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Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation

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SUMMARY

Background: There is a need for better tolerated drugs to normalize bowel function in chronic constipation. Prucalopride is a highly selective, specific, serotonin$_4$ receptor agonist with enterokinetic properties.

Aim: To evaluate the effects of prucalopride on bowel function, colonic transit and anorectal function in patients with chronic constipation.

Methods: Twenty-eight patients were enrolled in this double-blind, placebo-controlled, crossover study (prucalopride: 1 mg, $n = 12$; 2 mg, $n = 16$). Patients kept a bowel function diary. Colonic transit times and anorectal function (anal manometry, rectal sensitivity and rectal compliance) were assessed.

Results: Prucalopride (1 mg) compared to placebo significantly increased the mean number of spontaneous complete, spontaneous and all bowel movements per week. Prucalopride (1 mg) significantly decreased the percentage of bowel movements with hard/lumpy stools and straining and increased the urge to defecate. Prucalopride (1 and 2 mg) decreased the mean total colonic transit time by 12.0 h (prucalopride 42.8 h vs. placebo 54.8 h; $P = 0.074$). No statistically significant effects were found in any of the anorectal function parameters. Prucalopride was well tolerated. There were no clinically relevant changes in standard safety parameters.

Conclusions: Prucalopride significantly improves stool frequency and consistency, and the urge to defecate, and may decrease colonic transit times in patients with chronic constipation.

INTRODUCTION

Constipation is a very common gastrointestinal disorder.[1–4] However, many patients who present with constipation have no obvious dietary, systemic or local structural causes for their symptoms, i.e. they have idiopathic or functional constipation.[5]

The treatment of chronic functional constipation is a challenge, as current treatments, such as dietary adjustments and laxatives, do not always improve patients' symptoms, particularly those with a long history of constipation. Increased dietary fibre and laxatives can result in significant bloating, flatulence and distension,[6] or may be insufficient to improve the complaints of patients. There is therefore a need for more effective and better tolerated treatments that normalize bowel motility.

Functional constipation is often associated with impaired colonic motility. Moreover, in some patients with severe functional constipation, there is a decrease in the frequency and duration of high-amplitude propagating contractions (the human equivalent of giant migrating contractions),[7] and an associated reduction in the number of mass movements.[8] Delayed colonic transit can be measured adequately using radio-opaque

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markers. In such patients, a reasonable therapeutic approach would appear to be to stimulate intestinal motility.[9]

Prucalopride is a novel, highly selective, specific, serotonin$_4$ (5-hydroxytryptamine$_4$, 5-HT$_4$) receptor agonist with enterokinetic properties.[9–11] Stimulation of 5-HT$_4$ receptors facilitates cholinergic and non-adrenergic, non-cholinergic excitatory neurotransmission,[12] and this mechanism has been proposed to explain the enterokinetic properties of prucalopride.[13] Pre-clinical studies have shown that prucalopride stimulates the peristaltic reflex[14] and dose dependently enhances the occurrence of giant migrating contractions in the colon of a canine model,[15] which suggest that it might be suitable for the treatment of disorders associated with dysmotility of the small or large bowel.

Studies with prucalopride in healthy volunteers showed that it increased stool frequency and improved stool consistency, and shortened the colonic transit time,[10, 11] but did not alter anorectal function.[11]

The aim of this study was to evaluate the efficacy and tolerability of prucalopride (1 or 2 mg) on bowel function, gastrointestinal transit time and anorectal function in patients with chronic functional constipation.

MATERIALS AND METHODS

This single-centre, randomized, double-blind, placebo-controlled, crossover trial was conducted between May 1996 and June 1998. It was performed in accordance with Good Clinical Practice and the Declaration of Helsinki, and Ethics Committee approval was granted before commencement. Written informed consent was obtained from all patients before entry to the trial.

Patients

Male and female patients, aged 18–70 years, with a history of chronic functional constipation (see definition below) which was causing disability, with the patient's occupational, social and recreational activities governed by constipation and efforts to attain relief, and who had experienced poor results with routine laxatives and diet counselling, were eligible for inclusion. Patients also had to have a normal inhibition pattern of the external anal sphincter during straining.

