Ondansetron Decreases Vomiting Associated With Acute Gastroenteritis: A Randomized, Controlled Trial

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ABSTRACT. *Objective.* **Relatively little research has examined the role of antiemetic agents in the treatment of acute gastroenteritis. The use of the selective 5-HT_3 receptor antagonists (eg, ondansetron) offers a potentially valuable treatment option. The objective of this study was to evaluate the efficacy of ondansetron for the treatment of vomiting associated with acute gastroenteritis in children.**

Methods. **A randomized, double blind, placebo-controlled trial was conducted in the emergency department of a tertiary-care children's hospital. Eligible patients were 1 month to 22 years old and required intravenous fluids for gastroenteritis. Of 172 patients approached, 107 were enrolled (54 to intravenous ondansetron, 53 to placebo). The mean age was 5.3 years, and 53% of the patients were male. The frequency of vomiting, admission rate, and occurrence of complications were measured.**

Results. **After drug administration, 38 (70%) of the 54 patients in the ondansetron group had complete cessation of vomiting compared with 27 (51%) of the 53 patients in the placebo group. Sixteen (30%) of the 53 patients in the placebo group required admission compared with 14 (26%) of the 54 in the ondansetron group. An analysis of previously untreated patients with a measured serum carbon dioxide ≥15 mEq/L showed that 11 (23%) of the 47 who received placebo were admitted compared with 3 (7%) of the 43 who received ondansetron. No significant complications were detected.**

Conclusions. **Intravenous ondansetron decreases vomiting in children with gastroenteritis. In addition, ondansetron reduces the need for admission in those who are treated at an initial visit to the emergency department and have a measured serum carbon dioxide ≥15 mEq/L. The safety and low cost of this therapy suggests that ondansetron can be valuable in treating gastroenteritis in children.** *Pediatrics* **2002;109(4). URL: http://www.pediatrics.org/cgi/content/full/109/4/e62;** ***pediatric, gastroenteritis, vomiting, ondansetron, antiemetic.***

ABBREVIATIONS. ED, emergency department; CO_2, carbon dioxide.

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Approximately 30 million children in the United States develop acute gastroenteritis every year. Of these, 3 million seek evaluation by physicians, and a large number of these patients are treated in emergency departments (EDs). An estimated 220 000 children younger than 5 years are hospitalized every year for treatment of dehydration secondary to acute gastroenteritis.[1–6]

Current recommendations for the treatment of acute gastroenteritis focus primarily on the correction of dehydration and electrolyte abnormalities. Oral rehydration is the preferred therapy in mild to moderate dehydration, whereas intravenous fluids are recommended in more severe cases. Administration of an antiemetic drug, which could safely suppress vomiting, would be useful in promoting successful oral rehydration. Although several studies have shown some benefit with the use of antiemetic medications, including prochlorperazine, promethazine hydrochloride, and metoclopramide, clinical experience with these drugs has revealed an unacceptably high incidence of adverse effects, such as sedation and extrapyramidal reactions.[7–12] Reflecting this unfavorable clinical experience, we could find no recent review articles or guidelines in which the use of antiemetic agents for the treatment of childhood gastroenteritis was encouraged. Recent guidelines published by the American Academy of Pediatrics for the treatment of gastroenteritis expressed concerns about the frequency of adverse effects such as sedation and extrapyramidal reactions, seen with older antiemetics.[1] Although a number of investigators have examined newer antiemetic agents such as ondansetron in other areas of clinical practice where mitigation of nausea and vomiting is the goal, few studies have been done to identify agents that can control the vomiting associated with acute gastroenteritis in the ambulatory setting.[13–19] The main objective of this trial was to study the safety and efficacy of ondansetron, a recently developed 5-HT_3 receptor antagonist, in the treatment of the vomiting associated with gastroenteritis in children seen in a pediatric ED.

METHODS

The study design was a double-blind, randomized, placebo-controlled clinical trial. This investigation was performed in the Children's Hospital Boston ED between May 15, 1999, and May 1, 2000. This ED has a census of approximately 50 000 visits annually.

