ORIGINAL ARTICLE

Oral Ondansetron for Gastroenteritis in a Pediatric Emergency Department

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ABSTRACT

BACKGROUND

Vomiting limits the success of oral rehydration in children with gastroenteritis. We conducted a double-blind trial to determine whether a single oral dose of ondansetron, an antiemetic, would improve outcomes in children with gastroenteritis.

METHODS

We enrolled 215 children 6 months through 10 years of age who were treated in a pediatric emergency department for gastroenteritis and dehydration. After being randomly assigned to treatment with orally disintegrating ondansetron tablets or placebo, the children received oral-rehydration therapy according to a standardized protocol. The primary outcome was the proportion who vomited while receiving oral rehydration. The secondary outcomes were the number of episodes of vomiting and the proportions who were treated with intravenous rehydration or hospitalized.

RESULTS

As compared with children who received placebo, children who received ondansetron were less likely to vomit (14 percent vs. 35 percent; relative risk, 0.40; 95 percent confidence interval, 0.26 to 0.61), vomited less often (mean number of episodes per child, 0.18 vs. 0.65; $P<0.001$), had greater oral intake (239 ml vs. 196 ml, $P=0.001$), and were less likely to be treated by intravenous rehydration (14 percent vs. 31 percent; relative risk, 0.46; 95 percent confidence interval, 0.26 to 0.79). Although the mean length of stay in the emergency department was reduced by 12 percent in the ondansetron group, as compared with the placebo group ($P=0.02$), the rates of hospitalization (4 percent and 5 percent, respectively; $P=1.00$) and of return visits to the emergency department (19 percent and 22 percent, $P=0.73$) did not differ significantly between groups.

CONCLUSIONS

In children with gastroenteritis and dehydration, a single dose of oral ondansetron reduces vomiting and facilitates oral rehydration and may thus be well suited for use in the emergency department.

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In the United States, gastroenteritis accounts for more than 1.5 million pediatric outpatient visits and 200,000 hospitalizations annually.[1] Although oral-rehydration therapy is recommended for children with mild-to-moderate dehydration,[1] it remains underused. Clinicians who provide care in emergency departments are more likely to choose intravenous over oral rehydration when vomiting is a major symptom.[2] In one survey, 36 percent of pediatricians reported that vomiting was a contraindication to oral rehydration.[3] Thus, a safe and effective method of controlling vomiting is likely to increase the use and success rate of oral rehydration.

In a previous study of oral ondansetron (Zofran, GlaxoSmithKline) in children with gastroenteritis, six doses of oral elixir or placebo were administered over a period of 48 hours.[4] Although vomiting was reduced among children receiving ondansetron in the emergency department, the rates of diarrhea and return visits to the emergency department were increased.[4] We conducted a study to determine whether the administration of a single orally disintegrating ondansetron tablet to children with vomiting and dehydration as a result of gastroenteritis would control vomiting with minimal side effects.

METHODS

PATIENTS

The study was a prospective, double-blind, randomized comparison of ondansetron and placebo to control vomiting among children 6 months through 10 years of age. The trial was conducted in the emergency department of Children's Memorial Hospital in Chicago from January 1, 2004, through April 11, 2005. The study was approved by the hospital's institutional review board.

All children with symptoms consistent with gastroenteritis were screened for eligibility by the supervising physician. Eligible children had at least one reported episode of nonbilious, nonbloody vomiting within the four hours preceding triage, at least one episode of diarrhea during the illness, and mild-to-moderate dehydration (Table 1). The exclusion criteria were a body weight of less than 8 kg, severe dehydration, underlying disease that could affect the assessment of hydration (such as renal failure or hypoalbuminemia), a history of abdominal surgery, hypersensitivity to ondansetron, and previous enrollment in the study. If the child was deemed eligible for the study, a research assistant was contacted. Research assistants were on call from 8 a.m. until midnight, and overnight coverage was provided by the principal investigator. A log was kept of all children asked to enroll in the study, and any reasons for refusal were recorded. Written informed consent was obtained from the parents or guardians of all children. All 33 supervising physicians working in the emergency department participated in screening, and 10 research assistants were involved in the project.

