USE OF PROPHYLACTIC ONDANSETRON WITH INTRAVENOUS OPIOIDS IN EMERGENCY DEPARTMENT PATIENTS: A PROSPECTIVE OBSERVATIONAL PILOT STUDY

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Abstract—Background: The current literature suggests that the prophylactic use of antiemetics is ineffective at preventing nausea or vomiting caused by opioids in the emergency department (ED). While there is no data evaluating ondansetron’s efficacy for preventing opioid-induced nausea and vomiting, this practice remains common despite a lack of supporting evidence. Objectives: This study aimed to identify if prophylactic ondansetron administered with intravenous (IV) opioids prevents opioid-induced nausea or vomiting. Methods: This prospective observational study was conducted in the ED at two academic medical institutions. Patients were eligible for enrollment if they were prescribed an IV opioid with or without IV ondansetron and absence of baseline nausea. Patients' level of nausea was evaluated at baseline, 5 min, and 30 min after an IV opioid was administered and then observed for 2 hours. Results: One hundred thirty-three patients were enrolled, with 90% of patients presenting with a chief complaint of pain. Sixty-four (48.1%) patients received an IV opioid alone and 69 (51.9%) patients received both IV ondansetron and an IV opioid. Twenty-three (17.3%) patients developed nausea caused by opioid administration. One (0.75%) patient had an emetic event and 3 (2.3%) patients required rescue antiemetics during their observation period. Rate of nausea was similar between treatment groups 5 min after the opioid was administered \( (p = 0.153) \). There was no statistical difference in emesis, rescue medication requirements, or nausea severity between treatment groups. Conclusion: Our trial found that ondansetron did not appear to be effective at preventing opioid-induced nausea or vomiting. These findings and previous literature suggest prophylactic ondansetron should not be given to ED patients who are receiving IV opioids. © 2017 Elsevier Inc. All rights reserved.

Keywords—emesis; nausea; ondansetron; opioids; pain

INTRODUCTION

In 2011, the Centers for Disease Control and Prevention (CDC) estimated that 11 million people presented to emergency departments (EDs) in the United States (US) with a chief complaint of uncontrolled pain. According to the CDC report, approximately 54 million doses of analgesia were administered to ED patients, and 25 million were opioids. In addition, an estimated 27 million antiemetics were administered, of which 17 million (63%) were ondansetron (Zofran; GlaxoSmithKline, Brentford, London) (1). All opioids approved by the US Food and Drug Administration carry a warning that nausea and vomiting may occur, with evidence varying in degree of prevalence.
Opioids bind directly to the chemoreceptor trigger zone and activate the central nervous system vomiting center, inducing nausea or emesis (2). Previous studies have shown a low incidence of opioid-induced nausea and vomiting in ED patients, ranging from 2% to 20.2% (3–8).

Given the potential for opioids to induce nausea and vomiting, it is not uncommon for prophylactic antiemetics to be administered concurrently with opioid analgesics in the ED, despite limited evidence to support this practice. In a randomized, double-blind, placebo-controlled trial performed in a New Zealand ED, patients received either placebo or metoclopramide with IV morphine administration (5). While not statistically significant, the authors found a clear trend toward an increase in vomiting when patients received metoclopramide compared with placebo (5.4% vs. 1.9%, p = 0.17). A similar study performed in a United Kingdom ED determined that metoclopramide did not prevent nausea and vomiting associated with IV morphine use (6). Both groups of researchers concluded that nausea and vomiting is not a common adverse event from IV opioids and did not warrant pretreatment with antiemetic therapy. A 2014 trial from India evaluated the efficacy of promethazine, metoclopramide, ramosetron (a 5HT-3 antagonist), or placebo to prevent opioid-induced nausea or vomiting (7). The trial concluded that there was no difference in preventing nausea or vomiting between ramosetron, metoclopramide, or promethazine vs. placebo. In fact, patients treated with placebo had a trend toward less nausea compared to all treatment groups.

