Single vs. double dose of a proton pump inhibitor in triple therapy for Helicobacter pylori eradication: a meta-analysis


Authors' objectives
To compare the efficacy of a single versus double dose of a proton-pump inhibitor (PPI) in triple therapy for Helicobacter pylori (H. pylori) infection.

Searching
MEDLINE was searched in June 2001 for studies reported in English, French or Spanish. The search terms used were reported. Abstracts submitted to the American Gastroenterological Association congresses between 1995 and 2001, and abstracts obtained from the European Helicobacter pylori Study Group congresses between 1996 and 2001 dealing with H. pylori treatment, were handsearched. The reference lists of retrieved original studies and the authors' personal databases were also assessed for further studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The included studies had to have reported sufficient data to enable an evaluation of the patients’ baseline characteristics and inclusion and exclusion criteria to be eligible for inclusion.

Specific interventions included in the review
Studies of eradication therapy (triple therapy) using double versus single doses of PPIs were eligible for inclusion. The interventions being compared had to differ only in terms of the dose of PPI. In addition, the antibiotics used in the eradication therapy had to have been administered twice daily (b.d.) and consist of a combination of two of the following: clarithromycin, metronidazole or tinidazole and amoxicillin. Studies that compared different doses of antibiotics were excluded. The PPIs used by the included studies were lansoprazole (30 or 60 mg), pantoprazole (40 or 80 mg), omeprazole (20 or 40 mg) and rabeprazole (20 or 40 mg). The different antibiotic combinations used were: clarithromycin (250 mg b.d.) and metronidazole (400 mg b.d.); clarithromycin (250 mg b.d.) and metronidazole (500 mg b.d.); amoxicillin (1 g b.d.) and clarithromycin (500 mg b.d.); amoxicillin (1 g b.d.) and clarithromycin (250 mg b.d.); amoxicillin (500 mg three times a day, t.d.s) and clarithromycin (500 mg t.d.s.); amoxicillin (500 mg t.d.s.) and clarithromycin (200 mg b.d.). The duration of treatment ranged from 7 to 14 days.

Participants included in the review
Studies of participants with H. pylori infection, which had been confirmed using rapid urease test, histology or urea breath test, were eligible for inclusion.

Outcomes assessed in the review
Studies that reported the H. pylori eradication rate, as determined by histology or urea breath test, at least 4 weeks after the end of treatment were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Three reviewers independently assessed the abstracts of the articles identified by the search for inclusion.

Assessment of study quality
The studies were scored for quality using the criteria developed by Chalmers et al., which evaluate the design, implementation and analysis of RCTs. Studies presented as abstracts (n=2) were not scored. The remaining studies were given a quality score that ranged from zero to one, with maximum-quality studies rating one. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.
Data extraction
Three reviewers independently extracted the data and resolved any disagreements by consensus. The eradication rates of H. pylori were calculated by intention-to-treat (ITT) and per protocol analyses.

Methods of synthesis
How were the studies combined?
The studies were combined using Peto's (fixed-effect) method to calculate the pooled Peto odds ratios (ORs) and 95% confidence interval (CIs) for the H. pylori eradication rates.

How were differences between studies investigated?
Heterogeneity was assessed using the Q test, with a cut-off p-value of 0.10.

Data on the eradication rates were analysed separately for the PPIs lansoprazole and pantoprazole, but not for omeprazole and rabeprazole due to insufficient data. A separate subgroup analysis for different combinations of antibiotics (amoxicillin plus clarithromycin, and metronidazole plus clarithromycin at low dose) were also performed. Studies that tested 7-day schedules of triple treatment were also analysed separately.

Results of the review
Eleven studies met the inclusion criteria. Two studies were subdivided into two parts because they analysed four branches of treatment with different durations of eradication therapy. The total number of participants included was 2,391. Seven studies examined lansoprazole (n=1,414), 3 pantoprazole (n=555), 2 omeprazole (n=251) and 1 rabeprazole (n=240).

The quality of the included articles ranged from 0.24 (‘acceptable’) to 0.74 (‘well designed’).

The pooled analysis showed that double doses achieved higher H. pylori eradication rates than single doses in both the ITT (83.9% versus 77.7%; OR 1.51, 95% CI: 1.23, 1.85, P<0.01) and per protocol (88.8% versus 80.5%; OR 1.96, 95% CI: 1.51, 2.47, P<0.01) analyses. Heterogeneity was of borderline significance (P<0.10), but diminished with the exclusion of one small study (P=0.23); the main results remained unchanged.

A double dose of PPI was also found to be superior to a single dose in the subgroup analysis of lansoprazole (ITT analysis OR 1.52, 95% CI: 1.16, 2.00, P<0.01); pantoprazole (ITT analysis OR 1.76, 95% CI: 1.19, 2.58, P<0.01); 7-day therapy (ITT analysis OR 1.37, 95% CI: 1.09, 1.72, P not stated); and the combination of clarithromycin (500 mg) and amoxicillin (1 g) antibiotics (5 studies; ITT analysis OR 1.73, 95% CI: 1.38, 2.18, P not stated). There was no significant difference (2 studies) between single and double doses of PPIs for the combination of clarithromycin (250 mg) and metronidazole (500 mg) antibiotics.

Authors' conclusions
A double dose of PPI was superior to a single dose when used in combination with clarithromycin and amoxicillin as triple therapy for H. pylori eradication. However, in triple therapy comprising a PPI, clarithromycin and metronidazole, the need for a double dose of PPI was unclear.

CRD commentary
The review included a clear objective as well as predefined inclusion and exclusion criteria. Only one electronic database was searched and no attempt was made to look for unpublished studies. This means that some important information may have been missed and publication bias cannot be ruled out. The study selection and data extraction processes were carried out in triplicate, which helps to reduce errors and reviewer bias. The quality of the included studies was assessed, but the process used was unclear. Relevant details of the primary studies were tabulated along with brief comments on the quality of each study (plus the overall score). The studies were pooled using a fixed-effect model, despite the heterogeneity between the studies, which may not have been appropriate. However, this is unlikely to affect the overall conclusions, which appear to follow from the results presented.
Implications of the review for practice and research
The authors stated that a formal meta-analysis comparing different PPIs is warranted. They stated that it seems reasonable to await the results of studies of triple therapy using clarithromycin and metronidazole as second-line therapy before recommending otherwise promising schedules (due to concerns about drug resistance in H. pylori status).

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