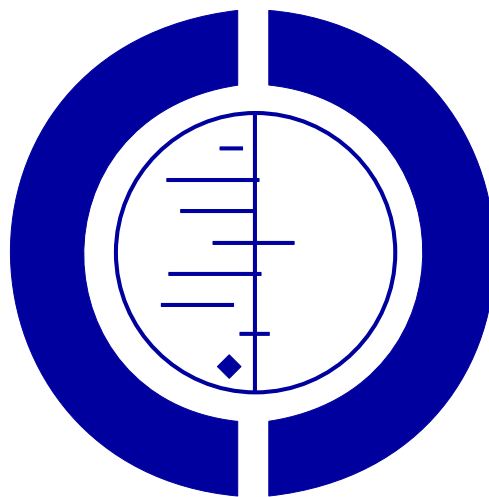


Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents (Review)

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Status: *New*

This record should be cited as:

Alhashimi D, Alhashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005506. DOI: 10.1002/14651858.CD005506.pub2.

This version first published online: 19 July 2006 in Issue 3, 2006.

Date of most recent substantive amendment: 23 March 2006

ABSTRACT

Background

Vomiting caused by acute gastroenteritis is very common in children and adolescents. Treatment of vomiting in children can be problematic and the use of antiemetics remains a controversial issue. There have been concerns expressed about apparently unacceptable levels of side effects such as sedation and extrapyramidal reactions, which are associated with some of the earlier generation of antiemetics.

Objectives

To assess the effectiveness of antiemetics on gastroenteritis induced vomiting in children and adolescents.

Search strategy

We searched the Cochrane Central register of Controlled Trials (CENTRAL), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register (searched 28 July 2005), MEDLINE (1966 to July 2005) and EMBASE (1980 to July 2005). Published abstracts from conference proceedings from the United European Gastroenterology Week and Digestive Disease Week were handsearched. Members of the Cochrane UGPD Group were contacted for details of any ongoing or relevant unpublished clinical trials.

Selection criteria

Randomised controlled trials comparing antiemetics and/or placebo in children and adolescents, under the age of 18, with vomiting due to gastroenteritis.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects data was collected from the studies.

Main results

Two trials involving 181 participants were included. Although no data were available for the precise time to cessation of vomiting (the primary outcome specified in the protocol for this review), one trial reported that the proportion of patients without vomiting over a 24 hour period was higher in the ondansetron and metoclopramide groups than placebo. In the second trial, ondansetron ensured complete anti-emesis for 8/12 (67%) patients within the first 4 hours and in 7/12 (58%) patients in the first 24 hr period. A few secondary outcomes were reported in the included trials.

Authors' conclusions

The small number of included trials provided some, albeit weak and unreliable, evidence which appeared to favor the use of ondansetron and metoclopramide over placebo to reduce the number of episodes of vomiting due to gastroenteritis in children. The increased incidence of diarrhea noted with both ondansetron and metoclopramide was considered to be as a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.

BACKGROUND

Epidemiology

Acute gastroenteritis is the leading cause of vomiting in children under three years of age and is a very common reason for children and adolescents attending emergency departments. Although vomiting is a fairly frequent occurrence in the younger child, it tends to be less prevalent in older children (Taylor 1999). Vomiting is usually accompanied by diarrhea and each year in the United States over 200,000 children aged less than five years require admission for treatment of dehydration secondary to gastroenteritis (Herikstad 2002). There is a similar pattern in the UK, with acute gastroenteritis in children under five years accounting for 20% of General Practitioner consultations and resulting in 24,000 hospital admissions annually (Flake 2004).

Vomiting is usually defined as a violent expulsion of gastric contents through the mouth. The act of vomiting requires the coordinated contractions of the abdominal muscles coupled with a diminished esophageal sphincter pressure and esophageal dilatation, with the stomach itself playing a somewhat passive role.

Dehydration, which is the decrease in total body water through a reduction in both the intracellular and extracellular fluid volumes, is an important cause of morbidity in children with vomiting (AAP1996). The clinical manifestations of dehydration are closely related to intravascular volume depletion which may lead to complications including irreversible shock, intractable seizures, and renal failure.

Starvation caused by reduced caloric intake in children with vomiting can lead to ketonemia, which in turn may lead to further dehydration.

Aetiology

Gastroenteritis attributable to viruses or bacteria occurs in the U.K. at a rate of 1.2 infections per person per year and is most common in the autumn and winter (Taylor 1999). The incidence in other developed countries is likely to be similar but may possibly be even higher in developing countries. The rotavirus, calcivirus, astrovirus, reoviruses, and adenoviruses are most commonly implicated. Bacterial causes may include *Staphylococcus aureus*, *Salmonella*, *Bacillus cereus*, or *Clostridium perfringens*. However, in developing countries, the rotavirus remains the most common cause of vomiting in children under 3 years of age (Doan 2003).

