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Alosetron, a 5-HT$_3$ receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers

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SUMMARY

Background: Alosetron is a potent and selective 5-HT$_3$ receptor antagonist, which has been shown to be beneficial in the treatment of female patients with non-constipated irritable bowel syndrome.

Aims: To investigate the effect of alosetron on whole gut, small bowel and colonic transit in patients with irritable bowel syndrome (Study 1) and healthy volunteers (Study 2).

Subjects: Thirteen patients with irritable bowel syndrome and 12 healthy volunteers.

Methods: Both studies were randomized, double-blind, placebo-controlled with a two-way crossover design, in which each subject received alosetron (2 mg b.d. administered orally) or placebo for 8 days. Mean whole gut transit was determined from the excretion of radiopaque markers; small bowel transit was determined from rise in breath hydrogen after a meal; and colonic transit and segmental transit were evaluated from abdominal X-ray. In addition, colonic transit was calculated by subtracting small bowel transit time from whole gut transit time.

Results: Alosetron increased colonic transit time by prolonging left colonic transit in both patients with irritable bowel syndrome and controls. This resulted in a tendency for the whole gut transit to be delayed in irritable bowel syndrome patients ($P = 0.128$), which was confirmed in controls ($P = 0.047$).

Conclusion: Alosetron delays colonic transit by prolonging left colonic transit. These results add to the body of evidence suggesting that alosetron should have a therapeutic role in patients with non-constipated irritable bowel syndrome.

INTRODUCTION

Irritable bowel syndrome is a common and distressing functional gastrointestinal disorder that affects 10–20% of adults at any one time and accounts for up to half of a gastroenterologist's workload.[1–4] Despite its prevalence, current therapy is unsatisfactory and many patients are refractory to treatment. Lack of adequate treatment to date has been mainly due to a poor knowledge of the aetiology and pathophysiology of irritable bowel syndrome. However, recent advances have suggested that it may be caused by a dysregulation of central/enteric nervous system function leading to abnormalities in the visceral sensitivity of the gut.[5, 6] This sensory dysfunction might result in even normal physiological events, such as contractions of the gut, being sensed abnormally. The dysfunction may also trigger a number of inappropriate reflexes which alter gastrointestinal motility, secretion and absorption, thus causing the wide variety of symptoms so often associated with this condition.[7] For instance, some irritable bowel syndrome patients with loose bowels have been shown to have accelerated transit through the small and large bowel.[8]

The mechanisms underlying sensory and motor dysfunction are unclear, but there is evidence that 5-hydroxytryptamine (5-HT) acting through the 5-HT

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type 3 (5-HT_3) receptor may play an important role.[9] For example, the 5-HT_3 receptor antagonist, granisetron has been shown to reduce rectal sensitivity and the motor response to a meal in patients with irritable bowel syndrome.[10] Ondansetron, another 5-HT_3 antagonist, increases rectal compliance and colonic transit time, and improves stool consistency in patients with irritable bowel syndrome.[11–14] More recently, alosetron, a potent selective 5-HT_3 receptor antagonist, has been shown to increase colonic compliance and the distension volume required to induce pain in irritable bowel syndrome patients.[15] Furthermore, alosetron has been shown to reduce abdominal pain and improve bowel function in female patients with non-constipated irritable bowel syndrome.[16–18]

It was the purpose of this study to investigate the effect of alosetron (2 mg b.d. administered orally) on whole gut, small bowel and colonic transit in both patients with irritable bowel syndrome (Study 1) and healthy volunteers (Study 2).

