Aliment Pharmacol Ther 2002; 16: 1347–1356.

Prucalopride, a systemic enterokinetic, for the treatment of constipation

A. V. EMMANUEL, A. J. ROY, T. J. NICHOLLS & M. A. KAMM
St. Mark's Hospital, Harrow, Middlesex, UK

Accepted for publication 20 February 2002

SUMMARY

Background: Laxatives are frequently ineffective in treating constipation. An alternative therapeutic approach is to target serotonin-4 receptors, which are involved in initiating peristalsis.

Aim: In a double-blind, placebo-controlled trial, to assess the efficacy and safety of a systemically active serotonin-4 agonist, prucalopride.

Methods: Seventy-four women with constipation were stratified into slow or normal transit groups, and each group was randomized to receive either placebo or 1 mg prucalopride daily for 4 weeks. A bowel function diary was maintained. Whole-gut and orocaecal transit, visceral sensitivity, quality of life and psychological state were assessed before and after treatment.

Results: Prucalopride, not placebo, increased spontaneous stool frequency ($P = 0.008$) and reduced time to first stool ($P < 0.001$). Prucalopride reduced the number of retained markers in all patients compared to placebo ($P = 0.004$). Prucalopride reduced the mean number of retained markers in slow transit ($P = 0.069$), but did not alter the marker count in normal transit ($P = 0.86$). Orocaecal transit was accelerated by prucalopride, not placebo ($P = 0.004$). Prucalopride, not placebo, increased rectal sensitivity to distension (urge volume, $P = 0.01$) and electrical stimulation ($P = 0.001$). Prucalopride significantly improved several domains of the Short Form Health Status Survey and the disease-specific quality of life. Adverse effects were similar for prucalopride and placebo.

Conclusions: Prucalopride improves symptoms, upper gut transit and gut sensitivity in constipated patients with both slow and normal transit. It improves transit in patients with slow transit. These changes are associated with improved well-being.

BACKGROUND

Constipation is one of the most common digestive complaints with a prevalence of up to 20% in the developed world.[1–3] In addition to impaired physical health, chronic functional constipation is associated with psychological morbidity and impaired social functioning,[4–7] resulting in a considerable negative impact on the quality of life and well-being.[8]

Patients with constipation vary in their symptom pattern and underlying physiological abnormality. Patients with slow transit usually have a reduced bowel frequency.[9, 10] Those with normal transit tend to have normal bowel frequency but an excessive need to strain, their symptoms relating mainly to disturbed anorectal function.[11] In patients with slow colonic transit, gastric emptying and small bowel transit are often slow,[12] suggesting a panenteric disorder. The treatment of constipation and its associated symptoms might be more effective if upper and lower gut function could be enhanced.

The current treatment of constipation centres on dietary fibre supplementation and laxative use,[13] but such treatments are often poorly tolerated. Increasing dietary fibre intake can result in significant bloating and flatulence, often without improving bowel frequency in

Correspondence to: Professor M. A. Kamm, St. Mark's Hospital, Northwick Park, Watford Road, Harrow, Middlesex, HA1 3UJ, UK.
E-mail: kamm@ic.ac.uk

patients with severe constipation.[11] Laxatives often lose their effectiveness with time,[13, 14] and clinical studies have shown a lack of universal benefit for any single agent.[15, 16] The predominant effects of both fibre and laxatives are thought to be restricted to the colon. There is a need for more effective and better tolerated drugs that normalize bowel function.

Prucalopride is a highly selective and potent serotonin-4 receptor agonist which facilitates cholinergic and excitatory non-adrenergic, non-cholinergic neurotransmission.[17] The drug is well absorbed and acts via a systemic mechanism to initiate peristalsis,[18] enhancing the occurrence of giant migrating contractions and accelerating colonic propulsion.[19] Because some patients with constipation are known to have fewer giant migrating contractions,[20] the drug might be expected to play a useful role in the treatment of functional constipation.

Prucalopride has been shown to accelerate whole-gut transit in healthy volunteers,[21, 22] with a marked and consistent effect on stool frequency and consistency.[21] Subsequent healthy volunteer studies have confirmed that prucalopride stimulates colonic transit, and enhances gastric emptying and small bowel transit, suggesting that it may also improve upper gut function and associated symptoms.[22, 23]

The aim of this randomized, double-blind, placebo-controlled study was to investigate the efficacy, physiological effects and safety of prucalopride in functional constipation, both slow and normal transit. We also assessed the extent to which the quality of life could be improved by pharmacological therapy for functional constipation.

METHODS

Patients

Consecutive female patients aged over 18 years, with a greater than 6-month history of constipation, were enrolled. Functional constipation was defined as either two or fewer spontaneous bowel actions in a week or the need to strain at defecation on at least a quarter of occasions.[24] Patients were screened by physical examination, electrocardiograph, urinalysis and routine serology. Patients had to have a body mass index between 18 and 28. All patients had undergone a normal structural examination of their colon within 1 year of the trial.