Constipation was defined according to the Thompson criteria[1] as the presence of two or more of the following criteria for at least 6 months: two or less spontaneous bowel movements (a bowel movement was considered to be spontaneous if it was not preceded within the previous 24 h by the intake of a laxative); lumpy (scybala) and/or hard stools for $\geq 25\%$ of the time; sense of incomplete evacuation for $\geq 25\%$ of the time; straining at defecation for $\geq 25\%$ of the time.

Exclusion criteria included: drug-induced constipation; secondary causes of constipation (e.g. endocrine, metabolic or neurological disorders); previous abdominal surgery (except hysterectomy, surgery for Meckel's diverticulum, appendectomy, cholecystectomy, inguinal hernia repair, splenectomy, nephrectomy or fundoplication); and anismus thought to be the primary cause of constipation. Patients with megacolon or megarectum, known or suspected organic disorders of the large bowel (e.g. obstruction, carcinoma or inflammatory bowel disease) or active proctological conditions thought to be responsible for constipation were also excluded, as were patients who were pregnant, breast-feeding, not using acceptable methods of birth control or who had known illnesses or conditions that might interfere with adequate assessment of the investigational drug.

Study design

All medication, except those drugs specified below, was stopped at least 14 days before the study. During the 2-week run-in period, the patients' bowel habits were documented and their constipation confirmed. Patients were instructed not to change their diet and fibre intake during the trial, and were also asked to avoid hot/spicy foods. Alcohol was not permitted during the study.

Concomitant treatment with agents known to influence bowel habit (e.g. anticholinergics, prokinetics, calcium-, ferrous-, bismuth-, magnesium- or aluminium-containing compounds) or laxatives (except rescue medication, see below) was not allowed. Patients receiving oral contraceptives, tricyclic agents or calcium channel blockers were required to continue treatment at the same dose for the duration of the study.

Rescue medication (bisacodyl, standard dose 15 mg) was allowed if ≥ 3 days had elapsed without a bowel movement. If this dosage was insufficient, an increase in dose was allowed. However, if this did not result in stools, tap water or phosphate enema was used.

After the run-in period, patients were randomized to two treatment groups. Group 1 received prucalopride (1 mg) or placebo, while group 2 received prucalopride (2 mg) or placebo, in a crossover design, which consisted of five 2-week periods: run-in (i.e. no treatment); prucalopride (1 or 2 mg) or placebo; wash-out (i.e. no treatment); placebo or prucalopride (1 or 2 mg); run-out (i.e. no treatment).

Efficacy assessments

The primary efficacy parameter was the transit time, which was measured during the second week of each treatment period according to a modified Metcalf method.[16] Patients swallowed 10 radio-opaque markers with their breakfast on six consecutive days (days 8–13 of each treatment period), and those markers remaining in the colon on day 14 were counted via a single abdominal X-ray.

The X-ray was used to calculate the mean or total colonic transit time (MCTT), and the segmental transit times of the right colon (RCTT), left colon (LCTT) and rectosigmoid (RSTT).[17] The basic formula for calculating MCTT is:

$$\mathrm{MCTT} = \sum_{i=1}^{6} n_i[(t_{(i+1)} - t_i)]/N$$

where n_i is the number of markers of a particular shape present on the film ($i = 1, 2, 3, 4, 5, 6$), N is the number of markers of each shape taken ($N = 10$ for all types), t_i is the time of intake of marker i ($i = 1, 2, 3, 4, 5, 6$) and t_7 ($t_{(i+1)}$ for $i = 6$) is the time of the abdominal X-ray. Assuming that $(t_{(i+1)} - t_i) = 24$ h for all i, and $N = 10$, the formula can be simplified to:

$$\mathrm{MCTT} = 2.4 \sum_{i=1}^{6} n_i = 2.4n$$

For segmental transit times (RCTT, LCTT and RSTT), the same formula was applied by counting the number of markers in each segment.

