Early heartburn relief with proton pump inhibitors: a systematic review and meta-analysis of clinical trials

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CRD summary
This review assessed proton-pump inhibitors for the relief of heartburn within 1 to 2 days. The authors concluded that proton pump inhibitors may improve symptoms within 24 hours, but most patients will not experience relief in the first 1 or 2 days. Apart from the limited search, this was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy of proton-pump inhibitors (PPIs) for heartburn relief within the first 1 to 2 days of treatment.

Searching
MEDLINE (1966 to June 2004) and EMBASE (1980 to June 2004) were searched without language restrictions; the search terms were reported. Abstracts were excluded, and pharmaceutical companies and the U.S. Food and Drug Administration were not contacted for unpublished studies. The reference lists of previous systematic reviews were screened.

Study selection
Study designs of evaluations included in the review
Studies with 20 or more patients per treatment arm were eligible for inclusion. Uncontrolled studies were not excluded a priori.

Specific interventions included in the review
Studies of PPIs were eligible for inclusion. Studies of chronic maintenance treatment, intermittent treatments and 'on demand' treatment were excluded. The included studies used omeprazole (10 to 20 mg/day), esomeprazole (20 to 40 mg/day), lansoprazole (15 to 30 mg/day) and rabeprazole (10 to 20 mg/day). In all of the included studies co-treatment with antacids was allowed but histamine2-receptor antagonists were not.

Participants included in the review
Studies of adults with acute heartburn, erosive oesophagitis, nonerosive gastroesophageal reflux disease (GERD) and/or symptomatic GERD were eligible for inclusion. Studies of patients with GERD symptoms refractory to standard or high-dose antisecretory treatment with histamine-receptor antagonists or PPIs were excluded, as were studies of patients with erosive oesophagitis which did not provide adequate information about baseline heartburn.

Outcomes assessed in the review
Studies were eligible if they reported either the number or percentage of patients with complete heartburn relief on day 1 or 2 of treatment, as assessed using a pre-specified symptom tool. The primary review outcome was the number of patients at day 1 with resolution of heartburn within the previous 24-hour period (overall, daytime and night-time). The secondary review outcomes were resolution of heartburn on day 2 (overall, daytime and night-time) and sustained resolution of heartburn on days 1 and 2. The review defined sustained heartburn resolution as an absence of heartburn in the previous 24-hour period that lasts for 7 consecutive days. All but two of the included studies assessed heartburn symptoms on day 1 or 2 using a written patient diary; other studies used a telephone interactive voice response system.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and any disagreements were resolved by consensus.
Assessment of study quality
Clinical trials were assessed and scored using the Jadad scale, which considers the reporting of randomisation, allocation concealment, blinding and handling of withdrawals. The maximum possible score was 5 points. Two reviewers independently assessed validity and any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. Data on the number of participants, the number with heartburn at baseline, and the number with complete and sustained heartburn relief at days 1, 2 and 28, were extracted. Where possible, the authors calculated the proportion of maximal benefit achievable on day 1 or day 2 (defined as the proportion of patients with resolution of heartburn on day 1 or 2 divided by the proportion with resolution at day 28). Where necessary, both authors estimated the percentages of patients with outcomes of interest from graphs and mean percentages were estimated.

Methods of synthesis
How were the studies combined?
Sample size-weighted mean proportions of patients with the outcomes of interest were calculated separately, along with 95% confidence intervals (CIs), for PPI and placebo. Pooled proportions were calculated separately on days 1 and 2 for individual PPIs and for all PPIs combined. Pooled relative risks (RRs) with 95% CIs were calculated for PPI versus placebo and for PPIs versus each other using a random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. Separate meta-analyses were performed for individual PPIs and for double-dose PPI versus single-dose PPI. The meta-analyses of daytime and night-time heartburn relief were repeated after excluding the non-randomised study; this was a post hoc decision. The meta-analysis was also repeated including only patients with erosive oesophagitis and nonerosive reflux disease.

Results of the review
Eighteen studies were included (at least 21,000 patients with GERD received PPIs). There were 17 RCTs and 1 non-randomised study with no control group.

Fourteen studies scored 3 or more for quality out of a maximum of 5 on the Jadad scale. Fifteen studies were double-blinded.

At day 1 of PPI treatment, complete 24-hour relief of heartburn occurred in 0.31 (95% CI: 0.30, 0.32; based on 13,980 patients), daytime relief in 0.49 (95% CI: 0.48, 0.50; based on 7,497 patients), night-time relief in 0.55 (95% CI: 0.53, 0.56; based on 9,479 patients) and sustained heartburn relief in 0.21 (95% CI: 0.20, 0.22; based on 11,197 patients).

The proportion of maximal response (response at day 28) achieved in the first 24 hours was 0.37 (95% CI: 0.35, 0.39; based on 3,819 patients).

Placebo was significantly less effective than PPI for 24-hour relief on day 1 (RR 0.41, 95% CI: 0.29, 0.58).

Single-dose PPI treatment was significantly less effective than double-dose PPI for 24-hour heartburn relief on day 1 (RR 0.82, 95% CI: 0.74, 0.92).

The subgroup analysis showed that omeprazole 20 mg was less effective than lansoprazole 30 mg and esomeprazole 40 mg for 24-hour sustained relief on day 1. Lansoprazole and esomeprazole were similarly effective for daytime, night-time and 24-hour heartburn relief. The results were reported.

Authors' conclusions
PPIs may improve symptoms from the first day of treatment, but most patients will not experience relief in the first 1 or 2 days of PPI treatment.
CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and outcomes; initial inclusion criteria for the study design were broad. Restricting the search to published studies listed in two databases plus reference lists might have resulted in the omission of other relevant studies and raised the possibility of publication bias; attempts were made to minimise language and publication bias. Methods were used to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. The validity of the clinical trials was assessed using criteria designed for RCTs and the results of this assessment were reported.

Statistical heterogeneity was assessed and the studies were appropriately pooled using meta-analysis. A subgroup analysis was used to examine the influence of various factors. Apart from the limited search, this was a well-conducted review and the authors' conclusions are likely to be reliable.

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

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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.