Aliment Pharmacol Ther 1999; 13: 1419–1427.

# *Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients*

R. H. JONES[1], G. HOLTMANN[2], L. RODRIGO[3], R. S. B. EHSANULLAH[4], P. M. CROMPTON[5], L. A. JACQUES[4] & J. G. MILLS[4]

[1]*Department of General Practice, Guy's, King's and St Thomas' School of Medicine, London, UK,* [2]*Department of Internal Medicine, University Hospital of Essen, Germany,* [3]*Gastroenterology Service, Hospital Central de Asturias, Oviedo, Spain,* [4]*Gastroenterology Clinical Development, and* [5]*Clinical Statistics, Glaxo Wellcome Research and Development, Stockley Park, UK*

Accepted for publication 15 September 1999

## SUMMARY

*Background*: Irritable bowel syndrome is one of the most common gastrointestinal disorders, yet no therapy convincingly controls the multiple symptoms of this syndrome.

*Aim*: To compare the efficacy and tolerability of the new 5-$HT_3$-receptor antagonist alosetron and the smooth muscle relaxant mebeverine in a double-blind, multicentre, randomized trial.

*Methods*: Six hundred and twenty-three nonconstipated females with irritable bowel syndrome were randomized to receive alosetron 1 mg twice daily ($n = 319$) or mebeverine 135 mg three times daily ($n = 304$) for 12 weeks, followed by a 4-week post-treatment period. The primary efficacy end-point was monthly responders for adequate relief of irritable bowel syndrome related abdominal pain and discomfort (defined as patients reporting adequate relief on at least 2 out of 4 weeks). Secondary end-points included assessments of bowel function, including urgency, stool frequency and stool consistency.

*Results*: There were significantly more responders in the alosetron group compared with mebeverine at months 2 and 3 ($P < 0.01$). Compared with mebeverine, the alosetron group experienced significant decreases in proportion of days with urgency and mean stool frequency, and had firmer stools within 1 week of starting treatment. A similar proportion of patients reported adverse events in the two treatment groups.

*Conclusions*: In nonconstipated female irritable bowel syndrome patients, alosetron is significantly more effective than mebeverine in improving symptoms.

## INTRODUCTION

Irritable bowel syndrome is one of the most common gastrointestinal disorders,[1, 2] and has substantial impact on patients' quality of life and medical resource use.[3, 4] Irritable bowel syndrome is reported to account for 20–50% of referrals to gastroenterologists.[5] Estimates of the prevalence of irritable bowel syndrome in the general population are as high as 20%, with a clear predominance in female patients.[6]

The most recent report of the Committee on Functional Bowel Disorders (Rome II) describes irritable bowel syndrome as a group of functional bowel disorders in which abdominal discomfort or pain is associated with defaecation or a change in bowel habit, and with features of disordered defaecation.[7] Irritable bowel

*Correspondence: Jane Mills, Gastroenterology Clinical Development Glaxo Wellcome Research and Development, Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK.*
*E-mail: JGM0522@Glaxo.Wellcome.co.uk*

syndrome patients may experience diarrhoea (diarrhoea-predominant subtype), constipation (constipation-predominant subtype), or alternation between the two (alternating subtype).

Effective treatment of irritable bowel syndrome remains a challenge to primary care physicians and gastroenterologists. Evaluating the efficacy of irritable bowel syndrome treatments is difficult due to the range of patient symptoms, and assessment of therapy is complicated by the significant placebo responses of patients in clinical trials.[8, 9] Furthermore, no currently available therapeutic agent effectively controls the multiple symptoms of irritable bowel syndrome.[7, 8] Thus, new therapeutic strategies addressing diverse irritable bowel syndrome symptoms are needed.

The potent and selective 5-$HT_3$ receptor antagonist, alosetron, is effective in alleviating pain and improving bowel function in irritable bowel syndrome patients. In recent placebo controlled clinical trials, alosetron was well tolerated and improved abdominal pain and discomfort, urgency, stool frequency and stool consistency in nonconstipated and diarrhoea-predominant female irritable bowel syndrome patients.[10–12] 5-$HT_3$ receptors mediate reflexes that control gastrointestinal motility and secretion, as well as the perception of bowel function.[13] Although the precise mechanism of action of alosetron is unknown, alosetron may modulate pain by altering the initiation, transmission or processing of extrinsic sensory information from the gastrointestinal tract, and modulate bowel peristaltic and secretory function by affecting intrinsic sensory neurones.[13] As a class, 5-$HT_3$ receptor antagonists slow colonic transit, increase colonic compliance and increase pain thresholds during colorectal distension.[14–17]

The antispasmodic compound mebeverine is a methoxybenzamine derivative widely used in irritable bowel syndrome management.[18] Mebeverine may alter contractile activity as well as small bowel motor activity in irritable bowel syndrome patients,[19] and is thought to decrease motility and intraluminal bowel pressure via a direct effect on smooth muscle cells.[20] Few large, well-controlled studies of mebeverine have been conducted in irritable bowel syndrome patients. However, within the limitations of their study design, most published reports provide some evidence to support the efficacy of mebeverine in relief of abdominal pain and discomfort.

