Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis - a mixed treatment comparison of randomized controlled trials

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CRD summary
This review concluded that 40mg esomeprazole appeared to have higher healing rates than licensed standard- and double-dose proton pump inhibitors, for severe erosive oesophagitis. The evidence presented appeared to support these conclusions, but the reliance on indirect mixed treatment comparisons and the poor reporting of trial characteristics, make it difficult to assess the reliability of the findings.

Authors' objectives
To assess the effectiveness of licensed standard doses of proton pump inhibitors in comparison with double-doses for the healing of severe erosive oesophagitis.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in October 2008 for full papers and abstracts published in English. Search terms were reported; a search filter for randomised controlled trials was used.

Study selection
Randomised controlled trials (RCTs) comparing endoscopic healing data for a European-licensed healing dose of a proton pump inhibitor with at least one alternative European licensed healing dose of a proton pump inhibitor, in patients with severe grades of erosive oesophagitis, were included in the review. Eligible trials had to assess outcomes at four weeks or eight weeks or both.

Included trials assessed the following proton pump inhibitors: 40mg esomeprazole, 30mg lansoprazole, 20mg omeprazole, 40mg omeprazole, and 40mg pantoprazole.

Direct head-to-head comparisons in included trial were available for: 40mg omeprazole versus 20mg esomeprazole; 40mg omeprazole versus 20mg omeprazole; 40mg esomeprazole versus 40mg pantoprazole; 40mg esomeprazole versus 30mg lansoprazole; 30mg lansoprazole versus 20mg omeprazole; and 30mg lansoprazole versus 40mg omeprazole.

The trials included patients with severe erosive oesophagitis defined as grades C and D in the Los Angeles classification system or comparable grades in other erosive oesophagitis classification systems (e.g. grades 3 and 4 in the Savary-Miller classification system).

The authors did not state how papers were selected for review or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the quality of each trial according to the following criteria: randomisation, allocation concealment, method of blinding and lost to follow-up. Any discrepancies were resolved through discussion. Only those trials that were judged to be of clearly adequate quality or possibly adequate quality were included in the analysis.

Data extraction
Four and eight week healing data for severe grades of oesophagitis were extracted on an intention-to-treat basis. Where intention-to-treat data were not available, all cases were assumed not be healed at four or eight weeks.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Data were pooled using a mixed treatment comparison carried out using a Bayesian Markov Chain Monte-Carlo model. Odds ratios (ORs) with 95% credible intervals (CrI) were reported using a random-effect model for each treatment dose in comparison with 20mg omeprazole. Statistical heterogeneity was assessed. Data were adjusted for year of publication and consistency was assessed using the posterior mean residual deviance. A sensitivity analysis using the alternative model at four and eight weeks was used to assess the impact of using alternative models. Unadjusted results for the fixed-effects model were presented at four weeks and the unadjusted results for the random-effects model were presented at eight weeks.

Results of the review
Twelve RCTs (n=5186 patients) were judged to be of sufficient quality to be included in the analysis. Sample sizes ranged from 66 to 1,286 patients.

Esomeprazole 40mg was associated with significantly higher healing rates at four weeks (OR 1.84, 95% CrI 1.50 to 2.22) and eight weeks (OR 1.91, 95% CrI 1.13 to 2.88).

None of the other proton pump inhibitors that were investigated had significantly higher healing rates than omeprazole 20mg. Levels of statistical heterogeneity were low.

There was insufficient data to include rabeprazole 20mg in the analysis (no identified trials that provided data for healing at four and/or eight weeks).

Sensitivity analyses using alternative models reported similar results and year of publication did not appear to be significant parameters in the analysis.

Authors' conclusions
Results from mixed treatment comparisons suggested that 40mg esomeprazole had higher healing rates than licensed standard- and double-dose proton pump inhibitors for severe erosive oesophagitis.

CRD commentary
This review answered a clearly defined review question. A number of relevant databases were searched for relevant studies, but only published English language studies were included in the review, so there was a risk of both publication and language bias. The risk of reviewer error and bias appeared to be relatively low, given the involvement of more than one reviewer when selecting studies and assessing their methodological quality; however it was unclear how many reviewers extracted the study data.

Relevant criteria were used to assess the quality of the trials, but the results of the assessment were not reported. Therefore it was difficult to assess the reliability of the individual trials, although the authors stated that they only included trials of sufficient quality. Given the use of indirect methods to compare the included interventions, few trial and population details were reported. This made it difficult to assess the reliability of the effect sizes, as analysis methods rely on the assumption of homogeneity and consistency amongst the included trials. Levels of statistical heterogeneity were reported to be low and further analyses were carried out to investigate the effects of other potential modifying factors. However, the results of indirect comparisons are only suggestive of relative effectiveness and are not as reliable as evidence from good quality head-to-head RCTs.

Overall, the evidence presented supported the review conclusions, but the reliance on indirect evidence and the poor reporting of trial characteristics, make it difficult to assess the reliability of the findings.

Three of the reviewers disclosed that they were full-time employees of AstraZeneca UK Ltd (the review sponsors).

Implications of the review for practice and research
Practice: The authors stated that 40mg esomeprazole is the most effective standard-dose proton pump inhibitor for the healing of erosive oesophagitis and is likely to offer substantial benefits to patients for whom previous standard-dose proton pump inhibitor therapy has failed.
Research: The authors did not state any implications for research.

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