Ondansetron Use in the Pediatric Emergency Department and Effects on Hospitalization and Return Rates: Are We Masking Alternative Diagnoses?

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Study objective: We evaluate the effect of ondansetron use in cases of suspected gastroenteritis on the proportion of hospital admissions and return visits and assess whether children who receive ondansetron on their initial visit to the pediatric emergency department (ED) for suspected gastroenteritis return with an alternative diagnosis more frequently than those who did not receive ondansetron.

Methods: This is a retrospective review of visits to 2 tertiary care pediatric EDs with an *International Classification of Diseases, Ninth Revision* diagnosis of vomiting or gastroenteritis. A logistic regression model was developed to determine the effect of ondansetron use during the initial pediatric ED visit on hospital admission, return to the pediatric ED within 72 hours, and admission on this return visit. For patients who returned within 72 hours and were admitted, hospital discharge records were reviewed. The proportions of alternative diagnoses, defined as a hospital discharge diagnosis that was not a continuation of gastroenteritis or vomiting, were compared between the groups.

Results: During the 3-year study period (2005 to 2007), 34,117 patients met study criteria. Ondansetron was used for 19,857 (58.2%) of these patients on their initial pediatric ED visit. After controlling for differences between the groups, patients who received ondansetron were admitted on their initial visit less often: odds ratio (OR) 0.47 (95% confidence interval [CI] 0.42 to 0.53). However, those who received ondansetron were more likely to return to the pediatric ED within 72 hours (OR 1.45; 95% CI 1.27 to 1.65) and be admitted on the return visit (OR 1.74; 95% CI 1.39 to 2.19). The proportions of alternative diagnoses at hospital discharge were not significantly different in the group that received ondansetron on the initial pediatric ED visit (14.9%) compared with the group that did not (22.4%) (absolute difference 7.5% [95% CI −0.5% to 16.4%).

Conclusion: Ondansetron use in the pediatric ED reduces hospital admissions for suspected gastroenteritis and vomiting. However, children who receive ondansetron in the pediatric ED appear more likely to return to the pediatric ED and be admitted on this return visit than their counterparts. Furthermore, the use of ondansetron does not appear to be associated with increased risks of masking serious diagnoses in children. [Ann Emerg Med. 2010;55:415-422.]

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INTRODUCTION

Gastroenteritis accounts for more than 1.5 million pediatric outpatient visits and 220,000 hospitalizations in the United States annually.[1-4] Oral rehydration therapy is the preferred method to rehydrate patients and is endorsed by the World Health Organization and other major health organizations.[1,5] However, oral rehydration therapy remains underused and patients often receive intravenous rehydration. In fact, one survey demonstrated that 36% of pediatricians believed that vomiting was a contraindication to oral rehydration therapy.[6,7] Practice guidelines for the treatment of gastroenteritis recommend oral rehydration therapy for mild to moderate

Editor's Capsule Summary

What is already known on this topic

Small studies suggest that ondansetron reduces hospital admission in children with gastroenteritis. There are concerns that use of this agent may hinder the diagnostic process.

What question this study addressed

The authors retrospectively compared hospital admission, return within 72 hours, admission on return, and alternative diagnoses between 34,117 children receiving (58%) or not receiving (42%) ondansetron for vomiting presumably caused by gastroenteritis.

What this study adds to our knowledge

Patients receiving ondansetron were less likely to be admitted but more likely to return within 72 hours and be admitted on return. Overall, fewer children in the ondansetron group (5.3% versus 7.3%) were admitted during the episode of illness. Ondansetron use was not associated with increased alternative diagnoses.

