Original Contribution

The use of ondansetron for nausea and vomiting after head injury and its effect on return rates from the pediatric ED

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Abstract

Background: The use of ondansetron in children with vomiting after a head injury has not been well studied. Concern about masking serious injury is a potential barrier to its use.

Objective: The aim of this study was to evaluate the use of ondansetron in children with head injury and symptoms of vomiting in the pediatric emergency department (PED) and its effect on return rates and masking of more serious injuries.

Design/Methods: Visits to 2 PEDs from 2003 to 2010 with a diagnosis of head injury were evaluated retrospectively. Patients discharged home after a head computed tomography (CT) are the primary cohort for the study. A logistic regression model was used to analyze ondansetron’s effects on the likelihood of return to the PED within 72 hours for persistent symptoms. A secondary analysis was performed on patients with a diagnoses of head injury who did not receive a head CT and were discharged.

Results: A total of 6311 patients had a diagnosis of head injury, had a head CT performed, and were discharged from the PED. The use of ondansetron increased significantly from 3.7% in 2003 to 22% in 2010 (P < .001). After controlling for demographic/acuity differences, receiving ondansetron in the PED was associated with a lower likelihood of returning within 72 hours (0.49, 95% confidence interval [0.26-0.92]). In patients with head injury who did not have a head CT performed and were sent home, the use of ondansetron in the PED was not associated with an increased risk of missed diagnoses.

Conclusion: Ondansetron use in children with a CT scan who are dispositioned home is relatively safe, does not appear to mask any significant conditions, and significantly reduces return visits to the PED.

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1. Background

Ondansetron is a widely used antiemetic in children. Its efficacy in cases of vomiting due to gastroenteritis has been widely established in the medical literature [1-8]. Because ondansetron’s effectiveness as an antiemetic has been demonstrated in the literature and its costs have gone down [9], it has become more widely used in the pediatric population [10,11]. In fact, ondansetron was 1 of the top 200 prescribed generic medications in 2008, with prescriptions up more than 58% from the previous year [10,11].

Although gastroenteritis accounts for a significant number of the patients who receive ondansetron, it has been demonstrated to be effective in limited patient populations other than acute gastroenteritis [12,13]. Recent studies show that administration of ondansetron before...
procedural sedation or oral contrast may be beneficial in preventing and treating vomiting in children [11,12,14]. There are rare case reports of ondansetron being used effectively in posttraumatic head injuries associated with vomiting [15]. Recent published studies have shown that ondansetron, while being predominately used for vomiting from gastroenteritis, is now frequently being used for diagnoses other than gastroenteritis [11].

Head injuries that present for evaluation to the pediatric emergency department (PED) have a wide variability in severity and symptoms. Alterations in mental status, a prolonged loss of consciousness, or persistent episodes of vomiting often lead clinicians to pursue imaging studies to exclude clinically important traumatic brain injuries (cTBI) [16]. If imaging does not identify cTBI and the patient continues to have symptoms of nausea or vomiting after the injury, the use on ondansetron may be helpful in symptom relief and may limit the return of patients to the PED for continued symptoms after the head injury. To date, no studies have evaluated the effects of ondansetron after head injury and its effects on return rates to the PED.

A clinical dilemma also exists in those patients who present with vomiting after a head injury, in whom the clinician has a low suspicion for cTBI. There are known risks to computed tomography (CT) imaging of the brain in children [17], so limiting unnecessary imaging in patients at low risk is of paramount importance. Using ondansetron in these cases where clinical suspicion may be low, to alleviate symptoms of nausea and vomiting after a head injury, has theoretical efficacy. However, its use in this scenario may be limited by the concern about masking a more serious injury and is a potential barrier to its use. This is especially true if no radiographic imaging precedes the ondansetron use.

There are few data in the literature that study the frequency of ondansetron use in patients with head injury for symptom relief without first obtaining diagnostic imaging. Furthermore, no data exist in the literature regarding the frequency of missed intracranial diagnoses in patients who are treated for vomiting after head injury in the PED and discharged home. These cases are rare, but masking such potentially serious diagnoses through the use of an antiemetic is of concern to clinicians caring for children.

The primary goal of this study was to examine a large cohort of patients with a diagnosis of head injury seen in the PED and discharged home to determine the effect of ondansetron use during the initial PED visit on returns to the PED within 72 hours. A secondary goal was to determine whether ondansetron use affects the rates at which significant missed diagnoses of cTBI occur in patients who return to the PED.

