Effectiveness of proton pump inhibitors in nonerosive reflux disease

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CRD summary
This review assessed the use of proton-pump inhibitors (PPIs) to relieve the symptoms of nonerosive reflux disease (NERD). The authors concluded that PPIs have a lesser effect in NERD than in erosive oesophagitis, and that symptoms tended to improve throughout the 4-week period. Insufficient data were presented to assess the appropriateness of pooling the studies, hence any conclusions may not be reliable.

Authors' objectives
To assess the effectiveness of proton-pump inhibitors (PPIs) for the relief of symptoms of nonerosive reflux disease (NERD), and also to assess the effects of PPIs in patients with NERD compared with patients with erosive oesophagitis (EE).

Searching
MEDLINE and HealthSTAR were searched for studies published in English between 1980 and 2002; the search terms were reported. Searches of the Food and Drug Administration website and of abstracts presented during the American College of Gastroenterology and Digestive Disease Week conferences (between 1999 and 2001) were also conducted. The reference lists of relevant reports were checked and physicians and researchers were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared acute treatment with PPI monotherapy with placebo were eligible for inclusion. The included studies used rabeprazole, esomeprazole, omeprazole and pantoprazole. Some studies had multiple treatment arms.

Participants included in the review
Studies of adults (aged 18 years or over) with NERD, i.e. symptoms of gastroesophageal reflux disease and negative upper endoscopy, were included if the patients had oesophagitis grade 0 or 1. The included studies used different systems to classify patients. The reviewers categorised patients into three groups: patients with negative endoscopy; patients with erythema and friability but no erosions; and all patients. For the comparison of PPI treatment in patients with NERD and EE, placebo-controlled studies of patients with endoscopically confirmed EE (Hetzel-Dent grades 2 to 4) were eligible and were included.

Outcomes assessed in the review
Studies that assessed the resolution of symptoms were eligible for inclusion. The review assessed:

heartburn resolution, defined as either complete or sufficient resolution;

complete resolution, defined as no heartburn during the previous 7 days); and

sufficient (or satisfactory) heartburn resolution, defined as less than 1 day of moderate heartburn during the previous 7 days.

The outcomes for patients with NERD were reported at 1, 2 and 4 weeks (where data permitted). Only complete resolution at 4 weeks was assessed for patients with EE.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and any disagreements were resolved by consensus. Inter-rater reliability was assessed using the kappa statistic.

**Assessment of study quality**  
The validity of RCTs of patients with NERD was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding, and the handling of withdrawals. The maximum possible score was 5 points. The authors did not state who performed the validity assessment.

**Data extraction**  
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted for all outcome measures for all time periods reported on an intention-to-treat basis, and were used to calculate the risk difference (‘therapeutic gain’) between treatment and placebo groups.

**Methods of synthesis**  
How were the studies combined?  
The studies were combined by meta-analysis using Bayesian modelling. Pooled risk differences (RDs) and 95% confidence intervals (CIs) were calculated for each outcome at each time point. In addition, pooled symptomatic response rates with 95% CIs were calculated separately for patients with NERD and patients with EE treated with PPI and placebo.

How were differences between studies investigated?  
Some differences were taken into account in the various meta-analyses, but statistical heterogeneity was not assessed.

**Results of the review**  
Seven RCTs (with 12 treatment arms) were used to assess heartburn resolution in patients with NERD (n=1,854). Two RCTs were used to assess the effects of PPIs in patients with EE (n=705).

Studies of NERD scored 4 or 5 out of 5 for quality.

PPIs in NERD.  
Patients treated with PPIs were significantly more likely to achieve complete or sufficient control of heartburn compared with placebo-treated patients. In general, the pooled RD between PPI and placebo groups ranged from 0.3 to 0.35 for sufficient control, and from 0.25 to 0.3 for complete control. Higher proportions of patients achieved sufficient resolution than achieved complete resolution, and sufficient resolution was achieved sooner than complete resolution.

PPIs in patients with NERD compared with EE.  
In an indirect comparison, complete resolution of heartburn symptoms at 4 weeks was more common in patients with EE than in those with NERD (56% versus 37%, \(P<0.00001\)). There was no significant difference between patients with NERD or EE in response rates with placebo (9.5% versus 7.5%, \(P>0.05\)).

**Authors’ conclusions**  
PPIs have a lesser effect in patients with NERD than in those with EE. There was a trend towards greater improvements in symptoms in patients with NERD throughout the 4 weeks of treatment.

**CRD commentary**  
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication bias. Restricting the
studies to English language reports raises the possibility of language bias. Two reviewers independently selected studies, which reduces the potential for reviewer bias and errors. However, the methods used to assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias in these processes. Only RCTs were included and validity was assessed using established criteria.

The studies were combined using meta-analysis techniques. However, there was insufficient details of the methods used for the meta-analysis, no assessment of statistical heterogeneity and no accompanying meta-analysis graphs. It was therefore not possible to judge whether or not the meta-analysis was appropriate. In addition, the methods used to deal with multiple comparison groups sharing a control group were not described. The evidence presented appears to support the authors’ conclusions but, since the review methods were not clearly reported and insufficient data were presented to assess the appropriateness of pooling the studies, any conclusions may not be reliable.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need to consider increasing the duration of future trials in patients with NERD beyond 4 weeks and to assess sufficient as well as complete heartburn relief.

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