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The Efficacy of Cisapride *vs.* Placebo and Diet in Patients with Chronic Constipation

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A B S T R A C T

The effects of cisapride (10 mg three times daily) on the stool evacuation characteristics, laxative consumption (symptom diary) and motility pattern (rectoanal manometry) were assessed in patients with chronic idiopathic constipation who fulfilled Rome II criteria. After a 14-day basal period on a diet rich in fiber (phase I), patients were treated with placebo (n=20) or cisapride (n=19) (phase II). Anorectal manometry was performed at the end of each phase. The study was controlled, randomized and double blind. Side effects related to the use of cisapride were noted and found to be mild. Cisapride and placebo increased stool frequency from 4 (1–11) to 7 (14–12) ($p<0.001$) and from 4 (2–10) to 6 (2–11) ($p<0.05$) per week, respectively. Straining was decreased from 69.0% to 39.7% in the cisapride ($p<0.0001$) group, and from 79% to 35% ($p<0.0001$) in the placebo group. Both cisapride and placebo decreased the feeling of incomplete evacuation from 91.7% to 37.5% ($p<0.0001$) and from 82.7% to 39.2% ($p<0.0001$), respectively. Cisapride reduced the need of laxatives and showed a tendency to normalize stool consistency but did not influence any other symptom or bowel motility parameter.

***Key words**: constipation, cisapride, motility*

Introduction

Constipation is one of the most frequent symptoms in gastroentrology[1]. Symptoms compatible with constipation are found in 3%–20% of the population, and the prevalence increases to 20%–25% in the elderly[2–4]. Although physicians often

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focus mainly on the infrequency of bowel movements in the definition of constipation, patients have a broader set of complaints[5]. Conventionally, constipation may be defined by three parameters: symptoms, measurements of defecation, and physiologic measurements[6].

Attempts to characterize a common underlying motor abnormality have led to disappointing conclusions. Investigations report either increased or reduced, and even normal intraluminal pressure changes of the sigmoid colon, and the same results are reported regarding the reactivity of the internal anal sphincter to rectal distention[7,8]. The differences in findings could be the result of a poor definition of constipation and heterogeneity of the patients examined[9]. In most cases, constipation can be treated with dietary manipulation, simple laxatives or enemas[1]. There is a group of patients in whom medicamentous treatment is unsatisfactory and where stimulant laxatives quickly lose their effect and may cause myenteric plexus damage[10]. One approach to the management of chronic constipation consists of stimulation, as physiological as possible, of the intestinal motility.

Cisapride is a benzodiazepine that has been developed as a prokinetic directed primarily to the upper bowel. It has also been extensively used in the treatment of constipation, the results being quite equivocal, and concerns about its safety caused it to be withdrawn from the market in the USA in July 2000[11–21].

The aim of this study was to determine the efficacy of cisapride as short-term therapy for chronic idiopathic constipation.

Patients and Methods

The study included two phases performed over 6 weeks. Phase I termed baseline phase lasted two weeks and was followed by four-week treatment with placebo or cisapride administered in a randomized and double-blind manner (phase II). Throughout the study, patients were encouraged to take a fiber-rich diet.

A questionnaire was used to define the number of stools *per* week without any treatment, and to detect the occurrence of abdominal distension, straining at stools, pain on defecation, hard stools, absence of need to defecate, and need to maneuver to expel stool.

During the study (phases I and II) patients kept a symptom diary in which they could report each bowel movement, consistency of stool according to the Bristol Stool Form Scale, straining at defecation, and sensation of incomplete evacuation if present. They could also report laxative or other drug intake and side effects during the treatment phase. Patients older than 18 with 3 or fewer spontaneous bowel movements *per* week or a combination of two of the three symptoms (straining at defecation, lumpy and/or hard stools, and incomplete evacuation over at least two years) were encouraged to enter the baseline phase unless they met the exclusion criteria.

