The importance of clarithromycin dose in the management of Helicobacter pylori infection: a meta-analysis of triple therapies with a proton pump inhibitor, clarithromycin and amoxycillin or metronidazole

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Authors' objectives
To examine the effect of seven-day triple therapies with a proton pump inhibitor, clarithromycin and amoxycillin or metronidazole for Helicobacter pylori (H pylori) eradication and evaluate which dose of clarithromycin is more effective for eradicating H pylori infection.

Searching
Published articles and abstracts in the English language were sought in the MEDLINE database (1986 to March 1998) using textwords or MeSH terms "Helicobacter pylori, clarithromycin, eradication". A search was also conducted of PubMed (Internet) with search terms "pylori, clarithromycin, eradication". A manual review of all abstracts from the following major international meetings held in the past two years (1996 and 1997) was also performed: American Digestive Disease Week; American College of Gastroenterology; British Society of Gastroenterology; European Helicobacter pylori Study Group IX and X International workshop; and 5th and 6th United European Gastroenterology Week. All papers retrieved from major relevant journals were scanned for additional articles.

Study selection
Study designs of evaluations included in the review
Clinical trials with a combination of a specified triple therapy given for seven days and with at least ten patients per treatment arm were included. The following were excluded: duplicated publications; studies without raw data or other treatment durations; and studies without a clearly defined follow-up duration for eradication confirmation.

Study designs included in the review were head to head comparative trials, randomised controlled trials (RCTs), cohort, and open study trials.

Specific interventions included in the review
Triple therapies which included the following drugs were studied: a proton pump inhibitor at recommended doses (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg); clarithromycin (250 mg b.d. or 500 mg b.d.); and amoxycillin (PAC combination) or metronidazole (PMC combination) given for seven days. Extended use of a proton pump inhibitor was allowed for ulcer healing. Studies with doses of clarithromycin other than 500 mg b.d. or 250 mg b.d. were excluded.

Participants included in the review
Patients with H pylori infection, including those with peptic ulcers and gastritis were included. Patients who had failed previous eradication treatment were excluded.

Outcomes assessed in the review
The primary outcome was H pylori eradication confirmed at least 4 weeks after treatment by at least one reliable method (culture or histology or urea breath test). Adverse events and drop-out rates due to adverse events were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

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

**Data extraction**
The following data were extracted onto a computerized database: first author; country of study; study design; source of publication; patient population; treatment regime and drug doses; follow-up methods; number of patients with H pylori infection treated, evaluated and cured; and number of patient with adverse events or who dropped out due to adverse events. The authors do not state how many of the reviewers performed the data extraction.

**Methods of synthesis**
How were the studies combined?
Pooling was performed by combining all raw data from each individual study to determine pooled rates and 95% confidence intervals (CIs) of the following:

- H pylori eradication; adverse events; and drop outs due to adverse events.

How were differences between studies investigated?
The influence of the following factors on the results was examined: clarithromycin dose (250 mg b.d. or 500 mg b.d.); dosing frequency of proton pump inhibitor (q.d.s. and b.d.); and study design (all clinical trials, head to head comparative trials, RCT, or cohort or open study trials). Analysis was by per protocol analysis and by intention to treat analysis. Statistical heterogeneity was not assessed.

**Results of the review**
A total of 82 studies (31 papers and 51 abstracts) involving 110 treatment arms (6123 patients) were included.

Results from the intention-to-treat analysis are reported.

Proton pump inhibitor, clarithromycin and amoxycillin (PAC combination).

Proton pump inhibitor, clarithromycin and metronidazole (PMC combination) given for seven days.

PAC combination (proton pump inhibitor, clarithromycin and amoxycillin).

Overall pooled eradication rate was 84.6% (95% CI: 81.6%, 87.7%).

Dose of clarithromycin (39 treatment arms with 2455 patients for clarithromycin 500 mg and 16 treatment arms with 766 patients for clarithromycin 250 mg): Pooled eradication rates were significantly higher with clarithromycin 500 mg compared to clarithromycin 250 mg (86.6% versus 78.2%; P < 0.0001). Head to head comparative trials gave similar results (4 trials with 192 patients for clarithromycin 500 mg and 4 trials with 193 patients for clarithromycin 250 mg): eradication rates 89.6% for 500 mg dose versus 79.8% for 250 mg dose.