A baseline dehydration score (Table 1) was assigned to all children. The score could range from 6 to 21, with higher scores indicating more severe dehydration. Children under 24 months of age were evaluated for all seven items used to determine the score, and those 24 months of age or older were evaluated for six (their ability to produce tears was not evaluated).[7-14] It was determined a priori that children under 24 months

Table 1. Dehydration Score.*

Variable	Normal or Mild Dehydration (1 Point)	Moderate Dehydration (2 Points)	Severe Dehydration (3 Points)
Pinch-retraction time†	Immediate	Slow (≤2 sec)	Very slow (>2 sec)
Feeling of skin to the touch	Normal	Dry	Clammy or cool
Condition of buccal mucosa	Moist	Dry	Very dry
Tears‡	Present	Reduced	None
Heart rate§	Within normal limits	Mild tachycardia (≤10% above normal)	Moderate tachycardia (>10% above normal)
Urine¶	Normal amount and color	Reduced amount or darker in color	None passed for >6 hr
Mental status	Thirsty, alert	Drowsy, irritable, restless	Limp, lethargic

* Higher scores indicate more severe dehydration. Scores range from 7 to 21 for children under 24 months of age and from 6 to 18 for children 24 months of age or older. Children under 24 months of age with scores of 10 to 17 and those 24 months of age or older with scores of 8 to 15 were considered to have mild-to-moderate dehydration. Those under 24 months of age with scores of 18 or more and those 24 months of age or older with scores of 16 or more were considered to be severely dehydrated.

† To assess pinch-retraction time, the examiner pinches a small fold of skin on the lateral abdominal wall at the level of the umbilicus and estimates the time it takes for the skin to resume its normal shape.[5]

‡ Only children under 24 months of age were evaluated for tears.

§ The normal heart rate was based on values published by Davignon et al.[6]

¶ The amount and color of the urine were reported by the parent.

of age with scores of 10 to 17 and those 24 months of age or older with scores of 8 to 15 would be considered to have mild-to-moderate dehydration and to be in need of rehydration. For analysis, dehydration scores for children 24 months of age or older were standardized so that they were on the same scale as those for children under 24 months of age.

RANDOMIZATION

The patients were randomly assigned in blocks of six to receive ondansetron or placebo and were stratified according to the dose of medication. An independent statistician provided the code to the pharmacy, which dispensed in an opaque bag a weight-appropriate dose of active drug or a placebo of similar taste and appearance. The weight-based dose was 2 mg for children weighing 8 to 15 kg, 4 mg for children weighing more than 15 kg and up to 30 kg, and 8 mg for children weighing more than 30 kg. GlaxoSmithKline supplied the tablets but had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data.

STUDY INTERVENTION

The bedside nurse administered the medication while the research assistant was outside the room to ensure that the research assistant, physician, child, and caregivers remained unaware of the treatment assignment. A tablet was placed on the top of each child's tongue, and the child was instructed to swallow five seconds later. Children who were unable to adhere to these instructions were assisted by the nurse until they swallowed. Since the tablet dissolves in seconds and does not require the coadministration of liquids, aspiration was not considered to be a risk. Children who vomited within 15 minutes after receiving the medication were given a second dose. A 1-hour period of intense oral rehydration was initiated 15 minutes after administration of the medication; the oral rehydration period then continued until disposition was determined (i.e., whether the child was admitted or sent home). In keeping with the World Health Organization (WHO) recommendations on oral rehydration, the caregivers were instructed to limit the amount of fluid given to 30 ml of oral electrolyte solution (Enfalyte, Mead Johnson Nutritionals) every five minutes.[15] After the oral-rehydration period was completed, the treating physician resumed management. If the treating physician chose to administer intravenous fluids, the protocol specified the administration of 20-ml boluses of 0.9 percent normal saline per kilogram of body weight, each given over a period of 30 minutes.