Patients with megacolon, faecal impaction, external rectal prolapse, solitary rectal ulcer or an active proctological condition causing constipation were excluded. Patients with known severe co-morbidity and those who had received care for an eating disorder were ineligible. The use of concomitant medication which might alter gut motility was prohibited. Other standard exclusion criteria applied. All subjects gave written informed consent and ethical approval was granted by the Harrow Ethics Committee.

Trial design

Patients kept a bowel habit diary throughout the 6 weeks of the study, comprising a 2-week drug-free run-in period followed by 4 weeks of treatment. Constipation was confirmed during the run-in period by means of the bowel function diary. Patients were stratified into slow or normal transit groups on the basis of a whole-gut transit study. They were then randomized to receive double-blind treatment with oral prucalopride, 1 mg, or placebo. Prior to treatment and at the end of the treatment period, the following were assessed: whole-gut transit, orocaecal transit time, rectal sensitivity, serological analysis and quality of life and psychological questionnaires. Placebo and prucalopride were presented identically as brown capsules to be taken as a single morning dose. As rescue medication, patients were allowed up to 15 mg of bisacodyl if no stools had been passed for three consecutive days, and this dose could be increased by a further 15 mg after consultation with the investigator.

Sample size calculation

Using data from previous studies, a median shift of gut transit of + 9 h (equivalent to + 7 markers) on placebo and − 14 h (equivalent to − 12 markers) on prucalopride was expected; this represents a difference of 19 markers (equivalent to 23 h) between the two groups. The standard deviation was 32 h. Based on these figures, to obtain a statistical difference at the level of 5% significance (two-tailed) with 80% power, and assuming a normal distribution with equal variances, it was calculated that 33 subjects would be required in each treatment group. Assuming a dropout rate of 20%, 40 subjects per treatment arm had to be recruited. Within each transit stratum, there would be 20 patients randomized to each treatment arm.

Symptoms and bowel function

At baseline, prior to the start of treatment and after 2 and 4 weeks of treatment, patients were asked to rate the following: most troublesome gut symptom on a six-point Likert scale (absent, very mild, mild, moderate, severe, could not be worse); overall severity of their constipation using a 100-mm visual analogue scale (0, absent; 100, could not be worse). Patients completed a 100-mm visual analogue scale after 2 and 4 weeks of treatment to assess their perceived efficacy of the treatment received (0, no response; 100, could not be more effective). At the end of the double-blind treatment, the investigator made a global assessment of treatment efficacy on a five-point Likert scale (very bad, bad, moderate, good, very good).

The bowel function diary recorded medication intake, frequency of defecatory urge and, for each bowel movement, the date and time, consistency (watery, −2; soft, −1; normal, 0; hard, 1; lumpy, 2), degree of straining (none, 0; little, 1; much, 2; lot, 3; could not be worse, 4) and sensation of incomplete evacuation. Diary data of the occurrence of adverse events were recorded. Full serology, electrocardiograph and vital signs were monitored at the start of the study and at the end of double-blind treatment for safety monitoring.

Whole-gut transit

A radio-opaque marker study was performed at the end of the run-in period and at the end of the double-blind treatment period.[10] Five sets of 20 radiologically distinct markers (P & A Mauch, Switzerland) were taken at 24-h intervals and an abdominal X-ray was recorded 120 h after the ingestion of the first set.

Stratification into slow or normal transit. Retention of more than the normal range for any one of the first three sets of markers reflects slow whole-gut transit.[10] This criterion was used to stratify patients prior to randomization.

Assessment of the effect of treatment. The final two sets of markers were used to assess the change in whole-gut transit in those with normal transit constipation, because in these patients most of the first three sets of markers would have passed through the gut by the time of the X-ray.[21] The assessment of the change in transit in those with slow transit was performed by studying the first three sets of markers only, because the last two sets were likely to still be present in the gut at the time of X-ray in these patients. The assessment of transit was performed blind to the treatment. Subjects were not permitted to use laxatives, suppositories or enemas during the 5-day period of the transit studies.

Orocaecal transit

This was calculated using the method of O'Brien *et al.*[25] Briefly, 20 g of lactulose was mixed with 400 g of heated cream of chicken soup (Heinz) and hydrogen in the exhaled breath was measured. Samples were obtained every 10 min and analysed immediately (EC60 Gastrolyser, Bedfont Instruments, Kent, UK). Orocaecal transit was taken as the time of the first reading of three consecutive samples that showed a breath hydrogen concentration of at least double the baseline.