The present randomized, double-blind clinical trial compared the efficacy and tolerability of alosetron and mebeverine in nonconstipated female irritable bowel syndrome patients. Multiple symptoms of irritable bowel syndrome were assessed, including the adequate relief of pain and discomfort, and improvements in bowel function (including urgency, stool frequency and stool consistency) in patients treated with alosetron (1 mg twice daily) or mebeverine (135 mg three times daily) for 12 weeks.

## METHODS

### *Patients*

Female irritable bowel syndrome patients aged 18 years or older with symptoms that fulfilled the Rome I criteria for irritable bowel syndrome[21] for at least 6 months were eligible to enter screening for the study. Research ethics committees at all sites approved the protocol, and all patients provided written informed consent.

Normal physical examinations (including sigmoidoscopy/colonoscopy), blood counts, serum chemistries and thyroid stimulating hormone levels, together with negative occult blood and ova/parasite stool tests, were required for patient eligibility. Patients were excluded if they were lactose intolerant and their symptoms were not controlled by diet; if they had an unstable medical condition or if another gastrointestinal condition existed; if there was a major psychiatric disorder or substance abuse within the previous 2 years; if there was evidence of nonskin malignancy within the previous 5 years; if an investigational drug was used within 30 days of the screening phase; if they were pregnant, breast-feeding or of childbearing potential and not using approved methods of contraception; or if a prohibited concurrent medication was used within 7 days prior to entering the screening phase. Prohibited concurrent medications included those likely to interfere with gastrointestinal function (including laxatives), or with the study analyses.

### *Study design*

A sufficient level of pain and appropriate stool consistency (for details see below) were confirmed in eligible patients prior to randomization during a 2-week screening period. Physicians assessed patients' baseline predominant disturbance in bowel function as diarrhoea-predominant, alternating or constipation-predominant.

The study was double-blinded and placebo-matched. Patients were randomized 1:1 to 12 weeks of oral

treatment with either encapsulated alosetron tablets 1 mg twice daily plus matched placebo once daily, or encapsulated mebeverine hydrochloride (Colofac; Solvay Healthcare Ltd, UK), 135 mg three times daily, taken before meals. A 4-week post-treatment period followed. Laboratory evaluations and adverse events were recorded at the 4, 8 and 12-week (or final) treatment visits.

*Data collection*

Daily and weekly symptom data were collected using an electronic touch-tone telephone based system during the screening, treatment and follow-up periods.[22] Severity of abdominal pain and discomfort was assessed on a daily basis using a five point scale (0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe), and was required to average between 1 and 3.3 for entry into the study. Stool consistency data were recorded daily as: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery, and were required to be greater than 2.5 for entry into the study. Absence of stool was assigned a consistency value of zero.

During the treatment and follow-up phases, patients were asked weekly if they had obtained adequate relief of their irritable bowel syndrome pain and discomfort during the previous 7 days.

*Statistical analysis*

The sample size was chosen with 90% power at the $\alpha = 0.05$ level of significance. The number of patients per treatment group needed to detect a 15% difference in proportion of patients with adequate relief between alosetron and mebeverine was 244 per group, assuming the proportion with adequate relief in the mebeverine treatment group was 40%. A target sample size of 300 patients per treatment group was chosen to allow for a 20% drop-out rate.

The primary efficacy parameter was the proportion of patients with adequate relief of irritable bowel syndrome pain and discomfort for at least 2 weeks per month ('monthly responders'). Analyses were by intention-to-treat; using the last observation carried forward principle for months with no data. Patients with no data in month 1 were assumed to be nonresponders for adequate relief. Missing weeks in a month with data were assigned as no relief. Analyses were performed using the Mantel–Haenszel test stratifying by geographical cluster.[23]

As a supportive analysis, the proportion of patients with weekly adequate relief of irritable bowel syndrome pain and discomfort was compared between treatment groups using the Mantel–Haenszel test as above.

Additional measures of pain included the proportion of pain and discomfort-free days. The proportion of pain and discomfort-free days was determined for baseline and at monthly intervals during the treatment and follow-up period. Changes from baseline in the two treatment groups were compared for each month of the treatment phase using the van Elteren extension of the Wilcoxon rank sum test stratified by cluster.[24]

The mean daily stool consistency scores and daily number of bowel movements were calculated at baseline (for the 2-week screening period), and for each week of the treatment and follow-up phases. In addition, the percentage of days on which patients experienced a sense of urgency was calculated at baseline and for the same weekly intervals. For each parameter, changes from baseline in the two treatment groups were compared using van Elteren's test stratified by cluster.[24]

The proportion of patients reporting adverse events was compared between treatment groups using Fisher's exact test.