2. Methods

This is a retrospective cross-sectional study of all visits to 2 tertiary care PEDs with a primary diagnosis of head injury, based on International Classification of Diseases Ninth Revision (ICD-9) billing codes. These PEDs are the only tertiary care pediatric emergency facilities in the area and together treat more than 120,000 pediatric acute care visits annually. Patient visits were evaluated for an 8-year period from January 1, 2003, to December 31, 2010. All visits for children between 6 months old and 18 years old were eligible for evaluation. In both study institutions, ondansetron use less than 6 months of age is uncommon, given the potential for other complex diagnoses in younger children, so this age group was not included for analysis. This study received approval from the hospital institutional review board at both study sites.

2.1. Selection of participants

The codes of interest of the ICD-9 were selected a priori to represent the primary diagnoses of head injury. Visits were selected for analysis if one of the preselected ICD-9 codes was entered for the visit. These codes were as follows: 959.01 (head injury not otherwise specified), 310.2 (post-concussive syndrome), 536.2 (head injury with persistent vomiting), 784 (injury to head/neck), 920 (contusion face/scalp), 850 (concussion with and without loss of consciousness), 850 to 854 (intracranial injury without skull fracture), and 800 to 804 (skull fracture).

2.2. Data collection and processing

For each patient visit, data were electronically abstracted from the medical record into a study database. Cases were selected for abstraction if the PED diagnosis was one of the previously selected ICD-9 codes. We collected data on disposition status (admission, operating room, or discharge home), demographic variables (age, weight, primary language, sex, race, and payor status), acuity level (based on Emergency Services Index [ESI] 5-level triage categories), whether laboratory tests were obtained, use of CT scan of the head, and whether or not the patient received ondansetron while in the PED. The ESI triage system is based on patient acuity and resource needs, where level 1 is the highest acuity and 5 is the lowest acuity [13]. Although the results of serum laboratory tests were not available to stratify patient acuity, ordering laboratory tests was used as an indicator of patient acuity. The route of ondansetron administration (oral or intravenous) and whether or not a prescription for ondansetron was given for home use were also recorded. Both oral dissolving tablets and liquid doses are included in the oral dosing category. Whether a patient received a prescription for ondansetron on discharge from the PED was routinely noted in the patient medical record as all discharge prescriptions are generated through an electronic medical record. Differences in demographic and acuity variables were compared between those patients who received ondansetron on their initial PED visit and those who did not.
Patient visits with an ICD-9 diagnosis of head injury were grouped in 2 different cohorts for analysis. To examine whether the use of ondansetron had any effect on return rates to the PED, we examined patient visits where a head CT was performed and the patient was discharged to home. Return rates to the PED within 72 hours were compared between those who received ondansetron on the first visit and those who did not. The rationale for this subgroup analysis was to examine return characteristics for a similar group who had acuity high enough to warrant a CT scan. This group also universally had no evidence of traumatic intracranial injury on CT, so the possibility of a missed diagnosis as a reason for return was minimized. During the study period, the ordering of CT scans was at the sole discretion of the ordering physician, and there were no formal clinical guidelines or protocols on CT use at the study sites. There were no screening or approval processes from the radiology department regarding orders for CT scans.

To control for suspected differences in acuity and demographic variables between those who were given ondansetron and those who were not, a logistic regression model was developed to analyze ondansetron’s effects on the proportion of PED returns. The demographic variables controlled for included age, primary language, sex, ethnicity, and payor status. Age was coded as a continuous value. Primary language was coded as primarily English or non-English, sex was coded as male or female, and ethnicity was coded as white or nonwhite. Payor status was divided into 2 categories: public (public and uninsured) or private. The acuity variables controlled for included ESI triage level (ordinal values 1-5) and serum laboratory testing. The remaining acuity variables were coded as dichotomous variables in the model. Missing data in the regression analysis were handled by listwise deletion and were not analyzed.