Intestinal irritation caused by gastroenteritis appears to be the main stimulus for vomiting. As the virus invades the mucosal cells of the upper gastrointestinal tract, it disrupts the normal sodium and osmotic intracellular balance and intracellular fluids are lost producing cellular fluid depletion. Paralysis of the bowel develops with resultant abdominal distension which induces further vomiting.

Vomiting, from whatever cause, occurs because of the stimulation of the two centers located in the brain, the chemoreceptor trigger zone and the vomiting center. The vomiting center, which controls

and integrates the act of vomiting, is located close to other centers which regulate respiration, vasomotor, and other autonomic functions and that may play an additional role in vomiting.

Stimuli are received by the vomiting centre from the gastrointestinal tract, from other parts of the body and the chemoreceptor trigger zone (Feldman 1989). In turn, the vomiting centre stimulates the salivation center, respiratory center, and the pharyngeal, gastro-intestinal and abdominal muscles, which then leads to vomiting (Friedman 1998).

The chemoreceptor trigger zone (CTZ) may receive stimuli from bacterial toxins or from metabolic abnormalities that occur with uremia, but it cannot independently mediate the act of vomiting (Brunton 1996). Instead impulses from the CTZ are relayed to the vomiting center, which coordinates the various physiological functions involved in vomiting.

Treatment

Vomiting associated with acute gastroenteritis is a distressing symptom for children and their parents. When faced with distraught parents, pediatricians may find themselves compelled to administer medication to stop children from vomiting. Treatment of vomiting in children is a controversial issue. Although the American Academy of Pediatrics stated in its position statement on the management of acute gastroenteritis in young children that it did not specifically evaluate the use of antiemetic drugs, it did confirm that there was a consensus of opinion that antiemetic drugs are not recommended and that physicians should be aware of their potential side effects (AAP1996).

Antiemetic medications are known to alleviate vomiting by inhibiting the body's chemoreceptor trigger zone (CTZ) or by a more direct action on the brain's vomiting centre.

A wide range of medicines have been used as antiemetics in children. These medications include: dopamine (D2) antagonists, serotonin or 5-hydroxytryptamine (5-HT₃) antagonists, anticholinergic agents, antihistamines, benzodiazepines, corticosteroids, and cannabinoids (Brunton 1996).

Several studies have investigated the effectiveness of prochlorperazine, promethazine hydrochloride, and metoclopramide as antiemetic medications. However, there have been concerns expressed about some of the adverse effects, such as sedation and extrapyramidal reactions, that have been associated with some of these medications. Quite surprisingly, very few of these reports relate directly to children, and the frequencies of such adverse events in pediatric populations are somewhat difficult to determine. The adverse effects of metoclopramide in young children have been well documented and may include fatigue and such extrapyramidal phenomena as dystonia, dyskinesia, akathisia, opisthotonos, and oculogyric crises (Taylor 1999).

Choosing between these therapeutic agents involves the careful consideration of a number of factors, including their effectiveness, their side effect profiles and cost.

Rationale for a systematic review

Concerns have been expressed about the side effects of antiemetics prescribed to children with vomiting. Several randomised control trials have investigated the effectiveness of different antiemetics but to the present time there has not been a systematic review of the evidence for the effectiveness of these medicines.

OBJECTIVES

The objective of this review was to provide reliable evidence regarding the clinical effectiveness and safety of antiemetics prescribed for vomiting due to gastroenteritis by comparing clinical outcomes expressed as cessation of vomiting and the eventual resumption of oral rehydration therapy.

The following null hypothesis was tested: for gastroenteritis induced vomiting there is no difference in the time taken to achieve cessation of vomiting between patients taking antiemetics as compared to those who have received placebo or nothing.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We only considered randomised controlled clinical trials in this review.

Types of participants

Studies which had recruited children and adolescents who were under the age of 18 and who presented with vomiting and a confirmed clinical diagnosis of gastroenteritis.

Any studies in which patients were vomiting as a result of general anaesthesia or due to chemotherapy were excluded. In addition, studies in which patients were suffering from surgical conditions (for example, acute appendicitis/pelvic abscess, inflammatory bowel disease), or systemic infections (such as urinary tract infections, pneumonia, meningitis), or metabolic conditions (diabetes mellitus or any other previously diagnosed disorders, including immunodeficiency) were excluded.