## RESULTS

*Study population and demography*

The two treatment groups were similar with regard to the distribution of age, race, physical characteristics and irritable bowel syndrome characteristics (Table 1). Six hundred and twenty-three of 1153 patients screened at 123 sites were randomized from 112 sites in 11 European countries, Israel, South Africa, New Zealand and Australia. Screening failures resulted primarily from failure to meet the pain and stool consistency entry criteria. Patient progression through the study is presented in Figure 1. Seventy-nine per cent (251/319) and 81% (246/304) of patients in the alosetron and mebeverine groups, respectively, completed the study. The incidences, and reasons for, premature discontinuation of patients from the study were similar in the two treatment groups, and are shown in Figure 1.

Eighty per cent of patients were at least 80% compliant with study medication at all months. Patient compliance with treatment was similar in the two groups.

*Adequate relief of pain and discomfort*

The proportion of monthly responders for adequate relief was greater in the alosetron group compared with

Table 1. Summary of demographic and baseline characteristics of study patients

| | Alosetron ($n$ = 319) | Mebeverine ($n$ = 304) |
|---|---|---|
| Age (mean years ± s.d.) | 44.2 ± 13.7 | 44.5 ± 13.9 |
| Ethnic origin [no. (%)] | | |
| Caucasian | 315 (99) | 298 (98) |
| Asian | 1 (< 1) | 1 (< 1) |
| Other | 3 (< 1) | 5 (2) |
| Height (mean cm ± s.d.) | 163.7 ± 7.1 | 163.5 ± 6.6 |
| Weight (mean kg ± s.d.) | 67.5 ± 12.4 | 68.2 ± 16.0 |
| Irritable bowel syndrome parameters | | |
| Time since onset of symptoms (mean years) | 9 | 10 |
| Diarrhoea-predominant [no. (%)] | 232 (73) | 217 (71) |
| Alternating [no. (%)] | 76 (24) | 73 (24) |
| Constipation predominant [no. (%)] | 11 (3) | 14 (5) |
| Pain severity* (mean ± s.d.) | 2.00 ± 0.61 | 2.07 ± 0.57 |
| Sense of urgency** (mean ± s.d.) | 66.9 ± 29.0 | 67.8 ± 29.6 |
| Stool consistency*** (mean ± s.d.) | 3.46 ± 0.59 | 3.46 ± 0.54 |
| Stools per day (mean ± s.d.) | 2.67 ± 1.44 | 2.76 ± 1.66 |

* Pain severity scale: 0 = none; 1 = mild; 2 = moderate; 3 = intense; 4 = severe.
** Values represent the percentage of days with symptoms.
*** Stool consistency scale: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery.

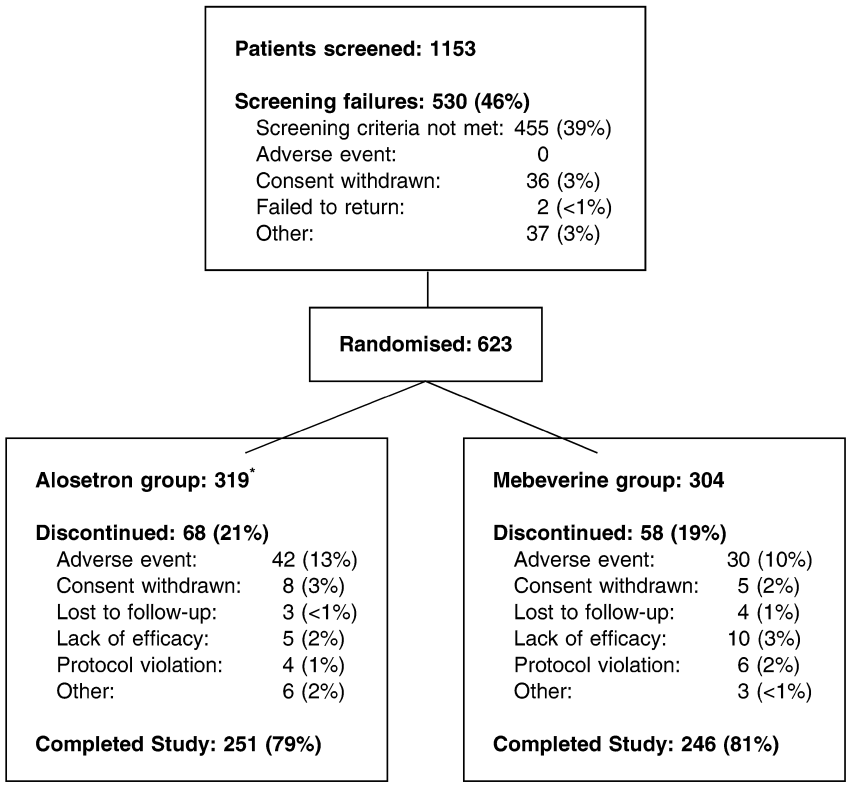


Figure 1. Flowchart of patient progression through the study. Reasons for screening failures and discontinuation from study are indicated.

the mebeverine group for all months of treatment, and the difference reached statistical significance in months 2 and 3: month 1 (46% vs. 39%, respectively; $P = 0.081$); month 2 (56% vs. 43%, respectively; $P = 0.001$); month 3 (58% vs. 48%, respectively; $P = 0.009$).

