Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D): a multicentre, parallel-group, randomised placebo-controlled trial

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Declared competing interests of authors: none

Published March 2015
DOI: 10.3310/eme02020

Scientific summary

Treatment of diarrhoea-predominant irritable bowel syndrome
Efficacy and Mechanism Evaluation 2015; Vol. 2: No. 2
DOI: 10.3310/eme02020

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Irritable bowel syndrome (IBS) is a heterogeneous condition, characterised by abdominal pain/discomfort and disturbed bowel habit. There is an interaction between gut pathology and disturbed central processing of visceral afferent signalling in this group of patients. Patients may suffer from both diarrhoea (with accelerated transit) and constipation (when transit is delayed), with around one-third of them having a mixed bowel pattern with episodes of both diarrhoea and constipation. Both subtypes exhibit hypersensitivity to rectal distension. Although the majority of patients with IBS have mild symptoms and are commonly managed in the community, there is a small proportion of patients who have moderate to severe symptoms, who are referred to secondary care for further investigations and management of their symptoms. Most treatments are based on symptom control rather than a 'cure', owing to lack of understanding of the underlying mechanisms. However, there have recently been reports of 'immune activation' in the mucosa of patients with diarrhoea-predominant irritable bowel syndrome (IBS-D), such as increased mast cell numbers and release of proinflammatory mediators, for example tryptase and histamine. This has been supported by animal studies that clearly show mast cell activation by psychological stress, associated with the development of visceral hypersensitivity, a key feature of IBS in humans. Although some reports have linked severity of pain to the number of mast cells in close proximity to nerves, a link between symptoms and mast cell numbers or mediators released from mucosal biopsies has not been seen in recent mechanistic studies. Other human studies have reported increased in immune cells, such as T lymphocytes and enterochromaffin cells, particularly in postinfectious IBS. There have been three small pilot randomised placebo-controlled trials and one open-labelled study suggesting that mesalazine slow-release granule formulation (2 g; PENTASA®, Ferring Pharmaceuticals Ltd), 5-aminosalicylic acid (5-ASA), may improve symptoms of IBS, such as abdominal pain and improvement in bowel habit, particularly in patients with postinfective irritable bowel syndrome (PI-IBS). One small study with just 20 patients showed a reduction in mast cell numbers following treatment.

Objectives

Our clinical primary outcome was to compare the effect of mesalazine with placebo on stool frequency. Secondary clinical outcomes were to assess the effect of mesalazine on abdominal pain, stool consistency, urgency and satisfactory relief of IBS symptoms. The primary mechanistic outcome was to assess change in mast cell percentage area stained after treatment with mesalazine. Secondary mechanistic outcomes were to assess mast cell tryptase release, volume of fasting small bowel water, faecal tryptase and calprotectin.

Methods

All participants met the modified Rome III criteria for IBS-D. Organic diseases were excluded with normal blood tests and sigmoidoscopy/colonoscopy. Participants taking non-steroidal anti-inflammatory drugs or 5-ASA compounds were excluded from the study. All participants were randomised after a 2-week baseline stool diary. All participants completed a 12-week stool diary and at the end of each week they recorded the presence of 'satisfactory relief of IBS symptoms'.

Results

Our large multicentred, parallel group, randomised placebo-controlled trial of mesalazine for treatment of IBS-D, which randomised 136 subjects, was powered to detect a significant difference in bowel frequency but has shown no clinical benefit over placebo in patients with IBS-D. Mechanistic assessments showed no significant changes in mast cell numbers or mast cell mediators released from mucosal biopsies. We did not find that the rate of release of mast cell products from a colonic biopsy was a useful biomarker, as it failed to correlate with any symptoms. Mesalazine did not cause significant changes in fasting small bowel water content, faecal tryptase or calprotectin. There was, however, a small number ($n = 13$) of patients with IBS-D who met the criteria for PI-IBS and who showed significant clinical benefit of treatment with mesalazine. This requires confirming in a further larger and more adequately powered study.

Conclusion

This study does not support any clinically meaningful benefit or harm of mesalazine compared with placebo in unselected IBS with diarrhoea. If there is a subgroup that benefits it is likely to be those with postinfective IBS and a trial of such patients, particularly those with more severe diarrhoea. Therefore, a more precise subtyping based on underlying disease mechanisms is needed to allow more effective targeting of treatment in IBS.

Trial registration

This trial is registered as ISRCTN76612274.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) Programme, a MRC and NIHR partnership.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 09/20/16. The contractual start date was in October 2010. The final report began editorial review in May 2014 and was accepted for publication in December 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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