Selective stimulation of colonic transit by the benzofuran 5HT₄ agonist, prucalopride, in healthy humans

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Abstract

Background—Prucalopride (R093877) is a selective and specific 5HT₄ agonist, the first of a new chemical class of benzofurans, with gastrointestinal prokinetic activities *in vitro*.

Aims—To evaluate the effects of prucalopride on gastrointestinal and colonic transit.

Methods—A validated scintigraphic technique was used to measure gastrointestinal and colonic transit over 48 hours in 50 healthy volunteers. For seven days, each subject received a daily dose of 0.5, 1, 2, or 4 mg prucalopride, or placebo in a double blind, randomised fashion. The transit test was performed over the last 48 hours.

Results—There were significant accelerations of overall colonic transit at 4, 8, 24, and 48 hours ($p < 0.05$) and proximal colonic emptying $t_{1/2}$ ($p < 0.05$). The 0.5, 2, and 4 mg doses of prucalopride were almost equally effective and accelerated colonic transit compared with placebo. Prucalopride did not significantly alter gastric emptying ($p > 0.5$) or small bowel transit (overall $p = 0.12$). The medication appeared to be well tolerated during the seven day treatment of healthy subjects.

Conclusion—Prucalopride accelerates colonic transit, partly by stimulating proximal colonic emptying, but does not alter gastric or small bowel transit in healthy human subjects. Prucalopride deserves further study in patients with constipation. (Gut 1999;44:682-686)

Keywords: benzofuran; prucalopride; motility; transit; colon; gastrointestinal

Prucalopride (R093877) is a benzofuran derivative and a specific 5HT₄ agonist that has been shown to facilitate cholinergic neurotransmission.¹ It enhances colonic contractility, including giant contractions in dog colon *in vivo*.² In phase I studies in humans, single doses of up to 4 mg orally, subcutaneously, and intravenously were well tolerated with no clinically relevant effects on laboratory or cardiovascular safety parameters.³

Constipation is a common problem,⁴⁻⁶ and colonic motility disorders are increasingly recognised.⁷⁻¹² However, treatments are relatively ineffective for the more severe forms of constipation, as in paraplegia or Parkinson's disease.¹³⁻¹⁶ In some patients, slow transit constipation is associated with colonic inertia,^{17,18} and if medically intractable, requires colectomy with ileorectostomy.¹⁹ There is a need for effective stimulants of colonic motility for such patients; an effective colonic prokinetic would be a useful addition to the currently available medical treatments for slow colonic transit. To be considered a candidate for such a role, it is important to perform pharmacodynamic studies of any new drug, including dose-response studies, and to characterise the mode of its action.

Thus, the aim of this study was to evaluate the effects of prucalopride on gastrointestinal and colonic transit in healthy subjects.

Materials and methods

SUBJECTS

Fifty three healthy subjects were recruited by public advertisement. Each subject completed a validated bowel disease questionnaire²⁰ and was screened for any chronic gastrointestinal symptoms. Inclusion criteria were: 18 to 65 year old males and females; females of childbearing potential required negative pregnancy test within 48 hours of study; no present or previous chronic gastrointestinal illness; and no previous abdominal surgery except appendectomy or hernia repair. Exclusion criteria were: abdominal surgery other than appendectomy or hernia repair; positive gastrointestinal symptoms on bowel disease questionnaire; use of medications that may alter gastrointestinal motility; and OTC (over the counter) medication within seven days of study.

Abbreviations used in this paper: 5HT₄, 5-hydroxytryptamine; WGTT, whole gut transit time.

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Figure 1 Experimental procedure.

Table 1 Effect of prucalopride on gastric and small bowel transit

Dose	n	G _{LAG} (min)	G _{FER} (%/min)	SBTT 10% (min)
Placebo	9	53 (6)	0.5 (0.01)	88 (20)
Prucalopride				
0.5 mg	11	43 (5)	0.53 (0.02)	72 (15)
1 mg	9	53 (8)	0.53 (0.02)	69 (17)
2 mg	11	50 (5)	0.55 (0.02)	83 (20)
4 mg	10	47 (5)	0.55 (0.02)	121 (16)

Data expressed as mean (SEM).

G_{LAG} = gastric emptying lag time (time for emptying 10% of meal).

G_{FER} = slope of fractional gastric emptying rate.

SBTT = small bowel transit time.

