Treatment of chronic constipation with cisapride and placebo

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SUMMARY The effect of cisapride (20 mg bid), a new prokinetic drug, on bowel habits and laxative consumption was studied in patients with idiopathic painless constipation and chronic laxative intake. After a four week base line period, spontaneous defecation (frequency without laxative intake) and total defecation (total frequency) were measured. Patients with a spontaneous defecation of less than three stools per week entered the treatment period and were randomly assigned to double blind treatment with either cisapride (n=64) or placebo (n=62). After eight weeks of treatment, a four week run out phase on single blind placebo medication was conducted. Cisapride and placebo increased spontaneous stool frequency from 1.1 ± 0.2 SEM to 3.0 ± 0.2 per week ($p < 0.001$) and from 1.2 ± 0.1 to 1.5 ± 0.2 ($p > 0.05$), respectively. Laxative consumption was decreased from 3.6 ± 0.3 to 1.8 ± 0.2 doses/week by cisapride ($p < 0.001$) and from 3.3 ± 0.3 to 2.8 ± 0.3 by placebo ($p < 0.05$). Both drugs improved constipation as assessed by the patient by means of a visual analogue scale, but cisapride did so to a larger extent than placebo. The effects of cisapride partly outlasted active medication by at least four weeks. It is concluded that cisapride improves bowel habits in patients with idiopathic constipation and reduces laxative consumption.

Chronic constipation is a common complaint in Western medicine.^{1,2} An underlying disorder such as Hirschsprung's disease, diabetic autonomous neuropathy, or idiopathic intestinal pseudoobstruction can rarely be found. In most cases the feeling of being constipated may be because of a discrepancy between the expectation of the patient and the reality with respect to bowel frequency and stool volume.

Although bran is, at least in non-constipated subjects, effective in enhancing faecal bulk and thus stool frequency,³⁻⁷ adherence to a diet rich in fibre is generally poor.^{4,8} Therefore, laxatives are frequently used by these patients.^{2,8} Chronic laxative consumption, however, may damage the colonic muscle layer

and lead to a true colonic cause of constipation.^{9,10} Thus, a vicious circle is initiated. A new prokinetic drug was recently developed which, in contrast with drugs such as metoclopramide and domperidone, stimulates also motility of the lower gastrointestinal tract.¹¹⁻¹³ In the present trial cisapride was studied to see if it was able to reduce laxative intake in patients with chronic laxative abuse.

Methods

STUDY DESIGN

The study lasted for 16 weeks and consisted of three phases. The first phase was called base line phase and lasted for four weeks. It was followed by an eight weeks treatment phase during which either placebo or cisapride were given in a randomised and double blind manner. Finally, placebo was given single blindly to all patients for four further weeks (run out phase).

Patients reporting regular laxative consumption because of constipation of at least one years duration

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were encouraged to enter the base line phase unless one or more of the following exclusion criteria were fulfilled: lower abdominal or rectoanal pain related or unrelated to defecation; intermittent diarrhoea; organic disease of the colon such as tumours, strictures, and acute or chronic inflammatory diseases; organic diseases of the rectum and anus such as fissures, fistulas, perianal abscesses, and eczema of the perianal skin; regular intake of antacids or of opioid, anticholinergic, anticonvulsant, antidepressant, or neuroleptic drugs; psychosis; hypothyroidism or hyperparathyroidism; malignant diseases; pregnancy or lactation; and bedridden patients. Organic diseases of colon, rectum, and anus were assumed to be absent when an actual digital rectal examination and a barium enema or colonoscopy during the preceding year showed normal findings. Colonic diverticular without signs of diverticulitis, however, did not lead to exclusion from the trial. The patients were told about the potential harmful effects of chronic laxative consumption and about the rationale of the intended study. They were encouraged to take a diet rich in fibre such as wholemeal bread or supplements of wheat bran. Patients agreeing to participate received a diary card for the next four weeks (base line phase). Each bowel movement and each laxative intake had to be marked on the card separately for each day. Three different symbols were used to define the consistency of the passed stools as 'hard', 'normal', or 'liquid', respectively. At the end of four weeks the diary card of the base line phase was reviewed. Patients suspected of not completing the card properly were excluded from the study.

When fulfilling the following definition of constipation patients entered the treatment phase: during the base line phase less than three stools per week had been passed spontaneously. Defecation was not considered to be spontaneous when induced by laxative intake. Defecation was defined to be induced by a laxative when occurring the day or the day after intake. Patients entering the treatment phase were randomly assigned to double blind treatment with either 20 mg of cisapride bid (R 51519, Janssen Pharmaceutica, Beerse/Belgium) or matching placebo tablets. Randomisation had been carried out in blocks of 10 in order to ensure even distribution of treatments over the participating centres. Patients were seen at the end of the fourth and the eighth week of the treatment phase, respectively. Between each of two visits a diary card had to be completed as described above. After the end of the treatment phase the patients were followed up for four further weeks with single blind placebo treatment. A fourth and last diary card was completed and was returned at a final visit.

