Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication

CRD summary
This review concluded that high-dose proton pump inhibitors appeared more effective than standard-dose as part of a seven-day triple therapy regimen for eradication of Helicobacter pylori infection. These conclusions may not be reliable due a risk of missing data, apparent methodological weaknesses in the included studies and the borderline significance of many of the findings.

Authors' objectives
To compare the effectiveness of high-dose proton pump inhibitors (PPI) with standard in triple therapy for the eradication of Helicobacter pylori.

Searching
PubMed, Web of Knowledge, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL were searched from January 1990 to September 2007. Search terms were reported in an appendix. Digestive Disease Weekly (1990 to 2007), United European Gastroenterology Week (1992 to 2007) and European Helicobacter Study Group Congress (1995 to 2007) abstracts were searched. Study authors were contacted for additional studies. Reference lists of relevant reviews were screened.

Study selection
Randomised controlled trials (RCTs) that compared a standard dose of a PPI twice a day with a high-dose twice a day regimen in otherwise similar triple therapies for eradication of Helicobacter pylori were eligible for inclusion in the review. Triple therapy had to combine a PPI, clarithromycin and either metronidazole or amoxicillin for at least seven days. Examples of standard- and high-dose regimens were reported in the review. Before treatment, Helicobacter pylori infection had to be determined by biopsy and/or urea breath test (UBT). The primary outcome was intention-to-treat eradication of Helicobacter pylori evaluated by biopsy and/or UBT at least four weeks after the end of treatment. Secondary outcomes were per protocol eradication and adverse events.

PPI regimens compared in the included studies were: 20mg esomeprazole versus 40mg esomeprazole; 20mg omeprazole versus 40 mg esomeprazole; 40mg pantoprazole versus 40 mg esomeprazole; 20mg omeprazole versus 40mg omeprazole; and 40mg esomeprazole versus 20mg omeprazole, 40mg pantoprazole and 20mg rabeprazole. Included participants were treated for seven days. All except one of the included triple therapies included amoxicillin plus clarithromycin twice a day. All included patients had either an ulcer or non-ulcer dyspepsia. Adverse events were assessed mainly by interview.

Studies were screened for inclusion by two reviewers.

Assessment of study quality
Two reviewers independently assessed the validity of each study using the Jadad scale of randomisation, blinding and dropouts/withdrawals plus an additional criterion of adequacy of allocation concealment. Studies were awarded yes or no for each criterion. Discrepancies were resolved through consensus.

Data extraction
Data were extracted independently by two reviewers and used to calculate relative risks (RRs) with 95% confidence intervals (CIs); discrepancies were resolved through discussion.

Methods of synthesis
Studies were grouped by outcome and pooled relative risks with 95% CIs calculated using a fixed-effect model (or a random-effects model where there was significant heterogeneity). Number-needed-to-treat (NNT) was calculated.
Statistical heterogeneity was assessed using the Q test and \( I^2 \) statistic; scores of 50% or more were considered heterogeneous. Further analyses excluded studies considered to be outliers and studies that compared different and same generation PPI drugs.

**Results of the review**

Six RCTs (n=1,703) were included in the review. Sample sizes ranged from 104 to 576. Randomisation methods were adequate in three RCTs. Allocation concealment was adequate in only one RCT. None of the studies were double-blind. Patient withdrawals were described in all studies.

A significant difference in mean intention-to-treat eradication rate (RR 1.09, 95% CI 1.01 to 1.17; six RCTs) was reported in favour of high-dose PPI (cure rate 82%) in comparison with standard-dose PPI (cure rate 74%). This analysis was associated with evidence of significant heterogeneity (\( I^2=55\% \)) and publication bias.

Sensitivity analyses showed that both publication bias and heterogeneity (\( I^2=14.4\% \)) were reduced by removal of one study (RR 1.06, 95% CI 1.00 to 1.12, \( I^2=\)not reported; five RCTs). Similar effects were observed for per protocol eradication rates with no evidence of publication bias.

Subgroup analyses showed significant differences in eradication rates in favour of first generation standard-dose PPIs (20mg omeprazole) versus second generation high-dose PPIs (40mg pantoprazole) (RR 1.12, 95% CI 1.04, 1.20; four RCTs). There was no significant difference between standard- and high-dose PPIs of the same generation (three RCTs, \( I^2=0\% \)). A planned analysis to compare effect sizes in ulcer and non-ulcer patients was not possible due to a lack of studies.

No severe adverse events were reported. There was no statistically significant difference in the mild to moderate adverse event profiles between high-dose and standard-dose treatment groups.

**Authors' conclusions**

High-dose PPI appeared more effective than standard dose for eradication of *Helicobacter pylori* infection in seven-day triple therapy.

**CRD commentary**

This review answered a clearly defined review question. A number of relevant literature sources were searched. It was unclear whether there were language restrictions and so the risk of language bias was unknown. The authors own comments and in some cases analyses suggested a risk of publication bias; it was unclear how reliable publication bias tests were given the small number of included studies. The risk of reviewer error and bias was low as the authors ensured that each stage of the review process involved two independent reviewers. The validity of the studies was assessed using relevant criteria. Many studies had methodological weaknesses that put them at risk of bias. Methods used to combine the studies appeared valid, although a number of the analyses showed evidence of significant statistical heterogeneity and some effects were of borderline statistical significance. Attempts to investigate potential sources of heterogeneity and assess effect sizes in different groups of studies were hampered by the small number of included studies.

Overall, the authors’ conclusions may not be reliable due the risk of missing data, the apparent methodological weaknesses of the studies and the borderline significance of many of the findings.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further evidence was required to confirm that the safety profile of high-dose PPI was similar to standard-dose PPI and confirm the higher efficacy of high-dose PPIs compared with standard. Further studies were required to determine whether high-dose PPIs improved the effectiveness of longer triple therapies and other alternative *Helicobacter pylori* treatment schedules in comparison with standard triple therapy.
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