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Selective 5-hydroxytryptamine antagonism: a role in irritable bowel syndrome and functional dyspepsia?

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SUMMARY

Background: Abnormalities of gut motility and visceral pain perception are both thought to be involved in the pathogenesis of irritable bowel syndrome and may be susceptible to modulation by drugs affecting the various 5-HT receptor subtypes. The aim of this study was to investigate the therapeutic potential of a 5-HT_3 antagonist in irritable bowel syndrome.
Methods: Fifty patients with irritable bowel syndrome were treated with ondansetron, a highly selective 5-HT_3 antagonist, in a double-blind, placebo-controlled cross-over study. In addition to assessing its effect on the classical symptoms of irritable bowel syndrome (abdominal pain, distension and disordered bowel habit) its effect on symptoms often seen in irritable bowel syndrome, but more commonly associated with functional dyspepsia, was also examined.
Results: Ondansetron reduced bowel frequency ($P = 0.035$) and improved stool consistency ($P = 0.002$) in diarrhoea predominant irritable bowel syndrome and did not cause a deterioration of bowel habit in constipation predominant subjects. No statistically significant improvement was seen for abdominal pain or distension, although those patients who did respond were approximately twice as likely to be taking ondansetron than placebo. It was also found that ondansetron significantly improved the upper gastrointestinal symptoms of post-prandial epigastric discomfort ($P = 0.008$), flatulence ($P = 0.022$) and heartburn ($P = 0.003$).
Conclusion: The results of this study justify evaluation of the therapeutic potential of selective 5-HT antagonists in both functional dyspepsia and irritable bowel syndrome.

INTRODUCTION

Neural control of gastrointestinal function is now believed to be mediated by a combination of extrinsic innervation from the autonomic nervous system and via the enteric nervous system at a local level. The enteric nervous system contains large quantities of 5-HT which is thought to be an important neurotransmitter affecting gut function.[1] At least five sub-types of 5-HT receptor have been identified in the gastrointestinal system often with apparently opposing actions.[2,3] One particular subtype, the 5-HT_3 receptor, is widely distributed in the gut at post-synaptic vagal and sympathetic nerve endings as well as within the enteric nervous system.[4] In man, there is evidence to suggest that 5-HT_3 receptor antagonists can increase colonic transport time[5,6] and reduce post-prandial colonic motility as well as increasing rectal pain thresholds to balloon distension in irritable bowel syndrome patients.[7] These properties suggest that this class of drug may have a role in the treatment of irritable bowel syndrome, particularly as the gastrointestinal symptoms of this condition are thought to be related to a combination of disordered motility and altered visceral sensitivity.[8]

It was once believed that the symptoms of irritable bowel syndrome originated solely from the colon. However, it is now clear that many patients complain of 'non-colonic' upper gastrointestinal symptoms similar to functional dyspepsia and furthermore suffer from more

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general features, such as lethargy, urinary symptoms and backache, not obviously connected with the gut.[9] It was the purpose of this study to evaluate the effect of ondansetron, a specific 5-HT_3 antagonist, on the symptoms of irritable bowel syndrome, including both colonic and 'non-colonic' manifestations of the disorder.

MATERIALS AND METHODS

Patients

Fifty patients (11 men and 39 women, age range 22–65 years) entered the study. All patients fulfilled the 'Rome Working Team' guidelines for the diagnosis of irritable bowel syndrome and, in addition, had normal haematological and biochemical indices and no abnormal findings on either barium enema or colonoscopy.[10] The diagnosis of irritable bowel syndrome had been made a median of 48 months (range 8–360 months) prior to study recruitment. At entry into the study, a detailed history of bowel habit was taken to allow separation into diarrhoea (28 subjects) or constipation (20 subjects) predominant sub-groups. Only two of the 50 patients recruited could not be classified into one of these two sub-groups. Written informed consent was obtained and the protocol approved by the South Manchester District Ethics Committee.

Study design

This was a randomized, double-blind, placebo-controlled cross-over study. Trial design consisted of an initial 2-week 'baseline' period followed by two treatment periods of 4 weeks separated by a 2-week 'washout' phase. During the treatment periods patients received ondansetron 4 mg orally three times daily, as ondansetron hydrochloride dihydrate, or matching placebo in random order. No treatment was given during 'baseline' or 'washout' periods. All other medication for irritable bowel syndrome was discontinued before the study.

