Are proton pump inhibitors the first choice for acute treatment of gastric ulcers: a meta analysis of randomized clinical trials

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Authors' objectives
To compare gastric ulcer healing rates for patients treated with a proton-pump inhibitor (PPI), an histamine 2-receptor antagonist or placebo.

Searching
MEDLINE, and the Cochrane Library were searched using the following keywords: 'proton pump inhibitors', 'PPI', 'rabeprazole', 'omeprazole' 'esomeprazole', 'lansoprazole' 'pantoprazole', 'ranitidine'; 'healing rates', 'gastric ulcer', 'stomach ulcer', 'gastric ulcer disease', 'peptic ulcer', 'peptic related disorders'; and 'clinical trials', 'randomized clinical trials' and 'multicenter studies'. In addition, medical journals were handsearched and the reference lists of other meta-analyses, monographs, pharmacoconomic studies and reviews were examined. The search included papers published in any language between January 1990 and July 2001.

Study selection
Study designs of evaluations included in the review
All double-blind, randomised clinical controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
Short-term treatment (less than 6 months) with a PPI (omeprazole, rabeprazole, pantoprazole, esomeprazole or lansoprazole), compared with an histamine 2-receptor antagonist (ranitidine) or placebo. A range of different regimens were reported depending upon the actual drug used. The recommended daily dose was 30 mg/day for lansoprazole, 20 mg/day for omeprazole, and 40 mg/day for pantoprazole. Further details were provided in the paper. No study on esomeprazole met the inclusion criteria for the review. PPIs combined with antibiotics or with treatment for Helicobacter pylori were excluded from the review.

Participants included in the review
Participants with an endoscopically-confirmed diagnosis of gastric ulcer were eligible for inclusion in the review; those with concomitant duodenal ulcers or gastric ulcers complicated with haemorrhage or perforation, were not. The mean age of the participants was 56 plus or minus 1.5 years. Approximately half of the participants smoked, although few studies analysed healing rates by smoking status.

Outcomes assessed in the review
Ulcer improvement and healing rates had to be assessed by endoscopy. Healing was defined by 95% of the included studies as the complete re-epithelialisation of the ulcer crater, or as the endoscopic disappearance of the ulcer crater with no visible mucosa breaks in the remaining studies (5%). Efficacy results were reported at different time points, ranging from 2 to 8 weeks. Clinical symptoms assessed by day and/or night pain were also assessed.

How were decisions on the relevance of primary studies made?
Two researchers independently reviewed the papers.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, but any differences in the data retrieved were
resolved through consensus between the two researchers.

Data were extracted under the following categories: study design, population characteristics, diagnosis, severity, PPI and comparator treatment regimens, healing rates and clinical symptoms, alcohol consumption, smoking and caffeine use. The results were retrieved for both intention to treat and per protocol analysis. If the study authors reported per protocol results only and mentioned the initial number of participants in the study, the healing rates for the intention to treat analysis were estimated.

Methods of synthesis
How were the studies combined?
The healing rate ratio (RR) was calculated for each trial by dividing the healing rate of the PPI by the rate with the comparator at the specified time point. Chi-squares and confidence intervals (CIs) were calculated using the exact method described by Miettinen (see Other Publications of Related Interest). As there was no statistically significant evidence of heterogeneity, the healing rates for each treatment were pooled across trials by time point. The overall healing rates of lansoprazole, omeprazole and pantoprazole at 4 and 8 weeks were estimated by pooling the rates for the recommended daily dosage for each drug. Rabeprazole was pooled at 3 and 6 weeks using a dose of 20 mg/day. The overall RR were assessed using the Mantel-Haenszel chi-squared test and 95% CIs were calculated using the exact method (see Other Publications of Related Interest). It was not possible to pool the clinical symptoms because different symptoms were reported in each study, at different time points, and also the method used to collect the data varied.

The RR point estimates were plotted against year of publication and sample size to assess the possibility of publication bias, but no trend was identified. Data from abstracts for which a full report could not be obtained were excluded from a secondary analysis.

How were differences between studies investigated?
The Wald chi-squared was used to test for statistical homogeneity; a p-value of less than 0.05 was considered to be significant for all results. There were no adjustments for multiple comparisons. To identify any studies that had a disproportionate influence on the summary treatment effect, individual studies were deleted one at a time.

Results of the review
Sixteen randomised trials (n=3,762) were included in the review. Of these, 4 (n=973) compared a PPI with a placebo, 9 (n=2,193) compared a PPI with ranitidine, although none comparing rabeprazole with ranitidine met the inclusion criteria, and 3 (n=596) compared a newer PPI (lansoprazole, pantoprazole or rabeprazole) with omeprazole. Six trials in total studied omeprazole, 4 studied lansoprazole, 3 rabeprazole and 3 pantoprazole. No study on esomeprazole met the inclusion criteria.

The overall healing rates varied between the studies, but were consistently lower for participants receiving placebo treatment, for whom the ulcer did not heal during the course of the trial; the maximum recorded as healed was 39% of the participants in any of the trials. Higher healing rates were observed after treatment with ranitidine, but ulcers remained for 52% of the participants. For participants receiving PPIs, 67% had healed ulcers by the end of the trial. Compared with placebo, lansoprazole and omeprazole improved the pooled healing RR at each time point. In relation to ranitidine, the pooled RR of PPIs (lansoprazole, omeprazole and pantoprazole) was also increased at both 4 (1.33, 95% CI: 1.24, 1.42) and 8 weeks. Individual trials showed more improvement or resolution of pain, day pain and night pain with the new PPIs (rabeprazole, pantoprazole and lansoprazole) in comparison with omeprazole. For example, 82% of the participants with pain in one study improved with rabeprazole, versus 65% with omeprazole, at 6 weeks. No evidence of publication bias was found.

Authors' conclusions
Treatment with PPIs resulted in higher healing rates than ranitidine or placebo. The first-line drug therapy for patients diagnosed with gastric ulcer should, therefore, be one of the newer PPIs, in preference to an histamine 2-receptor antagonist.
CRD commentary
The review question and the study selection criteria were clearly stated. The literature search included only the MEDLINE and the Cochrane Library databases, although no language restrictions were applied and additional searches were undertaken; these included handsearches of medical journals and checks of reference lists. The authors provide relatively few details on the methodology of the literature review, and no information on any methods for assessing the validity of the primary studies.

The range of statistical tests described seemed to be appropriate. Some of the results of these tests were presented graphically and in tabular format, but there was little narrative presentation of these findings, in terms of the actual data from which the RRs were calculated, the RRs or the CIs. It was unclear from the authors’ sensitivity analysis in which abstracts were excluded, whether the data included in this review were, therefore, taken from conference abstracts only. It was also unclear as to which secondary analyses the single identified abstract was excluded from.

The authors’ conclusions seem appropriate in the light of the data they present.

Implications of the review for practice and research
Practice: The authors state that the first-line drug therapy for patients diagnosed with gastric ulcer should be one of the newer PPIs, in preference to an histamine 2-receptor antagonist.

Research: The authors state that further research should aim to determine the appropriate PPI maintenance doses, and to understand the factors influencing healing and relapse rates.

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