FOLLOW-UP

On days 3 and 7 after randomization, a research assistant telephoned the child's family and asked, using a standard script, whether the child had returned to an emergency department, had received intravenous-fluid treatment, had had any additional symptoms, or had been hospitalized. The records of Children's Memorial Hospital were reviewed to confirm caregivers' reports. If the research assistant was unable to reach a caregiver on the designated day, attempts were continued daily for two weeks after enrollment of the child.

OUTCOME MEASURES

The primary outcome was the proportion of children in each group who vomited while receiving oral-rehydration therapy. A vomiting episode was recorded by the research assistant when the forceful expulsion of stomach contents occurred. Episodes separated by no more than two minutes were counted as a single episode. Nonproductive retching, spilling of oral contents, and drooling were not considered vomiting. The secondary outcomes were the number of episodes of vomiting during oral-rehydration therapy and the rates of intravenous rehydration and hospitalization.

ADVERSE EVENTS

The research assistant, treating physician, and nurses monitored patients for adverse events from enrollment to disposition from the emergency department. A treatment-related adverse event was one considered by at least two of the three physician investigators to be possibly, probably, or definitely related to the study drug. Although a significantly increased frequency of diarrhea in the emergency department was considered an adverse event, generalized symptoms related to the underlying illness (fever, vomiting after discharge, diarrhea, or fatigue) were not considered to be adverse events. A data and safety monitoring board reviewed adverse outcomes in a blinded fashion.

STATISTICAL ANALYSIS

We estimated that the enrollment of 214 children would provide the study with a statistical power of 90 percent to detect a change from 35 percent

in the control group to 15 percent in the treatment group in the proportion of children who vomited during oral rehydration, given a two-sided type I error of 0.05. The calculation included a 10 percent adjustment for nonadherence of the caregiver to the therapy.[16]

Baseline characteristics of the two groups were compared by the chi-square or Fisher's exact test for proportions and the t-test for continuous variables. We used generalized estimating equations to account for the random effect that decision making by individual physicians might have had on the outcomes of interest, since the assumption of independence might not have been true for all outcomes.[17] Logistic models were used for the dichotomous outcomes of vomiting and intravenous hydration. A cumulative logit model was used for the ordinal outcome of the number of vomiting episodes, with the number of episodes defined as zero, one, two, or greater than or equal to three.[17] Since only nine children were hospitalized, Fisher's exact test was used to compare proportions between groups.

Because the child's age, race, and sex, the time of day, the presence or absence of fever, the hydration score, and the amount of fluid administered could influence the response to the study medication, these factors were included in all models. Other variables that were included when appropriate were the number of episodes of vomiting and diarrhea during oral-rehydration therapy and, in the 24 hours before triage, weight change, length of stay in the emergency department, and the type of physician caring for the child (pediatric emergency physician vs. urgent care physician). Because of sample-size limitations, the effect of each of these variables was determined individually. Those with a significant effect at the 0.2 level were included in multiple-predictor models. The treatment group (ondansetron or placebo) was included in all models. For the primary outcome of vomiting, the best four-predictor model based on deviance statistics was determined. Poisson models were used for length of stay in the emergency department and the number of episodes of diarrhea in the emergency department. A mixed-effects linear regression model was used for the outcomes of volume of oral-rehydration fluid and volume of intravenous fluid administered, with the physician as the random effect. Variables with significant interactions were considered together.[18]

The statistical model used for the primary outcome of vomiting, the mixed-effects models for outcomes based on physician's decision making, and the rule for including multiple predictors in regression models were specified in advance. For the number of vomiting episodes, we initially proposed using a Poisson model, but data analysis revealed that the Poisson distribution did not provide a good fit and that a cumulative logit model was more appropriate.