After the initial history and physical examination, patients underwent the following tests: complete blood count, thyroid hormones, serum glucose, creatinine, hepatic enzymes, calcium, potassium, sodium, electrocardiography (ECG), barium enema with proctosigmoidoscopy or colonoscopy, and study of rectal motility. Patients with organic disease of the colon and rectum, psychosis, hypothyroidism, hyperparathyroidism, malignant disease, pregnancy or lactation, or using a drug that could produce constipation were excluded. Organic diseases of the colon, rectum and anus were assumed to be absent when digital rectal examination and barium enema or colonoscopy during the preceding year showed normal findings. Colonic diverticula without signs of diverticulitis, however, did not lead to exclusion

from the trial. A normal rectoanal inhibitory reflex to rectal distention was present in all patients. None of the patients was taking any constipating medication or had a concurrent illness associated with constipation.

Anorectal function was assessed by means of a side-opening water perfused catheter connected to Albyn Medical Griffon transducers and recorder. The maximum resting pressure was considered as the highest pressure in the anal canal at rest, recorded by the pull-through technique. The reported values are the mean of three recordings. Squeeze pressure was obtained by asking the patient to maximally contract the external anal sphincter while the probe was inserted through the anal canal. There were three separate trials and maximal pressures from each transducer were averaged. Reflex inhibition was elicted by distending a rectal balloon with different volumes of air. Balloon distention was used to detect the threshold (smallest volume of rectal distention) for common sensations, the first detectable sensation (rectal sensory threshold), the sensation of urgency to defecate, or the sensation of pain (maximum tolerable volume). Manometric results were compared before and after treatment period.

Patients entering the treatment phase were randomly assigned to double blind treatment with either 10 mg of cisapride tid or matching placebo tablets. The Ethics Committee of the General Hospital »Sveti Duh«, Zagreb, approved the study protocol. A written informed consent was obtained from all patients prior to entry in the study. Qualitative data were recorded as frequency and percentage, and qualitative data as median and interval. Statistical comparisons between groups were made with the use of nonparametric Mann-Whitney U test for independent samples. Differences within the groups were tested with Wilcoxon test.

Results

Thirty-nine patients fulfilled the definition of constipation and entered the treatment phase. Patient data are given in Table 1. Duration of constipation varied from 2 to 16 years (median 5 years) in the cisapride group, and from 2 to 30 years (median 5.5 years) in the placebo group. Fifty-one percent of the patients were regularly using laxatives. Forty-one percent of all study patients had spontaneous bowel movements. This study was a prospective, double-blind, placebo controlled, randomized cross-over comparison of the effects of cisapride 10 mg tid or placebo. Details about the symptoms from the questionnaire and diary cards during the baseline period are given in Figure 1.

TABLE 1
BASIC CHARACTERISTICS OF STUDY GROUPS

	Cisapride (N = 19)	Placebo (N = 20)	Statistical difference
Women (N)	15 (78.9%)	14 (70.0%)	$\chi^2 = 0.0744$ ns
Age (yrs.)	40 (19–76)	40.5 (21–71)	t = 0.1125 ns
Height (cm)	166 (150–190)	167 (157–181)	t = 0.1408 ns
Weight (kg)	65 (47–95)	71.5 (50–100)	t = 1.2663 ns
Smokers (N)	6 (31.6%)	6 (30.0%)	$\chi^2 = 0.0577$ ns
Victims of violence (N)	5 (26.3%)	6 (30.0%)	$\chi^2 = 0.0101$ ns
Physical activity (N)	7 (36.8%)	2 (10.0%)	$\chi^2 = 2.5872$ ns

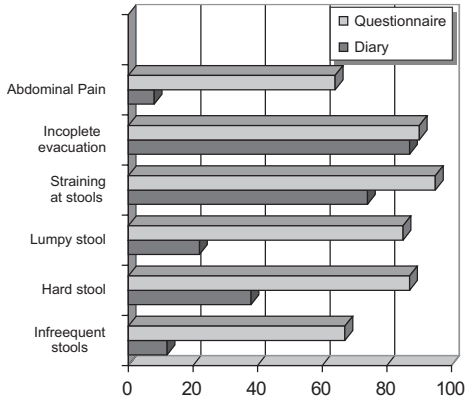

Fig. 1. Symptoms and signs of constipation.

