Ondansetron is safe and effective for prehospital treatment of nausea and vomiting by paramedics

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ABSTRACT

Objective. The objectives were to evaluate the safety and efficacy of ondansetron in the out-of-hospital treatment of undifferentiated nausea or vomiting. Methods. Patients with severe nausea or intractable vomiting who were transported by paramedic-staffed ambulances in eight California counties were treated with intravenous (IV), intramuscular (IM), or oral dissolving tablet (ODT) administration of ondansetron. Data were collected prospectively for a six-month period using an online database. Prospectively defined outcome measures were 1) efficacy as measured by a quantitative visual analog nausea scale and 2) incidence of adverse effects. There were no control or placebo groups. Results. Data was collected for 2072 patients, but one patient did not receive the medication. Therefore, Ondansetron was administered to 2,071 patients (3.7% of transported patients). Most patients were adult, with only 66 patients less than 18 years old. Of the 2,071 patients, 1,320 (64%) received IV administration, 77 (4%) received IM administration, and 674 (33%) received ODT administration of ondansetron. Intravenous administration resulted in the largest improvements in nausea scores (mean 4.4; 95% confidence interval [CI] 4.2, 4.5), followed by IM (mean 3.6; 95% CI 3.0, 4.3) and ODT (mean 3.3; 95% CI 3.1, 3.5). Overall, the mean decrease in nausea score was 4.0 (95% CI 3.9, 4.1; p < 0.001) on a 10-point scale. After medication administration, four patients had mild hypotension, one had hypertension, two had itching or rash, and one had a brief episode of supraventricular tachycardia that resolved spontaneously. Conclusions. Ondansetron is safe and effective for out-of-hospital treatment of nausea and vomiting when administered by paramedics via the IV, IM, or oral route. When available to paramedics, ondansetron is used frequently. Key words: antiemetic; paramedic; ondansetron; nausea; vomiting

INTRODUCTION

Nausea and vomiting are common complaints affecting patients treated by paramedics in the prehospital setting. One report estimated that 5% of patients treated in the prehospital setting suffered from nausea and/or vomiting.1 Nausea is often a significant concern, as many patients consider nausea to be a more uncomfortable symptom than pain.2 Furthermore, transport in the back of an ambulance may induce nausea and vomiting in patients prone to motion sickness or worsen symptoms in patients already experiencing nausea.3 In many emergency medical services (EMS) systems, the paramedic scope of practice does not address this well. Diphenhydramine may be used as an antiemetic, but is rarely used for that purpose in the emergency department, causes drowsiness, and does not have proven efficacy.4 A previous California EMS study of the treatment of motion sickness with diphenhydramine or metoclopramide was terminated in 2008 with a limited number of enrolled patients. A pilot study of droperidol for motion sickness during ambulance transport5 showed promise, but use of this medication has decreased because of a Food and Drug Administration (FDA) black box warning of the risk of QT prolongation.

Ondansetron is a 5-hydroxytryptamine3 (5-HT3) receptor antagonist that has been used safely and effectively for the treatment of undifferentiated nausea and vomiting in the emergency department, inpatient, and outpatient settings.6–10 Since FDA approval of generic ondansetron in 2006, the cost of the medication has declined considerably to just over $1.00 per dose.11 Low cost and proven in-hospital safety and efficacy make ondansetron an attractive therapeutic option during prehospital care and interfacility transfer.

Although ondansetron is used in a number of EMS jurisdictions across the United States, there is a paucity of data regarding prehospital use. In 2008, Warden et al. reported improvement in nausea and vomiting after intravenous (IV) or intramuscular (IM) administration of ondansetron by paramedics in the prehospital setting.2 Unfortunately, in this study, complete data were available for only 198 of 953 patients and data were not collected on adverse events.

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The purpose of this study was to confirm the finding that ondansetron is effective in alleviating nausea and vomiting in the prehospital environment as well as to evaluate the use of the ondansetron oral dissolving tablet (ODT) in a large prospective cohort of patients with undifferentiated nausea and vomiting. We also sought to collect prospective data on adverse events observed after administration of ondansetron by paramedics to patients during ambulance transport.

METHODS

Study Design

This was a prospective, observational, nonrandomized study with the objective of evaluating the utilization, safety, and efficacy of the out-of-hospital IV, IM, and oral administration of ondansetron in the treatment of undifferentiated nausea or vomiting. Paramedic treatment protocols were modified so that all patients without a contraindication who met clinical criteria were candidates to receive the medication. All patients were transported by paramedic-staffed ambulances. There were no control or placebo groups.

