Use of cisapride in patients with non-ulcer dyspepsia: a meta-analysis of randomized trials

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Authors' objectives
To assess the safety and efficacy of cisapride in non-ulcer dyspepsia (NUD) compared with placebo, H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs).

Searching
The authors searched MEDLINE (1966 to 1999), HealthSTAR (1975 to 1999), TOXLINE (pre-1965 to 1999), EMBASE (1974 to 1999), and Current Contents (1990 to 1999) using search strategies which are detailed in the appendices of the review along with the strategy for regular DIALOG alerts from MEDLINE, HealthSTAR, TOXLINE, EMBASE, Current Contents Search, Pascal, Pharmaceutical News Index (PNI) and Adis LMS Drug Alerts. The Cochrane Library was searched (issue number 4, 1998). The authors also manually searched the reference lists from retrieved articles and abstracts from Gastroenterology (1989 to 1998) were also searched manually. The authors contacted the manufacturer of cisapride for information regarding unpublished studies. The searches do not state any language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Data from the first phase of crossover trials were considered for inclusion.

Specific interventions included in the review
Cisapride (10 mg tid/qid, or 30 mg/day or doses ranging from 4 to 20 mg tid/qid) compared with one or more of the following: placebo, H2 receptor antagonists (H2RAs) such as ranitidine (300 mg/day or 150 mg bid), cimetidine (200 mg qid), nizatidine (300 mg/day) or metoclopramide (10 mg tid), for a duration of no less than two weeks. No comparisons of cisapride with proton pump inhibitors (PPIs) were available.

Participants included in the review
Adult patients (aged greater than 21 years) diagnosed for non-ulcer dyspepsia (NUD) in which involvement of definite structural factors such as esophagitis, chronic gastric or duodenal ulcer and gastric erosion for the symptoms of dyspepsia had been eliminated by upper gastro-intestinal endoscopy.

Outcomes assessed in the review
Outcomes measures included:
1. The number of patients experiencing significant improvement on a global symptom scale (good and/or excellent response).
2. The number of patients showing significant improvement (or complete reduction) in specific symptoms such as epigastric pain, early satiety, nausea, belching, and bloating (at the end of the trial period for each arm of the study).

How were decisions on the relevance of primary studies made?
A single researcher made an initial review of the studies for inclusion. Two reviewers then independently made a final selection of the relevant studies. Disagreements were resolved by discussion.

Assessment of study quality
The authors used the 5-point, 3-item Jadad scale to assess the validity of the relevant studies (see Other Publications of Related Interest no.1). Studies were scored 0 to 5 points in total, with 5 being the highest quality and 0 the lowest. Two reviews independently assessed the relevant studies for validity. Reviewers were not blinded to author, year and journal of publication.
**Data extraction**

Two reviewers extracted data independently using a pre-designed extraction form. The completed forms were cross-checked and any disagreements were resolved by consensus.

The degree of agreement between reviewers was estimated by Kappa.

Data were extracted for the categories: biographical details, trial design, patient characteristics (e.g. age, history of NUD, history of alcohol and NSAIDs use), dosages, treatment period and outcomes.

**Methods of synthesis**

How were the studies combined?

Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Peto fixed-effect model. A random-effects calculation was also used but showed similar results so the fixed-effect results are reported.

The presence of publication bias was assessed by using a funnel plot.

How were differences between studies investigated?

Between-trial heterogeneity was evaluated using the Cochran Q statistic.

Sensitivity analyses were performed to investigate the effects of trial quality, country of publication, language of publication, studies published in supplements and effect of placebo run-in before randomisation. For the secondary outcome measure, the sensitivity analysis was performed by estimating the effect size using the random-effects model.

**Results of the review**

Twenty-four RCTs were included in the review. Twenty RCTs compared cisapride with placebo (6,964 participants, 6,201 randomised to cisapride and 763 randomised to placebo), three RCTs compared cisapride with H2 antagonists and one RCT compared cisapride with H2 antagonists and placebo. The latter four RCTs were combined into one group of cisapride (294 participants) compared with H2 antagonists (306 participants). No studies of cisapride with PPI were available.

