Oral Dimenhydrinate Versus Placebo in Children With Gastroenteritis: A Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: Dimenhydrinate, an antihistaminic agent, is a widely used drug in Canada and Europe. It limits stimulation of the vomiting center via the vestibular system. Multiple studies have shown its effectiveness in the treatment of vertigo and postoperative nausea and vomiting.

WHAT THIS STUDY ADDS: Dimenhydrinate, when given orally, did not significantly decrease the frequency of vomiting in children with acute gastroenteritis compared with placebo. The reported adverse effect proportions were similar for the dimenhydrinate and placebo groups.

abstract

OBJECTIVE: To evaluate the efficacy and safety of oral dimenhydrinate in the treatment of acute gastroenteritis.

METHODS: This was a randomized, double-blind, placebo-controlled trial conducted in the emergency department of a pediatric university-affiliated center. Children 1 to 12 years old who presented to the emergency department with at least 5 episodes of vomiting in the previous 12 hours and diagnosed with acute gastroenteritis were block-randomized to receive oral dimenhydrinate (1 mg/kg; maximum: 50 mg) every 6 hours for 4 doses or placebo for 4 doses. The primary outcome measure was treatment failure as defined by the occurrence of ≥2 episodes of vomiting in the 24 hours after administration of the first dose of the study medication.

RESULTS: During the study period, 209 patients met inclusion criteria, but 50 refused to participate and 7 were missed. Eight participants were lost to follow-up, and 144 were thus included in the primary analysis. Of these patients, 74 were randomized to receive dimenhydrinate and 70 placebo. The proportions of patients showing failure of treatment were similar for both treatment groups: dimenhydrinate, 31% (23 of 74); placebo, 29% (20 of 70) (difference: 0.02 [95% confidence interval: −0.12 to 0.17]). There were no differences between the 2 groups in rates of intravenous catheter insertion, mean number of episodes of vomiting or diarrhea, abdominal pain, nausea, duration of symptoms, revisit rates, or parental absenteeism. The proportions of adverse effects were similar in both groups (53% vs 54%).

CONCLUSIONS: The prescription of oral dimenhydrinate did not significantly decrease the frequency of vomiting in children with acute gastroenteritis compared with placebo. Pediatrics 2012;129:1050–1055

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Acute gastroenteritis is one of the most common pediatric problems worldwide. Vomiting is a common symptom in children with infectious gastroenteritis. The benefit of oral rehydration with a glucose electrolyte solution during gastroenteritis is well recognized as the mainstay treatment modality. Although it prevents dehydration, this measure does not decrease unpleasant symptoms, such as nausea and vomiting, experienced by children. Achieving control of these symptoms could be beneficial not only for the patient’s comfort but also because it could prevent further dehydration by limiting fluid loss and facilitating oral rehydration. Dimehydrinate, an over-the-counter, widely used drug in Canada and Europe, is an ethanalamine derivative antihistamine. It limits stimulation of the vomiting center by the vestibular system, which is rich in histamine receptors. Multiple studies have shown dimehydrinate’s effectiveness in the treatment of postoperative nausea and vomiting in children. It is also used for the treatment of vertigo in children. Furthermore, it is inexpensive to administer, with an average cost of US $0.30 per dose. The principal adverse effects of dimehydrinate are drowsiness, dizziness, and anticholinergic symptoms. Restlessness and insomnia have also been described in children.

A previous study by Uhlig et al evaluated the efficacy and safety of dimehydrinate in children with gastroenteritis. They reported that dimehydrinate administration to children with none/mild dehydration reduced the frequency of vomiting. It did not, however, improve oral rehydration or clinical outcomes. Their decision to assess rectal administration may limit the generalizability and validity of their findings, particularly to children with diarrhea.

To our knowledge, no data have been published on the efficacy of oral dimehydrinate in controlling emesis in children with acute gastroenteritis. We hypothesized that the children treated with oral dimehydrinate during an acute episode of gastroenteritis would experience fewer episodes of vomiting than children who received placebo. The objective of our study was to evaluate the efficacy and safety of oral dimehydrinate in the treatment of vomiting due to acute gastroenteritis in children.

METHODS

We conducted a randomized, double-blind, placebo-controlled clinical trial in a pediatric university-affiliated hospital emergency department (ED) with a patient census of ~80,000 visits per year. To be eligible, children had to experience “some” dehydration secondary to a diagnosis of gastroenteritis according to the treating physician, be aged from 1 to 12 years, and present with >5 episodes of vomiting in the preceding 12 hours. In addition, to be included, patients had to be evaluated by 1 of the 4 participating pediatric ED physicians while they attended in the ED. Exclusion criteria were as follows: (1) preexisting chronic medical condition such as gastrointestinal disease (malabsorption or inflammatory bowel disease); malignancy; diabetes mellitus; cardiac, endocrine, immunologic, or neurologic disorder; (2) suspected surgical abdomen or gynecologic condition, urinary tract infection, migraine, or meningitis; (3) use of medication other than acetaminophen or ibuprofen in the previous 48 hours; (4) history of allergy or adverse reaction to dimehydrinate; (5) severe dehydration requiring immediate intravenous fluid therapy; and (6) hematemesis or hematochezia.

