

Project Title:	Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome(IBS-D)
Project Ref:	09-20-16
Cost:	£724,082
Lead Applicant & Institution:	Professor Robin Spiller Wolfson Digestive Diseases Centre University of Nottingham
Start Date:	Anticipated 1 September 2010
Plain English Summary:	<p>The Irritable Bowel Syndrome (IBS) affects around 10% of the population who at some time suffer from abdominal pain or discomfort, bloating and irregular bowel habit. IBS patients' bowel habit varies with approximately 1/3rd having mainly diarrhoea (IBS-D), 1/3rd mainly constipation and 1/3rd a mixed bowel habit.</p> <p>Current surveys show that most patients are dissatisfied with treatment. Mesalazine is an inexpensive safe drug widely used to treat bowel inflammation in ulcerative colitis. Recently, there have been several small studies suggesting benefit in IBS. Since 4 out of 5 studies have been in IBS-D we propose to focus on this subgroup who suffer increased bowel frequency with urgency which are among the most disabling of IBS symptoms. One small study showed that Mesalazine reduced the number of mast cells in the large bowel but this was underpowered (n=20) and needs confirming as do the other studies which were either not double blinded or not placebo controlled. Mast cells release substances which have been shown to excite nerves responsible for intestinal pain and their number correlate with the pain severity in IBS.</p> <p>Each patient will receive 12 weeks treatment with identical looking pills containing either Mesalazine or an inert substance (placebo). Before and after taking the treatment, patients will have a flexible endoscope passed into the lower bowel and a small scraping (called a biopsy) removed from the lining of the bowel which will then be examined under the microscope to count the number of inflammatory and mast cells. We will also measure substances released by the biopsy including mast cell products which may cause symptoms.</p> <p>We will find out whether Mesalazine compared with placebo reduces the stool frequency and improves the patients' overall IBS symptoms. We will also look to see whether it reduces the number of mast cells or reduces the secretion of mast cell products from the biopsies. These products increase the tone of the small bowel which makes the bowel narrower and the passage through it faster. We will assess this from a MRI scan of the abdomen looking at the size of the small bowel.</p>

	<p>This simple, highly patient acceptable, non-invasive test may predict who should receive this treatment. If at the end of the trial patients feel they have benefited from treatment then we will be able to prescribe it for them. Our study could explain why Mesalazine works which should allow better targeting of this inexpensive safe treatment for a large group of patients who currently have no satisfactory treatment.</p>
<p>Abstract:</p>	<p><u>Design:</u> A randomised, placebo-controlled, parallel group design evaluating the effect of Mesalazine on IBS symptoms, mast cell numbers and secretion, and small bowel tone in IBS-D patients.</p> <p><u>Study Population:</u> 108 IBS-D patients aged 18-75 years meeting Rome III criteria.</p> <p><u>Planned Intervention:</u> 12 weeks Mesalazine 800 mgs tds compared with placebo. Patients will complete a daily symptom diary for two weeks prior to randomisation and then during the 12 weeks of treatment. At randomisation and at 12 weeks, they will undergo 1)flexible sigmoidoscopy and biopsy to allow quantification of numbers of mucosal inflammatory and mast cells per high powered field. Biopsies will also be incubated and release of inflammatory mediators measured 2) MRI scanning both fasting and for 4 hours postprandially to assess small bowel water content and indirectly intestinal tone. Patients will also complete validated anxiety, depression and somatisation questionnaires at entry.</p> <p><u>Primary Outcome Measures:</u></p> <p><u>Clinical:</u> Reduction in stool frequency, averaged over weeks 11 and 12 compared with average of 2 weeks prior to randomisation.</p> <p><u>Mechanistic:</u> Reduction in mucosal mast cell counts.</p> <p><u>Secondary Outcome Measures:</u></p> <p><u>Clinical:</u></p> <ol style="list-style-type: none"> 1. Decrease in IBS symptom severity score 2. % patients achieving satisfactory relief of IBS symptoms <p><u>Mechanistic:</u></p> <ol style="list-style-type: none"> 1. Change in mast cell tryptase release from mucosal biopsy 2.Reduction in stool mast cell tryptase concentrations 3.Change in small bowel tone a) fasting b) average 0-4 hrs post prandially <p><u>Assessment and Follow-Up:</u> Since Mesalazine is expected to have 1-2 months to have its full effect the assessment will be by means of daily stool diary analysed in the last 2 weeks. Visits are planned at 2, 4, 8 and 12 weeks for safety monitoring.</p> <p><u>Proposed Sample Size:</u> 96 patients based on the primary end point of stool frequency. Our previous study on IBS-D patients gives a mean stool frequency of 3.1 (SD 2.0). Our study will have an 80% power to detect such an effect at the 1% significance level (90% at 5% significance). Allowing for a 10% dropout we will recruit 108.</p> <p><u>Statistical Analysis:</u> Analysis of the Primary outcome measure will be performed using an Analysis of Covariance in the form of a General Linear Model incorporating terms for baseline frequency, treatment arm, centre, age, diet and gender. All analyses will be performed using the current version of Stata.</p>

	<p>Project Time Table: 0-6 Months: Set up and regulatory approval. 6-24 Months: Recruitment: 70 in Nottingham and 40 in Manchester. We have recruited 25 IBS patients in the first 6 months of this year and see 450 new IBS patients /year with 700 IBS-D/ year at the Manchester centre. 27 Months : Last patient out, lock database and undertake final analysis 27 – 33 Months: Complete analysis 33 – 36 Months: Write up and publish.</p>
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Project website: (if applicable)	To follow
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