Patients who were between the ages of 1 month and 22 years, had vomiting from acute infectious gastroenteritis, and were identified as requiring intravenous fluids for rehydration were eligible

for enrollment. This age range was selected to capture the population of patients seen at our institution. An attending physician in pediatric emergency medicine made the diagnosis of apparent infectious gastroenteritis and then determined the need for intravenous fluids on a clinical basis. Because the primary goal was the control of emesis, patients were enrolled only when they had had 3 or more episodes of vomiting in the previous 24 hours. Typically, the vomiting associated with gastroenteritis precedes the diarrheal symptoms of this disease.[3] To help ensure that our study population reflected clinical practice, we did not require the presence of diarrhea and/or fever for enrollment as long as the overall clinical picture, as determined by an experienced practitioner, was gastroenteritis. Because the study protocol included telephone follow-up, access to a home telephone or pager was required. Patients were excluded when they had received any antiemetic therapy within 72 hours of enrollment or had a history of hepatic disease or a past adverse drug reaction to ondansetron. Patients were also excluded when they had diarrhea that had been present for >7 days; a history of chronic gastrointestinal disease; or any preexisting active medical condition, such as congenial heart disease, malignancy, immunodeficiency, cystic fibrosis, sickle cell anemia, or diabetes mellitus. The presence of headache or a focal neurologic examination was also an exclusion criteria.

One of 3 trained research assistants conducted patient enrollment Monday through Friday from 4 to 11 PM and on Saturday and Sunday from noon to 5 PM. At other times, patient enrollment was performed by 1 of the study investigators. Patients who were believed to have infectious gastroenteritis by clinical assessment and to be in need of intravenous fluids, as judged by the emergency physician, were approached for study enrollment. A questionnaire detailing demographics, history of present illness, medical history, allergies, and medications was completed, and written informed consent was obtained. A log of all patients who were approached for enrollment was kept, and reasons for refusal were recorded. After enrollment, intravenous fluids were instituted as an initial 20-mL/kg bolus of 0.9% saline followed by 5% dextrose in 0.45% saline solution at twice the patient's maintenance rate. Serum electrolytes, blood urea nitrogen, and creatinine were obtained on all patients in accordance with previously designed practice guidelines. Children with symptoms suggestive of bacterial enteritis (eg, grossly bloody stools, fever above 39.0°C) underwent stool swab for white blood cells, stool guaiac, and stool cultures. Other laboratory studies were obtained at the discretion of the treating physician.

A computer randomization code was produced by a member of the medical school's center for clinical investigation. Blocking was used in groups of 4, 6, or 10 as generated randomly by computer to ensure that equal numbers of patients were enrolled in both the control group and the treatment group throughout the study. This randomization code was controlled by the center for clinical investigation and provided to the pharmacy for drug distribution. All providers except the pharmacist were blinded to group assignment until after data analysis. The study investigators remained blinded until after complete statistical analysis was performed to test the primary and secondary outcome measures. The pharmacy provided a single syringe, labeled "gastroenteritis study drug," that contained either ondansetron (Zofran Injection; Glaxo Wellcome Inc, Research Triangle Park, NC) calculated to provide a dose of 0.15 mg/kg (maximum of 8 mg) or an equal volume of 0.9% saline solution. The appearance of ondansetron is indistinguishable from that of 0.9% saline. The contents of the syringe were administered intravenously over 2 minutes, followed by 3 to 5 mL of a 0.9% saline flush. Drug administration was performed during the initial fluid bolus. Repeat doses of the study drug were not given, and no other antiemetic medications were allowed during patient enrollment. Antipyretics were given when indicated for fever. Other medications given to the patient either during the visit or after discharge were recorded. All patients were kept in the ED for at least 1 hour after drug administration before final disposition was made. This length of time was determined by the pharmacologic profile of ondansetron. The antiemetic properties of intravenous ondansetron has been shown in previous studies to be <20 minutes.[20,21] Decisions on repeat fluid boluses, duration of fluid administration, and need for hospital admission all were left to the discretion of the attending physician. In accordance with preexisting institutional practice guidelines at our institution, patients with a measured serum carbon dioxide (CO_2) of ≤14 mEq/L or a history of intravenous hydration for the same illness were generally admitted. Both of these factors are believed to indicate a more serious level of dehydration and need for hospitalization. Information collected by the study investigators was not used in determining the need for hospital admission.