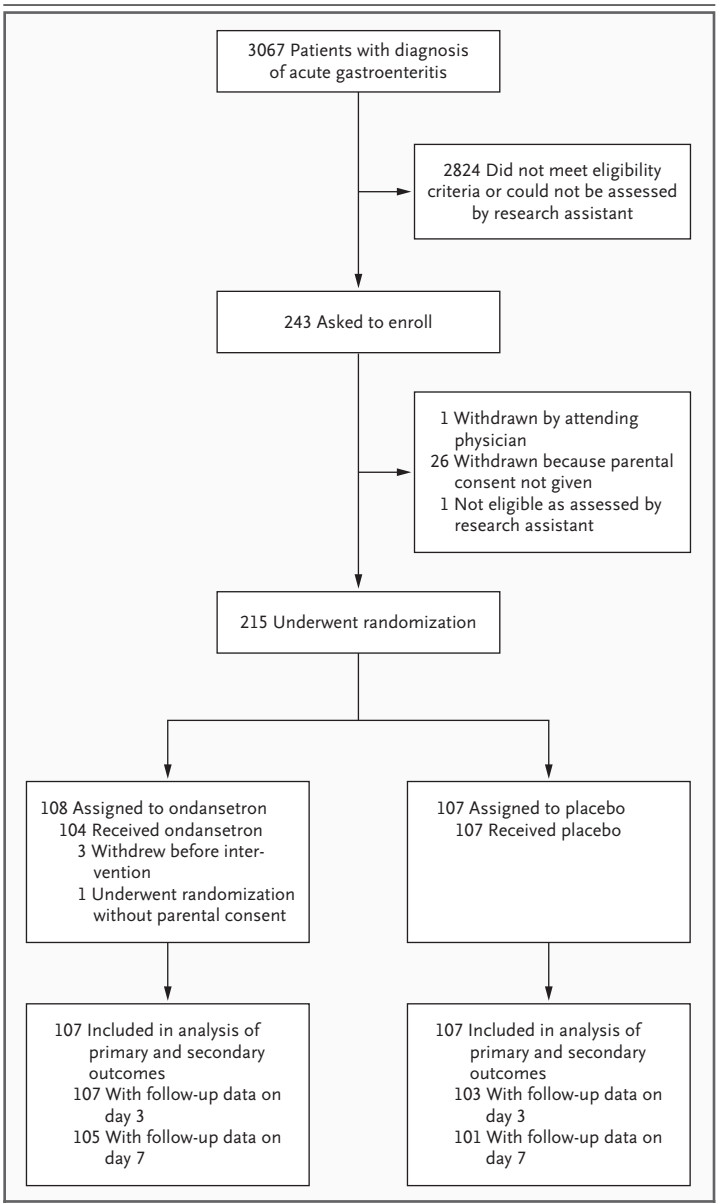

Figure 1. Enrollment and Outcomes.

The primary outcome was vomiting during oral rehydration in the emergency department after the receipt of ondansetron or placebo. The secondary outcomes were the mean number of episodes of vomiting, the rate of treatment with intravenous rehydration, and the rate of hospitalization.

Table 2. Baseline Characteristics of the Patients.*

Characteristic	Ondansetron Group (N=107)	Placebo Group (N=107)
Male sex — no. (%)	60 (56)	62 (58)
Age — mo	26±21	30±20
Weight — kg	13.1±5.3	13.7±5.5
Heart rate — beats/min	141±20	140±17
Dehydration score — no. (%)†		
9–10	29 (27)	24 (22)
11–12	51 (48)	58 (54)
13–14	20 (19)	20 (19)
15–16	7 (7)	5 (5)
Urinary measurements‡		
Specific gravity	1.026±0.007	1.025±0.006
Ketones	2.6±1.6	2.6±1.5
Vomiting — no. of episodes in preceding 24 hr	9.0±6.0	9.3±6.8
Diarrhea — no. of episodes in preceding 24 hr	5.8±4.5	6.2±5.2
Serum values at catheterization§		
Sodium — mmol/liter	138.8±6.7	136.8±2.9
Potassium — mmol/liter	4.2±0.5	4.1±0.5
Bicarbonate — mmol/liter	17.1±3.4	17.5±3.2
Blood urea nitrogen — mg/dl	16.4±10.0	18.3±6.4
Creatinine — mg/dl	0.49±0.12	0.54±0.14
Glucose — mg/dl	91±24	92±24