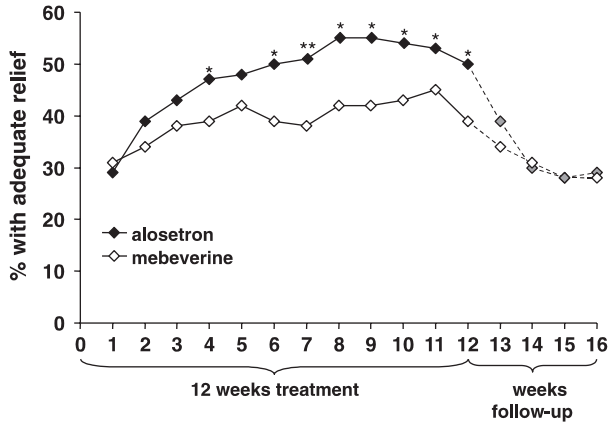


Figure 2. Per cent of patients with adequate relief of irritable bowel syndrome pain and discomfort on a weekly basis during treatment with alosetron or mebeverine, and during the post treatment follow-up. (Significantly different from mebeverine, * $P < 0.05$; ** $P < 0.001$.)

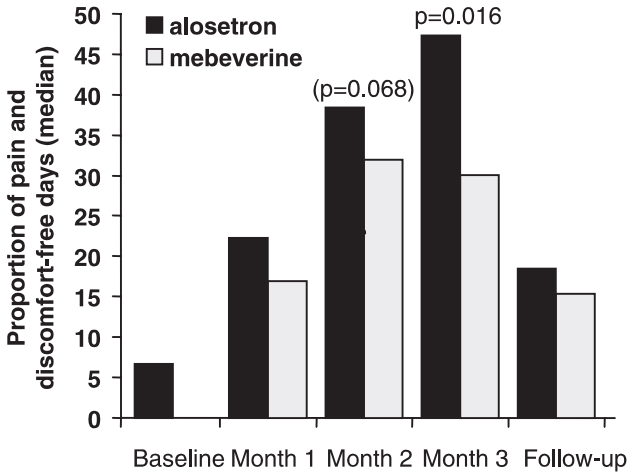


Figure 3. Median proportion of pain and discomfort free days at baseline, during treatment and during follow-up in patients in the alosetron and mebeverine treatment groups. (Statistical significance of differences determined relative to baseline values.)

The percentage of patients in the alosetron and mebeverine groups with adequate relief of pain and discomfort reported each week is shown in Figure 2. The percentage of patients with adequate relief was numerically greater in the alosetron group compared with mebeverine by week 2 and the difference reached statistical significance by week 4. Symptoms rapidly worsened following cessation of treatment. There was no difference in the treatment response between irritable bowel syndrome sub–types (interaction test for diarrhoea-predominant vs. alternator, $P = 0.822$)

The median proportion of pain and discomfort-free days at baseline, and during each month of treatment and follow-up, is shown in Figure 3. In the third month the change from baseline was significantly greater for alosetron treated patients ($P = 0.016$).

*Bowel function*

The alosetron treatment group experienced significant decreases in the proportion of days with urgency and mean stool frequency, and had firmer stools compared with the mebeverine group. Figures 4, 5 and 6 show the effects of alosetron and mebeverine on urgency, stool frequency and stool consistency, respectively.

Compared with mebeverine, alosetron provided significantly greater improvement in bowel function parameters within the first week of treatment. Improvement with alosetron was sustained throughout the subsequent weeks of treatment and symptoms worsened within 1 week of treatment cessation. Bowel function parameters during the follow-up phase were similar between the alosetron and mebeverine groups, with the exception of weeks 13 and 14 stool consistency scores ($P < 0.05$).

*Safety*

Adverse events reported by 5% or more of patients in any treatment group are shown in Table 2. Adverse events were reported by 69% (220/318) and 64% (196/304) of patients in the alosetron group and mebeverine group, respectively, a difference that was

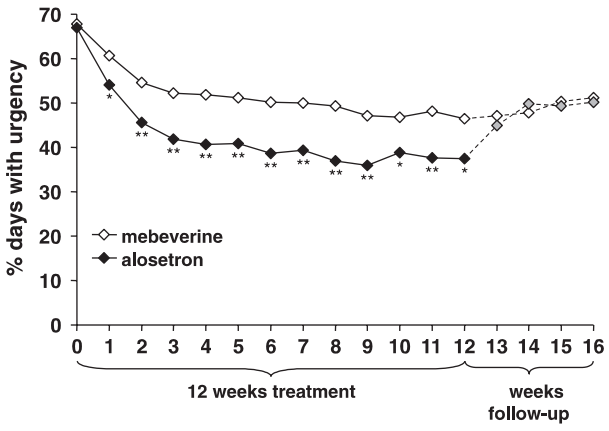


Figure 4. Mean proportion of days with urgency in irritable bowel syndrome patients during treatment with alosetron 1 mg b.d. or mebeverine 135 mg t.d.s., or during post treatment follow-up. (Significantly different from mebeverine, * $P < 0.05$; ** $P < 0.001$.)

