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

Ching Lam,1 Wei Tan,2 Matthew Leighton,2 Margaret Hastings,3 Melanie Lingaya,1 Yirga Falcone,1 Xiaoying Zhou,4 Luting Xu,5 Peter Whorwell,3 Andrew F Walls,4 Abed Zaitoun,6 Alan Montgomery2 and Robin C Spiller1*

1National Institute for Health Research (NIHR) Nottingham Digestive Diseases Biomedical Research Unit, Nottingham University Hospitals NHS Trust, Nottingham, UK
2Clinical Trials Unit, University of Nottingham, Nottingham, UK
3Neurogastroenterology Unit, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK
4Immunopharmacology Group, University of Southampton, Southampton, UK
5FRAME Laboratory, University of Nottingham, Nottingham, UK
6Histopathology, Nottingham University Hospitals NHS Trust, Nottingham, UK

*Corresponding author

Declared competing interests of authors: none

Published March 2015
DOI: 10.3310/eme02020
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)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www-publicationethics.org). Editorial contact: nihredit@southampton.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

**EME programme**

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting ‘science driven’ studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

**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.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2015. This work was produced by Lam et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Efficacy and Mechanism Evaluation Editor-in-Chief

Professor Raj Thakker  May Professor of Medicine, Nuffield Department of Medicine, University of Oxford, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen’s University Management School, Queen’s University Belfast, UK

Professor Aileen Clarke  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson  Director of NETSCC, HTA, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Professor Elaine McColl  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk