Aliment Pharmacol Ther 1997; 11: 561–568.

Zamifenacin (UK-76, 654), a potent gut M_3 selective muscarinic antagonist, reduces colonic motor activity in patients with irritable bowel syndrome

L. A. HOUGHTON*, J. ROGERS†, P. J. WHORWELL*, F. C. CAMPBELL‡, N. S. WILLIAMS† & J. GOKA§

**Department of Medicine, University Hospital of South Manchester, Manchester, UK; †Department of Surgery, Royal London Hospital, London, UK; ‡Department of Surgery, Ninewells Hospital, Dundee, UK; and §Pfizer Central Research, Sandwich, Kent, UK*

Accepted for publication 13 February 1997

SUMMARY

Background: Zamifenacin is a new potent gut M_3 selective muscarinic antagonist developed for possible use in irritable bowel syndrome.

Methods: In this multicentre, double-blind, parallel group, placebo-controlled study, the effect of a single dose of zamifenacin 10 mg or 40 mg on both fasting (30 min) and fed (60 min) colonic motor activity was assessed in 36 patients with irritable bowel syndrome (aged 25–68 years; 19 male). Colonic motility was recorded using a five-channel solid-state catheter introduced by colonoscopy to a depth of 35 cm in an unprepared colon.

Results: Zamifenacin 40 mg profoundly reduced colonic motility, particularly after the meal ($P < 0.05$). This was reflected by a significant reduction in the mean amplitude of contractions, number of contractions, percentage duration of contractions, activity index and the motility index ($P < 0.05$). A smaller reduction in all the motility parameters was obtained with 10 mg zamifenacin, but these changes were not statistically significant. Three patients each on placebo and zamifenacin reported side-effects, but these were mild and transient.

Conclusion: A single 40 mg dose of zamifenacin significantly reduces colonic motility in irritable bowel syndrome patients without significant antimuscarinic effects. The results of this study confirm that the concept of developing selective antimuscarinic agents may be a promising approach to the treatment of irritable bowel syndrome. Not only would such compounds benefit from not having the usual side-effects of anticholinergics but they might also offer much more in the way of dose flexibility.

INTRODUCTION

The pathophysiology of irritable bowel syndrome is poorly understood, but studies have suggested that disordered motility of both the small[1–3] and large bowel,[4–8] and abnormalities in gut visceral sensation,[9–15] may play important roles. The most consistent motor abnormality in the small bowel is a marked increase in 'cluster activity' seen in the wakeful state but not during sleep,[1–3] whilst in the colon motility in many patients appears to be exaggerated, particularly after meals.[4–8] The main defect of visceral sensation appears to be hypersensitivity, and this has been demonstrated in the entire length of the gastrointestinal tract in patients with irritable bowel syndrome.[3, 9–15]

Current therapy is far from satisfactory, ranging from modifications in diet to pharmacological intervention.

Correspondence to: Dr L. A. Houghton, Department of Medicine, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK.

The most commonly used drugs are the antispasmodics of which the antimuscarinic agents are an important example. However, the efficacy and dosing of these latter agents is significantly limited by lack of end-organ selectivity resulting in unacceptable atropine-like side-effects.

Zamifenacin (UK 76, 654) is a new gut-selective M_3 muscarinic receptor antagonist, equipotent to atropine but with few of its side-effects.

The aim of this study was to assess the inhibitory effect of zamifenacin on colonic motility in patients with irritable bowel syndrome.

MATERIALS AND METHODS

Patients

Forty-eight patients (aged 25–68 years; 19 male) with irritable bowel syndrome were screened for the study; 35 at the Manchester centre, five at the Dundee centre and eight at the London centre. All patients had a history of abdominal pain, together with abdominal distension and altered bowel habit (constipation, diarrhoea or alternating) for at least 2 years, and none had any evidence of organic disease based on standard investigations (criteria similar to those suggested by the 'Rome' Irritable Bowel Working Party[16]). No patient was taking any drug known to affect gastrointestinal motility nor were they dependent on, or abusing, analgesic medication or minor tranquillizers. Patients in whom anticholinergic drugs were contra-indicated or who drank more than two units of alcohol per day were excluded from the study. Female patients were either post-menopausal or surgically sterilized.