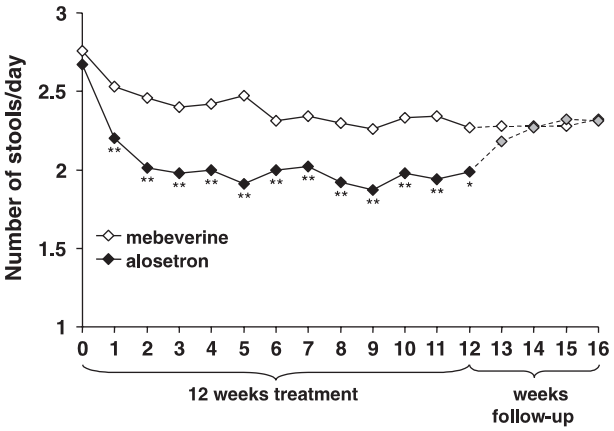


Figure 5. Stool frequency in irritable bowel syndrome patients during treatment with alosetron 1 mg b.d. or mebeverine 135 mg t.d.s., or during post treatment follow-up. (Significantly different from mebeverine, $^{*}P < 0.01$; $^{**}P < 0.001$.)

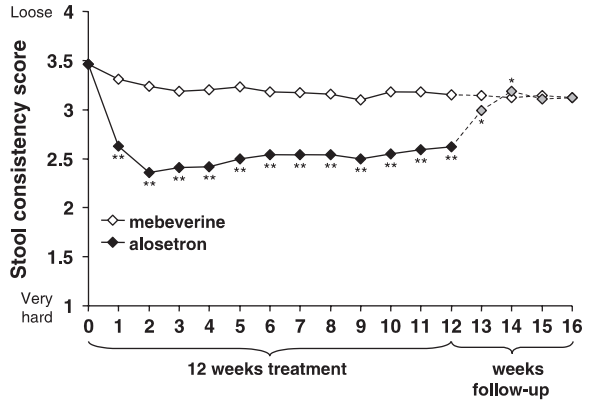


Figure 6. Stool consistency in irritable bowel syndrome patients during treatment with alosetron 1 mg b.d. or mebeverine 135 mg t.d.s., or during post treatment follow-up. Scale: 1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery. (Significantly different from mebeverine, $^{*}P < 0.05$; $^{**}P < 0.001$.)

not statistically significant. Constipation was the most commonly recorded adverse event in the alosetron treated group (22%). Seventy-one patients reported 87 events of constipation; the majority were reported within 2 weeks of starting treatment and the median duration was 7 days. Seventy per cent of the events were described as of mild or moderate severity.

With the exception of constipation in the alosetron group, and ear, nose and throat complaints in the mebeverine group, adverse event profiles between the alosetron and mebeverine treated groups were similar.

Forty-two patients (13%) in the alosetron group and 30 patients (10%) in the mebeverine group withdrew from the study due to adverse events. The adverse event associated with the majority of these withdrawals in the alosetron group was constipation (23/42), although the majority of patients reporting constipation remained in the study (48/71).

Nineteen of the 30 withdrawals in the mebeverine group were attributed to a wide range of gastrointestinal adverse events (including abdominal pain, nausea, constipation and diarrhoea).

Serious adverse events were reported for 3% of patients in both the alosetron (11/318) and the mebeverine (8/304) treatment groups. With the exception of one report of erosive gastritis and one report of colitis/sigmoiditis in the alosetron group and two reports of abdominal pain and discomfort and one of constipation in the mebeverine group, none of the serious adverse events was considered to be drug-related. Laboratory values were not significantly changed by alosetron or mebeverine treatment.

## DISCUSSION

The results of this multicentre, randomized, double-blind study in nonconstipated female irritable bowel syndrome patients confirm the efficacy of alosetron in the relief of abdominal pain and discomfort and improvement in bowel function in this patient population. Alosetron provided significantly greater therapeutic benefit than mebeverine.

Mebeverine hydrochloride is widely used in the management of irritable bowel syndrome. It is believed to act directly on smooth muscle cells to reduce sodium influx,[20] and indirectly limit calcium influx and resultant muscle contraction. Mebeverine may also indirectly limit potassium efflux and prevent prolonged reflex muscle relaxation.[25] Studies in patients with irritable bowel syndrome demonstrated both a reduction in pelvic colonic activity,[20] and altered small bowel activity resulting from an increase in the phase 2 motility index, a decrease in propagation velocity, and increase in duration of phase 3 of the migrating motor complex.[19]

Evaluation of the early placebo-controlled studies conducted with mebeverine is difficult. End-points were not standardized and the majority of studies were small, a factor that is a major limitation in a condition where the placebo response is extremely variable and often high. Nevertheless, a meta-analysis of five studies concluded that treatment with mebeverine is associated with a significant reduction in abdominal pain and global symptom improvement.[26] These conclusions are

