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Effect of prucalopride, a new enterokinetic agent, on gastrointestinal transit and anorectal function in healthy volunteers

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SUMMARY

Background: Prucalopride (PR) is a novel 5-HT_4 agonist enterokinetic compound.
Aim: To evaluate its effect on bowel function, gut transit and anorectal function in healthy volunteers using a double-blind, placebo-controlled crossover study.
Methods: Twenty-four healthy volunteers (12 men, 12 women, mean age 25 years, range 20–53 years) were randomly assigned to 1 mg/placebo or 2 mg/placebo (PL). The trial consisted of five consecutive 1 week periods: no drug treatment, PR treatment or PL, washout, PL or PR, no treatment. Subjects maintained a diary of bowel function during the entire study period. Total intestinal transit time (TITT), mean colonic transit time (MCTT) and anorectal function (anal manometry, rectal sensitivity and rectal compliance) were assessed at the end of both treatment periods. Electrocardiography and blood sampling were performed for safety analysis; blood sampling was also used to check compliance.
Results: No subjects withdrew from the study. Treatment with PR 2 mg showed a statistically significant increase in mean number of weekly stools (11.5 vs. 7.1 compared to PL, $P = 0.04$) and in the percentage of loose/watery stools (48 vs. 12% compared to PL, $P=0.005$). Within 1 week, stool frequency and consistency returned to baseline values when treatment was stopped. MCTT was shortened significantly with both doses, i.e. from 35 h on PL to 25 h on PR 1 mg ($P=0.01$) and from 43 h on PL to 22 h on PR 2 mg ($P=0.02$). Anorectal function was unaffected by PR. Transient and moderate headache occurred in nine subjects during PR treatment and in six subjects during PL treatment.
Conclusion: Prucalopride is well tolerated by healthy subjects and has a marked and consistent effect on stool frequency and consistency, and on colonic transit. In the present study prucalopride did not affect visceral sensitivity or sphincter function. It holds promise for patients with slow transit constipation.

INTRODUCTION

Constipation is a common disorder.[1–4] A large number of subjects presenting with constipation have no obvious dietary, systemic or local structural causes for their symptoms, i.e. they are mostly identified as suffering from idiopathic or functional constipation.[5] Treatment of chronic idiopathic constipation is a challenge, because dietary adjustments are often not enough to improve the patient's health. A reasonable therapeutic approach to the problem of chronic idiopathic constipation is to stimulate intestinal motility.[6]

Prucalopride (formerly known as R093877) is a benzofurancarboxamide derivative that stimulates gastrointestinal enterokinetic activity in gastric, small intestinal and colonic smooth muscle, as has been demonstrated in both *in vitro* and *in vivo* animal studies (data on file, Janssen Research Foundation). It probably enhances both cholinergic and non-adrenergic,

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non-cholinergic (NANC) neurotransmission.[7] Prucalopride may be suitable for the treatment of disorders associated with dysfunction of the small or large bowel. In studies with single or repeated doses of prucalopride in healthy volunteers, it was well tolerated and no clinically relevant changes in the investigated laboratory and cardiovascular parameters were observed (data on file, Janssen Research Foundation). Recently, its enterokinetic effects were demonstrated in healthy volunteers.[8, 9]

The aim of this study was to evaluate the tolerability and the effect of prucalopride on bowel function, gastrointestinal transit time and anorectal function in healthy volunteers.

MATERIALS AND METHODS

This was a single-centre, randomized, double-blind, placebo-controlled crossover trial using two doses of prucalopride. Twenty-four healthy volunteers (12 men, 12 women, mean age 25 years, range 20–53 years) were entered into the trial. They were randomly assigned to two groups: volunteers in group 1 were treated for 1 week with 1 mg prucalopride and placebo, and those in group 2 with 2 mg prucalopride and placebo in a crossover design. Evaluation took place at the end of each treatment period and consisted of defecatory symptoms (kept in a diary), colonic transit time by means of a marker study and anorectal manometry, blood analysis and electrocardiography. In order to standardize the two treatment weeks as much as possible, subjects were asked to consume a similar meal pattern as during the first treatment period. Subjects were asked to avoid hot or spicy foods. Alcohol was not permitted during the study.

