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Beta-blockade in irritable-bowel syndrome—an assessment in anxious patients with diarrhoea

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SUMMARY

It is not common practice to target therapy to specific subgroups of patients with irritable-bowel syndrome. It was the purpose of this study to assess the effect of β-adrenoceptor blockade in patients with irritable-bowel syndrome characterized by anxiety and diarrhoea using a double-blind, cross-over design. Compared with placebo, 10 mg of bisoprolol appeared to have no significant beneficial effect upon either symptomatology, anorectal sensitivity or whole-gut transit time. However, active therapy did not adversely effect the symptoms of irritable-bowel syndrome. Beta-blockade does not appear useful in the treatment of irritable-bowel syndrome but can be prescribed without fear of exacerbating symptoms if indicated for other reasons.

INTRODUCTION

Therapeutic trials in irritable-bowel syndrome (IBS) usually fail to take account of the fact that there may be subgroups of the disorder with differing pharmacological responsiveness. A sizeable proportion of patients with this condition exhibit a high level of psychological abnormality, frequently taking the form of heightened anxiety.[1,2] It is common experience, even in healthy individuals, that stress or anxiety-provoking situations may lead to urinary or bowel frequency and patients with IBS often attribute exacerbations of their disorder to stressful life events.[3,4]

It is therefore tempting to suggest that reducing the level of anxiety in patients with irritable-bowel syndrome in whom anxiety is a prominent feature may lead to a symptomatic improvement. Beta-adrenoceptor blockade reduces some of the somatic features of anxiety and is currently used in its treatment.[5] The aim of this study was to investigate whether bisoprolol, a β_1-adrenoreceptor-blocking agent, was effective in relieving symptoms of irritable-bowel syndrome in subjects in whom anxiety and diarrhoea were predominant. Such patients have recently been shown to have increased rectal sensitivity to distension,[6] so the effect of treatment with bisoprolol on ano-rectal manometry and whole-gut transit time was also assessed.

METHODS

Patients

Patients were considered eligible for the study only if they reported diarrhoea-predominant irritable-bowel syndrome with at least two loose bowel motions per day. In addition, all subjects fulfilled the criteria of irritable-bowel syndrome as defined by the International IBS Working Team.[7] All suitable subjects were screened for active psychopathology with the Hospital Anxiety and Depression questionnaire[8] and only those scoring 8 or greater for anxiety recruited to the study.

Ten patients (seven women and three men; age range 19–56 years) fulfilled the criteria for entry. The study was of a randomized, double-blind, cross-over design. An initial treatment-free baseline period of 2 weeks without any prophylactic medication was followed by two 4-week treatment periods separated by a 2-week washout phase. Patients were randomized to receive either bisoprolol 10 mg daily or matching placebo during the first treatment period and the alternative during the second.

Symptom scores

Subjects were seen at 2-weekly intervals during the study period. Each patient recorded daily on diary cards details of abdominal pain, distension, bowel habit and stool consistency. Symptom severity was scored over a range of 0–4 for each feature and the overall score per week determined by totalling the recorded daily scores. In addition, a record was kept by each patient of their daily bowel habit. The total number of bowel actions per day was further subdivided into three categories according to consistency: loose or watery, formed or normal, and hard or very hard. At each hospital visit a global assessment of symptom severity over the preceding 2 weeks was also made by the same physician monitoring the patient.

Anorectal manometry

Standard anorectal manometry was performed at the end of the initial baseline period and after each treatment phase. An air-filled balloon was inserted into the rectum and the volume required to produce the sensations of gas, stool, urgency and discomfort recorded. The rectal pressures corresponding to these volumes were also recorded.

Anxiety scores

Anxiety levels were assessed at the start of the study, at the end of the initial baseline period and after each treatment phase. Anxiety was rated using both the Hospital Anxiety and Depression Questionnaire and the short version of the Anxiety Symptom Rating Test.[8]

Whole-gut transit time

During the baseline period and at the end of each treatment phase whole-gut transit time was measured by oral ingestion of a 'Brilliant Blue' stool marker. The time taken until first appearance and disappearance of the marker in the stool was recorded.

Compliance
All unused drugs were returned for tablet counting at each visit.

Statistics

Statistical comparison was made by repeated-measures analysis of variance. Specific differences between visits were investigated using Tukey's critical range test. Some measurements were found to follow a log-normal distribution and in these cases a log transformation was carried out prior to analysis.

RESULTS

Results of symptom scores are given in Table 1. The order in which patients took the active phase and placebo did not affect the results and so results are shown with the treatment phase first for ease of presentation. Treatment with bisoprolol did not significantly alter any recorded disease parameter. Thus the abdominal pain, distension and overall symptom scores assessed by the patients themselves and the physicians overall assessment were no different before or after active treatment or placebo. Bisoprolol therapy also had no effect upon the total number of bowel actions per day (Table 1). Stool consistency did not change over the study period compared with placebo. Assessments of levels of anxiety and depression were similar after active treatment to placebo and baseline values (Table 1).