Rectal sensitivity

The assessment of rectal sensation was performed by both mucosal sensitivity to electric current and distension. The former was assessed using a 1-cm bipolar ring electrode (21L10, Dantec, UK), mounted on a 14G Foley catheter and inserted 10 cm above the anal verge; it was connected to a constant current stimulator (Neuromatic2000M*C*, Dantec, UK) with application of a gradually increasing current (mA) at 10 Hz for 500-ms pulses. The latter was assessed by ramp distension of a compliant balloon to obtain volumes for threshold sensation and urgency sensation and the maximum tolerable volume.[26]

Quality of life and psychological status

Patients completed three questionnaires at the end of the run-in and double-blind treatment periods. These consisted of: (i) two quality of life questionnaires: one generic (Short Form Health Status Survey, SF-36[27]) and one condition-specific (Chronic Idiopathic Constipation Questionnaire, comprising four domains — symptom burden, daily life functioning, feelings and treatment satisfaction — with a total score of between 0 and 205; data on file, Janssen Research Foundation); and (ii) the Hospital Anxiety and Depression Scale.[28] Patients completed the questionnaires at the beginning of the visits, in a quiet room, having been given an assurance of confidentiality and anonymity.

Compliance

All subjects had a plasma drug trough level measured on the final day of the double-blind treatment period. Compliance was also determined by counting the returned unused blister packs of medication.

Statistical analysis

Treatment group comparability was analysed using descriptive statistics, which were also calculated per stratum. The chi-squared test was used to compare treatment groups for nominal parameters, and the Mann–Whitney *U*-test was used for ordinal and continuous parameters. Data which were assessed to be normally distributed were analysed by *t*-test. All statistical analysis was interpreted at the 5% level (two-tailed). Efficacy parameters were compared by analysis of covariance (ANCOVA). Comparisons of treatments were carried out using ancova with the baseline number of markers as the only covariate. Comparisons were performed on baseline, end of double-blind treatment (diary) and end-point (last measurement on treatment) data.

RESULTS

Patients

The disposition of the patients is shown in Figure 1. Eighty-seven consecutive patients were screened, of whom 10 were not enrolled due to lack of consent ($n = 7$), absence of symptoms of constipation on run-in diary ($n = 2$) or co-existent faecal incontinence ($n = 1$). Three of the remaining 77 patients had no efficacy data due to being lost to follow-up or due to withdrawal with adverse events. The 74 remaining patients (placebo, 37; prucalopride, 37) were randomized. Nineteen per cent had two or fewer bowel actions per week and the rest needed to strain excessively.

There were no significant differences between the placebo- and prucalopride-treated groups, except that significantly ($P = 0.040$) more placebo-treated patients reported using laxatives in the previous 6 months. There were no significant demographic differences between normal and slow transit patients when compared within prucalopride- and placebo-treated groups.

Efficacy assessment

Symptoms. Prucalopride, not placebo, treatment produced a significant reduction in the patients' subjective assessment of constipation severity compared to baseline (visual analogue scale reduction: -27 vs. -3, respectively; $P < 0.001$). Patients reported a significant beneficial effect with prucalopride compared with placebo (mean visual analogue scale scores of 65 vs. 21, respectively; $P < 0.001$).

At baseline, there were no intergroup differences in the patients' assessment of the severity of their main gut symptom. However, by week 2, this had improved significantly ($P = 0.002$) in the prucalopride-treated patients, and this difference was more significant ($P < 0.001$) after 4 weeks of treatment.