The total intestinal transit time was calculated by counting the number of differently shaped markers in the first stool on day 14.[18]

Secondary efficacy parameters measured were diary parameters and anorectal function tests.

Patients kept daily diaries for the entire 10-week study, in which they recorded the date and time of each bowel movement, stool consistency (lumpy, hard, normal, loose or watery), urgency (yes or no; if yes, patients recorded the number of times per day), straining (none, a little or much), sensation of incomplete evacuation (yes or no) and severity of abdominal pain (none, mild, moderate or severe). Patients also recorded whether each bowel movement was spontaneous (i.e. not induced by a laxative within the previous 24 h) and complete (i.e. associated with a sense of complete evacuation).

Patients were also asked to note the time and date of marker intake in their diaries, but it appeared that many patients neglected to do so. For this reason, the investigator conducted a blind review of all X-rays after the trial was over. This review showed that, even though the time and date of intake had not been recorded, the patients had taken their markers. It was therefore decided to include all X-rays in the colonic transit time analysis.

The review also revealed that two X-rays deviated from the others in that all markers of the last 4–6 intakes were located together in the right colon, indicating that the patient had taken the markers all together shortly before the X-ray was obtained. The two X-rays, which appeared to belong to different patients in the prucalopride (2 mg)/placebo group, were excluded from the final colonic transit time analysis. All anorectal function tests were performed on the last day of each treatment period. Maximum basal pressure, maximum squeeze pressure and anal sensitivity were measured according to methods developed in our laboratory and reported previously.[19, 20] Volumes and pressures of rectal sensitivity, e.g. first sensation, urge to defecate and maximum tolerated volume, were recorded.[19]

Safety and tolerability

Standard laboratory safety tests were performed at the start and end of the study and after each treatment period. Blood pressure, heart rate and electrocardiogram recordings were measured at the start of the study and 3 h after drug administration on day 14 of each treatment period. Adverse events were monitored throughout the trial.

Statistical analysis

Because this was a pilot efficacy study, exploratory statistical analysis was used. All statistical tests were two-tailed and interpreted at the 5% level of significance.

The placebo and active treatment periods were compared using analysis of variance, including fixed effects for period and treatment and a random patient effect. In addition, the placebo and active treatment periods were compared using Koch's non-parametric analysis for two-period crossover designs.

RESULTS

Patients

Of the 28 patients randomized to receive treatment (prucalopride (1 mg)/placebo group, $n = 12$; prucalopride (2 mg)/placebo group, $n = 16$), three discontinued treatment prematurely because of adverse events during prucalopride treatment in the first period, and one was uncooperative with continuing treatment after the first period (placebo); all four patients were in the prucalopride (2 mg)/placebo group.

The patients' demographic data and clinical characteristics are summarized in Table 1. The history of constipation did not differ in the two dose treatment groups, except that the duration of constipation was longer in the prucalopride (1 mg) sequences (group 1: 23.6 years for prucalopride–placebo and 20.0 years for placebo–prucalopride) than in either of the prucalopride (2 mg) sequences (group 2: 16.3 years and 11.6 years, respectively, for prucalopride–placebo and placebo–prucalopride).

Compliance with the study medications was excellent during each treatment period in both groups (all median capsule intakes 7.0 per week).

Colonic transit time

Colonic transit times were analysed in 25 patients, i.e. 20 patients with two observations and five patients with only one observation. The results for these patients are shown in Table 2 and Figure 1. The estimated MCTTs were 10.8 h shorter after prucalopride (1 mg) compared with placebo (37.0 h vs. 47.8 h) and 15.2 h shorter after prucalopride (2 mg) compared with placebo (48.4 h vs. 63.5 h). None of the differences were statistically significant. MCTT measured during placebo treatment was higher in group 2 than in group 1.

When both prucalopride and placebo groups were combined, the estimated mean total MCTT was 12.0 h shorter with prucalopride than with placebo (42.8 h vs. 54.8 h; $P = 0.074$) (Figure 1).

