Ondansetron for irritable bowel syndrome with diarrhoea: randomised controlled trial

David Gunn,[1,2] Rabia Topan,[3] Ron Fried,[4] Ivana Holloway,[5] Richard Brindle,[5] Suzanne Hartley,[5] Lorna Barnard,[5] Maura Corsetti,[2] S Mark Scott,[3] Adam Farmer,[6] Ayesha Akbar,[7] Maria Eugenicos,[8] Nigel Trudgill,[9] Kapil Kapur,[10] John McLaughlin,[11] David S Sanders,[12] Arvind Ramadas,[13] Peter Whorwell,[14] Lesley Houghton,[15] Phil G Dinning,[16] Qasim Aziz,[3] Alexander C Ford,[17,18] Amanda Farrin[5] and Robin Spiller[1,2*]

[1]NIHR Nottingham Digestive Diseases Biomedical Research Centre, University of Nottingham, Nottingham, UK
[2]Nottingham Digestive Diseases Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
[3]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[4]Department of Gastroenterology and Hepatology, University of Zurich, Zurich, Switzerland
[5]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK
[6]Royal Stoke Hospital, University Hospitals of North Midlands NHS Trust, Stoke, UK
[7]St Mark's Hospital, Harrow, UK
[8]University of Edinburgh, Western General Hospital, Edinburgh, UK
[9]Sandwell and West Birmingham NHS Trust, Birmingham, UK
[10]Barnsley Hospital NHS Foundation Trust, Barnsley, UK
[11]University NHS Foundation Trust, Manchester, UK
[12]Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield Wythenshawe Hospital, Manchester, UK
[13]Tees Valley Hospital, Middlesbrough, UK
[14]University of Manchester, Manchester, UK
[15]St James's University Hospital, Leeds, UK
[16]Discipline of Surgery and Gastroenterology, Flinders Medical Centre, Flinders University, South Australia, Australia
[17]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK
[18]Leeds Gastroenterology Institute, Leeds Teaching Hospitals Trust, Leeds, UK

[*]Corresponding author robin.spiller@nottingham.ac.uk

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Scientific summary

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Scientific summary

Background

Irritable bowel syndrome (IBS), which affects around 10% of the population, accounts for 1.8 million consultations/year in primary care in England and Wales (0.6 million patients). Symptoms of IBS with diarrhoea (IBS-D) include frequent, loose or watery stools with associated urgency, which can severely limit socialising, travelling and eating out, with resulting marked reduction in quality of life and loss of work productivity. Around one-third of all IBS patients meet Rome criteria for IBS-D. When patients are asked to rank symptoms in order of importance, the erratic bowel habit is rated first, followed by abdominal pain and, for those with diarrhoea, urgency.

Ondansetron, a 5-hydroxytryptamine-3 ($5HT_3$) receptor antagonist, has an excellent safety record for over 20 years as an antiemetic, but is only exceptionally used in the treatment of IBS-D. It has, however, been shown to slow colonic transit and in a small randomised, placebo-controlled, crossover pilot study, benefited patients with IBS-D. While the current trial was ongoing, a separate trial in the USA using a fixed dose bimodal release formulation (3 mg ondansetron +9 mg delayed release formulation) also reported improvement in stool consistency but not pain.

Objectives

Our primary aim was to determine the efficacy of generic ondansetron compared to placebo in controlling the symptoms of IBS-D using the US FDA-recommended combined end point in which a responder is defined as a patient who met the response criteria for both pain and bowel habit for 6 out of 12 weeks of the trial. Secondary end points included its effect on the characteristic abnormalities of stool consistency, frequency and urgency as well as abdominal pain, satisfactory relief of IBS symptoms, mood and use of rescue medication and to determine the effect of 12 weeks ondansetron over the 1 month after discontinuation, as well as safety.

The study also included mechanistic studies to examine the correlation of rectal sensitivity and compliance, faecal bile acids (FBAs) and proteases and postprandial sigmoid motility with the baseline symptoms of our IBS-D patients. We also attempted to determine whether ondansetron significantly altered these biomarkers compared to placebo.

