A double-blind study of nicardipine in irritable bowel syndrome

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Previous studies have suggested that calcium antagonists inhibit colonic motility and therefore may have therapeutic potential in irritable bowel syndrome. This possibility was assessed in a double-blind cross-over trial of the calcium antagonist nicardipine in 62 patients with irritable bowel syndrome. Nicardipine significantly decreased whole gut transit time ($P = 0.02$) in constipated patients, but there was no effect on transit time in those with diarrhoea, or an alternating bowel habit. However, significant effects on general well-being, abdominal pain, abdominal distension or bowel habit were not observed. This study suggests that nicardipine does not have a useful therapeutic effect in irritable bowel syndrome.

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Introduction

Irritable bowel syndrome is one of the commonest conditions seen in gastroenterological practice [1–3] yet its treatment remains far from satisfactory [4,5]. Although the pathophysiological basis for its symptomatology remains unclear, there is evidence that exaggerated motor activity of both the large [6] and small bowel [7,8] may be important. Therapeutic intervention in irritable bowel syndrome is therefore often directed towards decreasing intestinal motility and, at present, this is usually mediated through using anticholinergic pathways.

Studies in patients with irritable bowel syndrome have suggested that calcium channel blocking agents reduce colonic motor activity following meal ingestion [9–11], suggesting that they may have a therapeutic role in this condition. We report a double-blind controlled trial of the calcium antagonist nicardipine in patients with irritable bowel syndrome.

Patients and methods

Sixty-two patients with irritable bowel syndrome (57 women, five men, age range 19–65 years, mean 40.1 years) were recruited from the outpatient department. Diagnosis of irritable bowel syndrome was based on the presence of non-menstrual abdominal pain and distension, together with an abnormal bowel habit (diarrhoea, 19 patients; constipation, 19 patients; alternating diarrhoea and constipation, 24 patients). Diarrhoea was defined as the passage of three or more loose stools per day and constipation as less than three stools per week or frequent straining. All patients had normal haematology, biochemistry, sigmoidoscopy and, in those over 40 years of age, contrast radiology or colonoscopy. The mean duration of symptoms prior to entry into the trial was 7.2 years (range 6 months–25 years) and these were present on at least 3 days per week. Most patients had received multiple previous therapies for irritable bowel syndrome (mean 3.4, range 1–7 years).

The study was performed as a double blind cross-over trial. After a 2-week run-in period during which patients took placebo, they were randomized into a 4-week treatment period receiving either nicardipine or matching placebo. After a further 2-week placebo phase, they crossed over to the alternative treatment phase. The initial dose of nicardipine was 60 mg per day but patients were instructed to increase the dose to 90 mg per day after 2 weeks if symptoms were still present. Follow-up visits were performed at 2-weekly intervals.

Throughout the study, patients entered details of their bowel habit, the severity of abdominal pain and distension and their general well-being on daily diary cards. Severity of abdominal pain and distension was scored on a 0–3 scale with 0 = none, 1 = mild, 2 = moderate, and 3 = severe; general well-being was also scored on a 0–3 scale with 0 = very well, 1 = well, 2 = unwell, and

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3 = very unwell. 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. Whole gut transit time was assessed during the baseline period and in each of the 4-week study periods using a carmine marker technique in which patients ingested 720 mg of dye at 0900 hours on the study day and recorded the time at which their stools first became discoloured.

Results were analysed on an 'intent to treat' basis and included only patients who completed at least 2 weeks of the second treatment period. The statistical analysis was performed using an analysis of covariance for a two-period crossover design with statistical significance set at the 5% level. Both clinical and transit data were analysed to ensure that an order effect was not affecting the results obtained. The patients gave written consent before entering the study which was approved by the district ethical committee.

Results

Fifty-one patients completed at least 2 weeks of the second treatment period and were therefore available for analysis (diarrhoea, 17; constipation, 16; alternating, 18). There were no significant differences in the age or male:female ratio in the bowel habit sub-groups. Of those patients not included in the analysis, four withdrew in the run-in period before receiving any medication, two withdrew in the wash-out period between treatments, four were withdrawn whilst taking nicardipine (three adverse event, one non-compliance) and one was withdrawn during the placebo treatment phase (lack of efficacy). There were also six late withdrawals on nicardipine in the final 2 weeks of the trial (two inefficacy, two adverse events, two concomitant illness).

The results of the study are summarized in Table 1. There was little change in the severity of abdominal pain on either nicardipine or placebo in any of the sub-groups. Abdominal distension was also unaltered by treatment in patients with constipation or an alternating bowel habit. In those with diarrhoea, there was a slight improvement in distension on nicardipine, and a worsening on placebo. The between-treatment difference reached statistical significance ($P = 0.02$) but was of a magnitude unlikely to be of clinical importance. No significant changes in well-being occurred on either treatment.

Table 2 summarizes the changes in whole gut transit times in each of the bowel habit subgroups. Nicardipine caused a significant reduction ($P = 0.02$) in those patients presenting with constipation. However, no change in whole gut transit was noted in patients presenting with diarrhoea or an alternating bowel habit (Fig.1.).

Table 1. Summary of study results.