A multicenter trial conducted in nine countries assessed the safety and efficacy of ondansetron for the treatment of nausea and vomiting induced by opioid exposure (8). A total of 2574 patients who received an IV opioid in the ED were included, of which 520 patients (20.2%) developed nausea or emesis caused by the opioid. The 520 patients with nausea or emesis were enrolled to receive either placebo, 8 mg of ondansetron, or 16 mg of ondansetron. The trial found that one dose of either 8 mg or 16 mg of ondansetron controlled emesis in 62% and 69% of the patients, respectively. The authors concluded that ondansetron was effective at treating opioid-induced nausea and vomiting, but should be preserved for patients complaining of nausea or vomiting. For ED patients presenting with nausea, a 2011 randomized, placebo-controlled, double-blind superiority trial was unable to detect statistical differences between ondansetron, promethazine, metoclopramide, or placebo in nausea reduction (9).

To our knowledge, published research assessing the efficacy of prophylactic antiemetic therapy has only been evaluated outside of the United States, and none of these studies included ondansetron (4–7). Prophylactic ondansetron has been studied in the postoperative setting and in settings involving patient-controlled analgesia with mixed results, but has never been studied for antiemetic prophylaxis caused by opioid-induced nausea and vomiting in the ED (10–13). Despite a lack of supporting evidence, it remains common practice to pretreat patients with antiemetic therapy before they receive IV opioids. While ondansetron is generally well tolerated, it does have some concerning adverse effects, including QTc prolongation (14). The primary purpose of this study is to determine if prophylactic ondansetron reduces opioid-induced nausea and vomiting.

METHODS

This prospective, observational study was approved by the Institutional Review Boards at Banner University Medical Center Phoenix and Banner University Medical Center Tucson. Patients were eligible for enrollment if they were ≥18 years of age, had a medication order for an IV opioid (fentanyl, morphine, or hydromorphone), spoke English, and did not have nausea at baseline. Patients were excluded if they received any antiemetic therapy other than IV ondansetron, reported an allergy to ondansetron, presented with altered mental status, were breastfeeding or pregnant, received an opioid or antiemetic within 24 hours before presentation to the ED, or were unable to consent. Convenience sampling was used based on study team availability in the ED. Enrollment began in November 2015 and continued until January 2016. Trained ED study nurses acted as collaborators and helped to identify eligible patients. The decision to use an opioid analgesic, the type of opioid used, and the use of prophylactic ondansetron use were all done solely at the discretion of the treatment team before screening or enrollment in the study. Pharmacists used an electronic ED patient tracking board (Cerner or Epic) to identify patients with orders for an IV opioid with or without IV ondansetron. Patients were consented either before the IV opioid was administered or immediately after (within 5 min) to ensure that no delay in therapy occurred because of study enrollment. The investigators assessed nausea or presence of emesis at baseline, 5 min after opioid administration, and again at 30 min after opioid administration. Nausea was assessed using a verbally administered 11-point numeric rating scale (NRS) (Figure 1). The data collection tool and example NRS are available in the Figure 2. Patients were

![Figure 1. Numeric rating scale for severity of nausea.](Image)
monitored for ≤2 hours after the opioid was administered to capture antiemetic requirements or emesis. The secondary objectives were to determine if ondansetron would reduce the number of emetic events, examine if ondansetron would prevent the need for additional antiemetic medications, and identify if there was a difference in nausea between morphine, fentanyl, and hydromorphone. Discrete variables were analyzed using Fisher’s exact and McNemar’s tests.

RESULTS

One hundred thirty-three patients were enrolled between November 2015 and January 2016. Sixty-nine (51.8%) patients received ondansetron with an IV opioid and 64 (48.2%) patients received only an IV opioid. The average age in both treatment groups was 48 years, and 90% had a chief complaint of pain (Table 1). Every patient that received ondansetron during this study was given an initial dose of 4 mg and had a baseline nausea score of 0. Fourteen (20.3%) patients in the ondansetron and opioid group complained of nausea vs. nine (14.1%) patients in the opioid monotherapy group (p = 0.343; Table 2). The overall incidence of opioid-induced nausea was 17.3%. Five minutes after the opioid was given, there was no difference in nausea between the ondansetron and opioid group when compared to the opioid monotherapy (7.2% vs. 12.5%; p = 0.308). Thirty minutes after the opioid was administered, nausea was more present in patients treated with an opioid and ondansetron compared with opioid monotherapy (15.9% vs. 4.6%; p = 0.047).

