

# Efficacy of intravenous ondansetron to prevent vomiting episodes in acute gastroenteritis: a randomized, double blind, and controlled trial

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## Abstract

Acute gastroenteritis is one of the most common infectious diseases of childhood. Its symptoms are vomiting, diarrhea, and dehydration. In the emergency ward, intravenous rather than oral rehydration is usually preferred because of the high likelihood of emesis. Treatments to reduce emesis are of value in improving the rehydration procedure. Our study is a double-blind randomized trial and proposes the use of ondansetron as an anti-emetic drug to treat children with acute gastroenteritis. Seventy-four in-patients, aged 3 months to 15 years, were enrolled and randomly assigned to an ondansetron or placebo group. Inclusion criteria were the diagnosis of acute gastroenteritis and the absence of other diseases or allergies to drugs. A single bolus (0.15 mg/kg) of ondansetron was injected intravenously; normal 0.9% saline solution was used as a placebo. This treatment induced vomiting cessation in the ondansetron group significantly in comparison to the placebo group. The length of the hospital stay and the oral rehydration fluid volume were similar in the two groups and no adverse effects were noticed. Thus, safety, low cost, and overall benefit of ondansetron treatment suggests that this drug can be administered successfully to children with acute gastroenteritis.

## Introduction

Acute gastroenteritis is a common illness in childhood. Frequently caused by viruses, its symptoms include vomiting, diarrhea, abdominal pain, and fever. No therapy is suggested for viral infections, while dehydration caused by diarrhea and emesis should be treated vigorously.<sup>1</sup> In emergency departments, physicians usually choose intravenous over oral rehydration when vomiting is the most impor-

tant symptom, even if oral rehydration is recommended for mild to moderate dehydration.<sup>2</sup> Thus, reducing emesis is the first goal to assure the preference and the success rate of oral dehydration.<sup>3</sup> Anti-emetic treatments could have potential benefits but some concerns about the adverse effects, such as extrapyramidal symptoms or lethargy, discourage their use.<sup>4</sup> Ondansetron is a novel anti-emetic drug currently used to treat nausea and vomiting associated with antineoplastic therapies in children and adults.<sup>5</sup> Its activity as a serotonin 5-HT<sub>3</sub> receptor antagonist prevents extrapyramidal effects.<sup>5</sup> For this reason, ondansetron has been studied for a possible use in acute gastroenteritis in children. Ondansetron has shown greater effectiveness in reducing vomiting when compared with metoclopramide, a common anti-emetic or placebo, but has an increased incidence of diarrhea.<sup>6</sup> Furthermore, intravenous ondansetron administration in a double-blind trial in the emergency department has significantly reduced emesis, diarrhea, and hospital admission rates, confirming the cost-benefit ratio associated with this pharmaceutical approach.<sup>7</sup> Based on this preliminary evidence, our present study shows the result of a single dose of intravenous ondansetron in the in-patient setting in Thai children.

## Materials and Methods

Our study was a prospective, double-blind, randomized comparison between ondansetron and a placebo to reduce emesis in children affected by acute gastroenteritis. The trial was conducted at the pediatric in-patient ward of the Srinakharinwirot University Hospital from January 2008 to October 2008. The Ethics Committee of the Faculty of Medicine at the Srinakharinwirot University approved the protocol study. Children, from 3 months to 15 years old, who vomited more than three times in the 24 hours prior to admission and had acute gastroenteritis symptoms, were eligible for the study. Parents or legal guardians of children who met eligible criteria were asked to sign a written informed consent form. Treatment with any anti-emetic drug within 24 hours before enrolment or any history of a chronic medical condition such as hepatic disease, cardiovascular disease, chronic respiratory disease, immunodeficiency, tumors, diabetes mellitus, chronic gastrointestinal conditions, behavioral or psychiatric problems, or other neurological conditions were considered as exclusion criteria. Children who had a history of any drug allergy were also excluded. After enrolment, demographic characteristics and clinical data were recorded by nursing staff. Weight to the nearest 100 g and height to

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Contributions: both authors of this collaborative work defined the research theme. SR designed the methods and experiment, carried out the experiment, analyzed the data, interpreted the results, and wrote the paper. LR co-designed the experiment, and co-worked on associated data collection and their interpretation. Both authors have contributed to, read, and approved the manuscript.

