Aliment Pharmacol Ther 1999; 13: 1437–1444.

5-HT$_4$ receptor antagonism in irritable bowel syndrome: effect of SB-207266-A on rectal sensitivity and small bowel transit

L. A. HOUGHTON, N. A. JACKSON, P. J. WHORWELL & *S. M. COOPER
*Department of Medicine, University Hospital of South Manchester, Manchester, UK; and *SmithKline Beecham Pharmaceuticals, Harlow, UK*

Accepted for publication 27 June 1999

SUMMARY

Background: Pre-clinical studies indicate that the 5-hydroxytryptamine (5-HT)$_4$ receptor may be involved in the pathophysiology of irritable bowel syndrome and that antagonism of this receptor may be an effective therapeutic strategy.
Aim: To investigate the effects of SB-207266-A, a selective 5-HT$_4$ receptor antagonist on rectal sensitivity and small bowel transit in patients with irritable bowel syndrome.
Methods: Eighteen patients with diarrhoea-predominant irritable bowel syndrome and a history of increased rectal sensitivity were randomized to receive either SB-207266-A (20 mg) or placebo for 10 days. Following a washout period, patients were then crossed over to receive the alternative therapy for 10 days. Rectal sensitivity and orocaecal transit time were assessed on day 10 of each treatment period. In addition, patients were asked whether they had experienced any changes in their symptoms.
Results: Fifteen patients completed the study. SB-207266-A significantly increased orocaecal transit time towards normal (placebo: 5.3 h (4.0–7.2 h), mean (IQR) vs. SB-207266-A: 6.5 h (4.8–8.0 h); $P = 0.027$) and tended to decrease rectal sensitivity (volume to discomfort 89 mL (60–150 mL), geometric mean (IQR) vs. 107 mL (75–150 mL); $P = 0.134$). Eleven out of 15 patients reported symptomatic improvements with SB-207266-A but none with placebo. SB-207266-A was well tolerated.
Conclusion: Our results support a role for the 5-HT$_4$ receptor in the pathophysiology of irritable bowel syndrome and suggest that the selective 5-HT$_4$ antagonist, SB-207266-A, is worthy of further evaluation in this disorder.

INTRODUCTION

Irritable bowel syndrome is a common condition characterized by recurrent abdominal pain and disordered bowel function occurring in the absence of any identifiable cause. The mechanisms underlying the symptoms of irritable bowel syndrome are not yet fully understood but there is growing evidence to suggest that the gastrointestinal tract may be abnormally sensitive to normal physiological events. This is based on observations that patients with irritable bowel syndrome often report a reproduction of their typical pain and associated spasm when the sigmoid colon is stretched or distended during endoscopic or radiological examination and have lower sensory thresholds to experimental balloon distension of the gut.[1–7] Although most of these studies have been conducted in the rectum,[1–5] there is evidence to support increased sensitivity to mechanical distension throughout the gastrointestinal tract.[6, 7] The mechanisms underlying this hypersensitivity remain to be elucidated but could involve the enteric, visceral afferent/efferent, spinal and/or central nervous systems.

Correspondence to: Dr L. A. Houghton, Department of Medicine, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 2LR, UK.

Numerous neuroactive substances have been implicated in the induction and maintenance of the visceral hypersensitivity associated with irritable bowel syndrome.[8] Among these, 5-hydroxytryptamine (5-HT) is thought to be a likely contender,[9] acting at least partly via the 5-HT_4 receptor. Thus, although 5-HT_4 receptor antagonism appears to have little or no effect on normal gut function,[10–21] activation of the 5-HT_4 receptor does increase the sensitivity of the peristaltic reflex[16, 17] and evoke chloride secretion[22, 23] in isolated gut preparations. Moreover, 5-HT_4 receptor antagonists have been shown to inhibit the induction of peristaltic activity by 5-HT in conscious dogs[24] and in distal colonic tissue taken from guinea-pigs.[10] In addition, they prevent increases in defecation induced by stress or 5-hydroxytryptophan (5-HTP) in rats[25] and mice[14, 15] and suppress the nociceptor response to colorectal distension in rats in which the colorectum has been irritated with acetic acid,[25] possibly via positive coupling with tetrodotoxin-insensitive Na^+ channels in capsaicin-sensitive unmyelinated neurones.[26] Thus, 5-HT_4 receptor antagonism may have potential in the treatment of functional bowel disorders, such as irritable bowel syndrome.