All patients gave full informed consent for the study to be carried out and the study was approved by all relevant ethical committees.

Experimental protocol

This was a multicentre, randomized, double-blind, placebo-controlled, parallel group study run in two cohorts. The first cohort was randomized to zamifenacin 40 mg or placebo, and the second to zamifenacin 10 mg or placebo. The two placebo groups were combined for statistical analysis. Each patient underwent a screening assessment in which colonic motility was measured over a 90-min period; 30 min basal and 60 min postprandial after a standard meal providing 1042 kcal (503 kcal fat, 317 kcal carbohydrate, 222 kcal protein) consumed within 15 min. Only those patients who satisfied all inclusion/exclusion criteria and exhibited an unequivocal colonic motor response to the meal were randomized to treatment. Within 4 weeks of screening, the patients underwent a second colonic motility assessment, after dosing with either zamifenacin 40 mg, zamifenacin 10 mg or placebo, 30 min before the start of recording.

Electrocardiograph, pulse and blood pressure measurements were taken pre-dose and 0.5, 1.0, 1.5, 2.0 and 2.5 h after dosing. In addition, throughout the study the patients were asked to report any side-effects and to indicate whether these were mild, moderate or severe.

Measurement of colonic motility

After at least a 10-h fast, a solid-state catheter (Gaeltec Ltd, Isle of Skye, UK), with five pressure transducers situated 0, 5, 10, 15 and 20 cm from its distal end and radially arranged around its circumference, was positioned colonoscopically in an unprepared bowel to a distance of 35 cm from the anus with minimal air inflation. During withdrawal of the colonoscope, suction was applied to remove any air introduced into the colon at endoscopy. No sedation was used and no patient complained of undue discomfort during the procedure.

The solid-state catheter was connected to an IBM-PC computer via an analog-digital converter (PC-Polygraph; Synectics Medical, Stockholm, Sweden), and the data stored and analysed using Synectics Medical software (Polygram Lower GI Edition, version 5.0).

Analysis of data

The preprandial period was defined as the 30 min prior to the test meal, periprandial as the 30 min starting at the beginning of the test meal and postprandial as the final 30 min of the recording period. Each of these periods was analysed to yield values for: (i) the number of pressure waves greater than 20 mmHg; (ii) the mean amplitude of pressure peaks; (iii) the percentage duration of activity calculated as the sum of the duration of individual pressure waves expressed as a percentage of each epoch; (iv) the motility index calculated as the product of mean amplitude and percentage duration of activity in each 30-min epoch; and (v) the activity index (i.e. area under the curve calculated by integration of the curve).

The effect of the meal on colonic motility was assessed by comparing the pre- and peri-meal periods, and the peri- and post-meal periods using the Wilcoxon matched-pairs signed-rank test.

The effects of zamifenacin 10 mg, zamifenacin 40 mg and placebo on changes in colonic motility were compared using the non-parametric Kruskal–Wallis analysis of variance test on the changes between the screening and study days. Paired comparisons between each of the active treatment groups and the placebo group were made using the Wilcoxon rank-sum test for two independent groups. Prior to the main analysis described, the placebo patients from the two consecutive groups were compared using the Wilcoxon rank-sum test and, as they were not significantly different, they were combined into one placebo group. Differences were considered to be significant at the 5% level.

RESULTS

Of the 48 patients who underwent the screening assessment, 36 were randomized to treatment: nine patients receiving 40 mg zamifenacin, nine patients 10 mg zamifenacin and 18 patients placebo control. Of the 12 non-randomized patients, three had abnormal laboratory results which were not related to the study drug, five did not meet selection criteria, one asked to be withdrawn and three violated the protocol by testing positive for substance abuse.