EXPERIMENTAL DESIGN

Figure 1 details the experimental procedure. A parallel group, dose-response study was performed, with 10 subjects being randomised to each treatment: placebo, 0.5 mg, 1.0 mg, 2.0 mg, or 4.0 mg per day prucalopride as a single dose. Subjects were dosed with medication daily at the same time in the morning, half an hour before breakfast for seven days; a 48 hour transit test was performed on days 5–7.

TRANSIT MEASUREMENTS

On the day of transit measurements, the study medication was administered at a standardised time, 60 minutes prior to administration of the capsule containing radiolabelled particles. An adaptation of an established scintigraphic method was used to measure gastrointestinal and colonic transit.^{21–25} Briefly, ¹¹¹In adsorbed on activated charcoal particles was delivered to the colon by means of a methacrylate coated, delayed release capsule.²⁵ The capsule was ingested following an overnight fast. After the capsule emptied from the stomach (documented by its position relative to radioisotopic markers placed on the anterior iliac crests), a radiolabelled meal was ingested. In this meal,

^{99m}Tc sulphur colloid was used to label two scrambled eggs, which were eaten with one slice of whole wheat bread and one glass of whole milk (1.25 MJ). This meal facilitated measurement of gastric and small bowel transit. Subjects ingested standardised meals for lunch and dinner at four and eight hours after the radiolabelled meal. Abdominal images, relative to the time of meal ingestion, were obtained every 15 minutes for the first two hours, then every 30 minutes for the next four hours; scans were obtained at 8, 24, and 48 hours.

DATA AND STATISTICAL ANALYSIS

A variable region of interest program was used to quantitate the counts in the stomach and each of four colonic regions: ascending, transverse, descending, and combined sigmoid and rectum. These counts were corrected for isotope decay, tissue attenuation, and cross talk (downscatter) of ¹¹¹In counts in the ^{99m}Tc window.^{22–24}

The primary summaries for comparison of transit profiles were obtained: gastric lag time, post-lag gastric emptying slope (fractional emptying rate), small bowel transit time (t_{10%}), and colonic geometric centre at 4, 8, 24, and 48 hours. The geometric centre is the weighted average of counts in the different colonic regions (ascending (AC), transverse (TC), descending (DC), rectosigmoid (RS)) and stool. At any time, the proportion of colonic counts in each colonic region is multiplied by its weighting factor as follows: (%AC × 1 + %TC × 2 + %DC × 3 + %RS × 4 + % stool × 5)/100 = geometric centre.

Thus, a high geometric centre implies faster colonic transit; a geometric centre of 1 implies

Figure 2 Effect of prucalopride on overall colonic transit (geometric centre) at 4 (A), 8 (B), 24 (C), and 48 (D) hours. ANOVA shows significant overall drug effect (at least one dose at each time point; * $p < 0.05$) at all times. Dunnett's test shows significant effects of the 0.5 and 2.0 mg doses versus placebo.

Figure 3 Effect of prucalopride on proximal colonic emptying half time; the drug has an overall significant effect on $t_{1/2}$; the $t_{1/2}$ values observed with the 0.5 and 2.0 mg doses are significantly lower than those with placebo (Dunnett's test, * $p < 0.05$).

that all isotope is in the ascending colon; and a geometric centre of 5 implies that all isotope is in the stool.

The $t_{1/2}$ of proximal colonic emptying (combined ascending and transverse regions) was also estimated. A $t_{1/2}$ of 48 hours was assumed if there was less than 50% emptied by 48 hours, the time of the last scan performed in this study. This applied to three subjects in the placebo group, and one subject in each of three prucalopride groups: 1, 2, and 4 mg.

Statistical analysis was by one way analysis of variance (ANOVA) with subsequent Dunnett's test for comparison of the effects of each dose versus placebo. Data are presented as mean (SEM); $p < 0.05$ was considered significant.