The primary aim of this study was therefore to assess the effect of a potent, selective, orally active, long-acting 5-HT_4 receptor antagonist, SB-207266-A (N-(1-butyl-4-piperidinylmethyl)-3,4-dihydro-2H-[1,3]-oxazino-[3,2-a]-indole-10-carboxamide hydrochloride), on rectal sensitivity and small bowel transit in patients with diarrhoea-predominant irritable bowel syndrome and a history of rectal hypersensitivity. In addition, a number of anorectal manometric parameters were measured, and a global assessment of symptoms and adverse events experienced was carried out.

METHODS

Patients

Eighteen patients with irritable bowel syndrome (12 male, 6 female) aged 23–67 years (mean age 47 years) were enrolled into the study. All patients had diarrhoea-predominant irritable bowel syndrome, as defined by the Rome criteria,[27] and a clinical history of increased rectal sensitivity, defined as an inability to tolerate a balloon distension volume of more than 125 mL (approximately 1 s.d. below the mean for a departmental non-irritable bowel syndrome population). No patient had co-existent disease and had normal biochemistry, haematology, urinalysis and 12-lead electrocardiography. In addition, all patients had a negative rigid sigmoidoscopy within the previous 24 months, and patients aged 45 years or over had a negative barium enema and/or a negative colonoscopic examination. Female patients were either post-menopausal or surgically sterilized.

With the exception of two patients who continued to take ranitidine and cimetidine for chronic indigestion, none of the patients had taken prescribed medication in the 2 weeks preceding the first dosing day, or had taken over-the-counter medication in the 48 h prior to the first dosing day. All patients drank below the recommended alcohol limit (< 21 units/week or had an average daily intake of less than 3 units), had not participated in a trial of any drug in the 3 months prior to the start of the study, and in the case of male patients did not attempt to father a child in the 3 months following the start of the study. The study was approved by South Manchester Medical Research Ethics Committee and all patients gave written informed consent.

Using estimates of within-subject variation from previous departmental studies of patients with irritable bowel syndrome and healthy volunteers, it was calculated that a sample size of 16 patients would give the study 80% power, at the 5% significance level, to detect a change of 115 mL (approximately 30%) in rectal distension volume to induce 'discomfort' and a change of 81 min in orocaecal transit.

Protocol design

The study was conducted as a double-blind, placebo-controlled, randomized trial with a two-part crossover, repeat-dose design. Patients were randomized to receive either 20 mg of SB-207266-A or placebo orally once daily for 10 days. Following a washout period of at least 14 days, patients were then crossed over to receive the alternative therapy for a further 10 days.

On day 10 of each treatment period, rectal sensitivity and anorectal motility to balloon distension and orocaecal transit were assessed. In addition, during each treatment period, patients were prompted for information on adverse experiences.

Rectal sensitivity and anorectal motility to balloon distension. On the morning of the study, the patients were placed in the left lateral position and a narrow