MATERIALS AND METHODS

Subjects

Study one (S3BB2006). Thirteen patients with irritable bowel syndrome (nine female, four male) aged 23–56 years (mean age 40.2 years) were enrolled. All patients were diagnosed according to the Rome I Criteria and had been suffering from symptoms for at least 6 months, with symptoms occurring on at least 3 days in each of the 4 weeks before the study.[19] No patient had coexistent disease and all had normal biochemistry, haematology, urinalysis, stool culture, and if aged over 40 years and presenting for the first time with irritable bowel syndrome, normal barium enema or colonoscopy. Patients were excluded if they: had severe constipation (one or less bowel movement per week); a history of gastrointestinal surgery (other than appendicectomy, cholecystectomy and hiatus hernia repair); had gastrointestinal symptoms related to or exacerbated by the consumption of milk or milk products; or were taking drugs that might modify gastrointestinal function, such as analgesic medication, tranquillizers or antidepressents. Female patients were also excluded if they were pregnant or breast feeding, and females of child bearing potential had to be taking adequate contraceptive measures (if on oral contraceptives, these must have been taken for at least 3 months prior to entry into the study). With the exception of bulking agents and lactulose, on which the patients had to have been stabilized, all other medication for irritable bowel syndrome together with caffeine containing drinks were stopped 48 h before the study. All patients drank below the recommended alcohol limit (< 21 units/week), smoked < 5 cigarettes per day, and had not participated in a trial of any drug within the previous 30 days or during the study. Moreover, they were also asked to abstain from smoking from midnight on study day 5 and all patients were asked to maintain their usual diet throughout the study.

Study two (S3BB2005). Twelve healthy male volunteers, aged 20–37 years (mean 24.4 years) were enrolled. All volunteers had normal laboratory investigations (see Study 1) plus negative drug abuse testing. Restrictions on medication, alcohol, caffeine and cigarettes were as above. However, volunteers were not allowed to have participated in a drug trial within the previous 4 months or during this study.

The studies were approved by South Manchester Medical Research Ethics Committee and all subjects gave written informed consent.

Study design and procedure

Both studies were single-centre, randomized, double-blind, placebo-controlled and two-way crossover in design. Each subject was randomized to receive either alosetron 2 mg b.d. or placebo (at 09.00 hours and 21.00 hours) for 8 days.[16] Following a washout period of at least 3 weeks, subjects were crossed over to receive the alternative treatment for a further 8 days.

On the first day of each treatment period subjects attended the Clinical Investigation Laboratory between 09.30 and 10.00 hours and were issued with their first study medication for days 1–4 and three different shapes of radio-opaque polythene markers (24 of each). The three types of markers were cut from polythene tubing (Portex Ltd, Hythe, Kent, UK) to be cylinders of identical mass and were used to measure whole gut transit time and segmental colonic transit using the method of Metcalf *et al.* (see below.)[20] The external and internal diameters, and lengths of the cylinders were $4.5 \times 3.0 \times 1.3$ mm (marker 1), $3.0 \times 2.0 \times 3.0$ mm (marker 2) and $2.0 \times 1.0 \times 5.0$ mm (marker 3). The subjects ingested the morning dose with 100 mL of water whilst in the laboratory and were instructed to

take the next medication at 21.00 hours, and then at 09.00 hours and 21.00 hours on the following 3 days. They were also instructed to swallow the first 24 markers (marker 1) on day 2, the second 24 markers (marker 2) on day 3 and the third 24 markers (marker 3) on day 4 with 100 mL of water at 10.30 hours each morning (i.e. one and a half hours after taking the morning dose of study medication). Finally, the subjects were issued with stool collection kits consisting of air-tight opaque containers, collection bags and toilet supports for the collection bags, and their use explained.[21] Subjects were asked to collect their stools over the next 4 days (days 2–5) and label each stool sample with the time and date of collection.

On day 5, fasted subjects re-visited the laboratory between 09.00 hours and 09.30 hours and brought with them all stools collected since day 1. They were given the day 5 study medication with 100 mL of water and a plain abdominal X-ray was taken for assessment of colonic segmentation of the polythene markers. One and a half hours after dosing, the subjects ingested a solid test meal consisting of three sausages, 60 g mashed potato and 120 g of baked beans within 5 min with 50 mL water. The baked beans acted as a source of unabsorbable carbohydrate for the hydrogen breath test (see below) which measures mouth to caecum transit. At the end of day 5, subjects were issued with further study medication (days 6–8), stool collection containers and bags for the next 3 days, and told to bring the stool samples to the laboratory on day 9.

