Impact of a Pharmacist Implemented Protocol on Overall Use of Alvimopan (Entereg®) and Length of Stay in Laparoscopic Colorectal Surgeries

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Abstract: The primary objective of this study is to assess the impact of a pharmacist-implemented protocol on number of post-operative alvimopan doses. The secondary objective of this study is to assess LOS (length of stay), in days, before and after protocol implementation. A retrospective chart review was conducted from October 2015 through March 2016 for all laparoscopic colorectal surgeries. Number of post-operative alvimopan doses received and LOS was recorded for each patient that received at least one dose of alvimopan. Comparative data, before protocol implementation, from November 2014 through June 2015 were analyzed against the study data. Number of post-operative alvimopan doses and LOS were recorded. The mean number of doses was 6.41 in the comparator group and 4.25 in the study group (probability size \( P < 0.001 \)), which did meet statistical significance. Although the secondary objective was not statistically significant, LOS slightly decreased as the mean LOS was 5.01 days in the comparator group versus 4.49 days in the study group (\( P = 0.256 \)). At the current price of $120 per capsule, close to $30,000 was saved during the study period, projecting an annual cost savings of approximately $68,000. Results from this study show that pharmacists can play a vital role in cost savings and ensuring appropriate use of certain high-risk medications, like alvimopan, without increasing overall length of stay.

Key words: Alvimopan, pharmacist-implemented, colorectal, cost savings.

1. Introduction

POI (post-operative ileus) is defined as the transient cessation of bowel motility after GI (gastrointestinal) or other surgery. POI is a common cause of morbidity and prolonged patient recovery, leading to increased hospital costs, utilization of healthcare resources and higher readmission rates. POI is thought to be a multifactorial phenomenon brought on by inflammation from surgical manipulation, opioid use and endogenous hormones that all work to slow down GI motility [1]. Characteristics of POI can include abdominal pain, nausea and vomiting, and diet intolerance. Recent studies show that 20% of patients undergoing laparoscopic GI surgery will develop POI, increasing their length of stay by approximately five days. It is estimated that approximately $1,500,000,000 is spent annually to manage the total hospital costs that go along with POI [2, 3]. It was once thought that restricting oral feedings would help prevent nausea and vomiting, as well as protect the anastomosis from the stress of digesting food, allowing it time to heal. However, several studies have shown that earlier oral feedings have led to quicker GI recovery times, fewer post-operative complications, and consequently shorter hospital stays. Proper nutrition is necessary for wound healing and therefore a vital piece in the recovery process [4].

Alvimopan (Entereg®) is a peripherally acting, mu-opioid, receptor antagonist indicated to accelerate the time to upper and lower GI recovery following surgeries that include partial bowel resection with primary anastomosis. Acting peripherally, alvimopan has shown to accelerate the time to GI recovery by antagonizing mu-opioid receptors in the GI tract. Due to its inability to penetrate the CNS (central nervous system) and its large molecular size, alvimopan still
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allows analgesia to take place due to its inability to act on the mu-opioid receptors found in the central nervous system. In-vitro binding also shows that alvimopan binds with a high affinity to the mu-opioid receptor, but it has little to no activity towards the delta-opioid or kappa-opioid receptors [5]. The most common adverse reaction seen in patients taking alvimopan was dyspepsia (incidence ≥ 1.5%). Alvimopan 12 mg should be administered orally 30 min to 5 h prior to surgery, followed by 12 mg orally twice daily, beginning on post-operative Day 1, for a maximum of seven days, or 15 total doses. According to the FDA (Food and Drug Administration), there are no dosage adjustments for elderly patients, those with mild-moderate hepatic impairment or mild-severe renal impairment. It is recommended that these patients be monitored for adverse reactions. Alvimopan is not recommended in patients with severe hepatic impairment or those with end-stage renal disease. Contraindications to alvimopan therapy include patients who have taken therapeutic doses of opioids for more than seven consecutive days prior to taking alvimopan. In addition, patients recently exposed to opioids are expected to be more sensitive to the effects of alvimopan and may experience abdominal pain, nausea, vomiting and diarrhea. Alvimopan therapy is also not recommended in patients with a complete GI obstruction or in patients undergoing surgery for complete bowel obstruction. All patients receiving alvimopan therapy should be monitored for adverse reactions.

Alvimopan is restricted to a total of 15 in-hospital doses and is associated with a REMS (Risk Evaluation and Mitigation Strategy) program. This program, E.A.S.E.® (Entereg® Access Support and Education), is to ensure that only certified hospital pharmacies are dispensing alvimopan, and appropriate staff and physicians are educated on the medication. The E.A.S.E® program was brought about to limit the cumulative number of doses which a patient may receive due to the increased risk of myocardial infarction with prolonged use [6]. A Phase-3, double-blind, placebo-controlled study, conducted over 12 months, using alvimopan 0.5 mg vs. placebo in patients with chronic non-cancer pain, showed an increased number of myocardial infarctions in the alvimopan group compared to placebo, 1.3% vs. 0%, respectively [7]. In this study, the majority of myocardial infarctions occurred in the first four months of therapy. A causal relationship has not been established [6].

In 2014, SJMC (St. John Medical Center) Pharmacy dispensed 1,102 doses of alvimopan, costing approximately $126,000. Current usage of alvimopan at SJMC for 2015 was approaching the annual usage of 2014, in just the first six months of the year. Increased use of alvimopan at SJMC was attributed to growth of the colorectal surgery service, as well as a less stringent discontinuation process. A pharmacist-initiated protocol, which will be discussed below, was put into place to ensure proper use of alvimopan and limit any unnecessary spending that results from unwarranted doses.

As previously mentioned, alvimopan use at SJMC had been increasing due to an increased number of colorectal surgeries and lack of regimented discontinuation by prescribers. Formerly, alvimopan doses could be held at nursing discretion if a patient was tolerating their GI soft diet and having bowel movements, through a nursing notification to pharmacy, but this seldom occurred. Typically, alvimopan was discontinued from the medication profile at the physician’s discretion. At a majority of the time, a patient would be tolerating a GI soft diet and having bowel movements, yet he would still be receiving alvimopan inappropriately, leading to increased exposure to this high-risk medication and increased usage of a high-cost medication.

A pharmacist-driven initiative, with physician input, was put into place ensuring alvimopan therapy would be discontinued at the appropriate time. As mentioned previously, early oral feedings have shown...
to accelerate the time to GI recovery; Therefore, accelerated diet orders were made available for the colorectal surgeons to advance feedings for patients they deemed appropriate. Order sets were also updated to ensure that every patient without contraindications received a pre-operative dose of alvimopan, as well as post-operative doses, twice daily, until bowel function was restored, or a maximum of 15 doses, whichever happened first. Furthermore, physicians agreed to hold the alvimopan dose just prior to the administration of a soft diet order to help cut unnecessary doses. Therefore, if the soft diet was tolerated, an unnecessary dose of alvimopan was not given in the morning prior to the patient receiving their breakfast tray, cutting back on at least one dose of alvimopan, if not more. In addition, pharmacists also began reviewing contraindications for every patient on alvimopan therapy on post-operative Day 1. The colorectal surgeons reviewed contraindications to alvimopan therapy for their respective patients pre-operatively, while the pharmacist was able to serve as a double-check in the post-operative period.

2. Methods

The research protocol received exempt status from St. Vincent Medical Center IRB (Investigational Review Board) in November 2015. Retrospective data were collected from October 2015 to March 2016. The data included number of post-operative doses of alvimopan and length of stay, in days. Patient identifiers were not collected. All data were stored in a web-based database. Informed consent was not required because no changes were made to current practice.

During the study period, patients received alvimopan 12 mg orally twice daily post-operatively until toleration of a GI soft diet or bowel movements were presented. Nurses, under physician orders, agreed to hold alvimopan doses prior to initiation of a GI soft diet in order to cut down on unnecessary alvimopan exposure. Pharmacists already reviewed contraindications to alvimopan therapy on post-operative day one for all patients receiving therapy. Colorectal surgeons reviewed contraindications to alvimopan therapy pre-operatively for their respective patients.