How this might change clinical practice

Ondansetron may be useful in the treatment of children with vomiting presumably caused by gastroenteritis, without masking alternative diagnoses.

dehydration but no pharmacologic therapy for vomiting.[5] However, vomiting and gastroenteritis symptoms are distressing to families, and at least half of all physicians caring for children with gastroenteritis report prescribing antiemetic agents.[8,9]

In the last several years, the use of ondansetron has become a useful adjunct in the treatment of acute gastroenteritis in the pediatric emergency department (ED). Ondansetron, a selective 5-hydroxytryptamine3 receptor antagonist, acts at chemoreceptors in the peripheral and central nervous system to alleviate nausea,[10-14] which has been shown in numerous well-designed studies in children to reduce episodes of vomiting in the pediatric ED, reduce the need for intravenous fluid rehydration, and improve oral intake in the pediatric ED.[10,11,15-18] Existing studies differ in whether the use of ondansetron is able to reduce hospitalization rates or the length of the pediatric ED stay.[10,11,15,19] Available studies show that, after patients are treated with ondansetron in the pediatric ED, there is either no significant difference in return rates to the pediatric ED within the next 48 hours[10] or a slightly increased rate of return for those patients treated with ondansetron.[11] However, existing studies that have examined return rates are limited by their small sample size.[10,11,17,20] A recent meta analysis by DeCamp et al,[19] examining 5 studies with a total of 612 patients, determined that there was no significant difference in return visitation rates between the 2 groups. However, the relative rarity of a return visit limits the ability to draw any conclusions from groups of this size.

No clear data exist in the literature about the frequency with which patients who are treated for vomiting or gastroenteritis in the pediatric ED and discharged home return for care with an alternative diagnoses (ie, appendicitis, intussusception) that is not simply a progression of gastroenteritis. These cases are rare, but masking such potentially serious diagnoses through the use of an antiemetic is of great concern to clinicians caring for children. The majority of published studies have prospectively enrolled fewer than 400 patients each and were not powered to analyze these clinically important outcomes.[15,17,19]

The primary goal of this study was to examine a large cohort of patients who had vomiting or gastroenteritis and who were treated in the pediatric ED to determine the effect of ondansetron use during the initial pediatric ED visit on hospital admission, return to the pediatric ED within 72 hours, and admission on this return visit. A secondary goal was to determine whether ondansetron use affects the rates at which significant alternative diagnoses such as appendicitis or intussusception occur in patients who return to the pediatric ED.

MATERIALS AND METHODS

Study Design

This is a retrospective cross-sectional study of all visits to 2 tertiary care pediatric EDs with a primary diagnosis of vomiting or gastroenteritis, according to *International Classification of Diseases, Ninth Revision* (*ICD-9*) billing codes. These pediatric EDs are the only tertiary care pediatric emergency facilities in the area and together treat more than 120,000 pediatric acute care patients annually. Patient visits were evaluated for a 3-year period, from January 1, 2005, to December 31, 2007. All visits for children between 3 months and 18 years of age were eligible for evaluation. In both study institutions, ondansetron use at less than 3 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.

Selection of Participants

ICD-9 codes of interest were selected a priori to represent primary diagnoses of either vomiting alone or vomiting with diarrhea presumed to be caused by gastroenteritis. Patients with diarrhea alone were not included. Visits were selected for analysis if one of the 9 preselected *ICD-9* codes was entered for the visit. These codes were 008.8 (viral gastroenteritis not otherwise specified), 009.1 (enteritis, gastroenteritis of presumed infectious origin), 009.0 (infectious colitis, enteritis and gastroenteritis), 536.2 (persistent vomiting), 558 (unspecified noninfectious gastroenteritis), 558.9 (unspecified noninfectious

gastroenteritis), 787.0 (nausea and vomiting), 787.01 (nausea with vomiting), and 787.03 (vomiting alone).

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 pediatric ED diagnosis was one of the above selected *ICD-9* codes. We collected data on disposition status (admission or discharge home), demographic variables (age, weight, primary language, sex, race, and payer status), acuity level (based on Emergency Services Index 5-level triage categories), use of intravenous fluids, whether serum laboratory tests (defined as nonbedside CBC count or serum electrolyte level testing) or abdominal radiographs were obtained, and whether or not the patient received ondansetron while in the pediatric ED. The Emergency Services Index triage system is based on patient acuity and resource needs, where level 1 is the highest acuity and 5 is the lowest acuity.[21-23] Although the results of serum laboratory tests were not available to stratify patient acuity, ordering laboratory tests, abdominal radiographs, or giving intravenous fluids 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 pediatric ED was routinely noted in the patient chart because 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 pediatric ED visit and those who did not.