Diary

Changes in bowel habit after treatment with prucalopride (1 or 2 mg) or placebo are shown in Table 3. Treatment with prucalopride (1 mg) resulted in a significant ($P \leq 0.05$) increase in the frequency of spontaneous complete, spontaneous and all bowel movements per week compared with placebo. Similar increases were not seen in the prucalopride (2 mg) group.

Prucalopride (1 mg) also significantly ($P \leq 0.05$) decreased the percentage of bowel movements associated with hard/lumpy stools, decreased the percentage of bowel movements with little/much straining and increased the urge to defecate. The changes with prucalopride (2 mg) were smaller than those with

Table 1. Baseline demographics and clinical characteristics of study population. All values are expressed as mean ± S.E.M., except where indicated

Variable	Group 1 ($n = 12$)	Group 2 ($n = 16$)
Gender (% female)	92	88
Age (years)	42.4 (4.61)	37.5 (3.63)
Weight (kg)	66.6 (2.79)	62.5 (3.06)
Height (cm)	168.0 (2.34)	167.4 (1.80)
History of constipation		
Duration (years)	19.9 (5.04)	14.3 (2.32)
Age at first consultation (years)	28.3 (4.72)	26.8 (4.43)
Previous 6 months		
Time between stools (days)	6.3 (1.16)	7.6 (1.27)
Frequency of BMs (number/week)	2.0 (0.51)	3.9 (1.32)
Laxative use (%)	100	100
Inadequate therapeutic effect (%)	100	94

BM, bowel movement.

Table 2. Colonic transit times (least-square means; 95% confidence intervals) in the second week of treatment with prucalopride (1 or 2 mg) or placebo

	Group 1			Group 2		
	Prucalopride 1 mg ($n = 12$)	Placebo ($n = 12$)	Difference	Prucalopride 2 mg ($n = 12$)	Placebo ($n = 13$)	Difference
MCTT (h)	37.0 (14.6–59.5)	47.8 (26.0–69.6)	−10.8 (−30.3–8.8)*	48.4 (23.0–73.7)	63.5 (37.6–89.5)	−15.2 (−39.1–8.7)†
RCTT (h)	10.4 (2.7–18.0)	15.2 (7.7–22.7)	−4.8 (−10.5–0.9)	14.5 (2.7–26.4)	16.1 (4.0–28.2)	−1.6 (−12.5–9.2)
LCTT (h)	11.3 (−2.6–25.3)	18.6 (5.2–32.0)	−7.3 (−23.4–8.9)	13.1 (2.3–23.8)	20.1 (9.2–31.1)	−7.1 (−16.6–2.5)
RSTT (h)	14.6 (2.9–26.3)	14.0 (2.5–25.5)	+ 0.6 (−6.0–7.1)	21.5 (10.0–32.9)	27.0 (15.4–38.7)	−5.6 (−14.0–2.8)

MCTT, mean total colonic transit time; RCTT, right colonic transit time; LCTT, left colonic transit time; RSTT, rectosigmoid transit time. Least-square means and P values obtained from crossover mixed model, including factors for sequence, period and treatment.
* $P = 0.24$.
† $P = 0.18$.