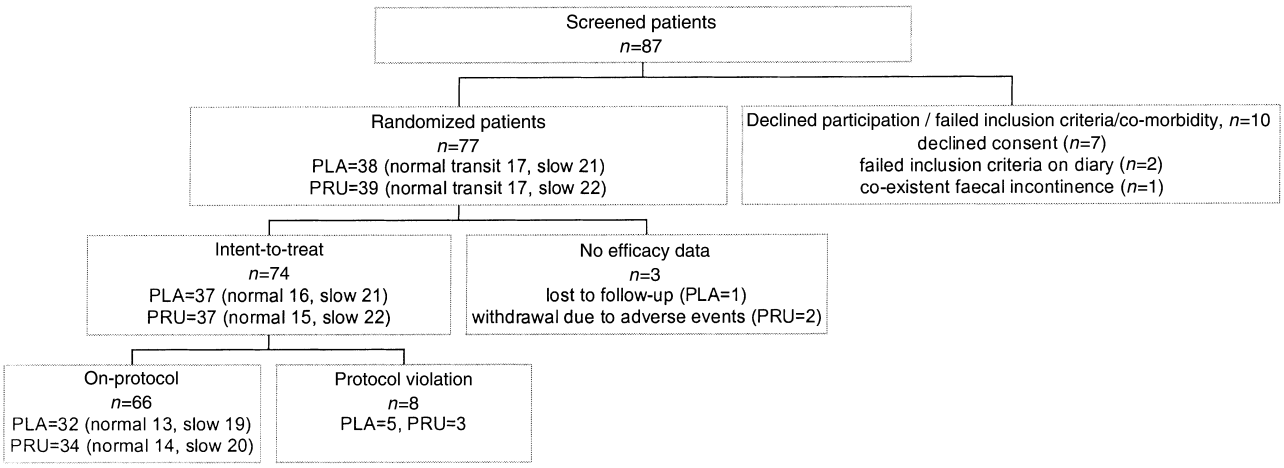

Figure 1. Trial profile. PLA, placebo-treated patients; PRU, prucalopride-treated patients.

Bowel function (diary data). The time to first bowel movement after the first intake of drug was significantly ($P < 0.001$) shorter for prucalopride than placebo (Table 1). The marked hastening of time to the first bowel movement was apparent across the spectrum of all patients, as demonstrated by the decrease in time for the 25th, 50th and 75th quartiles. Prucalopride significantly ($P < 0.001$) increased the average weekly frequency of spontaneous bowel movements (Table 1). There was also a significant ($P < 0.001$) increase in the urge to defecate.

During the run-in period, the average consistency of spontaneous bowel movements was 0.7 (− 1, soft; 0, normal; 1, hard) in both groups. This decreased significantly over the 4-week treatment period with prucalopride compared with placebo (− 0.6 vs. − 0.1, respectively; $P < 0.001$). No other diary parameter showed any statistically significant difference between prucalopride and placebo.

Whole-gut transit (Table 2): analysis using all ingested markers (total 100) — within-group analysis. Prucalopride significantly reduced the average number of retained markers in all patients (62 vs. 51, pre- vs. on treatment; $P = 0.004$). This was not seen on placebo (64 vs. 62; $P = 0.76$). Prucalopride (but not placebo) also reduced the median number of retained markers in slow transit patients ($n = 22$) from 45 to 31 ($P = 0.07$), but did not alter transit in patients with normal transit ($n = 15$) (26 vs. 25, $P = 0.86$).

Table 1. Effects of treatment on bowel function (± s.d., where appropriate) based on diary data

	Intention-to-treat		
	Placebo ($n = 36$)‡	Prucalopride ($n = 37$)	P value
Average weekly frequency of spontaneous bowel movements*			
Baseline	5.7 ± 4.4	5.9 ± 5.8	N.S.
End of treatment	5.0 ± 3.6	7.6 ± 5.7	0.019
Change	− 0.7 ± 2.6	1.8 ± 2.7	< 0.001
Time to first spontaneous bowel movement (h.min)†			
25th quartile	6.30	1.20	
50th quartile	24.20	3.50	
75th quartile	69.00	23.55	< 0.001

N.S., not significant.
* Spontaneous, not induced by laxative within the previous 24 h.
† Data not available for one prucalopride-treated patient as time of ingestion of first dose of drug was not recorded by patient.

Whole-gut transit (Table 2): analysis using all ingested markers (total 100) — between-group analysis. When analysing the data from all five sets of markers with both transit groups combined, prucalopride significantly reduced the absolute number of retained markers after 4 weeks of treatment compared with placebo (51 vs. 62, respectively; $P = 0.018$). Prucalopride, not placebo, significantly reduced the number of retained markers after 4 weeks of treatment when compared with baseline (11 vs. 1, respectively; $P = 0.033$).

Whole-gut transit (Table 2): analysis using first three sets of markers (total 60) in slow transit and last two sets of markers (total 40) in normal transit. In patients with slow transit, there was a trend for prucalopride to reduce the absolute number of retained markers after 4 weeks of treatment compared with placebo (31 vs. 42, respectively; $P = 0.069$). In patients with normal transit, no effect of prucalopride could be observed in the absolute number of retained markers after 4 weeks of treatment compared with placebo (25 vs. 30, respectively; $P = 0.66$).

Prucalopride treatment resulted in 22% (8/37) of patients changing from slow to normal transit compared with only 5% (2/37) in the placebo group ($P = 0.10$). Of the 74 patients, eight used laxatives during the transit study (placebo, $n = 5$; prucalopride, $n = 3$), leaving 66 who strictly followed the protocol. In this population, 21% (7/34) of prucalopride-treated and 3% (1/32) of placebo-treated patients changed from slow to normal transit ($P = 0.04$).

Orocaecal transit. This was significantly accelerated by prucalopride, not placebo. The mean prucalopride-associated reduction in orocaecal transit was from 76 to 54 min compared with 71 to 72 min with placebo ($P = 0.004$). Changes were significant both in comparison with placebo and baseline ($P < 0.001$).

