Adverse events with bismuth salts for Helicobacter pylori eradication: systematic review and meta-analysis

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CRD summary

The authors concluded that bismuth used in the eradication of *Helicobacter pylori* was safe and well tolerated. The only adverse event occurring significantly more often with bismuth was dark stools. This was a well-conducted review, but deficits in the trial quality may have led to an underestimation of the adverse events.

Authors' objectives

To assess the safety of bismuth salts used in *Helicobacter pylori* (*H. pylori*) eradication therapy.

Searching

MEDLINE (1966 to October 2007), EMBASE (1988 to October 2007), the Cochrane Library and Current Contents were searched for relevant studies. Search terms were reported and there were no language restrictions. Additional studies were sought by manually checking the reference lists of identified studies. Digestive Disease Week, United European Gastroenterology Week and the European *Helicobacter* Study Group conference abstract books were handsearched (2000 to 2007).

Study selection

Studies were eligible if they were randomised controlled trials of bismuth monotherapy compared with acid suppression therapy alone, placebo, or no treatment; or bismuth could be given in combination with antibiotics or antibiotics and acid suppression therapy as part of a recognised eradication regimen compared with the same dose and duration of the co-treatment without bismuth. Accepted treatments included bismuth triple therapy (in combination with two antibiotics), quadruple therapy (two antibiotics plus acid suppression therapy), or ranitidine bismuth citrate dual (with one antibiotic) or triple (two antibiotics) therapy. Participants had to be *H. Pylori* positive adults (over 16 years) taking any bismuth compound for more than one day. Trials assessed bismuth toxicity using medical databases, face-to-face or telephone interviews, symptom diaries, or questionnaires.

The included trials were conducted in Europe, Asia, the USA, South America, and Australia. Twenty percent of the trials used more than one bismuth-containing regimen. The duration of therapy ranged between seven and 56 days, with a total daily dose of between 400mg and 2,100mg. The following treatments were used: ranitidine bismuth citrate, tripotassium dicitrato bismuthate, bismuth subsalicylate, bismuth subnitrate, and colloidal bismuth subcitrate. Comparison interventions included proton pump inhibitors, H_2-receptor antagonists, antibiotics, and placebo. Mean age of participants was between 36.7 and 50.5 years and the percentage of male patients was between 32 and 78.

Two reviewers performed the searches. Titles and abstracts were screened and those judged to be potentially eligible for inclusion were assessed using pre-designed eligibility forms. In case of disagreement between the two reviewers, a third reviewer was consulted and agreement was reached by consensus.

Assessment of study quality

The quality of the studies was assessed using the following criteria: method of assessment of occurrence of adverse events (interview, diary, or questionnaire), method of randomisation, method of allocation concealment, blinding of assessor to patient allocation.

Data extraction

Two reviewers extracted the data concerning the total number of adverse events and the number of specific adverse events, using specially developed forms. The details of trial and patient characteristics were recorded. The proportion of patients reporting any adverse event and the proportion with specific adverse events were calculated. Data extraction was checked by a third reviewer. The verified data were entered into an Excel spreadsheet, which was also checked by the third reviewer.

Methods of synthesis

A meta-analysis of dichotomous adverse event outcomes was conducted using a random-effects model, where sufficient data were available. Adverse events with bismuth versus control regimen were expressed as relative risks (RRs) with 95% confidence intervals (CIs). The number needed to harm was calculated from the risk difference derived from the meta-analysis and, where significant, this was reported. Funnel plots were used to examine potential publication bias.

Heterogeneity was assessed using the I^2 statistic. The sources of heterogeneity were assessed in sensitivity analyses on trial setting, country of origin, type and dose of bismuth salt used, mean age of patients, and their sex.

Results of the review

Thirty-five studies were included in the meta-analysis (n=4,763 patients with *H. pylori*). Three of the quality criteria were; randomisation described, allocation concealment described, and double-blind. One of the 35 studies fulfilled all three of these criteria, six fulfilled two of the criteria, 12 fulfilled one, and 16 fulfilled none. The process of collecting adverse event data was unclear in 21 of the studies.

There were no serious adverse events, such as death or neurotoxicity, in any arms of any of the included studies. Overall, there was no significant difference in any adverse events between bismuth-containing regimens and control ones (RR 1.01, 95% CI 0.87 to 1.16). There was no significant difference in abdominal pain (RR 1.06, 95% CI 0.64 to 1.74), diarrhoea (RR 1.01, 95% CI 0.72 to 1.42), dizziness (RR 1.18, 95% CI 0.81 to 1.72), headache (RR 1.31, 95% CI 0.81 to 2.11), metallic taste (RR 1.02, 95% CI 0.81 to 1.28), nausea and/or vomiting (RR 1.16, 95% CI 0.89 to 1.52), or adverse events leading to withdrawal of therapy (RR 0.86, 95% CI 0.54 to 1.37). The only difference was observed for dark stools, with significantly more dark stools seen with bismuth therapy (RR 5.06, 95% CI 1.59 to 16.12; four trials), with a number needed to harm of 7.5 (95% CI 4 to 71). There was statistically significant heterogeneity for some of the outcomes, but no obvious causes were found.

When considering only trials with patients treated for one month or more (11 trials), a significant additional effect was seen for diarrhoea (RR 1.72, 95% CI 1.14 to 2.60), but the differences for the other adverse events remained non significant. Most patients received treatment for only one to two weeks.

Authors' conclusions

Bismuth used in the eradication of *H. pylori* was safe and well tolerated. The only adverse event occurring significantly more often with bismuth was dark stools.

CRD commentary

This systematic review addressed a clear research question and was supported by appropriate inclusion criteria. Measures were taken to avoid reviewer bias and error in the review process. The literature search included relevant databases, with no language restriction, and search terms were reported. Sensitivity analyses were carried out when results were heterogeneous. Information on the participants included in the trials was limited. The included trials had serious quality problems and none met all the quality criteria specified.

The authors' conclusions followed from the data presented, but deficits in the trial quality and the collection of adverse event data may have led to an underestimation of these adverse events.

Implications of the review for practice and research

The authors made no specific recommendations for research or practice.

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