

A Randomized Clinical Trial Comparing Oral Ondansetron With Placebo in Children With Vomiting From Acute Gastroenteritis

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Study objective: Vomiting in children suffering from acute gastroenteritis interferes with the oral rehydration process and equally frustrates parents and health care providers. Adjuncts such as promethazine and metoclopramide are less than optimally effective and are associated with side effects. Ondansetron, a 5-HT₃ receptor antagonist marketed as Zofran, is a safe and effective antiemetic used extensively in oncology and postoperative patients. We evaluate the effect of the antiemetic ondansetron versus placebo on the clinical outcome of patients with vomiting from gastroenteritis in a pediatric emergency department.

Methods: This was a randomized, prospective, double-blind clinical trial in a university-affiliated children's hospital ED. Children between the ages of 6 months and 12 years who had vomited at least 5 times during the preceding 24 hours were randomized to receive either oral ondansetron or a taste- and color-matched placebo. Oral rehydration was commenced 15 minutes later at 5 mL/min per standard oral rehydration protocols. Patients were discharged after they voided and continued standard oral rehydration at home with the introduction of a bananas, rice, applesauce, and toast (BRAT) diet after the first 24 hours. Any patient requiring admission was considered a treatment failure, and no further doses were given. Discharged patients were given 5 additional doses to be used every 8 hours, and they were contacted by telephone 24 and 48 hours after discharge to record the number of episodes of vomiting and diarrhea. The parents were also required to complete a diary of the same information, which was mailed to the investigators for confirmation of the telephone data.

Results: One hundred forty-five patients were enrolled, of whom 51% (n=74) were randomized to ondansetron. At baseline, age distribution, sex, and severity of illness did not differ between the ondansetron and placebo groups. During the observation period in the ED, the median number of episodes of

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vomiting was 0 in both groups, but the rank sum of vomiting episodes was significantly lower in the ondansetron group ($P=.001$). The number of episodes of emesis in the ED after enrollment ranged from 0 to 7 in the placebo group and 0 to 2 in the ondansetron group. During the 48 hours of follow-up, the median number of episodes of vomiting remained 0, with no statistically significant difference between the groups. There was no statistically significant difference in the rank sum of episodes of diarrhea in the ED between the groups ($P=.622$); however, during the next 48 hours, the patients in the ondansetron group had significantly more diarrhea than the placebo group. A lower proportion of patients receiving ondansetron compared with placebo required intravenous fluid therapy ($P=.015$). The admission rate was also lower in patients receiving ondansetron ($P=.007$). The revisit rate was higher in the ondansetron group compared with the placebo group ($P=.047$).

Conclusion: Ondansetron was effective in reducing the emesis from gastroenteritis during the ED phase of oral rehydration and in lowering the rates of intravenous fluid administration and hospital admission.

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INTRODUCTION

Acute gastroenteritis is a common disease resulting in significant morbidity in young children. The recommended first-line treatment is oral rehydration, unless contraindications exist such as persistent vomiting, ileus, obtundation, shock, or impending shock.¹ Oral rehydration has been proven safe and cost-effective and is the recommended first-line therapy for acute gastroenteritis by the American Academy of Pediatrics (AAP).² Parents often become discouraged even with one episode of emesis during the rehydration phase, despite overall oral rehydration failure rates of 5% to 20%.³⁻⁵ Multiple drugs have been tried to assist oral rehydration, with varying degrees of success and complicating side effects. The use of promethazine (Phenergan) is widespread but has a failure rate of 31% and results in mild to moderate drowsiness in 71% of patients with gastroenteritis.^{6,7} This interferes with the oral rehydration process and the assessment of lethargy. Promethazine is also associated with extrapyramidal side effects. Metoclopramide has also been tried, but low efficacy and the relatively high incidence of side

effects, such as somnolence, nervousness, irritability, and dystonic reactions, have limited its use.⁸