All patient return visits to either of the 2 study pediatric EDs within 72 hours that resulted in an admission to the hospital were analyzed in detail with a manual chart review. In addition to the above demographic and acuity variables, the pediatric ED record from the initial visit for these patients was further examined (by A.S.) to determine the documentation of abdominal pain on physician examination, temperature greater than 38°C (100.4°F), whether or not the patient had diarrhea, and duration of vomiting. Hospital charts from these visits were also manually reviewed by this reviewer (A.S.) to determine hospital discharge diagnosis. The authors met before data abstraction to define the specific variables of interest, and data from these charts were extracted into a standardized abstraction form. If notes in the chart had discrepancies about the presence of abdominal pain or duration of symptoms, the attending physician notes were used. If temperature was noted multiple times in the chart, the highest temperature was used. The reviewer was blinded as to whether or not patients had received ondansetron on their initial pediatric ED visit at the chart review (hospital charts reviewed did not have records of medication dosing given in the pediatric ED). Hospital discharge diagnoses were classified as progression of initial disease (persistent vomiting or gastroenteritis) or an alternative diagnosis that was not deemed a continuation of gastroenteritis or vomiting (ie, appendicitis, intussusception, or intracranial tumor). A second reviewer evaluated a random 20% sample of these return visits and agreed in all cases with the initial classification. A 72-hour return period was chosen because deterioration caused by persistence of gastroenteritis symptoms or worsening symptoms of an alternative diagnosis should manifest within this period.

To control for suspected differences in acuity and demographic variables between those who received ondansetron and those who did not, a logistic regression model was developed to analyze ondansetron's effects on the proportion of admissions and hospital returns. The demographic variables controlled for included age, weight, primary language, sex, race, and payer status. Age and weight were coded as continuous values. Primary language was coded as primarily English or non-English, sex was coded as male or female, and race was coded as white or nonwhite. Payer status was divided into 2 categories, public (public and uninsured) or private. The acuity variables controlled for included Emergency Services Index triage level (ordinal values 1 to 5), use of intravenous fluids, abdominal radiographs, and laboratory testing. These 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.

Outcome Measures

The primary outcomes were the need for hospitalization and return visits to the pediatric ED within 72 hours. A secondary outcome was the rate of alternative diagnoses in patients who returned to the pediatric ED within 72 hours and were hospitalized.

Primary Data Analysis

We created 3 logistic regression models analyzing patient visits to the pediatric ED. Our first model was used to analyze hospitalization rates at the initial pediatric ED patient visit and included the above acuity and demographic variables, in addition to whether or not the patient had received ondansetron on that visit. The second model was constructed to evaluate return visits to the pediatric ED within 72 hours and included the same variables as above, with the addition of whether the patients had received a prescription for ondansetron on their initial pediatric ED visit. The third model was developed to analyze the return patient visits with alternative diagnoses. This model included the same variables as model 2, with the addition of the data gathered by the chart review, including presence of abdominal pain, temperature greater than 38°C (100.4°F), diarrhea, and duration of vomiting. Because of potential differences between the 2 study sites, we clustered the analysis by site but observed no significant differences, so we report only the aggregate results. To further control for variability in care between different providers, we considered clustering the analysis by provider, but the large number of providers included in the data set precluded this approach. We stratified the models

by the route by which ondansetron was given (oral or intravenous) to determine whether this affected the strength of the associations. In the analysis of alternative diagnoses, we stratified data by age to determine whether patients who received ondansetron at younger ages were more likely to return with alternative diagnoses.

Regression diagnostics (C-statistic and Hosmer and Lemeshow goodness-of-fit test) were performed on the above models. The Hosmer and Lemeshow goodness-of-fit test for our models allowed us to accept the null hypothesis that our models were a good fit.[24] For the models, we then determined which variables might have significant interaction terms and added each category of interaction term to the models. The interaction terms were not significant and the trends in the probabilities did not change, and we therefore present our models without interaction terms.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) are shown to represent the strength of the associations for regression model output. Comparison between the proportions of alternative diagnoses in the groups is represented by the absolute differences in the proportions and the 95% CI between the 2 independent proportions. All statistical analyses were performed with the Statistical Package for the Social Sciences (version 15.0; SPSS, Inc., Chicago, IL).