Types of intervention

Active interventions

We considered any antiemetics administered orally, IV or as suppositories at any dosage, prescribed to terminate or reduce vomiting.

Control

Administration of placebo or nothing prescribed to terminate vomiting.

Types of outcome measures

Primary

- The primary outcome for this review was the time taken from the first administration of the treatment measure till cessation of vomiting

Secondary

We also considered the following secondary outcomes for this review.

- Parental satisfaction as assessed by questionnaire or interview
- Number of subjects who had been admitted due to intractable vomiting
- Number of subjects who required intravenous fluids
- Time taken to reduction of episodes of vomiting
- Number of subjects who revisited
- Number of subjects resumed oral rehydration.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Upper Gastrointestinal and Pancreatic Diseases Group methods used in reviews.

Searches were conducted on 28th July 2005 to identify all published and unpublished randomised controlled trials. There were no language or date restrictions in the electronic searches.

ELECTRONIC SEARCHES

The search strategy for this review was constructed by using a combination of MESH subject headings and textwords relating to the use of antiemetics for the treatment of gastroenteritis in children.

Trials were identified by searching the following electronic databases - The Cochrane Central Register of Controlled Trials - CENTRAL (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) on The Cochrane Library (Issue 2 2005), MEDLINE (1966 to July 2005) and EMBASE (1980 to July 2005).

To identify randomized controlled trials, the following search was combined with the Cochrane highly sensitive search strategy phases one two and three, as contained in the Cochrane Reviewers' Handbook 4.2.5 (Higgins 2005).

gastroenteritis.tw.
exp rotavirus infections/
exp norwalk virus/
exp vomiting/
vomit\$.tw.
exp diarrhea, infantile/
diarrhea.tw.
diarrhoea.tw.
exp dehydration/

dehydrat\$.tw.
 or/30-40
 exp antiemetics/
 exp dopamine antagonists/
 (dopamin\$ adj2 antagonists).tw.
 chlorpromazine.tw.
 droperidol.tw.
 domperidone.tw .
 metoclopramide.tw.
 haloperidol.tw.
 prochlorperazine.tw.
 promethazine.tw.
 exp serotonin antagonists/
 serotonin adj2 antagonist\$.tw.
 dolasetron.tw .
 granisetron.tw.
 ondansetron.tw.
 tropisetron.tw.
 exp anticholinergic agent/
 scopolamine.tw.
 exp antihistamines/
 buclizine.tw.
 cyclizine.tw.
 dimenhydrinate.tw.
 diphenhydramine.tw.
 trimethobenzamide.tw.
 meclizine.tw.
 BENZODIAZEPINES/
 lorazepam.tw .
 exp corticosteroids/
 dexamethasone.tw.
 methylprednisolone.tw.
 exp cannabinoids/
 cannabinoid\$.tw.
 marijuana.tw.
 marinol.tw.
 or/42-75
 infan\$.tw.
 child\$.tw.
 neonat\$.tw.
 pediatric\$.tw.
 paediatric\$.tw.
 juvenile\$.tw.
 or/77-82
 41 and 76 and 83
 84 and 29

MANUAL SEARCHES

Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials. Published abstracts from conference proceedings from the United European Gastroenterology Week (published in *Gut*) and Digestive Disease Week (published in *Gastroenterology*) were handsearched.

In addition members of the Cochrane UGPD Group and experts in the field were contacted and asked to provide details of any ongoing clinical trials and any relevant unpublished materials.

METHODS OF THE REVIEW

Assessment of search results

The abstracts of studies resulting from the searches were independently assessed by two reviewers (DAH/ZF) and all irrelevant studies were excluded. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, were obtained. Studies not matching our inclusion criteria were excluded and their details and reasons for their exclusion were noted in the 'Characteristics of excluded studies'.

Assessment of methodological quality

Each of the two reviewers then graded the selected studies separately and every study reporting a randomised controlled clinical trial was assessed using a simple contingency form. The criterion grading system described in the Cochrane Reviewers' Handbook 4.2.5 (Higgins 2005) was followed. The gradings were compared and any inconsistencies between the reviewers in the interpretation of inclusion criteria and their significance to the selected studies were discussed and resolved.

