (p<0.001). With regards to length of stay, 7 ± 2.6 days in the treatment group and 7.2 ± 2.2 days in the control group (p=0.792).[5] The difference in total hospital cost saw no difference between the two groups (p>0.81).[5]

Absher *et al.* assessed the use of alvimopan in laparoscopic and open bowel resections. The authors discovered that patients who were given alvimopan had a mean 1.8 day shorter post-operative length of stay (p=0.01) and lower rates of nasogastric tube insertion (p<0.001).[6] A multivariate analysis showed a statistically significant reduction in post-operative length of stay by 1.2 days (p=0.01).[6] In comparison to the study by Barletta *et al.,* the authors found improved recovery with alvimopan in open colectomy but not laparoscopic colectomy.[7] The two types of colectomy procedures were assessed on the basis of whether or not alvimopan was administered. Both colectomy procedures saw no difference for the development of post-operative ileus.[7] However, the length of stay for open colectomy was significant with alvimopan (5.6 ± 2.5 vs. 6.8 ± 3.3 days, p=0.009) compared to laparoscopic colectomy with alvimopan (3.9 ± 1 vs. 3.7 ± 1.4 days, p=0.305).[7]

A retrospective study assessed the dosing of alvimopan by not administering the pre-operative dose.[8] The authors evaluated patients

Table 2: Number of doses received by alvimopan patients

Number of Doses	Alvimopan patients
1	7
3	2
4	3
5	10
6	5
7	1
8	5
9	2
10	1
11	2
12	2
Average duration of therapy (days)	3.55

Table 3: Primary outcomes with and without alvimopan

Outcome	No Alvimopan (n=976)	Alvimopan (n=271)	p-value
Post-operative Ileus	32.5%	33.3%	0.46

Table 4: Primary Outcomes with and without alvimopan

Characteristic	Group 1: No Alvimopan (n=40)	Group 2: Alvimopan (n=40)	p-value
30-day Readmission	0	7.5%	0.07
Length of Stay	7.65	5.92	0.036
Length of post-operative stay (days)	6.68	5.85	0.26
Time to tolerate diet post-op (days)	2.26	2.07	0.767
Time to first bowel movement post-op (days)	3.77	2.55	0.0331
Number of bowel movements (n)	5	6	
Use of laxatives (n)			0.0009
No	28	39	
Yes	12	1	
Use of anti-emetics (n)			0.356
No	13	17	
Yes	27	23	

that underwent elective bowel resection with primary anastomosis without colostomy or ileostomy. Three groups of patients were included in the study: (1) patients that received alvimopan doses pre-operatively and post-operatively, (2) patients that received alvimopan without a pre-operative dose, and (3) matched cohort patients who did not receive alvimopan.[8] When compared to controls, alvimopan with or without pre-operative doses time to discharge was significant, $p<0.001$ and $p=0.03$ respectively.[8] Patients without pre-operative dose also still had a faster time to bowel movement (71 vs 97 hr, $p=0.006$) and faster time to diet (17 vs 54 hr, $p<0.001$) when compared to controls.[8] When comparing alvimopan without pre-operative dose to alvimopan doses before and after surgery, time to discharge was significant ($p=0.03$).[8] Alvimopan appears to be provide benefit even without the pre-operative dose.

Harbaugh *et al.* assessed the use of alvimopan in patients that received alvimopan doses before and after surgery. The authors found a significant difference in prolonged ileus ($p<0.001$) and shorter length of stay ($p<0.001$).[9] Study patients were compared to control patients (no alvimopan doses) with propensity matching. A similar study assessed the doses of alvimopan looking at 43 patients with alvimopan and 37 patients without alvimopan.[10] The multivariate analysis showed a short time with GI recovery ($p<0.05$) when patients received alvimopan even when adjusting for variables.[10]