Mouth to caecum transit. Mouth to caecum transit for the head of the meal was determined by breath hydrogen analysis using a method similar to Levitt.[22] End expiratory breath samples were taken before ingestion of the solid meal and at 10-min intervals thereafter. Breath hydrogen content was determined using a breath hydrogen monitor containing an electrochemical detector. A rise in breath hydrogen of 3 p.p.m. sustained for 30 min was considered to mark the time when the head of the meal reached the caecum.

Whole gut transit. The mean whole gut transit of each of the three markers (or mean mouth-to-anus transit) was calculated from the number and time of excretion for each marker using the formula described by Hinton *et al.*[21] The numbers and types of each polythene marker were determined by radiography of the stool samples. The average mean whole gut transit time was calculated from these three measurements using the following equation:

$$\frac{\left(\sum_{i=1}^{n} x_i t_{xi} / \sum_{i=1}^{n} x_i\right) + \left(\sum_{i=1}^{n} y_i t_{yi} / \sum_{i=1}^{n} y_i\right) + \left(\sum_{i=1}^{n} z_i t_{zi} / \sum_{i=1}^{n} z_i\right)}{3},$$

where t is the time from ingestion of markers to defaecation, x is the number of markers from day 2 passed at time t_x, y is the number of markers from day 3 passed at time t_y, z is the number of markers from day 4 passed at time t_z and n is the number of stools.[20]

Colonic transit (CT). This was calculated in two ways: (i) CT1, by subtracting the mouth to caecum transit time from the average mean whole gut transit time; and (ii) CT2, from the equation of Metcalf *et al.* for calculating the mean colonic transit from the three radio-opaque polythene markers on a single abdominal X-ray.[20]

Segmental colonic transit. The transit time for the right, left and rectosigmoid colon was calculated using the second colonic transit time equation (CT2) for each of the three sections of the colon.

Safety assessments

Laboratory assessments of haematology, clinical chemistry and urine chemistry together with blood pressure and pulse rate were carried out pre-study, day 1, day 9 and post-study. In addition, a full physical examination was performed pre- and post-study, and adverse events were recorded at each visit.

Statistical analysis

Non-parametric methods (Wilcoxon rank-sum tests) appropriate for a two-period crossover design of study were used to analyse the data.[23] For each efficacy parameter analysed, medians and ranges are presented along with a point estimate (median) of the treatment difference and the corresponding 95% confidence interval.[24]

The analyses were based on subjects with data for both periods, and a test for any carry-over effect was included. In the event that significant carry-over effects were found data were analysed for the first treatment period only.

Table 1. Effect of alosetron on transit parameters in patients with irritable bowel syndrome (Study 1)

	Placebo	Alosetron	*P*
WGT (marker 1; h)	67.5 (20.6, 124.7)	81.9 (13.9, 158.8)	0.093
WGT (marker 2; h)	66.6 (16.3, 137.4)	72.8 (23.8, 144.0)	0.066
WGT (marker 3; h)	51.9 (15.9, 119.3)	54.1 (13.3, 120.0)	0.471
MWGT (h)	58.9 (17.8, 113.8)	72.2 (20.0, 140.9)	0.128
SBT (min)	335.0 (190.0, 490.0)	330.0 (200.0, 510.0)	0.513
CT1 (h)	53.2 (13.0, 107.6)	64.2 (15.5, 135.6)	0.036
CT2 (h)	37.5 (1.0, 67.0)	49.0 (1.0, 72.0)	0.065
LCT (h)	11.5 (0, 23.0)	22.5 (0, 52.0)	0.006
RCT (h)	7.0 (1.0, 23.0)	6.5 (0, 31.0)	0.571
RST (h)	8.0 (0, 24.0)	4.5 (0, 23.0)	0.378

Results expressed as median (range).
WGT = whole gut transit, MWGT = mean whole gut transit, SBT = small bowel transit, CT1 = colonic transit, calculated by subtracting mouth to caecum transit time from the average mean whole gut transit, CT2 = colonic transit, calculated from the equation of Metcalf *et al.*,[20] LCT = left colonic transit, RCT = right colonic transit, RST = rectosigmoid transit.

RESULTS

Of the 13 patients with irritable bowel syndrome who entered Study 1, one withdrew after the first treatment period through personal choice and of the 12 healthy volunteers who entered Study 2, one failed to return for the second treatment period.