The following parameters of methodological quality were assessed:

- Randomisation: was graded as adequate (A), unclear (B), inadequate (C). Adequate (A) included any one of the following methods of randomisation: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. Methods of randomisation utilising any of the following: case record number, date of birth or alternate numbers were judged as inadequate(C).
- Concealment of allocation: was graded as adequate (A), unclear (B), inadequate (C) or concealment not used (D). Adequate (A) methods of allocation concealment included either central randomisation or sequentially numbered sealed opaque envelopes. This criterion was considered inadequate (C) if there was an open allocation sequence and the participants and trialists could foresee the upcoming assignment.
- Blinding of outcomes assessment: whether persons assessing the outcome of care were aware of which treatment the participant received, was graded as yes, no and unclear (detection bias).
- Handling of withdrawals and losses - if there was a clear description given of the difference between the two groups of losses to follow up was graded as yes (A), unclear (B) and no (C) (attrition bias).

Data collection

Study details and outcomes data from randomised controlled clinical trials that met the inclusion criteria were collected using a form which was designed for this purpose, then entered into the 'Characteristics of included studies' table in RevMan 4.2.2 by each reviewer sequentially, and were automatically checked for differences. Data was only included when there was agreement. All disagreements were discussed and resolved by consensus. Dunia Alhashimi (DAH) held the master copy.

The following details were extracted.

- (1) Study methods: method of allocation, masking of participants and outcomes, exclusion of participants after randomisation and proportion of losses to follow-up.
- (2) Participants: country of origin, sample size, age, sex, inclusion and exclusion criteria.
- (3) Intervention: type of antiemetic; dose, frequency and route.
- (4) Control: placebo or nil.
- (5) Outcomes: any primary and secondary outcomes which had been specified *a priori* in the 'types of outcomes measures' section of the protocol.
- (6) Adverse effects: any adverse effects related to any clinically diagnosed hypersensitivity or other adverse reactions or side effects to the antiemetics were noted.

This information was used to help us assess heterogeneity and the external validity of the trials.

Data synthesis

Due to significant clinical heterogeneity and the paucity of data in the few included studies, we were unable to do a meta-analysis of the extracted data and therefore only provide a descriptive summary of results of the individual trials.

Sensitivity analyses

There were insufficient included studies in this systematic review and therefore no attempt was made to conduct a sensitivity analysis.

DESCRIPTION OF STUDIES

Finding the trials

The search strategy identified 2443 references (the Cochrane Library = 644, MEDLINE = 628, EMBASE = 1171). After examination of the titles and abstracts of these references, all but six studies were eliminated and excluded from further review. Full text copies of the six remaining studies were obtained and subjected to further evaluation.

The Ginsberg study was a non randomised controlled trial and it was withdrawn from further review (Ginsburg 1980). The Debray trial was translated from French into English and was then assessed against the inclusion criteria specified for this review (Debray 1990). The participants in this trial included children and infants vomiting from either bacterial or viral infectious diseases, of which less than half (49%) had vomiting attributable to gastroenteritis whereas the remaining participants were vomiting due

to bronchitis or 'other'. As over half of the participants in this study were not suffering with gastroenteritis and the authors failed to provide any separate data for those children with vomiting induced by gastroenteritis, this study is awaiting further assessment. We have written to the authors to try to obtain the missing data and, on the basis of any additional information we receive, this review will be updated accordingly.

The inclusion criteria in our protocol specified that the participants should be children and adolescents up to the age of 18 years. Although the mean age of participants in the Reeves trial was 5.3 years, this trial did include patients up to the age of 22 years, which we considered are neither children nor adolescents (Reeves 2002). As it was not clear from the text how many of the participants were over the age of 18 years, we have written to the trialists asking for clarification as to how many of the participants fall outside our inclusion criteria of 18 years of age. This trial is awaiting further assessment pending a reply from the trialists. The Van Eygen trial did not include any of our primary or secondary outcomes and was therefore excluded from further assessment (Van Eygen 1979).

Even though the two remaining studies (Ramsook 2002; Cubeddu 1997) did not address the primary outcomes specified in the protocol for this review and therefore did not totally match our inclusion criteria, it was considered that their inclusion and the reporting of their results, some of which matched our secondary outcomes, might help to provide some evidence towards answering this research question. (see table of 'Characteristics of Included Studies' and 'What's new').

Summary of trial details

The study by Ramsook et al was a randomized double blind clinical trial conducted in the emergency department of a university-affiliated hospital in Texas, USA (Ramsook 2002). The participants comprised 145 children (82 males, 63 females), who were aged between six months and 12 years. The baseline characteristics of age, sex distribution and episodes of vomiting were similar in both the intervention and placebo groups.

Eligibility for the study required participants to have a clinically confirmed diagnosis of gastroenteritis, at least five episodes of vomiting with or without diarrhea, and to have not received any antiemetics in the preceding 24 hrs. The presence of any serious underlying chronic systemic conditions or the necessity for immediate rehydration resulted in the automatic exclusion of any patients.