Setting

The trial took place simultaneously in four local EMS agencies (LEMSAs) comprising eight California counties: Santa Barbara County, Inland Counties EMS Agency (San Bernardino, Inyo, and Mono Counties), Coastal Valleys EMS Agency (Napa, Sonoma, and Mendocino Counties), and El Dorado County. The eight counties cover 44,000 square miles, with a combined population of 3.3 million and a combined annual call volume of 313,000.

Protocol

Paramedics were provided a 90-minute training program, facilitated by their service provider’s education staff or base hospital, consisting of a PowerPoint (Microsoft, Inc., Redmond, WA) presentation, demonstration, skill competency evaluation, and written examination. The curriculum included drug pharmacology, patient selection, and the use of the nausea scale.

A standardized protocol was implemented that allowed paramedics to administer ondansetron without online medical control. Inclusion criteria were 1) age 4 years or greater and 2) severe nausea or intractable vomiting. The only exclusion criterion was known sensitivity to ondansetron or other 5-HT3 antagonists. Paramedics were encouraged to administer the drug by the IV route when possible. Patients without an IV line were given the medication IM or orally (i.e., ODT). The route was selected by the paramedic, with assistance of the base hospital where LEMSA protocol required. The dose was 4 mg IV/IM/oral for all ages (4 years or greater). A second dose was allowed in the protocol under standing orders or with online medical control, depending on LEMSA protocols. A third dose required an online medical control order. The California Emergency Medical Services Authority approved the study protocol and added ondansetron to the state optional scope of practice for an 18-month evaluation period with mandatory data collection and reporting. Because the medication was considered standard medical care, and data were initially collected for state evaluation purposes, written patient consent was not required. Analysis of the data for publication was approved by the institutional review board at Arrowhead Regional Medical Center.

Outcome Measures

The primary outcome measures were the change in severity of nausea as reported by the patient and any adverse effect experienced by the patient after administration of ondansetron. A 10-point visual analog scale was used before and after each dose of the medication to quantitatively evaluate changes in the patient’s degree of nausea. Paramedics recorded the number the patient pointed to when shown the printed visual analog scale. The scale was taken from the work of Craig Warden, MD.1

All patients with adverse or untoward effects were identified both by the treating paramedic and during the clinical review of each case by a representative of the LEMSA or service provider under supervision of the study coordinators. All possible adverse reactions were reviewed by the provider medical director and these data were entered into the online data tool.

Medical Oversight

Paramedics were required to successfully complete a training session and pass a postcourse examination before being authorized to administer the medication. A quality improvement (QI) data-collection form was completed after all uses, and these were reviewed by a QI coordinator. All unusual events were reviewed by the medical directors of the advanced life support (ALS) provider and LEMSA.

Data Collection

Data were collected using a structured data-collection form designed by the investigators. After each patient contact in which ondansetron was administered, the treating paramedic completed a data-collection form and/or electronic patient care record (PCR). These forms were reviewed by the provider QI coordinator and verified against the PCR. If discrepancies were present, the prehospital care report was used. After
verification, de-identified data from the forms were entered by QI coordinators into a password-protected online electronic database (www.surveymonkey.com).

Data from the electronic online database was downloaded as an Excel spreadsheet (Microsoft, Inc.) and imported into STATA/IC 10.1 (StataCorp LP, College Station, TX) for analysis.

**Statistical Methods**

Changes in nausea score were presented as mean changes with exact confidence intervals (CIs). P-Values for the changes in nausea scores were calculated using the Wilcoxon signed-rank test. Differences in improvement of nausea scores by route of administration were compared using the Wilcoxon rank-sum (Mann-Whitney) test. The a priori significance level was set at alpha = 0.05.

**RESULTS**

All eligible patients transported between November 15, 2008, and May 15, 2009, were included. Data were submitted for 2,072 subjects. All 2,072 records had complete premedication and postmedication nausea scores. The intent-to-treat analysis included 2,001 subjects who received one dose, 70 subjects who received two doses, and one subject who did not receive any medication. Subjects with an initial nausea score of 0 (19 cases in which ondansetron was given preventatively) were excluded from the effectiveness analysis but were included in the analysis of adverse events.

Subject ages ranged from 2 years (1 patient, out of protocol, interfacility transfer with physician order) to 100 years. Sixty-six subjects were less than 18 years old. The age distribution of the study patients is available in Figure 1. Sixty-four percent of the subjects were female and 36% were male.

