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Prucalopride Improves Bowel Function and Colonic Transit Time in Patients With Chronic Constipation: An Integrated Analysis

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OBJECTIVES: Constipation is often characterized by slow colonic transit, but the relationship between colonic transit time (CTT) and symptoms is unclear. The aims of this study were to investigate the effect of prucalopride, a 5-hydroxytryptamine receptor-4 agonist, on CTT and assess the relationship between CTT and symptoms.

METHODS: This was an integrated analysis of three randomized, placebo-controlled, phase 2 dose-finding trials of prucalopride in patients with chronic constipation (ClinicalTrials.gov identifiers: NCT00617513; NCT00631813; and NCT00596596). Measurements of CTT were analyzed using radio-opaque markers at the start and end (4 or 12 weeks) of treatment. At these visits, patients assessed the presence and severity of their symptoms.

RESULTS: In total, 280 patients had CTT measurements before and at the end of treatment and were included in the analysis. Their mean age was 43 years, 93% were women, and mean duration of constipation was 19 years. After a once daily treatment with prucalopride 2 mg ($n=98$) and 4 mg ($n=70$), CTT was reduced by 12.0 h (95% confidence interval (CI): -18.9, -5.1) and 13.9 h (95% CI: -20.5, -7.4), respectively; CTT increased by 0.5 h (95% CI: -4.5, 5.5) with placebo ($n=112$). At the end of the trial, symptoms including bloating/flatulence/distension and straining were rated as severe or very severe by a higher proportion of patients with slow or very slow CTT (>48 h) than by those with normal CTT.

CONCLUSIONS: There was a clear relationship between increased CTT and increased symptom severity in patients with chronic constipation. Treatment with prucalopride accelerated CTT in these individuals.

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INTRODUCTION

Constipation is a common, often chronic, gastrointestinal problem that has a significant negative impact on health-related quality of life (1,2). Chronic constipation is diagnosed using the Rome III criteria (3) or, more commonly in clinical practice, by the patient's symptoms of infrequent, difficult, or unsatisfactory bowel evacuation.

Prevalence estimates for chronic constipation vary more according to definition than to geography, but are generally between 10 and 15% for developed countries (4,5). It is thought that the majority of patients with constipation experience slow-transit constipation, in which the rate of colonic transit is reduced (6); however, a relationship between symptoms

of constipation (stool consistency and frequency of bowel movements) and colonic transit time (CTT) has never been convincingly demonstrated.

Prucalopride is a selective, high-affinity, 5-hydroxytryptamine receptor-4 agonist with gastrointestinal prokinetic properties. The high affinity and selectivity for 5-hydroxytryptamine receptor-4 differentiates prucalopride from older generation compounds, such as cisapride and tegaserod, and minimizes the potential for target-unrelated side effects (7,8). Phase 3 clinical trials have shown prucalopride to be effective in improving stool frequency (9–11) and it is also effective in reducing abdominal and stool-related symptoms associated with constipation (12). In the European Union, prucalopride is approved for the

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symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. The recommended dose is 2 mg once daily for adults or 1 mg once daily for patients who are over 65 years old.

A consistent effect of prucalopride on CTT has not yet been reported in patients with chronic constipation. Some phase 2 trials have shown that prucalopride treatment results in decreased orocecal transit time (13) and reduced CTT (14,15), but other phase 2 trials have reported a less conclusive effect of prucalopride on CTT (16,17).

The aims of this study were twofold: first, to evaluate the effects of prucalopride on CTT in a large population, and, second, to assess the relationship between CTT and symptoms of constipation. To address these aims, an integrated analysis was performed that combined CTT data obtained from three placebo-controlled phase 2 trials before and after prucalopride treatment.

METHODS

Population

The present study is an integrated analysis of patient data from three randomized, placebo-controlled, phase 2 dose-finding trials in patients with chronic constipation (INT-1, INT-2, and USA-3; ClinicalTrials.gov identifiers: NCT00617513; NCT00631813; and NCT00596596) (14,18,19). An integrated analysis approach was used to provide as much data as possible for addressing the study aims.

Design of the phase 2 trials

The main inclusion criterion for these trials was chronic constipation, defined as two or fewer spontaneous complete bowel movements (SCBMs) per week in combination with straining, sensation of incomplete evacuation, or hard stools for $\geq 25\%$ of stools. Secondary constipation was the main exclusion criterion.

For each trial, there was a run-in period of 4 weeks. Patients were then treated with either placebo or prucalopride once daily for 4 weeks (INT-1 and USA-3) or for 12 weeks (INT-2). Key trial objectives were to assess CTT; the number of SCBMs per week; stool consistency (measured on a 5-point scale from -2 (watery) to $+2$ (very hard)); and symptom severity. CTT was measured at baseline (before the first dose of investigational product) and at the end of treatment. All patients maintained a daily bowel symptom diary, and subjective assessments by the patient of symptom severity and stool consistency were made at every fortnightly visit.