Once eligibility and exclusion criteria were confirmed and written informed consent was obtained, a standardized questionnaire detailing demographic characteristics, medical history, and symptoms of present illness was completed. The intervention of interest consisted of the administration of oral dimehydrinate or placebo at a dosage of 1 mg/kg per dose every 6 hours for 4 doses, with a maximum dose of 200 mg/day. The first dose was given in the ED by the regular ED nurses, and the patients were kept under observation. If the patient vomited within 5 minutes after drug ingestion, a second dose was given. This interval was based on the pharmacokinetics of oral dimehydrinate, which produces an initial response within 15 minutes.

Fifteen minutes after the drug administration, oral rehydration was offered with a standardized rehydration solution at a rate of 0.2 mL/kg per minute. During the ED stay, degree of dehydration, number of emesis and diarrheal episodes, quantity of fluid consumed, need for intravenous rehydration, and length of stay were recorded. Vomiting was defined as a forceful expulsion of stomach contents or an involuntary effort to do so. Drooling, spitting, productive cough, and food spilling were not considered vomiting episodes. Nausea was defined as feeling the need to throw up.

Complementary investigations, need for intravenous rehydration, duration of observation, discharge, and hospitalization decisions were left to the discretion of the attending physician.

After patient discharge from the ED, parents were instructed to give the medication every 6 hours for an additional 3 doses, to continue oral rehydration. Telephone follow-ups were conducted by a research assistant on days 1, 3, and 7 and, if necessary, every second day until the patient was symptom free, to assess patient’s status via a standardized questionnaire.

A randomization table was used to generate block randomization of variable size. Randomization was stratified according to category of age (<8 and ≥8 years) to prevent uneven distribution of ages. All providers, patients,
parents, and research assistants were blinded to group assignment until completion of data analysis. To do so, the pharmacy provided a bottle labeled “GAG study drug” precalculated to provide a dose of 3 mg/mL of dimenhydrinate or a color-, taste-, and odor-matched placebo in identical packaging. Medication kits were consecutively numbered and assigned to the patients according to their stratum and the order of recruitment. At the pharmacy, the patient’s identification was coded so that only a user having the access code would have been able to identify patients’ allocation.

The primary outcome measure was treatment failure as defined by the occurrence of ≥2 episodes of vomiting in the 24 hours after administration of the first dose of the study medication. The secondary outcomes were as follows: (1) intravenous fluid administration; (2) hospitalization; (3) the number of episodes and duration of vomiting and diarrhea; (4) the elapsed time before complete resolution of gastroenteritis symptoms; (5) reported adverse effects; (6) ED revisits within 7 days; and (7) parental work absenteeism.

The data were collected via the ED medical records, the standardized questionnaires filled by investigators during the ED stay, and telephone interviews. Data were entered in an Excel data file (Microsoft Corporation, Redmond, WA). Based on previously reported data, we estimated that ~70% of patients would have ≤1 episode of emesis in the 24 hours after the first medication dose. We prospectively defined that the minimal improvement which would be clinically significant would be to improve the success rate from 70% to 90% for the participants in the intervention group. We therefore calculated that we would need 60 patients per group to have a power of 80% with an α error of .05. However, to compensate for possible dropouts, we recruited at least 75 patients per group. Patients’ characteristics and outcomes were compared using the Mann–Whitney U test and the χ² test for categorical variables and Student’s t test for continuous variables. To account for the effect of multiple comparisons, a Bonferroni estimation was applied to consider that a result would be statistically significant. Accordingly, all results of the 7 secondary outcomes would be declared significant at a P = value of .05/7 = .007.

Analysis followed an intention-to-treat approach with the exclusion of patients lost to follow-up. A sensitivity analysis evaluating worst-case and best-case scenarios was performed to account for patients lost to follow-up. We estimated that the worst-case scenario would imply a 25% dropout.

The study was approved by our institutional review board, and all patients/guardians provided written informed consent to participate in the study.

**RESULTS**

A total of 209 patients were eligible for inclusion while the designated physicians were attending in the ED between April 2005 and October 2010. Seven patients were missed and of the remaining 202 patients who were approached, 50 refused to participate (Fig 1). Of the 152 recruited patients, 8 patients were lost to follow-up. A total of 144 participants were thus included in the primary analysis using an intention-to-treat approach. Of these, 74 were randomized to the dimenhydrinate group and 70 to the placebo group.

The baseline characteristics of study participants are described in Table 1. Participants in both groups had similar demographic and clinical characteristics.

As reported in Table 2, the proportions of participants with ≥2 vomiting episodes were similar for both treatment groups: dimenhydrinate, 31% (23 of 74); placebo, 29% (20 of 70) (difference: 0.02 [95% confidence interval (CI): –0.12 to 0.17]). Data were unknown for 2 participants in the treatment group and 6 in the placebo group. Accordingly, the worst-case scenario would lead to a difference of proportion of treatment failure of 0.07 (95% CI: –0.08 to 0.21) in favor of dimenhydrinate whereas the best-case scenario would lead to a difference of proportion of treatment failure of 0.04 (95% CI: –0.11 to 0.18) in favor of placebo.