Emesis is a complicated process involving several anatomic regions, receptors, and neurotransmitters. Stimulation of these vomiting regions is mediated by neurotransmitters such as serotonin, dopamine, opiates, choline, and histamines, and the blocking of these receptors is presumed to be the mechanism of existing antiemetics. Serotonin receptor subtypes (ie, 5-HT₃) receptors are found in high concentration in both the peripheral and central nervous system, especially the chemoreceptor trigger zone (CTZ). More than 80% of the total body 5-HT is contained in the enterochromaffin cells of the gastrointestinal mucosa in the area of the vagal afferent nerves.⁹ Vomiting in gastroenteritis probably results from gut mucosal damage induced by viral or bacterial pathogens, triggering the release of serotonin from enterochromaffin cells that act through receptors on the vagal afferent nerves. These nerves stimulate the vomiting center and the CTZ to induce emesis similar to chemotherapy-induced damage to the gut mucosa. In addition, metabolism of cytotoxic drugs may produce metabolites that directly stimulate the CTZ, thereby causing delayed emesis, and it is possible that similar metabolites are produced in gastroenteritis.¹⁰

Ondansetron, a selective 5-HT₃ receptor antagonist marketed as Zofran, is a safe and effective antiemetic used extensively in oncology and postoperative patients.¹¹⁻¹⁴ Ondansetron was first synthesized in 1983 and became available for clinical use in 1991.¹⁵ It is completely and rapidly absorbed from the gastrointestinal tract after oral administration, with the drug being first detected in plasma 30 minutes after administration of an oral dose but with the time to peak concentration in adults being 1.7 to 2.2 hours.¹⁶ As a result of first-pass metabolism, its bioavailability is only approximately 60%, compared with ondansetron given by intravenous infusion over a 15-minute period.¹⁶ Hepatic oxidative metabolism accounts for more than 95% of ondansetron clearance, and it does not accumulate with repeated oral administration. The cerebral 5-HT₃ receptor binding site of ondansetron is the area postrema, which contains the CTZ. Ondansetron also acts peripherally in the upper gastrointestinal tract, where it blocks 5-HT₃ receptors on vagal afferent nerve terminals.¹⁰ The use of ondansetron in acute gastroenteritis was first reported by Cubeddu et al,¹⁷ who used a single intravenous dose and compared its effect with metoclopramide and placebo in the ensuing 24 hours. In the ondansetron group, the frequency of emesis was lower, and a larger proportion had no emesis in the subsequent 24 hours.

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In the randomized, controlled trial described here, we studied the role of oral ondansetron in patients presenting to a pediatric emergency department with acute gastroenteritis. We report the effect of oral ondansetron on clinical outcomes including frequency of vomiting, oral rehydration, and hospital admission.

MATERIALS AND METHODS

This was a randomized, controlled trial designed to test the hypothesis that the administration of oral ondansetron to patients with acute gastroenteritis leads to a clinically relevant reduction in vomiting (emesis) and rates of intravenous fluid administration. The primary outcome measures were the frequency of emesis during the 48-hour period after enrollment and the rates of intravenous fluid administration. The secondary outcomes were admission rates and the frequency of diarrhea.

A true random allocation procedure was designed using standard random number allocation tables. The pharmacy research section assigned treatment or placebo according to this individual randomization. The study was double-blind in that neither the investigators (including persons administering the drug, the ED staff, and the outcome assessors) nor the patients and their families knew of the treatment assignment. On enrollment, the pharmacy provided the drug or a color-, taste-, and odor-matched placebo in identical packaging according to the randomization code. The pharmacy team was not privy to the enrolled patients or the outcome measures. This code remained locked within the pharmacy research section and was broken and revealed to the investigators only at the close of the study.

Study participants were recruited from the ED at Texas Children's Hospital, Houston, TX. Both informed parental consent and patient assent, where appropriate, were obtained. This study was approved by the Institutional Review Board.

A clinical definition of gastroenteritis as the presence of vomiting with or without diarrhea was used.^{18,19} Patients were eligible for entry if they were 6 months to 12 years of age, had at least 5 episodes of vomiting in the preceding 24 hours, and did not receive any antiemetics. Patients were excluded if they had underlying chronic conditions (eg, malignancy, gastroesophageal reflux, migraine), possible appendicitis, urinary tract infection, or severe gastroenteritis requiring immediate intravenous fluids.