Table 1. Demographic and acuity characteristics of patients who did and did not receive ondansetron on the initial pediatric ED visit for vomiting or gastroenteritis.

Demographics and Acuity Characteristics	Received Ondansetron in the Pediatric ED (n=19,857)	Did Not Receive Ondansetron (n=14,260)
Mean age, y	4.2	3.8
Mean weight, kg	19	17.9
Sex, %		
Male	53.4	51.3
Female	46.6	48.7
Race, %		
White	39	29
Nonwhite	61	71
Primarily English speaking, %	79	86
Patients with Medicaid, %	24	36
Median ESI triage level*	2	2
Received intravenous fluids, %	18	16
Abdominal radiographs obtained, %	6.4	8.5
Laboratory studies obtained, %	39	36

ESI, Emergency Services Index.
*ESI 5-level triage categories An ESI triage level of 1 is the highest acuity and 5 is the lowest acuity.

RESULTS

During the 3-year study period, 34,117 patients met study entry criteria. Ondansetron was used for 19,857 (58.2%) patients on their primary visit to the pediatric ED, and a prescription for ondansetron was given to 11,624 (34.1%) of patients. Of those who received ondansetron in the pediatric ED, 85.7% received the oral formulation, whereas 14.3% received an intravenous dose. Patients receiving an ondansetron dose in the pediatric ED were on average older, weighed more, were less likely to be primarily English speaking, were more often male, were more likely white, and were less likely to be Medicaid patients than their counterparts who did not receive ondansetron in the pediatric ED (Table 1). Median Emergency Services Index acuity levels were similar between the groups. Patients who received ondansetron in the pediatric ED also received fewer abdominal radiographs than their counterparts but received intravenous fluids and had laboratory studies performed slightly more often (Table 1). Of the 34,117 records, 1,455 (4%) had missing data that were excluded from the regression analysis. The majority of data were missing from the language, race, and weight variable fields.

Before controlling for acuity or demographic variables, patients who received ondansetron (n=19,857) on their initial pediatric ED visit were admitted less often than their counterparts who did not receive ondansetron (n=14,260) (3.7% versus 6.4%). However, those who received ondansetron were more likely to return to the pediatric ED within 72 hours (6.2% versus 4.7%) and be admitted on the return visit (25.9% versus 21.4%). The overall admission rate (combining admissions on initial and repeated visit) for those receiving ondansetron on the initial visit was 5.3% compared with 7.3% in the group that did not receive ondansetron (Table 2).

After controlling for differences between the groups, patients who received ondansetron were admitted on their initial visit less often (OR 0.47; 95% CI 0.42 to 0.53) (Table 3). However, those who received ondansetron were more likely to return to the pediatric ED within 72 hours (OR 1.45; 95% CI 1.27 to 1.65) (Table 4) and be admitted on the return visit (OR 1.74; 95% CI 1.39 to 2.19) (Table 5). After controlling for demographic and acuity differences, being given a prescription for ondansetron had no effect on the proportion of returns or readmissions. 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.

During the study period, a total of 443 patients (1.3%) returned to the pediatric ED within 72 hours and were subsequently admitted to the hospital on this visit. Of these 443 patients, 309 (70%) had received ondansetron on their initial pediatric ED visit and 134 (30%) had not. Seventy-six of the 443 patients (17.2%) ultimately received an alternative diagnosis on discharge from the hospital. The proportions of alternative diagnoses at hospital discharge were not significantly different in the group that received ondansetron on the initial pediatric ED visit (14.9%) compared with the group that did not receive ondansetron on the initial visit (22.4%) (absolute difference 7.5% [95% CI −0.5% to 16.4%). Similarly, proportions of alternative diagnoses at hospital discharge were not significantly different in the group that received an

Table 2. Hospitalization and 72-hour return rates in patients who did and did not receive ondansetron on the initial pediatric ED visit for vomiting or gastroenteritis.*