Rectal sensitivity. Prucalopride significantly ($P \leq 0.001$) altered the rectal sensitivity to electrical stimulation, the sensation of urgency and the maximum tolerated volume to distension compared with placebo (Table 3), for the groups as a whole. This effect was observed in patients with both slow and normal transit.

Investigator assessment. At the end of the 4 weeks of treatment, the therapeutic effect was rated as 'very good', 'good' or 'moderate' in 81% (29/36) of prucalopride-treated patients compared to 31% (11/36) of placebo-treated patients ($P < 0.001$). Nine prucalopride-treated patients were rated as having had a 'very good' response compared to one placebo-treated patient.

Table 2. Effects of treatment on whole-gut transit. Numbers show the mean of the absolute number of retained markers at baseline and at the end of treatment (week 4) and the mean change between the end of treatment and baseline (± s.d., where appropriate)

	Intention-to-treat		
	Placebo	Prucalopride	*P* value
Analysis of all 5 sets of markers			
All patients (n = placebo; prucalopride)			
Baseline (n = 37; 37)	63.8 ± 30.9	61.9 ± 30.8	N.S.
Week 4 (n = 36; 36)	61.8 ± 30.2	51.2 ± 29.6	0.018
Change vs. baseline	− 1.1 ± 21.3	− 11.2 ± 21.8*	0.033
Slow transit (n = placebo; prucalopride)			
Baseline (n = 21; 22)	87.7 ± 13.5	83.4 ± 16.8	N.S.
Week 4 (n = 20; 22)	80.3 ± 20.5	66.1 ± 26.9	0.065
Change vs. baseline	− 6.9 ± 20.1	17.3 ± 23.7*	N.S.
Normal transit (n = placebo; prucalopride)			
Baseline (n = 16; 15)	32.6 ± 14.8	30.4 ± 14.9	N.S.
Week 4 (n = 16; 14)	38.8 ± 24.1	27.8 ± 14.8	N.S.
Change vs. baseline	6.2 ± 21.1	− 1.6 ± 14.6	N.S.
Analysis of selected sets of markers†			
Slow transit (n = placebo; prucalopride)			
Baseline (n = 21; 22)	47.9 ± 13.2	44.8 ± 15.3	N.S.
Week 4 (n = 20; 22)	41.7 ± 17.3	30.5 ± 21.1	0.069
Change vs. baseline	− 5.7 ± 15.9	− 14.3 ± 20.5*	N.S.
Normal transit (n = placebo; prucalopride)			
Baseline (n = 16; 15)	28.1 ± 10.5	26.1 ± 10.6	N.S.
Week 4 (n = 16; 14)	29.6 ± 10.8	24.5 ± 11.0	N.S.
Change vs. baseline	1.4 ± 12.9	− 0.57 ± 11.8	N.S.

N.S., not significant.
*Significant change from baseline ($P < 0.05$).
†Sets 1, 2 and 3 for slow transit and sets 4 and 5 for normal transit.

Table 3. Changes in rectal sensitivity to distension and electrical stimulation vs. baseline (baseline and post-treatment values in parentheses) in an intention-to-treat analysis for all patients in placebo- and prucalopride-treated groups. Results presented as mean ± s.d.

	Intention-to-treat		
	Placebo (n = 36)	Prucalopride (n = 37)	*P* value
Mean change in anal electrosensory threshold (mA)	+ 0.1 ± 0.7 (7.2 → 7.3)	− 0.3 ± 1.0 (8.6 → 8.3)	N.S.
Mean change in rectal electrosensory threshold (mA)	+ 0.7 ± 2.5 (19.6 → 20.2)	− 1.3 ± 2.8 (20.4 → 19.1)	0.001
Mean change in rectal initial sensation volume — distension (mL)	+ 1.9 ± 13.5 (48 → 50)	− 1.8 ± 14.5 (55 → 54)	N.S.
Mean change in rectal urge sensation volume — distension (mL)	+ 2.8 ± 15.3 (105 → 108)	− 7.9 ± 19.0 (111 → 104)	0.010
Mean change in rectal maximum tolerated volume — distension (mL)	+ 6.3 ± 23.5 (200 → 208)	− 15.9 ± 30.1 (191 → 177)	< 0.001

N.S., not significant.

Quality of life and psychological status. Neither of the treatment groups differed significantly at baseline for any of the subscales of the SF-36. Following treatment, there was a statistically significant ($P = 0.019$) difference in favour of prucalopride compared with placebo in the domain of 'body pain'. In the Chronic Idiopathic Constipation Questionnaire, significant ($P < 0.05$) intergroup differences in favour of prucalopride were

found for satisfaction with bowel frequency, activities of daily life and satisfaction with treatment. The overall Chronic Idiopathic Constipation Questionnaire score improved by 27 points (9%) with prucalopride and by 8 points (3%) with placebo ($P < 0.001$).