Figure 1 shows the effect of the standard meal on colonic motility during the screening assessment in the 36 patients randomized to treatment. All parameters significantly increased in response to the meal (pre- vs. peri-meal; $P < 0.0001$). However, during the post-meal period there was a significant decrease in all but mean amplitude with respect to the peri-meal period; although all values remained higher than during the pre-meal period.

Compared with placebo, 40 mg zamifenacin reduced all motility parameters measured pre-, peri- and post-prandially, although the pre- and periprandial activity index and the preprandial motility index did not reach statistical significance (Figures 2 and 3). This reduction in activity was particularly evident during the post-prandial period. A smaller reduction in motility was

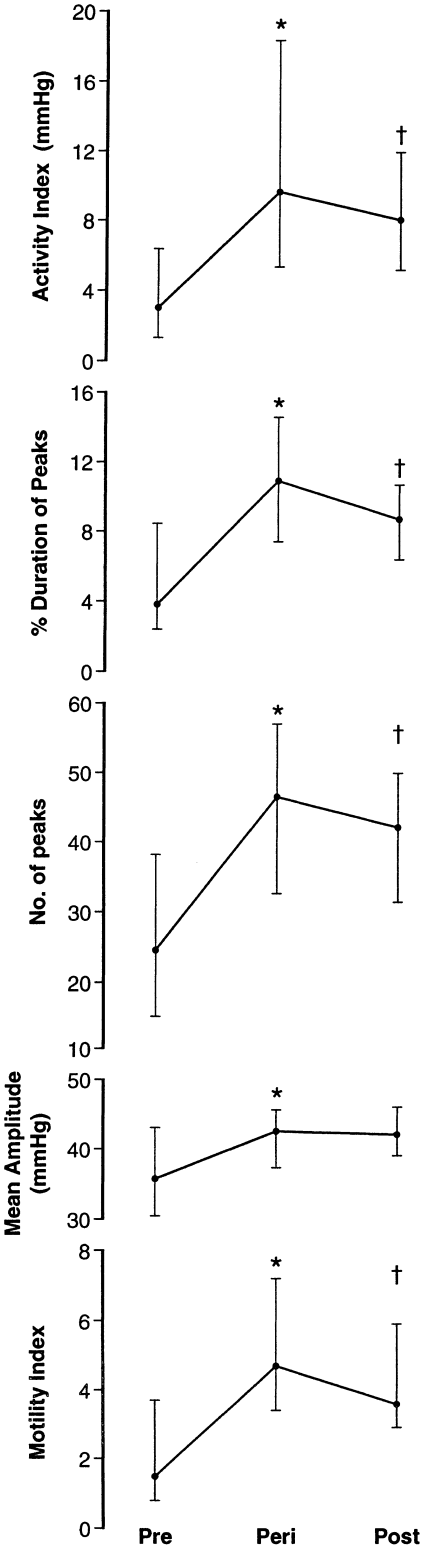

Figure 1. The effect of the standard meal on all the colonic motility parameters assessed. Data are expressed as median plus interquartile range. * Statistically significantly different from preprandial, $P < 0.001$. † Statistically significantly different from periprandial, $P < 0.02$.