Methods

Treatment of irritable bowel syndrome using titrated ondansetron trial (TRITON) was a multisite, parallel-group, randomised, double-blinded, placebo-controlled trial, with embedded mechanistic studies within selected sites. Our aim was to determine the superiority of ondansetron compared with placebo. We aimed to randomise 400 patients with IBS-D on a 1 : 1 basis to receive either ondansetron or placebo. Both treatments were administered for 12 weeks in oral doses ranging from 4 mg every third day to 24 mg daily. Dose titration was undertaken in the first 2 weeks of the study to avoid constipation, which at a standard dose occurs in one-quarter of patients. This was achieved by frequent consultation with the research nurse, starting with 1 × 4 mg tablet per day and increasing in increments every 2 days to a maximum of 2 tablets thrice daily. If constipation developed, the treatment was stopped to allow the return of bowel movements and then restarted at a lower dose, typically one every alternate day or one every second day. Rescue medication of loperamide was discouraged but allowed exceptionally for uncontrolled diarrhoea and was documented in the daily diary.

The primary outcome of response for both reduction in pain intensity and improvement in stool consistency was assessed over the 12 weeks post randomisation. Secondary and safety outcomes were measured up to 16 weeks post randomisation. Symptoms that were recorded daily included (1) stool consistency and abdominal pain (measured by both paper diary and daily text message); (2) stool frequency, urgency of defaecation, use of rescue medication (defined as the use of loperamide) over 12 weeks of treatment and the answer to the question in the diary 'Overall, have you had satisfactory relief from your IBS symptoms in the past week?'.

Irritable bowel syndrome symptom severity [measured by the IBS Severity Scoring System (IBS-SSS)], dyspepsia [using the Short Form Leeds Dyspepsia Questionnaire (SFLDQ)], quality of life and mood [using the IBS Quality of Life (IBS-QOL) and Hospital Anxiety and Depression Scale (HADS) questionnaires], and somatic symptoms [using the Patient Health Questionnaire 12 Somatic Symptoms (PHQ-12) questionnaire] were assessed by patient-reported questionnaires at the baseline and 12 weeks post randomisation.

The trial also assessed possible underlying mechanisms of any effect of ondansetron on changes in the primary and secondary end points. Whole gut transit was measured at baseline and 12 weeks using radio-opaque markers and an abdominal X-ray. High-resolution manometry was performed at baseline and after 8–11 weeks of treatment at two centres to assess whether ondansetron decreased the number of high-amplitude propagating contractions (HAPCs) or increased the percentage time occupied by cyclical retrograde propagated contractions. Barostat assessment was performed at baseline and after 8–11 weeks of treatment at two centres in order to assess if ondansetron increases rectal compliance or decreases sensitivity (manifested as increased pressure thresholds for pain and urgency). Stool samples were assessed for faecal water % (FW), faecal protease (FP) and FBAs.

Clinical results

The study closed early due to slow recruitment with just 80 patients randomised; 37 to ondansetron and 43 to placebo. Four patients discontinued ondansetron and one placebo during 12-week randomised treatment. Four were excluded from the per-protocol population due to major protocol violations.

In the intention to treat (ITT) analysis, 15 patients (40.5%) on ondansetron achieved the primary end point response [95% confidence interval (CI) 24.7% to 56.4%], compared to 12 (27.9%) patients on placebo (95% CI 14.5% to 41.3%), $p = 0.19$, adjusted OR 1.93 (0.73, 5.11). Response for pain intensity reduction was achieved by 17 (46.0%) on ondansetron (95% CI 29.9% to 62.0%) and 16 (37.2%) on placebo (95% CI 22.8% to 51.7%), $p = 0.32$, adjusted OR 1.61 (0.63 to 4.12). Response for stool consistency improvement was reported by 25 (67.6%) on ondansetron (95% CI 52.5% to 82.7%) and 22 (51.2%) on placebo (95% CI 36.2% to 66.1%), $p = 0.07$, adjusted OR 2.45 (0.92, 6.52). Overall use of the rescue medication, loperamide, was 39.5% ($n = 17$) on placebo compared with 18.9% ($n = 7$) on ondansetron. However, by week 12, loperamide use fell to 13.5% on ondansetron versus 25.6% on placebo. Average stool consistency in the final month of treatment fell significantly more on ondansetron than placebo, adjusted mean difference −0.5 [standard error (SE) 0.25, 95% CI (−1.0 to −0.02), $p = 0.042$]. Ondansetron improved the dyspepsia score (SFLDQ) significantly more than placebo; the largest reduction being in symptoms of indigestion and nausea. The adjusted mean difference in the total score compared to placebo was −3.2 points [SE 1.43, 95% CI (−6.1, to −0.4), $p = 0.028$]. Ondansetron was well tolerated with most adverse reactions being mild or moderate and not significantly greater than on placebo. The commonest was constipation, reported in 32% on ondansetron and 23% on placebo, of which 75% and 80%, respectively, were rated as mild. Just two patients withdrew citing constipation as the cause.