multi-lumen polyvinyl catheter (4 mm outer diameter, Arndorfer Medical Specialities Inc., Greendale, WI) was inserted into the rectum and positioned with two side holes in the rectum (4.5 and 15.0 cm from the anal verge) and three side holes in the anal sphincter (0.5, 1.0 and 2.0 cm from the anal verge). Although the catheter was narrow and flexible, it was sufficiently stiff to prevent kinking and acute bending during manual passage through the anus and correct positioning in the rectum. Each side hole was perfused with distilled water at a rate of 0.2 mL/min (Arndorfer Medical Specialities Inc.) and connected via water-filled transducers to a polygraph recorder and visual display unit (Synectics Medical, Stockholm, Sweden). A 6 cm length of distensible latex tubing was tied to the catheter between 5 and 11 cm from the anal verge and used to distend the rectum. The pressure within the balloon was monitored using a water-filled non-perfused channel situated 8 cm from the anal verge. After a 10 min rest period, the rectal balloon was serially inflated with air at 10, 20, 40, 60, 80, 100 mL, and then in 25 mL increments until the patient experienced discomfort. Each inflation was maintained for 1 min and was separated by at least 1 min, during which the balloon was totally deflated. During the procedure, the patients were asked to mark on a standard form the nature of any sensations felt (e.g. open bowels, urgency and discomfort). Although the patients were informed of the nature of sensations they might experience at the beginning of the study, they were not aware of the timing of the balloon distensions or prompted about the sensations during the studies.

Small bowel transit. Following the rectal sensitivity and anorectal motility assessment, orocaecal transit of a physiological test meal was evaluated. This was measured as the time from ingestion of a standard meal of three Frankfurter sausages, 60 g of mashed potato and 120 g of baked beans (consumed within 5 min with 50 mL water) to an increase in breath hydrogen of at least 10 ppm sustained for 30 min. Breath hydrogen was measured using a modified Haldane–Priestley tube[28] and baseline breath hydrogen was defined as the median value of five consecutive readings all within a 5 ppm range.

Symptom assessment. In order to assess any general change in irritable bowel syndrome symptomatology during a treatment period, a global evaluation was made at the first visit and repeated daily by telephone on days 2–9 and in person on day 10. At the same time any adverse events were recorded as well as being documented hourly (up to 4 h after dosing) on the first day of dosing for each treatment period.

Safety assessments. Laboratory assessments of haematology, clinical chemistry and urine chemistry were carried out pre-study, before dosing on day 1 and approximately 2 h after dosing on day 10 of each treatment period, and at follow-up.

Blood pressure and pulse rate were measured pre-study, before and 1, 2, 3 and 4 h after dosing on day 1 of each treatment period, 4 h after dosing on day 10 of each period, and at follow-up. 12-lead ECG was performed pre-study, before and 4 h after dosing on day 1 of each treatment period, approximately 2 h after dosing on day 10 of each period, and at follow-up.

Data analysis

The following measurements were derived from the rectal distension study: the lowest balloon volumes to induce the sensations of 'open bowels or desire to defecate', 'urgency' and 'discomfort'; the compliance of the rectum (calculated from the volume:pressure relationship at 60 mL distension); low and high rectal motility indices (calculated by measuring the areas under the rectal pressure profiles obtained 4.5 and 15 cm, respectively, from the anal verge while the balloon was inflated to a volume of 60 mL); basal anal pressure; and the lowest distension volumes required to induce relaxation of the internal anal sphincter (IAS) and to cause sustained relaxation throughout the period of distension. In addition, orocaecal transit time from breath hydrogen values was measured as described above.

Statistical analysis

Patients were entered into the statistical analysis for a given variable only if they had evaluable data for that variable from both treatment periods. Comparisons between treatments were made by means of analysis of variance (ANOVA), which was used to calculate *P*-values and also to generate point estimates and 95% confidence intervals either for the ratio between values obtained with SB-207266-A and those obtained with placebo (in the case of the rectal distension volumes to induce the sensations of 'open bowels',

'urgency' and 'discomfort', and the anorectal motility variables), or for the difference between values obtained with SB-207266-A and those obtained with placebo (in the case of orocaecal transit time).

RESULTS

Of the 18 patients enrolled into the study, one withdrew before the start of dosing for personal reasons. A further two patients withdrew at the end of their first period of treatment, again for personal reasons. The remaining 15 patients (aged 34–67 years; 4 female) finished both treatment periods and attended the follow-up assessment, and were therefore considered to have completed the study.

Orocaecal transit

Orocaecal transit time was significantly increased from the relatively fast time of 5.3 h under control conditions to a more normal time of 6.5 h after SB-207266-A ($P = 0.027$) (Figure 1, Table 1).