Patients were randomized to either the oral ondansetron (strawberry flavor) group or the taste- and color-matched placebo group. The dose of ondansetron was based on

oncology data, in which 4 mg (children) or 8 mg (adults) is given 30 minutes before chemotherapy and then every 8 hours for 1 to 2 days.²⁰ The doses of ondansetron used in this study for gastroenteritis were 2 mL (1.6 mg) every 8 hours for patients aged 6 months to 1 year, 4 mL (3.2 mg) every 8 hours for patients aged 1 to 3 years, and 5 mL (4 mg) every 8 hours for patients aged 4 to 12 years. Oral rehydration was initiated 15 minutes after the first dose of ondansetron or placebo at 5 mL/min, according to standard oral rehydration protocols.^{21,22} Our rehydration protocol used unflavored pedialyte as the first-choice fluid, the only electrolyte solution available to us at that time. Although pedialyte is a maintenance solution by AAP recommendations, it has been successfully used as a rehydrating solution in mild to moderately dehydrated patients.^{23,24} For patients who refused this fluid because of palatability, a mixture of Gatorade and Pedialyte (Ross Nutritionals, Columbus, OH) or Gatorade alone was tried. This applied mainly to school-aged children in whom the lower electrolyte composition of Gatorade and the mixture of Gatorade and Pedialyte was accepted. There was a written rehydration protocol that listed the order of fluid choices and the fluids to avoid (water, soda, juices, coffee, and tea). Patients were reassessed at 30-minute intervals and discharged after they successfully tolerated oral fluids and voided in the ED. They continued standard oral rehydration therapy with introduction of a bananas, rice, applesauce, and toast (BRAT) diet after the first 24 hours.²⁵ Those patients who vomited more than 3 times were reevaluated by a physician, and intravenous fluids were given, followed by reinitiation of oral rehydration 30 to 60 minutes later. Additionally, intravenous fluids were given if the patient refused oral intake according to the rehydration protocol. Any patient receiving intravenous fluids who had persistent vomiting or who still refused oral fluids was admitted. These patients were considered treatment failures and were not given additional doses because of the variability of inpatient management among different physicians. For those patients discharged home, the total number of medication doses was 6 (first dose in the ED and then every 8 hours for 2 days).

In the ED, the number of episodes of emesis and diarrhea was documented, as was the administration of intravenous fluids and admission to the hospital. Attempts were made to contact all participants by telephone at 24 and 48 hours after discharge to record the number of episodes of vomiting and diarrhea during these intervals. The parents were also required to complete a diary of this same information and mail it to the investigators for confirmation of the telephone information. Any return visits

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to the ED were noted, along with the reason for the revisit.

Inclusion criteria required at least 5 episodes of vomiting in the prior 24 hours, and a treatment success was defined as 2 or less episodes of vomiting per day in the 2 days after enrollment. Based on a 2-group comparison of proportions, with an estimated success rate of 80% in the ondansetron group and 60% in the placebo group, a sample size of 91 was calculated for each group. Because of time constraints relating to the gastroenteritis season, the study was terminated before achieving the calculated sample size. The intention-to-treat analysis principle was followed. The χ^2 test, Student's *t* test, and Wilcoxon rank sum test were used to compare between the groups variables at the nominal, interval, and ordinal level of measurement, respectively. Statistical significance was set at a *P* value of less than .05. Analyses were conducted with the SAS (SAS Inc., Cary, NC) statistical software.

RESULTS

A total of 145 patients were recruited into the study; 74 were randomized to ondansetron and 71 to placebo. At baseline, age distribution, sex, and severity of illness, as measured by the number of episodes of vomiting in the 24 hours before enrollment, were similar between the ondansetron and placebo groups (Table 1).