Dosing frequency of proton pump inhibitor (PPI) with clarithromycin 250 mg (11 treatment arms with 571 patients for PPI b.d. and 5 treatment arms with 195 patients for PPI): Pooled eradication rates were significantly higher with PPI twice daily compared to PPI once daily (81.1% versus 69.7%; P <= 0.001).

PMC combination (proton pump inhibitor, clarithromycin and metronidazole).

Overall pooled eradication rate was 87.2% (95% CI: 84.8%, 89.5%).

Dose of clarithromycin (15 treatment arms with 836 patients for clarithromycin 500 mg and 40 treatment arms with 2057 patients for clarithromycin 250 mg): No significant difference in eradication rates with clarithromycin dose (86.7% versus 88.3%). Head to head comparative trials also showed no significant difference (4 trials with 324 patients for clarithromycin 500 mg and 4 trials with 318 patients for clarithromycin 250 mg): eradication rates 88.9% for 500 mg dose versus 87.4% for 250 mg dose (P = 0.6503).
Dosing frequency of proton pump inhibitor (PPI) with clarithromycin 250 mg (13 treatment arms with 585 patients for PPI twice daily and 27 treatment arms with 1472 patients for PPI once daily): Pooled eradication rates were significantly higher with PPI twice daily compared to PPI once daily (88.7% versus 81.7%; \( P \leq 0.001 \)).

Study design.

There was no significant difference in eradication rates between RCTs and cohort or open trials with respect to clarithromycin dose and frequency of dosing for PMC or PAC combination therapy.

Adverse events.

Treatment related drop-outs (58 studies with 69 treatment arms and 4266 patients) and adverse events (49 studies with 55 treatment arms and 3469 patients):

PAC combination (proton pump inhibitor, clarithromycin and metronidazole): 33.7% reported adverse events and 1.2% dropped out. Significantly more patients on clarithromycin 500 mg compared clarithromycin 250 mg experienced adverse events (39.7% versus 30%; \( P < 0.0001 \)) though no significant difference in drop-outs (1.7% versus 1%; \( P = 0.3356 \)).

PAC combination (proton pump inhibitor, clarithromycin and amoxycillin): significantly lower rates of adverse reactions than in PMC group (21.4% versus 33.7%; \( P < 0.0001 \)). Drop-out rates were similar to those of the PMC group (1.8% versus 1.2%; \( P = 0.1264 \)). No significant differences were found in either adverse event rates according to clarithromycin dose.

Authors’ conclusions

Seven day triple therapies with a proton pump inhibitor, clarithromycin and amoxycillin or metronidazole are highly effective therapies for the eradication of H. pylori. Clarithromycin 500 mg b.d. should be used in these combinations to achieve the best treatment results, which can minimise the subsequent development of bacterial resistance to clarithromycin and metronidazole.

CRD commentary

The aims and inclusion criteria were stated. Attempts were made to locate published studies as well as abstracts reported at conferences. However no attempt was made to locate unpublished studies thus raising the possibility of publication bias. Analysis was reported on a per protocol and an intention to treat basis. Sensitivity analyses were conducted to determine the effect of various factors on the results. Some limitations of the review were discussed.

By limiting the literature search to studies published in the English language, some relevant studies may have been omitted. No details were given of methods used to assess studies for relevance and study validity was not assessed. The authors do not state what model (random-effects or fixed-effect) was used to combine studies. Heterogeneity was not formally assessed and so it is not clear whether it was appropriate to pool studies. Examination of results from the "head to head" comparative trials examining the effect of clarithromycin dose on eradication rates suggests heterogeneity across studies was present. By pooling individual results any within-trial comparability was lost. It was not stated how missing values in the individual studies were dealt with in the intention to treat analysis.

In view of the above limitations, the conclusion should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors state that clarithromycin 500 mg b.d. should be used in combination with a proton pump inhibitor and amoxycillin or metronidazole all given twice daily to achieve the best results and minimise the subsequent development of bacterial resistance to clarithromycin.

Research: The authors state that future studies should report eradication rates by both per-protocol and intention-to-treat analysis and to provide raw data on adverse events and drop-outs.
Bibliographic details

PubMedID
10383500

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Amoxicillin /administration & dosage; Clarithromycin /administration & dosage; Drug Therapy, Combination; Enzyme Inhibitors /administration & dosage; Helicobacter Infections /drug therapy; Helicobacter pylori; Humans; Metronidazole /administration & dosage; Proton Pump Inhibitors

AccessionNumber
11999001397

Date bibliographic record published
28/02/2001

Date abstract record published
28/02/2001

Record Status
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.