* Plus–minus values are means ±SD. There were no significant differences between the groups.
† Higher values indicate more severe dehydration.
‡ A total of 100 urine samples were obtained for analysis. Urinary ketone values are reported as 0 to 4+, with higher values indicating increasing ketonuria.
§ The measurements were performed on serum samples obtained at the time of insertion of the intravenous catheter in 48 patients (15 in the ondansetron group and 33 in the placebo group). To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert values for creatinine to millimoles per liter, multiply by 88.4. To convert values for glucose to millimoles per liter, multiply by 0.05551.

Relative risks and 95 percent confidence intervals are presented for all results. Analyses were performed with SAS software (version 9.1) according to the intention-to-treat principle. All P values are two-sided, with a P value of less than 0.05 used to indicate statistical significance, without adjustment for multiple comparisons.

RESULTS

PARTICIPANTS

During the study period, 243 potentially eligible patients were identified by the supervising physicians (Fig. 1). One child did not meet the criteria for dehydration after evaluation by the research assistant, and one child was withdrawn by the supervising physician because of severe dehydration. The caregivers of 26 children declined to participate. A total of 215 children were randomly assigned to treatment, 108 to ondansetron and 107 to placebo. There were no significant differences in baseline characteristics between the groups (Table 2).

Three children in the ondansetron group were withdrawn before receiving study medication. Database analysis revealed that one child in the placebo group did not meet the eligibility criteria. The only patient whose data were not analyzed was a child who was accidentally assigned to ondansetron before parental consent had been obtained and whose family chose not to participate.

Five children who received ondansetron vomited within 15 minutes. Each of these children was given a second dose, which was tolerated. Three children who received placebo vomited within 15 minutes. The parents of two of these children refused to allow a second dose to be given; the remaining child was given a second dose, which was tolerated.

OUTCOME

Of the 107 children in each group whose data were analyzed, 15 who received ondansetron vomited while receiving oral-rehydration therapy, as compared with 37 who received placebo (14 percent vs. 35 percent, P<0.001) (Table 3). After adjustment for the type of physician providing care, the relative risk was 0.40 (95 percent confidence interval, 0.26 to 0.61). The mean number of episodes of vomiting was significantly lower among children who received ondansetron than among those who received placebo (0.18 vs. 0.65, P<0.001). This difference remained significant after adjustment for the type of physician providing care (relative risk, 0.30; 95 percent confidence interval, 0.18 to 0.50).

Fifteen children in the ondansetron group (14 percent) and 33 in the placebo group (31 percent) received intravenous rehydration (P=0.003). The interaction effect between treatment group and whether a child vomited was significant (P=0.009); thus, separate models were used for children who vomited and those who did not. Among the 92 children in the ondansetron group and the 70 children in the placebo group who did not vomit, in-

Table 3. Outcome Measures.*

Outcome	Ondansetron Group (N=107)	Placebo Group (N=107)	Relative Risk (95% CI)†	P Value‡
Vomited during oral rehydration — no. (%)	15 (14)	37 (35)	0.40 (0.26–0.61)	<0.001
Mean no. of vomiting episodes	0.18	0.65	0.30 (0.18–0.50)	<0.001
Vomiting episodes per patient — no. (%)				
0	92 (86)	70 (65)		<0.001
1	12 (11)	21 (20)		0.13
2	2 (2)	7 (7)		0.17
≥3	1 (1)	9 (8)		0.02
Intravenous rehydration — no. (%)	15 (14)	33 (31)	0.46 (0.26–0.79)	0.003
Hospitalization — no. (%)	4 (4)	5 (5)	0.80 (0.22–2.90)	1.00
Oral-rehydration fluid consumed — ml	239±112	196±92		0.001
Intravenous fluid administered — ml/kg	38±8.9	46±9.1		0.002
Length of stay in emergency department — min	106±53	120±63		0.02