OUTCOME MEASURES

Primary outcome

Patients' symptoms were assessed by the same clinician at 14-day intervals during the study. The severity of abdominal pain and abdominal distension during the preceding week were scored on a four-point scale, as were the non-colonic symptoms, nausea, heartburn, post-prandial discomfort, flatulence (belching), lethargy, back pain and urinary symptoms (Table 1). Stool consistency was scored on a five-point scale, and the number of bowel actions per day were also recorded (Table 1).

Table 1. Outcome measures

Symptoms	Score
Irritable bowel syndrome symptoms	Scale 0–3
Abdominal pain	None = 0
Abdominal distension	Mild = 1
	Moderate = 2
Non-colonic symptoms	Severe = 3
Post-prandial discomfort	
Heartburn	
Flatulence	
Nausea	
Lethargy	
Backache	
Urinary symptoms—frequency	
—urgency	
—urge incontinence	
Bowel habit	Scale 1–5
Stool consistency	Watery = 1
	Loose = 2
	Formed = 3
	Hard = 4
	Very hard = 5
Bowel actions	Number per day

Additional measures

Patients recorded their bowel habit daily on diary cards using a similar scoring system (Table 1).

Daily dietary fibre intake was assessed and recorded at each visit throughout the study. Patients were also requested not to alter their diet during the study period.

Patient anxiety and depression levels were assessed using the Hospital Anxiety and Depression Scale which was administered at the beginning and end of each treatment period.[11]

STATISTICAL METHODS

The effects of ondansetron and placebo were compared by assessing the data for the week up to day 1 and the week up to day 28 for each treatment period. The data were analysed for the study group as a whole and for the

Table 2. Symptom improvement

Symptoms	Improved on: Ondansetron only	Placebo only	Both	Neither	Relative odds*
Abdominal pain†	11	5	5	26	2.31 N.S.
Abdominal distension	14	8	1	26	1.75 N.S.
Post-prandial discomfort	13	3	9	15	4.49 $P = 0.008$
Flatulence	15	5	6	23	3.03 $P = 0.022$
Heartburn	10	1	7	7	10.58 $P = 0.003$

* Relative odds indicate the likelihood of symptom improvement on ondansetron alone vs. placebo alone.
† Two patients recorded 'none' both on day 1 and day 28. Their data for this symptom have been excluded.
Note: numbers may not add up to 50 (see text).

Table 3. Stool consistency

	Improvement on: Ondansetron only	Placebo only	Both	Neither	Relative odds*
Overall	21	4	3	12	5.38 $P < 0.001$
Diarrhoea	13	2	3	6	8.17 $P < 0.002$
Constipation	7	2	0	6	3.67 N.S.

* Relative odds indicate the likelihood of improvement on ondansetron alone compared with placebo alone.

constipation and diarrhoea predominant sub-groups. Data for improvement in symptom severity and changes in stool consistency recorded at clinic visits were analysed by the same statistical methods. Improvement/change was defined as a shift of at least one grade in the scoring system for symptoms or a change towards normality for stools. The four outcomes (change on ondansetron only, placebo only, change on both or change on neither) were analysed using log-linear models for binary cross-over data.[12] This procedure included the Hills–Armitage test for interaction between treatment and period and Prescott's test for treatment differences.

Estimates of the relative odds for improvement on ondansetron vs. placebo were derived from the log-linear analysis (Tables 2 and 3).

The changes in the average number of bowel actions per day recorded on patient diary cards were analysed using non-parametric methods for the cross-over design study based on Wilcoxon Rank sums (Table 4).[13] The analysis included tests for treatment carry over and period effects. No significant effects were found.

The data for a patient scoring zero for a specific symptom prior to a treatment period were excluded from the analysis for that particular symptom only. Thus, the numbers in Table 2 do not necessarily add up to the total number of patients in the study.

Results are presented as means and standard deviations for data which have an approximate normal distribution (Hospital Anxiety and Depression Scale, dietary fibre) and as medians and ranges for data which have a non-normal distribution (symptom severity, bowel actions, etc.).

Table 4. Bowel actions per day

		Median (interquartile range)		
		Day 1	Day 28	Treatment difference
Overall	Ondansetron	2 (1–3)	1 (1–2)	
	Placebo	1 (1–2)	2 (1–2)	N.S.
Diarrhoea	Ondansetron	2 (1–4)	1 (1–3)	
	Placebo	2 (1–4)	2 (1–3)	$P = 0.035$
Constipation	Ondansetron	1 (1–1.5)	1 (1–2)	
	Placebo	1 (1–1.5)	1 (1–2)	N.S.

RESULTS

Forty-nine of the 50 patients originally randomized completed the study. A single patient was withdrawn after the first treatment period because of incorrect allocation of study medication.