Diary

Subjects kept a diary for a total of 5 weeks, starting 1 week before the first treatment period and continuing until 1 week after the second treatment period, to record bowel habits. Time of each bowel movement, stool consistency, straining, sensation of incomplete evacuation and abdominal pain were recorded each day using a 4-point scale: no/mild/moderate/severe.

Colonic transit time

The colonic transit time was measured according to Metcalf *et al.*[10] Subjects ingested six sets of radio-opaque markers at 12 h intervals on days 4–6 of each treatment period. A single abdominal X-ray was performed on day 7. Afterwards, the mean colonic transit time (MCTT), and the segmental transit times of the right colon (RCTT), left colon (LCTT) and rectosigmoid colon (RSTT) were calculated.[10, 11] By collecting the first stool on day 7 of treatment and counting the number of markers of each type present (by means of stool radiograph), the total intestinal transit time (TITT) was calculated.[12]

Anorectal function tests

The maximal basal pressure (MBP), maximum squeeze pressure (MSP), functional sphincter length (SL), distention reflex (DR) and anal sensitivity were measured according to methods described previously.[13, 14] Furthermore, volumes and pressures of rectal sensitivity, e.g. first sensation to filling of the rectum, urge to defecate and maximal tolerated volume, were recorded.[14]

Statistics

Data were analysed using the Wilcoxon test and Fisher's exact test (two-tailed). A P-value of < 0.05 was considered significant. The placebo and the active treatment were compared for each group separately using the non-parametric Koch's analysis for two-period crossover designs.

RESULTS

No subjects dropped out of the study. There was a slight gender imbalance between the two groups (in group 1 five women out of 12 volunteers, in group 2 seven of 12). No concomitant disorders were present that could have an influence on the course of the trial. In general, no statistically significant period or carry-over effects were observed.

Colonic transit time

The MCTT was shorter after prucalopride treatment than after placebo treatment (Table 1). Compared to placebo, the MCTT was 10 h shorter in group 1 (from 35 to 25 h, $P = 0.01$), and 21 h shorter in group 2 (from 43 to 22 h, $P = 0.02$). Segmental transit times also changed after treatment: the RCTT was 6 h shorter in group 1 ($P = 0.07$) and 9 h shorter in group 2 ($P = 0.03$) compared to placebo. The LCTT was 2 h shorter in group 1 ($P = 0.22$) and 6 h shorter in group

Table 1. Colonic transit times (hours) after 1 week of treatment with 1 or 2 mg prucalopride compared to placebo

		MCTT	RCTT	LCTT	RSTT
Group 1	1 mg prucalopride	25.3 (15.7–35.0)	9.0 (5.3–12.7)	6.3 (2.5–10.1)	10.1 (3.3–16.9)
	Placebo	35.1 (27.4–42.7)	14.7 (10.7–18.8)	8.2 (2.8–13.6)	12.1 (5.3–18.9)
	Δ	9.7 (3.7–15.7)*	5.8 (0.4–11.1)	1.9 (−1.3–5.1)	2.0 (−4.1–8.2)
Group 2	2 mg prucalopride	22.2 (12.1–32.2)	11.2 (5.9–16.5)	4.3 (1.1–7.6)	6.6 (1.9–11.3)
	Placebo	42.7 (32.1–53.2)	20.1 (15.2–25.1)	10.1 (5.7–14.4)	12.5 (7.6–17.4)
	Δ	20.5 (7.3–33.7)†	8.9 (2.3–15.4)‡	5.7 (1.1–10.4)†	5.9 (−1.1–12.9)

*$P = 0.01$, †$P = 0.02$, ‡$P = 0.03$.
Data presented as mean (95% confidence interval); Δ, difference in means (positive value means decrease in colonic transit time).
MCTT, mean colonic transit time; RCTT, right colonic transit time; LCTT, left colonic transit time; RSTT, rectosigmoidal transit time.

Table 2. Mean colonic transit time (MCTT; hours) in males compared to females

	Males ($n = 12$)	Females ($n = 12$)	P-value
Placebo	31.1 (24.3–37.9)	46.6 (37.5–55.8)	0.01
Prucalopride (1 or 2 mg o.d.)	19.1 (11.8–26.4)	28.4 (17.3–39.5)	N.S.
Δ (hours)	12.0 (1.9–22.1)*	18.2 (7.0–29.4)†	N.S.
Δ (%)	35.1 (12.8–57.3)*	38.3 (11.9–64.8)‡	N.S.

*$P = 0.005$, †$P = 0.007$, ‡$P = 0.016$.
Data presented as mean (95% confidence interval); Δ, difference placebo–prucalopride.

2 ($P = 0.02$) compared to placebo. For the RSTT and TITT, no statistically significant differences were found in either group. Women had a longer MCTT than men during the placebo phase (Table 2). During treatment with prucalopride (1 or 2 mg) the effect on colonic transit was equal for both sexes, the MCTT being reduced by the same percentage. In both sexes, the decrease in MCTT was statistically significant.

Diary

Data on bowel habits are given in Table 3. In group 2 a significant increase in the number of times with urge to defecate and stool frequency was observed. Furthermore, the stool consistency changed significantly. These changes were not significant in group 1. In both groups no changes were observed in the percentage of stools associated with straining or with incomplete evacuation.

Anorectal function

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

Adverse effects

The medication was well tolerated in general. Adverse effects (AEs) are listed in Table 5. The most frequently mentioned AEs were gastrointestinal events and headache. These were also fairly frequent during treatment with placebo. In group 1, 11 subjects (92%) mentioned at least one AE during or after prucalopride treatment, and six subjects (50%) during or after placebo treatment. In group 2, 10 subjects (83%) mentioned at least one AE during or after prucalopride treatment, and eight subjects (67%) during or after placebo treatment. None of the results of the haematological and biochemical analysis or urinalysis prompted further investigations or medical interventions. No statistically

Table 3. Changes in bowel habit during treatment with 1 or 2 mg prucalopride compared to placebo

	Group 1 ($n = 12$)			Group 2 ($n = 12$)		
	Prucalopride 1 mg	Placebo	P-value	Prucalopride 2 mg	Placebo	P-value
Stool frequency (weekly)	11.1 (7.8–14.3)	9.0 (7.2–10.8)	0.47	11.5 (8.2–14.8)	7.1 (6.1–8.0)	0.04
Watery stools (%)	32 (16–49)	18 (2–34)	0.42	48 (29–67)	12 (−1–24)	0.005
Straining (%)	48 (25–71)	53 (31–76)	0.57	65 (45–85)	72 (53–91)	0.07
Incomplete evacuation (%)	29 (9–48)	27 (8–46)	0.81	37 (15–60)	33 (9–57)	0.57
Time till first stool (hours)	12 (10–13)	12 (10–13)	0.81	13 (12–14)	13 (11–14)	0.47

Data presented as mean (95% confidence interval).

Table 4. Anorectal function after 1 week of treatment with 1 or 2 mg prucalopride as compared to placebo

	Group 1 (n = 12)			Group 2 (n = 12)		
	Prucalopride 1 mg	Placebo	P-value	Prucalopride 2 mg	Placebo	P-value
MBP	58 (48–69)	54 (45–62)	0.29	58 (49–67)	61 (54–67)	0.33
MSP	99 (55–143)	100 (65–136)	0.57	68 (50–85)	72 (51–93)	0.41
SL	3.7 (2.8–4.5)	3.4 (2.7–4.0)	0.65	3.3 (2.7–4.0)	3.8 (3.3–4.2)	0.30
FSV	84 (53–114)	81 (60–102)	0.87	61 (40–83)	64 (41–86)	0.81
FSP	19 (13–25)	22 (14–30)	0.37	12 (8–17)	23 (15–31)	0.11
Urge volume	175 (143–206)	177 (133–221)	0.87	175 (124–226)	153 (109–197)	0.15
Urge pressure	23 (17–30)	28 (18–38)	0.17	22 (13–30)	29 (17–41)	0.57
MTV	247 (208–286)	240 (186–295)	0.94	241 (186–295)	212 (157–266)	0.30
MTP	34 (27–40)	39 (26–51)	0.34	32 (20–44)	37 (25–49)	0.69
AS	3.6 (2.6–4.7)	2.7 (2.1–3.2)	0.13	2.4 (1.5–3.3)	2.7 (1.7–3.7)	0.09

MBP, maximum basal pressure; MSP, maximum squeeze pressure; SL, sphincter length; FSV, first sensation volume; FSP, first sensation pressure; MTV, maximum tolerable volume; MTP, maximum tolerable pressure; AS, anal sensitivity.
Data presented as mean (95% confidence interval).

