The influence of in vitro, nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-Helicobacter pylori regimens: a meta-analysis

Authors' objectives
To determine the influence of nitroimidazole resistance (NIR) on the efficacy of treatment for Helicobacter pylori (H. pylori) infections.

Searching
Searches were conducted of the following: MEDLINE database; all abstracts submitted to the Digestive Disease Week, United European Gastroenterology Week, meetings of the British Society of Gastroenterology; and major H. Pylori meetings of 1993 to 1997. A manual search was conducted of all the 1993 to 1997 issues of the main gastroenterological journals and references of all articles found were reviewed.

Study selection
Study designs of evaluations included in the review
Clinical trials and reviews on the treatment of H. pylori infection were included if they provided adequate data about the medication, dose frequency, total daily dose, duration of treatment, and eradication results in relation to nitroimidazole susceptibility.

Specific interventions included in the review
The following nitroimidazole containing treatment regimes were included: bismuth based triple therapy consisting of a bismuth compound, a nitroimidazole (metronidazole, ornidazole or tinidazole) and either tetracycline or amoxycillin; proton pump inhibitor (PPI) based triple therapy consisting of a PPI, a nitroimidazole (metronidazole or tinidazole), and either amoxycillin or clarithromycin; quadruple therapy consisting of a PPI, bismuth compound, tetracycline or amoxycillin and either metronidazole or tinidazole; and a one week ranitidine bismuth citrate based triple therapy. Duration of bismuth-based therapy ranged from 4 to 28 days; PPI-based triple therapy including studies ranging from 7 to 14 days, and quadruple therapy ranged from 1 to 12 days.

Participants included in the review
Patients being treated for H. Pylori infection were studied.

Outcomes assessed in the review
Eradication of H. pylori was assessed in relation to nitroimidazole susceptibility. Methods of ascertainment of eradication included either two or more biopsy-based tests of carbon thirteen or carbon fourteen urea breath test, four or more weeks after the end of treatment. Nitroimidazole susceptibility was assessed using disk diffusion, the E-test or agar dilution.

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 authors performed the selection.

Assessment of study quality
The authors do 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 authors performed the data extraction.
Methods of synthesis

How were the studies combined?
The pooled estimate of the odds ratio (OR) for treatment failure and for per protocol eradication results and 95% confidence intervals was calculated for each medication group using the logit method with weighting according to the inverse variance of the study.

How were differences between studies investigated?
Individual studies were grouped within medication groups according to duration of treatment. Funnel plots were constructed to assess bias with plot asymmetry being analysed using a linear regression approach.

Results of the review

Twenty studies (27 treatment arms with 1691 patients) assessed bismuth based triple therapy.

Thirty-eight studies (48 treatment arms with 2454 patients) assessed PPI based triple therapy.

Fifteen studies (16 treatment arms with 678 patients) assessed quadruple therapy.

One study (38 patients) assessed ranitidine bismuth citrate based triple therapy.

Bismuth based triple therapy: NIR was significantly associated with treatment failure. OR = 5.9 (95% CI: 4.1, 8.3). Eradication rates in susceptible strains = 89% (95% CI: 80%, 97%) compared to rates in resistant strains = 64% (95% CI: 52%, 77%) with P < 0.01. Funnel plot was significantly skewed suggesting smaller studies were overestimating the effect of NIR compared to larger studies. NIR was significantly associated with treatment failure in sub-groups classified by specific drug used and duration: amoxycillin for 7 days (AMO7): OR = 15.8 (95% CI: 6.9, 36.2); amoxycillin for 14 days (AMO14): OR = 5.3 (95% CI: 2.3, 14.8); tetracycline for 7 days: OR = 13.4 (95% CI: 5.1, 35.6); and tetracycline for 14 days: OR = 3.2 (95% CI: 2.0, 5.3).

Pooled eradication rates in relation to nitroimidazole susceptibility with classical bismuth-based therapy reported as susceptible vs resistant (AMO7: P = 0.001; AMO14: P = 0.32; TET7: P = 0.08; TET14: P = 0.16). Funnel plots for AMO7 did not suggest any bias (intercept -21 (95% CI: -115, 75)). In TET 14 funnel plot was skewed (intercept -36 (95% CI: -62, -7.5)). Numbers in other subgroups were insufficient to assess funnel plots.

