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

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
The objective of this review is to provide reliable evidence regarding the clinical effectiveness and safety of antiemetics for vomiting due to gastroenteritis by comparing clinical outcomes expressed as cessation of vomiting and the eventual resumption of oral rehydration therapy. Additionally, we will look into the number of children and adolescents who had be admitted to hospital and the number of subjects who required intravenous fluids.
The following null hypothesis will be 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.

BACKGROUND

Epidemiology

Acute enteric illness 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 common occurrence in the younger child it tends to be less prevalent in older children (Taylor 1999). Vomiting is usually accompanied by diarrhoea and each year in the United States over 200,000 children aged less than 5 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 5 years accounting for 20% of GP consultations and resulting in 24,000 admissions annually (Flake 2004).
Vomiting is usually defined as the 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 further worsens the dehydration.

Aetiology

Gastroenteric illnesses attributable to viruses or bacteria occur in the UK at a rate of 1.2 infections per person per year and are most common in the autumn and winter (Taylor 1999).Figures in other developed countries are likely to be similar however it maybe 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 the rotavirus remains the most common cause of vomiting in children under 3 years of age in developing countries (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 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 by itself it cannot mediate the act of vomiting (Brunton 1996). Impulses from the CTZ are relayed to the vomiting center, which coordinates the various physiological functions involved in vomiting.

Treatment

Vomiting associated with acute enteric infections is a distressing symptom for children and their parents. Pediatricians often find themselves compelled to administer medication when faced with distraught parents who want to stop their child from vomiting. Treatment of vomiting in children is a controversial issue. Although the American Academy of Pediatrics didn't specifically evaluate the use of antiemetic drugs, in its position statement on the management of acute gastroenteritis in young children, it stated that consensus of opinion was that antiemetic drugs are not needed and that physicians should be aware of their potential side effects (AAP1996).

Anti-emetic medications alleviate vomiting by inhibiting the body's chemoreceptor trigger zone (CTZ) or by direct action on the brain's vomiting centre.

A wide range of pharmaceutical agents 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 clinical experience with these drugs has revealed an unacceptably high incidence of adverse effects, such as sedation and extrapyramidal reactions. 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 appear to be particularly common and may include fatigue and such extrapyramidal phenomena as dystonia, dyskinesia, akathisia, opisthotonos, and oculogyric crises (Taylor 1999).

Choosing between these therapeutic agents involves careful consideration of many factors, including their effectiveness, side effect profiles, physician familiarity, and cost.

Rationale for a systematic review

There are sufficient concerns about the side effects of antiemetics prescribed to children with vomiting. A few randomised control trials have been conducted which investigated the effectiveness of different antiemetics but there are currently no systematic reviews.

OBJECTIVES

The objective of this review is to provide reliable evidence regarding the clinical effectiveness and safety of antiemetics for vomiting due to gastroenteritis by comparing clinical outcomes expressed as cessation of vomiting and the eventual resumption of oral rehydration therapy. Additionally, we will look into the number of children and adolescents who had be admitted to hospital and the number of subjects who required intravenous fluids.

The following null hypothesis will be 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 will only consider randomised controlled clinical trials (RCTs) in this review.

Types of participants

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

We will exclude studies in which patients were vomiting as a result of general anaesthesia or due to chemotherapy. Additionally, studies in which patients are suffering from surgical conditions e.g.:acute appendicitis/pelvic abscess, inflammatory bowel disease, or systemic infections e.g.: urinary tract infections, pneumonia, meningitis, metabolic conditions e.g.. diabetes mellitus or any other previously diagnosed disorders, including immunodeficiency ,will be excluded.

Types of intervention

Active interventions

Administration of any systemic antiemetics at any dosage, prescribed to terminate or reduce vomiting. These may be administered orally, IV or as suppositories.

Control

Administration of placebo or nothing prescribed to terminate vomiting.

Types of outcome measures

Primary

- Time taken from first administration of treatment measure till cessation of vomiting

Secondary

- 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 will be conducted to identify all published and unpublished randomised controlled trials. Articles published in any language will be included.

Trials will be 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 and the Cochrane Pain, Palliative and Supportive care Group Trials Register) on The Cochrane Library. Also MEDLINE, EMBASE, Web of Science, BIOSIS and LILACS (Latin American and Caribbean Center on Health Sciences Information) will be searched.

The search strategy for the review will be constructed by using a combination of MESH subject headings and textwords relating to the use of antiemetics for the treatment of gastroenteritis in children. The standard Cochrane search strategy filter for identifying randomised controlled trials will be applied to all searches.

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

METHODS OF THE REVIEW

Assessment of search results

Two reviewers (DAH/ZF) will independently assess the abstracts of studies resulting from the searches. 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, will be obtained. All irrelevant records will be excluded and details of the studies and the reasons for their exclusion will be noted.

Assessment of methodological quality

Each reviewer will then grade the selected studies and every study reporting a randomised controlled clinical trial will be assessed using a simple contingency form and will follow the criterion grading system described in the Cochrane Reviewers' Handbook 4.2.0 (Higgins 2005). The gradings will be compared and any inconsistencies between the reviewers in the interpretation of inclusion criteria and their significance to the selected studies will be discussed and resolved.

We will assess the following parameters of methodological quality:

- Randomisation: graded as adequate (A), unclear (B), inadequate (C). Adequate (A) will include 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. Inadequate method of randomisation (C) utilising any of the following: case record number, date of birth or alternate numbers will be judged as inadequate.
- Concealment of allocation: graded as adequate (A), unclear (B), inadequate (C) or concealment not used (D). Adequate (A) methods of allocation concealment would include either central randomisation or sequentially numbered sealed opaque envelopes. This criterion will be considered inadequate (C) if there is an open allocation sequence and the participants and trialists can foresee the upcoming assignment.
- Blinding of outcomes assessment: whether persons assessing the outcome of care were aware of which treatment the participant received, will be graded as yes, no and unclear (detection bias).
- Handling of withdrawals and losses - was there a clear description given of the difference between the two groups of losses to follow up which will be graded as yes (A), unclear (B) and no (C) (attrition bias).

Data collection

Study details from randomised controlled clinical trials meeting the inclusion criteria will be entered into the 'Characteristics of included studies' table in RevMan 4.2.8 by each reviewer separately and cross checked.

The following details will be extracted.

(1) Study methods: method of allocation, masking of participants and outcomes, exclusion of participants after randomisation and proportion of follow-up losses.

(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: primary and secondary outcomes mentioned in the section of outcome measures.

(6)Adverse effects : We will report on any specific adverse effects related to any clinically diagnosed hypersensitivity or other adverse reactions to the antiemetics.
Additionally we will include any Quality of Life or Patient Reported Outcomes measures reported in the trials.

This information will be used to help us assess heterogeneity and external validity of the trials.
Outcome data will be collected using a predetermined form designed for this purpose. Extracted data will be entered into RevMan 4.2.2 by each reviewer sequentially and automatically checked for differences. Zbys Fedorowicz (ZF) will hold the master copy. Data will only be included if there is an independently reached consensus. Any disagreement will be discussed and if required a third reviewer will be consulted.

Data synthesis
We plan to assess heterogeneity by looking at the characteristics of the studies, by examining the types of participants, the interventions and outcomes. We will follow the UGPD Group statistical guidelines on publication bias and examine the forest plot of the results and the chi squared test.
The data will be analysed by ZF using RevMan and reported according to Cochrane Collaboration criteria. Pooling of data will only occur if the included studies have similar interventions taken by similar participants. We will present relative risks for outcomes and odds ratios for adverse effect outcomes.
Relative risk, the number needed to treat and their 95% confidence intervals will be calculated for all dichotomous data.
For synthesis and meta-analysis of any quantitative data we will use the fixed and random effects models as appropriate. If it is established that there is significant heterogeneity between the studies we will use the random effects model.

Sensitivity analyses

If there are sufficient included studies we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies of lower methodological quality and any unpublished studies. In addition, sensitivity analyses may be undertaken to examine the effect of allocation concealment, blind outcome assessment and completeness of follow up.

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.

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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) will be responsible for: Data collection for the review Screening 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 Interpretation of data Writing the review. (ZF) and (DAH) will be 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 will also be the guarantor for the review.
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