At each visit the patient assessed his state with respect to constipation by means of a visual analogue scale.^{14,15} A horizontal line of 100 mm length was labelled at its left end 'as bad as always', at its right end 'could not be better'. In addition, the patient was asked which of the items stool frequency, stool consistency, ease of defecation, and need for laxatives had responded best to treatment. Blood pressure, heart rate, and body weight were registered and the patient was asked for possible side effects of treatment. The returned diary cards were checked for completeness and the returned tablets were counted. Patients suspected of not having completed the card properly or returning more than one third of the tablets were excluded from the study.

The protocol of the study had been approved by the ethical committee of the University Clinics of Munich.

PATIENTS

The study population consisted of outpatients seen by the members of the Bavarian Constipation Study Group. The Group consists of eight physicians working in private practice. Each of the members referred at least 10 patients. From the 140 patients entering the base line phase 126 fulfilled the definition of constipation and entered the treatment phase. Details of the patients are given in the Table.

STATISTICAL ANALYSIS

Individual means of the variables recorded on the diary cards were calculated for each week of the trial. Group means are given with SEM. The ratings obtained by means of the visual analogue scale were evaluated as follows. The line of 100 mm length was divided in 10 segments of 10 mm each, and the number of ratings falling into each segment was counted. Statistical comparisons were made with the Wilcoxon's rank-sum-test. Paired analysis was used when appropriate.

Results

GENERAL CHARACTERISTICS OF PATIENTS AND BASE LINE PHASE

Two thirds of the patients were women. All but 24 patients (19%) regularly used laxatives. The main constituent of two thirds of the laxatives used were anthraquinones, the rest containing bisacodyl or sodiumpico sulphate as the active component. The treatment groups were well matched (Table). Also, there was no difference between the groups during base line with respect to any measured variable.

TREATMENT PHASE

Treatment was well tolerated in both groups. No

Table Details of the patients in the treatment groups

	Cisapride	Placebo
Total no	64	62
Women (n)	38	37
Mean age (years)	49.5±1.7	51.4±1.8
Mean body weight (kg)	70.9±1.3	71.5±1.6
Smokers (n)	22	22
Regular physical activity*	41	43
Duration of constipation (years)	5.1 (1-20)	6.0 (1-57)
Laxative consumers	53	49
Bran intake	36	38
Stools/week†	2.2±0.1	2.2±0.1

*Number of patients doing either physical work or daily gymnastics;
†patient's estimate for the time before the base line phase.

change in blood pressure, heart rate, and body weight were observed. The following side effects were reported: nausea, one patient on cisapride, one on placebo; dyspepsia, one patient on cisapride; anxiety, one patient on placebo. During treatment two patients from each group were withdrawn for lack of compliance. Six other patients, two on cisapride and four on placebo, refused to continue treatment because of lack of effect.

Total stool frequency was not affected by placebo (Fig. 1). Laxative consumption was reduced from a mean of 3.3 ± 0.3 doses/week during base line to 2.8 ± 0.3 during the second half of the placebo treat-

Fig. 1 Time course of total (open symbols) and spontaneous stool frequency (closed symbols) in patients treated with cisapride (circles) and placebo (squares), respectively. Placebo response of spontaneous stool frequency is significant when compared with base line ($p < 0.05$). Cisapride was superior to placebo during weeks 9-12 ($p < 0.01$) and during run out ($p < 0.05$) for both pairs of curves.

Fig. 2 Time course of laxative consumption in patients treated with cisapride (circles) and placebo (squares), respectively. When compared with base line, laxative intake is decreased during treatment and run out in the cisapride ($p < 0.01$) and placebo ($p < 0.05$) group. During weeks 9-12 laxative intake is lower in cisapride treated patients than in placebo treated patients ($p < 0.05$).

ment phase ($p < 0.05$), and three patients became free from laxatives. This led to an increased spontaneous stool frequency. Cisapride increased stool frequency by 50% from base line to the second half of the treatment phase (Fig. 1). Concomitantly, seven patients became free from laxatives, mean laxative intake fell by half (Fig. 2), and three fourths of defecations occurred spontaneously. The most pronounced effect of active treatment was on stool consistency where placebo was completely ineffective (Fig. 3). The effects of cisapride developed progressively during treatment, whereas placebo effects when present remained constant.

RUN OUT PHASE

No differences were observed between treatment and run out phase in the placebo group. Switching from cisapride to placebo, however, led to a partial loss of treatment effects during the next one to two weeks. Thereafter, a new steady state was reached for the rest of the time which was still significantly different from control values.

