

What is the role of antiemetics for children with acute gastroenteritis in the developing world?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: : What is the role of antiemetics for children with acute gastroenteritis in the developing world?

The WHO Pocketbook of Hospital Care for Children recommends that "anti-emetics should not be given to young children with acute or persistent diarrhoea or dysentery: they do not prevent dehydration or improve nutritional status and some have dangerous, sometimes fatal, side-effects. (Pocketbook chapter 5, page 110).

INTRODUCTION

Gastroenteritis is a particularly common paediatric illness. Rotavirus is the most common cause of severe gastroenteritis and accounts for an estimated 139 million episodes worldwide each year in children under 5 years of age. Annually, 25 million clinic visits and 2 million hospitalizations can be attributed to rotavirus gastroenteritis. Rotavirus is responsible for nearly half a million deaths per year. Children in developing countries account for 82% of these deaths.[1]

Vomiting limits the success of oral rehydration in acute gastroenteritis leading to an increased need for prolonged emergency department stays, hospitalization and use of intravenous rehydration. Antiemetics therefore have significant potential to lessen the burden of gastroenteritis for both the patient and the health care system. In general the use of antiemetics in children with gastroenteritis has been limited by concerns of adverse effects such as sedation and extra pyramidal effects.

If there is to be a role for antiemetics in acute gastroenteritis in the developing world then there must be evidence to suggest that these medications are effective, have a clinically acceptable adverse effect profile and are cost effective.

METHODS

To address this question relevant articles were identified using a search of the MEDLINE database from 1970 to August 2007 using key words developing countri*, child*, antiemetic* and gastroenteritis as well as the Clinical Queries filter. A total of 1127 potentially relevant publications were identified. The Clinical Queries filter limited the number of articles to 142. The

abstracts for all of these articles were read as well as the entire article if there was any doubt about the relevance of the publication. Only cohort studies or randomized controlled trials were accepted for review. A total of six relevant trials were identified as well as one Cochrane Review. All of the trials included were level 1b. Protocols for treatment of gastroenteritis in children published by the US Centers for Disease Control and the American Academy of Pediatrics were also reviewed.

RESULTS

A randomized double blind trial comparing domperidone, metaclopramide and placebo suppositories was conducted by Van Eygen et al.[2] Sixty children admitted to hospital with vomiting associated with gastroenteritis were evaluated. The study drug was given at the start of the trial and then up to 3 more times in the subsequent 24 hours. No adverse events are reported in the 24 hour period of the study. Those in the domperidone group were less likely to require further doses ($P=0.055$ compared with metaclopramide, $P<0.05$ compared with placebo). Domperidone was statistically better at reducing nausea, vomiting, anorexia and abdominal pain compared to placebo ($P\leq 0.05$ or better). In this small study no adverse events were identified within the 24 hour study period.

Cubbedu et al.[3] compared IV ondansetron, IV metaclopramide and placebo in a small study double blind randomized controlled trial. Thirty six children aged 6 months to 8 years with vomiting associated with gastroenteritis were enrolled. Those treated with ondansetron had fewer episodes of emesis in first 24 hours ($P=0.048$) compared to placebo and were more likely to have no episodes of emesis over 24 hours ($P=0.039$). No statistically significant benefit to metaclopramide was demonstrated. More diarrhea was seen in the treatment groups when compared to placebo ($P=0.013$ for ondansetron and $p=0.004$ for metaclopramide). Adverse events reported included drowsiness (>90% of patients in all groups), cough (25% in ondansetron group and 8% in metaclopramide group) and tremor seen in one patient treated with metaclopramide.