The primary outcomes recorded were the frequency of vomiting episodes after drug administration and the need for hospitalization. A vomiting episode was defined as any episode of forceful expulsion of stomach contents. Nonproductive retching, spilling of oral contents during feeding, and drooling were not considered vomiting episodes. Vomiting episodes were recorded by the research assistant or investigator while the patient was in the ED. After patients left the ED, the frequency and timing of vomiting episodes and other symptoms were determined from inpatient nursing flow sheets and home symptom journals, completed by parents and/or adult patients. Standardized telephone follow-up was performed 5 to 7 days after patient enrollment. Vomiting episodes were tabulated in 24-hour blocks starting from the time of drug administration until reported cessation of vomiting. After the initial analysis of hospitalization rate was performed, a subgroup analysis was performed, limited to those patients who did not fulfill the requirements for admission in the established clinical practice guidelines (CO_2 ≤14 mEq/L, previous visit for fluid therapy). Secondary outcomes included duration of vomiting symptoms after drug administration, number and duration of diarrhea symptoms, frequency of return visits to an urgent or emergency care center, need for readministration of intravenous fluids, and need for later hospital admission. Length of stay in the ED, duration and amount of intravenous fluids given, and duration of hospitalization were also recorded, as were any observed complications. Although specific safety parameters were not measured, data collection was constructed to help identify potential complications. All potential complications noted from chart review, symptom journal, and telephone follow-up were recorded. To help ensure complete data collection and to help confirm that the initial clinical diagnosis of gastroenteritis was correct, we followed all patients by telephone until resolution of their vomiting symptoms.

The study sample size was calculated as follows. On the basis of a retrospective review of ED records, we anticipated that 40% of the patients in the control group would be admitted to the hospital for treatment of gastroenteritis. We sought to detect a 50% reduction in admission rate after use of ondansetron, ie, reduction in admission rate to 20% or less. At the end of the gastroenteritis season in 2000, an independent statistical advisor and study monitor reevaluated the sample size calculation. The advisor noted that admission rates were lower than anticipated in the control group, thus invalidating our a priori sample size estimate. A more accurate sample size of 106 total patients was calculated. On the basis of this more realistic sample size calculation and the desire not to delay significantly the availability of study results by waiting to enroll additional patients during the next gastroenteritis season, we decided to stop enrollment at the end of the 2000 gastroenteritis season. This decision was made before release of the randomization codes and unblinding of the investigators. The Children's Hospital Committee on Clinical Investigation approved this study and the modification described above. Statistical analyses were performed using the Statistical Package for the Social Sciences (Windows Version 9.0.0; SPSS, Inc, Chicago, IL) and consisted of the χ^2 or Fisher exact test for categorical variables; an unpaired, 2-tailed Student t test for continuous variables; and the Mann-Whitney U test for ordinal variables. Significance was established at $P < .05$.

RESULTS

During the study period from May 1999 to May 2000, 172 children between the ages of 1 month and 22 years were approached for study enrollment. Of these, 107 (62%) provided informed consent. Of these 107 patients, 105 (98%) received the study drug; 2 (2%) did not complete the study because of loss of or failure to obtain intravenous access before drug or fluid administration. All 107 patients were included for data analysis as an intent-to-treat population (Fig 1).