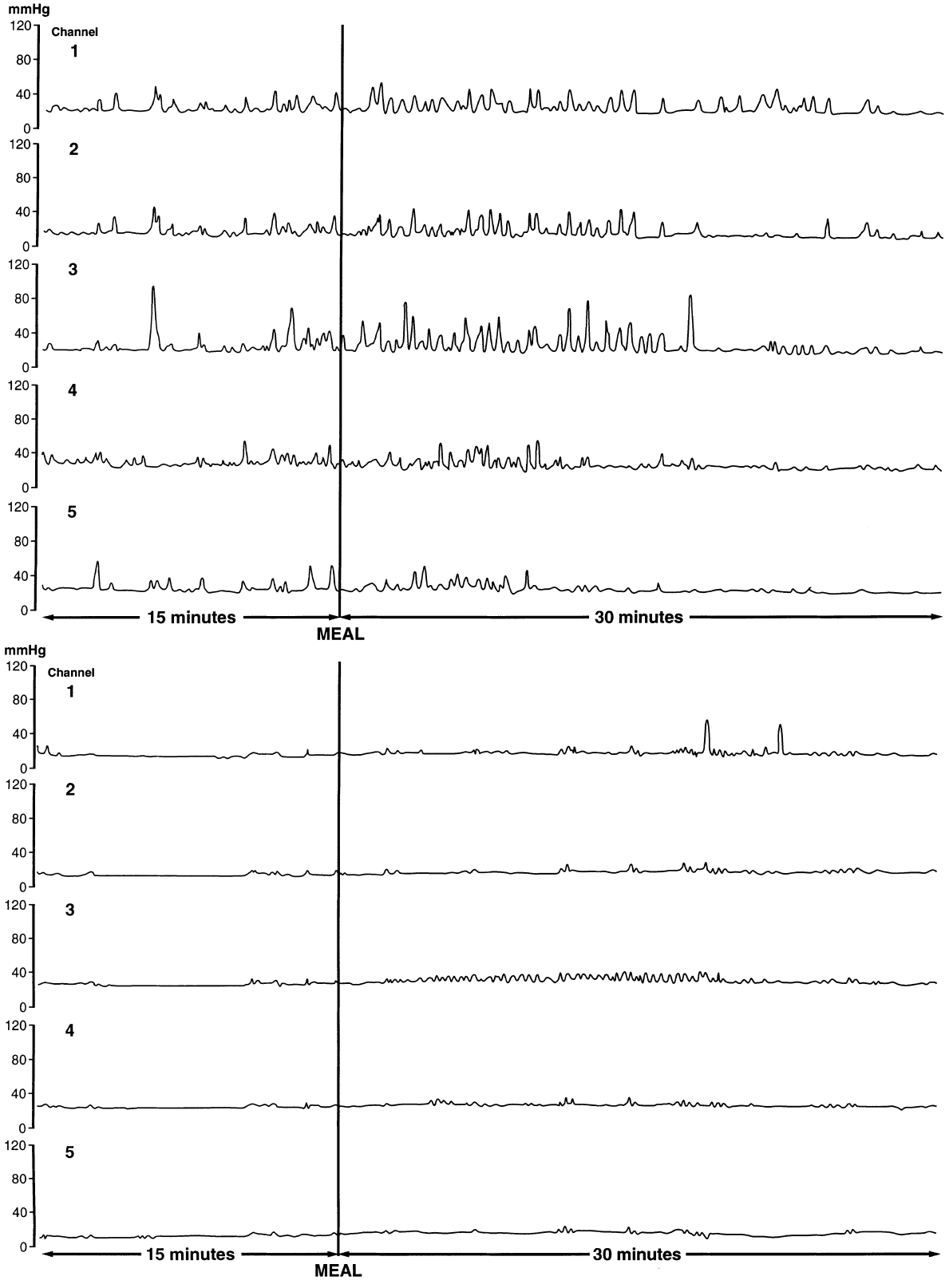

Figure 2. The effect of the standard meal on colonic motility during the screening visit (top tracing) and the effect of 40 mg zamifenacin pre- and post-meal ingestion (bottom tracing) in the same patient. Channels 1–5 represent motility recordings obtained from pressure transducers situated 35, 30, 25, 20 and 15 cm from the anal verge.