Of the 2,072 patients, 1320 (64%) received IV, 77 (4%) received IM, and 674 (33%) received ODT administration of ondansetron. One patient did not receive ondansetron due to IV malfunction. The initial dose was 4 mg for all IM and ODT administrations and for all but 4 IV administrations. Three adult subjects received a 2-mg IV dose and one 2-year-old subject received a 1-mg IV dose. The lower doses were given with medical control order and were included in all analyses.

Of 2,053 subjects with nausea, 1,634 (80%) had improvement of nausea after the medication, 395 (19%) had no change in nausea after the medication, and 24 (1%) had worsening of their nausea after the medication (Fig. 2). For all patients with nausea, the nausea score declined from a preadministration mean of 7.7 to a postadministration mean of 3.7, for a mean improvement of 4.0 (95% CI 3.9, 4.1; p < 0.001) (Table 1). In patients who improved, the mean improvement in nausea score was 5.1 (95% CI 4.9, 5.2; p < 0.001).

Intravenous administration resulted in the largest improvements in nausea scores (mean 4.4; 95% CI 4.2, 4.5), followed by IM (mean 3.6; 95% CI 3.0, 4.3) and ODT (mean 3.3; 95% CI 3.1, 3.5) (Table 1). The difference for IV vs. IM was 0.8 (p = 0.03); the difference for IM vs ODT was 0.3 (p = 0.353); and the difference for IV vs. ODT was 1.1 (p < 0.001).

**TABLE 1.** Change in Nausea Score, by Route of Administration

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>n</th>
<th>Mean Baseline Nausea Score</th>
<th>Mean Posttreatment Nausea Score</th>
<th>Mean Improvement in Nausea Score</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2,053</td>
<td>7.7</td>
<td>3.7</td>
<td>4.0</td>
<td>3.9, 4.1</td>
</tr>
<tr>
<td>IV</td>
<td>1,307</td>
<td>7.8</td>
<td>3.5</td>
<td>4.4</td>
<td>4.2, 4.5</td>
</tr>
<tr>
<td>IM</td>
<td>77</td>
<td>8.4</td>
<td>4.8</td>
<td>3.6</td>
<td>3.0, 4.3</td>
</tr>
<tr>
<td>ODT</td>
<td>669</td>
<td>7.4</td>
<td>4.1</td>
<td>3.3</td>
<td>3.1, 3.5</td>
</tr>
</tbody>
</table>

CI = confidence interval; IV = intravenous; IM = intramuscular; ODT = oral dissolving tablet.
TABLE 2. Adverse Events after Ondansetron Administration

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Dose</th>
<th>Route</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>F</td>
<td>4 mg</td>
<td>ODT</td>
<td>Nausea/vomiting, BP 118/82 to 86/68 mmHg</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>4 mg</td>
<td>IV</td>
<td>Nausea/vomiting, BP 130/94 to 90/60 mmHg</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>4 mg</td>
<td>IV</td>
<td>Nausea, BP 162/145 to 98/57 mmHg</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>4 mg</td>
<td>IV</td>
<td>Nausea/vomiting, hypotension resolved with 400 mL IV NS</td>
</tr>
<tr>
<td>88</td>
<td>F</td>
<td>4 mg</td>
<td>IV</td>
<td>Nausea, BP 159/89 to 210/88 mmHg</td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>4 mg</td>
<td>IV</td>
<td>Immediate erythema/pruritus at IV site, resolved with diphenhydramine</td>
</tr>
<tr>
<td>67</td>
<td>F</td>
<td>4 mg</td>
<td>IV</td>
<td>Diffuse pruritus without rash</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>4 mg</td>
<td>ODT</td>
<td>Transient PSVT at 170 bpm for 5–10 seconds, self-terminated</td>
</tr>
</tbody>
</table>

BP = blood pressure; F = female; IV = intravenous; M = male; NS = normal saline; ODT = oral dissolving tablet; PSVT = paroxysmal supraventricular tachycardia.

Eight patients (0.4% of the total) had postadministration changes that were evaluated as potential adverse medication reactions (Table 2). There were four episodes of hypotension, all mild, three of which were in patients who were vomiting. There was one episode of hypertension. There were two suspected allergic reactions, one with localized erythema and pruritus, and one with generalized pruritus only, neither with changed vital signs. There was one episode of paroxysmal supraventricular tachycardia (PSVT), in a patient without a history of cardiac dysrhythmias, that resolved within 10 seconds without treatment.

To determine overall frequency of use, the cases in the months of March and April were compared with the total number of transported patients. Utilization of ondansetron by county EMS system ranged from 0.5% to 6.7% of all patient transports, with the overall use of ondansetron in 3.7% of 29,426 patients transported during this two-month period.

