Oral domperidone: double blind comparison with placebo in irritable bowel syndrome

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SUMMARY Symptom scores, stool data, and the transit of a standard, solid meal were measured in 25 patients with irritable bowel syndrome during baseline conditions and after four weeks treatment with placebo and domperidone in the form of a double-blind cross-over trial. All patients had previously undergone a comprehensive series of diagnostic investigations and had failed to respond to dietary supplementation with coarse wheat bran (10–30 g daily). Compared with placebo treatment, domperidone had no significant effect on gastric emptying, small bowel or whole gut transit times, stool weight, frequency, or consistency. Most symptoms improved significantly with both placebo and domperidone treatments, compared with the baseline period, but there was no significant difference between placebo and domperidone for any of the symptoms. Abdominal distension, however, was reported on more days per week during domperidone treatment ($p=0.02$). The findings in this study do not support the use of domperidone in the management of irritable bowel syndrome.

In a recent study¹ we measured the time taken for a solid meal to pass through the stomach, small intestine, and colon in 61 patients with irritable bowel syndrome. Those who complained predominantly of diarrhoea had rapid small bowel and colonic transit, while those who presented with constipation had slow small bowel and colonic transit. In addition, 74% of patients who reported abdominal pain during the transit test did so as meal residues entered the colon. These findings suggest that disturbances in the transit of food through the small intestine, as well as the colon may be responsible for some of the symptoms experienced by patients with irritable bowel syndrome. It might follow, therefore, that an agent which influences transit through the small and/or large intestine could be helpful in the management of some patients with irritable bowel syndrome. Domperidone is a specific, potent, peripheral dopaminergic antagonist² known to enhance gastric emptying^{3,4} and accelerate small bowel transit.⁴ Moreover, the results of a recent clinical trial suggest that it may have a beneficial role in the treatment of irritable bowel syndrome.⁵

The purpose of this study was to determine

whether domperidone can influence the transit of a meal through the stomach, small intestine and colon in patients with irritable bowel syndrome and whether the drug has any advantages over placebo in the management of symptoms in irritable bowel syndrome.

Methods

SUBJECTS

All the patients were referred to the gastrointestinal clinic at the Royal Hallamshire Hospital with symptoms of abdominal pain and bowel disturbance suggestive of a diagnosis of irritable bowel syndrome.^{6,7} Patients were included in the study only if their symptoms had persisted for at least six months and were present on at least three days per week. A full history, clinical examination (including sigmoidoscopy), and a comprehensive series of screening examinations (Table 1) relevant to their presenting symptoms were carried out and patients were not accepted for the trial if there was any evidence of organic disease, past or present.

Finally, each patient underwent a four week trial of dietary supplementation with coarse wheat bran (10–30 g daily) and entered the drug trial only if they had failed to respond to bran.

Thirty-one patients (28 women, three men:

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Table 1 Screening investigations

Full blood count + ESR
Plasma urea/electrolytes/calcium
Liver function tests
Rectal biopsy
Stool microscopy + culture
Barium meal + follow through
Barium enema
Thyroid function tests
* Faecal fat excretion
* Serum folate + vitamin B12
* Schilling test
* ¹⁴ C-Glycocholate breath test
* Lactose tolerance test
* Urinary 5-hydroxy-indole acetic acid

* Indicates those investigations carried out only on the patients who complained of diarrhoea.

median age 31 years, range 19–61 years) satisfied these criteria and entered the study. Each patient signed a form giving consent for the study to be carried out. Female subjects within the reproductive years, were studied only if they were not pregnant and were taking a reliable form of contraception. Approval for the study protocol was granted by the Ethical Subcommittee of the Sheffield Area Health Authority (Teaching) (Southern District) in November 1980.

The spectrum of symptoms at presentation is indicated in the Figure.

STUDY DESIGN

The study consisted of a three week baseline period during which no treatment was given, followed by a double-blind cross-over trial comparing domperidone with an identical placebo, each taken for four weeks in random order. These two limbs of

the cross-over drug trial were separated by a two week wash out period, during which open placebo treatment was given.