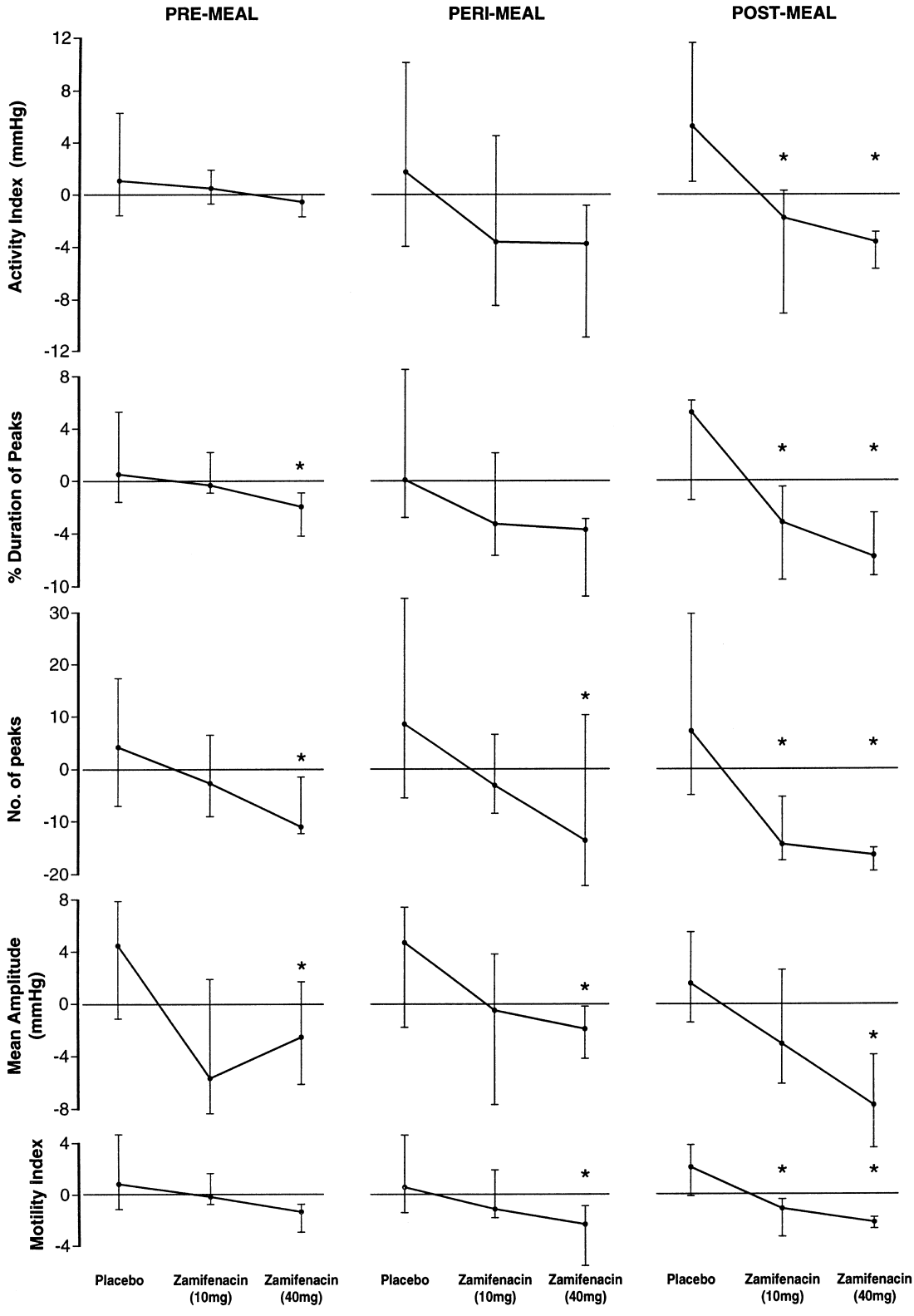

Figure 3. The changes in all colonic motility parameters from screening to study days for all three treatment groups (zamifenacin 40 mg, zamifenacin 10 mg and placebo). Data are expressed as median changes from screening to study day plus interquartile range.
* Statistically significant difference from placebo, $P < 0.05$.

seen after 10 mg zamifenacin, although statistical significance was only found for the postprandial activity index, percentage duration of peaks, the number of peaks and the motility index ($P < 0.05$).

Side-effects

Three patients each on placebo and zamifenacin (two on 40 mg and one on 10 mg) reported side-effects. These consisted of mild blurred vision, dizziness, nausea, dry mouth, shivering and palpitations. One placebo patient reported mild blurred vision and the rest headache, vomiting and muscular pain.