Baseline data showed that 37 (50%) of the patients in the ondansetron and 40 (56.33%) in the placebo group had up to 10 episodes of vomiting in the preceding 24 hours (Table 01). In addition, 37 (50%) patients in the ondansetron group and 31 (43.66%) in the placebo group had more than 10 episodes of vomiting.

Randomization was to oral ondansetron (74) or taste and colour matched placebo (71). The patients received ondansetron 1.6mg for those aged six months to one year, 3.2mg aged one to three years and 4mg aged four to 12 years, or placebo eight hourly. Each

received a total of six doses of the ondansetron or placebo of which a single dose was taken in the emergency department followed by an additional five doses taken eight hourly for up to 48 hours when discharged to home.

Oral rehydration therapy, consisting of unflavored Pedialyte, was started 15 minutes after the first dose of ondansetron or placebo was administered in the emergency room. Patients were only discharged after they were able to successfully tolerate oral fluids and after successful rehydration. At the end of the 24 hour period, all the patients were progressively weaned onto a diet consisting of bananas, rice, applesauce and toast (BRAT). A total of 13 patients with persistent vomiting who had received intravenous fluids and refused oral fluids were admitted and classified as treatment failures.

Ondansetron group.

Out of 74 patients who were enrolled in the trial, one patient who developed a rash after the first dose was withdrawn, seven were lost to follow up and two were eventually admitted. Only 64 out of the 73 patients completed the 24-hour follow up. A total of 62 patients completed the trial at 48 hours.

Placebo group.

Out of 71 patients who entered the trial, four were lost to follow up, 11 were admitted and only 56 completed the 24-hour follow up. There were a further five losses to follow up at 48 hours. A total of 51 patients successfully completed the trial at 48 hours.

Although the trialists recorded the proportion of participants without vomiting during the emergency department stay, and the first 24-hour and second 24-hour period, they did not provide the precise time to cessation of vomiting which was the primary outcome specified for this systematic review.

The only secondary outcomes specified for this review and included in this trial were the rates of intravenous fluid administration, and admission for each group. The trial did not include any assessment of parental satisfaction.

The only adverse effects reported in this trial were the frequency of diarrhea.

The Cubeddu study was a randomized double-blind placebo-controlled clinical trial conducted in a children's hospital in Venezuela (Cubeddu 1997). All 36 participants (21 males, 15 females) aged six months to eight years were hospitalised for a minimum period of 24 hours during the course of the trial. They were only enrolled in the trial if they had been diagnosed with acute gastroenteritis which was confirmed by a positive stool analysis for adenovirus or rotavirus. All but two of the participants had positive stool cultures for rotavirus, adenovirus or bacteria.

The participants in the groups were comparable for gender and food intake but were not balanced for age, height, weight and degree of hydration.

The inclusion criteria specified for this study required participants to have had at least two vomiting episodes (either spontaneous or oral-rehydration induced) within one hour, where a vomiting

episode was defined as an expulsion of stomach contents and was recorded as a single vomit or retch or any number of continuous vomits and/or retches with a minimum one minute interval separating each episode. Retching was defined as an attempt to vomit that was not productive of any stomach contents.

Participants were excluded if they had severe dehydration, seizures, significantly elevated rectal temperatures, had received any parenteral antiemetic medication in the six hours previously or were diagnosed with a parasite-induced gastroenteritis.

Three groups of 12 children in each group were randomised to either ondansetron hydrochloride dihydrate (0.3mg/kg), metoclopramide hydrochloride (0.3mg/kg), or sterile saline solution (placebo) administered as a single intravenous dose. Oral rehydration, consisting of a solution of sodium, potassium, citrate and glucose, was started 30 minutes after administration of either antiemetic or control and continued at 30 minute intervals for up to four hours. No food was permitted during this rehydration period but it was gradually introduced based on the individual status of the patient (i.e. their level of hydration, the presence or absence of retching and/or diarrhea).

Treatment failures were defined as patients who had experienced two vomiting episodes in any 90 minute period 1-8 hours after the administration of the intervention, or had three episodes during the hour following the end of administration of the study treatment.

In this study, treatment failures at 0-4hrs included four (33%) who had received placebo, two (17%) metoclopramide and one (8%) who had received ondansetron. And at 0-24 hrs; four (33%) who received placebo, five (42%) metoclopramide and two (17%) who had received ondansetron. Treatment failures accounted for 50% of the participants in this study.