Results

SUBJECTS

Fifty three participants were enrolled: two dropped out because of headache and diarrhoea; a third subject's data were lost due to technical error, but this subject was replaced with another healthy control. The study population consisted of 50 healthy volunteers (14 men and 36 women; mean age 33 years, range 18–55 years). All subjects completed the transit studies. The methacrylate capsule failed to dissolve in two subjects; thus, their counts were not dispersed through the four colonic regions, but the capsule location in the colon on sequential scans was easily identified by virtue of the position relative to the dispersed ^{99m}Tc counts from the meal that outlined the colon. While the contents of the capsule were not dispersed, all counts were assumed to be in the

Table 2 Adverse events in two or more subjects during treatment with prucalopride

	Prucalopride				
	Placebo (n=9)	0.5 mg (n=11)	1 mg (n=9)	2 mg (n=11)	4 mg (n=10)
Diarrhoea	2	3	8	6	8
Constipation	1	0	0	0	1
Flatulence	3	2	1	6	4
Nausea	0	0	1	1	5
Abdominal pain	1	1	3	4	3
Headaches	3	3	6	6	4
Menstrual disorder*	0	0	0	2	1
Dizziness	0	0	1	1	0
Skeletal pain	0	1	0	1	0
ECG nodal arrhythmia	0	0	0	1	1
Total no of subjects with adverse events	5	8	9	9	9

*Breakthrough menstrual bleeding or reduced blood loss on day 1 of menstruation.

Table 3 Diarrhoea observed during treatment with prucalopride

	n	No with diarrhoea	Mild	Moderate	Severe
Placebo	9	2	0	1	1
Prucalopride					
0.5 mg	11	3	2	1	0
1 mg	9	8	4	2	2
2 mg	11	6	4	2	0
4 mg	10	8	1	3	4

colonic region identified from the ^{99m}Tc image. Two other subjects failed to attend for the 24 hour scan but otherwise had complete data.

GASTRIC AND SMALL BOWEL TRANSIT

There was no significant overall effect of the tested doses of prucalopride compared with placebo on gastric emptying. Similarly, the ANOVA showed a lack of significant overall effect on small bowel transit ($p = 0.12$). There was wider variability of small bowel transit times. Table 1 gives a summary of these results.

OVERALL COLONIC TRANSIT

Prucalopride significantly accelerated overall colonic transit (geometric centre) between 4 and 48 hours. Dunnett's test showed that the 0.5 mg/day dose accelerated transit at all times tested; the 2.0 mg/day dose caused significant acceleration of colonic transit at 24 and 48 hours. At 48 hours, colonic transit with the 4.0 mg dose was also significantly accelerated relative to placebo (fig 2).

PROXIMAL COLONIC EMPTYING

Figure 3 shows the effects of prucalopride on the $t_{1/2}$ of proximal colonic emptying. The numbers of censored data (48 hour $t_{1/2}$ for those with less than 50% emptying) in each group were: three placebo, one 1 mg/day, one 2 mg/day, and one 4 mg/day. This means that it was assumed that the $t_{1/2}$ was 48 hours for three subjects given placebo whose proximal colon had not emptied 50% at 48 hours; the censored value of 48 hours was assumed for one subject in each of the three other active treatment groups. The overall drug effect on $t_{1/2}$ proximal colonic emptying was significant ($p < 0.025$) and the 0.5 and 2 mg doses were associated with significantly lower $t_{1/2}$ values compared with placebo ($p < 0.05$).

ADVERSE EFFECTS

Table 2 shows the adverse effects noted in the study according to dose of prucalopride received. The most frequent adverse effects were diarrhoea (see also table 3), headache, flatulence, nausea, and abdominal pain. Two subjects dropped out of the study at their own request because of headache and diarrhoea. There was no difference in the frequency of adverse effects induced by the different doses of prucalopride.

Discussion

This study in healthy volunteers shows that prucalopride has no significant effects on gastric or small bowel transit; however, it significantly accelerates overall colonic transit

and the emptying of the ascending and transverse colon. The dose related effects in healthy volunteers suggest that a dose between 0.5 and 2.0 mg/day may be the most effective with no significant incremental acceleration with the 4 mg/day dose. These observations are indicative of the dose ranges that are worthy of further study in disease states such as constipation, where further clarification of the dose-response may be obtained. The lack of effects on gastric and small bowel transit contrasts with the previous observations in healthy volunteers with another 5HT₄ agonist prokinetic agent, cisapride. Indeed, several papers convincingly show acceleration of solid emptying²⁶⁻³⁰ and of small bowel transit²⁶ by cisapride in healthy subjects, but its effects on colonic transit are less prominent in healthy subjects.³¹ The less specific effects of previously studied 5HT₄ agonists had raised questions concerning the role of 5HT₄ receptors in colonic motility. In fact, the results of this study provide evidence that 5HT₄ receptors are involved in the control of human colonic motility in vivo.