Electrocardiograph measurements showed no evidence of tachycardia and there were no clinically significant changes in blood pressure. There was only one report of a possibly treatment-related laboratory test abnormality and this occurred in one of the patients who had received placebo treatment. This patient had raised lactate dehydrogenase (LDH) accompanied by muscular pain for 4 days after treatment. As there were no abnormalities in liver function tests, the raised LDH may have been of muscular origin.

DISCUSSION

This study has shown that zamifenacin, a selective M_3 muscarinic receptor antagonist, is effective at reducing distal colonic motility, particularly postprandially, in patients with irritable bowel syndrome. In addition, the atropine-like side-effects usually associated with such drugs were minimal, suggesting that zamifenacin has much greater gut selectivity than conventional anticholinergics.

It is now believed that both abnormal motility and visceral sensitivity of the small and large bowel play important roles in the pathophysiology of irritable bowel syndrome.[1–15] Motility disturbances tend to be more prevalent following stimulation of the intestine by, for example, meal ingestion,[5, 6] balloon distension,[9, 11–13] or intravenous infusion of cholecystokinin or pentagastrin.[17] In particular the colonic motor response to food appears to be exaggerated,[4–8] and in some patients associated with abdominal pain.[8] However, abnormal motility does not always correlate well with symptomatology and this could be accounted for by disordered visceral hypersensitivity. It is now known that the whole of the gastrointestinal tract is more sensitive in patients with irritable bowel syndrome than in normal healthy volunteers,[9–15] and it may be that this could lead to contractions whose amplitudes are within the normal range being perceived as painful events. A further confounding factor may be the effect of exogenous stimuli such as stress. Many patients claim that stress exacerbates their symptoms, and it has been shown that stress increases colonic motility in patients with irritable bowel syndrome,[2, 18, 19] although in some studies this response has been shown to be no more exaggerated than in normal healthy volunteers.[4, 20] Emotion, in the form of anger, has also been shown to enhance rectal visceral sensitivity.[21] The role of frank psychopathology is far less clear, as although it is common in hospital attenders with irritable bowel syndrome it is now known that non-consulters with irritable bowel syndrome exhibit the same prevalence of psychological problems as the normal population.[22–24]

These various observations have led to therapy being directed at either increasing stool bulk, controlling stress and anxiety levels, reducing motility and normalizing gut visceral sensitivity, although it should be noted that this latter approach is still at a developmental stage. Unfortunately the conventional treatments that are at present available suffer a number of drawbacks. Bulking agents can often exacerbate symptoms, and results from controlled trials of antidepressants have been conflicting; some demonstrating an improvement in both the overall well-being and irritable bowel syndrome symptomatology, while others show either only an increase in ability to cope with symptoms or no improvement at all.[25–29] Anxiolytic drugs have not been fully assessed but there is no convincing evidence that these are effective in irritable bowel syndrome.[30] Antimuscarinics at doses that are effective at reducing motility are often associated with unwanted atropine-like side-effects. Thus, although most trials have shown some improvement in well-being,[31–37] only a few have shown a beneficial effect on abdominal pain and in most of these it was relatively minor.[31–35] Various serotonin (5HT) receptor subtypes may be involved in the perception of visceral sensation and, to date, attempts to modulate hypersensitivity have largely focused on the $5HT_3$ receptor.[38–41] However, although granisetron has been shown to reduce rectal sensitivity to balloon distension in patients with irritable bowel syndrome,[42] other studies have not been able to show an effect of either oral or intravenous ondansetron on rectal and stomach visceral sensation in normal healthy volunteers.[43, 44] Furthermore, clinical trials of ondansetron

on diarrhoea-predominant irritable bowel syndrome have been rather disappointing.[40, 41] Thus, there is currently a strong need for more effective forms of therapy for irritable bowel syndrome particularly as it represents such a large work load for gastroenterologists as well as primary care physicians.[45–47]

The results of this study show that a selective M_3 receptor antagonist can significantly inhibit food-stimulated distal colonic motility with relatively minor anticholinergic side-effects. Therefore the development of such compounds, which may not only reduce the strength of abnormal contractions but also minimize the perception of normal motility in a viscerally hypersensitive subject, is a promising approach to the treatment of irritable bowel syndrome.