Table 5. The most frequently mentioned adverse effects

	Group 1 (n = 12)		Group 2 (n = 12)	
	Prucalopride (1 mg o.d.)	Placebo	Prucalopride (2 mg o.d.)	Placebo
Abdominal pain	8	7	9	4
Headache	6	1	3	5
Diarrhoea	1	0	5	1

significant changes were found in blood pressure, heart rate or body weight. Also, no relevant ECG abnormalities were found at the start and end of the trial.

DISCUSSION

Prucalopride is a novel enterokinetic drug belonging to the group of benzofuran derivatives, which has an excitatory effect on 5-HT_4 receptors. *In vitro* animal studies have shown that cholinergic and non-adrenergic, non-cholinergic (NANC) neurotransmission is facilitated. Both mechanisms are important in the regulation of colonic motility. Briejer *et al.* have demonstrated that prucalopride is able to enhance gastric as well as small intestinal and colonic motility.[7, 15, 16] In healthy men, it has been shown that prucalopride shortens orocaecal and total gut transit time, resulting in an increased stool frequency and looser stools.[9]

This study contains the first data on the efficacy of prucalopride in healthy male and female volunteers.[8] We found that the effects on gastrointestinal motility were dose-dependent, the best effect being seen with 2 mg orally administered once daily. Although Emmanuel *et al.*[9] found no dose-dependent effect in 16 healthy volunteers, this effect has been observed in previous studies with 0.5, 1 and 2 mg prucalopride (data on file, Janssen Research Foundation). The enterokinetic action of prucalopride was evident within 1 day of the start of the treatment, and persisted during the 7 days of the treatment. After termination of the prucalopride treatment, bowel habits appeared to normalize within 2 or 3 days. The enterokinetic action was demonstrated both by the objective measurement of colonic transit time and by subjective (diary) parameters. The acceleration of colonic transit was evident: mean colonic transit time and also segmental transit times of the right and left hemicolon were markedly reduced by prucalopride. A significant finding was that prucalopride's effects on colonic transit were the same in both men and women. This is important, because women have known slower colonic transit times than men.[17] This was supported by our data, showing a slower colonic transit time in women during placebo treatment. The effect on colonic transit time also reflected significantly on bowel habit: stool frequency was increased and stools became more loose or watery during the entire treatment period.

Anorectal function was unaffected by prucalopride. Anal sphincter pressures, anorectal sensitivity and rectal compliance were unchanged by prucalopride treatment in healthy volunteers, which is in line with previous results.[9] Effects on anorectal function have been described for various drugs, such as cisapride and loperamide.[17–21] Cisapride, a motility-stimulating agent, was believed to diminish the rectal distention threshold,

thus inducing an urge to defecate in chronically constipated patients.[17] However, these results were not confirmed by Enck *et al.* in healthy volunteers.[20] Instead, they found a lowered anal resting pressure, which they ascribed to a direct action of cisapride on the smooth muscle cells. Prucalopride, however, had no effect either on rectal sensitivity or on anal pressures. Therefore, the anal sphincters and changed rectal perception probably play no role in the increased stool frequency seen in healthy volunteers. Future studies will show if this also holds for constipated patients.

In this study, prucalopride was generally well tolerated in healthy volunteers. No serious adverse effects were encountered and the gastrointestinal adverse effects (abdominal cramps, diarrhoea) are probably related to the enterokinetic action of prucalopride. No clinically relevant changes in blood biochemistry, urinalysis, blood pressures, heart rate or ECG were found.

In conclusion, prucalopride is a new, potent enterokinetic compound with a marked dose-related effect on colonic transit time and bowel habit in healthy volunteers. In this study prucalopride shortened colonic transit time significantly in both men and women. Furthermore, stool frequency increased and stools became looser during treatment with prucalopride. Treatment with prucalopride did not change anorectal function. Overall, treatment with prucalopride was well tolerated and, besides headache, adverse effects were mainly related to its enterokinetic action. It holds promise for patients with constipation.

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