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Double-blind study of an α_2 agonist in the treatment of irritable bowel syndrome

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SUMMARY

A double-blind crossover trial of the α_2 agonist lidamidine hydrochloride in 72 patients with irritable bowel syndrome is reported. Lidamidine was found to have no significant effect on frequency and severity of abdominal pain or abdominal bloating. It did cause a statistically significant reduction in frequency of defaecation ($P = 0.005$), but this was of a degree unlikely to be of clinical importance. Although α_2 agonists inhibit gastrointestinal motility in animals this study suggests that lidamidine hydrochloride does not have a useful therapeutic role in irritable bowel syndrome.

INTRODUCTION

Although the pathophysiology of the irritable bowel syndrome has yet to be defined clearly, there is evidence that disordered colonic motility may account for some of its symptomatology.[1] Therapeutic agents, therefore, are often directed towards decreasing motor activity of the colon, usually through an anti-cholinergic effect. The response to treatment, however, is unpredictable and often unsatisfactory.[2]

Studies in experimental animals have suggested that α_2 adrenoreceptor

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agonists inhibit gastrointestinal motility[3,4] and may therefore be of benefit in patients with irritable bowel syndrome. We report a double-blind controlled trial of lidamidine hydrochloride (Rorer Inc. Washington, PA), an α_2 agonist, in patients with irritable bowel syndrome.

PATIENTS AND METHODS

Seventy-two patients with irritable bowel syndrome (62 women, 10 men, age range 18–64 years) were recruited from the out-patient department. Diagnosis of irritable bowel syndrome was based on the presence of abdominal pain and distension together with an abnormal bowel habit (diarrhoea, 19 patients; constipation, 24 patients; alternating diarrhoea and constipation, 29 patients). All patients had normal haematology, biochemistry, sigmoidoscopy and, in those over 40 years, contrast radiology or colonoscopy.

The study was performed as a double-blind crossover trial. After a 2-week washout period, during which patients took placebo, they were randomized into a 4-week period receiving either lidamidine or matching placebo (corn starch). The initial dose of lidamidine was 8 mg/day but patients were instructed to increase the dose to 16 mg/day after 2 weeks if symptoms were still present. This was followed by a further 2-week washout on placebo, and a final 4-week phase during which patients received the opposite therapy to that given in the initial treatment period.

Throughout the study patients entered details of their bowel habit, and the severity and frequency of abdominal pain and distension on diary cards. Severity of abdominal pain and distension was scored daily on a 0–3 scale with 0 = none, 1 = mild, 2 = moderate and 3 = severe. These scores were totalled for each 7 days so that a mean weekly score on a 0–21 scale could be calculated for each parameter. Follow-up visits were performed every 2 weeks at which patients were asked to score the severity of heartburn, nausea and post-prandial discomfort over the preceding fortnight on a 0–3 scale and the physician recorded a subjective evaluation of overall efficacy.

Results were analysed on an intent to treat basis and included only patients with data in both periods. The statistical analysis was performed using an analysis of covariance for a two-period crossover design.[5] Significant effects uncovered by this analysis were investigated in detail using appropriate multiple comparison tests. Statistical significance was set at the conventional 5% level. The patients gave written consent before entering the study which was approved by the district ethical committee.

RESULTS

Data from 57 patients were available for the final crossover analysis. Six patients were withdrawn whilst taking lidamidine: three due to adverse reactions and three

Table 1. Summary of study results

	Placebo		Lidamidine		Between treatment
	Baseline	End study	Baseline	End study	*P* value
Pain					
Frequency (episodes/week)	8.9	8.6	9.3	8.5	0.798
Severity (score/week)	9.1	9.9	9.3	8.9	0.152
Distension (score/week)	11.1	10.6	10.5	10.8	0.512
Bowel habit (stools/week)	11.3	12.5	12.1	10.5	0.005
Global assessment (%)					
Much improved	—	21	—	26	—
Slightly improved	—	31	—	24	—
Unchanged	—	33	—	31	—
Worse	—	15	—	19	—

lost to follow-up. Four patients withdrew whilst on placebo: two due to adverse reactions, one because of inefficacy, and one lost to follow-up. Five patients were not evaluable because of data deficiencies.

The results of the study are summarized in Table 1. There was little change in the frequency of abdominal pain on either lidamidine or placebo. Severity of pain improved marginally on lidamidine, and slightly worsened during the placebo phases, but neither change reached statistical significance. The response to treatment was similar in patients presenting with constipation, diarrhoea or an alternating bowel habit.

Abdominal distension was also little changed by treatment with either lidamidine or placebo and no significant changes in heartburn, nausea or post-prandial discomfort occurred on either placebo or lidamidine.

The average weekly number of bowel movements decreased from baseline on lidamidine, but was increased by placebo. Although the difference reached statistical significance ($P = 0.005$) the changes were relatively small (Table 1) and not of a degree to be useful clinically. Detailed examination of the data suggested that the reduction in defaecation by lidamidine occurred mainly in those with diarrhoea rather than in the constipated patients. However, the number of subjects in the subgroups was too small for any meaningful statistical comparison to be made.

Global evaluation of efficacy revealed no significant difference between lidamidine and placebo. Approximately a quarter of patients were rated much improved, but 50% were unchanged or worse (Table 1).

DISCUSSION

This study suggests that the α_2 agonist, lidamidine, is not effective in reducing abdominal pain and distension in patients with irritable bowel syndrome. It did

cause a reduction in frequency of defaecation, as noted previously in studies of acute and chronic diarrhoea,[6,7] but this was of a degree unlikely to be of clinical significance.

In the gut the primary result of α_2 receptor stimulation is inhibition of acetylcholine release. α_2 Receptors are located pre-synaptically on cholinergic nerves and also post-synaptically on epithelial cells.[1] α^2 Receptor agonists might therefore be expected to influence many gastrointestinal functions mediated through acetylcholine release, such as intestinal motility and secretion. Studies in animals have revealed inhibition of both small intestinal and colonic motility by lidamidine.[1,2] However, studies in humans have shown that lidamidine does not significantly affect small bowel transit time,[8,9] suggesting that its anti-diarrhoeal action is largely due to inhibition of secretion rather than affecting small intestinal motility. It has been suggested that in humans α_2 agonists may act more on the colon rather than the small bowel by inhibiting contractile activity. Although doubt remains concerning the origin of the symptoms of irritable bowel syndrome, episodes of gastrointestinal spasm have been shown to correlate with the onset of abdominal pain.[10] The results of the present study suggest that lidamidine does not inhibit colonic motor activity to a degree which is clinically useful in humans.

In comparison to previous therapeutic trials in irritable bowel syndrome,[2] there was little placebo effect noted in the present study. Although 20% of patients felt 'much improved' whilst on placebo, individual symptoms changed little from baseline. This anomaly was not due to improvement in other gastrointestinal symptoms that may be associated with irritable bowel syndrome as anorexia, heartburn, nausea and post-prandial discomfort also demonstrated no clinically significant changes. The improvement probably reflects the support and intensive follow-up associated with a clinical trial and emphasizes the importance of assessing efficacy in terms of individual symptoms, rather than solely in terms of global improvement.

It appears, therefore, that α_2 agonists may not be useful in the treatment of irritable bowel syndrome unless more potent or specific examples of this class of drugs can be developed.

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