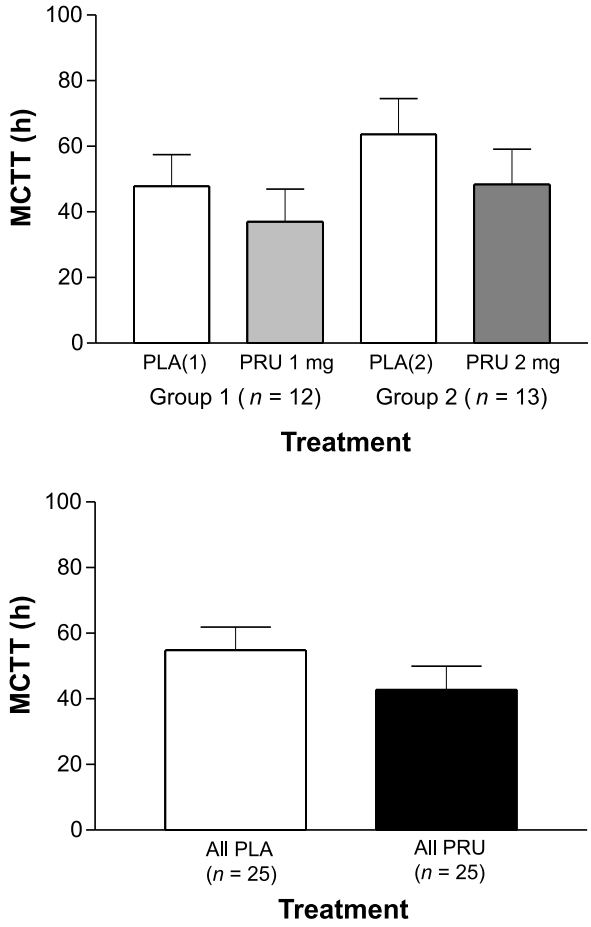

Figure 1. Estimated mean colonic transit times (MCTT; least-square means ± S.E.M.). PRU, prucalopride; PLA, placebo.

1 mg and were not statistically significant compared with placebo.

Anorectal function

No statistically significant changes were found in any of the parameters of anal manometry, anal sensitivity and rectal compliance after treatment with prucalopride (1 or 2 mg) compared with placebo (Table 4).

Safety and tolerability

Prucalopride (1 or 2 mg) was generally well tolerated with an adverse event profile similar to that of placebo. Most adverse events were mild or moderate in severity and resolved spontaneously. The most frequent adverse event was headache, which was reported by six prucalopride and three placebo patients, and by one

Table 3. Bowel habit parameters (means; 95% confidence intervals) after 2 weeks of treatment with prucalopride (1 or 2 mg) or placebo

	Group 1			Group 2		
	Prucalopride 1 mg ($n = 12$)	Placebo ($n = 12$)	*P* value	Prucalopride 2 mg ($n = 12$)	Placebo ($n = 13$)	*P* value
Average number of BMs/week						
SCBMs	2.6 (1.13–4.16)	1.2 (0.39–1.95)	0.011	2.0 (0.37–3.59)	1.7 (−0.25–3.63)	N.S.
SBMs	8.1 (5.21–11.07)	5.3 (3.36–7.33)	0.026	6.3 (3.66–9.02)	5.8 (1.38–10.16)	N.S.
All BMs	8.8 (5.73–11.96)	5.6 (3.70–7.43)	0.028	6.9 (4.35–9.45)	7.0 (2.71–11.29)	N.S.
Consistency of BMs						
Normal (%)	34.4 (19.8–49.0)	30.9 (13.3–48.5)	N.S.	31.1 (15.2–47.0)	37.8 (22.3–53.3)	N.S.
Hard/lumpy (%)	18.8 (4.1–33.5)	50.4 (30.1–70.8)	0.011	22.7 (4.7–40.7)	40.4 (18.0–62.8)	N.S.
BMs with little/much straining (%)	66.3 (44.9–87.7)	81.9 (65.9–97.9)	< 0.046	87.0 (75.5–98.6)	90.3 (77.4–103.2)*	N.S.
Urge to defecate(number/week)	6.9 (4.0–9.8)	4.7 (2.9–6.6)	0.035	10.1 (4.0–16.3)	8.5 (2.6–14.3)	N.S.
Sense of complete evacuation (%)	35.0 (17.7–52.3)	34.0 (10.0–58.0)	N.S.	29.4 (9.5–49.3)	41.0 (14.2–67.8)	N.S.
Time to first BM (h/min)	8:43 (−1:04–18:31)	19:04 (−1:55–40:04)	N.S.	22:50 (1:20–44:21)†	38:25 (4:27–72:22)	N.S.

S, spontaneous (i.e. not induced by a laxative within the previous 24 h); C, complete (i.e. associated with a sense of complete evacuation); BM, bowel movement; N.S., not significant. *P* values obtained from mixed model.