Symptom severity

As can be seen from Table 2 there was no significant effect of ondansetron on either abdominal pain or abdominal distension. However, when an improvement was observed the patient was approximately twice as likely to be taking ondansetron than placebo. No significant differences emerged in either the diarrhoea predominant or constipation predominant sub-group.

In contrast the symptoms for post-prandial discomfort, heartburn and flatulence significantly improved with ondansetron.

All other non-colonic symptoms failed to show any significant differences between ondansetron and placebo, and, therefore, in the interests of clarity the data are not included.

Bowel habit

Tables 3 and 4 summarize the results for changes in stool consistency and bowel frequency.

For the group as a whole ondansetron produced a significant improvement in stool consistency although this was largely accounted for by changes in the diarrhoea predominant subjects (Table 3). With respect to bowel frequency, ondansetron showed no effect in the group overall but significantly reduced the frequency in the diarrhoea predominant group (Table 4). Ondansetron did not have any deleterious effects on the bowel habit of constipation predominant subjects.

Hospital Anxiety and Depression Scale scores

The Hospital Anxiety and Depression Scale scores at baseline, mean (s.d.): anxiety 9.2 (5.2) and depression 5.9 (3.8) did not differ significantly between the two treatment order groups.

There was no significant change after treatment with either ondansetron (mean change: anxiety −0.8, depression 0.1) or placebo (mean change: anxiety 0.2, depression −0.1).

Dietary fibre intake

Dietary fibre intake remained constant between the two treatment periods. The average daily intake varied between 20 and 21 g (s.d. = 8 g).

DISCUSSION

Ondansetron had a clear beneficial effect on the bowel habit in diarrhoea predominant patients. This observation is consistent with a previous report of loose and watery stools improving in subjects with irritable bowel syndrome and diarrhoea during treatment with ondansetron, although this was at the higher dose of 16 mg t.d.s.[6] A likely explanation for this effect of ondansetron on bowel function is an increase in colonic transit time[4,5] which has been reported in both healthy controls[5] and patients with diarrhoea predominant irritable bowel syndrome.[6] Prolonged colonic transit time would allow an increase in water absorption in the colon so hardening stool consistency, but other possible effects of 5-HT_3 antagonists, such as alteration of rectal sensitivity,[7] may also be involved. In our study, no deterioration in bowel habit was reported by those patients with constipation. This is of importance since if this class of drug is going to be used in treating irritable bowel syndrome it is likely to be given to patients with varying bowel habit.

The effect of ondansetron on abdominal pain and

distension was less clear although it should be noted that in a large proportion of patients these symptoms did not respond to either placebo or ondansetron. This is unusual considering the high placebo response rates often reported for symptomatic improvement in irritable bowel syndrome studies,[14] although it is more in accordance with our own observations on the placebo response in irritable bowel syndrome trials.[15] However, it is of interest that when a patient did appear to improve with treatment they were approximately twice as likely to be taking ondansetron than placebo.

The finding that a 5-HT_3 receptor antagonist was helpful in the treatment of symptoms of functional dyspepsia in irritable bowel syndrome patients was unexpected. While upper gastrointestinal endoscopy was not performed on all the patients in the study and therefore an absolute guarantee that no peptic ulcer disease existed cannot be given, the recognized association of functional upper gastrointestinal problems with irritable bowel syndrome makes functional dyspepsia the most likely explanation for their symptoms. The pathophysiology of functional dyspepsia is not well understood and is probably multifactorial. Thus, the mechanism by which ondansetron could be mediating its benefit must remain speculative but could include an effect on gastric emptying,[16] or even a central effect.[17]

Klein has suggested that trials in irritable bowel syndrome should be of a parallel design.[14] However, cross-over studies have the advantages of maximizing placebo–drug differences, allowing a smaller number of patients to be studied, being much less costly and minimizing the problem of variability between patients which is a particular difficulty with irritable bowel syndrome. Furthermore, because they allow smaller numbers to be studied they can be undertaken in single centres which ensures greater homogeneity of recruited patients. Thus, the cross-over design is ideal for a preliminary study,[15] such as this one, aimed at establishing whether a drug has any activity in irritable bowel syndrome provided care is taken to guard against carry-over effects and that the sample size is adequate. When our study was analysed carry-over effect was looked for and ruled out and sample size was ample as indicated by the fact that statistical differences were detected.

Thus, this trial has shown that ondansetron appears to have activity against some of the symptoms of functional bowel disorders suggesting that 5-HT antagonists are worthy of further evaluation for this indication.

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