Hospitalization and 72-Hour Return Rates	Received Ondansetron in the Pediatric ED (n=19,857)	Did Not Receive Ondansetron (n=14,260)	95% CI for Difference
Hospitalization rates on initial pediatric ED visit (%)			
Not admitted	19,115 (96.3)	13,347 (93.6)	−2.7 CI (–3.1 to –2.2)
Admitted	742 (3.7)	913 (6.4)	
Return rates to the pediatric ED within 72 h (%)†			
Did not return	17,923 (93.8)	12,720 (95.3)	1.5 CI (1.0 to 2.0)
Returned	1,192 (6.2)	627 (4.7)	
Hospitalization rates of patients who return to the pediatric ED within 72 h (%)†			
Not admitted	883 (74.1)	493 (78.6)	4.5 CI (0.4 to 8.5)
Admitted	309 (25.9)	134 (21.4)	
Hospitalization rates on either initial pediatric ED visit or return visit within 72 h (%)			
Not admitted	18,806 (94.7)	13,213 (92.7)	−2.0 CI (–2.5 to –1.5)
Admitted	1,051 (5.3)	1,047 (7.3)	

*95% CI for difference represents the absolute difference and the associated 95% CI of that difference.
†Total denominator excludes those patients who were admitted on the initial visit.

Table 3. OR of admission to the hospital on initial visit after being treated for vomiting or gastroenteritis.

Variable	OR	95% CI
Received ondansetron on initial pediatric ED visit	0.47	0.42-0.53
Age, y	0.96	0.93-1.01
Weight	1.0	0.99-1.01
Primary language	0.96	0.78-1.18
Sex	0.95	0.85-1.06
Race	1.55	1.36-1.76
Payer status	1.41	1.23-1.62
ESI level	1.66	1.56-1.76
Intravenous fluids given	5.34	4.68-6.10
Abdominal radiographs obtained	2.45	2.15-2.79
Serum laboratory tests obtained	9.89	7.71-12.70
P value HL GOF test	.225	

HL GOF, Hosmer-Lemeshow goodness of fit.

Table 4. OR of return to the pediatric ED within 72 hours after being treated for vomiting or gastroenteritis.

Variable	OR	95% CI
Received ondansetron on initial pediatric ED visit	1.45	1.27-1.65
Age, y	0.87	0.83-0.91
Weight	1.0	0.99-1.01
Primary language	0.89	0.77-1.02
Sex	0.94	0.85-1.05
Race	0.87	0.76-0.99
Payer status	1.19	1.04-1.36
ESI level	0.99	0.92-1.06
Intravenous fluids given	1.35	1.13-1.61
Abdominal radiographs obtained	0.99	0.79-1.24
Serum laboratory tests obtained	0.96	0.83-1.10
Received Prescription for Ondansetron	0.99	0.87-1.13
P value HL GOF test	.127	

Table 5. OR of return to the pediatric ED and admission within 72 hours after being treated for vomiting or gastroenteritis.

Variable	OR	95% CI
Received ondansetron on initial pediatric ED visit	1.74	1.39-2.19
Age, y	0.88	0.82-0.94
Weight	1.0	0.99-1.01
Primary language	1.11	0.82-1.49
Sex	0.99	0.82-1.19
Race	1.79	1.44-2.22
Payer status	1.56	1.24-1.96
ESI level	1.52	1.36-1.69
Intravenous fluids given	1.61	1.23-2.14
Abdominal radiographs obtained	0.87	0.62-1.24
Serum laboratory tests obtained	0.71	0.56-0.91
Received prescription for ondansetron	0.85	0.68-1.06
P value HL GOF test	.198	

ondansetron prescription on their initial visit (17.1%) compared with the group that did not (17.2%) (absolute difference 0.1% [95% CI –7.9% to 7.4%]) (Table 6). Among the 443 patients, the presence of temperature greater than 38°C (100.4°F), diarrhea, and duration of vomiting in those patients with and without alternative diagnoses was not significantly different. However, patients with an alternative diagnosis were more likely to have physician documentation of abdominal pain during the initial pediatric ED visit, 26% versus 13.5% (absolute difference 12.5% [95% CI 2.2% to 25.4%]). After controlling for the presence of abdominal pain on examination, fever, diarrhea, and duration of vomiting, in addition to the above demographic and acuity variables, ondansetron use in the pediatric ED (OR 0.63 [95% CI 0.32 to 1.24]) or the presence of a prescription (OR 1.38 [95% CI 0.73 to 2.62]) was not associated with an increased odds of an alternative diagnosis on the return visit.