This trial produced no data for the exact time to cessation of vomiting and therefore did not address the primary outcome of this review. Although the trial provided no explicit data for the precise time taken for a reduction in the number of episodes of vomiting (which was one of our secondary outcomes), it did indicate the number of vomiting episodes experienced by the participants over the 0-24 hour period.

Neither any revisit or readmission data nor any assessments of parental satisfaction were reported. All participants were orally rehydrated and none of them received any intravenous fluids.

Adverse events were noted in all treatment groups which included episodes of diarrhea, general drowsiness, a cough which was experienced by a few of the patients in both groups and tremor experienced by one patient in the metoclopramide group.

Further details of these trials can be found in the table 'Characteristics of included studies'.

METHODOLOGICAL QUALITY

The Ramsook study was a well conducted clinical trial in which the intervention (oral ondansetron) and control (placebo) groups were assigned before the experiment through the use of standard random number allocation tables (Ramsook 2002). The medications were blinded, randomized, and packaged by a pharmacy. Assignment to either the oral ondansetron (strawberry flavour) intervention or the taste and colour matched placebo was carried out by the pharmacy research section according to the predetermined randomization procedure. The randomization code was locked away and was only broken and revealed to the assessors at the conclusion of the trial. Triple blinding was achieved in this trial as neither the trialists, the emergency department staff, patients and carers nor the outcomes assessors were aware of the treatment assignment in this study. Randomization and allocation concealment were both graded as adequate (A).

The authors followed the intention-to-treat principle and presented a Trial Randomisation Flow diagram which comprehensively charted the path of all the participants through the study, and all patients lost to the trial were accounted for satisfactorily. This trial was supported in part by a grant from Glaxo Wellcome Research and Development.

In the Cubeddu study it was stated that the participants were randomly assigned to interventions and control, but the method used to achieve randomisation was not mentioned by the trialists and therefore this criterion was graded as (B) unclear (Cubeddu 1997). The trialists confirmed that blinding of investigators was achieved through the preparation of the study medication by a pharmacist not involved in patient care and therefore the allocation concealment in this study was graded as (A) adequate. There was no indication from the study details if persons assessing the outcomes of care were blinded to which treatment the participants received (detection bias), and thus this criterion was graded as unclear.

The report was fairly explicit about the losses due to 'treatment failures' and was graded as (A) clear.

It was stated that two of the authors of this trial obtained funding from Glaxo Wellcome.

There were a number of differences in the conduct of the two included studies:

- All patients in the Cubeddu study were hospitalised for 24 hours, whereas in the Ramsook study any patient who was hospitalised was considered a treatment failure and took no further part in the study.
- In the Cubeddu study, a diagnosis of either bacterial or viral gastroenteritis was confirmed by stool analysis, the diagnosis in Ramsook was less clear with the clinical definition of gastroenteritis as "the presence of vomiting with or without diarrhea".
- The studies were conducted over different time periods. In the Ramsook study, the patients were discharged to home care after

the initial observation period in the emergency department and were followed up for up to 48 hrs, whereas the Cubeddu study was completed in 24 hours, after which all the participants were discharged and received no further care.

Hospitalisation of all the participants in the Cubeddu study ensured they were more closely observed and that data collection was more likely to be complete (Cubeddu 1997). Conversely a greater reliance was placed on the participants and their carers in the study by Ramsook (Ramsook 2002). These participants were asked to complete a diary recording the number of episodes of vomiting and diarrhea in the 24 hour follow up period. Although the patients were contacted by telephone 24 and 48 hours after discharge, compliance with medication, oral rehydration and the BRAT diet guidelines could not be assured. The parents were required to complete a diary which was then mailed to the trialists to confirm the data which had previously been obtained over the telephone. The trialists did indicate that 10-15% of patients were lost to follow up of telephone and mail-in diary.

RESULTS

The primary outcome specified in the protocol for this review was the time taken from the administration of the treatment measure until cessation of vomiting. None of the included trials provided any data addressing this outcome but some of the secondary outcomes were reported.

The Ramsook 2002 study.

Primary outcome: time to cessation of vomiting

This report did indicate that the number of participants who received ondansetron and had no vomiting was greater than those who received placebo during the emergency department stay and during the first and second 24-hour period (Table 02). However it was not explicit about the precise time to cessation of vomiting in each person in each group during the study period.

Secondary outcomes: Admission and revisit rate, intravenous rehydration

Two participants in the placebo and 11 in the ondansetron group who had persistent vomiting, or refused oral rehydration, or were administered intravenous fluids were subsequently admitted (Table 03). Although no exact data were made available, the trialists confirmed that a smaller proportion of patients in the ondansetron group compared with placebo required intravenous fluid therapy. The revisit rate was higher in the ondansetron group (4/74; 5.41%), two for persistent vomiting and two for persistent diarrhea, compared with the placebo group (0/71) $P=.047$. This trial did not include any assessment of parental satisfaction.