Rectal sensitivity and anorectal motility

Although SB-207266-A increased the distension volume required to induce the sensation of 'discomfort' by approximately 20% compared with placebo, this difference did not reach statistical significance ($P = 0.13$) (Figure 2, Table 1). Likewise, there were no significant differences in the volumes required to induce the sensations of 'open bowels' ($P = 0.46$) or 'urgency' ($P = 0.94$) between SB-207266-A and placebo administration (Figure 2, Table 1).

Examination of Figure 2, however, shows that four patients had become 'normo-sensitive' (represented by broken lines) by the time of randomization (although all patients were rectally sensitive before enrolment into the study). Interestingly, retrospective analysis of the remaining 11 'sensitive' patients showed that eight exhibited a reduction in rectal sensitivity after SB-207266-A compared with placebo administration.

SB-207266-A appeared to have no significant effect on any of the other anorectal motility parameters measured (Table 1).

Symptoms and adverse experiences

Of the 15 patients who completed the study, 11 reported a global improvement in their irritable bowel syndrome symptoms following treatment with SB-207266-A but not following treatment with placebo. One patient reported an improvement with placebo but not with SB-207266-A, and two reported improvements with both treatments. The remaining patient reported a mild exacerbation of symptoms with both SB-207266-A and placebo.

The main improvements in symptoms reported by the patients receiving SB-207266-A were an increase in the firmness of stools, a decrease in the frequency of bowel movements, and reductions in abdominal pain and bloating.

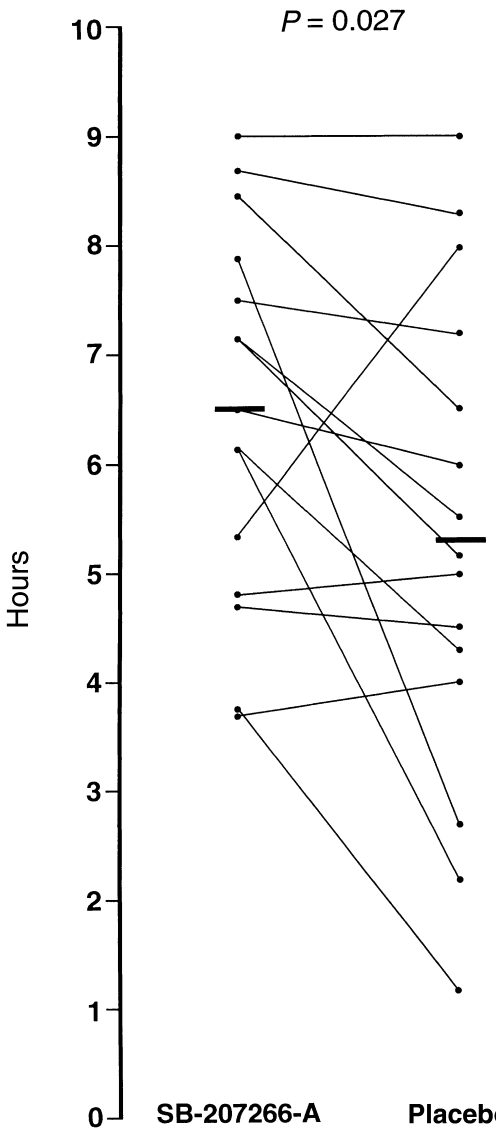

Figure 1. Effect of SB-207266-A on orocaecal transit time. Bars represent the means.