LAXATIVE USERS AND NON-USERS

Cisapride increased stool frequency in non-users only during active treatment (Fig. 4). A moderate

Fig. 3 Normal (=not hard) stools as percentage of total stools passed in patients treated with cisapride (circles) and placebo (squares), respectively. No liquid stools were recorded by the patients during either phase. Cisapride values are significantly higher for both treatment and run out phase when compared with either base-line or corresponding placebo values (all $p < 0.01$).

Fig. 4 Stool frequencies in patients treated with cisapride stratified in laxative users ($n=53$) and non-users ($n=11$). Closed circles, total frequency in users; closed squares, spontaneous frequency in users; open circles, frequency in non-users. Total frequencies significantly differ between users and non-users during base line and run out ($p < 0.01$).

increase of total frequency in laxative users was maintained during run out. Spontaneous frequency in users increased three fold ($p < 0.01$) and was similar during the second half of the treatment phase and during run out. In the placebo group, no clear cut differences between laxative users and non-users were seen.

SUBJECTIVE ASSESSMENT BY THE PATIENT

Both placebo and cisapride treatment were considered to be effective by the patients as assessed by the visual analogue scale (Fig. 5). Cisapride, however, was more effective than placebo during treatment and run out. Stool frequency was the variable considered by the patients to have responded best to treatment (36 patients in the cisapride and 12 in the placebo group). Only 12 and 9 patients, respectively, considered stool consistency, and five and six patients, respectively, the need for laxatives to have responded best.

Discussion

More than 5% of apparently healthy people complain of constipation and regularly use laxatives.^{1,2}

Fig. 5 Self assessment by the patients by means of the visual analogue scale at the four control visits. Broken lines, placebo; solid lines, cisapride. Both treatments are effective when compared to base line (all $p < 0.01$), but cisapride is superior to placebo during treatment ($p < 0.001$) and run out ($p < 0.05$).

The definition of constipation in published studies ranges from merely subjective criteria (the patient claims to be constipated)¹ over specific complaints such as straining at stool or passing scybala² to precise definitions ($\leq$ three stools/week).⁶ The latter definition, however, seems pseudo precise because it does not take into consideration that laxative use may confound the assessment of 'true' bowel habits. We therefore felt that recording both total and spontaneous stool frequency, and laxative consumption would be necessary to evaluate the effect of a test drug on bowel habits. In addition, stool consistency as assessed by the patient proved to be a sensitive measure for the patients wellbeing with respect to bowel function.

Our sample was inhomogeneous in that some patients did not take laxatives at all, while others took more than 10 doses per week. Our definition of constipation, however, allowed to include the total spectrum of these patients. The use of laxatives was purposely not forbidden because this would have resulted in non-controllable non-compliance.

During a base line period bowel habits were assessed prospectively as retrospective estimates by the patients as to frequency of stools and laxative intake are not reliable. In addition, the base line phase allowed the quantitation of the expected¹⁶ placebo effects: placebo did not affect total stool frequency and stool consistency, but reduced laxative consumption and thus enhanced spontaneous stool frequency. These effects were maintained throughout the observation period. In contrast, changes induced by active treatment and exceeding placebo effects developed progressively during the treatment phase. Cisapride not only affected stool frequency and laxative intake, but also stool consistency. In fact, stool consistency was the factor which differed most between treatment and control group. The patients do not seem to be aware of this, however, because most of them claimed stool frequency to have responded best to treatment. The time course of the subjective rating by means of the visual analogue scale paralleled the objective data of spontaneous frequency, stool consistency, and, inversely, laxative consumption. The patients thus well appreciate the objective changes of bowel function.

To our knowledge this is the first study showing an effect on bowel movements of a drug which is not a laxative. Domperidone, an antidopaminergic prokinetic drug, has been found to be ineffective in constipated patients with the irritable bowel syndrome.¹⁷ Cisapride may at least in part act by decreasing towards normal the thresholds for the inhibitory relaxation reflex and the defecation reflex¹³ which are increased in patients with idiopathic constipation.¹⁸ Further studies will have to show whether

cisapride works by affecting defecation alone, or by speeding transit in other colonic segments as well, and whether different types of idiopathic constipation¹⁹ react differently to the drug. The mode of action of cisapride has not been fully elucidated as yet. It releases acetylcholine from the nerve endings of the myenteric plexus, but additional effects on the colon seem also possible.¹²

Cisapride comparably increased stool frequency in both laxative users and non-users during active treatment. During run out, however, stool frequency in non-users returned to nearly base line, whereas in users the effects of cisapride outlasted active treatment by at least four weeks. It is conceivable, therefore, that medication for a certain time allows definite reduction or even stopping of laxative consumption and hence interrupts the vicious circle maintained by laxative abuse. To answer this question longer treatment and longer follow-up after stopping treatment are mandatory.

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