Meta-analysis: sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment

Jafri N S, Hornung C A, Howden C W

CRD summary
The review concluded that sequential therapy appeared superior to standard triple therapy for eradication of Helicobacter pylori infection among patients naive to treatment for the infection. This was a well conducted review and the authors’ conclusion appeared reasonable but it was based on a small number of studies, some of which were of low-quality, and there was evidence of publication bias.

Authors' objectives
To compare sequential therapy with standard triple therapy for Helicobacter pylori (H. pylori) infection.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases were searched to October 2007. Search terms were reported. In addition Internet searches using Google Scholar were conducted and references lists were scanned for additional studies. Review articles, presentations and abstracts of relevant conference proceedings were hand searched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) comparing 10-day sequential therapy for H. pylori infection with 7 or 10 day standard triple therapy were eligible for inclusion. Only studies where all participants were H. pylori treatment-naive and had not used a proton-pump inhibitor, ranitidine bismuth citrate, other histamine-2-receptor antagonist or antibiotics in the preceding month were eligible. Diagnosis of H. pylori infection had to be conducted using histological evaluation, biopsy urease test, faecal antigen test or urea breath test. Eradication had to be evaluated by the same methods a minimum of 4 weeks after treatment. Included studies had a defined length of treatment and reported an objective measurement of morbidity.

Most of the included trials compared sequential therapy with a triple-therapy regimen including a proton pump inhibitor. One trial compared sequential therapy with a triple-therapy regimen containing ranitidine bismuth citrate. The majority of the trials were conducted in single centres in Italy. The mean age of participants ranged from 9.9 years to 70 years (where reported) with 51% being male.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which evaluated randomisation, concealment of allocation, blinding and withdrawals. The maximum possible score was 5 points. RCTs scoring 3 or more points were rated as high quality.

Three reviewers independently assessed validity and resolved disagreements through discussion.

Data extraction
Data were extracted onto a standardised form independently by three reviewers. Disagreements were resolved through discussion. Data on rates of eradication and incidence of side effects were extracted. Study authors were contacted for missing data. The relative risk reduction was calculated together with corresponding 95% confidence interval (CI) to compare the benefits of sequential therapy in comparison with standard triple therapy. The absolute risk reduction was also calculated with corresponding CIs to evaluate the potential clinical value of sequential therapy compared to standard triple therapy.
Methods of synthesis

Results from individual studies were combined to provide an overall estimate of the relative treatment effect using a random-effects model where statistical heterogeneity was present. For homogeneous studies, a Mantel-Haenszel fixed-effects model was utilised. Heterogeneity was assessed using the $I^2$ statistic. Sensitivity analyses were performed to evaluate differences in effect by trial quality, patient age, diagnosis (peptic ulcer disease versus non-ulcer dyspepsia), smoking status, resistance to clarithromycin/imidazoles or both, duration of triple therapy and adherence. Publication bias was assessed by visual inspection of funnel plots and using Egger, Begg and Mazumdar’s tests.

Results of the review

Ten RCTs (n=2,747) were included in the review. One trial scored the maximum 5 points for methodological quality, four trials scored 3 points, three trials scored 2 points and two trials scored one point. Three RCTs failed to describe the randomisation process, six RCTs were open label, only one RCT was reported to be double-blind, and four RCTs failed to adequately describe withdrawals.

Pooled crude H. pylori eradication rates (10 RCTs, n=2,747) for sequential therapy were 93.4% (95% CI: 91.3, 95.5, n=1363) and for standard triple therapy were 76.9% (95% CI: 71, 82.8, n=1,384). This resulted in a relative risk reduction of 71% (95% CI: 64, 77) and an absolute risk reduction of 16% (95% CI: 14, 19) in favour of sequential therapy. There was no evidence of statistical heterogeneity ($I^2 = 0\%$).

Similar results were reported in sub group analyses with sequential therapy appearing superior to standard therapy when stratified by trial quality, ulcer healing, diagnosis (peptic ulcer disease, nonulcer disease), patient age, smoking status, resistance to clarithromycin, imidazoles or both, duration of triple therapy and method of diagnosis.

Inspection of the funnel plot showed evidence of significant publication bias in favour of sequential therapy. Neither the Begg or Egger test showed any significant evidence of publication bias.

Adverse events (7 RCTs): Both treatments reported similar adverse events. The most common adverse events were diarrhoea, abdominal pain and glossitis.

Authors' conclusions

Sequential therapy appeared superior to standard triple therapy for eradication of H. pylori infection among patients naïve to treatment for the infection.

CRD commentary

The review question was clear and supported by detailed inclusion criteria. Several relevant sources were searched and attempts were made to minimise language bias. Some attempts were made to locate unpublished studies, however formal assessment showed evidence of significant publication bias. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was not clear whether similar steps were taken in study selection. Validity was assessed using an established checklist. The methods used to combine studies appeared appropriate and no evidence of statistical heterogeneity was found. The authors appropriately discussed individual aspects of study quality and report some limitations of the review including only one study being double-blind, the majority of participants being from one country (Italy), the fact that one study was performed in children only, some RCTs had small samples sizes and a number were of low methodological quality. This was a well conducted review and the authors’ conclusion appeared reasonable but it was based on a small number of studies, some of which were of low-quality, and there was evidence of publication bias.

Implications of the review for practice and research

Practice: the authors did not state any implications for practice.

Research: the authors stated that further RCTs are required to confirm the superiority of sequential therapy in comparison to existing treatment regimen before becoming standard treatment for treatment-naïve patients.

Funding
One author received funding from the manufacturers Meretek, Tap, Takeda, Santarus, Novartis and AstraZeneca; no external funding was received for this review.

**Bibliographic details**

**PubMedID**
18490667

**Original Paper URL**

**Additional Data URL**
http://gut.bmj.com/content/56/10/1353

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Bacterial Agents /administration & dosage; Drug Administration Schedule; Drug Therapy, Combination; Helicobacter Infections /drug therapy; Helicobacter pylori; Humans; Proton Pump Inhibitors; Sensitivity and Specificity; Treatment Outcome

**AccessionNumber**
12009100108

**Date abstract record published**
31/03/2009

**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.