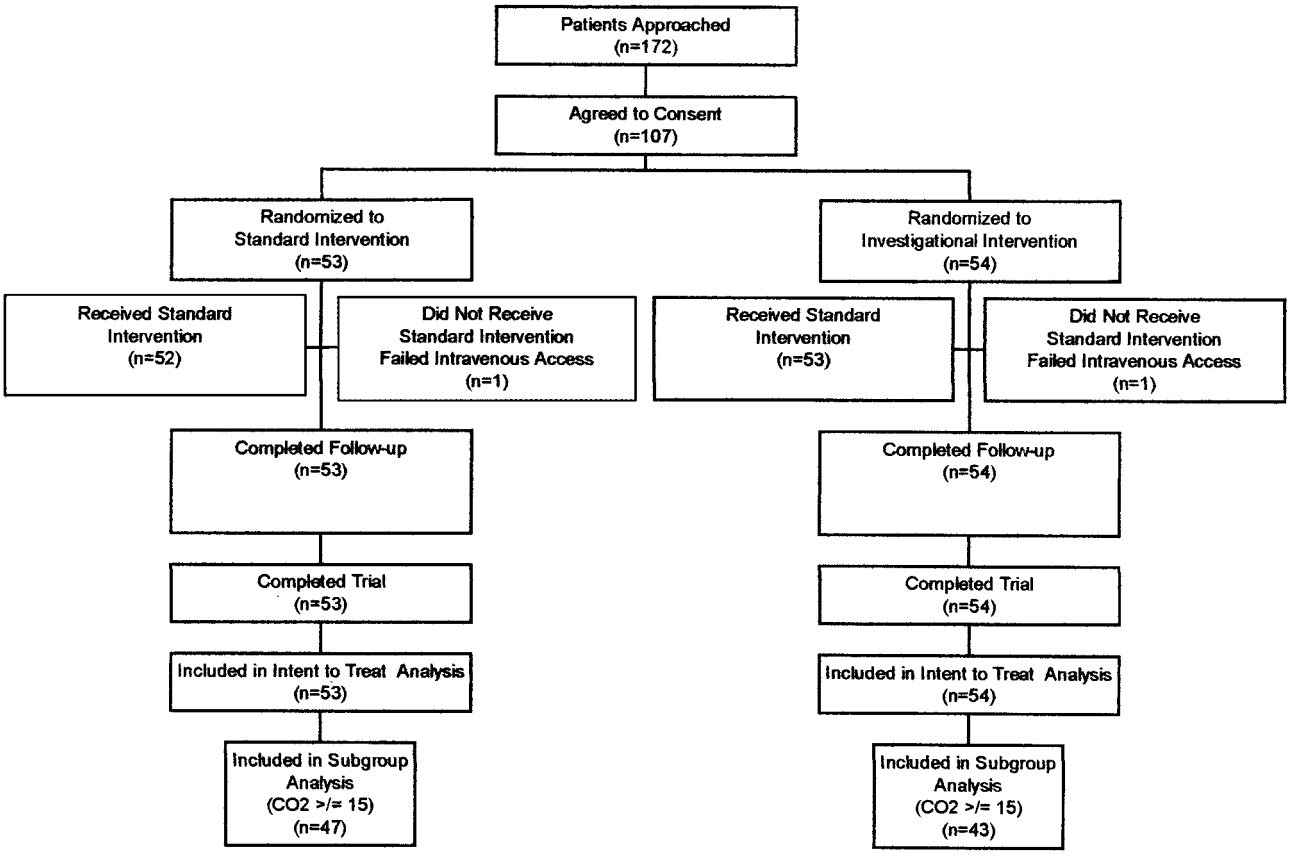

Fig 1. Profile of randomization and allocation of patients.

Of the 107 patients, 53% were male with a mean age of 5.3 years (standard deviation: ±4.9). The ondansetron group had 54 patients, and the placebo group had 53. No significant differences were noted between the 2 groups with respect to patient demographics, duration and frequency of symptoms, presence of fever, presence of other medical problems, or a previous visit to a physician (Table 1). A significantly higher proportion of patients randomized to ondansetron had a measured serum CO_2 of ≤14

TABLE 1. Demographic Characteristics of the Study Population

	Ondansetron (N = 54)	Placebo (N = 53)
Age (y ± SD)	4.7 ± 4.2	6.2 ± 5
Age range	3 mo–19 y	7 mo–22 y
Gender (% male)	52	55
Race (%)		
White	50	55
Black	9	15
Hispanic	33	26
Other	8	4
Insurance type (%)		
Private	74	66
Public	26	32
No insurance	0	2
Vomiting in previous 24 h (median [range])	7 (3–30)	8 (3–40)
Presence of diarrhea (%)	57	60
Diarrhea in previous 24 h (median [range])	4.5 (1–20)	3 (1–20)
Fever in ED (% above 38.5°C)	9	6
Presence of other medical problems (%)	20*	21*
Previous visit to a physician (%)	48	47
Serum sodium above 145 mEq/L (%)	0	2
Serum CO_2 <15 (%)	20†	4†
BUN/creatinine above 20 (%)	87	77
Urine specific gravity above 1.030 (%)	7	4

SD indicates standard deviation; BUN, blood urea nitrogen.
* The most commonly reported underlying medical condition was asthma.
† There were no statistically significant differences between the 2 study groups with the exception of measured serum CO_2 ($P < .01$).

mEq/L (11 [20%] of 54 vs 2 [4%] of 53; $P < .01$), suggesting more severe illness.