ACKNOWLEDGEMENT

This study was funded by Pfizer Central Research, UK.

REFERENCES

1 Thompson DG, Laidlow JM, Wingate DL. Abnormal small bowel motility demonstrated by radiotelemetry in a patient with irritable colon. Lancet 1979; ii: 1321–3.
2 Kumar D, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. Lancet 1985; ii: 973–7.
3 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 1987; 92: 1885–93.
4 Wangel AG, Deller DJ. Intestinal motility in man. III. Mechanisms of constipation and diarrhoea with particular reference to the irritable colon syndrome. Gastroenterology 1965; 48: 69–84.
5 Connell AM, Avery Jones F, Rowlands EN. Motility of the pelvic colon. IV. Abdominal pain associated with colonic hypermotility after meals. Gut 1965; 6: 105–12.
6 Sullivan MA, Cohen S, Snape WJ. Colonic myoelectrical activity in irritable bowel syndrome: effect of eating and anticholinergics. New Engl J Med 1978; 298: 878–83.
7 Narducci F, Bassotti G, Granata MT, *et al*. Colonic motility and gastric emptying in patients with irritable bowel syndrome. Effect of pretreatment with octylonium bromide. Dig Dis Sci 1986; 31: 241–6.
8 Holdstock DJ, Misiewicz JJ, Waller SL. Observations on the mechanism of abdominal pain. Gut 1969; 10: 19–31.
9 Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973; 14: 125–32.
10 Whitehead WE, Holtkotter B, Enck P, *et al*. Tolerance for rectosigmoid distension in irritable bowel syndrome. Gastroenterology 1990; 98: 1187–92.
11 Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. Gut 1990; 31: 458–62.
12 Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhoea-predominant and constipation-predominant patients. Dig Dis Sci 1980; 25: 404–13.
13 Prior A, Sun W-M, Read NW. Irritable bowel syndrome: differences between patients who show rectal sensitivity and those who do not. Eur J Gastroenterol Hepatol 1993; 5: 343–9.
14 Costantini M, Sturniolo GC, Zaninotto G, *et al*. Altered esophageal pain threshold in irritable bowel syndrome. Dig Dis Sci 1993; 38: 206–12.
15 Francis CY, Houghton LA, Whorwell PJ, Morris J, Bradbury J. Enhanced sensitivity of the whole gut in patients with irritable bowel syndrome. Gastroenterology 1995; 108: 601.
16 Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disorders and functional abdominal pain. Gastroenterol Int 1992; 5: 75–91.
17 Snape WJ, Carlson GM, Matarazzo SA, *et al*. Evidence that abnormal myoelectrical activity produces colonic motor dysfunction in irritable bowel syndrome. Gastroenterology 1977; 72: 383–7.
18 Welgan P, Meshkinpour H, Beeler M. Effect of anger in colon motor and myoelectric activity in irritable bowel syndrome. Gastroenterology 1988; 94: 1150–6.
19 Whorwell PJ, Houghton LA, Taylor EE, Maxton DG. Physiological effects of emotion: assessment via hypnosis. Lancet 1992; 340: 69–72.
20 Narducci F, Snape WJ, Battle WM, London RL, Cohen S. Increased colonic motility during exposure to a stressful situation. Dig Dis Sci 1985; 30: 40–4.
21 Houghton LA, Cooper P, Jackson NA, Whorwell PJ. Visceral sensation and emotion: a study using hypnosis. Gastroenterology 1995; 108: 3470(Abstract).
22 Greenbaum D, Abitz L, VanEgeren L, Mayle J, Greenbaum R. Irritable bowel syndrome prevalence, rectosigmoid motility and psychometrics in symptomatic subjects not seeking physicians. Gastroenterology 1983; 84: A1174(Abstract).
23 Drossman DA, McKee DC, Sandler RS, *et al*. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and non-patients with irritable bowel syndrome. Gastroenterology 1988; 95: 701–8.
24 Whitehead WE, Bosmajian L, Zonderman AB, Costa PT, Schuster MM. Symptoms of psychological distress associated with irritable bowel syndrome. Comparison of community and medical clinic samples. Gastroenterology 1988; 95: 709–14.
25 Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. Lancet 1994; 344: 39–40.
26 Lancaster-Smith MJ, Prout BJ, Pinto T, Anderson JA, Schiff AA. Influence of drug treatment on the irritable bowel syndrome and its interaction with psychoneurotic morbidity. Acta Psychiatr Scand 1982; 66: 33–41.
27 Myren J, Groth H, Larssen SE, Larsen S. The effect of trimipramine in patients with irritable bowel syndrome: a double blind study. Scand J Gastroenterol 1982; 17: 871-5.