Side effects:

Apart from diarrhea the only other side effect reported in this trial was the development of a macular rash in one patient who had received ondansetron.

The Cubeddu 1997 study.

Primary outcome: time to cessation of vomiting

Although this report did not provide the precise time to cessation of vomiting for participants in any of the groups, it did indicate that the proportion of patients experiencing no vomiting in the time period 0-24 hours was higher in the ondansetron group 7/12 (58%) than placebo 2/12 (17%) and 4/12 (33%) in the metoclopramide group $P = .039$ (Table 04).

Ondansetron ensured complete anti-emesis for 8/12 (67%) patients within the first 4 hours and in 7/12 (58%) patients in the first 24 hr period.

Secondary outcomes: Admission and revisit rate, intravenous rehydration

Intravenous fluid therapy for diarrhea induced fluid loss was given to 3 (25%) patients in the ondansetron group and to 1 (8%) in the metoclopramide group during the first 24 hour period after treatment.

No data was available for either admission beyond the study period or revisit rates. The trialists did not include any data on assessment of parental satisfaction.

Side effects:

Adverse events were noted in all treatment groups. All patients in the study experienced at least one episode of diarrhea but compared with placebo there were significantly more episodes of diarrhea in the ondansetron ($P = .013$) and metoclopramide ($P = .004$) groups in the first 24 hours although there was no significant difference between these two groups.

Other side effects included general drowsiness in 90% of the patients, a cough experienced by a few patients in both groups and tremor by one patient in the metoclopramide group.

DISCUSSION

Whilst recognising the methodological limitations of the two studies, the incompleteness of their data, the likelihood of publication bias and the comparative unreliability of the evidence, we have still chosen to include them but advise caution in the interpretation of their results. We expect that, with a response from the trialists in either of the studies which are awaiting assessment, we will be able to add to and improve on the rather distinct lack of data available for the planned outcomes specified in the protocol of this review.

The AAP guidelines (AAP1996), published almost 10 years ago, stated that there was a consensus of opinion that antiemetics were not needed for the management of vomiting due to gastroenteritis in children. It was thus somewhat disappointing to see a lack of robust clinical trials to either support or refute this opinion and both of these included trials provide little or no direct evidence to support the necessity of any immediate changes to that guidance. The AAP guidelines did also warn that clinicians should be aware of certain potential, but unspecified, adverse effects associated with antiemetics, yet both of these studies, whilst reporting some side

effects, appeared to indicate that other than diarrhea all of the drugs were reasonably well tolerated.

This review included two trials which were industry funded and provided some weak and unreliable evidence regarding the clinical effectiveness and safety of antiemetics prescribed for children vomiting due to gastroenteritis.

AUTHORS' CONCLUSIONS

Implications for practice

It appears that ondansetron may reduce the amount of acute vomiting as well as reducing the number of children who required intravenous rehydration, and admission for acute gastroenteritis. However this conclusion is only based on two studies. In addition, participants in the ondansetron group did have more diarrhoea than in the placebo group, but the amount is likely not clinically significant. The two included trials reported on two possible routes of administration for two antiemetics; either oral or intravenous ondansetron or intravenous metoclopramide. It is conceivable that in the presence of persistent vomiting the intravenous single dose of ondansetron, if available, may offer some advantages over the oral route particularly in that the intravenous route is most likely to obviate any further irritation to the gastric mucosa.

Implications for research

In view of the likelihood of a higher incidence of gastroenteritis in developing countries the importance of further research into the effectiveness and cost effectiveness of antiemetics cannot be underestimated, particularly if this may lead to a reduction in the frequency with which costly intravenous fluids and hospitalisation are required.

Future research should also focus on outcomes that are of relevance to patients and thus the time to cessation of vomiting rather than a reduction in the number of episodes of vomiting as outcomes would appear to be more appropriate.

POTENTIAL CONFLICT OF INTEREST

There are no financial conflicts of interest and the reviewers declare that they do not have any associations with any parties who may have vested interests in the results of this review.