Table 2. Summary of most common* drug-related adverse events and reasons for withdrawal from the study for patients treated with alosetron or mebeverine

| Adverse event | Alosetron $n = 318$ $n$ (%) | Mebeverine $n = 304$ $n$ (%) | $P$-value |
|---|---|---|---|
| Total patients with one or more adverse event | 220 (69) | 196 (64) | 0.233 |
| Gastrointestinal | 150 (47) | 99 (33) | < 0.001 |
| Constipation | 71 (22) | 8 (3) | ND** |
| Nausea | 23 (7) | 26 (9) | ND |
| Abdominal pain and discomfort | 29 (9) | 17 (6) | ND |
| Neurology | 55 (17) | 59 (19) | 0.534 |
| Headache | 31 (10) | 44 (13) | ND |
| Ear, nose and throat | 29 (9) | 46 (15) | 0.026 |
| Viral infections | 7 (2) | 19 (6) | ND |
| Lower respiratory | 40 (13) | 30 (10) | 0.311 |
| Viral infections | 24 (8) | 17 (6) | ND |
| Musculoskeletal | 23 (7) | 33 (11) | 0.125 |
| Pain | 10 (3) | 18 (6) | ND |
| Skin | 28 (8) | 20 (7) | 0.540 |
| Non-site specific | 38 (12) | 33 (11) | 0.706 |
| Malaise and fatigue | 19 (6) | 15 (5) | ND |
| Total patients with one or more drug-related adverse event | 128 (40) | 82 (27) | < 0.001 |
| Patients withdrawn from study due to adverse event | 42 (13) | 30 (10) | 0.211 |

* Incidence > 5%.
** ND: not determined for individual adverse events.

supported by the results of a large study (1147 patients) in general practice[27] and a recent study in which 300 patients diagnosed on the basis of the Rome I criteria were treated with mebeverine capsules 200 mg twice daily for 8 weeks.[28] Studies with mebeverine have included patients with all types of bowel habit, and 'normalization' of bowel habit is generally reported.

The efficacy of alosetron was evaluated in two dose ranging studies,[10, 11] and recently confirmed in a large placebo controlled study.[12] $5HT_3$-receptor antagonists are known to slow colonic transit and so, with the exception of the first dose-ranging study, patients with constipation-predominant irritable bowel syndrome were excluded. In the second dose-ranging study, alosetron 1 mg twice daily significantly increased the proportion of females, but not males, reporting adequate relief of abdominal pain and discomfort. The efficacy of alosetron in nonconstipated females was confirmed in a large placebo controlled study where it was shown to increase the proportion of patients with adequate relief of irritable bowel syndrome pain and discomfort, as well as producing firmer stools, and reducing stool frequency and days with urgency.[12] Improvements in all end-points were seen within the first few weeks of treatment and were maintained throughout the 12-week treatment period.

The reason for an apparent difference in efficacy between men and women remains unknown and is the subject of ongoing investigation with larger numbers of male irritable bowel syndrome patients. However, because the majority of patients presenting for treatment are female, the present study, as well as the primary efficacy studies, were conducted only in women.

The present study sought to address some of the criticism of previous investigations with potential irritable bowel syndrome therapies. The population was defined by the Rome I criteria,[21] and a 2-week screening period confirmed inclusion of patients with abdominal pain and discomfort of measurable severity. The study was powered to detect a difference of clinical relevance between treatments, and the primary end-point was a patient-based assessment collected regularly, and in real time, over a 12-week treatment period. Adequate relief of abdominal pain and discomfort is highly correlated

with other measures of symptom relief, e.g. pain severity, proportion of pain-free days and urgency.[29, 30]

There was an increase in the numbers of patients reporting adequate relief of abdominal pain and discomfort in both treatment groups within 2 weeks of starting treatment. After 4 weeks, the difference between alosetron and mebeverine was statistically significant, and the benefit was maintained throughout the remainder of the treatment period.

Previous studies have shown that urgency is one of the most distressful symptoms of irritable bowel syndrome.[31] The proportion of days per week with urgency was reported to be approximately 70% at baseline in both treatment groups. A significantly greater reduction in days with urgency was observed after 1 week of treatment with alosetron compared with mebeverine. Within 4 weeks, the proportion of days with urgency reported by patients treated with alosetron was reduced to about 40%. This therapeutic advantage was also sustained throughout treatment. Mebeverine had little effect on stool frequency or consistency, whereas treatment with alosetron resulted in a rapid reduction in stool frequency and firming of stools.

The negative impact of IBS on a patient's ability to function normally and sense of well being is increasingly recognized. In a placebo controlled study alosetron 1 mg b.d. was associated with significant improvements in 8 of the 9 scales of a disease-specific health-related quality of life instrument (IBSQOL).[32] Interpretation of QoL data collected in multinational studies is often confounded by cultural differences and a limited population from each contributing country. Country specific analyses of data collected during this study will form the basis of a separate report.