Table 6. Proportions of alternative diagnoses in those patients treated for vomiting or gastroenteritis who returned and were admitted to the hospital within 72 hours.*

	Received Ondansetron in the Pediatric ED	Did Not Receive Ondansetron	Absolute Differences (95% CI)†
Continuation of gastroenteritis, %	263 (85.1)	104 (77.6)	7.5 (−0.5 to 16.4)
Alternative diagnosis, %‡	46 (14.9)	30 (22.4)	
	Received Ondansetron Prescription	**Did Not Receive Ondansetron Prescription**	
Continuation of gastroenteritis, %	136 (82.9)	231 (82.8)	0.1 (−7.9 to 7.4)
Alternative diagnosis, %‡	28 (17.1)	48 (17.2)	

*Total includes those 443 patients who were initially discharged but returned and were admitted within 72 hours of the initial pediatric ED visit.
†95% CI represents the 95% CI of the absolute difference between the proportion point estimates.
‡Alternative diagnosis defined as a hospital discharge diagnosis not deemed a continuation of gastroenteritis or vomiting.

Table 7. Proportions of specific alternative diagnoses in those patients treated for vomiting or gastroenteritis who returned and were admitted to the hospital within 72 hours.*

Final Hospital Diagnosis	Received Ondansetron in the Pediatric ED, % (n=309)	Did Not Receive Ondansetron, % (n=134)	Absolute Differences, % (95% CI)†
Appendicitis	4.2	2.2	2 (−2.5 to 5.2)
Intussusception	2.3	2.2	0.1 (−4.0 to 2.8)
Bacteremia	1.0	3.7	2.7 (−0.05 to 7.5)
Pyelonephritis	1.6	1.5	0.1 (−3.8 to 2.5)
Small bowel obstruction	0.6	1.5	0.9 (−1.2 to 4.7)
Intracranial tumor	1.0	0.0	1 (−1.0 to 2.8)

*Alternative diagnosis defined as a hospital discharge diagnosis not deemed a continuation of gastroenteritis or vomiting. Total includes those 443 patients who were initially discharged but returned and were admitted within 72 hours of the initial pediatric ED visit.
†95% CI represents the 95% CI of the absolute difference between the proportion point estimates.

The 6 most common alternative diagnoses were appendicitis (16/76), intussusception (10/76), bacteremia (8/76), pyelonephritis (7/76), small bowel obstruction (4/76), and intracranial tumor (3/76). The proportion of each specific diagnosis was not significantly different in the group that had received ondansetron on the initial pediatric ED visit compared with those who did not (Table 7).

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

LIMITATIONS

There are several potential limitations to this study. The study design was a retrospective chart review of pediatric ED visits. Ultimately, given the large numbers needed to enroll to examine the proportion of return visits and alternative diagnoses after ondansetron use, the retrospective study design, in spite of its inherent limitations, is the preferred methodology. Despite these limitations, because of the diverse and large patient population studied, results from this study should be generalizable to other pediatric emergency facilities as well and EDs that are not pediatric specific. The retrospective nature also allows the study to evaluate actual pediatric practice patterns concerning ondansetron usage among a large group of emergency physicians who were not aware of or influenced by the study.

Children given ondansetron may be sicker patients who a pediatric emergency physician feels need intervention (medication, intravenous fluids, laboratory testing). The differences between the group given ondansetron and those who did not receive ondansetron both in acuity and demographic variables are controlled for to the best of our ability in the logistic regression model. In fact, the median Emergency Services Index levels in these 2 groups are identical. However, there are likely other factors such as the level of dehydration, severity of the gastroenteritis, or access to timely primary care follow-up that are not controlled for in this model that may confound the results of the study. Certainly these other unaccounted-for differences in acuity could contribute to the differences that have been shown. Although only 4% of the data had missing values, it is possible that these missing data bias the results.

Furthermore, the physicians at these study sites used their own clinical discretion to give ondansetron, dose the medication, administer intravenous fluids or laboratory testing,

and admit or discharge patients. Because of the large number of providers in the study cohort, physician variability in management could not be completely controlled for in this analysis.