ACKNOWLEDGEMENTS

The reviewers would like to thank Janet Lilleyman, the Review Group Coordinator of the Cochrane UGPD Group, for her support throughout this review. We also are very grateful to Iris Gordon for her tireless effort in developing the search terms and strategy and running the searches for this review. Madame Ricks of the

British School of Bahrain also very kindly undertook the translation of the French study into English for which we are extremely grateful.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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TABLES

Characteristics of included studies

Study	Cubeddu 1997
Methods	A randomised double blind placebo-controlled parallel group study. Method of randomisation not specified.
Participants	Children aged 6 months to 8 years
Interventions	A single IV dose of Ondansetron (0.3mg/kg) or metoclopramide (0.3mg/kg) or placebo(sterile saline)
Outcomes	Primary outcome: a single vomit or retch or any number of continuous vomits and/or retches
Notes	Treatment failures at 0-4hrs: four (33%) placebo, two (17%) metoclopramide and one (8%) ondansetron. At 0-24hrs: four (33%) placebo, five (42%) metoclopramide and two (17%) ondansetron. This study was supported by Glaxo Wellcome Research and Development
Allocation concealment	A – Adequate

Study	Ramsook 2002
Methods	A prospective double blind randomised study. Random allocation tables were used to assign treatment or placebo. Treatment was blinded randomised and packaged by a pharmacy.
Participants	Children between the ages of 6 months and 12 years
Interventions	Oral Ondansetron 2mL(1.6mg) for ages 6 months to 1 yr, 4mL (3.2mg) aged 1-3yrs, and 5mL (4mg) aged 4-12 (all 8 hourly) or placebo. Oral rehydration was started 15 mins after the initial dose at 5mL/min according to standard accepted protocols.
Outcomes	Primary outcomes: frequency of vomiting during the 48hour period after enrollment and rates of intravenous fluid administration. Secondary outcomes: admission rates and frequency of diarrhea.
Notes	One patient who developed a rash was withdrawn after the first dose. A total of 13 patients, who had received intravenous fluids, had persistent vomiting and who had to be subsequently admitted, were classified as treatment failures. Study funding was obtained from Glaxo Wellcome.
Allocation concealment	A – Adequate

Characteristics of excluded studies

Ginsburg 1980 This was a non randomised controlled study.

Van Eygen 1979 No outcomes matching those specified in the protocol of this review.

ADDITIONAL TABLES

Table 01. Baseline characteristics 24hr preceding the study (Ramsook 2002)

Emesis episodes	Ondansetron group	Placebo group
less than 10	37(50%)	40(56.33%)
more than 10	37(50%)	31(43.66%)

Table 02. Proportion of patients without vomiting (Ramsook 2002)

Time period	Ondansetron group	Placebo Group
ED Stay	64 (87%)	46 (65%)
First 24 hours	37 (58%)	30 (54%)
24 -48 hours	43 (70%)	30 (59%)

Table 03. Admission rate including the number requiring intravenous fluids (Ramsook 2002)

Ondansetron Group	Placebo Group
2	11

Table 04. Participants with no vomiting 0-24hr (Cubeddu 1997)

	Ondansetron(n=12)	Metoclopramide(n=12)	Placebo (n=12)
No vomiting	7 (58%)	4 (33%)	2 (17%)

GRAPHS AND OTHER TABLES

This review has no analyses.

COVER SHEET

Title	Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents
Authors	Alhashimi D, Alhashimi H, Fedorowicz Z
Contribution of author(s)	Dunia Alhashimi(DAH) and Zbys Fedorowicz (ZF) were responsible for: Designing the review Co-ordinating the review Performing previous work that was the foundation of current study. (DAH) (ZF)and Hakima Alhashimi (HAH) were responsible for: Data collection for the review Screening the search results Screening retrieved papers against inclusion criteria Appraising quality of papers Abstracting data from papers Obtaining and screening data on unpublished studies Entering data into RevMan Analysis of data

	<p>Interpretation of data Writing the review. (ZF) and (DAH) were responsible for: Organising retrieval of papers Writing to authors of papers for additional information Providing additional data about papers. (DAH) conceived the idea for the review and is the guarantor for the review.</p>
Issue protocol first published	2005/4
Review first published	2006/3
Date of most recent amendment	23 May 2006
Date of most recent SUBSTANTIVE amendment	23 March 2006
What's New	In view of the absence of any trials addressing the primary outcome of this review, 'the time taken from the first administration of treatment measure to cessation of vomiting', we report only on the outcomes presented in the two included trials, which specifically refer to some of the secondary outcomes specified in the protocol of this review. Two trials are awaiting assessment and if data relevant to the outcomes of this review become available we will update the review accordingly.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	28 July 2005
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD005506.pub2
Cochrane Library number	CD005506
Editorial group	Cochrane Upper Gastrointestinal and Pancreatic Diseases Group
Editorial group code	HM-UPPERGI