Analysis of the Hospital Anxiety and Depression Scale revealed no significant intergroup differences in changes from baseline for either anxiety or depression subtotals or the total score. At baseline, the patients did not fulfil scores for clinical anxiety or depression. The mean baseline anxiety scores for the prucalopride- and placebo-treated groups were 9.5 ± 0.7 and 9.1 ± 0.7, respectively, and 6.0 ± 0.6 and 6.0 ± 0.7 for depression scores, respectively. There were within-group changes in favour of prucalopride in the depression subtotal ($P = 0.02$) and in the total Hospital Anxiety and Depression Scale score ($P = 0.02$).

Compliance

Compliance with trial medication was excellent and comparable in both groups (mean weekly capsule intake 6.6 vs. 6.9 for prucalopride and placebo, respectively). This was confirmed in all patients for whom serology was available. Mean plasma trough levels of prucalopride were 2.12 ng/mL (s.d., 1.12 ng/mL).

Safety

Overall, 77% of prucalopride- and 66% of placebo-treated patients reported one or more adverse events. The most frequently reported were gastrointestinal. In particular, diarrhoea (10%) and flatulence (21%) were more common with prucalopride than placebo, whilst abdominal pain and nausea occurred with similar frequency in both groups. The most common non-gastrointestinal adverse event was headache, which was reported with similar frequency in both prucalopride- (49%) and placebo-treated (42%) groups. Severe adverse events were reported in similar proportions of patients (36% vs. 34% for prucalopride and placebo, respectively). Three prucalopride-treated patients withdrew from treatment because of adverse events: one due to back pain and nausea, one due to abdominal pain and diarrhoea, and one due to diarrhoea and vomiting. All three recovered fully within 2 days of cessation of treatment. No clinically relevant differences in vital signs, electrocardiographic parameters or laboratory values were observed between the groups at the end of 4 weeks of treatment.

DISCUSSION

The results of this double-blind, placebo-controlled study demonstrate the safety and efficacy of prucalopride for the treatment of patients with chronic functional constipation. Four weeks of treatment with prucalopride, 1 mg, hastens colonic transit in patients in whom it is slow and improves symptoms in all patients.

We have previously published the first description of prucalopride, a substituted benzamide, as having enterokinetic properties in healthy volunteers.[21] There were marked effects on stool frequency and consistency, accompanied by the acceleration of both upper gut and colonic transit. The present study extends these observations to patients with chronic functional constipation.

In this single centre trial of consecutive patients, we studied only females because women account for three-quarters of patients who consult with constipation.[1, 11, 29] A 4-week treatment period was chosen to take account of any cyclical symptom or transit changes.[30, 31] A 1-mg dose was chosen because the previous healthy volunteer study showed no difference in the effects of 1 mg and 2 mg,[21] and the higher dose was associated with a greater risk of adverse events.[32] Because prucalopride has a half-life of around 24 h,[33] once-daily dosing was employed in this study.

To ensure that the trial closely paralleled normal clinical practice, only newly referred patients were enrolled, and the study was analysed by intention-to-treat. Of the 87 screened patients, only two were found on collection of screening diary data not to have symptoms consistent with constipation. This suggests that, in contrast to other observations,[34, 35] patients' self-reported symptoms at presentation are sufficient to diagnose constipation, and the maintenance of a formal diary is of additional value in only a minority of patients.

Prucalopride increased the frequency of spontaneous bowel movements from a mean of six to eight per week. There was an associated increased frequency of urge to defecate and a trend towards a reduced need to strain and improved stool consistency. Prucalopride resulted in a stool within 4 h in half of all patients.

In addition to the objective improvement in symptoms, patients rated prucalopride treatment as significantly more effective than placebo. Prucalopride-treated patients reported a greater subjective improvement in symptoms compared with placebo-treated patients. This improvement was evident within 2 weeks of starting treatment and was sustained with continued treatment. Additionally, the overall clinical impression of the investigator was that 4 weeks of treatment with prucalopride was favourable in over 80% of patients compared with 31% in the placebo group.

A simple count of the total number of retained markers in all patients (unstratified by transit) showed that prucalopride, but not placebo, significantly reduced the number of markers by 11, equivalent to an acceleration of transit by 13 h. The change in the mean number of retained markers with placebo was one, demonstrating the robust reproducibility of this technique for assessing whole-gut transit, and the minimal effect of placebo in functional constipation.