Onset of nausea was different between the two treatment groups. Six patients in the ondansetron and opioid group who did not report nausea at 5 min developed nausea 30 min after the opioid was given. There were no patients in the opioid monotherapy group reporting a higher nausea score at 30 min compared to their score at 5 min. A Fisher’s exact test was performed to compare the timing of nausea onset in patients who experienced nausea and patients who received ondansetron and an opioid reported more nausea 30 min after the opioid was administered (p = 0.022; Table 3). There was no difference in nausea development between the two groups 5 min after the opioid was administered. In addition, there was no difference in nausea severity based on patient-reported numeric rating scores between treatment groups at 5 or 30 min after opioid administration (Figure 2).

Fisher’s exact tests were performed to evaluate differences in emesis and rescue medication requirements between the two groups. There was one (0.75%) emetic event during patient observation, and it occurred in the opioid monotherapy group. Two patients required rescue medication in the opioid monotherapy group who received ondansetron and an opioid reported more nausea 30 min after the opioid was administered (p = 0.608).

Patients were enrolled if they received an IV dose of fentanyl (25–100 mcg), morphine (4–8 mg), or hydromorphone (0.5–2 mg). The average dose of morphine administered was 4.5 mg, the average hydromorphone dose was 1.0 mg (7 morphine mg equivalents), and the average fentanyl dose was 50 mcg (5 morphine mg equivalents). There was no difference found in nausea severity between the two groups.

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Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ondansetron Plus Opioid (n = 69)</th>
<th>Opioid (n = 64)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>48.6 (15.8)</td>
<td>48.3 (17.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Female, %</td>
<td>56.5</td>
<td>43.7</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal/pelvic pain, %</td>
<td>39.6</td>
<td>34.3</td>
<td>NS</td>
</tr>
<tr>
<td>Arm/leg pain, %</td>
<td>13.0</td>
<td>12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Back/neck pain, %</td>
<td>11.5</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>Chest pain, %</td>
<td>13.0</td>
<td>20.0</td>
<td>NS</td>
</tr>
<tr>
<td>Headache, %</td>
<td>1.5</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Throat/tooth pain, %</td>
<td>5.7</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Trauma, %</td>
<td>5.7</td>
<td>9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Other, %</td>
<td>7.2</td>
<td>12.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant; SD = standard deviation.

Table 2. Incidence of Nausea

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients, % (n/N)</th>
<th>Opioid Plus Ondansetron, % (n/N)</th>
<th>Opioid Alone, % (n/N)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>17.3 (23/133)</td>
<td>20.3 (14/69)</td>
<td>14.1 (9/64)</td>
<td>0.343</td>
</tr>
</tbody>
</table>

Table 3. Onset of Nausea

<table>
<thead>
<tr>
<th>Group</th>
<th>Nausea Onset at 5 Min</th>
<th>Nausea Onset at 30 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron plus opioid, % (n/N)</td>
<td>33.3 (3/9)</td>
<td>66.7 (6/9)</td>
</tr>
<tr>
<td>Opioid monotherapy, % (n/N)</td>
<td>75.0 (6/8)</td>
<td>0 (0/8)</td>
</tr>
<tr>
<td>p value</td>
<td>0.153</td>
<td>0.022</td>
</tr>
</tbody>
</table>
promethazine, ramosetron, and metoclopramide) nausea in all three prophylactic antiemetic groups. Bhowmik et al. showed a paradoxical increased rate of patients that received opioid monotherapy (5,7). Interestingly, patients that received an opioid and ondansetron were more likely to be nauseous at 30 min compared to patients in the opioid monotherapy group. Ondansetron reaches peak serum levels approximately 25 min after administration (17). Therefore, one would expect nausea to be less common in the ondansetron and opioid group at 30 min. Previous studies have similarly found that patients pretreated with antiemetics were more likely to develop nausea compared to patients that received opioid monotherapy (5,7). Bhowmik et al. showed a paradoxical increased rate of nausea in all three prophylactic antiemetic groups (promethazine, ramosetron, and metoclopramide) compared with placebo (7). They explained this phenomenon as multifactorial, possibly caused by uncontrolled pain, vagal stimulation, or underlying disease state (7). We suspect that patients may have developed nausea caused by uncontrolled pain. Because the rate of nausea and emesis was rare, the use of ondansetron likely did not make a difference. Moreover, the psychological component of a nurse explaining to the patient that they are receiving a medication for nausea/emesis prophylaxis before administration may also play a role in the increased incidence of surveyed nausea at 30 min. Alternatively, given the observational nature and limited patient population of this study, it is possible that some intangible factor not identified in our baseline characteristics led to the identification and treatment of patients who were more likely to develop nausea after administration of an opioid.