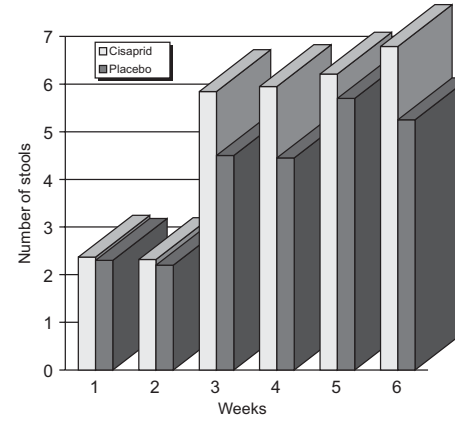

Fig. 2. Frequency of spontaneous stools during the study.

The two patient groups were well matched. Treatment was well tolerated. Side effects were defined as any extra sensation felt during the study and were mild in general. The most common side effects were blotting, abdominal cramps, nausea, headache, dizziness and fatigue. The number of side effects recorded *per* patient *per* week increased from 5.65 during the baseline phase to 13.9 during the treatment phase in the placebo group, and from 7.89 to 24.1 in cisapride group. So, cisapride increased total stool frequency from 4 (1–11) to 7 (14–12) ($p<0.001$) and placebo from 4 (2–10) to 6 (2–11) ($p<0.05$) *per* week.

Cisapride increased the number of spontaneous stools from 3 (0–7) in the baseline phase to 7 (3–11) ($p<0.001$), and placebo from 2 (0–8) to 5.5 (0–11) ($p<0.01$) *per* week (Figure 2). Laxative consumption was reduced from 2.21 doses/week during the baseline phase to 0.37 during the treatment phase in the cisapride group. Twelve of 14 patients in the cisapride group who had been using laxative in the baseline period turned free from laxatives (McNemar test, $\chi^2 = 7.6923$; $p< 0.01$). In the placebo group, three patients turned laxative-free (non significant), and laxative consumption was reduced from 2.05 the in baseline phase to 1.05 doses/week in the treatment phase (Figure 3).

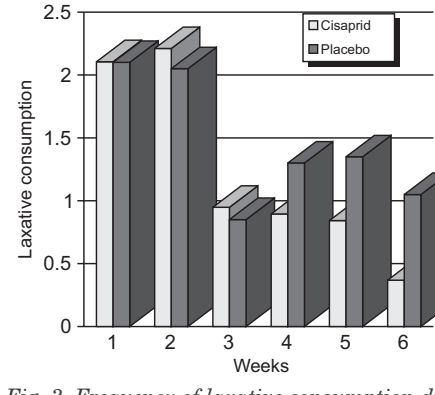

Fig. 3. Frequency of laxative consumption during the study.

The effect of cisapride developed progressively during the course of treatment, whereas placebo effects when present remained constant. Straining on bo- wel movements was decreased from 69.0% to 39.7% with cisapride ($p<0.0001$), and from 79% to 35% with placebo ($p<0.0001$). Both cisapride and placebo decreased the

TABLE 2
TYPES AND FREQUENCY OF STOOLS IN STUDY WEEKS 2 AND 6

Stool type*	Cisapride N (%)	Placebo N (%)	Statistical significance
1–2	14 (11.7)	20 (14.7)	t = 0.715 ns
3–5	99 (82.5)	92 (67.7)	t = 2.725 p<0.01
6–7	7 (5.8)	24 (17.6)	t = 2.891 p<0.01