To examine cases where the use of ondansetron may have masked a more serious diagnosis, we examined all patients with head injury who did not have a head CT performed on the initial visit and were sent home. A missed diagnosis was defined as a skull fracture or intracranial hemorrhage not diagnosed on the index visit. To evaluate missed diagnoses, all patient return visits to either of the 2 study PEDs within 72 hours in those patients without a head CT performed on the initial visit were analyzed in detail with a manual medical record review. In addition to the previously mentioned demographic and acuity variables, the PED record from the initial visit for these patients was further examined (by author J.S.) to determine the documentation of the number of episodes of vomiting, duration between head injury and PED presentation, history of loss of consciousness, and presence of abnormal neurologic examination findings. Hospital electronic medical record (EMR) medical records from these visits were also individually reviewed by this reviewer (author J.S.) to determine hospital discharge diagnosis and needs for surgical intervention. The authors met before data abstraction to define the specific variables of interest, and data from these medical records were extracted into a standardized abstraction form. If notes in the medical record had discrepancies about the presence of vomiting or duration of symptoms, the attending notes were used. The reviewer was blinded as to whether or not patients had received ondansetron on their initial PED visit at the time of the medical record review (hospital medical records reviewed did not have records of medication dosing given in the PED). Discharge diagnoses on the repeat visit were classified as consistent with postconcussive syndrome, a missed intracranial diagnosis that was not diagnosed on the initial visit, or a diagnosis unrelated to the head injury. A 72-hour return period was chosen because deterioration due to worsening symptoms of an alternative diagnosis should manifest within this period. A second reviewer evaluated a random 20% sample of these return visits and agreed in all cases with the initial classification.

2.3. Outcome measures

The primary outcome was the return visit rate to the PED within 72 hours. The secondary outcome was the rate of missed cases of skull fracture or intracranial hemorrhage in patients who returned to the PED within 72 hours and were hospitalized.

2.4. Primary data analysis

We created 2 logistic regression models analyzing patient visits to the PED. Our first model was used to analyze 72-hour return rates in the cohort who received a CT scan and were discharged home. This model included the previously mentioned acuity and demographic variables in addition to whether or not the patient had received ondansetron on the initial visit in the PED or a prescription for ondansetron at discharge. A second model was developed to analyze return patient visits with a missed diagnosis in whom a head CT was not done on the index visit (defined as a skull fracture or intracranial hemorrhage not diagnosed on the index visit). This model included the same variables as model number 1, with the addition of the data gathered by the medical record review including: number of episodes of vomiting, duration between head injury and PED presentation, history of loss of consciousness, and presence of abnormal neurologic examination findings. Because of potential differences between the 2 study sites, we stratified the analysis by site but saw no significant differences, so we report only the aggregate results. To further control for variability in care between different providers, we considered stratifying the analysis by provider, but the large number of different providers included in the data set precluded this approach. In the analysis of missed diagnoses, we stratified data by age to determine if patients at younger ages who received ondansetron were more likely to return with alternative diagnoses.

Regression diagnostics (c statistic and Hosmer and Lemeshow goodness-of-fit test) were performed on the
Ondansetron for nausea and vomiting after head injury

3. Results

3.1. Cohort who had a head CT performed

During the study period, 28,271 patients were seen with an ICD-9 diagnosis representing head injury. Of these, 6,676 (24%) had a head CT performed in the PED. Of those who had a head CT performed, 365 were admitted (5.5%) and 6,311 (94.5%) were ultimately discharged home from the PED during the period. Among discharged patients, 1,228 (19.4%) were given ondansetron in the PED and 616 (9.7%) patients received a prescription for ondansetron at PED discharge. Of those who received ondansetron in the PED, 84% received the oral formulation, whereas 16% received an intravenous dose. Patients receiving an ondansetron dose in the PED were more likely white and less likely to be Medicaid patients compared with their counterparts who did not receive ondansetron in the PED (Table 1). Median age and ESI acuity levels were similar between the groups. Patients who received ondansetron in the PED had laboratory tests performed at a similar rate to those who did not receive ondansetron (Table 1). The use of ondansetron in the study group increased significantly over time from a rate of 3.7% in 2003 to 22.4% in 2010 (P for trend < .001; Fig.). During this same period, the rate of head CT performed in the same cohort of patients with a head injury diagnosis decreased (P < .01) as the rate of ondansetron use increased [8].

Of those discharged patients who did not receive ondansetron in the PED, 138 (2.7%) patients returned to the PED within 72 hours compared with 14 (1.1%) patients in the group who received ondansetron (P < .001). The reasons for return were predominantly for post–concussive-related symptoms of vomiting, headache, or ataxia; 114 (2.1%) of the return visits were directly related to postconcussion symptoms in the group that did not receive ondansetron compared with 10 (0.08%) return visits for similar symptoms in the group that did receive ondansetron (P < .001).

