

In children with vomiting related to acute gastroenteritis, are antiemetic medications an effective adjunct to fluid and electrolyte therapy?

Part A: Evidence-based answer and summary*

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Vomiting is unpleasant and distressing for a child and for the parents. Vomiting can limit the effectiveness of oral rehydration therapy, and can increase the risk of dehydration, as well as the need for intravenous hydration and hospitalization. Antiemetic medications are commonly prescribed to treat vomiting in children with acute gastroenteritis (1-4). However, only a few efficacy studies (5-10) have been published on the use of antiemetic medications in paediatric gastroenteritis. These studies are summarized in Table 1.

In a Cochrane review, Alhashimi et al (11) reviewed three of the above five studies. The study by van Eygen et al (5) was excluded because the outcome measures were considered to be unsatisfactory. The study by Reeves et al (7) was also excluded, because patients up to 22 years of age were included. The studies by Cubeddu et al (6), Ramsook et al (8) and Freedman et al (9) were criticized by these Cochrane

reviewers, because the outcome measures were a reduction of emetic episodes rather than the precise time to cessation of vomiting. Alhashimi et al (11) concluded that the three trials provided some evidence, albeit weak and unreliable, that favoured the use of ondansetron and metoclopramide over placebo for the treatment of vomiting associated with childhood gastroenteritis. It was hoped that the study by Reeves et al (7) would be included in the review after the data from the adult patients were excluded from the analysis. The study by Stork et al (10) was not included in the review, presumably because the study had not been published at the time of the review.

In summary, all existing studies demonstrated that specific antiemetic medications were efficacious in reducing vomiting, as well as the need for intravenous fluid administration and possibly hospitalization of children with acute gastroenteritis.

TABLE 1
Double-blind, randomized, controlled studies on the use of antiemetics in the treatment of vomiting related to acute gastroenteritis

| Reference, year (yr) of publication | Patients (n) | Age | Study design | Outcome measures | Results | Comments |
|-------------------------------------|--------------|--------------|---|--|---|---|
| van Eygen et al (5), 1979 | 60 | 2-6 yrs | Children hospitalized with gastroenteritis were randomly assigned to receive a suppository that contained placebo, domperidone 30 mg or metoclopramide 10 mg at study entry, and up to three more times, as clinically warranted, throughout the 24 h study period. | Severity of nausea, vomiting, anorexia, abdominal pain and abdominal distension. | Children who received domperidone required fewer additional suppositories than children who received metoclopramide (P<0.05) or placebo (P<0.05). Nausea and vomiting were improved by domperidone. | No drug-related adverse events were reported. |
| Cubeddu et al (6), 1997 | 36 | 6 mo - 8 yrs | Children with acute gastroenteritis who had vomited twice within 1 h were randomly assigned to receive either a single intravenous dose of ondansetron (0.3 mg/kg) (n=12), metoclopramide (0.3 mg/kg) (n=12) or a normal saline placebo (n=12). | Frequency of emesis in the subsequent 24 h. | The number of emetic episodes experienced was significantly less (P=0.048) in the ondansetron group (mean=2) than in the placebo group (mean=5), and the proportion of patients who did not vomit was greater in the ondansetron group (58%) than in the placebo group (17%) (P=0.039). Compared with placebo, metoclopramide also reduced the number of emetic episodes, but the results did not reach statistical significance. | Significantly more episodes of diarrhea were reported during the first 24 h in the ondansetron (P=0.013) and metoclopramide (P=0.004) groups than in the placebo group. Otherwise, there was no difference in the number or type of adverse events in the three groups. |