Table 1. Effect of SB-207266-A on rectal sensitivity and anorectal motility to balloon distension and orocaecal transit time

	SB-207266-A	Placebo	*P*-value
*Oroceacal transit time (h)**	6.5 (4.8–8.0)	5.3 (4.0–7.2)	
	Difference	1.11 (0.15–2.08)	0.027
Rectal sensation (mL):			
Open bowels	40 (20–65)	35 (20–60)	
	Ratio	1.12 (0.81–1.57)	0.46
Urgency	75 (40–100)	74 (40–150)	
	Ratio	1.01 (0.71–1.36)	0.94
Discomfort	107 (75–150)	89 (60–150)	
	Ratio	1.20 (0.94–1.54)	0.134
Anorectal motility:			
Compliance (mL/cm H_2O)	7.58 (4.5–12.3)	8.04 (3.5–19.1)	
	Ratio	0.94 (0.45–1.98)	0.864
Rectal motility index (low)	112 (145–372)	262 (161–433)	
	Ratio	0.43 (0.11–1.66)	0.190
Rectal motility index (high)	200 (113–278)	211 (84–404)	
	Ratio	0.95 (0.49–1.85)	0.867
Basal anal pressure (mmHg)	74 (68–86)	73 (63–82)	
	Ratio	1.01 (0.92–1.11)	0.811
Initial IAS relaxation (mL)	12 (10–20)	13 (10–20)	
	Ratio	0.92 (0.68–1.23)	0.536
Sustained IAS relaxation (mL)	101 (70–156)	96 (55–156)	
	Ratio	1.05 (0.65–1.70)	0.796

Data expressed as geometric mean or *mean plus IQR. Data in brackets for 'ratio' and 'difference' values represents the 95% CI.

No serious adverse experiences were reported during the study, and there were no withdrawals because of adverse experiences. A summary of the adverse experiences reported by more than one patient is given in Table 2. Furthermore, no clinically significant changes occurred in vital signs, laboratory variables or 12-lead ECG data.

Relationship between sensory thresholds and symptoms

Of the 11 'sensitive' patients, 10 reported an improvement in symptoms, whilst of the four 'normo-sensitive' irritable bowel syndrome patients, three were non-responders to SB-207266-A.

DISCUSSION

The results of this study show that the selective 5-HT_4 receptor antagonist, SB-207266-A, significantly increased orocaecal transit time towards normal values and tended to decrease rectal sensitivity in a group of patients with diarrhoea-predominant irritable bowel syndrome and a history of rectal hypersensitivity. In addition, 11 of 15 patients reported an improvement in symptoms with SB-207266-A but not with placebo, and treatment with SB-207266-A was well tolerated.

The modest nature of the effect of SB-207266-A on rectal sensitivity may have been due, at least in part, to the fact that four of the patients enrolled into the study had become 'normo-sensitive' by the time of randomization. If these patients are excluded from the analysis, the effect of SB-207266-A becomes much more marked, as eight of the remaining 11 patients exhibited an increase in the sensory threshold for discomfort. Furthermore, 10 of these 'hypersensitive' patients reported a symptomatic improvement with SB-207266-A but not with placebo. It is interesting to note that three of the four 'normo-sensitive' patients under control

