**Authors' objectives**
To review the clinical pharmacology of ranitidine bismuth citrate (RBC) in the treatment of Helicobacter pylori (HP) infection and duodenal ulcer.

**Searching**
MEDLINE was searched from 1992 to January 1997 for articles published in the English language, using the keywords 'Tritec', 'ranitidine' and 'bismuth'. References pertaining to the treatment of duodenal ulcers or HP were extensively searched for additional sources.

**Study selection**
Study designs of evaluations included in the review
All articles pertaining to RBC were considered for inclusion. Emphasis was placed on randomised, double-blind trials. Priority was placed on data relating to regimes that were approved by the Food and Drug Administration for the treatment of duodenal ulcer in conjunction with HP infection.

Specific interventions included in the review
The interventions included the following: a combination therapy consisting of RBC (400 to 800 mg for 4 weeks) plus clarithromycin (250 mg four times daily or 500 mg three times daily for the first 2 weeks); placebo RBC plus placebo clarithromycin; placebo combined with one of the active agents; and RBC alone.

Participants included in the review
Participants with duodenal ulcer, including those with a single active duodenal ulcer diagnosed by endoscopy; and patients infected with HP. HP was identified by a positive culture, a positive histology, an urease breath test, or a rapid urease test.

Outcomes assessed in the review
The outcomes reported were: ulcer healing, eradication of HP infection, adverse effects, and ulcer recurrence 24 weeks after healing. Ulcer healing was judged as the complete re-epithelialisation of the mucosa with no erosion at the original ulcer site after 4 weeks' treatment. HP eradication was defined as at least two of the three tests performed at the end of treatment being negative, with or without a further negative result 4 weeks later, or as all tests being negative for longer than 4 weeks after the end of treatment.

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

**Assessment of study quality**
The author does not state that they assessed validity.

**Data extraction**
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Differences between the studies were discussed in the narrative summary of the results.

Results of the review
Four randomised controlled trials (RCTs) were included: 2 placebo-controlled RCTs (N=333) published in the US, and 2 further RCTs (N=327) published elsewhere.

The rate of HP infection in patients on entry was 68% for the US studies, versus 94% for the non-US studies.

US studies.
The ulcer healing rates at 4 weeks were: for the RBC (400 mg) and clarithromycin combination, 71 and 82%, (p<0.001 versus the placebo groups); RBC, 66 and 74%; for clarithromycin, 49 and 73%; and for placebo, 15 and 52%. HP eradication 4 weeks after therapy was: for the RBC (400 mg) and clarithromycin combination, 86 and 82% (p<0.01 versus the other 3 groups); for RBC, 0 and 0%; for clarithromycin, 24 and 36%; and for placebo, 0 and 0%.

Ulcer recurrence 24 weeks after healing (1 RCT, N=117) was: for the RBC (400 mg) and clarithromycin combination, 30%; for RBC, 77%; for clarithromycin, 36%; and for placebo, 80%.

Adverse effects: the discontinuation rate due to adverse effects ranged from 2 to 6% (1 RCT, N=204), with the highest rate occurring in the group receiving the double placebo.

Non-US studies.
The ulcer healing rates at 4 weeks were: for the RBC (400 mg) and clarithromycin combination, 88 and 89%; for the RBC (800 mg) and clarithromycin combination, 88 and 93%; and for RBC, 71 and 83%.

HP eradication 4 weeks after therapy was: for the RBC (400 mg) and clarithromycin combination, 82 and 94% (p<0.001 versus monotherapy); for the RBC (800 mg) and clarithromycin combination, 74 and 84% (p<0.001 versus monotherapy); and for RBC, 0 and 2%.

The occurrence of adverse reactions was: for the RBC (400 mg) and clarithromycin combination, 31 and 28%; for the RBC (800 mg) and clarithromycin combination, 35 and 25%; and for RBC, 23 and 29%.

Ulcer recurrence 24 weeks after healing (1 RCT, N unknown) was: for the RBC (400 mg) and clarithromycin combination, 6%; for the RBC (800 mg) and clarithromycin combination, 9%; and for RBC, 40%.

No details were provided in the original studies as to how the adverse reactions were classified, or how many were serious or resulted in discontinuation of the therapy.

Cost information
The relative costs of the different regimes for the treatment of ulcers were discussed.

Authors' conclusions
RBC in conjunction with clarithromycin achieved HP eradication rates of 82 to 94%, and duodenal ulcer healing rates of 71 to 89%, in clinical trials. RBC is given twice daily for 28 days and is associated with very low rates of patient noncompliance, or failure to complete therapy due to adverse effects. It is less expensive and may have lower ulcer healing rates than omeprazole plus clarithromycin, but it may be more effective in eradicating HP.
CRD commentary
This review was difficult to read. The review of the RCTs comprised only a part of an extensive discussion of the pharmacology of RBC. Much information on the pharmacology was presented. The authors considered the differing rates of HP infection between the non-US and the US trials to be potentially caused by the different diagnostic criteria, definitions and study populations.

By restricting the literature search to English language studies in one database, other relevant studies may have been omitted. No details were given of the methods used to select the primary studies or extract the data. The inclusion criteria were not clearly defined and validity was not assessed. No point estimate of the treatment effect (with 95% confidence intervals) was calculated. More comprehensive details of the primary studies would have been helpful, in particular, the patients' characteristics. Further information may have been available from the authors of the primary studies had they been approached. Information on the adverse reactions noted in the non-US studies would have been helpful. No comment was made on the heterogeneity of the results in the placebo arm of the US trials.

In view of the lack of details of the review process, i.e. validity assessment and the methods used, the author's conclusions cannot be considered to be supported by the evidence presented.

Implications of the review for practice and research
The author considered that community-based follow-up studies may clarify the effect of HP resistance and patient compliance on long-term ulcer relapse rates. In addition, they may help determine whether a preferable regime exists for the treatment of duodenal ulcer associated with HP infection.

Bibliographic details

PubMedID
9640487

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Ulcer Agents /administration & dosage /adverse effects /pharmacokinetics /pharmacology; Bismuth /administration & dosage /adverse effects /pharmacokinetics /pharmacology; Clinical Trials as Topic; Drug Interactions; Duodenal Ulcer /drug therapy /microbiology; Formularies as Topic; Helicobacter Infections /drug therapy; Helicobacter pylori; Humans; Ranitidine /administration & dosage /adverse effects /pharmacokinetics /pharmacology

AccessionNumber
11998001113

Date bibliographic record published
30/11/1999

Date abstract record published
30/11/1999

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.