The frequency of emesis during the ED observation period after enrollment ranged from 0 to 7 in the placebo group and from 0 to 2 in the ondansetron group. The median number of episodes of vomiting was 0 in both groups, but the rank sum of vomiting episodes was signif-

icantly lower in the ondansetron group (*P* = .001). The proportion of patients who had no vomiting after enrollment was greater for those receiving ondansetron compared with placebo during the ED stay (*P* = .004), although statistical significance was not retained beyond that period (Table 2).

At both the 24- and 48-hour follow-up, the median number of episodes of vomiting remained 0, with no statistically significant difference between the groups (Table 3). The number of patients excluded from analysis because of being lost to follow-up or because of admission is shown in the trial profile (Figure 1).

A smaller proportion of patients receiving ondansetron compared with placebo required intravenous fluid therapy (*P* = .015; Figure 2).

The mean duration of stay in the ED after enrollment was 3 hours with placebo and 2 hours with ondansetron (*P* = .069). The admission rate was lower in patients re-

Table 1.
Baseline characteristics of participants.

Characteristic	Ondansetron Group, n (%)	Placebo Group, n (%)
Age		
6 mo to 1 y	8 (10.82)	6 (8.45)
1-4 y	42 (56.76)	43 (60.56)
4-12 y	24 (32.43)	22 (30.99)
Sex		
Boys	45 (60.81)	37 (52.11)
Girls	29 (39.19)	34 (47.89)
Severity of illness (No. of vomiting episodes during the preceding 24 h)		
<10	37 (50)	40 (56.33)
≥10	37 (50)	31 (43.66)

Table 2.
Comparison of complete antiemesis between ondansetron and placebo groups.

Proportion of Patients With No Emesis	Ondansetron Group		Placebo Group		<i>P</i> Value
	N*	n (%)	N*	n (%)	
During ED Stay	74	64 (87)	71	46 (65)	.004
First 24-h period	64	37 (58)	56	30 (54)	.8
Second 24-h period	62	43 (70)	51	30 (59)	.2

*Denotes number of patients on whom follow-up data were obtained. Missing patients were excluded from analysis.

Table 3.
Comparison of the antiemetic effect between ondansetron and placebo groups.

Episodes of Emesis	Ondansetron Group			Placebo Group			<i>P</i> Value
	N*	Mean	Median	N*	Mean	Median	
During ED stay	74	0.18	0	71	0.83	0	.001
First 24-h period	64	0.75	0	56	0.96	0	.96
Second 24-h period	62	0.37	0	51	0.53	0	.86

*Denotes number of patients on whom follow-up data were obtained. Missing patients were excluded from analysis.

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ceiving ondansetron ($P=.007$; Figure 2). There was no statistically significant difference in the rank sum of episodes of diarrhea in the ED between the groups ($P=.622$); however, over the next 48 hours, the patients in the ondansetron group had significantly more diarrhea than those in the placebo group (Table 4). The revisit rate was higher in the ondansetron group (4/74; 5.41%) compared with the placebo group (0/71; 0%; $P=.047$). Two of the 4 patients returned for persistent vomiting, and 2 returned for persistent diarrhea. Only 1 of these 4 patients had any vomiting (2 episodes) during the period in the ED.