DISCUSSION

This large prospective study of prehospital use of ondansetron for undifferentiated nausea and vomiting is the first prehospital study to our knowledge to examine the ondansetron ODT compared with other routes of administration. This is the largest study to date to prospectively evaluate adverse effects after administration of ondansetron in the prehospital setting.

Our study supports the conclusion that patients with severe nausea and vomiting benefit from administration of ondansetron by paramedics to reduce their symptoms and increase comfort. The study did not have a control group. Ondansetron has been previously shown to be effective in the treatment of nausea and vomiting in controlled studies in other settings, and this study was designed to evaluate whether it had a similar effect for out-of-hospital patients. The mean overall reduction in scores on the nausea scale was from 7.7 to 3.7—for a mean decrease of 4.0. The nausea scale has not been validated and a clinically significant change has not been determined; however, for pain the clinically significant threshold (when patients report the pain to be a “little better” or “little worse”) has been reported to range from 1.3 to 2.8.

Adverse events in our study were very rare and were either minor or self-limited. Because we used both prospective reporting of adverse events by paramedics and nurse or physician review of all cases in which ondansetron was administered, we believe it is unlikely that we failed to detect a serious adverse reaction. Almost all (99.6%) of the patients receiving ondansetron had no reported adverse reaction. There were a total of eight (0.4% of all patients) possible adverse reactions observed. Three of the patients who were vomiting became mildly hypotensive. Since hypotension due to hypovolemia after protracted vomiting is common, it is not clear that this was a reaction to the medication. There were two mild allergic reactions and one brief episode of PSVT that resolved spontaneously. Because of the lack of a placebo or control group, we cannot conclude whether the adverse events observed were related to the study medication.

In this population, all three routes of administration resulted in a substantial reduction in the scores on the nausea scale. The reduction was greatest with the IV route (decrease of 4.4), followed by IM (3.6) and then oral (3.3). The apparent superiority of the IV route may be due to the combination of short transport times and longer time to onset of action for oral medications, and may therefore not be clinically significant.

There were few pediatric patients in the study group (66 less than 18 years old, 13 less than 17 years old), so we cannot be as certain about the safety and effectiveness of prehospital use of ondansetron in these age groups. There were no adverse events in patients under the age of 18 years in our study.

Our study protocol specified a 4-mg dose for all patients and all routes of administration. We also allowed one repeat dose without base physician consultation. We felt that using this universal dose was simple to learn and remember and could potentially reduce medication dosing errors than can occur with weight-based formulas.

Finally, we observed that, when available, ondansetron is used frequently by paramedics: 3.7% of the transported patients in March and April were...
treated with ondansetron. This is similar to a previous report. For our analysis of frequency of use, we analyzed the last two whole months of the trial to best approximate the steady-state use of this new medication. By March the drug had been used for several months and paramedics were comfortable in its use. We felt that this would give a more accurate indication of how frequently this medication would be used going forward and therefore would be a more useful estimate for service provider and EMS agency decision making.

**LIMITATIONS AND FUTURE RESEARCH**

The most significant limitation of this study was the lack of a placebo or other control group. This limited the ability of this study to evaluate the effectiveness of ondansetron in decreasing symptoms of nausea and vomiting. As all patients except for one received some form of ondansetron, we cannot exclude the possibility that the improvement in nausea score observed was due to a placebo effect. Given that the effectiveness of ondansetron in treating nausea and vomiting in the hospital setting is well established, we believe it is unlikely that all of the improvement in our study was due to placebo effect.

The lack of a control group also limited our ability to determine whether the adverse effects observed were due to ondansetron administration or whether the patients receiving ondansetron had a different rate of adverse effects compared with similar patients who did not receive the medication. Because we did not collect data on times of administration and times at which nausea scale measurements were taken, we were unable to control for time as a possible confounder. It is possible that patients with very short transport times had the second nausea measurement performed very soon after the medication was given, thus not allowing time for the medication to take effect.

Our study included a relatively low proportion of pediatric patients, limiting the conclusions that can be drawn about this population. Previous in-hospital studies have shown ondansetron to be safe and effective for pediatric patients, but prehospital use of ondansetron in children is an area that merits further investigation.

**CONCLUSIONS**

Ondansetron is safe and effective for out-of-hospital treatment of nausea and vomiting when administered by paramedics via the IV, IM, or oral route. When available to paramedics, ondansetron is used frequently, thus having potential to alleviate suffering for many patients.

**References**