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TABLE 1
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| Reference, year (yr) of publication | Patients (n) | Age | Study designs | Outcome measures | Results | Comments |
|-------------------------------------|--------------|---------------|--|---|---|--|
| <i>Continued from page 391</i> | | | | | | |
| Reeves et al (7), 2002 | 107 | 1 mo – 22 yrs | Patients seen in the emergency department with ≥ 3 episodes of gastroenteritis-related vomiting in the preceding 24 h were randomly assigned to receive intravenous ondansetron 0.15 mg/kg to a maximum of 8 mg (n=54) or an equal amount of normal saline placebo (n=53). | Frequency of vomiting post-treatment and need for admission. | Thirty-eight (70%) of patients in the ondansetron group had complete cessation of vomiting, compared with 27 (51%) in the placebo group (P=0.04). Sixteen patients (30%) in the placebo group required admission, compared with 14 (26%) in the treatment group (P=0.62). In a subgroup analysis that excluded patients who had a serum CO ₂ level ≤ 14 mEq/L or had previously received intravenous hydration, three of 43 (7%) patients who received ondansetron required admission, compared with 14 of 47 (23%) patients who received placebo (P=0.04). | No difference in adverse events was noted between groups. |
| Ramsook et al (8), 2002 | 145 | 6 mo – 12 yrs | Children seen in the emergency department with ≥ 5 episodes of gastroenteritis-related vomiting in the preceding 24 h were randomly assigned to receive either oral ondansetron (n=74) or a placebo. The doses of ondansetron were 1.6 mg, 3.2 mg and 4 mg for patients 6 mo – 1 yr of age, 1–3 yrs of age and 4–12 yrs of age, respectively, to be given every 8 h for up to two days. | Frequency of vomiting 48 h after enrollment, the need for intravenous therapy and admission. | The number of emetic episodes after enrollment ranged from 0–7 in the placebo group and from 0–2 in the ondansetron group. Eight patients in the ondansetron group versus 22 patients in the placebo group required intravenous therapy (P=0.015). The number of admissions was three in the ondansetron group versus 15 in the placebo group. | There was no statistically significant difference between the groups in the number of episodes of diarrhea that occurred while the child was in the emergency department. However, children in the ondansetron group had significantly more diarrhea over the next 48 h than the control group. The prolonged regimen of ondansetron treatment may account for the increase in diarrheal episodes. |
| Freedman et al (9), 2006 | 215 | 6 mo – 10 yrs | Children seen at the emergency department with ≥ 1 episode of gastroenteritis-related vomiting in the preceding 4 h and mild to moderate dehydration were randomly assigned to receive either oral ondansetron (n=108) or a placebo (n=107). The weight-based doses of ondansetron were 2 mg for children who weighed between 8 kg and 15 kg, 4 mg for children who weighed between ≥ 15 kg and < 30 kg, and 8 mg for children who weighed ≥ 30 kg. Children who vomited within 15 min after the medication were given a second dose. A 1 h period of intense ORT was initiated 15 min after the study drug had been administered, and ORT then continued until disposition was determined. | Proportion of children who vomited and frequency of vomiting while receiving ORT, the need for intravenous therapy and admission. | Children who received ondansetron were less likely to vomit than patients who received placebo (14% versus 35%), vomited less often (mean number of episodes per child 0.18 versus 0.65, respectively; P<0.001) and were less likely to be treated with intravenous hydration (14% versus 31%). The rates of hospitalization were 4% and 5%, respectively (P=1.00). | Children who received ondansetron had more episodes of diarrhea during ORT than those who received placebo (1.4 versus 0.5; P<0.001). The increase in diarrheal episodes might have resulted from the repeated use of ondansetron. |

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|-------------------------------------|--------------|---------------|--|--|--|--|
| <i>Continued from page 392</i> | | | | | | |
| Stork et al (10), 2006 | 166 | 6 mo – 12 yrs | Children seen at the emergency department with >3 episodes of gastroenteritis-related vomiting, mild to moderate dehydration and failed ORT were randomly assigned to receive intravenous ondansetron 0.15 mg/kg (n=46), intravenous dexamethasone 1 mg/kg (n=46) or placebo (normal saline, 10 mL) (n=44). These children also received intravenous normal saline 10 mL/kg/h–20 mL/kg/h. Oral fluid tolerance was evaluated at 2 h and 4 h. Those children who did not tolerate oral fluids at 4 h were admitted. | Need for hospitalization, tolerance of oral fluid. | Nine patients (20.5%) who received placebo, seven patients (14.9%) who received dexamethasone and two patients (4.4%) who received ondansetron required hospital admission. The result was significantly different for those who received ondansetron than from those who received placebo (P=0.02). Similarly, at 2 h, 39 (86.6%) ondansetron-treated patients tolerated oral hydration versus 29 (67.4%) placebo-treated patients. | The authors did not report whether ondansetron-treated patients had more episodes of diarrhea during the treatment period. |