After controlling for differences in age, sex, race, primary language, insurance, whether or not laboratory studies were performed, and ESI acuity level, being given ondansetron in the PED was associated with a lower likelihood of returning for postconcussive symptoms within 72 hours (OR, 0.49; 95% CI [0.26-0.92]). Being given ondansetron in the PED on the initial visit was not associated with admission on the return visit (OR, 0.52; 95% CI [0.23-1.18]). However, receiving a prescription for ondansetron had no effect on the proportion of returns or readmissions (OR, 1.17; 95% CI [0.49-2.83]). Furthermore, after controlling for differences in acuity and demographics, begin given ondansetron in the PED on the initial visit was not associated with admission on the initial visit (OR, 1.05; 95% CI [0.78-1.41]). The route by which ondansetron was given did not affect the strength of these associations. No interaction terms were found to be significant, and the trends in the probabilities did not change, and we therefore present our models without interaction terms (see Table 2).

3.2. Cohort who did not have a head CT performed

During the study period, 21,595 patients were seen in the PED with a diagnosis of head injury and were discharged home without a CT scan. Of these patients, only 433 (2.0%) were given ondansetron during the PED stay and 21,162 (98%) did not receive ondansetron. Of those 433 patients who received ondansetron in the PED, 2.8% returned to the PED within 72 hours compared with 1.8%, of the patients who did not receive ondansetron (P = .105). When controlled for differences in demographic and acuity variables as previously mentioned, ondansetron had no significant effect on return rates in this cohort (OR, 1.15; 95% CI [0.56-2.36]). On a medical record review of all 397 return visits within 72 hours, there were 26 patients admitted on the return visit. Of these returning patients, there were no patients with a missed diagnosis in the group that received ondansetron (0/433) compared with 7 patients with a missed diagnosis in the

<table>
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<tr>
<th>Variable</th>
<th>Received ondansetron in PED</th>
<th>Did not receive ondansetron in PED</th>
<th>P</th>
</tr>
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<tr>
<td>Median age (y)</td>
<td>6.8</td>
<td>6.7</td>
<td>.79</td>
</tr>
<tr>
<td>ESI acuity level, mean</td>
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<td>2.9</td>
<td>&lt;.001</td>
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<td>Insurance type</td>
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<td>31.4</td>
<td>&lt;.001</td>
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<td>Private (%)</td>
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<td>61.2</td>
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<tr>
<td>Self-pay (%)</td>
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<td></td>
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<tr>
<td>Ethnicity: white (%)</td>
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<td>&lt;.001</td>
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<td>Any laboratory done (%)</td>
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<td>10.2</td>
<td>.08</td>
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</table>
group that did not receive ondansetron (7/2162, or 0.04%; 
\( P = .36 \)). The missed diagnoses in the group that did not 
receive ondansetron all presented with persistent vomiting 
and included 2 subdural hematomas with skull fracture, 1 
epidural hematoma, and 4 skull fractures without intracranial 
hemorrhage. Only the single patient with an epidural 
hematoma needed operative management. Of 397 return 
visits, the number of episodes of vomiting, duration between 
head injury and PED presentation, history of loss of 
consciousness, and presence of abnormal neurologic exam-
ination findings in those patients with and without a missed 
diagnosis were not significantly different (Table 2).

We further stratified the group with missed diagnoses to 
determine if patients at younger ages who received 
ondansetron were more likely to return with these missed 
diagnoses. In age groups of patients younger than 1 year, 2 to 
4 years, and older than 4 years, the proportions of missed 
diagnoses were not significantly different in the groups that 
did and did not receive ondansetron on the initial PED visit 
(Table 3). Within the 72-hour period, there was also no 
significant difference in time to return to the PED between 
those patients with and without missed diagnoses.

4. Discussion

No previous studies have been published that examine the 
outcomes of patients who received ondansetron in the PED 
for nausea and vomiting after head injury and the effect on 
return visitation rates. In this study, in a large cohort of 
patients with closed head injury who had a head CT 
performed and were discharged home, ondansetron resulted 
in a significant reduction in return visitation rates for 
postconcussive symptoms. During the 8-year study period, 
there was a 6-fold increase in the use of ondansetron in 
patients with a diagnosis of head injury that presented to the 
PED and had a head CT performed. Despite a lack of 
evidence in the literature that ondansetron is effective in 
relieving postconcussive symptoms, providers in our study 
clearly feel increasingly comfortable with its use.