Patients were asked to take two tablets of domperidone (20 mg), or placebo, four times daily, half an hour before each meal and just before sleep. Any tablets remaining after each treatment period were returned to the investigators. These were counted to determine the actual number of tablets ingested.

Patients recorded the daily frequency and consistency (formed or unformed) of their stools and the daily incidence of three symptoms (urgency, distension, and pain) on diary cards throughout the whole study. In addition, they were interviewed by one of the authors (PAC) during the baseline period, after two weeks and four weeks of each treatment and also after the placebo 'wash out' period. On each occasion they were asked to rate each of their symptoms in terms of severity, as follows: well (1); slight (2); moderate (3); severe (4); incapacitating (5).

The transit of a standard, solid meal through the stomach, small bowel and colon was measured during the baseline period and during the fourth week of each drug treatment period. Finally, patients also indicated their overall preference for the first or second drug treatment at the end of the study.

MEAL TRANSIT STUDIES

In every case patients fasted overnight and the standard test meal was eaten at 9.30 am. In studies carried out during treatment periods, tablets were taken with a small amount of water half-an-hour before the test meal and at noon. Patients continued

taking the tablets until the stool collection was complete.

The test meal consisted of three Frankfurter sausages, mashed potato, baked beans, and homogenised pineapple with custard.⁸ Twenty-five microcuries (0.93 MBq) ^{99m}Tc-sulphur colloid and 50 segments (2 mm × 3 mm) of radiopaque plastic tubing were incorporated in the mashed potato.

Immediately after ingestion of the meal, the subject lay supine with the head resting on pillows and measurements of gastric emptying and small bowel transit time were recorded for at least six hours. Our technique has been described in detail elsewhere.^{1,8} Briefly, gastric emptying was measured by counting radioactivity over the stomach every 10 minutes, using a collimated crystal scintillator (Type DMI-2, Nuclear Enterprises Ltd, Edinburgh), which was positioned over the site of maximum counts, immediately after ingestion of the meal,⁹ and connected to a counter ratemeter. Small bowel transit time was determined by measuring the time from eating the meal to the sustained rise in breath hydrogen that occurred when the unabsorbed carbohydrate residues contained in the meal reached the colon and were fermented by colonic bacteria.¹⁰ No further food or drink was taken until measurements of small bowel transit time were complete. Subjects were then allowed to return home and asked to collect the results of each bowel movement in individual polythene bags, labelled with the time and date, for a period of at least 72 hours after the ingestion of the test meal. These were weighed and then radiographed to determine the number of markers present.¹¹ The time taken to void 50% of the markers after ingestion of the test meal provided an index of the whole gut transit time.

STATISTICAL ANALYSIS

Symptom scores were non-parametric and comparisons were made using the Wilcoxon's (paired) rank sum test. Transit measurements, stool weights, and stool frequencies were compared using Student's (paired) *t* test.

The χ^2 test was applied to the data showing the relative proportions of stools reported as unfarmed and days on which symptoms of urgency, distension or pain were reported. These proportions were then transcribed and shown as median percentages.

Results

Six patients withdrew or were withdrawn from the study during the first period of drug treatment. In one case (male) this was placebo treatment and he failed to attend for follow up. The other five cases

(female) had been taking domperidone. One of these patients failed to attend for follow up, but the other four were withdrawn because of side-effects (see Table 2); one complained of facial swelling and an exacerbation of abdominal pain and distension, one developed galactorrhoea and the other two mastalgia.

Transit measurements and symptom scores from these patients were not included in the analysis.

Twenty-five patients (23 women; two men) completed the study. Eleven patients were treated with domperidone followed by placebo, while 14 patients had these treatments in the reverse order.

Compliance was good: the number of doses taken according to the tablet counts was at least 90% of that recorded by the patients, in all but four patients in the case of placebo, and three patients in the case of domperidone.

