Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease

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CRD summary
This review concluded that treatment using high-dose proton-pump inhibitors is no more effective than placebo for the improvement or resolution of symptoms in adult patients experiencing laryngo-pharyngeal symptoms assumed to be related to gastro-oesophageal reflux disease. However, the between-study differences mean that the reliability of the authors’ conclusions is uncertain.

Authors’ objectives
To determine the effectiveness of treatment for reflux disease in adult patients with laryngeal or pharyngeal symptoms attributed to gastro-oesophageal reflux disease (GERD).

Searching
MEDLINE (1966 to September 2005), EMBASE (1974 to September 2005) and the Cochrane CENTRAL Register (to September 2005) were searched; the search terms were reported. Additional manual and electronic searches of abstracts of meeting proceedings from the American Gastroenterological Association (1975 to 2005), the United European Gastroenterology Federation (1992 to 2005) and the American Academy of Otolaryngology – Head and Neck Surgery Foundation (1994 to 2005) were conducted. No language restrictions were applied.

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

Specific interventions included in the review
Studies of medical or surgical anti-reflux treatment for laryngeal or pharyngeal symptoms assumed to be associated with GERD were eligible for inclusion. All of the included studies used proton-pump inhibitors (PPIs) such as pantoprazole (80 mg for 12 weeks), lansoprazole (60 mg for 12 weeks), omeprazole (80 mg for 12 weeks), rabeprazole (40 mg for 8 weeks) and esomeprazole (80 mg for 16 weeks). No studies assessing surgical interventions met the inclusion criteria for this review.

Participants included in the review
Studies of adults with laryngeal or pharyngeal symptoms lasting not less than 2 weeks and attributed to GERD were eligible for inclusion. Studies of patients with other specific identifiable causes of laryngeal or pharyngeal symptoms supported by physical examination and/or appropriate tests were excluded. The participants included in the study were all aged 18 years or older and were experiencing a variety of symptoms: cough, nocturnal cough, globus, sore throat, hoarseness, dysphonic attacks, frequent clearing of the throat and non-productive cough.

Outcomes assessed in the review
Studies that assessed the proportion of patients reporting an improvement in symptoms after treatment were eligible for inclusion. Definition of a ‘responder’ was taken as that chosen by the authors of the included studies.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements on inclusion through recourse to a third reviewer.

Assessment of study quality
Validity was assessed and scored (between 0 and 5) using the Jadad scale, which assesses randomisation, blinding and the handling of withdrawals. Two reviewers independently assessed validity and resolved any disagreements through recourse to a third reviewer.
Data extraction
Two reviewers independently extracted the data using a predefined form and resolved any disagreements through consensus, with the aid of a third reviewer where required. Data on the numbers of patients responding to a PPI and placebo were used to derive a relative risk (RR) for each study. An intention-to-treat analysis was conducted on evaluable patients.

Methods of synthesis
How were the studies combined?
The results from individual studies were combined and a pooled RR, with 95% confidence interval (CI), was calculated using the DerSimonian and Laird random-effects model. The number-needed-to-treat (NNT), with 95% CI, was calculated as the reciprocal of the pooled absolute risk reduction. Publication bias was visually assessed using a funnel plot and explored using the methods proposed by Egger.

How were differences between studies investigated?
Subgroup analyses were conducted to explore the effects of Jadad score and symptoms reported at baseline by the patients. Statistical heterogeneity was assessed using the chi-squared test.

Results of the review
Five studies (n=247) were included: four RCTs and one randomised controlled crossover trial. Only data from the first period of the randomised controlled crossover trial were included in the analysis.

Two studies scored 4 on the Jadad scale and three scored 5. There were no statistically significant differences between the PPI and placebo groups for improvement or resolution of symptoms (RR 1.18, 95% CI: 0.81, 1.74). There was no evidence of statistical heterogeneity.

The NNT was 54, which indicates that there was no clinically meaningful effect.

Subgroup analyses found that the results were similar to the overall analysis after evaluating Jadad score and type of patients’ symptoms at baseline (only cough versus multiple symptoms).

The funnel plot suggested the potential for publication bias.

Authors’ conclusions
Treatment using high-dose PPIs is no more effective than placebo for the improvement or resolution of symptoms in adult patients experiencing laryngo-pharyngeal symptoms assumed to be related to GERD.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. A limited range of databases was searched and unpublished material was not sought, so it is possible that some relevant studies could have been missed. In addition, the formal assessment of publication bias suggested that this was possibly present in the review. Methods were used to minimise reviewer error and bias in the study selection and data extraction processes. Two reviewers independently assessed validity using the Jadad criteria, thus reducing the potential for bias and errors, although only the composite score was presented; this makes it difficult for the reader to judge study validity for themselves.

The characteristics of the participants and interventions were adequately summarised. However, the authors limited their assessment of the crossover study to the first time period only; this results in the loss of data as crossover trials are powered such that data from all time periods are required. There was no evidence of statistical heterogeneity, although there were differences between the studies in terms of the definitions used for outcomes in individual studies and treatment regimen, including drug, dosage and duration of treatment; the pooling of studies using meta-analysis may not, therefore, have been appropriate. In summary, the between-study differences mean that the reliability of the authors’ conclusions is uncertain.
Implications of the review for practice and research

Practice: The authors stated there was no evidence to support prescribing PPIs for adult patients with laryngeal or pharyngeal symptoms presumed to be associated with GERD.

Research: The authors stated that further research is needed to identify the characteristics of patients who may respond to PPI treatment.

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