Proton pump inhibitor, clarithromycin and either amoxycillin or nitroimidazole: a meta-analysis of eradication of Helicobacter pylori


Authors' objectives
To compare two twice-daily (b.d.), one-week triple therapies for Helicobacter pylori eradication by conducting a meta-analysis. The two therapies were a combination of a proton-pump inhibitor (PPI), clarithromycin (C) and amoxycillin (A), and a combination of PPI, C and a nitroimidazole (N).

Searching
The authors searched PubMed up to September 1999 (the start date was unclear). Abstracts from the International Workshop on Gastroduodenal Pathology and Helicobacter pylori, and American Digestive Disease Week were handsearched from 1995 to 1999 using the search terms provided. Additional studies were identified by examining the references of reviews and retrieved studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
First-line triple therapy with a PPI (including omeprazole, lansoprazole and pantoprazole), C (250 or 500 mg) and either A (1 g) or N (including metronidazole and tinidazole, either 250 or 400 to 500 mg). Therapies were delivered twice-daily for 7 days. Only standard doses of PPI (20 mg b.d. omeprazole, 30 mg b.d. lansoprazole, or 40 mg b.d. pantoprazole) were included, although extended use was allowed when employed for ulcer healing.

Participants included in the review
Participants with peptic ulcer disease and/or non-ulcer disease, and healthy individuals were included in the review. No other participant characteristics were reported.

Outcomes assessed in the review
The eradication rates of H. pylori were determined by histology and/or carbon-13 urea breath test, at least 4 weeks after therapy.

How were decisions on the relevance of primary studies made?
The bibliographic searches were performed independently by two reviewers, although the authors do not state how other papers were selected for review or how many of the reviewers performed the remaining selections.

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

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following data were recorded in tables: type and dose of PPI; C, A and N doses; type of analysis and percentage of patients treated; and disease.

Methods of synthesis
How were the studies combined?
A meta-analysis was performed which combined the Peto odds ratio (OR) using a fixed-effect model. Separate analyses were performed for studies on an intention to treat (ITT) and per protocol (PP) basis. The authors reported using RevMan software for this analysis, which weighted the studies according to event rate and sample size. No formal methods were employed for assessing publication bias.

How were differences between studies investigated?
The chi-squared statistic was used to test for homogeneity using a p-value of 0.20. Subgroup analyses were performed for the comparisons between PPI-C-A and PPI-C-N at low doses of C (250 mg b.d.), and for the comparisons between PPI-C-A and PPI-C-N at high and low doses of C (500 and 250 mg b.d.), respectively. Subanalyses were only performed on studies on an ITT basis.

Results of the review
Twenty-two RCTs involving 5,663 participants were included in the review: 2,877 received the PPI-C-N combination and 2,786 received the PPI-C-A combination.

The comparison revealed no difference of eradication efficacy between the PPI-C-A and PPI-C-N regimens for studies employing ITT (OR 1.00, 95% CI: 0.83, 1.22) and PP (OR 0.98, 95% CI: 0.80, 1.20) analyses. The chi-squared test for homogeneity showed significant heterogeneity for both ITT (chi-squared 24, P<0.2) and PP (chi-squared 39, P<0.2) analyses.

The subgroup analyses of studies using ITT for the comparison between PPI-C-N and PPI-C-A at low C doses suggested that PPI-C-N was more effective in eradicating H. pylori than PPI-C-A (OR 0.68, 95% CI: 0.48, 0.98). The chi-squared test for homogeneity showed no significant heterogeneity between these studies (chi-squared 7.95, P>0.2).

The subgroup analyses of the studies using ITT analyses for the comparison between PPI-C-A at high C doses with PPI-C-N at low C doses showed no difference in their efficacy in eradicating H. pylori (OR 1.18, 95% CI: 0.93, 1.50). The chi-square test for homogeneity showed significant heterogeneity between these studies (chi-squared 16.27, P<0.2).

Authors’ conclusions
The authors conclude that one-week combination regimens of PPI plus C and either A or N are similarly effective in eradicating H. pylori. However at low C doses, N achieves better results.

CRD commentary
The authors stated the review question clearly. The inclusion criteria were stated but lacked detail concerning outcomes and participant characteristics. This make it difficult to appreciate for whom these interventions are useful. The authors described the methods used to assess eradication of H. pylori, but did not describe the parameters for inclusion. In addition, no details were provided of the number of reviewers involved in this decision-making, and thus selection bias may have been introduced. Finally, the duration of the interventions included was unclear since extended use of a PPI was allowed for ulcer healing. The literature search and description of search terms appeared adequate and some attempts were made to identify unpublished material. The search dates were unclear, and would make replication of the search difficult. No attempt was made to assess publication bias. No validity assessment was reported by the authors, although the inclusion criteria were restricted to RCTs. Given the apparent heterogeneity of the studies included in the review a quality assessment would have been informative. Study details were reported in tables and in the text, although patient characteristics were lacking and some studies appeared to have employed both ITT and PP analyses. The authors chose to pool data despite identifying significant heterogeneity, and these potential sources of heterogeneity were not addressed. Subgroup analyses were performed but only on RCTs that used ITT analyses. The authors provided information concerning the limitations of these analyses, although it is unclear why they chose to compare PPI-C-A and PPI-C-N at disparate C doses; any difference between eradication rates could be due to either differences in dosage or medication. There may be a potential conflict of interest as the authors of the review were also authors of one of the primary studies. The authors’ conclusions appear appropriate, although the data could have been investigated more thoroughly by including a quality assessment and investigating sources of heterogeneity.
Implications of the review for practice and research
The authors did not state any implications for further research and practice.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.