TRANSIT MEASUREMENTS (Table 3)

There were no significant differences in measurements of gastric emptying, small bowel transit time or whole gut transit time between either baseline and placebo periods or placebo and domperidone periods. Small bowel transit, however, was faster with domperidone treatment, compared with the baseline period ($p < 0.05$). There was no apparent differential effect of domperidone on measurements of transit which were initially at the slow end of the range during the baseline period compared with those that were towards the rapid end.

ANALYSIS OF DIARY CARDS AND STOOL WEIGHT (Table 4)

Treatment with placebo had no significant effect on

Table 2 Number of patients reporting side effects with placebo and domperidone

	Placebo	Domperidone
Palpitations	1	0
Chest tightness	1	0
Paresthesiae hands	1	0
Tremulousness	0	1
Leg cramps	0	1*
Lightheadedness	0	1
Headache	2	4
Blurred vision	1	0
Lethargy	1	2
Insomnia	0	1
Facial swelling	1	1*
Greasy hair	0	1
Increased salivation	0	1
Urinary frequency	0	4
Mastalgia (Galactorrhoea)	0	5(3)*

* Includes patients withdrawn from the study before undergoing placebo treatment.

Table 3 Results for gastric emptying, small bowel transit time and whole gut transit time during baseline, placebo and domperidone periods

	Baseline	Placebo	Domperidone
Gastric emptying (t-half) {hours}	1.6±0.2	1.5±0.2	1.6±0.2
Small bowel transit time {hours}	5.7±0.3	5.7±0.3	4.8±0.4*
Whole gut transit time {hours}	58±6	61±6	65±7

* Significant difference from baseline (means are shown ± SEM).

stool weight, stool frequency, or the incidence of symptoms of pain or distension, compared with the preceding baseline period. Urgency, however, was reported on fewer days ($p<0.05$) with placebo, although the proportion of stools described as unformed increased ($p<0.01$).

Compared with placebo, domperidone had no significant effect on stool weight, stool frequency, stool consistency or the incidence of symptoms of pain or urgency. Distension, however, was reported on more days per week with domperidone ($p=0.02$).

SYMPTOM SCORES (Figure)

For each symptom, the analysis of the response of that symptom to placebo and domperidone was confined to that sub-group of patients reporting that symptom as 'moderate', 'severe' or 'incapacitating' at presentation during the baseline period. This was intended to minimise any confusion arising from the 'non-response' of symptoms which were 'well' or 'slight' initially.

There was no significant difference in efficacy between placebo and domperidone for any of the symptoms studied. Compared with the baseline period, both treatments resulted in a significant

improvement in diarrhoea, pain, borborygmi, flatulence, and nausea. Placebo treatment was also associated with an improvement in urgency, whereas domperidone treatment was associated with an improvement in distension and belching.

There was no significant difference between symptom scores after two weeks and after four weeks of treatment with respect to either placebo or domperidone.

OVERALL RESPONSE

Twelve patients reported an overall improvement on domperidone, compared with placebo, but only four of these patients were sufficiently impressed with their response to continue with it after the study had finished. Six patients reported an overall deterioration with domperidone, but no change with placebo. The remaining seven patients preferred placebo to domperidone, although they did not dislike the latter treatment. These patients did not wish to continue with placebo treatment.

It was not possible to characterise 'responders' and 'non-responders' in terms of physiological measurements or presenting symptoms.

SIDE EFFECTS (Table 2)

A wide range of side effects were reported during both placebo and domperidone treatments. Three patients, however, were withdrawn from the study because of mastalgia and galactorrhoea in response to domperidone and two other women developed galactorrhoea on domperidone, although they completed the study. Four other women complained of urinary frequency on domperidone, whereas this was not reported with placebo.