The degree of agreement between two evaluators was high (K = 0.90 plus/minus (SE) 0.21).

Study quality:

Quality assessment showed that one study was of high quality score (5), 16 were of moderate quality score (3 to 4) and seven studies were of low quality score (0 to 2).

Studies comparing cisapride and placebo:

Cisapride was found to be more effective than placebo (OR 4.58, 95% CI: 3.58, 5.85) when assessing global excellent outcome only (n = 13, 1,354 participants). Statistically significant heterogeneity was found, p < 0.0016).

Cisapride was found to be more effective than placebo (OR 4.25, 95% CI: 3.42, 5.27) when assessing good and excellent response. Statistically significant heterogeneity was found, p < 0.001).

Cisapride was found to be more effective than placebo in the pooled estimate of effect size of individual symptoms of NUD (epigastric pain, early satiety, belching and bloating) with the exception of nausea. The OR calculated using a fixed-effect model for epigastric pain (n = 4, 127 participants) was 5.34 (95% CI: 2.60, 10.94).

The OR calculated using a fixed-effect model for early satiety (n = 4, 169 participants) was 2.85 (95% CI: 1.54, 5.24).

The OR calculated using a fixed-effect model for nausea (n = 4, 164 participants) was 1.39 (95% CI: 0.73, 2.62), which was not statistically significantly different.
The OR calculated using a fixed-effect model for belching (n = 3, 113 participants) was 4.13 (95% CI: 1.96, 8.69).

The OR calculated using a fixed-effect model for bloating (n = 4, 169 participants) was 3.13 (95% CI: 1.68, 5.81).

Results using a random-effects model were similar: epigastric pain, early satiety, belching, bloating and nausea were 6.06 (95% CI: 2.81, 14.83), 3.03 (95% CI: 1.42, 6.47), 4.54 (95% CI: 2.0, 10.34), 3.24 (95% CI: 1.67, 6.28), and 1.38 (95% CI: 0.72, 2.66) respectively. No statistically significant heterogeneity was found.

Studies comparing cisapride and H2 antagonists:

Cisapride did not differ significantly from H2 antagonists with an OR for global excellent outcome of 1.43 (95% CI: 0.98, 2.08) and for combined global excellent plus good of 1.13 (95% CI: 0.60, 2.13). There was no statistically significant heterogeneity observed across the studies used in these two outcome measures. No changes were observed with a sensitivity analysis using random effects.

The funnel plots obtained by plotting of log OR of primary outcomes versus precision (1/SE) of individual studies were not symmetrical suggesting that a systematic bias exists among the studies.

**Authors’ conclusions**
The authors state that the present meta-analysis indicates that cisapride is possibly effective in NUD. However, the findings of significant statistical and clinical heterogeneity among studies raises doubt about the efficacy of cisapride in NUD and, further, no significant difference was observed between cisapride and H2 antagonists.

**CRD commentary**
This is a good review. The authors have stated the research question and inclusion and exclusion criteria. The literature search appears to be very thorough. While it is unlikely that additional relevant studies were missed in these searches, the authors’ funnel plots did suggest that studies were missing in the plot of results.

The quality of the included studies was formally assessed. The authors also reported how the articles were selected, and who performed the selection and validity assessment. The authors reported who performed the data extraction and how this was performed, along with tests for agreement between reviewers.

The data extraction is reported in tables and discussed in the text of the review. The studies were statistically combined and heterogeneity was assessed as well as additional sensitivity analyses. Although significant heterogeneity was present, the authors still chose to combine the studies using a fixed-effect model.

The authors’ conclusions appear to follow from the results but the authors state that these should be viewed with caution because of the doubt raised by the significant heterogeneity between studies and that effect on the efficacy.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

**Bibliographic details**

**Original Paper URL**

**Other publications of related interest**

This additional published commentary may also be of interest. Cisapride for non-ulcer dyspepsia. Bandolier 2000;76:2-5.

**Indexing Status**
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.