Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials

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CRD summary
This review compared Pentasa 4 g/day with placebo for the treatment of mild to moderate Crohn's disease. The authors concluded that Pentasa reduced the Crohn's Disease Activity Index score in comparison with placebo, but the clinical significance is unclear. A limited search and poor reporting of review methods make it difficult to assess the robustness of the conclusions.

Authors' objectives
To undertake a meta-analysis of the results of randomised controlled trials (RCTs) of slow-release mesalamine (Pentasa) in the treatment of mild to moderate Crohn's disease.

Searching
MEDLINE was searched from 1986 to 1998; the search terms were not reported. The internal files of the marketing authorisation holders in the USA and Europe were also searched.

Study selection
Study designs of evaluations included in the review
Double-blind, placebo-controlled, RCTs were eligible for inclusion. All of the included trials were of 4 months' duration.

Specific interventions included in the review
Studies assessing 4 g of Pentasa were eligible for inclusion. The included studies all compared oral Pentasa at 4 g/day with placebo.

Participants included in the review
Studies of adult patients with active Crohn's disease were eligible for inclusion. The majority of the patients had either ileocolitis or ileitis. The average duration of disease was 8 to 10 years, and most patients were experiencing a chronic current episode (more than 28 days). The mean Crohn's Disease Activity Index (CDAI) ranged from 248 to 277 (values for individual patients ranged from 86 to 474). The average age of the patients ranged from 37 to 42 years, and most were women (range: 60 to 83%).

Outcomes assessed in the review
Studies using the CDAI as the primary outcome were eligible for inclusion. In all of the included studies CDAI values were calculated at baseline, then monthly for 4 months using information from patient diaries.

How were decisions on the relevance of primary studies made?
The authors did not state how decisions on the relevance of primary studies were made.

Assessment of study quality
The authors included only double-blind, placebo-controlled trials in the review; they did not state whether they performed any additional checks of study validity. They also performed an individual patient data (IPD) meta-analysis and contacted the drug license holder for relevant trials, but they did not state if they rechecked the raw data for errors.

The authors did not state how judgements of validity were made, or if any trials were excluded from the meta-analysis.
Data extraction
The authors did not state how many reviewers extracted the data from the study reports. For each study, the change (with standard error) from baseline in CDAI to 4 months was extracted for each treatment group and used to calculate the mean treatment difference and 95% confidence interval (CI). For all studies, patients without a 4-month visit had the last observation carried forward, while patients with no post-baseline measurements were assumed to have zero change.

Methods of synthesis
How were the studies combined?
The authors performed both a meta-analysis, using the results from the individual study reports, and a pooled IPD analysis.

For the meta-analysis, the differences in the mean change in CDAI between Pentasa and placebo were combined using a fixed-effect model, weighted by the inverse variance. The 95% CI of the weighted mean difference (WMD) was calculated using a normal approximation. This analysis was conducted for both the intention-to-treat and protocol correct (patients who did not violate the original study protocol) populations.

For the IPD analysis, the data were analysed using an analysis of covariance model. Change in CDAI was the outcome, and the model adjusted for baseline CDAI and study centre. If the same centre was included in more than one trial, then the model was also stratified by trial.

How were differences between studies investigated?
Study homogeneity in the meta-analysis of summary data was assessed using a statistical test (details were not reported) and forest plots were presented. Subgroup analyses were also conducted to examine the influence on the CDAI of response to prior oral steroid use, response to prior sulfasalazine use, duration of disease, duration of current episode, and gender. These factors were chosen because the study reports identified them as possible treatment effect modifiers (P<0.1). The IPD analysis was used to assess if the baseline disease severity (as measured by the baseline CDAI) had any impact upon reduction in CDAI.

Results of the review
Three studies (n=615) were included.

Meta-analysis: Pentasa was associated with a statistically significant improvement (a larger reduction) in CDAI compared with placebo (WMD -18, 95% CI: -35, -1, P=0.04). There was no evidence of statistical heterogeneity between the study results (P=0.12). This result was confirmed when the analysis was repeated for the protocol-correct patients (WMD -25, 95% CI: -46, -3, P=0.02) and there was also no evidence of statistical heterogeneity (P=0.18).

IPD analysis: this also found that Pentasa was associated with a statistically significant improvement in CDAI compared with placebo (WMD -25, 95% CI: -44, -6, P=0.01). The baseline CDAI was a significant predictor of treatment response (P<0.001), with patients with a higher baseline score experiencing a greater reduction in CDAI after treatment.

Subgroup analyses: the improvement associated with Pentasa was only statistically significant for patients who had experienced remission or benefit from prior steroid use (WMD -46, 95% CI: -74, -17, P=0.02), patients who had suffered from Crohn's disease for less than 7 or 8 years (WMD -39, 95% CI: -65, -13, P<0.001) and patients with an acute episode (less than 28 days) (WMD -42, 95% CI: -75, -9, P=0.01). There was no evidence of any differences between Pentasa and placebo in relation to prior sulfasalazine use or gender.

Authors' conclusions
Treatment of active Crohn's disease with Pentasa 4 g/day is superior to placebo in reducing the CDAI, but the clinical significance of the magnitude of this difference remains unclear.
CRD commentary
This meta-analysis had clear aims and study inclusion criteria. Limiting the search to one database and trials provided by the manufacturers might have resulted in the omission of other relevant studies. The search strategy was not described in full (the search terms were not reported), so the appropriateness of the strategy cannot be judged. It was unclear whether any language restrictions had been applied, thus the potential for language bias cannot be assessed. It was also unclear if any trials identified by the search were excluded from the meta-analysis, or why the maximum recommended daily dose of 4 g was used when there were other trials assessing lower doses that might have provided useful results. The methods used to select studies, assess study design and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias.

Only double-blind, placebo-controlled RCTs were eligible, but the authors did not state whether they made further quality checks of the data for the IPD analysis. The authors performed two meta-analyses: one using the results from the manufacturers' study reports and a supplementary analysis using the IPD. The main analysis of summary data was conducted on the intention-to-treat population and its results were confirmed by an additional analysis of the protocol-correct population. The statistical analysis methods used in the IPD analysis and to pool treatment differences seemed appropriate, although the pooling of individual treatment arms was not correct and these results should be treated cautiously. The subgroup analyses assessed factors identified in the original analyses as being potentially related to the treatment effect, and this seemed an appropriate approach. The limited search and lack of reporting of review methods make it difficult to confirm the robustness of the conclusions.

Implications of the review for practice and research
Practice: The authors stated that the subgroup analyses in this study did not provide sufficiently clear answers to inform clinicians which patient group should receive Pentasa 4 g/day. The clinical significance of the treatment difference observed is also unclear, as it is smaller than that usually needed to establish clinical efficacy.

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

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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.