* According to the Bristol Stool Form Scale

TABLE 3
POST-TREATMENT VALUES OF MANOMETRIC PARAMETERS IN CISAPRIDE AND PLACEBO GROUP

Parameter	Cisapride X (range)	Placebo X (range)	Statistical significance
Maximal resting anal canal pressures (mm Hg)	44.0 (20.0–76.7)	54.5 (27.7–96.0)	t = 1.7424 ns
Maximal squeeze anal canal pressures (mm Hg)	107.3 (42.3–200.7)	152.0 (59.7–272.0)	t = 1.7543 ns
Thresholds of IAS relaxation (ml)	20 (10–50)	20 (20–50)	t = 0.2940 ns
Amplitude of RAIR (mm Hg)	25 (10–40)	25 (5–73)	t = 0.5874 ns
Rectal sensory threshold (ml)	10 (10–30)	20 (5–30)	t = 0.3734 ns
Maximum tolerable volume (ml)	200 (80–300)	160 (90–300)	t = 1.0640 ns

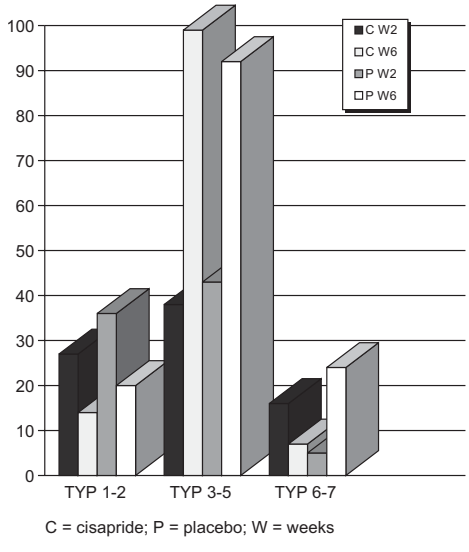

Fig. 4. Types of stools at weeks 2 and 6 of the study.

feeling of incomplete bowel movements from 91.7% to 37.5% (p< 0.0001) and from 82.7% to 39.2% (p< 0.0001), respectively. There was a statistically significant difference between the groups before and at the end of the treatment period. On cisapride, stool consistency showed a tendency to normalize (Table 2 and Figure 4).

At the end of the treatment phase, there was a statistically significant between-group difference in the parameters of manometric measurements (Table 3). The parameters of manometric measurement showed different tendencies in the study groups. In the cisapride group, most of the manometric parameter values decreased after the treatment as compared to the pretreatment values. In contrast, in the placebo group, the majority of values increased after the treatment period (Figure 5).

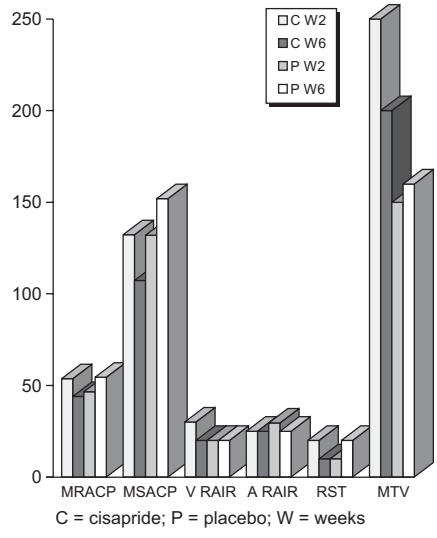

Fig. 5. Manometric parameters in study weeks 2 and 6 in cisapride and placebo group.

Discussion

The majority of constipated patients will experience symptom relief with dietary modification and simple osmotic laxatives. Patients with proven pelvic floor dysfunction (anorectal manometry, balloon expulsion study, defecography), if the symptoms are severe enough, should be considered as candidates for biofeedback. Some of those patients who do not respond are treated with aggressive laxative programs; however, their long-term use causes damage to the enteric nervous system which may prove irreversible. Refractory patients could be considered for surgery, although only few will be qualified after more extensive physiologic studies[1].