28 Heefner JD, Wilder RM, Wilson ID. Irritable colon and depression. Psychosomatics 1978; 19: 540–7.
29 Steinhart MJ, Wong PY, Zarr ML. Therapeutic usefulness of amitriptyline in spastic colon syndrome. Int J Psychiatry Med 1981–2; 11: 45–57.
30 Dotevall G, Groll E. Controlled clinical trial of mepiprazole in irritable bowel syndrome. Br Med J 1974; 4: 16–8.
31 Kruis W, Weinsierl M, Schussler P, Holl J. Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with irritable bowel syndrome. Digestion 1986; 34: 196–201.
32 Connell AM. Physiological and clinical assessment of the effect of the musculotropic agent meberverine on the human colon. Br Med J 1965; 2: 848–51.
33 Baume P. Mebervine, an effective agent in irritable bowel syndrome. Aust NZ J Med 1972; 2: 34–6.
34 Tasman-Jones C. Mebeverine in patients with irritable colon syndrome: double blind study. NZ Med J 1973; 77: 232–5.
35 Berthelot J, Centonze M. Etude controlee en double aveugle Duspatalin (Mebeverine) contre placebo, dans le traitement du colon irritable. Gaz Med Fr 1981; 88: 2341–3.
36 Piai G, Mazzacca G. Prifinium bromide in the treatment of the irritable colon syndrome. Gastroenterology 1979; 77: 500–2.
37 Rees WDW, Evans BK, Rhodes J. Treating irritable bowel syndrome with peppermint oil. Br Med J 1979; 2: 835–6.
38 Talley NJ. 5-Hydroxytrptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. Aliment Pharmacol Ther 1992; 6: 273–89.
39 Costall B, Naylor RJ. 5-Hydroxytryptamine new receptors and novel drugs for gastrointestinal motor disorders. Scand J Gastroenterol 1990; 25: 769–87.
40 Steadman C, Talley NJ, Phillips SF, Van Dyke C. Selective 5-hydroxytryptamine type 3 receptor antagonism with ondansetron as treatment for diarrhoea-predominant IBS: a pilot study. Mayo Clin Proc 1992; 67: 732–8.
41 Maxton DG, Haigh CG, Whorwell PJ. $5HT_3$ antagonists: a role in irritable bowel syndrome and non-ulcer dyspepsia. Gut 1991; 32: A1228(Abstract).
42 Prior A, Read NW. Reduction of rectal sensitivity and postprandial motility by granisetron, a $5HT_3$ receptor antagonist, in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1993; 7: 175–80.
43 Goldberg PA, Kamm MA, Setti-Carraro P, Van Der Sijp JRM, Roth C. $5HT_3$ antagonism does not modify visceral sensation or compliance in healthy subjects. Gastroenterology 1993; 104: A512(Abstract).
44 Wilmer A, Tack J, Coremans G, Janssens J, Vantrappen G. Effect of ondansetron, a $5HT_3$ receptor antagonist on perception of gastric distension and gastric compliance in healthy man. Gastroenterology 1993; 104: A603(Abstract).
45 Switz DM. What the gastroenterologist does all day. Gastroenterology 1976; 70: 1048–50.
46 Ferguson A, Sircus W, Eastwood MA. Frequency of functional gastrointestinal disorders. Lancet 1977; ii: 613–4.
47 Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. Lancet 1983; i: 632–4.