A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux
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CRD summary
This review assessed the efficacy of proton-pump inhibitors in the treatment of laryngopharyngeal reflux in adults. The authors concluded that there was insufficient evidence on which to base conclusions regarding the effectiveness of the intervention, and further randomised trials are required. Despite limitations to this review, the authors' cautious conclusions are justified give the data available.

Authors' objectives
To assess the efficacy of proton-pump inhibitors (PPIs) in the treatment of laryngopharyngeal reflux in adults.

Searching
MEDLINE (from 1966), EMBASE (from 1980) and the Cochrane Controlled Trials Register were searched up to October 2004; the search terms were reported. Additional references were identified from the reference lists of retrieved articles. No language restrictions were applied and no attempts were made to contact the drug manufacturers or to handsearch journals.

Study selection
Study designs of evaluations included in the review
Only double-blind randomised controlled trials (RCTs) with at least 10 participants, which suffered from less than 20% drop-out in any study arm and with no other unanticipated methodological flaws, were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared an oral PPI with placebo were eligible for inclusion. Studies that assessed the effectiveness of PPIs in combination with other potentially active interventions were excluded. The studies included in the review assessed the effectiveness of 40 mg twice daily doses of omeprazole and pantoprazole. The duration of treatment was 21 days and 30 days.

Participants included in the review
Eligible studies had to include individuals over the age of 18 years who were suffering from at least one of the following laryngopharyngeal reflux symptoms: hoarseness, excessive throat clearing, globus sensation, excessive phlegm, sore throat or chronic cough. Other causes had to be excluded and participants had to have experienced symptoms for at least 2 months. All eligible participants should have received 24-hour ambulatory oesophageal pH monitoring in order to confirm the presence of reflux. Both of the reported studies included patients who had experienced symptoms of chronic laryngitis for at least 3 months. Other causes were excluded by flexible laryngoscopy, and 24-hour dual-channel pH probe measurements were used to confirm the presence of reflux.

Outcomes assessed in the review
Eligible studies had to report a symptom score for laryngopharyngeal reflux, defined as a composite score of throat pain, hoarseness, foreign body sensation in the throat, throat clearing and cough. Other eligible outcomes included an improvement in endoscopic laryngeal signs or pH readings evaluated by 'pH metry'. The included studies used two different patient-assessed scoring systems: a visual analogue score (VAS) with between 0 to 1,400 points reflecting both the severity and frequency of symptoms, and a composite score between 0 and 72 derived from a 4-point symptom scale adjusted for the frequency of symptoms.

How were decisions on the relevance of primary studies made?
Two reviewers performed the literature searches, but the authors did not state how the papers were selected for the
review, or how many reviewers performed the selection.

Assessment of study quality
Five predefined methodological criteria (see Study Designs of Evaluations Included in the Review) were used to assess and screen studies for inclusion. The studies were also assessed for estimation of sample size and intention-to-treat analysis. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data from the included studies using predefined criteria. Any differences in opinion were resolved through discussion. All symptom scores were converted to a 10-point scale and the mean and standard deviation were calculated.

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects model to give a pooled weighted mean difference (WMD) with 95% confidence intervals (CIs).

How were differences between studies investigated?
A chi-squared test was used to assess statistical heterogeneity. Some clinical differences between the studies were also evident from the data tables and the text of the review.

Results of the review
Two RCTs (n=30 and n=21) were included in the review, one of which was a crossover study.

One RCT (n=30) assessed the effects of omeprazole and found that placebo treatment was associated with significantly greater reductions in laryngeal symptom scores compared with omeprazole (standardised mean difference, SMD -2.25, 95% CI: -3.19, -1.31). The other crossover RCT (n=21) found that pantoprazole was associated with a significantly greater increase in laryngeal symptom scores compared with control (SMD 1.10, 95% CI: 0.15, 2.06).

When the studies were pooled there was no significant difference between PPIs and placebo (WMD -0.440, 95% CI: -3.86, 2.71); significant heterogeneity was found (chi-squared test, p=0.00001).

Authors’ conclusions
There was insufficient evidence on which to base conclusions regarding the effectiveness of PPIs in the treatment of laryngopharyngeal reflux. The combined analysis of the included trials failed to show any significant positive effects of treatment with PPIs.

CRD commentary
This review answered a clear research question. The literature search covered all languages, therefore language bias is unlikely to be an issue. However, no specific attempts were made to identify unpublished articles, which suggests there may be a risk of publication bias. Some attempts were made to reduce error and bias in the processes of the review through the use of more than one reviewer; it is unclear though whether screening for inclusion and the validity assessment were carried out with similar rigour. There is also some doubt over the validity of the meta-analysis which pooled data from two studies with conflicting results. The authors acknowledged the heterogeneity between the patient populations. Despite the aforementioned limitations and given the paucity of data, the review's cautious conclusions about the insufficiency of the data are valid.

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

Research: The authors stated that well-designed, large, probably multicentre RCTs are required to further assess the effectiveness of PPIs in the treatment of laryngopharyngeal reflux.

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