Reeves et al.[4] conducted a randomized double blind control trial looking at the efficacy of IV ondansetron for the treatment of gastroenteritis associated vomiting in 107 children aged 1 month to 22 years. Children enrolled in this study were assessed as needing IV fluids suggesting either a significant degree of dehydration or significant vomiting. However, the criteria for this clinical decision were not defined. Those treated with IV ondansetron were more likely to cease vomiting (70% vs. 51%, $P=0.04$), and slightly less likely to be admitted to hospital (30% vs. 26%, $P=NS$). No significant adverse events were reported during the study period. Unfortunately the treatment and

Table 1: Description of Included studies

Study	Study Type	Participants	Intervention	Outcomes	Comments
Van Egan 1979	Double blind RCT	60 children ages 2 to 6 years	Suppository of domperidone (30 mg), metoclopramide (10 mg) or placebo given at start of trial and up to 3 times in the subsequent 24 hours	Children treated with domperidone were less likely to require further doses (P=0.055 compared with metoclopramide, P<0.05 compared with placebo). Domperidone was statistically better at reducing nausea, vomiting, anorexia and abdominal pain compared to placebo (P≤ 0.05 or better)	No adverse events were identified within the 24 hour study period
Cubeddu 1997	Double blind RCT	36 children ages 6 months to 8 years	Single IV dose of ondansetron (0.3mg/kg), metoclopramide (0.3mg/kg) or placebo (sterile saline)	Children treated with ondansetron had fewer episodes of vomiting in the first 24 hours compared to placebo (P=0.048) and were more likely to have no episodes of vomiting in the first 24 hours (P=0.039). More diarrhea was seen in treatment group when compared to placebo (P=0.013 for ondansetron and P=0.004 for metoclopramide)	No difference in the number or type of adverse events reported in the three groups.
Reeves 2002	Double blind RCT	107 children ages 1 month to 22 years	Single IV dose ondansetron (0.15 mg/kg) or placebo (saline)	Children treated with ondansetron were more likely to cease vomiting (70% vs. 51%, P=0.04) and slightly less likely to be admitted to hospital (30% vs. 26%, P=NS).	Only children who required IV therapy were included but the criteria used to make this decision was not outlined in the study. The treatment group was somewhat different than placebo group at the start of the trial in that they were more likely to be younger and have a lower serum pCO ₂ . No significant adverse events were reported during the study period.
Ramscook 2002	Double blind RCT	145 children ages 6 months to 12 years	Liquid ondansetron given every 8 hours for up to 6 doses (1.6 mg/dose for ages 6 months to 1 year, 3.2 mg/dose for ages 1-3 years, 4 mg/dose for ages 4-12 years) or placebo (colour and taste matched)	Children treated with ondansetron were more likely to cease vomiting during the ED stay (87% vs 65%, P=0.04) but the difference was not statistically significant over the 48 hour follow up. Children in the treatment group were less likely to need IV therapy (P=0.015) and less likely to be admitted (P=0.007).	Children in the treatment group were more likely to represent to the ED (5% vs 0%, P=0.047) and had more episodes of diarrhea in the first 24 hours (4.7 vs 1.4, P=0.02).
Freedman 2006	Double blind RCT	215 children ages 6 months to 10 years	Single dose oral dissolvable ondansetron (2mg for weights of 8 to 15kg, 4mg for weights greater than 15kg to up to 30kg and 8mg for weights greater than 30kg) or placebo (colour and taste matched)	Children who received ondansetron were less likely to vomit (14% vs. 35%, RR 0.40, 95% CI 0.26-0.61), tended to vomit less often (0.18 episodes/child vs. 0.65, P<0.001) and have greater oral intake (239 ml vs. 196 ml, P=0.001).	Both the treatment and placebo groups had similar rates of hospitalization (4% vs. 5%, P=1.0). Children in the treatment group had more episodes of vomiting compared with placebo (1.4 vs 0.5, P<0.001). No significant adverse events noted within 7 days.

Stork 2006	Double blind RCT	137 children ages 6 months to 12 years	Single dose IV dexamethasone (1mg/kg, max 15 mg) or ondansetron (0.15 mg/kg) or placebo (all diluted to 10ml)	Admission rates were reduced by ondansetron (4%) and dexamethasone (14%) compared to placebo (21%). The difference was statistically significant for ondansetron compared to placebo (RR=0.21, 95% CI of 0.05 to 0.81).	All groups received IV fluids. The study ended prematurely because of an increased number of patients who had already received antiemetics as outpatients precluding identification of previously untreated patients. No side effects were identified.
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placebo groups were somewhat different at the start of the trial. The treatment group tended to be younger and had lower serum CO₂ levels suggesting more severe disease in this group.