* Plus–minus values are means ±SD.
† The adjusted relative risk is reported for dichotomous outcomes. CI denotes confidence interval.
‡ All reported P values were adjusted as described in the text.

travenous hydration was less common in the ondansetron group (5 percent vs. 17 percent; P=0.01; relative risk, 0.32; 95 percent confidence interval, 0.13 to 0.77). Although, overall, children in the ondansetron group received a larger volume of oral-rehydration fluid and a smaller volume of intravenous fluid and had a shorter stay in the emergency department, hospital admission rates were similar in the two groups.

ADVERSE EVENTS

No cardiovascular or respiratory events occurred. Urticaria developed in one child in the placebo group. Children who received ondansetron had more episodes of diarrhea while undergoing oral rehydration than those who received placebo (1.4 vs. 0.5, P<0.001), even after adjustment for the number of episodes occurring before arrival. Follow-up, which was completed for 96 percent of the children (Table 4), did not reveal any additional adverse events. Kawasaki's disease was diagnosed in one child in the ondansetron group six days after randomization. The disease was not attributed to treatment.

DISCUSSION

We found that a single dose of ondansetron improves the success of oral rehydration in dehydrated children with gastroenteritis. The oral dose was well tolerated and resulted in a reduction of more than 50 percent in both the proportion of children who vomited during oral rehydration and the proportion treated with intravenous fluids. As compared with children who received placebo, children who received ondansetron had fewer episodes of vomiting, greater oral intake of fluids, and a shorter stay in the emergency department.

To prevent vomiting in 1 child, 5 children had to receive ondansetron (95 percent confidence interval, 3.2 to 10.6); to prevent 1 child from having to be treated by intravenous rehydration, 6 had to receive ondansetron (95 percent confidence interval, 3.6 to 17.0). These benefits were also reported in a previous study, which found that the administration of liquid ondansetron three times daily for two days reduced vomiting in the emergency department, the use of intravenous fluids, and the need for hospitalization among children.[4] However, that study did not report a reduction in vomiting after discharge, and children who were given ondansetron had significantly more episodes of diarrhea and return visits to the emergency department. We found that a single dose of oral ondansetron reduced vomiting and the need for intravenous fluids without any clinically significant adverse events.

Although there are no established criteria indicative of a need for intravenous rehydration, we

Table 4. Follow-up Data.*

Variable	Ondansetron Group (N=107)	Placebo Group (N=107)
Follow-up on day 3		
Completed follow-up — no./total no. (%)	107/107 (100)	103/107 (96)
Mean interval between enrollment and follow-up — days	3.7	3.7
Return visit to emergency department — no./total no. (%)	19/107 (18)	17/103 (17)
Intravenous rehydration — no./total no. (%)	13/107 (12)	10/103 (10)
Hospitalization — no./total no. (%)	6/107 (6)	6/103 (6)
Follow-up on day 7		
Completed follow-up — no./total no. (%)	105/107 (98)	101/107 (94)
Mean interval between enrollment and follow-up — days	7.8	7.9
Intravenous rehydration — no./total no. (%)	1/105 (1)	0/101
Hospitalization — no./total no. (%)	1/105 (1)	0/101
Follow-up on both days — no./total no. (%)		
Any return visit to emergency department	20/105 (19)	22/101 (22)
Any intravenous rehydration	14/105 (13)	10/101 (9)

* There were no significant differences between the groups.

found that fewer children in the ondansetron group than in the placebo group received intravenous fluids. Since the decision to administer intravenous fluids was made by the supervising physician, who was unaware of patients' treatment assignments, we believe this difference represents a true effect of treatment.