*$n = 11$.

†$n = 14$.

patient during both placebo and prucalopride (1 mg) treatment (Table 5). Other adverse events reported by more than two patients during treatment were abdominal pain, nausea, diarrhoea and flatulence. Three patients in the prucalopride (2 mg) group withdrew from treatment because of adverse events, which were predominantly gastrointestinal in nature (diarrhoea and headache, $n = 1$; abdominal pain, diarrhoea, flatulence, malaise and nausea, $n = 1$; headache and sensation of oedema (swollen hands, feet and face), $n = 1$). All these patients recovered after stopping the trial medication. No deaths or serious adverse events were reported during the study.

There were no clinically relevant changes in any of the standard laboratory or cardiovascular parameters measured.

DISCUSSION

The frequency of constipation in the population is not precisely known. Depending on the definition used, prevalence is reported to vary from 2% to 4% for infrequent stools and from 10% to 16% for excessive straining.[21–23] In nursing homes, frequencies seem to be higher: up to 20%.[24] Depending on the population studied and the definition used, it has been estimated that up to 15% of the normal population has symptoms associated with functional constipation, while 5–10% may experience outlet delay. However, the true prevalence may be even higher as many patients do not consult their doctors.[23, 25, 26]

The results of this double-blind, placebo-controlled, crossover study confirm the safety and efficacy of prucalopride (1 or 2 mg) in the treatment of chronic functional constipation. Because the study population was predominantly female and had a long history of not responding to laxatives or dietary counselling, it therefore reflected the normal population of patients with severe functional constipation.[6]

As it was not clear from previous studies in healthy volunteers, which had used doses of 1 and 2 mg,[10, 11] whether the effects of prucalopride on colonic transit were dose dependent; both doses were evaluated in this study. In the first study,[10] no dose dependence was found but, in the second,[11] the effects of prucalopride on gastrointestinal motility were dose dependent, with the 2 mg dose having greater effects. A study in healthy volunteers has shown that prucalopride (single and once-daily dosing with 1–6 mg) has a well-characterized,

Table 4. Anorectal function (means; 95% confidence intervals) in the second week of treatment with prucalopride (1 or 2 mg) or placebo

	Group 1		Group 2	
	Prucalopride 1 mg ($n = 12$)	Placebo ($n = 12$)	Prucalopride 2 mg ($n = 12$)	Placebo ($n = 13$)
MBP (mmHg)	61.3 (52.0–70.6)	64.7 (55.1–74.2)	70.8 (55.8–85.9)	65.4 (51.7–79.0)
MSP (mmHg)	66.3 (44.1–88.4)	64.6 (37.2–92.0)	59.6 (33.2–86.0)	50.8 (30.5–71.0)
FSV (mL)	130.8 (87.6–174.0)	141.9 (88.6–195.2)	105.7 (65.9–145.4)	120.8 (79.4–162.3)
FSP (mmHg)	31.6 (13.9–49.2)	21.5 (14.7–28.3)	20.2 (12.4–27.9)	22.5 (13.9–31.1)
Urge volume (mL)	234.8 (173.9–295.8)	233.2 (176.9–289.4)	204.0 (156.7–251.3)	213.5 (164.6–262.3)
Urge pressure (mmHg)	37.1 (23.8–50.3)	38.1 (22.7–53.5)	30.3 (17.6–42.9)	33.8 (22.7–44.9)
MTV (mL)	272.8 (201.9–343.6)	225.7 (151.6–299.9)	249.4 (200.4–298.5)	257.9 (208.5–307.4)
MTP (mmHg)	46.8 (30.6–62.9)	42.9 (28.1–57.7)	40.6 (22.9–58.3)	41.8 (30.4–53.3)
AS (mAmp)	4.7 (3.6–5.7)	5.1 (3.7–6.5)	3.5 (2.6–4.4)	4.7 (3.2–6.1)

MBP, maximum basal pressure; MSP, maximum squeeze pressure; FSV, first sensation volume; FSP, first sensation pressure; MTV, maximum tolerable volume; MTP, maximum tolerable pressure; AS, anal sensitivity.