	Run-in period	Placebo	Nicardipine	Between treatment *P* value
Diarrhoea (n = 17)				
pain	8.0	8.3	8.1	0.85
distension	10.1	10.9	9.0	0.02
bowel habit	17.0	15.9	16.9	0.47
Constipation (n = 16)				
pain	8.7	7.4	9.0	0.08
distension	12.5	11.6	12.3	0.46
bowel habit	7.3	7.8	7.6	0.89
Alternating (n = 19)				
pain	12.0	9.0	9.0	0.89
distension	12.9	12.2	12.5	0.62
bowel habit	10.1	10.6	11.1	0.46

Values for pain and distension on a 0–21 scale where 0 = no symptoms and 21 = severe symptoms each day of the week. Values for bowel habit represent mean number of stools per week.

Side effects suggestive of vasodilatation (headaches, erythema, oedema or palpitations) were seen in 19 patients whilst taking nicardipine, leading to five withdrawals from the study. Headache also occurred in seven patients during placebo therapy.

Discussion

This study shows that the calcium channel blocker nicardipine is not effective in reducing symptomatology in irritable bowel syndrome but does cause a significant reduction in whole gut transit time in those with constipation.

There is little clinical information available concerning the potential use of calcium antagonists in irritable bowel syndrome. One small clinical trial of the use of diltiazem has been published [12]. Compared with placebo, no

Table 2. Whole gut transit time results (h).

	Diarrhoea (n = 9)	Constipation (n = 12)	Alternating (n = 16)
Pre-study	33.3 ± 11.6	55.5 ± 11.8**	36.1 ± 3.4
Placebo	34.1 ± 9.0	47.5 ± 11.2*	34.1 ± 3.0
Nicardipine	32.7 ± 5.0	36.9 ± 5.3	28.9 ± 3.3
Between treatment *P* value	0.98	0.02	0.23

*$P < 0.05$ constipation versus diarrhoea. **$P < 0.01$ constipation versus diarrhoea. All results are expressed as mean ± s.e.m.

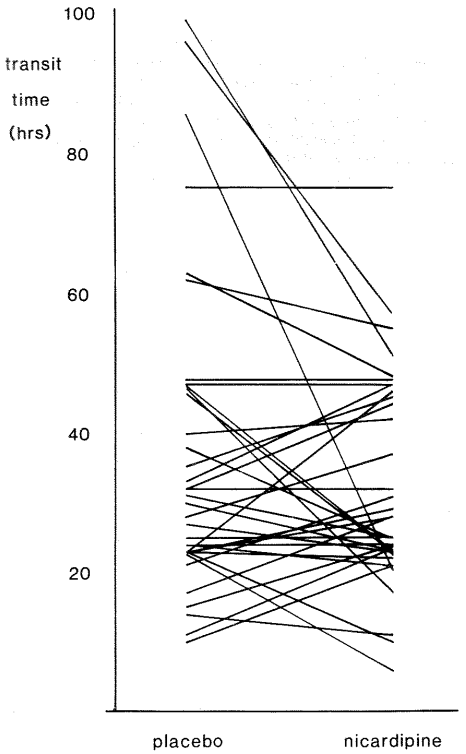

Fig. 1. Comparison of individual whole gut transit times on nicardipine and placebo.

significant improvement in global well-being, abdominal pain or bowel habit was noted, although a trend towards a decrease of diarrhoea was observed.

Whole gut transit was assessed using a dye technique rather than radio-opaque markers. The first appearance of dye has been shown to correlate well with the first appearance of radio-opaque pellets and appears reproducible within the limits set by the normal variability of whole gut transit times [13]. Because many of the patients in the present study were young women, the dye technique is preferable as the patient does not have to be exposed to radiation. The reduction in transit time noted during nicardipine therapy is of interest as it appears to apply only to those patients with initially prolonged transit. One of the mechanisms of constipation in irritable bowel syndrome is thought to be an increase in the segmental contractions of the colon [14]. As nicardipine has been shown to greatly reduce the contractile response of the colon to food in patients with irritable bowel syndrome [11], it may be that the change in whole gut transit seen in the present study was secondary to a reduction in segmental motor activity. However, it is also possible that contractions of both the small and large bowel may be the pathophysiological origin of pain in irritable bowel syndrome [8,15,16], yet nicardipine did not cause a decrease in the severity of this symptom. There are a number of possible explanations of this paradox. First, oral nicardipine may not achieve sufficient blood levels to inhibit the high amplitude contractile activity associated with abdominal pain. However, the patients who exhibited side effects secondary to vasodilatation, suggesting high blood levels of nicardipine, were found to be no more responsive than those without side effects. Second, the perception of pain in irritable bowel syndrome may be related more to visceral hypersensitivity which has been demonstrated in the small and large intestine of many patients with irritable bowel syndrome [17–19], and may not be affected by calcium channel blockers.

In comparison with previous therapeutic trials in irritable bowel syndrome [4,5], little placebo effect was noted in the present study. This may be related partly to the design of the study, since the baseline assessment was performed after 2 weeks on placebo in order to minimize any placebo effect occurring during the treatment phase. Most of the patient population had also previously failed to respond to multiple therapies for irritable bowel syndrome, although only a small number had taken part in other clinical trials.

In conclusion, the results of this study suggest that the calcium channel blocker nicardipine does not have a therapeutic role in the treatment of irritable bowel syndrome.

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