Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis

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CRD summary
This review concluded that a 10-day course of levofloxacin-based triple therapy is more effective and better tolerated than a 7-day course of bismuth-based quadruple salvage therapy for the treatment of persistent Helicobacter pylori infection. However, it is unclear how reliable the conclusions are, given the reliance on a small number of variable studies and the lack of a validity assessment.

Authors' objectives
To compare levofloxacin-based triple therapy and bismuth-based quadruple salvage therapy for the treatment of persistent Helicobacter pylori (H. pylori) infection. The authors also assessed the effects of duration and dosing schedules of levofloxacin-based triple therapy on eradication rates.

Searching
PubMed, EMBASE and the Cochrane Controlled Trials Register were searched up to April 2005 for English language publications; the search terms were provided. In addition, conference abstracts (dating from 2000 to 2005) and reference lists from retrieved articles were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Crossover trials appeared to have been excluded. The trials had to include intention-to-treat analysis. For the secondary analyses, prospective studies including randomised and non-randomised trials were eligible for inclusion.

Specific interventions included in the review
Studies that compared levofloxacin-based triple therapy (levofloxacin, amoxicillin and proton-pump inhibitor) with bismuth-based quadruple therapy (bismuth, tetracycline and metronidazole, plus either rabeprazole, pantoprazole, omeprazole or lansoprazole) were eligible for inclusion. Details of drug dosages were provided. The duration of treatment in both treatment groups was either 7 or 10 days.

Participants included in the review
Participants with persistent H. pylori infection and confirmed treatment failure to at least one prior course of standard triple therapy (as measured by urea breath testing or gastric mucosal biopsy) were eligible for inclusion.

Outcomes assessed in the review
The main outcome assessed was the eradication of H. pylori infection at least 4 weeks after treatment, as confirmed by urea breath testing or gastric mucosal biopsy. Other outcomes assessed were the incidence of adverse events and the incidence of therapy discontinuation due to adverse events. The secondary outcomes included eradication rates with 7 days of therapy versus 10 days of therapy, and eradication rates with levofloxacin 250 mg twice daily versus 500 mg once daily.

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

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

Data extraction
Two reviewers independently extracted the data and the level of agreement assessed. If not provided, the number of
patients in which H. pylori was successfully eradicated was calculated given the intention-to-treat and per protocol analyses. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
The pooled RR with 95% CIs was calculated using the DerSimonian and Laird fixed-effect model. The authors stated that they created scatter plots evaluating eradication rates against sample sizes to identify publication bias. Eradication rates for secondary outcomes were also pooled with 95% CIs. In addition, the authors used meta-regression and calculated an odds ratio to compare any between-group differences.

How were differences between studies investigated?
Statistical heterogeneity was assessed (p<0.10), but the test used was not described. A post hoc analysis was conducted which compared 10 days of levofloxacin-based triple therapy with 7 days of bismuth-based quadruple therapy.

Results of the review
Six RCTs (n=854) were included that evaluated primary outcomes. Eleven randomised and non-randomised trials evaluated treatment duration (n=547), and eight randomised and non-randomised trials evaluated dosage (n=447).

Levofloxacin-based triple therapy demonstrated significantly better H. pylori eradication rates in comparison with bismuth-based quadruple therapy (RR 1.18, 95% CI: 1.08, 1.29; 6 RCTs). However, significant heterogeneity was observed.

The post hoc analysis demonstrated that 10 days of levofloxacin-based triple therapy resulted in significantly better H. pylori eradication rates than 7 days of bismuth-based quadruple therapy (RR 1.41, 95% CI: 1.25, 1.59; 4 RCTs) (heterogeneity was not significant). Adverse events and discontinuation of therapy due to adverse events were reported to be less common with 10 days of levofloxacin-based triple therapy than 7 days of bismuth-based quadruple salvage therapy (4 RCTs): RRs 0.51 (95% CI: 0.34, 0.75) and 0.30 (95% CI: 0.10, 0.89), respectively (heterogeneity was not significant in both analyses).

Eradication rates were higher with 10-day therapy compared with 7-day therapy: 87% (95% CI: 82, 92) versus 68% (95% CI: 62, 74), respectively (11 trials). No difference in eradication rates were found when a twice daily dose of 250 mg levofloxacin was compared with a single daily dose of 500 mg.

Authors’ conclusions
A 10-day course of levofloxacin-based triple therapy is more effective and better tolerated than a 7-day course of bismuth-based quadruple therapy.

CRD commentary
This review addressed a well-defined question in terms of the interventions, participants, outcomes and study design. Several databases were searched and both published and unpublished studies were sought. The authors also attempted to assess publication bias. Only English language publications were included, thus potentially introducing language bias. Two reviewers extracted the data, thereby eliminating the chances for reviewer error and bias. The authors did not assess validity so it is unclear whether the data are reliable.

Details of the included studies were presented, but information on participant characteristics was lacking. The authors conducted a meta-analysis, but appropriately stated that the results should not have been pooled because of statistical heterogeneity. The authors have based their conclusions on post hoc subgroup analyses of the data. Overall, the findings of the review should be interpreted with caution since it is unclear how reliable the data are, given the lack of a validity assessment and the reliance on a small group of heterogeneous studies.

Implications of the review for practice and research
Practice: The authors stated that levofloxacin-based triple therapy provides an effective alternative to bismuth-based
quadruple therapy for the treatment of persistent H. pylori infection.

Research: The authors stated that an RCT comparing levofloxacin-based triple and bismuth-based quadruple therapy should be evaluated in countries not previously examined (i.e. the USA).

Funding
NIH Career Development Award.

Bibliographic details

PubMedID
16542284

DOI
10.1111/j.1572-0241.1998.455_t.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Amoxicillin /therapeutic use; Anti-Ulcer Agents /therapeutic use; Bismuth /therapeutic use; Drug Resistance, Bacterial; Drug Therapy, Combination; Gastritis /drug therapy; Helicobacter Infections /drug therapy; Humans; Levofloxacin; Metronidazole /therapeutic use; Ofloxacin /therapeutic use; Proton Pump Inhibitors; Randomized Controlled Trials as Topic; Tetracycline /therapeutic use

AccessionNumber
12006003367

Date bibliographic record published
12/04/2007

Date abstract record published
09/08/2008

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.