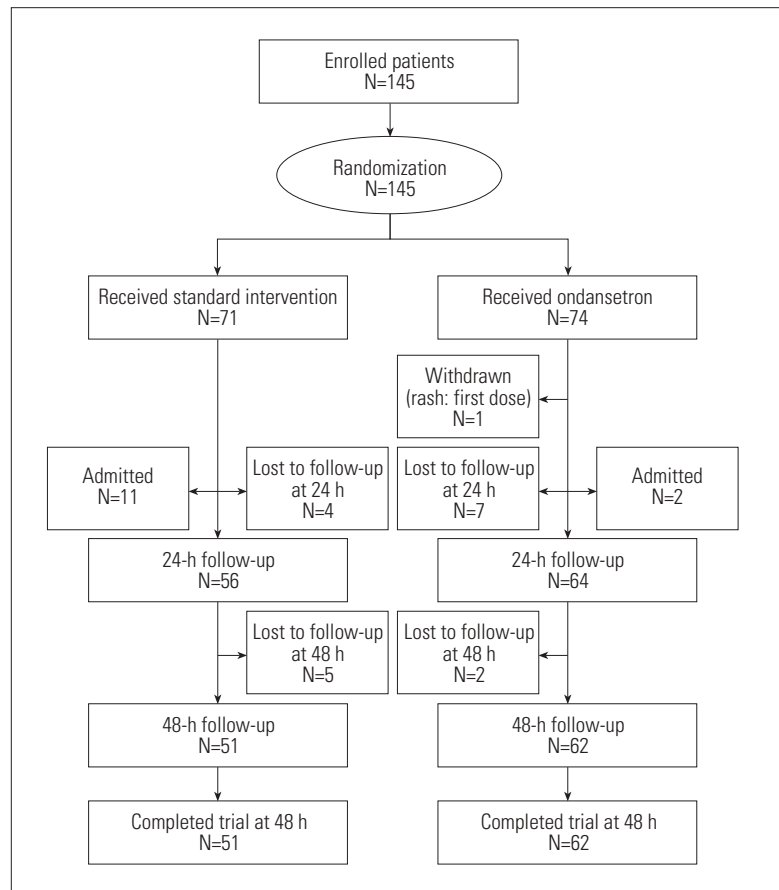
DISCUSSION

In this randomized, double-blinded, clinical trial, ondansetron did not reduce the overall frequency and proportion of patients with vomiting, except during the ED period. The most likely explanation is that the patients enrolled in the study were not sufficiently ill

(only ≥ 5 episodes of vomiting in the preceding 24 hours). In addition, patients with mild gastroenteritis often have their peak of vomiting on the first day of the illness. This may explain why both the treatment and placebo groups had a median number of zero episodes of emesis on follow-up. This finding may not apply to patients with more severe gastroenteritis who continue to vomit after the first day of the illness and may benefit from subsequent doses of ondansetron. More importantly, ondansetron resulted in a reduction of the frequency with which intravenous fluids and hospital admission were required.

Patients receiving ondansetron returned to the ED more often than those in the placebo group. Two patients returned because of persistent diarrhea. Although this has not been a problem in oncology or postoperative patients taking ondansetron, our patients with acute gastroenteritis had 3 times more diarrhea than those in the placebo group. This probably reflects a side effect of the drug in patients with increased motility from gastroenteritis as also reported by Cubeddu et al.¹⁷ Perhaps

Figure 1.
Trial profile of ondansetron in acute gastroenteritis.



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shorter dosing regimens might cause less diarrhea without compromising efficacy. Three out of these 4 patients had no vomiting during the ED period, implying that the ondansetron was successful as an antiemetic in the initial phase of rehydration, although it failed to prevent a return visit.

The only other side effect in this study was the development of a macular rash in 1 patient 30 minutes after receiving ondansetron without urticaria or respiratory symptoms. It was unclear whether this rash was drug related or a viral exanthem. With the exception of diarrhea, none of the manufacturer's listed side effects (headache, malaise, constipation, diarrhea, dizziness, abdominal pain, xerostomia, and weakness) were reported. These have been reported in adult patients taking 8 mg 3 times a day, with the most common being headache in 27% and all others being less than 10% (most <5%).²⁰ Accidental administration of ondansetron at 10 times the normal dose has been reported with no side effects (Micromedex, Greenwood Village, CO). Ondansetron has been well tolerated in pediatric studies including

those younger than 4 years of age, although pharmacokinetic data in these patients are lacking.²⁶

In this era of managed care and cost containment, alternatives to aggressive therapies and hospital admission are valuable to both patients and health care systems. Cost-effective analysis refers to the full economic evaluation in which drug acquisition costs and costs incurred using a particular treatment are assessed together with clinical efficacy. Cost-effectiveness studies comparing ondansetron with metoclopramide in oncology patients have shown that ondansetron administered three times a day is at least as cost-effective as metoclopramide, while twice-a-day regimens are more cost-effective.²⁷ Hospital acquisition costs for ondansetron are approximately US\$4.01 per milligram for intravenous ondansetron and less for oral preparations, but patient charges vary greatly nationwide.²⁸ Given the cost of intravenous fluid therapy, especially if it includes admission,⁵ single-dose ondansetron at a cost of less than US\$20 is an attractive alternative. Perhaps the most useful regimen would be a total of 3 doses during a 24-hour period, during which time oral rehydration can be successfully completed. The economic benefit of such a regimen remains speculative.