The study followed patients at the only 2 major tertiary care pediatric EDs in the area. It is possible that patients attended another emergency facility or consulted their primary care physician, rather than return to one of the study pediatric EDs. These missed patients would not be captured on the analysis of return visits. However, the 2 study facilities are the only major hospitals that admit pediatric patients, so the analyses should capture the majority of admissions and those with alternative diagnoses.

Finally, the study was unable to determine whether a patient who received a prescription for ondansetron in fact filled and used that prescription. Therefore, making a definitive conclusion on whether discharging a patient with a prescription for ondansetron prevents return visits to the pediatric ED for care is not possible.

DISCUSSION

To our knowledge, this is the largest study to date of ondansetron use in the pediatric ED. This study reinforces previous prospective randomized trials that show ondansetron decreases the probability of hospital admission on the initial pediatric ED visit.[11,19] However, in this large cohort, children who receive ondansetron in the pediatric ED appear more likely to return to the pediatric ED and be admitted on this return visit than their counterparts. Furthermore, this study shows that ondansetron use does not appear to mask significant alternative diagnoses in children.

Despite convincing evidence of ondansetron's effects on oral rehydration tolerance, masking a serious illness with antiemetic use is a clear concern for health care providers both in the ED and the primary care setting. To date, no studies have conclusively addressed this topic, likely because of the rare occurrence of such alternative diagnoses. Although any patient presenting with vomiting or diarrhea to the pediatric ED who is discharged could ultimately receive an alternative diagnosis on return visit, we hope that the results of this study can help reassure providers that the risks of these alternative diagnoses are not significantly worse when ondansetron is used. In fact, it approaches statistical significance that those who received ondansetron were less likely to receive an alternative diagnosis, suggesting that the initial ED assessment is usually correct.

The presence of vomiting and diarrhea together versus vomiting alone was not associated with an increased risk of alternative diagnoses. However, those patients with suspected gastroenteritis and abdominal pain on examination were more likely to return with an alternative diagnosis that those without. This is potentially a useful warning sign to clinicians.

The reasons for the increased returns to the pediatric ED may be that children who are given ondansetron have a more pronounced illness and are inherently more likely to return once discharged. In this study, the cohort of patients receiving ondansetron had similar acuity in terms of Emergency Services Index triage level as higher use of intravenous fluid, radiographs, and laboratory testing. Even though the regression model controls for some acuity factors, it is unable to control for all confounders that determine patient acuity. It is likely that these higher-acuity patients clinically improve once they receive a dose of ondansetron and tolerate oral rehydration. However, once the medication effect wears off after discharge, the children return for care. Before ondansetron use, these may be patients who would have been admitted for intravenous hydration at their initial visit. Therefore, ondansetron in some patients may simply be delaying hospital admission.

According to observations by Ramsook et al,[11] higher revisit rates among those treated with ondansetron were potentially caused by increased diarrhea episodes in those receiving ondansetron prescriptions. However, when patients who received ondansetron prescriptions were excluded from analysis, the strength of the association for a return within 72 hours was unchanged. It is possible that patients who received ondansetron in the pediatric ED but did not receive prescriptions had such a profound symptomatic improvement in the pediatric ED from ondansetron that they returned for further doses.

If the effects of ondansetron are so profound on the initial pediatric ED stay that they prevent hospital admission, one would expect the presence of a prescription for ondansetron to have a similarly strong effect, which we did not see in this study. Although a home prescription did not make a difference, there is the potential that the cost of the medication and availability (based on insurance coverage for the prescription) did not allow patients to have outpatient prescriptions filled. Unfortunately, this study was not able to determine whether patients filled the ondansetron prescription they were given.

Ondansetron became available generically in 2006, and since then acquisition costs have decreased.[25] This study was not designed to provide a formal cost analysis, but it is likely that ondansetron use in the pediatric ED has the potential to save significant costs in both hospitalization and resource utilization.

In this large cohort study, the independent use of ondansetron in the pediatric ED does not appear to be associated with increased risk of masking serious diagnosis in children with suspected gastroenteritis. This large cohort validates earlier smaller studies that ondansetron is associated with a lower proportion of hospital admissions. However, controlling for acuity and demographic variables, the study has also demonstrated that children who receive ondansetron in the pediatric ED appear more likely to return to the pediatric ED and be admitted on this return visit than their counterparts.