Before patient enrollment, the median number of vomiting episodes in the previous 24 hours for all patients was 7 episodes (range: 3–40). After drug administration, 38 (70%) of the patients in the ondansetron group had complete cessation of vomiting, compared with 27 (51%) in the placebo group ($P = .04$). For patients who continued to have vomiting, the median number of episodes after drug administration was 2 (range: 1–4) for the ondansetron group as compared with 4 (range: 1–46) for the placebo group ($P = .25$).

At the time of enrollment, 62 children (58%) had a history of accompanying diarrhea. No significant difference was seen between the treatment and control group with regard to pre- and postdiarrheal complaints. Both groups had a decrease in the number of diarrheal episodes and the total duration of diarrheal symptoms after enrollment.

Fourteen patients (26%) who received ondansetron were hospitalized at the time of enrollment versus 16 patients (30%) in the placebo group (P = NS). Of the 16 admitted patients in the placebo group, 2 had been seen in the ED and received intravenous fluids within the 48 hours preceding enrollment. An additional 3 of the patients in this group were noted to have a measured serum CO_2 of ≤14 mEq/L. In the ondansetron group, 2 of the patients who were admitted had been seen previously and had failed intravenous hydration and an additional 8 of the patients who were admitted had a measured serum CO_2 ≤14 mEq/L.

A subgroup analysis excluding those patients who 1) had a measured serum CO_2 ≤14 mEq/L, 2) had been seen previously for intravenous hydration, or 3) failed to complete enrollment because of lack of intravenous access left a total of 90 patients. Fourteen (16%) of these patients required admission; 3 (7.5%) of 43 patients who received ondansetron versus 11 (23%) of 47 patients in the placebo group ($P = .04$). The average length of hospitalization was 2 days for all admitted patients.

No significant intergroup difference was seen with regard to ED reevaluation or readmission rates (Table 2). Reanalysis of the data including these patients as treatment failures did not alter the results.

No significant differences were noted with regard to reported or observed complications between the 2 groups. Reported and observed complications after drug or placebo administration included abdominal pain (1 in the placebo group), "sinusitis" (1 in the placebo group), and rash (1 in the ondansetron group). One patient in the ondansetron group developed a diffuse nonurticarial rash 24 hours after drug administration while in the hospital. The rash resolved spontaneously and was attributed to his viral illness by his inpatient treating physicians, who were of course unaware of the patient's enrollment group. All patients with grossly bloody stools or a fever above 39.0°C underwent stool testing for leukocytes and bacterial culture (6 patients in the ondansetron group and 8 patients in the control group). Three cultures were positive for presumed bacterial pathogens, all for *Escherichia coli* 0157:H7. Two patients, 1 in each group, had a positive stool culture for *E coli* 0157:H7, which did not require additional treatment. Another patient in the ondansetron group was believed to require additional treatment and was readmitted after enrollment for hemolytic uremic syndrome. As this patient had a positive stool culture for *E coli* 0157:H7 at the time of initial enrollment, he was likely in the prodromal period for this disease. At last follow-up (8 months after hospital discharge), this child was well.

DISCUSSION

We found that adding ondansetron to standard intravenous rehydration therapy significantly decreased the amount of vomiting in children with gastroenteritis. Furthermore, we were able to show that in first-time treated children, with a measured serum CO_2 ≥15 mEq/L, ondansetron significantly decreased the hospital admission rate.