There were no statistical differences between the 2 groups for rate of intravenous insertion, mean number of episodes of vomiting and diarrhea, abdominal pain, nausea, duration of symptoms, revisit rates, and parental absenteeism.

The proportions of reported adverse effects were high but similar in both
The main adverse effect was drowsiness in 42% and 37% of the participants, respectively. A secondary, per-protocol analysis was performed among the 105 participants reporting the use of all 4 doses of medication. This analysis found no association between treatment arms and all outcomes of interest (Table 4).

Blinding was maintained as demonstrated by the fact that the physicians correctly identified the medication allocation in 44% of the participants in the intervention group and in 54% of the participants in the placebo group.

**DISCUSSION**

This study found that oral dimenhydrinate did not significantly decrease the frequency of vomiting in children with acute gastroenteritis compared with placebo. In addition, our study reported similar adverse effect proportions for dimenhydrinate and placebo, which suggests that it is a safe medication.

Our results are in agreement with a previous study conducted by Uhlig et al. that had evaluated the efficacy and safety of dimenhydrinate if given rectally. Their primary outcome was different from ours. It was defined as weight gain within 18 to 24 hours after randomization. They had also included patients with no dehydration and with less vomiting before enrollment than in our study. In their study, patients were also recruited from pediatric practices and not only ambulatory departments. They reported that the change of weight did not differ between children who received dimenhydrinate or placebo. However, the mean number of vomiting episodes between randomization and follow-up visit was 0.64 in the dimenhydrinate group and 1.36 in the placebo group. In total, 69.6% of the children in the dimenhydrinate group versus 47.4% in the placebo group were free of vomiting between randomization and the follow-up visit. Another limitation of their study was that dimenhydrinate was administered rectally. It is possible that the absorption of the medication was limited in patients with diarrhea.

In the past, it was suggested that dimenhydrinate might delay other diagnoses such as appendicitis; however, in our study no such instance were encountered. Furthermore, the reported adverse effect profiles were similar for dimenhydrinate and placebo. The hypothesized sedative effect of dimenhydrinate might have counteracted the emetic effect by reducing overall fluid intake. However, a similar frequency of drowsiness was reported in both study groups. The issue of the frequency of sedation attributed to dimenhydrinate was also negated in a previous study. Overall, dimenhydrinate seems to be safe in children.

Despite the multiple antiemetic drugs available in pediatrics, their use in gastroenteritis remains controversial.
it is known that ED clinicians do often use antiemetic agents to treat acute gastroenteritis in children, mainly to prevent further dehydration. There has been no study documenting the efficacy of many of these drugs in the treatment of children with acute gastroenteritis. This situation underscored the need for further research on the subject.

Recently, randomized clinical trials and meta-analyses have studied the efficacy and safety of ondansetron, a selective 5-HT3 receptor-blocking agent, in decreasing emesis in the ED. This agent had shown promising results in alleviating the frequency of vomiting in acute gastroenteritis. Reeves et al demonstrated a reduction in vomiting in children with acute gastroenteritis receiving one dose of 0.15 mg/kg of intravenous ondansetron compared with placebo. However, a reduction in the hospitalization rate was not observed. Ramsook et al studied the efficacy of oral ondansetron in acute gastroenteritis in children. The patients who received ondansetron required intravenous fluid less often and had fewer hospital admissions, but after discharge, had a similar number of emesis episodes, more diarrhea, and a higher revisit rate compared with those receiving placebo. Cubbedu et al evaluated the effect on emesis of a single dose of intravenous ondansetron versus metoclopramide versus placebo during acute gastroenteritis. Children in the metoclopramide group had equivalent vomiting episodes and more diarrhea compared with those receiving placebo. Patients treated with ondansetron had fewer vomiting episodes but more diarrhea than those receiving placebo. Finally, Al-Ansari et al failed to show a difference in the cessation of vomiting between intravenous metoclopramide versus intravenous ondansetron for children hospitalized for gastroenteritis.

Our study had several limitations. A priori, we had decided to recruit a convenient sample of patients available. The patients were considered eligible only when 1 of the 4 designated recruiting physicians was working in the ED. This decision could have led to the possibility of unintentional enrollment or ascertainment bias. No data were collected on missed and excluded patients during the study period. Therefore, we cannot comment on the external validity of our sample for the entire population of the children visiting an ED for suspected gastroenteritis. The study was conducted over a significant length of time because of the lack of a dedicated research assistant. Possible bias might also have been introduced because the recruiting physician was also the main medical caregiver deciding patient disposition. We did not perform routine stool cultures to identify infectious agents as well as laboratory tests. No clinical dehydration scale was systematically applied to evaluate patients’ degree of dehydration.

**CONCLUSIONS**

The prescription of oral dimenhydrinate did not significantly reduce the proportion of children experiencing recurrent vomiting in those experiencing acute gastroenteritis compared with placebo. No significant adverse effects were encountered with the use of dimenhydrinate in the study population.
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