Rectal visceral sensitivity was also unaffected by treatment with bisoprolol. The volumes of air required to elicit rectal sensation was not significantly different after active or placebo treatment (Table 2). Whole-gut transit time was rather variable but again no significant alteration was apparent on treatment with bisoprolol compared to placebo.

Treatment with 10 mg of bisoprolol produced no significant adverse events.

Table 1. Symptom and psychological scores during treatment with bisoprolol and placebo. There were no significant differences between the treatment and placebo groups

	Baseline	Bisoprolol	Placebo
Overall IBS Score	16.1	15.7	14.4
Pain	14.9	13.7	13.1
Distension	13.8	15.0	12.0
Bowel habit	19.1	13.7	13.1
% Loose Actions	71	47	48
Physician's Global Assessment	2.2	2.0	1.9
Anxiety Score	9.2	8.3	9.0
Depression Score	6.6	6.7	5.7
Anxiety Symptom Rating Score	26.0	28.2	24.8

Table 2. Mean (95% confidence interval) volume (ml) required to produce the rectal sensations of gas, stool, urgency of defaecation and discomfort. There were no significant differences between the treatment and placebo groups

Sensation	Baseline	Bisoprolol	Placebo
Gas	42	44	53
	(27,65)	(29,68)	(34,81)
Stool	66	79	79
	(42,105)	(50,124)	(50,124)
Urgency	115	119	109
	(87,154)	(89,158)	(82,145)
Discomfort	156	155	142
	(130,188)	(128,186)	(118,172)

DISCUSSION

There has been only one previous systematic assessment of the effect of β-blockade in IBS.[9] However, in that study patients were not subgrouped and no physiological measurements or assessment of anxiety was made. Our trial attempted to target a subset of IBS patients most likely to respond to β-blockade, namely those with anxiety and diarrhoea. Despite this there appeared to be no beneficial effect on their symptoms. The effect of β-blockade on rectal sensitivity has not been previously investigated. However, bisoprolol failed to modify anorectal responsiveness to distension, suggesting that the β-adrenergic system does not have a prominent role in mediating rectal visceral sensitivity.

One possible approach to treating the psychological aspects of IBS is the use of either antidepressants or anxiolytics. There are a number of drawbacks, particularly side-effects and dependency, associated with the use of these drugs and β-blockade is now a fashionable alternative. It was perhaps surprising that no change in anxiety levels was observed during treatment with bisoprolol. There are several possible explanations for this finding. First, although the anxiolytic efficacy of β-blockade is thought to be independent of selectivity, bisoprolol is very highly selective and may therefore be less beneficial in this respect. Alternatively, drug characteristics such as lipid solubility, intrinsic sympathomimetic activity and dosage may lead to subtle differences in effect. Lastly, the anxiety questionnaire may be more dependent on central features than the peripheral manifestations that are traditionally thought to be modified by β-blockade.[10]

The subjects selected for this study were those judged most likely to respond to therapy with β-blockade. Thus, the negative results obtained suggest that β-blockers do not have a therapeutic role in IBS. However, no exacerbation of symptoms was observed and therefore β-blockers are not contra-indicated in IBS patients prescribed them for other reasons.

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REFERENCES

1 Drossman DA, McKee DC, Sandler RS *et al.* Psychosocial factors in the irritable bowel syndrome. *Gastroenterology* 1988; **95:** 701–708.
2 Maxton DG, Morris JA, Whorwell PJ. Ranking of symptoms by patients with the irritable bowel syndrome. *Br Med J* 1989; **299:** 1138.
3 Creed F, Craig T, Farmer R. Functional abdominal pain, psychiatric illness, and life events. *Gut* 1988; **29:** 235–242.
4 Ford MJ, Miller PMcC, Eastwood J, Eastwood MA. Life events, psychiatric illness and the irritable bowel syndrome. *Gut* 1987; **28:** 411–421.
5 James I, Savage I. Beneficial effect of nadolol on anxiety-induced disturbances of performance in musicians. *Am Heart J* 1984; **108:** 1150–1155.
6 Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. *Gut* 1990; **31:** 458–462.
7 Thompson WG, Drossman D, Doteval G, Heaton K, Kruis W. Irritable bowel syndrome: guidelines for the diagnosis. IBS Working Team report, Rome 1988. *Gastroenterol Int* 1989; **2:** 92–95.
8 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–370.
9 Fielding JF. Timolol treatment in the Irritable Bowel Syndrome. *Digestion* 1981; **22:** 155–158.
10 Opie LH, Sonnenblick EH, Kaplan NM, Thadani U. Beta-blocking agents. In: Opie LH, ed. *Drugs and the Heart.* New York: Grune and Stratton, 1987: 1–18.