There are several limitations to this study. First, spontaneous remission of vomiting in a large proportion of enrolled patients suggests that the severity of illness for study inclusion should have been set at a higher level. Additionally, using a shorter time period, such as the presence of vomiting within the past 2 hours rather than during the prior 24 hours, may have identified patients most likely to benefit from an antiemetic. Second, the sample size may have been inadequate to detect small differences in the frequency of vomiting during the 48-hour period, especially because 10% to 15% of patients were

Figure 2.

Intravenous fluid administration and admission rates between ondansetron and placebo. IVF, Intravenous fluid.

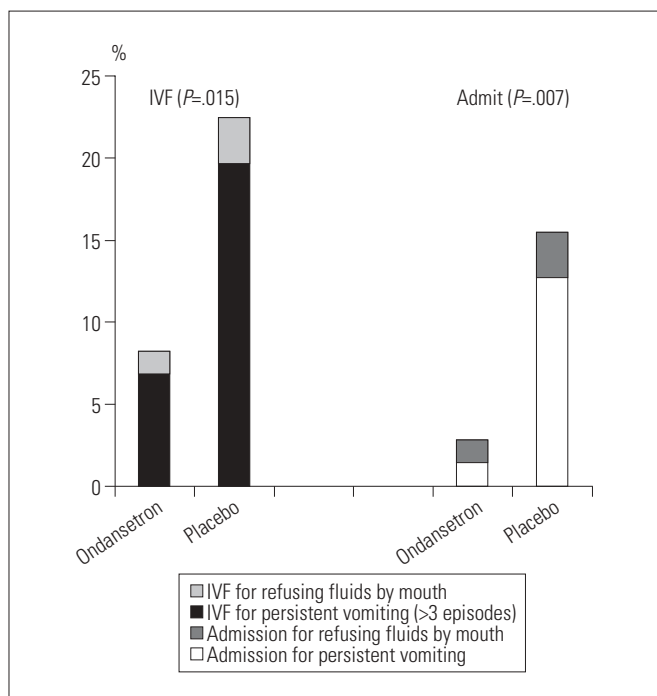


Table 4.

Comparison of diarrhea between ondansetron and placebo groups.

Episodes of Diarrhea	Ondansetron Group			Placebo Group			P Value
	N*	Mean	Median	N*	Mean	Median	
During ED stay	74	0.70	0	71	0.61	0	.622
First 24-h period	64	4.70	2	54	1.37	0	.002
Second 24-h period	62	2.98	0	51	0.96	0	.015

*Denotes number of patients on whom follow-up data were obtained. Missing patients were excluded from analysis.

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lost to follow-up by telephone and mail-in diary. Third, the elimination of diarrhea from the inclusion criteria may have led to enrollment of patients with uncomplicated gastritis rather than true gastroenteritis.¹⁹ For many clinicians, this distinction is academic and may not diminish the significance of the results of this study. Lastly, compliance with the medication, oral rehydration, and the BRAT diet guidelines could not be assured and may have influenced some outcome measures such as frequency of vomiting during the follow-up period.

In summary, ondansetron was effective in lowering the rates of intravenous fluid administration and hospital admission in patients with vomiting from acute gastroenteritis. Reduction in the frequency of vomiting was less significant and evident only during the ED stay.

Author contributions: CR and DM-S conceived the study, designed the trial, and obtained funding from GlaxoWellcome. CR, DM-S, and IS-C undertook recruitment, data collection, and supervision of the project. CAK provided statistical advice on design, sample size estimation, and analyzed the data. CR drafted the manuscript, and all authors contributed substantially to its revision. CR takes responsibility for the paper as a whole.

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