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the nearest millimeter were measured. To classify the hydration status, the World Health Organization criteria were adopted on admission; Table 1 summarizes the scale.

Participants were randomized in two groups by a computerized program using a block of two, and were assigned to the ondansetron group or placebo group. After intravenous blood access for baseline biochemistry and fluid resuscitation, patients received a single bolus of intravenous ondansetron (Zofran, Glaxo Wellcome Inc.) at the dose of 0.15 mg/kg up to the maximal dose of 8 mg over 2 min. Children who were assigned to the control group were treated intravenously with 0.9% of normal saline solution, the same amount as the ondansetron treatment, and over 2 min as well. Attending physicians were responsible for the treatment protocol and discharge from the hospital. The primary outcome was the number of vomiting episodes after drug administration. We defined a vomiting episode as a forceful expulsion of stomach contents that was separated from the previous one by

more than 2 min. Non-productive retching, spilling of oral contents, and drooling were not considered vomiting. The secondary outcomes were the volume of intravenous and oral rehydration fluid, length of hospital stay, and adverse effects. The results were presented descriptively as mean, SD, and percent values. The Pearson chi-square or Fisher exact test were used to compare proportions between the two groups. Continuous variables were compared by using a Student t-test. Comparison of ordinal variables between groups was done by the Mann-Whitney U test. Statistical analysis was performed with the SPSS 11.0 software package. The P-value of <0.05 was considered as statistically significant.

## Results

One hundred and eight potentially eligible patients were approached to enroll for the study. Of these, 74 patients accepted the invitation to join and were randomly assigned to two treatment groups: one treated with ondansetron and the other treated with the placebo, as a control. The mean age was 3.2 yr (SD 2.6; range 3 mth to 12 yr) and thirty-eight patients (51.4%) were boys. Firstly, we evaluated the clinical presentation in terms of the mean number of vomiting episodes during the 24 hr before admission, mean onset, and last vomiting incident before admission. Data are reported in Table 2.

Fifty-two children (70.3%) were graded as having mild dehydration by attending physicians at the time of admission. There were no significant differences in baseline characteristics including demographics, clinical presentations, and hematological and biochemistry parameters between the groups (Table 2). No patient had hypernatremia or hypokalemia. Severe metabolic acidosis (bicarbonate <15 mEq/L) on admission was reported in five and two patients in the ondansetron and placebo groups, respectively. Outcomes of treatment are presented in Table 3.

After drug administration, 30 (81.1%) patients in the ondansetron group completely ceased vomiting as compared to 9 (24.3%) patients of the placebo group ( $P<0.01$ ). The mean number of vomiting episodes after drug administration was significantly lower in the ondansetron group than in the placebo group (0.5 vs. 2.1,  $P<0.01$ ). Median time of complete cessation in the placebo group was 10 hr while emesis ceased immediately in the ondansetron group. No significant differences in length of hospital stay, volume of intravenous fluid, and oral rehydration fluid administration were observed between the groups. We did not observe any adverse effect in either group.

**Table 1. Scale of hydration status.**

	Symptoms
Normal or mild dehydration	No signs or symptoms
Moderate dehydration	Thirsty, restless or irritable behavior, decreased skin elasticity, sunken eyeballs
Severe dehydration	Shock or diminished consciousness, lack of urine output, cool and moist extremities, low blood pressure, rapid and feeble pulse