The effect of ondansetron on the 72-hour return rates 
among those patients who had a head CT performed is 
independent of whether or not that patient received a 
prescription for ondansetron on discharge. This indicates 
that the symptom relief that patients achieve from only a

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
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<td>PED site</td>
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<tr>
<td>Ethnicity</td>
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<td>Insurance type</td>
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<td>0.86-1.79</td>
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<tr>
<td>ESI acuity level</td>
<td>1.15</td>
<td>0.97-1.36</td>
</tr>
<tr>
<td>Any laboratory test done</td>
<td>1.55</td>
<td>0.97-2.45</td>
</tr>
<tr>
<td>Prescription for ondansetron given</td>
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<td>0.49-2.83</td>
</tr>
<tr>
<td>Zofran given in PED</td>
<td>0.48</td>
<td>0.26-0.92</td>
</tr>
</tbody>
</table>

* Controlled for age, primary language, sex, ethnicity, payor status, ESI triage category, whether serum laboratory tests were obtained, and whether or not patient received ondansetron prescription on initial PED visit.
In patients who did not have a head CT obtained in the PED and were discharged home, ondansetron was rarely used. This is likely due to clinicians concerns about masking symptoms of a more significant head injury. In those patients who did not have a head CT performed, receiving ondansetron in the PED resulted in a slightly higher unadjusted return rate to the PED in 72 hours, a trend opposite to what was seen in those patients with a head CT. This may indeed be due to the masking of nausea and vomiting in the PED. When the effects of the medication wear off, the symptoms may compel patients to return to the PED. Because these patients did not have intracranial imaging while in the PED (unlike their comparison cohort), they are likely concerned about their symptoms being due to an underlying missed diagnosis and, thus, to return to the PED. It is likely that, in these cases where ondansetron was used without a prior head CT, the treating physician may have informed patients that this treatment was not conventional and may have been more specific with patients about symptoms, warranting a need for return to the PED. When controlled for differences between the groups, the effect of ondansetron on return rates in this cohort is not significant. Despite these increased returns, there were no missed diagnoses of cTBI in the subgroup of patients without a head CT who received ondansetron in the PED. The cohort of patients is small (only 433), so making any definitive conclusions about the safety of ondansetron in children with head injuries without intracranial imaging is not possible. However, in our study, all cases of missed diagnoses were seen in patients who were not given ondansetron on the initial PED visit. These results should be viewed in light of the fact that our cohort of patients who received ondansetron without head CT imaging prior was small (only 433 of nearly 21 595 patients), and as such, our conclusions are limited. However, we hope that the results of this study can help reassure providers that, when paired with sound clinical judgment, the risk of these missed diagnoses is not significantly worse when using ondansetron [19-31].

### 5. Limitations

This study is limited in a number of important ways. Owing to this study design, we were unable to assess the physician reasoning behind giving ondansetron in the PED. Also, this study reflects practice at 2 local institutions where the physicians may have different practice variations in ondansetron use, which may not be generalizable to other institutions. However, given the large numbers of patients needed to enroll to examine trends in use over time, the retrospective design was the preferred methodology. Furthermore, the retrospective design allows the study to evaluate actual pediatric practice patterns in the use of ondansetron in a large group of emergency physicians who were not aware or influenced by the study.
Furthermore, as touched on previously, the group of patients with an ICD-9 diagnosis of head injury is a heterogeneous group of patients who may have sustained an isolated head injury or a more multisystem injury. In this heterogeneous group, a variety of clinical factors affects admission decisions, which may confound an analysis of whether ondansetron affects admission and return rates. By focusing primarily on discharged patients and controlling for acuity and demographic differences, we have tried to control for these differences.

6. Conclusion

During the study period, clinicians significantly increased their use of ondansetron for treatment of postconcussive symptoms—a use that has not been well described in the literature. In this large cohort study, the use of ondansetron in discharged patients with head injury who have head CT imaging performed has lower rates of return to the PED for discharged patients with head injury who have head CT literature. In this large cohort study, the use of ondansetron in discharged patients with head injury who have head CT

References


