A systematic review of efficacy and tolerability of mebeverine in irritable bowel syndrome

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CRD summary
The review concluded that mebeverine did not significantly improve the global symptoms of irritable bowel syndrome or relieve the associated abdominal pain, but it was mostly well tolerated, with no significant adverse events. Although the included trials were of high quality, the evidence was limited, so the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the safety and efficacy of mebeverine for irritable bowel syndrome.

Searching
PubMed, EMBASE, Scopus, and the Cochrane Library were searched up to June 2009 for publications in any language; search terms were reported. Google was also searched. Bibliographies of each retrieved article were handsearched.

Study selection
Controlled clinical trials that compared mebeverine (a musculotropic antispasmodic agent) with placebo for irritable bowel syndrome were eligible for inclusion. Case studies and cross-over studies were excluded. Trials were also excluded if they compared mebeverine with other active agents, if they used a combination of drugs, or if their outcomes did not relate to efficacy. However, trials of a high fibre diet or fibre supplementation with mebeverine and trials comparing different mebeverine dose regimes were included.

The primary outcomes were 'global assessment of symptoms by the patient or physician' (as defined by the included trials), or abdominal pain and distension. Trials were excluded if the outcomes were not clearly explained.

Most of the included trials compared 400mg/day mebeverine with placebo; one trial compared wheat bran plus 100mg/day mebeverine with placebo. Two trials compared different doses of mebeverine, 135mg/day with 200mg/day. Treatment duration ranged from three to 16 weeks. The included patients had all subtypes of irritable bowel syndrome, the percentage of males was 37%, and their mean age ranged from 32 to 56 years. Some trials recorded global improvement versus no improvement, whereas others evaluated the patient’s global assessment of relief. Where a trial lacked a definition of a global response, an assessment of a global improvement in symptoms was made.

Two reviewers selected studies for the review.

Assessment of study quality
Methodological quality was assessed using the Jadad score, which assessed randomisation, blinding, and whether withdrawals and drop-outs were described, using a 0 to 5 point score. A score of 2 or less indicated a low quality trial; 3 or more points indicated a high quality trial.

The authors did not specifically report how many reviewers performed the validity assessment.

Data extraction
Two independent reviewers extracted data using tables, with disagreements resolved by consensus. The numbers of events for each outcome were extracted in order to calculate relative risk (RR) and 95% confidence intervals (CI).

Methods of synthesis
Relative risks were pooled using either fixed-effect (Mantel-Haenszel) or random-effects models (DerSimonian and Laird) related to the presence of heterogeneity. Between trial heterogeneity was determined using the Cochrane Q statistic and L’Abbe plots.

Publication bias was assessed using funnel plots.
The regression of the normalised effect versus precision, and Kendall's test on the standardised effect versus variance was also determined.

**Results of the review**

Eight randomised controlled trials (RCTs) were included in the review (n=555 patients, range 30 to 184). Seven RCTs had a Jadad score of 4 or more points; the remaining RCT had a score of 3 points. Seven RCTs were double-blind, eight RCTs were randomised, and seven RCTs described randomisation appropriately. Four RCTs provided data on withdrawals and drop-outs.

**Mebeverine versus placebo**: There was no significant effect of mebeverine versus placebo for global or clinical improvement of symptoms (RR 1.13, 95% CI 0.59 to 2.16; five RCTs), with significant heterogeneity (p=0.002). The regression of the normalised effect versus precision and Kendall's test on the standardised effect versus variance were not significant (T=0.2). There was also no significant effect of mebeverine versus placebo on relief of abdominal pain (RR 1.33, 95% CI 0.92 to 1.93; three RCTs), with no significant heterogeneity (fixed-effect model). Adverse events were rare or unknown in four of the six RCTs, and at similar levels in the two remaining RCTs (an overall 24% in the mebeverine group compared with 22.5% in the placebo group).

**Mebeverine 200mg/day versus 135mg/day**: There was no significant difference in effect for global or clinical improvement of symptoms (RR 1.12, 95% CI 0.96 to 1.30; two RCTs) or for relief of abdominal pain (RR 1.08, 95% CI 0.87 to 1.34; two RCTs), with no significant heterogeneity (but a random effects model was used due to the low number of trials). One RCT found no serious adverse events; the other RCT found similar adverse events in both groups (59.5% in the 200mg/day group and 61.5% in the 135mg/day group).

**Authors' conclusions**

Mebeverine was mostly well tolerated, with no significant adverse events; however, its efficacy in global improvement of irritable bowel syndrome and relief of abdominal pain was not statistically significant.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, and study design, but the definition of relevant outcomes was not very precise. Relevant databases were searched, without language restrictions, but it appeared that unpublished studies were not considered, so some relevant trials may have been missed. Publication bias was assessed, but no details were reported. Efforts were made to reduce error and bias in data extraction, but it was not reported whether this process was applied to study selection and quality assessment.

Trial quality was assessed using suitable criteria; most of the included RCTs were of high quality. Relevant trial details were reported, but few specific descriptions of outcomes were reported. Statistical heterogeneity was assessed; there was evidence for heterogeneity for some outcomes. The statistical method used for the meta-analysis of the RCTs may not have been appropriate, since different measurements of outcome may have been combined.

Although the included trials were high quality, the evidence was limited, and whether the overall results were not significant due to a lack of power, as implied by the authors, is unclear.

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

**Practice**: The authors stated that, despite the non significant results of the review for mebeverine, it could be considered as clinically effective until more studies added power to the conclusions.

**Research**: The authors identified a need for RCTs of mebeverine for irritable bowel syndrome which consider different subtypes of the disease and the gender of patients.

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