Optimal sensitivity, according to whether the patient had normal or slow transit, was obtained by analysing only the numbers of markers in the relevant time frame — that is, in the 48 h prior to X-ray in those with normal transit and 120–72 h prior to X-ray in those with slow transit. This analysis showed that the improvement in whole-gut transit was seen only in those with slow transit and not normal transit constipation. In these patients, there was a reduction in marker count of 14 (approximately equivalent to 17 h). Although normal transit patients demonstrated a statistically significant difference in the mean number of retained markers, this had no clinical significance as it arose from a slight increase in the number of retained markers in the placebo group. Overall, 35% of slow transit patients treated with prucalopride normalized transit.

Prucalopride resulted in significant and consistent acceleration of orocaecal transit. A 29% acceleration of transit was seen with prucalopride. This technique does not allow the distinction to be made between hastened gastric and small intestinal transit.

In patients with constipation, prucalopride significantly and consistently heightened rectal sensitivity, both to distension and electrical stimulation. It is recognized that some patients with constipation may have an intrinsic sensory neuropathy[26, 36] and that slow transit is associated with the most profound sensory impairment.[37] It is possible that one of the beneficial mechanisms of the action of prucalopride in chronic functional constipation is an alteration of visceral sensation. Of relevance, this study demonstrated a trend towards an improved bodily pain score of the SF-36 and a reduction of abdominal bloating in prucalopride-treated patients. The ability of these drugs to modify visceral pain therefore deserves further investigation.

There is a well-recognized association between emotional and social factors and gut function.[38, 39] In particular, patients with constipation tend to have higher scores on scales of somatization, interpersonal sensitivity, anxiety and depression.[4, 5, 7] Using a general health questionnaire, the SF-36, and a rating scale specific for anxiety and depression in this study, we have shown that a drug-induced improvement in symptoms is associated with significant improvements in feelings of bodily pain in patients with constipation. There were additional trends towards improvement in the SF-36 domains of mental health and social functioning. Whether these changes in psychological and social functioning are primary or secondary to improvements in physical health cannot be ascertained from this study.

In the current study, prucalopride was well tolerated. Most adverse events were mild to moderate in severity and there were no clinically relevant effects on electrocardiographic, cardiovascular or laboratory parameters. The adverse event profile of prucalopride comprised primarily gastrointestinal symptoms, reflecting the colonic effects expected from a drug with enterokinetic properties. Headache was reported in approximately one-half of the study patients, with similar frequencies in the placebo and prucalopride groups. Eight per cent of prucalopride-treated patients withdrew from treatment due to adverse events, and all recovered fully within 2 days of stopping medication.

In conclusion, prucalopride enhances visceral sensitivity and significantly improves stool frequency and consistency and the need to strain in patients with slow and normal transit constipation. It hastens upper gut transit in all patients, of potential benefit in this panenteric disorder, and hastens colonic transit only in those in whom it is slow. Prucalopride is well tolerated and represents a new class of agent in the treatment of constipation.

ACKNOWLEDGEMENTS

This research was supported by Janssen Research Foundation, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