Mechanistic results

Results are expressed as mean (SD). Comparing baseline and week 12 showed ondansetron increased average whole gut transit 3.78 (9.1) hours on ondansetron significantly more than placebo −2.2 (10.3),

p = 0.01. Mean volume to reach urgency threshold using the barostat increased on ondansetron by 84 (61) ml and 38 (48) ml on placebo, n = 8; the difference was not significant, p = 0.26. Too few underwent manometry to allow meaningful assessment of the effect of ondansetron but anecdotally one patient who had a dramatic clinical improvement showed a loss of HAPCs and an increase in retrograde contractions, but this could have been due to chance. Ondansetron appeared not to significantly alter FP, though overall the increase in whole gut transit time from baseline to week 12 was correlated with a decrease in FP. There were no significant changes in FBAs and no evidence that ondansetron altered these though we did confirm that we had effectively excluded those with bile acid diarrhoea (BAD). The ratio of secondary to primary bile acids, a measure of bacterial metabolism of bile acids, increased substantially on ondansetron from 9.7 (7.08) to 21.4 (32.9) and less so on placebo from 22.84 (58.23) to 28.61 (31.42). However, owing to small numbers and wide variability these differences were not significant.

Limitations

Two previous studies in Nottingham had recruited 120 and 136 IBS-D patients within 2 years so we did not anticipate problems with recruitment. However, changes in referral pathways from primary to secondary care substantially reduced referrals to our coinvestigators who were all in secondary care, thus impairing recruitment. The power calculations required 400 to achieve 90% power to detect a 15% difference in primary end point, so the study is substantially underpowered. Use of loperamide did somewhat complicate interpretation since those on placebo used more rescue medication reducing the size of the effect on transit and stool consistency.

Conclusion

Despite being underpowered for our primary end point, our results are consistent with previous studies and confirmed ondansetron improves stool consistency but showed little effect on pain. Ondansetron significantly slowed whole gut transit time. Ondansetron reduced sensitivity to rectal distension more than placebo without altering compliance, but numbers were too small to achieve statistical significance. This could plausibly contribute to the reduction in urgency and stool frequency but needs repeating with larger numbers to be sure it was not due to chance. We found no evidence that rectal sensitivity was related to either faecal protease or bile acids. The manometry studies were underpowered but anecdotally ondansetron appeared to alter rectosigmoid motor patterns in a way that could reduce inflow of stool to the rectum.

Future work

We plan to do a simplified version of this trial, using an efficient and remote process, to overcome the changed referral pathways by recruiting in primary care. We will search for patients who have had a diagnosis of chronic diarrhoea and the recommended screening including a normal full blood count, a negative tissue transglutaminase (excluding coeliac disease) and a normal faecal calprotectin using software linked to primary care records. This will allow rapid screening of large numbers of patients to identify and approach patients with IBS-D who meet criteria to take part in a randomised trial of ondansetron or placebo, thus minimising barriers to recruitment. We would remove the pain threshold, which would increase the number of eligible patients and facilitate recruitment. Not allowing loperamide as rescue medication would simplify interpretation and dropouts would be treated as treatment failures. Further streamlining by removing all additional tests that were included in the current trial, as well as efficient trial processes, including e-consent, remote blood and stool samples (if required), and online questionnaires would also optimise recruitment.

Study registration

This trial is registered as ISRCTN17508514.

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