Limited literature is available evaluating the difference in nausea and vomiting between opioids, because most trials include only IV morphine. We planned to enroll a balanced opioid distribution, but providers more frequently ordered morphine (82%) at our institutions. In 2011, the CDC estimated that an equal distribution of IV morphine, IV hydromorphone, and IV fentanyl were administered in EDs around the United States (1). We anticipated a similar distribution for our study. Patients that received hydromorphone had a higher morphine equivalent dose when compared to patients receiving fentanyl and morphine (7.0 mg vs. 5.0 mg vs. 4.5 mg, respectively). Interestingly, the higher opioid dose in the hydromorphone group did not appear to affect the rate of nausea.

Table 4. Emesis and Rescue Medication Between Opioid Classes

<table>
<thead>
<tr>
<th>Event</th>
<th>Fentanyl, % (n/N)</th>
<th>Morphine, % (n/N)</th>
<th>Hydromorphone, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>0 (0/11)</td>
<td>0.9 (1/108)</td>
<td>0 (0/14)</td>
</tr>
<tr>
<td>Rescue medication</td>
<td>0 (0/11)</td>
<td>2.8 (3/108)</td>
<td>0 (0/14)</td>
</tr>
</tbody>
</table>

Table 4. Emesis and Rescue Medication Between Opioid Classes

or emesis between types of opioid. Morphine developed nausea most frequently in patients (19.4%) compared with fentanyl (9%) and hydromorphone (7.1%). The patient that had an emetic event during the trial received morphine without ondansetron. The three patients (2.8%) who required rescue medication all received morphine (Table 4).

DISCUSSION

Our study evaluated the efficacy of ondansetron to prevent nausea and vomiting before exposure to an IV opioid. In addition, we evaluated if ondansetron would reduce the requirement for rescue doses of antiemetic medications. There were no statistical differences in the rate of nausea, emesis, or rescue medications in either treatment group. Previous trials showed the lack of efficacy with prophylactic promethazine, ramosetron (not approved in the United States), and metoclopramide for patients presenting to the ED. This is the first study that assessed ondansetron’s efficacy for this indication in the ED and paves the way for larger randomized trials in the future.

The current literature estimates that 2.0% to 20.2% of ED patients will develop nausea or emesis caused by opioid exposure (3–8). The incidence of nausea was only seen in 23 (17.3%) patients and just one (0.75%) emetic event was recorded. Nausea occurred more frequently in the morphine (19.4%) group compared to fentanyl (9.1%) and hydromorphone (7.1%). The higher rates of nausea could be in part caused by the increased histamine release from morphine, because histamine activates the vestibular system, resulting in nausea and vomiting (15,16).

Interestingly, patients that received an opioid and ondansetron were more likely to be nauseous at 30 min compared to patients in the opioid monotherapy group. Ondansetron reaches peak serum levels approximately 25 min after administration (17). Therefore, one would expect nausea to be less common in the ondansetron and opioid group at 30 min. Previous studies have similarly found that patients pretreated with antiemetics were more likely to develop nausea compared to patients that received opioid monotherapy (5,7). Bhowmik et al. showed a paradoxical increased rate of nausea in all three prophylactic antiemetic groups (promethazine, ramosetron, and metoclopramide) compared with placebo (7). They explained this phenomenon as multifactorial, possibly caused by uncontrolled pain, vagal stimulation, or underlying disease state (7). We suspect that patients may have developed nausea caused by uncontrolled pain. Because the rate of nausea and emesis was rare, the use of ondansetron likely did not make a difference. Moreover, the psychological component of a nurse explaining to the patient that they are receiving a medication for nausea/emesis prophylaxis before administration may also play a role in the increased incidence of surveyed nausea at 30 min. Alternatively, given the observational nature and limited patient population of this study, it is possible that some intangible factor not identified in our baseline characteristics led to the identification and treatment of patients who were more likely to develop nausea after administration of an opioid.