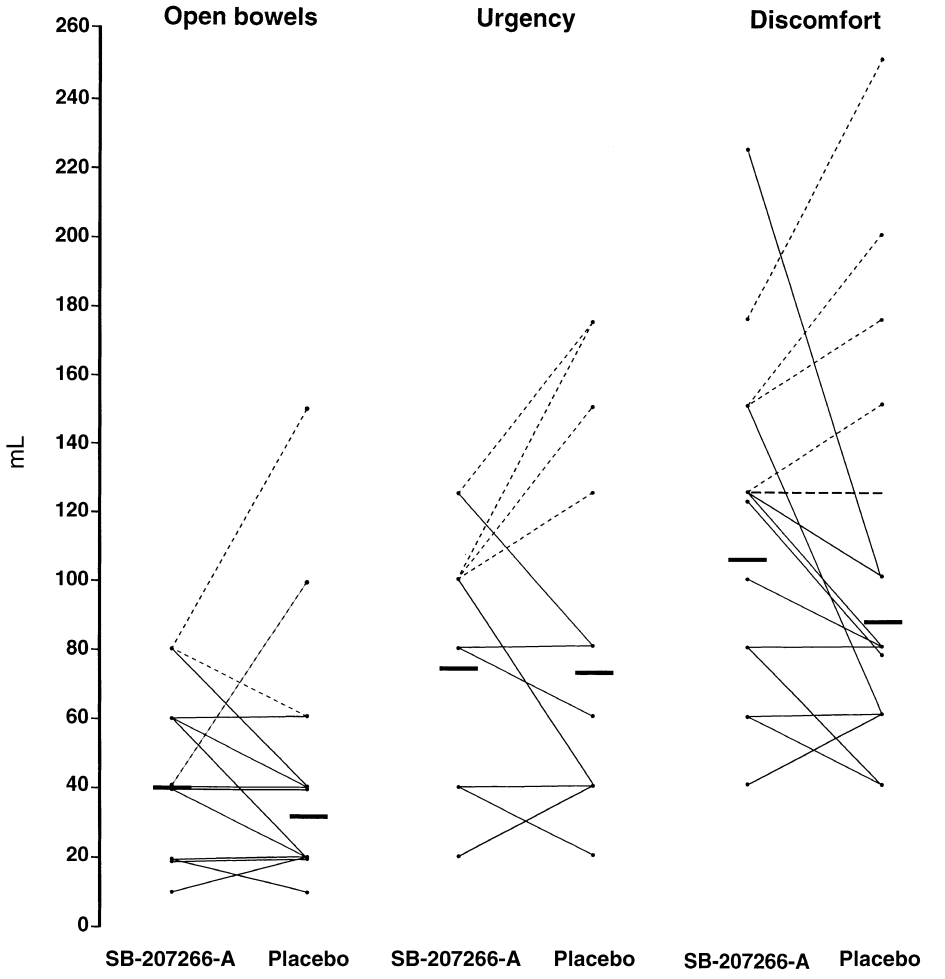

Figure 2. Effect of SB-207266-A on the balloon distension threshold of 'open bowels', 'urgency' and 'discomfort'. Bars represent the geometric means. Horizontal broken line at 125 mL represents the mean minus 1 s.d. for the departmental control range for the threshold to discomfort.

conditions were non-responders to SB-207266-A. These observations, together with the apparent 'normalization' in orocaecal transit with SB-207266-A, may suggest that this drug acts to normalize abnormal gut function rather than interfering with basal activity.

Table 2. Adverse experiences reported by more than one patient. Figures are the numbers of patients reporting each experience during each treatment

Adverse experience	SB-207266-A	Placebo
Headache	7	7
Constipation	3	—
Diarrhoea	1	2
Tenesmus	—	2
Coughing	1	2
Upper respiratory tract infection	2	2
Infection (viral)	1	1
A feeling of something present in rectum	1	1
Anal soreness	1	1
Abdominal pain	1	1
Fatigue	1	1

Indeed the majority of studies conducted to date have shown that this and other 5-HT_4 antagonists appear to have little or no effect on normal gut function. For example, they have been reported not to affect gastric[10] or colonic[11] motility in the dog, small intestinal motility in the rat,[12] gastrointestinal myoelectric activity in sheep[13] or defecation rate of mice.[14, 15] Furthermore, they do not appear to affect the normal peristaltic reflex[16–19] or the ascending and descending neural reflexes[20] in response to distension. A recent study in healthy man has also shown SB-207266-A to have no effect on gastric emptying, small bowel transit, pre- and postprandial colonic tone, colonic compliance or sensitivity to distension, although it may slightly delay colonic transit.[21] Thus, it appears that in general, the effects of 5-HT_4 antagonism only become apparent in either pathophysiological conditions or when

exogenous 5-HT is present in the system (see Introduction[14, 15, 24, 25]). With respect to the latter, it is interesting to note that plasma 5-HT concentrations are elevated after meals in patients with diarrhoea-predominant irritable bowel syndrome compared with healthy controls,[29] which is when most patients report that their symptoms are worse.