PPI based triple therapy: overall NIR was significantly associated with treatment failure. OR = 5.2 (95% CI: 3.8, 7.1). Eradication rates in susceptible strains = 93% (95% CI: 86%, 99%) compared to rates in resistant strains = 69% (95% CI: 60%, 79%) with P < 0.0001. The funnel plot was symmetrical suggesting no bias. NIR was significantly associated with treatment failure for the following sub-groups: AMO7: OR = 9.6 (95% CI: 5.2, 17.8); AMO10: OR = 4.2 (95% CI: 2.1, 8.3); AMO14: OR = 8.7 (95% CI: 4.0, 18.8); clarithromycin for 7 days (CLA7): OR = 3.5 (95% CI: 1.9, 6.3); but not for clarithromycin for 10 days (CLA10) where OR = 1.7 (95% CI: 0.5, 16.6), or clarithromycin for 14 days (CLA14): OR = 2.8 (95% CI: 0.5, 16.6). In nitroimidazole susceptible strains neither treatment duration nor the choice of second antibiotic influenced efficacy. Pooled eradication rates (AMO7 vs AMO10: P = 0.64; AMO7 vs AMO14: P = 0.85; AMO10 vs AMO14: P = 0.52; CLA7 vs CLA10: P = 0.90; CLA7 vs CLA14: P = 0.81; CLA10 vs CLA14: P = 0.91). Eradication rates for amoxycillin regimes = 93% (95% CI: 84%, 100%) vs clarithromycin containing regimes = 92% (95% CI: 82%, 100%) with P = 0.89.

Quadruple therapy: 8 of the fifteen included studies were by one author. Overall NIR was significantly associated with treatment failure. OR = 7.0 (95% CI: 3.1, 16.0). Eradication rates in susceptible strains = 91% (95% CI: 80%, 100%) compared to rates in resistant strains = 77% (95% CI: 53%, 100%) with P = 0.19. Funnel plot was symmetrical with a large confidence interval with intercept = -36 (95% CI: -91, +19). Susceptible vs resistant: (1 to 4 days) P = 0.23; 7 to 12 days P = 0.81.

Ranitidine bismuth citrate based triple therapy: efficacy was 100% in susceptible strains and 57% (4 out of 7 patients) in resistant strains (P = 0.0005 using Fisher's exact test).

Authors' conclusions
Nitroimidazole resistance decreases treatment efficacy. Treatment duration and choice of other drugs influence the impact of NIR on treatment efficacy. If NIR is present, a nitroimidazole-containing regime should be avoided or a quadruple regime should be given for more than one week.

CRD commentary
The aims and inclusion criteria were stated. The discussion included mention of some limitations of the review including the inability to exclude bias; several studies only published as abstracts; sub-groups too small to allow examination of dose and dosing frequency on efficacy; and the use of different methods of susceptibility testing.

More comprehensive details, such as keywords used, of the search strategy would have been welcome. It was not stated whether language restrictions were applied to primary studies. Methods used to select primary studies and extract data were not described. Examination of heterogeneity was limited to consideration of funnel plots of effect size against sample size. Without assessment of heterogeneity, it cannot be determined whether meta-analysis was appropriate. No information on individual studies was presented.

Without more comprehensive information about the primary studies and an assessment of validity of included studies, it cannot be considered that the evidence supports the authors conclusions.

Implications of the review for practice and research
Practice: The authors consider that nitroimidazole susceptibility data in the population or the individual patient are essential to determine the appropriate treatment regime for clinical practice. If NIR is present, a nitroimidazole-containing regime should be avoided. If this is not feasible, a regime with high intrinsic activity (such as quadruple therapy given for one week or more) should be chosen.

Research: The authors consider that further evaluation of a regime composed of ranitidine bismuth citrate with clarithromycin and nitroimidazole is needed and that studies investigating the efficacy of nitroimidazole regimes should provide data on nitroimidazole susceptibility.

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