As expected, constipation was the most commonly reported adverse event (22%) in the alosetron treatment group. However, this led to withdrawal of treatment in only a third of cases. Laxatives were not permitted during this study but might be expected to benefit some patients; a short drug holiday (maximum 4 days) was effective in all but a few patients who reported absence of stool for several consecutive days. Overall, both drugs were well tolerated.

In conclusion, alosetron was found to be effective in controlling both abdominal pain and bowel dysfunction in females with nonconstipated irritable bowel syndrome. Alosetron was significantly more effective than mebeverine in the control of multiple irritable bowel syndrome symptoms in this population.

## ACKNOWLEDGEMENTS

This study (protocol number S3BB3001) was sponsored by Glaxo Wellcome Research and Development, UK. We thank P. C. Ferriola, Glaxo Wellcome Inc., for writing and editing assistance. The authors thank the following investigators and their co-workers for their contribution to this study:

**Australia:** Professor I. Cook, Dr H. Debinski, Dr P. Desmond, Professor F. Dudley, Professor P. Gibson, Dr D. Hetzel, Dr J. Karrasch, Professor J. E. Kellow, Dr M. C. Ngu, Dr S. Roberts, Dr D. Routley, Dr P. Tagkalidis, Professor N. Yeomans.

**Belgium:** Dr D. de Looze, Dr M. Delforge, Dr M. Cabooter, Dr M. Castelain, Dr J. Ghilain, Professor G. Coremans, Dr R. Hannon, Dr P. Hoang, Dr A. Lakis, Dr V. Lamy, Professor M. Melange, Dr H. Naessens, Dr A. Van Gossum, Dr J. Van Isveldt.

**Denmark:** Dr L. A. Christensen, Dr J. Fallingborg, Dr L. Hendel, Dr E. Kristensen, Dr K. Ladefoged, Dr S. N. Rasmussen, Dr L. B. Rasmussen, Dr S. Rune, Dr W. Schradieck, Dr C. Thordal, Dr N. Thorsgaard.

**Germany:** Dr V. Aldinger, Dr N. Birke, Dr R. Jerwan-Keim, Dr M. Karaus, Dr H. Schoenekäs, Dr E. Schütz, Dr M. Schumacher, Dr H.-C. Treichel, Dr J. Wachter.

**Iceland:** Dr A. Bodvarsson, Dr H. Gudjonsson, Dr K. B. Orvar.

**Ireland:** Dr J. Crowe, Dr P. W. N. Keeling, Professor C. O'Morain.

**Israel:** Professor Z. Halpern, Dr J. Tiomnni.

**Netherlands:** Dr C. P. M. Dekkers, Dr A. A. M. Geraedts, Dr P. H. T. Koch, Dr J. L. Meijer, Dr C. Schop, Professor A. J. P. M. Smout, Professor R. W. Stockbrügger.

**New Zealand:** Dr M. L. Barclay, Dr M. R. Lane, Dr D. W. Shaw, Dr I. D. Wallace.

**Norway:** Dr P. Farup, Dr J. Fjøsne, Dr S. Wetterhus, Dr I. Wilhelmsen.

**South Africa:** Dr I. Berkowitz, Dr H. M. Bloch, Mr R. P. Mills, Dr H. R. Schneider, Dr M. O. Strimling, Dr T. A. Winter, Dr J. P. Wright.

**Spain:** Dr L. Bujanda, Dr A. M. Caballero, Dr J. Mones, Dr J. C. Porres, Dr R. Sainz-Samitier, Dr M. Villagrasa.

**Sweden:** Dr S. Björck, Professor R. Gillberg, Dr D.-A. Hallbäck, Dr E. Hertervig, Dr G. Lindberg, Dr G. Midhagen, Dr S. Nilsson, Dr H. Nyhlin, Dr A. Rönnblom, Dr L. Sidenvall, Dr T. Storskrubb.

**Switzerland:** Dr G. Egger, Dr S. Realini.

**United Kingdom:** Dr N. K. Ahluwalia, Dr M. E. Allerton, Dr K. D. Bardhan, Dr R. W. Chapman, Dr J. Collins, Dr A. Forbes, Dr D. Grimes, Dr S. Gunn, Dr I. Hart, Dr M. C. Horne, Dr J. O. Hunter, Dr D. A. Johnston, Dr R. Landray, Dr B. MacFarlane, Dr A. Mahmoud, Dr D. Maxton, Dr J. E. Miller, Dr S. Moore, Dr A. Morris, Dr J. B. Pailing, Dr J. Robinson, Dr G. Rubin, Mr D. Scrimgeour, Dr I. Smith, Dr S. D. Taylor, Dr R. Walker, Dr T. Wardle, Dr P. Whorwell, Dr J. Wilson, Dr G. R. Youngs.