The precise mode of action of SB-207266-A in irritable bowel syndrome remains to be elucidated. However, studies have shown that 5-HT$_4$ receptors are present throughout the gut and are associated with the enteric nervous system's AH (sensory) and S (inter- and motor) neurones, which when activated (e.g. with the abnormally high concentrations of 5-HT reported in irritable bowel syndrome) lead to long-term sensitization of the mechanisms regulating neurotransmitter release.[9, 30, 31] This results in an increased responsivity of the gut to mechanical and other stimuli,[9] a phenomenon often associated with irritable bowel syndrome. It therefore seems likely that SB-207266-A exerts its effects primarily by inhibiting this mechanism.

The recent Rome Working Partly recommendations on the conduct of clinical trials in functional bowel disorders[32] has suggested that a primary outcome measure based on more global features may be preferable to trying to score individual symptoms. Although our study was not intended to be a clinical trial, the opportunity was taken to record any symptom changes in a global manner. It is therefore interesting to note that the majority of patients did report an improvement with SB-207266-A when questioned in this way.

In conclusion, these data add further support to 5-HT and, more specifically, the 5-HT$_4$ receptor, playing an important role in the pathophysiology of irritable bowel syndrome. In addition, they suggest that this compound is worthy of further evaluation, and if successful, would represent the first attempt to treat this disorder by actually desensitizing the bowel rather than by suppressing its function.

ACKNOWLEDGEMENTS

Financial support for this study was provided by SmithKline Beecham Pharmaceuticals, Harlow, UK.

REFERENCES

1 Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973; 14: 125–32.
2 Prior A, Sorial E, Sun WM, Read NW. Irritable bowel syndrome: difference between patients who show rectal sensitivity and those who do not. Eur J Gastroenterol Hepatol 1993; 5: 343–9.
3 Whitehead WE, Holtkotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, Shabsin HS, Schuster MM. Tolerance for rectosigmoid distension in irritable bowel syndrome. Gastroenterology 1990; 98: 1187–92.
4 Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995; 109: 40–52.
5 Mayer EA, Munakata J, Mertz H, Lembo T, Bernstein CN. Visceral hyperalgesia and irritable bowel syndrome. In: Gebhert GF, ed. Visceral Pain, Progress in Pain Research and Management, Vol. 5. Seattle: IASP Press, 429–68.
6 Timble KC, Farouk R, Pryde A, Douglas S, Heading RC. Heightened visceral sensation in functional gastrointestinal disease is not site specific. Evidence for a generalised disorder of gut sensitivity. Dig Dis Sci 1995; 40: 1607–13.
7 Francis CY, Houghton LA, Whorwell PJ, Morris J. Enhanced sensitivity of the whole gut in patients with irritable bowel syndrome. Gastroenterology 1995; 108: A601 (Abstract).
8 Sanger GJ. Hypersensitivity and hyperreactivity in the irritable bowel syndrome: an opportunity for drug discovery. Dig Dis Sci 1999, in press.
9 Sanger GJ. 5-Hydroxytryptamine and functional bowel disorders. Neurogastroenterol Motil 1996; 8: 319–31.
10 Wardle KA, Bingham S, Ellis ES, Gaster LM, Rushant B, Smith MI, Sanger GJ. Selective and functional 5-hydroxytryptamine$_4$ receptor antagonism by SB-207266. Br J Pharmacol 1996; 118: 665–70.
11 Nagakura Y, Kamato T, Nishida A, Ito H, Yamano M, Miuyata K. Characterization of 5-hydroxytryptamine (5-HT) receptor subtypes influencing colonic motility in conscious dogs. Naunyn-Schmiedebergs Arch Pharmacol 1996; 353: 489–98.
12 Clayton NM, Gale JD. 5-HT$_4$ receptors are not involved in the control of small intestinal transit in the fasted, conscious rat. Neurogastroenterol Motil 1996; 8: 1–8.
13 Plaza MA, Arruebo MP, Murillo MD. Evidence for the involvement of 5-HT$_4$ receptors in the 5-hydroxytryptamine-induced pattern of migrating myoelectric complex in sheep. Br J Pharmacol 1997; 120: 1144–50.
14 Banner SE, Smith MI, Bywater D, Gaster LM, Sanger GJ. Increased defaecation caused by 5-HT$_4$ receptor activation in the mouse. Eur J Pharmacol 1996; 308: 181–6.
15 Hedge SS, Moy TM, Perry MR, Loeb M, Eglen RM. Evidence for the involvement of 5-hydroxytryptamine 4 receptors in 5-hydroxytryptamine-induced diarrhea in mice. J Pharmacol Exp Ther 1994; 271: 741–7.
16 Craig DA, Clarke DE. Peristalsis evoked by 5-HT and renzapride: evidence for putative 5-HT$_4$ receptor activation. Br J Pharmacol 1991; 102: 563–4.
17 Costall B, Naylor RJ, Tuladhar BR. 5-HT$_4$ receptor mediated facilitation of the emptying phase of the peristaltic reflex in the guinea-pig isolated ileum. Br J Pharmacol 1993; 110: 1572–8.
18 McLean PG, Coupar IM. 5-HT$_4$ receptor antagonist affinities of SB-207710, SB-205008 and SB-203186 in the human