Table 5. Incidence of adverse events (AE) during treatment with prucalopride (1 or 2 mg) or placebo

	Group 1		Group 2	
AE reported in ≥ 2 patients during treatment	Prucalopride 1 mg ($n = 12$)	Placebo ($n = 12$)	Prucalopride 2 mg ($n = 15$)	Placebo ($n = 13$)
Headache*	3	3	4	1
Abdominal pain*	1	2	4	1
Nausea	2	2	2	0
Diarrhoea	1	0	2	0
Flatulence*	1	1	2	0
Treatment withdrawals due to AEs	0	0	3	0

*One patient experienced AE during treatment with placebo and prucalopride (1 mg).

predictable, dose-proportional, pharmacokinetic profile with rapid, oral absorption. Furthermore, prucalopride is not associated with food interactions as concomitant food intake had no significant effects on its oral bioavailability (> 90%).[27, 28] Because prucalopride has a long elimination half-life, approximately 24 h, once-daily administration was used in our study.

Although both doses of prucalopride (1 and 2 mg) decreased the colonic transit time in our study, the differences were not statistically significant compared with placebo. However, despite randomization, the MCTT during placebo treatment for the prucalopride (2 mg) group was considerably longer than that for the prucalopride (1 mg) group, which may have affected the result with active treatment. In addition, because the transit studies were conducted during the second week of each treatment period, this may not have allowed sufficient time for prucalopride to show its full beneficial effects; most other published studies have involved at least 4 weeks of treatment.[29–31] The additional analysis of all patients with two valid MCTT assessments (both prucalopride and placebo) resulted in an overall 24% reduction (14 h) with prucalopride (1 and 2 mg) compared with placebo ($P = 0.057$). This is consistent with previous studies in patients with chronic constipation,[29, 30] which demonstrated that 4 weeks of once-daily prucalopride (0.5–4 mg) improved colonic transit.

In our study, prucalopride (1 mg) resulted in significant improvements in the average weekly number of bowel movements (spontaneous complete, spontaneous and all), stool consistency, the need to strain at defecation and the urge to defecate compared with placebo. Significant changes were not seen with prucalopride (2 mg), but this may have been influenced by the relatively high frequency of bowel movements in this group of patients during placebo treatment.

Anorectal function (anal sphincter pressure, anorectal sensitivity and rectal compliance) was unaffected by prucalopride in the present study. Similar results have

been found in studies in healthy volunteers.[10, 11] However, another study in patients with chronic constipation showed that 4 weeks of prucalopride (1 mg) significantly enhanced several parameters (both of distension and electrical stimulation) of rectal visceral sensitivity compared with placebo.[32]

Prucalopride was generally well tolerated in our study. The majority of adverse events were mild to moderate in severity, and there were no clinically relevant changes in blood biochemistry, urinalysis, blood pressure, heart rate or electrocardiogram. The most common adverse event with prucalopride was transient headache, which was reported by 29% of the prucalopride patients compared with 17% receiving placebo. Other adverse events experienced by prucalopride patients were mainly gastrointestinal in nature (abdominal cramps, diarrhoea, nausea and flatulence) and reflected the colonic effects expected from a drug with enterokinetic properties.[10, 11] The adverse event profile with prucalopride in our study was similar to that observed in previous studies in healthy volunteers[9, 10, 33, 34] and in patients with chronic constipation.[29–31]

In conclusion, once-daily administration of prucalopride was safe and effective for the treatment of patients with chronic functional constipation. Prucalopride (1 mg) significantly improved stool frequency and consistency and reduced the need to strain at defecation. The results suggest that it may also decrease MCTT in these patients. Although improvements with prucalopride (2 mg) were not always statistically significant compared with placebo, this probably reflects the refractory nature of the long-standing constipation in this patient population. Because treatment with prucalopride was also generally well tolerated, it therefore has potential in the management of chronic constipation.

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