Children who were given ondansetron and intravenous fluids were more likely to have complete cessation of vomiting symptoms compared with those who were given intravenous fluids and placebo (70% vs 51%; $P = .04$). A single, limited trial evaluating the antiemetic activity of ondansetron in the treatment of acute gastroenteritis showed similar results. Cubeddu et al[22] studied a total of 36 children

TABLE 2. Symptoms and Outcomes

	Ondansetron ($N = 54$)	Placebo ($N = 53$)	P Value
Follow-up			
Returned symptom journal	20 (37%)	23 (43%)	.92
Contacted by telephone	54 (100%)	53 (100%)	1.0
Patients with cessation of vomiting	38 (70%)	27 (51%)	.04
Median number of vomiting episodes	2 (range: 1–4)	4 (range: 1–46)	.25
Patients with diarrhea	22 (41%)	21 (40%)	.93
Median number of diarrhea episodes	5 (range: 1–37)	5 (range: 1–39)	.87
Duration of diarrheal symptoms (h)	60 (range: 12–113)	49 (range: 1–191)	.72
Patients admitted			
All patients	14 (26%)	16 (30%)	.62
Subgroup*	3/43 (7%)	11/47 (23%)	.04
Length of hospital stay (d)	2 (range: 1–4)	2 (range: 1–3)	.87
Return visits	4 (7%)	3 (6%)	.71
Admitted at return visit	2 (4%)	2 (4%)	1.0

* First-time patients with measured serum CO_2 ≥15.

with acute gastroenteritis. The children who were evaluated in their study received a standard dose of ondansetron, metoclopramide, or placebo in addition to oral rehydration therapy. The patients who received either of the antiemetic medications showed a statistically significant ($P < .05$) improvement in the number of emetic episodes, in the percentage of patients with no emetic episodes, and in the percentage of patients with treatment failures, when compared with saline placebo during the 24-hour study period. This study differed from our study in many important respects. The dose of ondansetron used was 0.3 mg/kg (compared with 0.15 mg/kg). Furthermore, patients in the Cubeddu study all were admitted for inpatient oral rehydration. The use of oral rehydration may account only for the higher proportion of patients with continued vomiting after drug treatment. Oral fluids when used to treat gastroenteritis, although effective for rehydration, have been shown to be associated with a higher number of vomiting episodes compared with intravenous hydration.[23] The brief (24-hour) period of data collection in the Cubeddu study makes it impossible to evaluate the potential for later return of symptoms or complications. Despite these differences, this earlier work is consistent with our findings.

Clear, objective criteria for identifying children who require hospitalization are not available. As noted previously, at our institution, patients with vomiting and diarrhea symptoms are admitted to the hospital when they return to the ED for a second visit after a trial of intravenous fluids and home management or when they have a measured serum $CO_2 \leq 14$ mEq/L. A subgroup analysis taking these factors into account found that ondansetron significantly reduced the rate of admission from 23% to 7% ($P = .04$).

Results of studies that evaluated hospital admission rate for gastroenteritis after rehydration vary widely. In a study of 42 patients with estimated mild to moderate dehydration, oral and intravenous rehydration were equally effective in preventing hospitalization (successful rehydration 82% vs 78%).[23] In another report, of 17 children who had mild to moderate dehydration and were rehydrated with intravenous fluids, none required admission.[24] Among 58 children who were aged 6 months to 13 years and had acute gastroenteritis and dehydration described by Reid and Bonadio,[25] 28% required admission because of inability to tolerate oral fluids despite intravenous hydration. In this same study, of the 42 patients (72%) who were discharged after intravenous hydration, 15% were subsequently readmitted after failure of outpatient management. As an additional factor, several studies have shown that admission rates can vary widely between institutions. One study noted up to an 18-fold difference in admission rates for children with gastroenteritis when comparing the admission practices of multiple, local EDs. The authors were unable to explain these differences on the basis of objective analysis of the various populations.[26] A study that compared children in Boston with those in New York noted an unexplainable 2- to 3-fold difference in admission rate for gastroenteritis.[27] Any study that uses an outcome that depends on a multitude of interrelated factors (eg, admission rate) may be difficult to generalize to other populations. Despite this, our study design allowed for a double-blind comparison of admission rates between virtually identical treatment and placebo groups. Thus, we would expect similar improvements in outcome to be realized at other institutions.