In our study patients who received alvimopan were more likely to undergo an elective surgery. Patients that did not receive alvimopan were assessed to have a more emergent case therefore limiting the proper administration of alvimopan. To account for this difference, patients were reevaluated by reviewing patients with a Charlson score zero. Most of the patients received alvimopan before and after surgery. We had a small number of patients that just received a pre-op dose or just a post-op dose. Conclusions are limited in regards to the significance of inconsistent dose administration before or after surgery and how it affects post-operative ileus occurrence. The effect on length of stay was assessed with regards to if patients had an elective/emergent surgery and/or if alvimopan was utilized. Length of stay was influenced more by if the surgical procedure was elective or emergent than if alvimopan was used. Patients with emergent procedures had a longer length of stay compared to patients undergoing elective procedures regardless if they received doses of alvimopan. Within our analysis patients with elective procedures are a length of stay of 5.68 days compared to patients with emergent procedures had a length of stay of 8.56 days. The hospital stay after surgery was not significantly different between patients that received alvimopan and those who did not. It might be reasonable to suggest that alvimopan should be given the most consideration in patients who undergoing elective surgery. The use of alvimopan did not manifest significant benefit to our patients, among a series of outcomes measured. With this evidence, the use of alvimopan may be warranted to patients that are elective and to be properly administered doses. More generally, this questions the use of alvimopan in everyday clinical practice when patients are admitted to the hospital. Alvimopan is not the only intervention that has demonstrated efficacy in managing incidence of post-operative ileus. Alternatives are being considered for prevention post-operative ileus through the use of enhanced recovery protocol or chewing gum. As with alvimopan, the various alternatives carry their own litany of indications, side effects, expenses, and workflow challenges. At our institution, careful evaluation of alvimopan's cost-benefit within context of the alternatives has led to restriction of the use of alvimopan.

It must not escape mention that alvimopan displayed efficacy for prevention of ileus in FDA-approved randomized clinical trials, else the FDA would not have approved its use. Such trials are, by necessity, rigorously managed. Patients are excluded for most deviations from an ideal state, as they must be for ascertaining potential benefit of any drug. Our work does not constitute a challenge to the FDA-approved findings. Our research setting differs markedly from that of a randomized clinical trial. Herein, we share results of analysis done in an operational context; a non-ideal state where imperfections occur in patient selection and doctor or patient compliance, where polypharmacy is commonplace, patients suffer from compound morbidities and are concurrently managed by multiple practitioners, expense constraints are real, and alternative therapies exist. This is the lens through which our findings should be viewed.

Our study does have limitations. A retrospective study by nature limits the external validity to other institutions. Our hospital procedures and protocols related to bowel surgeries are specific to our institution which may vary across clinical practice. We assessed a small population size of 80 patients when assessing specific outcomes. The study was also not powered which limits our conclusion regarding statistical significance.

CONCLUSION

Our retrospective chart review and medication use analysis showed little difference in outcome with the use of alvimopan. The development of post-operative ileus and 30-day readmission showed no difference. Our institution has limited the use of alvimopan based on our findings. Studies of a larger population looking at clinical outcomes with alvimopan are warranted how to utilize alvimopan in clinical practice with regards to administration and emergent/elective surgeries.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Kraft M, MacLaren R, Du W, Owens G. Alvimopan (Entereg) for the Management of Postoperative Ileus in Patients Undergoing Bowel Resection. PT 2010;35:44-9.
2. Schmidt WK. Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am L Surg 2001;182:27S-38S.
3. Alvimopan (Entereg) [package insert]. Merck Sharp & Dohme Corp.; Whitehouse Station (NJ): August 2015.
4. Berger NG, Ridolfi TJ, Ludwig KA. Delayed gastrointestinal recovery after abdominal operation- role of alvimopan. Clin Exp Gastroenterol 2015;8:231-5.
5. Gaines SL, Giroux K, Thomas S, Gregory JS. Real world efficacy of alvimopan on elective bowel resection patients: an analysis of statistical versus clinical significance. Am J Surg 2012;203:308-11.
6. Absher RK, Gerkin TM, Banares LW. Alvimopan use in laparoscopic and open bowel resections: clinical results in a large community hospital system. Ann Pharmacother 2010;44:1701-8.
7. Barletta JF, Asgeirsson T, El-Badawi KI, Senagore AJ. Introduction of alvimopan into an enhanced recovery protocol for colectomy offers benefit in open but not laparoscopic colectomy. J Laparoendosc Adv Surg Tech A 2011;21:887-91.
8. Winegar B, Cox M, Truelove D, Brock G, Scherrer N, Pass LA. Efficacy of alvimopan following bowel resection: a comparison of two dosing strategies. Ann Pharmacother 2013;47:1406-13.
9. Harbaugh CM, Al-Holou SN, Bander TS, Drews JD, Shah MM, Terjimanian MN, *et al.* A statewide, community-based assessment of alvimopan's effect on surgical outcomes. Ann Surg 2013;257:427-32.
10. Wang S, Shah N, Philip J, Caraccio T, Feuerman M, Malone B. Role of alvimopan (entereg) in gastrointestinal recovery and hospital length of stay after bowel resection. P&T 2012;37:518-25.