Mo Months; ORT Oral rehydration therapy

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Part B: Clinical commentary*

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Acute gastroenteritis continues to be associated with substantial morbidity in developed countries and has a significant mortality rate in developing countries (1,2). Poor nutrition status is associated with an increased risk (3). Dehydration is the most frequent and dangerous complication because of associated electrolyte imbalance and metabolic acidosis (3). Gastroenteritis-related vomiting remains a significant health problem. Prolonged or protracted vomiting is uncomfortable for patients and stressful for their families (1). Gastroenteritis-related vomiting increases the

risk of dehydration and electrolyte imbalance, as well as the need for intravenous hydration and hospitalization.

Vomiting is not a contraindication to oral rehydration therapy (ORT), but it can interfere with ORT (1,4). Chongbanyatcharoen (5) conducted a survey of physicians who had attended a short course entitled “Practical Approach to Common GI Problems”. At the end of the course, the physicians were surveyed about the possible reasons for failure of ORT. Sixty-one questionnaires were returned. Vomiting was the most common reason identified (86.9%).

Preliminary data suggest that the appropriate use of an antiemetic medication can minimize the need for intravenous therapy and also possibly the need for hospital admission (6-8). Given the high incidence of gastroenteritis, well-designed, large-scaled, multicentre, double-blind, placebo-controlled, randomized studies are needed to confirm the usefulness of antiemetic medications in the treatment of gastroenteritis-related vomiting. A cost-effectiveness analysis would provide useful information.

The decision to use any medication should be evidence based, and should take into consideration the clinical efficacy, potential adverse events and cost of treatment (1). Ondansetron shows promise as a first-line antiemetic medication. Use of ondansetron should be considered when vomiting interferes with ORT. Oral and single-dose ondansetron, rather than intravenous ondansetron, should be used if possible. The medication can be used for both inpatients and outpatients, but only after the patient has been clinically assessed. Prolonged ondansetron treatment is likely unnecessary, and such treatment may result in more diarrheal episodes, as shown in some of the reviewed studies. The medication should be used with caution in children whose diarrhea is a major concern.

Although unproven, use of this medication may also result in substantial cost savings by a reduction in the need

for intravenous hydration and hospitalization. Other potential cost savings can result from a reduction in time lost from work for parents or time lost from school for children (1). The cost of ondansetron is approximately \$5 for 2 mg, \$10 for 4 mg and \$20 for 10 mg (with a generic form of the 10 mg dose being \$10), plus the dispensing fee.

Other antiemetic medications, such as metoclopramide, are less efficacious in the treatment of gastroenteritis-induced vomiting and are associated with more adverse events than ondansetron. The adverse effects of metoclopramide include restlessness, drowsiness and dizziness, as well as extrapyramidal reactions such as dystonia, akathisia, oculogyric crisis and tardive dyskinesia.

In the clinical trials, children who received ondansetron experienced more episodes of diarrhea than children who received placebo. The increase in diarrheal episodes might have resulted from the repeated and prolonged use of ondansetron. Clinicians must balance the proven benefits of antiemetic therapy against the cost and risks of adverse events in patients with gastroenteritis-related vomiting (1). It should be emphasized that antiemetic agents are an effective adjunctive therapeutic agent in children requiring ORT, and their use by no means replaces the need for, nor should remove the emphasis from, the proper application of ORT.

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