Cisapride has been extensively used in the treatment of constipation, however, with controversial results[11–14]. According to Muller-Lissner, cisapride reduced or even discontinued laxative use, thus interrupting the vicious circle maintained by laxative abuse[12]. Because of concerns about its safety it was withdrawn from the market in the USA in July 2000. According to data published since 1993, 30 million US residents were taking the medication, and at the same time it was related to 111 deaths and 270 instances of irregular heartbeat were reported[18], however, but we think that cisapride is quite safe (if accompanied with due precaution measures). This study was conducted to evaluate the efficacy and side effects of short term therapy with cisapride. The baseline phase allowed for the quantification of placebo effects: placebo increased stool frequency, changed stool consistency and reduced laxative consumption. These effects were maintained throughout the observed period. In contrast, changes induced by the active treatment effects developed progressively during the treatment phase. Cisapride affected stool frequency and laxative intake. Stool consistency in the cisapride group showed a tendency toward normal, and reduction in the number of laxative users was recorded. There were no statistically significant differences between the effects of cisapride and placebo on other symptoms and bowel motility parameters.

In this study cisapride was not demonstrated to be superior to placebo in controlling the symptoms of constipation. It should be borne in mind that the placebo response was between 60% and 70%. Placebo response decreased with time. In this study we observed a decrease in stool frequency from week 4 to week 3 of treatment with placebo. Longer studies may obtain different results. Accordingly, short term treatment of constipated patients with cisapride is no more efficacious than placebo. Therefore, prescribing cisapride for this indication over a short period of time should better be avoided.

Other prokinetics have been developed with more selective actions on the colon. Tegaserod and prucalopride have shown promising results in idiopathic chronic constipation, however, additional studies are need to assess their toxicity and side effects[22,23].

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UČINAK CISAPRIDA NASPRAM PLACEBA I DIJETE U LIJEČENJU KRONIČNE KONSTIPACIJE

SAŽETAK

U bolesnika s kroničnom idiopatskom konstipacijom (prema Rimskim II kriterijima) ispitivan je učinak cisaprida (10 mg tri puta na dan) na defekacijske značajke, upotrebu laksativa (dnevnik simptoma) i motilitet (manometrija anorektuma). Nakon uvodnog razdoblja od 14 dana (I. faza) tijekom koje su svi bolesnici bili na dijeti obogaćenoj vlaknima, uslijedila je II. faza (kontrolirana, randomizirana, dvostruko slijepa faza u trajanju od 30 dana) u kojoj je jedna skupina bolesnika bila na placebu (n=20), a

druga na cisapridu (n=19). Nakon svake faze bolesnicima je učinjena anorektalna manometrija. Nuspojave vezane za liječenje cisapridom su bilježene, no nisu bile značajnije naravi. U objema skupinama ispitanika uočen je porast broja stolica na tjedan, i to u skupini na cisapridu sa 4 (1–11) stolice na 11 (12–14) stolica na tjedan ($p<0,001$), a u skupni na placebu sa 4 (2–10) na 6 (2–11) stolica na tjedan ($p<0,05$). Osjećaj naprezanja za vrijeme defekacije u bolesnika s konstipacijom smanjen je sa 69% na 39,7% skupine na cisapridu ($p<0,0001$), a u bolesnika na placebu sa 79% na 35% skupine ($p<0,0001$). U objema skupinama zabilježen je i pad incidencije nepotpunog pražnjenja, i to s 91,7% na 37,5% ($p<0,0001$) u skupini na cisapridu te s 82,7% na 39,2% ($p<0,0001$) u skupini na placebu. Cisaprid je smanjio potrebu za laksativom te pokazao tendenciju normaliziranja konzistencije stolice. Nije zabilježen utjecaj cisaprida ili placeba na druge simptome ili motilitetne parametre u bolesnika s idiopatskom konstipacijom.