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REFERENCES

1. King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52:1-16.
2. Burkhart D. Management of acute gastroenteritis in children. *Am Fam Physician*. 1999;60:2555-2563, 2565-2566.
3. Fleisher GR, Ludwig S. Infectious disease emergencies. In: Ludwig S, Fleisher GR, Henretig FM, et al, eds. *Textbook of Pediatric Emergency Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:757-762.
4. Kilgore PE, Holmn RC, Clarke MJ. Trends of diarrheal disease associated mortality in US children, 1968 through 1991. *JAMA*. 1995;274:1143-1148.
5. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics*. 1996;97:424-436.
6. Reis EC, Goepp JG, Katz S, et al. Barriers to use of oral rehydration therapy. *Pediatrics*. 1994;93:708-711.
7. Ozuah PO, Avner JR, Stein RE. Oral rehydration, emergency physicians, and practice parameters: a national survey. *Pediatrics*. 2002;109:259-261.
8. Szajewska H, Gieruszczak-Bialek D, Dyla GM. Meta-analysis: ondansetron for vomiting in acute gastroenteritis in children. *Aliment Pharmacol Ther*. 2206;50:393-400.
9. Kwon KT, Rudkin SE, Langdorf MI. Antiemetic use in pediatric gastroenteritis: a national survey of emergency physicians, pediatricians, and pediatric emergency physicians. *Clin Pediatr (Phila)*. 2002;41:641-652.
10. Freedman SB, Adler M, Seshadri R, et al. Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Engl J Med*. 2006;354:1698-1705.
11. Ramsook C, Sahagun-Carreon I, Kozinetz CA, et al. A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. *Ann Emerg Med*. 2002; 39:397-403.
12. Roila F, Feyer P, Maranzano E, et al. Antiemetics in children receiving chemotherapy. *Support Care Cancer*. 2005;13:129-131.
13. Kovac AL. Management of postoperative nausea and vomiting in children. *Paediatr Drugs*. 2007;9:47-69.
14. Food and Drug Administration. Prescribing information: Zofran (ondansetron hydrochloride). Available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_06_06_KP%20Ondansetron%20FDA%20label%208-22-06.pdf. Accessed April 20, 2009.
15. Alhashimi D, Al-Hashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database Syst Rev*. 2006;(4):CD005506.
16. Roslund G, Hepps TS, McQuillen KK. The role of oral ondansetron in children with vomiting as a result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: a randomized controlled trial. *Ann Emerg Med*. 2008;52:22-29.
17. Stork CM, Brown KM, Reilly TH, et al. Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Acad Emerg Med*. 2006;13:1027-1033.
18. Cubeddu LX, Trujillo LM, Talmaciu I. Antiemetic activity of ondansetron in acute gastroenteritis. *Aliment Pharmacol Ther*. 1997;11:185-191.
19. DeCamp LR, Byerley JS, Doshi N, et al. Use of antiemetic agents in acute gastroenteritis. *Arch Pediatr Adolesc Med*. 2008;162: 858-865.
20. Reeves JJ, Shannon MW, Fleisher GR. Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized controlled trial. *Pediatrics*. 2002;109:e62.
21. Brousseau DC, Mistry RD, Alessandrini EA. Methods of categorizing emergency department visit urgency: a survey of pediatric emergency medicine physicians. *Pediatr Emerg Care*. 2006;22:635-639.
22. Sarver JH, Cydulka RK, Baker DW. Usual source of care and nonurgent emergency department use. *Acad Emerg Med*. 2002;9: 916-923.
23. Tanabe P, Gimbel R, Yarnold PR, et al. Reliability and validity of scores on the Emergency Severity Index version 3. *Acad Emerg Med*. 2004;11:59-65.
24. Hosmer DW, Lemeshow S. Assessing the fit of the model. In: *Applied Logistic Regression*. Hoboken, NJ: John Wiley & Sons; 2000:140-144.
25. Food and Drug Administration. Prescribing information: Zofran (ondansetron hydrochloride). Available at: http://www.fda.gov/cder/ogd/approvals/ap1206.htm. Accessed April 2009.