Ondansetron did not reduce the hospitalization rate (4 percent overall). The failure to find a reduction in the hospitalization rate might be due to a lack of statistical power. Our study was powered, on the basis of previous data, to detect a reduction from 15 percent to 3 percent.[4,19] Thus, the detection of a significant effect of ondansetron on the rate of hospitalization might be more likely in settings in which this rate was higher.[4,19]

The total cost of the ondansetron used in this study, based on actual costs of $35.75 per 4-mg orally disintegrating tablet at Children's Memorial Hospital, would have been $3,825. The reduction in cost resulting from the avoidance of the insertion of intravenous catheters ($124.74 per child) and hospitalization ($1,900 per admission)[19] was $4,145. Thus, the use of ondansetron may reduce overall costs while providing individual benefits.

A total of 19 percent of children in the ondansetron group and 22 percent of those in the placebo group returned to the emergency department. Although these rates are higher than previously reported rates,[4,19] only about half of those who returned received intravenous fluids. We chose to analyze the data from children who became dehydrated and presented to the emergency department for care and not to focus on children who sought additional care from a primary care provider.

Other antiemetic agents used in the treatment of pediatric gastroenteritis, although frequently prescribed,[20] either have substantial side effects or have not been well studied. A review of a pharmaceutical database revealed that promethazine accounted for 92 percent of all antiemetic prescriptions filled for gastroenteritis.[20] Adverse events associated with promethazine include drowsiness (71 percent) and respiratory depression, dystonia, and neuroleptic malignant syndrome.[21-24] Neither promethazine nor prochlorperazine has been studied in children with gastroenteritis. However, in adults, promethazine is less effective than prochlorperazine.[24] Data from adults suggest that drowsiness (38 percent)[24] and akathisia (44 percent)[25] are common adverse events. Other agents, such as trimethobenzamide, metoclopramide, and dimenhydrinate, either have been shown to be ineffective[26] or have never been evaluated in children with gastroenteritis.[23]

Our data suggest that it is safe to administer oral ondansetron to children with gastroenteritis, with diarrhea being the most notable side effect. Since culture of specimens for viral and bacterial causes is not routinely performed in children with gastroenteritis, we cannot rule out the possibility that viruses or bacteria may explain the differences in the frequency of diarrhea between groups. However, this is unlikely, given the similar baseline characteristics of the two groups and the fact that Ramsook et al.[4] also noted an increased rate of diarrhea among children given ondansetron.

We used an unvalidated scale for dehydration because of the lack of an externally validated scale and the conclusion of a recent meta-analysis that individual signs of dehydration are imprecise and inaccurate.[5] Thus, we grouped commonly used signs and symptoms[7-9] to improve the diagnostic

characteristics in order to identify children with evidence of dehydration. The dehydration score was successful in this regard, since the ratio of blood urea nitrogen to creatinine exceeded 20 in 96 percent of the children who underwent venipuncture. A similar result was obtained in a previous study of intravenous rehydration: 82 percent of the children had a ratio of blood urea nitrogen to creatinine of more than 20.[19]

We chose not to use the WHO classification of dehydration (no dehydration, some dehydration, and severe dehydration),[15] because it does not work well as a research tool in settings in which very few children are severely dehydrated. It would not have allowed us to distinguish children with some dehydration who needed only reassurance and minimal rehydration from children with some dehydration who required rehydration.

The oral-rehydration period in the emergency department was limited to one hour to mimic routine clinical practice, in which prolonged periods of observation are impractical. Oral-rehydration therapy might have been deemed successful in some of the children in whom it was considered to have failed if they had been observed for four hours, as recommended by the WHO.[15]

We found that treatment with orally disintegrating ondansetron tablets was beneficial in children with vomiting and dehydration due to gastroenteritis. The ondansetron tablet is easy to administer, has few side effects, and is safe and effective. Therefore, it may be a useful therapy in the emergency department for children with vomiting and mild-to-moderate dehydration as a result of gastroenteritis.

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