On the basis of our data, approximately 8.5 children would need to be treated with ondansetron to prevent 1 hospitalization. This estimate, which is conservative, includes all children who received ondansetron in the study. The cost of ondansetron is approximately $26 per 4-mg vial. The total cost of ondansetron during this study was $1378 for 53 total vials. A random sampling (20%) of patients who required hospitalization during our study showed an average cost of $1900 per hospital admission, excluding ED charges. According to our analysis, we prevented 6 admissions during the course of the study. The cost reduction as a result of prevented admissions was approximately $11 400, yielding a savings of approximately $10 022 after deducting the cost for purchase of the drug. The use of ondansetron to control vomiting and promote successful outpatient management of gastroenteritis therefore represents a potential for significant cost savings in terms of actual dollars spent as well as the potential cost savings from time lost from work and/or school. Because ondansetron was administered to children who required placement of an intravenous line for rehydration, the additional expense is attributable only to the cost of the drug.

The safety profile of ondansetron, after numerous studies of its use in a wide variety of disorders, is favorable. Common side effects associated with the use of ondansetron include headache, diarrhea, constipation, fever, and malaise/fatigue.[20,21] In a study that evaluated the use of ondansetron in the treatment of postoperative emesis in 1900 patients, the incidence of the above side effects was similar to placebo.[28] Only rarely has ondansetron been associated with extrapyramidal reactions. Of the 3 reported instances of extrapyramidal reactions, all occurred in adults who were being treated for chemotherapy-induced nausea and vomiting.[29–31] All 3 were taking multiple medications; therefore, it is unclear whether ondansetron was the direct cause of these reactions. To our knowledge, no cases of extrapyramidal reactions have been reported in children. Allergic reactions have been reported in approximately 20 cases to date.[30–32] To our knowledge, no cases of serious morbidity have been described with the appropriate use of ondansetron.

There are several potential limitations of this study. Our data collection method, which used journal collection and telephone follow-up, has potential limitations. Although 60% of patients did not return a symptom journal, we were able to conduct a structured telephone interview for data collection on 100% of patients. Inaccuracies in symptom recall by family members may have influenced our results. Although we were able to show a significant decrease in vomiting in patients who received ondan-

setron when compared with those who received placebo, we were unable to make firm conclusions regarding the effect of ondansetron on hospitalization because of the size of the study population. Because all patients were given intravenous fluids in addition to ondansetron or placebo, we are unable to determine the effect of ondansetron alone in lieu of other therapy. A large proportion of patients with gastroenteritis improve after intravenous fluids alone. In fact, some patients may have recovered with aggressive oral rehydration therapy without the use of other therapy. Although the double-blinded, randomized design of the study should reduce the effect of confounding variables, the potential for unforeseen factors that may have influenced our results does exist. Despite the randomized nature of the study, we did note that by chance a higher proportion of patents in the ondansetron group had a measured serum CO_2 <15 (20% vs 4%). That patients with this degree acidosis are routinely admitted to our hospital for ongoing intravenous fluids likely influenced our results. Because the ondansetron group contained a higher proportion of these patents, we would expect any bias for admission to be placed against the ondansetron group.

In conclusion, our data demonstrate that single-dose ondansetron decreases vomiting in children with acute infectious gastroenteritis. Moreover, ondansetron reduced the need for admission in those who were treated at an initial visit to the ED and had a measured serum CO_2 ≥15 mEq/L. Although additional research is needed to determine drug safety and cost-effectiveness better, these encouraging findings suggest that ondansetron may have a role in the treatment of gastroenteritis in young children.

