Nitrofuran-based regimens for the eradication of Helicobacter pylori infection

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CRD summary
This review assessed furazolidone-based and nitrofurantoin-based regimens for the eradication of Helicobacter pylori infection and concluded that furazolidone-based primary triple therapies were less efficient than standard therapies. Furazolidone-based primary quadruple therapies were more efficient than furazolidone-based primary triple therapies. Given uncertainty over parts of the review process and study quality, the findings should be interpreted with caution.

Authors' objectives
To assess furazolidone-based (F) and nitrofurantoin-based (NF) regimens for the eradication of Helicobacter pylori (H. pylori) infection.

Searching
MEDLINE, EMBASE and Cochrane Controlled Trials Register were searched without language restrictions to August 2006; search terms were reported. A manual search of congress abstracts from five relevant bodies was undertaken from 1995 to 2005. Reference lists of retrieved articles were searched for additional studies.

Study selection
All studies using furazolidone/nitrofurantoin for the eradication of H. pylori were eligible for inclusion in the review. Only well-reported randomised controlled trials (RCTs) that included at least two treatment arms given as primary, secondary or third-line (rescue) regimens were included in the meta-analysis. Included studies were classified as assessing: primary treatment comprising triple combinations (proton pump inhibitors (PPI) plus furazolidone plus one other antimicrobial; H₂-histamine receptor blocker plus furazolidone plus one other antimicrobial; ranitidine bismuth citrate plus furazolidone plus one other antimicrobial; bismuth compound plus furazolidone plus one other antimicrobial); quadruple combinations containing furazolidone; other regimens (monotherapy, double combinations and one-day therapies); second-line regimens; third-line (rescue) regimens; and nitrofurantoin-based regimens. Patient characteristics were not reported, but most of the included studies came from Asia and South America. The primary outcome was the eradication of H. pylori infection. Side effects were also reported.

Two reviewers selected studies for inclusion in the review. Disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed using the Jadad scale for full papers and a scale developed by Timmer et al (2003) for abstracts; results were not reported. RCTs included in the meta-analysis comprised at least two treatment arms (including primary, secondary or rescue regimens) and specified numbers of patients treated, drug dose and schedule, randomisation method, blinding, side-effects, withdrawals and dropouts. The authors did not state how many reviewers performed the validity assessment.

Data extraction
H. pylori eradication rates were extracted on an intention-to-treat basis to calculate Peto odds ratios, relative risks and 95% confidence intervals (CIs). The percentage of side effects was also extracted.

The authors extracted data into a database and manually checked for errors, but did not state how many reviewers performed the data extraction.

Methods of synthesis
The pooled eradication rate was calculated for all treatment arms of similar regimens and expressed as weighted mean. The combined odds ratio and relative risk was calculated and the percentage of side effects was reported as a weighted mean for assessing the differences between the groups. Meta-analysis was based upon RCTs published as full papers.
Statistical heterogeneity was assessed by the $X^2$ test ($p \leq 0.05$). The influence of treatment duration and drug doses on the eradication rate were assessed through linear regression.

**Results of the review**

Thirty-seven journal articles and 14 abstracts were included, comprising 4,946 patients and 96 study arms.

There were some discrepancies between figures reported in the text and tables (latter used here). For furazolidone-based regimens compared with standard triple regimens the odds ratio was 2.34 (95% CI: 0.76 to 3.92) and relative risk was 1.61 (95% CI: 1.31 to 2.00); standard triple regimens were the superior regimen.

The pooled eradication rate of furazolidone-containing triple regimens was 76.6% (95% CI: 67.6 to 84.2). The pooled eradication rate of furazolidone and H$_2$-receptor containing triple regimens was 79.9% (95% CI: 67.8 to 89.9). The pooled eradication rate of furazolidone and bismuth-containing triple regimens was 84.5% (95% CI: 72.6 to 93.2); ranitidine bismuth plus furazolidone-based triple regimens compared with triple therapies were equally efficient. The pooled eradication rate of furazolidone-containing quadruple regimens was 83.4% (95% CI: 67.8 to 89.9).

Third-line (rescue) therapies containing furazolidone yielded a pooled eradication rate of 65.5% (95% CI: 56.3 to 75.5), which was significantly lower than the primary treatment (combined pooled eradication rate 80.3%, 95% CI: 69.6 to 88.7) and second-line regimens (pooled eradication rate 76.1%, 95% CI: 66.4 to 85.3).

Duration of treatment (three to five days versus seven days or 10 to 14 days) significantly influenced pooled eradication rate. Longer treatment durations had a higher pooled eradication rate. Dose of furazolidone had no significant influence on pooled eradication rate.

Combined odds ratio for all side effects of therapies containing furazolidone versus standard triple or quadruple therapies was 0.74 (95% CI: 0.32 to 1.98) and the combined relative risk was 0.84 (95% CI: 0.64 to 1.02); these indicated no difference in side-effects between treatments.

**Authors’ conclusions**

Furazolidone-based primary triple therapies were found to be slightly less efficient than standard therapies. Furazolidone-based primary quadruple therapies were more efficient than furazolidone-based primary triple therapies. The duration of treatment, but not furazolidone dose, influenced treatment outcome. Furazolidone was also efficient as a component of second-line or third-line therapies. Furazolidone-based therapies were as safe as standard therapies.

**CRD commentary**

The review question was clear, but inclusion criteria were not reported for participants. The adequate literature search was done without language restrictions, thus restricting the potential for language bias. It was unclear whether unpublished studies were sought, so some studies may have been missed. The use of trials published as full papers may, as acknowledged by the authors, have led to publication bias. More than one reviewer was involved in study selection, which reduced the potential for error and bias. An assessment of the quality of the included studies was undertaken, but the results were not reported; it was unclear how many reviewers were involved in the process and whether appropriate steps were taken to reduce bias. The assessment of study quality was used to inform the the selection of studies in the meta-analysis. It was not clearly reported how many authors were involved in data extraction, although checks for accuracy were undertaken. The methods used for the meta-analysis were poorly reported, therefore, it was unclear whether they were appropriate. Heterogeneity was assessed and subgroup analyses were undertaken relating to dose and duration of treatment. Given the uncertainty regarding the quality of the included studies and parts of the review process and analytical approach, the results should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that the use of furazolidone may be more reasonable as a primary quadruple therapy in low-income populations and was efficient as a component of second-line and third-line therapies in Asia, South America and Europe. Furazolidone-based therapies were as safe as the standard regimens.

**Research:** The authors did not state any implications for further research.
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