Study one—effect of alosetron in patients with irritable bowel syndrome

The average mean whole gut transit time was higher with alosetron compared with placebo, although this difference was not statistically significant (difference from placebo, 10.25 h; 95% CI, –3.9, 29.7 h; $P = 0.128$; Table 1). The difference from placebo in mean whole gut transit time for the individual markers was 13.0 h (–2.9, 41.0 h; $P = 0.093$) for marker 1, 11.1 h (–15.6, 24.5 h; $P = 0.066$) for marker 2 and 7.4 h (–20.5, 25.0 h; $P = 0.471$) for marker 3 (Table 1).

Examination of the transit times though the various regions of the gastrointestinal tract showed that alosetron increased colonic transit time (difference from placebo, CT1: 14.9 h [1.3, 29.4 h], $P = 0.036$; CT2: 11.5 h [–0.5, 17.0 h], $P = 0.065$), but had no effect on mouth to caecum transit time (7.5 min [–50.0, 115.0 min]; $P = 0.513$; Table 1). The delay in colonic transit appeared to be related to a highly statistically significant increase in left (14.5 h [4.0, 24.0 h]; $P = 0.006$) but not right (–0.8 h [–4.0, 2.0 h]; $P = 0.571$) or rectosigmoid (–4.8 h [–12.5, 5.5 h]; $P = 0.378$) colonic transit time (Table 1).

Study two—effect of alosetron in healthy volunteers

The average mean whole gut transit time was increased by alosetron compared with placebo (difference from placebo, 8.9 h [3.1, 16.0 h]; $P = 0.047$). The difference from placebo in mean whole gut transit time for the individual markers was 13.6 h (1.1, 24.7 h; $P = 0.047$) for marker 1, 15.8 h (3.2, 22.1 h; $P = 0.017$) for marker 2, and –0.3 h (–11.0, 8.3 h; $P = 0.917$) (Table 2). It must be noted, however, that unlike the patient data, there was evidence of a carry-over effect for markers 2 ($P = 0.047$) and 3 ($P = 0.047$; Table 3), and because of this a first treatment period only analysis was performed. This still showed that the transit of marker 2 ($P = 0.011$) but not marker 3 ($P = 0.144$) was delayed by the administration of alosetron (Table 4).

Alosetron also increased colonic transit time in healthy volunteers, as measured by CT1 (difference from placebo, 8.1 h [1.5, 16.6 h]; $P = 0.028$) but not CT2 (6.8 h [–8.0, 14.0 h]; $P = 0.201$; Table 2). Furthermore, alosetron appeared to have no significant effect on left (8.0 h [3.0, 13.0 h]; $P = 0.617$), right (–0.8 h [–7.5, 8.0 h]; $P = 0.579$) or rectosigmoid (–0.5 h [–12.0, 10.0 h]; $P = 0.927$) colonic transit time, or on mouth to caecum transit time (–10.0 min [–95.0, 90.0 min]; $P = 0.855$) in healthy volunteers (Table 2). Again, there was evidence of a carry-over effect for the measurements of CT1 ($P = 0.047$), CT2 ($P = 0.006$), left ($P = 0.097$), right ($P = 0.045$) and rectosigmoid ($P = 0.010$) colonic transit time (Table 3). Analysis of the first treatment period data only suggested that

Table 2. Effect of alosetron on transit parameters in healthy volunteers (Study 2)

	Placebo	Alosetron	*P*
WGT (marker 1; h)	32.7 (21.4, 65.5)	52.6 (9.3, 89.6)	0.047
WGT (marker 2; h)	34.6 (19.2, 65.6)	55.5 (30.6, 105.9)	0.017
WGT (marker 3; h)	49.3 (24.5, 82.6)	51.1 (22.4, 91.4)	0.917
MWGT (h)	46.7 (21.7, 62.1)	52.4 (26.4, 95.3)	0.047
SBT (min)	370.0 (210.0, 550.0)	310.0 (190.0, 640.0)	0.855
CT1 (h)	39.1 (14.2, 52.9)	45.8 (19.7, 92.1)	0.028
CT2 (h)	28.5 (6.0, 60.0)	41.0 (0, 62.0)	0.201
LCT (h)	6.0 (0, 15.0)	17.0 (0, 25.0)	0.617
RCT (h)	9.0 (0, 19.0)	6.0 (0, 27.0)	0.579
RST (h)	17.0 (0, 37.0)	17.0 (0, 26.0)	0.927

Results expressed as median (range).
WGT = whole gut transit, MWGT = mean whole gut transit, SBT = small bowel transit, CT = colonic transit, LCT = left colonic transit, RCT = right colonic transit, RST = rectosigmoid transit.