In a double blind, randomized controlled trial by Ramscook et al.[5] oral liquid ondansetron was evaluated in 145 children aged 6 months to 12 years who had vomited at least 5 times during 24 hours preceding presentation to ED. After discharge from ED participants were given 5 further doses to be taken 8 hourly at home. Those who received ondansetron were more likely to have no episodes of vomiting (87% vs. 65%, P=0.04) and more likely to have few episodes of vomiting (0.18 vs. 0.83, P=0.01) during the ED stay. However, the effect of reduced vomiting was not maintained beyond the ED stay. Those who received ondansetron were less likely to need IVT (P=0.015) and less likely to be admitted (p=0.007). Interestingly those in the treatment group had a higher rate of re-presentation to ED rate (5.41% vs. 0%, P=0.047) and had more episodes of diarrhea during the first 24 hours of the study (4.70 vs. 1.37, P=0.02). The only adverse event reported was a macular rash in one patient within 30 minutes of ondansetron administration.

Freedman et al.[6] conducted a double blind randomized control trial of a single dose of oral dissolvable ondansetron in 215 children aged 6 months to 10 years with vomiting, diarrhea and dehydration. Those who received ondansetron were less likely to vomit (14% vs. 35%, RR 0.40, 95% CI 0.26-0.61), tended to vomit less often (0.18 episodes/child vs. 0.65, P<0.001) and have greater oral intake (239 ml vs. 196 ml, P=0.001). Both the treatment and placebo groups had similar rates of hospitalization (4% vs. 5%, P=1.0). No significant adverse events during the 7 days following ondansetron were identified. However, the treatment group did have more episodes of diarrhea during oral rehydration (1.4 vs. 0.5, P<0.001).

In a double blind randomized control trial of 137 children ages 6 months to 12 years presenting to the emergency department Stork et al.[7] compared IV dexamethasone and ondansetron to placebo. Admission rates were decreased for both dexamethasone (14%) and ondansetron (4%) compared to placebo (21%). The difference was statistically significant for ondansetron compared to placebo (RR=0.21, 95% CI of 0.05 to 0.81). All participants in this study received IV fluids making it difficult to generalize the results to outpatient settings where IV fluids are not available or feasible. Interestingly, the study ended prematurely because of increased number of patients who had already received antiemetics as outpatients precluding identification of previously untreated patients. No side effects were identified but it was not clear how this was assessed.

A recent Cochrane Review assessed three studies[3],[5],[6] looking for evidence of effectiveness of antiemetics for vomiting associated with gastroenteritis in children and adolescents.[8] The conclusion drawn from this review is that "ondansetron may reduce the amount of acute vomiting as well as reducing the number of children who required intravenous hydration and admission for acute gastroenteritis". The authors

note that participants treated with ondansetron did have more diarrhea than controls but felt that the difference was not clinically significant.

The American Academy of Pediatrics endorses the US Centers for Disease Control position of discouraging the use of antiemetics in gastroenteritis by stating that "reliance on pharmacologic agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy, [and] can result in adverse events".[9],[1]

DISCUSSION

In general the use of antiemetics in paediatric gastroenteritis has been avoided due to concerns about central nervous system side effects from medications such as domperidone and metaclopramide. Recently there has been increased interest in the role of ondansetron in gastroenteritis. Ondansetron is a 5-HT₃-receptor antagonist that has a favourable side effect profile and has now been shown to be more effective than metaclopramide or dexamethasone. Freedman et al.[6] showed that a single dose of oral ondansetron in the ED can effectively decrease vomiting and improve the success of oral rehydration. The only adverse event identified in this study was an increase in diarrhea in the treatment group. So far this study provides the only evidence that a relatively safe, easy and effective treatment option exists for vomiting secondary to acute gastroenteritis exists in paediatrics. However, at an estimated cost of \$35 USD per 4 mg tablet this is unlikely to be a realistic option in developing countries.

SUMMARY

At this time there is some evidence that antiemetics may be safe and effective in gastroenteritis but there is still insufficient evidence that there is a significant cost benefit to their use in developing countries.

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