## REFERENCES

1 Jones R, Lydeard S. Irritable bowel syndrome in the general population. Br Med J 1992; 304: 87–90.
2 Harvey R, Read A, Salih Y. Organic and functional disorders in 2000 gastroenterology outpatients. Lancet 1983; 1: 632–4.
3 Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999; 60: 77–81.
4 Wells NE, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. Aliment Pharmacol Ther 1997; 11: 1019–30.
5 Farthing M. Irritable bowel, irritable body, irritable brain? Br Med J 1995; 310: 171–5.
6 Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997; 112: 2120–37.
7 Thompson W, Longstreth G, Drossman D *et al*. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(Suppl. II): 43–7.
8 Klein K. Controlled treatment trials in the irritable bowel syndrome: a critique. Gastroenterology 1988; 95: 232–41.
9 Pattee PL, Thompson WG. Drug treatment of the irritable bowel syndrome. Drugs 1992; 44: 200–6.
10 Bardhan K, Bodemar G, Geldof H *et al*. A double-blind placebo-controlled study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. Gastroenterology 1996; 110; A630 (Abstract).
11 Camilleri M, Mayer E, Drossman D *et al*. Improvement in pain and bowel function in female irritable bowel syndrome patients with alosetron, a 5–$HT_3$-receptor antagonist. Aliment Pharmacol Ther 1999; 13: 1149–59.
12 Mangel AW, Camilleri M, Chey WY *et al*. Treatment of female IBS patients with alosetron, a potent and selective $5HT_3$-receptor antagonist. Gastroenterology 1999; 116: A1036(Abstract).
13 Gershon M. Roles played by 5-hydroxytryptamine in the physiology of the bowel. Aliment Pharmacol Ther 1999; 13: 15–30.
14 Delvaux M, Louvel D, Mamet JP *et al*. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1998; 12: 849–55.
15 Goldberg PA, Kamm MA, Setti-Carraro P *et al*. Modification of visceral sensitivity and pain in irritable bowel syndrome by 5-$HT_3$ antagonism (ondansetron). Digestion 1996; 57: 478–83.
16 Prior A, Read NW. Reduction of rectal sensitivity and post-prandial motility by granisetron, a 5 $HT_3$-receptor antagonist, in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1993; 7: 175–80.
17 Zighelboim J, Talley NJ, Phillips SF *et al*. Visceral perception in irritable bowel syndrome. Rectal and gastric responses to distension and serotonin type 3 antagonism. Dig Dis Sci 1995; 40: 819–27.
18 Baume P. Mebeverine, an effective agent in the irritable colon syndrome. Aust N Z J Med 1972; 2: 34–6.
19 Evans PR, Bak YT, Kellow JE. Mebeverine alters small bowel motility in irritable bowel syndrome. Aliment Pharmacol Ther 1996; 10: 787–93.
20 Connell AM. Physiological and clinical assessment of the effect of the musculotropic agent mebeverine on the human colon. Br Med J 1965; 5466: 848–51.
21 Thompson W, Creed F, Drossman D *et al*. Functional bowel disorders and functional abdominal pain. Gastrointest J 1992; 5: 75–91.
22 Harding JP, Hamm LR, Ehsanullah RSB *et al*. Use of a novel electronic data collection system in multicenter studies of irritable bowel syndrome. Aliment Pharmacol Ther 1997; 11: 1073–6.
23 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of diseases. J Natl Cancer Inst 1959; 22: 719–48.
24 van Elteren P. On the combination of independent two sample tests of Wilcoxon. Bull Int Stat Inst 1960; 37: 351–61.
25 Dan Hertog A, Vanden Akker J. Modification of alpha 1-receptor operated channels by mebeverine in smooth muscle cells of guinea-pig taenia caeci. Eur J Pharmacol 1987; 138: 367–74.
26 Poynard T, Naveau S, Mory B *et al*. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 1994; 8: 499–510.
27 Le Gal M, Pelouz C. Colopathie fonctionelle. Une étude multicentrique rassemblant 1147 malades a confirmé l'efficacité de Duspatalin′ suspension, sur les symptômes de colopathie, ainsi qu'une bonne tolérance et une excellente acceptabilité. Impact Med 1989; 3: 70–3.
28 Guyot P. Efficacité de la mébévérine (Duspatalin′ 200 mg gélule) chez des patients présentant des troubles fonctionnels intestinaux: résultats d'une étude descriptive en fonction des différents sous-groupes symptomatiques. Act Méd Int Gastroentérol 1997; 11: 40–5.
29 Mangel AW, Hahn BA, Heath AT *et al*. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998; 26: 76–81.
30 Mangel AW, Northcutt AR, Kong S *et al*. Validation of adequate relief as an endpoint in irritable bowel syndrome. Gastroenterology 1999; 116: A1035(Abstract).
31 Northcutt A, Harding J, Kong S *et al*. Urgency as an endpoint in IBS. Gastroenterology 1999; 116: A1036(Abstract).
32 Watson MW, Lacey LA, McSorley D, Northcutt A, Mangel A. Impact of alosetron on health-related quality of life (HRQOL) in female patients with irritable bowel syndrome (IBS). Am J Gastroenteol 1999; 94: 2762 (Abstract 741).