Table 3. Effect of treatment sequence on transit parameters in which a carry-over effect was seen

	Placebo	Alosetron
WGT (marker 2; h)		
Alosetron → Placebo	44.4 (34.5, 65.6)*	61.1 (38.2, 73.0)*
Placebo → Alosetron	26.8 (19.2, 48.3)	38.3 (30.6, 60.6)
WGT (marker 3; h)		
Alosetron→Placebo	56.6 (34.9, 82.6)*	58.2 (49.9, 58.9)*
Placebo → Alosetron	30.5 (24.5, 63.4)	39.4 (22.4, 51.1)
CT1 (h)		
Alosetron → Placebo	45.1 (26.6, 52.9)*	49.2 (40.9, 65.3)*
Placebo → Alosetron	28.2 (14.2, 40.2)	31.4 (19.7, 54.4)
CT2 (h)		
Alosetron → Placebo	49.0 (16.0, 60.0)*	48.0 (33.0, 62.0)*
Placebo → Alosetron	23.5 (6.0, 32.0)	24.0 (0, 41.0)
LCT (h)		
Alosetron → Placebo	11.0 (5.0, 15.0)*	16.0 (12.0, 25.0)*
Placebo → Alosetron	3.0 (0, 7.0)	17.0 (0, 23.0)
RCT (h)		
Alosetron → Placebo	11.0 (4.0, 19.0)*	9.0 (3.0, 27.0)*
Placebo → Alosetron	3.0 (0, 14.0)	0 (0, 13.0)
RST (h)		
Alosetron → Placebo	24.5 (5.0, 37.0)*	20.0 (9.0, 26.0)*
Placebo → Alosetron	9.5 (1.0, 23.0)	12.0 (0, 23.0)

Results expressed as median (range).
WGT = whole gut transit, CT = colonic transit, LCT = left colonic transit, RCT = right colonic transit, RST = rectosigmoid transit, Alosetron → Placebo = Alosetron in 1st treatment period and placebo in 2nd treatment period, Placebo → Alosetron = Placebo in 1st treatment period and Alosetron in 2nd treatment period.
*Transit time was significantly longer after both alosetron and placebo, if alosetron was administered in the 1st treatment period.

alosetron does increase colonic transit time as measured by CT2 ($P = 0.004$) and left colonic transit time ($P = 0.004$; Table 4). The statistical interpretation of data for CT1 ($P = 0.006$), right ($P = 0.146$) and rectosigmoid ($P = 0.128$) colonic transit time was unaffected by this further analysis (Table 4).

Adverse experiences

Alosetron 2 mg b.d. was well tolerated by both irritable bowel syndrome patients and healthy volunteers and a summary of the adverse experiences reported by more than one subject is given in Table 5. No clinically significant changes occurred in vital signs or laboratory investigations.

DISCUSSION

Our data suggest that the 5-HT_3 receptor antagonist, alosetron, delays colonic transit probably by prolonging left colonic transit in both patients with irritable bowel syndrome and healthy volunteers. Furthermore, this effect results in a tendency for whole gut transit time to be increased. Alosetron, however, has no effect on mouth to caecum transit.

The small effect which alosetron had on the average mean whole gut transit time was probably because it was calculated from the mean transits of three markers, one of which (marker 3) did not appear to be significantly delayed by alosetron. The apparent lack of delay of marker 3 was most likely related to not all of the markers having been excreted by day 9.