The primary objective of this study was to assess the impact of a pharmacist-implemented protocol on number of post-operative alvimopan doses, before and after protocol implementation. The secondary objective of this study was to assess LOS (length of stay), in days, before and after protocol implementation. Statistical analysis was done for both the primary and secondary endpoints. A chi-square analysis was used to evaluate demographic data to ensure both sample groups (pre- and post-protocol implementation) were similar prior to running the primary variable. A Student’s t-test was used to analyze total post-operative doses of alvimopan, as well as compare length of stay post-operatively. Power was set at 80% (assumed extent $\alpha = 0.05$) to detect a difference of two doses, or one day of therapy, between the comparator group and the study group. The minimum sample size needed was 64 patients per group, to detect a reduction of two doses of alvimopan post-operatively post-protocol implementation.

3. Results

A total of 225 patients met inclusion criteria, 114 patients in the study group (post-protocol implementation) and 111 patients in the comparator group (pre-protocol implementation). No differences were noted between the two sample groups. The mean number of doses was 6.41 in the comparator group and 4.25 in the study group ($P < 0.001, 95\% \text{ CI (confidence interval)}: \widehat{\text{−1.441}, \text{−2.890}}$), which did meet statistical significance. Although the secondary objective was not statistically significant, LOS slightly decreased post-protocol implementation, as the mean LOS was 5.01 days in the comparator group versus 4.49 days in the study group ($P = 0.256, 95\% \text{ CI: 0.379}, \text{−2.894}$) (Table 1).
Table 1  Primary and secondary endpoint results.

<table>
<thead>
<tr>
<th>Items</th>
<th>Study group (n = 111)</th>
<th>Comparator group (n = 114)</th>
<th>P value</th>
<th>95% CI (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative alvimopan doses</td>
<td>4.25</td>
<td>6.41</td>
<td>&lt; 0.001</td>
<td>-1.441, -2.890</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>4.49</td>
<td>5.01</td>
<td>0.256</td>
<td>0.379, -2.894</td>
</tr>
</tbody>
</table>

4. Discussion

This study showed that pharmacists can make meaningful interventions in the post-operative setting that can impact patient care in a positive way. Previous studies have shown the efficacy that alvimopan can have in accelerating time to GI recovery in colorectal surgery. In contrast, studies have also found increased risk of myocardial infarction with prolonged use. Therefore, use of alvimopan must be for the appropriate indication and the shortest amount of time possible to avoid overexposure.

This study had many positive implications. Power was far exceeded, with 115 patients in the study group and 111 in the comparator group. The primary endpoint was statistically significant, showing a reduction in alvimopan usage of 2.16 doses per patient post-operatively, without leading to an increase in length of stay. By reducing the amount of alvimopan usage post-operatively, a cost-savings of approximately $30,000 resulted during the study period, projecting an annual cost savings of $68,000. This was only due to drug savings alone, not taking into account the shorter length of hospital stay in the post-protocol implementation group, or any adverse effects from prolonged exposure to alvimopan that could have led to escalated care and increased utilization of resources.

Nonetheless, there are several limitations to this study. Only patients who underwent laparoscopic colorectal surgeries were included, therefore excluding open colorectal procedures. Also, patients who went to intensive care unit floors post-operatively were excluded. These two factors alone excluded a high-risk subset of patients that could have benefited from inclusion into the study protocol. Furthermore, additional screening by a pharmacist for contraindications to alvimopan therapy was limited to the post-operative phase. Therefore patients had the potential to receive alvimopan pre-operatively in the setting of a contraindication. Future studies should include open colorectal surgeries and patients transferred to intensive care units post-operatively, as both of these patient populations are considered “high-risk” and could benefit from inclusion in the pharmacist-implemented protocol.

5. Conclusions

Based on the study result, pharmacists can have an impact in many areas regarding high-risk, high-cost medications in the post-operative setting. Unnecessary doses can be eliminated without increasing length of stay in post-operative laparoscopic colorectal surgery patients. In addition, this study demonstrated an area of cost-savings. Future studies should investigate the inclusion of “high-risk” patients, such as those who underwent open colorectal procedures, as well as patients who were transferred to intensive care units post-operatively. These patients are a unique subset of patients who could potentially benefit from the inclusion into the pharmacist-implemented protocol.

References

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