REFERENCES

1 Talley NJ, Weaver AL, Zinsmeister AR, *et al.* Functional constipation and outlet delay: a population based study. Gastroenterology 1993; 105: 781–6.
2 Sonnenberg A, Koch TR. Physician visits in the United States for constipation: 1958–1986. Dig Dis Sci 1989; 34: 606–11.
3 Talley NJ, O'Keefe EA, Zinsmeister AR, *et al.* Prevalence of gastrointestinal symptoms in the elderly: a population based study. Gastroenterology 1992; 102: 895–9.
4 Preston DM, Pfeffer J, Lennard-Jones JE. Psychiatric assessment of patients with severe constipation. Gut 1984; 25: A582–3.
5 Devroede G, Roy T, Bouchoucha M, *et al.* Idiopathic constipation by colonic dysfunction: relationship with personality and anxiety. Dig Dis Sci 1989; 34: 1428–34.
6 Leroi AM, Bernier C, Watier A, *et al.* Prevalence of sexual abuse among patients with functional disorders of the lower gastrointestinal tract. Int J Colorect Dis 1995; 10: 200–6.
7 Mason HJ, Serrano-Ikkos E, Kamm MA. Psychological morbidity in women with idiopathic constipation. Am J Gastroenterol 2000; 95: 2852–7.
8 Glia A, Lindberg G. Quality of life in patients with different types of functional constipation. Scand J Gastroenterol 1997; 32: 1083–9.
9 Hinton JM, Lennard-Jones JE. Constipation: definition and classification. Postgrad Med J 1968; 44: 720–3.
10 Evans RC, Kamm MA, Hinton JM, Lennard-Jones JE. The normal range and a simple diagram for recording whole gut transit time. Int J Colorect Dis 1992; 7: 15–7.
11 Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. Gut 1986; 27: 41–8.
12 van der Sijp JRM, Kamm MA, Nightingale JMD, *et al.* Disturbed gastric and small bowel transit in severe idiopathic constipation. Dig Dis Sci 1993; 38: 837–44.
13 Gattuso JM, Kamm MA. Review article: the management of constipation in adults. Aliment Pharmacol Ther 1993; 7: 487–500.
14 Cummings JH. The use and abuse of laxatives. In: Boucher IAD, ed. Recent Advances in Gastroenterology. London: Academic Press, 1976: 124–49.
15 Ashraf W, Park F, Lof J, Quigley EM. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. Aliment Pharmacol Ther 1995; 9: 639–47.
16 Jones M, Dubois D, Talley N. Laxatives in chronic constipation: a statistical meta-analysis [abstract]. Gastroenterology 1999; 116(4 Part 2): A67(Abstract).
17 Briejer MR, Akkermans LMA, Schuurkes JAJ. Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility. Pharmacol Rev 1995; 47: 631–51.
18 Grider JR, Foxx-Orenstein AE, Jin J-G. 5-Hydroxytryptamine$_4$ receptor agonists initiate the peristaltic reflex in human, rat and guinea pig intestine. Gastroenterology 1998; 115: 370–80.
19 Jin J-G, Foxx-Orenstein AE, Grider JR. Propulsion in guinea pig colon induced by 5-hydroxytryptamine (HT) via 5-HT$_4$ and 5-HT$_3$ receptors. J Pharmacol Exp Ther 1999; 288: 93–7.
20 Basotti G, Gaburri M, Imbimbo B, *et al.* Colonic mass movements in idiopathic chronic constipation. Gut 1988; 29: 1173–9.
21 Emmanuel AV, Kamm MA, Roy AJ, Antonelli K. Effect of a novel prokinetic drug, RO93877, on gastrointestinal transit in healthy volunteers. Gut 1998; 42: 511–6.
22 Bouras EP, Camilleri M, Burton DD, McKinzie S. Selective stimulation of colonic transit by the benzofuran 5HT$_4$ agonist, prucalopride, in healthy humans. Gut 1999; 44: 682–6.
23 Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterology 2001; 120: 354–60.
24 Drossman DA, Sandler RS, McKee DC, *et al.* Bowel patterns amongst subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. Gastroenterology 1982; 83: 529–34.
25 O'Brien JD, Thompson DG, Burnham WR, *et al.* Action of centrally mediated autonomic stimulation on human upper gastrointestinal transit: a comparative study of two stimuli. Gut 1987; 28: 960–9.
26 Kamm MA. Investigating constipation. Curr Med Lit (Gastroenterol) 1992; 11: 3–9.
27 McHorney C, Ware JE, Rogers E, *et al.* The validity and relative precision of MOS short and long form health status scales and Dartmouth COOP charts. Results from the medical outcomes study. Med Care 1992; 30: MS253–65.
28 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.
29 Heaton KW, O'Donnell LJD, Braddon FEN, *et al.* Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. Gastroenterology 1992; 102: 1962–8.
30 Prior A, Wilson K, Whorwell PJ, *et al.* Irritable bowel syndrome in the gynaecological clinic. Survey of 798 new referrals. Dig Dis Sci 1989; 34: 1820–8.
31 Kamm MA, Farthing MJG, Lennard-Jones JE, *et al.* Steroid hormone abnormalities in women with severe idiopathic constipation. Gut 1991; 32: 80–5.
32 Mannaert E, Van Bortel L, Woestenborghs R, van Peer A. Single-dose and once-daily pharmacokinetics and effects of food on prucalopride in humans [abstract]. Gut 1999; 45(Suppl. V): P0252.
33 Vant Klooster G, De Pauw M, Crabbé R. Tolerability, pharmacokinetics and pharmacodynamics of prucalopride in healthy volunteers [abstract]. Gut 1999; 45(Suppl. V): P0264.
34 Wald A, Hinds JP, Caruana BJ. Psychological and physiological characteristics of patients with severe idiopathic constipation. Gastroenterology 1989; 97: 932–7.
35 Wald A, Burgio K, Holeva K, Locher J. Psychological evaluation of patients with severe constipation: which instrument to use? Am J Gastroenterol 1992; 87: 977–80.

36 Knowles CH, Scott SM, Wellmer A, *et al.* Sensory and autonomic neuropathy in patients with idiopathic slow transit constipation. Br J Surg 1999; 86: 54–60.
37 de Medicis A, Badiali D, Corazziari E, *et al.* Rectal sensitivity in chronic constipation. Dig Dis Sci 1989; 34: 747–52.
38 Wolf S, Wolf HG. Experimental study of changes in gastric function in response to varying life experiences. Rev Gastroenterol 1947; 14: 419–26.
39 Almy TP. Experimental studies on the irritable colon. Am J Med 1951; 10: 60–7.