Although statistically there was evidence of a carry-over effect in some parameters in Study 2 (healthy volunteers), carry-over effects due to alosetron are unlikely as there was at least a 3-week wash out period between treatments and no similar carry-over effect was seen in Study 1 (irritable bowel syndrome patients). It is

Table 4. Analysis of first treatment period data only from healthy volunteers

	Placebo	Alosetron	*P*
WGT (marker 2; h)	26.8 (19.2, 48.3)	61.1 (38.2, 73.0)	0.011
WGT (marker 3; h)	30.5 (24.5, 63.4)	58.2 (49.9, 58.9)	0.144
CT1 (h)	28.2 (14.2, 40.2)	49.2 (40.9, 65.3)	0.006
CT2 (h)	23.5 (6.0, 32.0)	48.0 (33.0, 62.0)	0.004
LCT (h)	3.0 (0, 7.0)	16.0 (12.0, 25.0)	0.004
RCT (h)	3.0 (0, 14.0)	9.0 (3.0, 27.0)	0.146
RST (h)	9.5 (1.0, 23.0)	20.0 (9.0, 26.0)	0.128

Results expressed as median (range).
WGT = whole gut transit, CT = colonic transit, LCT = left colonic transit, RCT = right colonic transit, RST = rectosigmoid transit.

Table 5. Adverse experiences reported by more than one subject. Figures are the numbers of subjects reporting each experience during treatment

	Irritable bowel syndrome patients		Healthy volunteers	
	Placebo (n = 12)	Alosetron (n = 13)	Placebo (n = 12)	Alosetron (n = 11)
Constipation	2 (17%)	4 (31%)	—	6 (55%)
Diarrhoea	—	—	2 (17%)	—
Abdominal pain and discomfort	3 (25%)	2 (15%)	2 (17%)	—
Nausea	—	2 (15%)	—	—
Headache	2 (17%)	4 (31%)	—	2 (18%)
Dizziness	2 (17%)	—	—	—

highly unlikely that any alosetron, which has around a 60% bioavailability and a plasma elimination half life of 1.5 h, remained in the body after a 3-week wash-out period. It is therefore difficult to explain why transit times appeared to be longer after alosetron and placebo if the alosetron was taken in the first treatment period, whereas the transit times tended to be shorter when placebo was taken in the first treatment period. However, when a first treatment period analysis only was performed, the results were similar except for the colonic transit time calculated from X-ray (CT2) and left colonic transit (LCT) which were both significantly delayed by alosetron, confirming the results from Study 1.

No explicit statistical adjustments were made for the multiple comparisons performed in these studies, but the relatively high proportion of significant/borderline results obtained, probably excludes the possibility of finding these results by chance. This is further supported by the fact that our results are consistent with previous studies on other 5-HT_3 receptor antagonists, suggesting that 5-HT_3 blockade generally has little effect on the small intestine but does alter the function of the large intestine.[12, 25–29] The precise mechanisms responsible for this delay in transit are unclear, but other studies have shown that alosetron and other 5-HT_3 receptor antagonists can increase fluid absorption, reduce smooth muscle tone and decrease the phasic activity of the distal gut.[10, 11, 13, 15, 16, 30–35]

Irrespective of the mechanisms involved, the prolongation of colonic transit time by alosetron suggests that it may be clinically useful in the treatment of irritable bowel syndrome patients who have loose bowels and/or urgency of defaecation. Furthermore, recent clinical trials support this suggestion and have shown that alosetron significantly improves various aspects of bowel habit (urgency, consistency and frequency) as well as abdominal pain and discomfort in patients with non-constipation predominant irritable bowel syndrome.[18] These preliminary data are encouraging and support the suggestion by Humphrey that the pharmacodynamic profile of alosetron makes this 5-HT_3 receptor antagonist a suitable candidate in the treatment of this condition.[9]

Finally, alosetron was generally well tolerated and adverse events were mostly related to mild constipation and/or headache. It is interesting to note that patients in general reported more adverse events, both after administration of alosetron and placebo compared with

the healthy volunteers. Analysis of laboratory data and measurements of blood pressure and heart rate were all within normal limits.

In conclusion, the results of these two placebo-controlled studies demonstrate that alosetron 2 mg b.d. delays colonic transit time by prolonging left colonic transit, which should be of benefit for patients with non-constipation predominant irritable bowel syndrome.

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