**Table 2. Demographic description of ondansetron and placebo groups.**

	Ondansetron (N=37)	Placebo (N=37)
Age (yr); mean±SD	3.4±2.8	3.0±2.5
Median (range)	2.6 (0.3-12.0)	2.3 (0.3-10.4)
% Boy	21 (56.8)	17 (45.6)
Weight (kg)	14.9±6.1	12.8±4.2
Height (cm)	97.4±16.6	92.7±20.0
Number of vomiting in previous 24 hr; mean±SD	6.7±4.5	7.5±3.9
Last vomiting prior to admission; hr±SD	3.1±3.5	2.4±2.2
Onset of vomiting prior to admission; hr ± SD	23.2±21.6	28.4±24.6
Presence of diarrhea; n (%)	18 (48.6)	27 (73.0)
Number of diarrhea episodes in previous 24 hr; median (range)	4.2±3.0	6.1±4.7
Fever >38.5°C; n (%)	3 (8.1)	7 (18.9)
Previous visit to a physician; n (%)	17 (45.9)	20 (54.0)
Hydration status; n (%)		
Mild or no dehydration	26 (70.3)	26 (70.3)
Moderate dehydration	11 (29.7)	11 (29.7)
Sodium (mEq/L)	134.7±2.1	135.8±3.3
Potassium (mEq/L)	4.2±0.4	4.1±0.7
Bicarbonate (mEq/L)	18.9±4.1	18.5±3.7
BUN	15.0±5.0	13.5±5.5
Creatinine	0.5±0.2	0.5±0.2
Urine specific gravity	1.018±0.005	1.017±0.006
Hematocrit (%)	34.8±2.5	35.4±3.3
Hemoglobin (g/dL)	11.8±0.9	12.0±1.4
White blood cell count	9439±4587	9299±5620

**Table 3. Outcomes measurements.**

	Ondansetron (N=37)	Placebo (N=37)	P
Number of vomiting episodes; n (%)			
Mean±SD	0.5±.2	2.1±1.9	<0.01
Median (range)	0 (0-5)	2 (0-7)	<0.01
Cessation of vomiting	30 (81.1)	9 (24.3)	<0.01
1 episode	3 (8.1)	5 (13.5)	
2 episodes	1 (2.7)	10 (27.0)	
≥3 episodes	3 (8.1)	13 (35.1)	
Last vomiting after drug administration; hr			
Mean±SD	4.2±11.3	13.5±13.6	<0.01
Median (range)	0 (0-53)	10 (0-56)	<0.01
Intravenous fluid received (mL/kg/hr); mean±SD	4.3±1.3	4.1±1.4	0.65
Oral rehydration solution (mL/kg/hr); mean±SD	1.9±1.7	1.3±1.0	0.15
Length of hospital stay (hr); mean±SD	53.8±61.3	60.5±46.6	0.60

## Discussion

Our study provides evidence that an intravenous dose of ondansetron could be useful in reducing emesis associated to acute gastroenteritis. We have investigated 74 children, aged from 3 months to 15 years, admitted to the pediatric ward with a diagnosis of moderate or severe dehydration, in accordance with the World Health Organization guidelines. Previous studies enrolled children as outpatients;<sup>7,8</sup> however, we chose to enroll children in the in-patient setting in order to minimize the difference in the rehydration procedure and, in general, in overall treatment. Furthermore, we reduced the interference from a single physician by counting the number of vomiting episodes after treatment and complete emesis cessation as primary outcomes. In addition, we analyzed the length of hospital stay, volume of intravenous fluid, and oral fluid administration as secondary outcomes, without observing any significant differences between the ondansetron and placebo groups.

Results reported in our study show agreement with those of previous clinical studies conducted in the emergency department. We decided to use a single intravenous dose because no solution is available for this medication and it may have been difficult to orally

administer a tablet to young children. Intravenous ondansetron treatment (0.15 mg/kg) favors vomiting cessation in 70% of patients in comparison to 51% of the placebo group and, consequently, reduces the need for admission to the pediatric ward.<sup>7</sup> This positive effect may compensate for the cost of the drug, which is not cheap. Furthermore, oral ondansetron treatment shows that children vomit less often and tolerate an oral rehydration procedure better.<sup>8</sup> In addition, a higher mean incidence of diarrhea in an oral ondansetron group has been described, while intravenous treatment seems to decrease episodes of diarrhea.<sup>7,8</sup> There is no evidence of other adverse effects in cardiovascular or respiratory systems.<sup>8</sup> A possible limitation of these studies is the inclusion criteria; indeed, considering a set number of vomiting episodes within the previous 24 hours could have included patients with milder cases of acute gastroenteritis, inducing a too optimistic evaluation of the ondansetron treatment. However, current evidence demonstrates clinical benefits in the use of ondansetron as an anti-emetic in children with acute gastroenteritis.

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