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REFERENCES

1. American Academy of Pediatrics, Provisional Committee on Quality Improvement and Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics*. 1996;97:424–435
2. Burkhart D. Management of acute gastroenteritis in children. *Am Fam Physician*. 1999;60:2555–2563, 2565–2566
3. Fleisher GR. Infectious disease emergencies. In: Fleisher GR, Ludwig S, eds. *Textbook of Pediatric Emergency Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:757–762
4. Kilgore PE, Holman RC, Clarke MJ, et al. Trends of diarrheal disease associated mortality in US children, 1968 through 1991. *JAMA*. 1995; 274:1143–1148
5. Lieu TA, Black SB, Rieser N, et al. The cost of childhood chickenpox: a parents' perspective. *Pediatr Infect Dis J*. 1994;13:173–177
6. Halloran ME, Cochi SL, Lieu TA, et al. Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States. *Am J Epidemiol*. 1994;140:81–104
7. DeGrandi T, Simon JE. Promethazine-induced dystonic reaction. *Pediatr Emerg Care*. 1987;3:91–92
8. Krstenansky PM, Petree J, Long G. Extrapyramidal reaction caused by ondansetron [letter]. *Ann Pharm*. 1994;28:280
9. Mathews HG III, Tancil CG. Extrapyramidal reaction caused by ondansetron [letter]. *Ann Pharm*. 1996;30:196
10. Leary PM. Adverse reactions in children. Special considerations in prevention and management. *Drug Saf*. 1991;6:171–182
11. Bateman DN, Darling WM, Boys R, et al. Extrapyramidal reactions to metoclopramide and prochlorperazine. *Q J Med*. 1989;71:307–311
12. Boulloche J, Mallet E, Mouterde O, et al. Dystonic reactions with metoclopramide: is there a risk population? *Helv Paediatr Acta*. 1987;42: 425–432
13. Morris RW, Aune H, Feiss P, et al. International, multi-center, placebo-controlled study to evaluate the effectiveness of ondansetron vs. metoclopramide in the prevention of post-operative nausea and vomiting. *Eur J Anaesthesiol*. 1998;15:69–79
14. Splinter WM, Rhine EJ. Prophylaxis for vomiting by children after tonsillectomy: ondansetron compared with perphenazine. *Br J Anaesth*. 1998;80:155–158
15. Axelrod RS. Antiemetic therapy. *Compr Ther*. 1997;23:539–545
16. Roila F, Del Favero A. Antiemetics revisited. *Curr Opin Oncol*. 1997;9: 321–326
17. Ettinger DS. Preventing chemotherapy-induced nausea and vomiting: an update and review of emesis. *Semin Oncol*. 1995;22:6–18
18. Dicato M. Mechanisms and management of nausea and emesis [editorial]. *Oncology*. 1996;53(suppl 1):1–3
19. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis. *Cancer*. 1995;76:343–357
20. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet*. 1995;29:95–109
21. Wilde MI, Markham A. Ondansetron: a review of its pharmacology and preliminary clinical findings in novel applications. *Drug Eval*. 1996;52: 773–794
22. Cubeddu LX, Trujillo LM, Talmaciu I, et al. Antiemetic activity of ondansetron in acute gastroenteritis. *Aliment Pharmacol Ther*. 1997;11: 185–191
23. Issenman RM, Leung AK. Oral and intravenous rehydration of children. *Can Fam Physician*. 1993;39:2129–2136
24. Moineau G, Newman J. Rapid intravenous rehydration in the pediatric emergency department. *Pediatr Emerg Care*. 1990;6:186–188
25. Reid SR, Bonadio WA. Outpatient rapid intravenous rehydration to correct dehydration and resolve vomiting in children with acute gastroenteritis. *Ann Emerg Med*. 1996;28:318–323
26. Connell FA, Day RW, LoGerfo JP, et al. Hospitalization of Medicaid children: analysis of small area variations in admission rates. *Am J Public Health*. 1981;71:606–613
27. Perrin JM, Homer CJ, Berwick DM, et al. Variations in rates of hospitalization of children in three urban communities. *N Engl J Med*. 19894; 320:1183–1187
28. Bryson JC. Clinical safety of ondansetron. *Semin Oncol*. 1992;19(suppl 15):26–32
29. Camp-Sorrel D. Managing an extrapyramidal reaction caused by ondansetron. *Oncol Nurs Forum*. 1995;22:718–719
30. Chen M, Tanner A, Gallo-Torres H. Anaphylactoid-anaphylactic reactions associated with ondansetron [letter]. *Am J Psychiatry*. 1995;152: 1101
31. Madera J, Sanz S, Perez CI, et al. Urticaria and angioedema caused by ondansetron. *Allergy*. 1995;50(suppl):26:214
32. Kossey JL, Kwok KK. Anaphylactoid reactions associated with ondansetron. *Ann Pharmacother*. 1994;28:1029–1030