Our study has revealed several findings that are consistent with the observations of Emmanuel *et al.*³² despite major differences in experimental design and methods used in the two studies. Emmanuel *et al* showed that 1 and 2 mg of prucalopride accelerated whole gut transit time and the drug was well tolerated, results that are confirmed in our study. Furthermore, they did not observe dose responsiveness in either acceleration of transit or adverse effects, as the effects of 1 mg seemed greater than those of 2 mg prucalopride. However, Emmanuel *et al* also observed acceleration of oro-caecal transit measured by the lactulose-hydrogen breath test. We do not believe that differences in experimental design (multiple crossover versus parallel group) are responsible for the differences in these studies.

However, the methods used to measure transit were quite different. The lactulose breath test measures oro-caecal transit of a liquid marker and cannot really differentiate effects on gastric versus small bowel transit. In contrast, we have assessed transit of solids. The radio-opaque marker transit test used by Emmanuel *et al* addresses whole gut transit time (WGTT) in contrast to the regional specificity obtained with scintigraphic measurements. The WGTT measurements were based on marker ingestion at 12 hourly intervals for three days and an abdominal x ray on day 4; the treatment and placebo arms compared the number of intra-abdominal markers ingested 24 and 36 hours previously. We are unaware of any validation studies of these measurements used to assess colonic transit. Nevertheless, the results of our study appear to corroborate the main findings on colonic transit and adverse effects reported by Emmanuel *et al*, and specifically, the lack of a clear dose-response relation.

The acceleration of overall colonic transit is at least partly due to acceleration of proximal colonic emptying. This is a promising effect as previous studies have shown delayed proximal

colonic emptying in patients with idiopathic constipation.¹⁰⁻¹¹ The two doses of prucalopride that significantly altered proximal colonic emptying had an effect on overall colonic transit, suggesting that proximal colonic emptying may be the main action of the agent in the colon of healthy subjects. These studies also confirm the data from in vitro studies and animal studies in vivo.³³ Intravenously administered prucalopride induced high amplitude contractile clusters in the proximal colon and inhibited this contractile activity more distally, with a maximum effect noted at 0.31 mg/kg. These observations suggest that its main propulsive actions may be in the proximal colon.³³

Some 5HT₄ agonist prokinetics stimulate 5HT_{2A} and 5HT₃ receptors.³⁴ In vitro studies performed to date suggest that prucalopride (R093877) is specific and selective for 5HT₄ receptors and that it is devoid of affinity to M3 cholinergic receptors, 5HT_{2A} and 5HT₃ receptors, and cholinesterases.¹ In vivo canine colonic studies confirm the selectivity of the effects on 5HT₄ receptors, as the selective and potent 5HT₄ antagonist, GR125487, completely prevented the effects of the benzofuran, R093877.²

The reason for the lack of a dose-response effect of prucalopride on colonic transit is unclear from studies reported to date. The lack of a greater effect of the 4 mg over the 0.5 and 2.0 mg doses in our study may reflect the attenuation of signal by G protein coupled receptors,³⁵ which characterise serotonin receptors.³⁶ However, it is interesting to note that the dose dependent effects of prucalopride on colonic giant migrating or clustered contractions were more clearly demonstrable with the intravenous than with the oral administration of the drug in dogs.³³ Briejer *et al* noted a sigmoid dose-response curve in the dose range 0.001 to 1.25 mg/kg, with the linear part of the curve between 0.02 and 0.31 mg/kg.³³ While it is difficult to extrapolate dose effects in a canine model to the human, the fact that several healthy subjects developed diarrhoea and accelerated colonic transit with 0.5, 2.0, and 4.0 mg prucalopride suggests these dosages may also be effective if administered to patients with slow colonic transit. In the future, we shall appraise the dose related effects of prucalopride in constipated patients and those with slow colonic transit.

The fact that prucalopride did not affect gastric and small bowel motility in healthy subjects does not preclude its potential beneficial effects in pathological states (for example, delayed gastric emptying) and this needs further evaluation. In a canine model of lidamide (α_2 agonist) induced delayed gastric emptying, oral and intravenous prucalopride accelerated gastric emptying.³⁷ It is worth noting, for example, that, in some studies, other prokinetics were ineffective in accelerating gastric emptying in health,³⁸ whereas they have been shown to be effective in patients with delayed gastric emptying.³⁹

In summary, prucalopride (R093877) is effective in selectively accelerating colonic

transit without significant adverse effects during administration for one week in healthy humans. It deserves further study as a colonic motility stimulant in patients with constipation.

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