Discussion

The efficacy of drug treatment in irritable bowel syndrome is difficult to assess. Symptoms may mimic those in other conditions and are often intermittent, varying from patient to patient and within the same patient. Many of the symptoms respond readily to reassurance, dietary change, or placebo treatment.⁷ It is therefore essential to minimise diagnostic uncertainties, define the patient group carefully, to exclude those patients whose symptoms respond to simple reassurance or dietary change and finally to compare the effects of the active drug with those of an identical placebo.

In the present trial, patients with infrequent or intermittent symptoms were excluded to minimise the possibility that any apparent response to therapy could be owing to the usual fluctuation in symptoms and all patients underwent a comprehensive screen of investigations to exclude underlying organic

Table 4 Diary card data and stool weights during baseline, placebo and domperidone periods

	Baseline	Placebo	Domperidone
Daily stool frequency	1.4±0.3	1.2±0.2	1.2±0.2
Percent stools reported as 'unformed' (median)	25	36*	33*
Incidence of pain (days/week)	4.3	4.4	4.4
Incidence of distension (days/week)	2.7	3.0	3.6*†
Incidence of urgency (days/week)	0.9	0.6*	0.8
Daily stool weight (grams)	98±18	88±13	77±21

* Significant difference from baseline.

† Significant difference from placebo (means are shown ± SEM).

disease. Finally, only those patients who had not responded to reassurance and dietary advice were studied, as it could be argued that drug therapy would otherwise be unjustified. The incorporation of a baseline period before the drug trial provided a means for discerning placebo response from response to the active drug and analysis of the symptoms according to their severity at presentation was intended to help the clinician to answer the question, 'How will this drug affect this particular presenting symptom?' Comparison of this mode of analysis with a more conventional analysis of overall change in mean symptom scores did not alter the symptomatic response to domperidone compared with placebo qualitatively, but it seriously underestimated the true placebo responses.

Although previous studies have shown that domperidone accelerates the emptying of liquid meals¹² and barium⁴ from the stomach in man and 'normalises' gastric emptying delayed by apomorphine^{12, 13} we were unable to show that oral domperidone had any significant effect on the gastric emptying of solid food in patients with irritable bowel syndrome. In one study in dogs, intravenous domperidone had no effect on the gastric emptying rate of a solid meal but did reverse delayed gastric emptying due to concurrent dopamine infusion.¹⁴

Oral domperidone treatment (ranging from 10 mg tds to 20 mg qds) over several weeks has been shown to be effective for upper gastrointestinal symptoms of dyspepsia^{5, 15-21} and nausea and vomiting.^{22, 23} Moreover, one study⁵ has suggested that domperidone (10 mg qds) was superior to placebo for a wide range of symptoms in irritable bowel syndrome. In all of these studies patients were selected on the basis of the demonstration, or suggestion of, delayed gastric emptying, and the majority of patients, even in the 'irritable bowel syndrome' study, had an underlying organic disease such as peptic ulceration, endoscopic oesophagitis or biliary disease. Another study of 60 irritable bowel syndrome patients already taking a high fibre diet²⁴ showed no significant difference between placebo and domperidone treatments. Side effects were remarkable for their absence in all of these studies.

Our patients had been carefully screened for organic disease, did not exhibit delayed gastric emptying (Table 3) and upper gastrointestinal symptoms were not predominant (Figure). None of our physiological measurements was significantly influenced by domperidone treatment, although small bowel transit time was significantly faster with domperidone, compared with the baseline period, but not compared with placebo (Table 3). This

virtual lack of physiological effects in our patients may explain our finding that domperidone did not differ significantly from placebo in relieving any of the symptoms under consideration, even those of a dyspeptic nature. Although many of the symptoms we studied showed a pronounced placebo response, however, this response was not associated with any physiological changes.

Our conclusion, therefore, is that domperidone is no better than placebo for the management of the common symptoms in irritable bowel syndrome.

Although domperidone might be expected to produce galactorrhoea because of its effect on prolactin,^{19, 25} the authors are aware of only one report of this side effect.²⁰ The high incidence in our study is worrying, particularly as it occurred in a group of patients receiving the treatment for an essentially benign condition.

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