colon, rat oesophagus and guinea-pig ileum peristaltic reflex. Naunyn-Schmiedeberg's Arch Pharmacol 1995; 352: 132–40.
19 Sanger GJ, Smith MI, Wardle KA, Banner SE. SB-207266; 5-HT_4 receptor antagonism in human isolated gut and prevention of 5-HT-evoked sensitisation of peristalsis and increased defaecation in animal models. Neurogastroenterol Motil 1998; 10: 271–9.
20 Yuan SY, Bornstein JC, Furness JB. Investigation of the role of 5-HT_3 and 5-HT_4 receptors in ascending and descending reflexes to the circular muscle of guinea-pig small intestine. Br J Pharmacol 1994; 112: 1095–100.
21 Bharucha AE, Camilleri M, Ferber I, Zinsmeister AR. Effects of serotonin (5-HT_4) receptor antagonist on gastrointestinal (GI) transit, colonic motor and sensory function in health. Gastroenterology 1999; 16: G4170 (Abstract).
22 Moore BA, Sharkey KA, Mantle M. Role of 5-HT in cholera toxin-induced mucin secretion in the rat small intestine. Am J Physiol 1996; 270: G1001–9.
23 Kellum JM, Budhoo MR, Siriwardena AK, Smith EP, Jebraili SA. Serotonin induces Cl^- secretion in human jejunal mucosa *in vitro* via a non-neuronal pathway at a 5-HT_4 receptor. Am J Physiol 1994; 267: G357–63.
24 Bingham S, King BF, Rushart R, Smith MI, Gaster L, Sanger GJ. Antagonism by SB-204070 of 5-HT-evoked contractions in the dog stomach: an *in vivo* model of 5-HT_4 receptor function. J Pharm Pharmacol 1995; 47: 219–22.
25 Pichat P, Baudot X, Lechevalier P, Angel I. Inhibition by 5-HT_3 and 5-HT_4 antagonists of stress-induced colonic dysfunction and visceral pain in the rat. Gastroenterology 1996; 110: A735 (Abstract).
26 Cardenas CG, Del Mar LP, Cooper BY, Scroggs RS. 5-HT_4 receptors couple positively to tetrodotoxin-insensitive sodium channels in a subpopulation of capsaicin-sensitive rat sensory neurons. J Neurosci 1997; 17: 7181–9.
27 Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. Gastroenterol Int 1992; 5: 75–91.
28 Levitt MD. Production and excretion of hydrogen gas in man. N Engl J Med 1969; 28: 122–7.
29 Bearcroft CP, Perrett D, Farthing MJG. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. Gut 1998; 42: 42–6.
30 Sanger GJ, Gaster LM. 5-HT_4 receptor antagonists. Exp Opin Ther Patents 1994; 4: 1.
31 Ford APDW, Clarke DE. The 5-HT_4 receptor. Med Res Rev 1993; 13: 633–62.
32 Van Zanten S, Talley N, Whorwell PJ, *et al*. Design of treatment trials on functional gastrointestinal disorders. Gut (Suppl.) 1999, in press.