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The primary limitations of the trial are the inherent limitations of an observational study—primarily the nonrandomized, unblinded study design. Treatment allocation was performed independent from the investigators, and while there were no differences in baseline demographics, there is always the possibility that some factor not considered in our study design influenced the use of an antiemetic. In addition, the unblinded nature of our study design limits our ability to rule out the placebo effect on the incidence of nausea in either group. Both factors could help to explain the unexpected trend.
towards an increased incidence of nausea in patients receiving ondansetron. While this trial design does introduce some limitations, securing institutional review board approval for a randomized controlled trial at our institutions was not feasible because the committee believed patients would feel obligated to enroll for treatment of their immediate pain or administering ondansetron or placebo without patient consent would be unethical. Another limitation is our inability to generalize because of the size of this pilot study and use of convenience sampling. To reduce sampling error, investigators recruited and trained ED nurses to help with evaluating and enrolling patients. More patients than anticipated had baseline nausea at presentation, regardless of indication, causing exclusion. Previous research from Paoloni and Talbot-Stern and Greenwald et al. found that nausea may be directly proportional to the rate of pain the patient is experiencing (3,18). Patients in our study were not matched based on type or severity of pain; therefore, it is possible that patients in the ondansetron and opioid group had more uncontrolled pain inducing nausea. To evaluate nausea, we used an NRS because it has been used previously to describe nausea (19). The NRS tool relies on patient reporting and has significant interpatient variability. In addition, many of the ED providers were aware of this study, which may have altered their prescribing patterns during enrollment. Another limitation of our trial is that we did not attempt to collect data on adverse effects of ondansetron, such as QTc prolongation. Our trial was observational in nature, and many patients did not receive an electrocardiogram before treatment and even fewer had an electrocardiogram after treatment.

CONCLUSION

Our study observed no difference in nausea, vomiting, or rescue medication requirements in patients that received prophylactic ondansetron with an IV opioid compared to opioid monotherapy. While more than one-sixth of the patients experienced some form of nausea after IV opioid treatment, the overall incidence of emesis was extremely rare in patients presenting to the ED without baseline nausea. Additional studies with large numbers of patients are warranted. These observations and previous literature suggest that ondansetron should be reserved for patients who are experiencing nausea or vomiting. Providers should consider withholding prophylactic ondansetron to patients who are receiving IV opioids in the ED and instead reserve ondansetron therapy for patients that develop nausea and vomiting. This will prevent exposing patients to potential unwarranted adverse drug reactions and may result in significant cost savings.

Acknowledgments—Richard D. Gerkin, MD, provided statistical advice and analyzed the data as an acknowledged contributor.

REFERENCES

ARTICLE SUMMARY

1. Why is this topic important?
Given the potential for opioids to induce nausea and vomiting, it is not uncommon for prophylactic antiemetics to be administered concurrently with opioid analgesics, despite limited evidence to support this practice. Published research assessing the efficacy of prophylactic antiemetic therapy for opioid-induced nausea and vomiting has never evaluated ondansetron, one of the most commonly administered medications in emergency departments, and despite a lack of supporting evidence, it remains common practice to pretreat patients with antiemetic therapy before receiving intravenous (IV) opioids.

2. What does this study attempt to show?
This study aimed to identify if prophylactic ondansetron administered with IV opioids prevents opioid-induced nausea or vomiting.

3. What are the key findings?
One hundred thirty-three patients were enrolled with 23 (17.3%) patients that developed nausea caused by opioid administration. One (0.75%) patient had an emetic event and three (2.3%) patients required rescue antiemetics during their observation period. There was no difference in emesis, nausea, rescue medication requirements, or nausea severity between treatment groups.

4. How is patient care impacted?
These observations and previous literature suggest that ondansetron should be reserved for patients who are experiencing nausea or vomiting. Providers should consider withholding prophylactic ondansetron to patients receiving IV opioids in the ED and instead reserve ondansetron therapy for patients who develop nausea and vomiting. This will prevent exposing patients to potential unwarranted adverse drug reactions and may result in significant cost savings.