Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis. A comparison of esomeprazole with other PPIs

Edwards S J, Lind T, Lundell L

CRD summary
This review compared the effectiveness of esomeprazole with other standard-dose proton-pump inhibitors for the treatment of reflux oesophagitis, and found that 40 mg esomeprazole is the most effective treatment currently available. Overall, the findings of the review appear to be supported by the data, but caution is advised given the levels of unexplained statistical variation detected between the studies.

Authors' objectives
To compare the effectiveness of esomeprazole with other proton- pump inhibitors (PPIs) for the treatment of reflux oesophagitis.

Searching
The Cochrane CENTRAL Register, BIOSIS Previews, EMBASE and MEDLINE were searched up to February 2005; the search terms were reported. Unpublished and published trials were eligible for inclusion, but non-English language studies were excluded.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review. The authors also stated that the studies had to meet their quality criteria.

Specific interventions included in the review
Studies comparing 40 mg of esomeprazole with a licensed dose of any other European-approved PPI were eligible for inclusion. The included studies used the following comparators: 30 mg lansoprazole, 20 mg omeprazole and 40 mg pantoprazole.

Participants included in the review
Studies of individuals with oesophagitis were eligible for inclusion. Oesophagitis had to be defined using the Los Angeles classification A to D, or grades 2 to 4 in older classification systems such as the Savary-Miller classification. The authors excluded trials if they focused on a restricted range of oesophagitis, although such trials were included in a secondary analysis.

Outcomes assessed in the review
Eligible studies had to assess endoscopic healing at 4 and/or 8 weeks. A protocol change was made to extend this to include a secondary analysis of endoscopic healing rates according to the baseline grade of oesophagitis.

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

Assessment of study quality
The methods of randomisation and concealment of allocation were used to assess the quality of the studies. Two reviewers independently carried out assessments and a third party resolved any disagreements. The studies were scored as either 'clearly adequate' (A) or 'clearly inadequate' (B).
Data extraction
One reviewer extracted the data and two other reviewers independently checked the accuracy of the data extraction.

Relative risks (RRs) with 95% confidence intervals (CIs) were extracted or calculated for endoscopic healing at 4 and 8 weeks using intention-to-treat (ITT) data. ITT was defined as ‘patients being analysed in the treatment arm that they entered at randomisation regardless of whether they drop-out, receive the incorrect treatment or withdraw before completion of the trial’; the data were recalculated if the study authors used any alternative definitions.

Methods of synthesis
How were the studies combined?
The studies were combined and a pooled RR with 95% CIs calculated using a fixed-effect analysis. Publication bias was assessed using funnel plots and the Egger method (regression of normalised effect versus precision).

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared and I-squared tests. Analyses were also planned to investigate the effects of study quality and the use of a random-effects pooling method. Where significant heterogeneity was detected, subgroup analyses were carried out based on drug comparator and dose.

Results of the review
Six RCTs (n=13,572) were included. Data from 2 excluded RCTs (n=1,228) were also included in some analyses.

Esomeprazole (40 mg) showed a significant improvement in the healing rates of reflux oesophagitis at both 4 weeks (RR 0.92, 95% CI: 0.90, 0.94, p<0.00001) and 8 weeks (RR 0.95, 95% CI: 0.94, 0.97, p<0.00001) in comparison with combined standard-dose PPIs. However, significant heterogeneity was detected at both 4 and 8 weeks; further analysis suggested that the majority of this heterogeneity was due to the inclusion of the third largest trial (n=2,425). Subgroup analyses showed that 40 mg esomeprazole was associated with a significant improvement in healing rates in comparison with 30 mg lansoprazole at 4 weeks (RR 0.95, 95% CI: 0.95, 0.98, p<0.001) and 8 weeks (RR 0.96, 95% CI: 0.94, 0.99, p<0.0009), with 20 mg omeprazole at 4 weeks (RR 0.88, 95% CI: 0.85, 0.91, p<0.0001) and 8 weeks (RR 0.93, 95% CI: 0.91, 0.95, p<0.0001), and with 40 mg pantoprazole at 4 weeks (RR 0.93, 95% CI: 0.89, 0.96, p=0.0002) and 8 weeks (RR 0.97, 95% CI: 0.95, 1.00, p=0.03). No trials compared 20 mg rabeprazole with 40 mg esomeprazole.

Sensitivity analyses.

The results remained similar when 2 excluded RCTs with limited grades of oesophagitis were included, and when a random-effects model was used.

Baseline grade of oesophagitis.

At both 4 and 8 weeks, esomeprazole showed a significant additional benefit over standard-dose PPIs for the more severe grades of oesophagitis. This effect increased in size with increasing severity of the disease.

No significant publication bias was detected at either 4 or 8 weeks.

Authors’ conclusions
Evidence suggests that 40 mg esomeprazole is the most effective treatment currently available when compared with other standard PPI treatments.

CRD commentary
This review answered a clearly defined question. A number of databases were searched and steps were taken to assess the possibility of publication bias. Although no evidence of publication bias was detected, the reliability of these tests is unclear given the small number of included studies, and no specific attempts to locate unpublished material were made. The exclusion of non-English language publications also suggests that the findings might be subject to language bias.
Some attempts were made to reduce the risk of bias and error when extracting the study data and assessing the quality of the studies. However, it is unclear whether similar precautions were taken when assessing the eligibility of the studies.

The studies were all grouped together for the primary analyses and, as such, a significant level of statistical heterogeneity was reported. Some attempts were made to investigate the cause of this heterogeneity but no definitive cause was identified, although one large trial appeared to be responsible for the majority of the heterogeneity. The authors also included two excluded studies in secondary analyses. Overall, the findings of the review appear to be supported by the data, but caution is advised given the levels of unexplained statistical heterogeneity detected.

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

Practice: The authors stated that where the choice of PPI is restricted by formulary listings, esomeprazole and the least expensive alternative PPI appear to be the best supported treatments.

Research: The authors did not state any implications for research.

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