Laxatives were not permitted during the trials, except for the use of bisacodyl as a rescue medication if the patient had not passed stool for at least 3 consecutive days. The use of laxative rescue medication was not permitted during the CTT measurements (baseline and end of treatment).

Transit time measurements and analysis

CTT was measured using a slightly modified version of the Metcalf method (20,21). A capsule containing 10 radio-opaque

markers was given to the patient every day for 6 consecutive days (INT-1 and INT-2) or a capsule of 24 markers was taken on each of 3 consecutive days (USA-3), with each capsule containing markers of a different shape. The exact times at which the doses were taken were recorded in the daily bowel symptom diaries. A single abdominal X-ray taken on the day after the administration of final dose of markers (immediately before the start of treatment or at the end of treatment) was used to calculate CTT based on the number of markers present, according to the Metcalf method (20,21).

Integrated study design

The present study includes participants from these phase 2 trials who were treated with a placebo or prucalopride 2 or 4 mg and for whom there were valid measurements of CTT before and at the end of treatment. Post-treatment CTT measurements were combined irrespective of treatment duration. This was not expected to affect the results, as other clinical efficacy outcomes were similar at week 4 and at the end of the 12-week trial.

Patients with a CTT of 48 h or less were defined as having normal colonic transit, patients with a CTT of more than 48 h were defined as having slow colonic transit, and patients with a CTT of more than 96 h were defined as having very slow colonic transit. These thresholds were set on the basis of clinical experience and evidence from previous trials, which have shown mean normal CTTs in adults without constipation to be less than 48 h, and upper normal limits for CTTs to be less than 96 h (21–23). Individual symptoms and stool consistency were analyzed using the results of questionnaires taken at the same time that CTT measurements were carried out, before and at the end of treatment. Symptom definitions were pooled for this analysis, as shown in **Table 1**, because symptom definitions differed slightly among trials.

Statistical analyses

Response to treatment was defined in the same way as in the phase 3 pivotal trials of prucalopride (9–11): patients were defined as responders when they had a mean of three or more SCBMs per week over the whole double-blind treatment period. Descriptive statistics for CTT before and at the end of treatment, and the change from baseline in CTT, were calculated for all patients, for those with slow or very slow CTT and normal CTT at baseline, and for responders and nonresponders in each treatment group. Significance of the change from before treatment to the end of treatment in each group was evaluated by a paired *t*-test. The comparisons between treatment groups and the placebo group were evaluated with the two-sample *t*-test.

Symptom scores were linked with CTT values that were assessed at the same time. Stool consistency was analyzed using data recorded at the same time as that at which the CTT measurements were carried out. Statistical comparisons were carried out using a Cochran–Mantel–Haenszel test, assessing a nonzero correlation. Statistical analyses were performed using Statistical Analysis System (SAS) software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient population and characteristics

From the 651 patients who completed the three phase 2 trials, 280 (43%) were eligible for inclusion in this study because they had a CTT measurement taken both before and at the end of treatment with placebo, prucalopride 2 mg, or prucalopride 4 mg (Table 2).

Of the 280 patients included in the integrated analysis, 112 were treated with placebo, 98 with prucalopride 2 mg, and 70 with prucalopride 4 mg (Table 2). Their mean age was 43 years

(range: 18–70 years), and they had a mean duration of constipation of 19 years (range: 0.5–64 years). Most patients (93%) in this study were women. These baseline characteristics were comparable across the three treatment groups, and were similar to the overall population enrolled in the three phase 2 trials, in which there was a mean age of 42 years, a mean duration of constipation of 18.3 years, and a preponderance of women (92%).

CTT measurements

Mean baseline CTT across all groups was ~66 h (Table 2). Overall, 70% of patients had a slow or very slow CTT at baseline (i.e., >48 h) and 30% had a normal CTT. The proportions of patients with slow or very slow CTTs at baseline were similar across the three treatment groups. Compared with CTT measurements before treatment and an increase in CTT of 0.5 h (95% confidence interval (CI): -4.5, 5.5, $P > 0.05$) at the end of treatment in the placebo group, CTTs at the end of treatment were significantly reduced in the prucalopride 2 and 4 mg groups by 12.0 h (95% CI: -18.9, -5.1; $P < 0.001$) and 13.9 h (95% CI: -20.5, -7.4; $P < 0.001$), respectively (Figure 1a). The change in CTT was not significantly different between trials, as evaluated using a general linear model.

For the subgroup of patients with a slow or very slow CTT at baseline ($n = 196$, 70%), larger reductions of 23.4 h (95% CI: -31.2, -15.6; $P < 0.001$) and 20.4 h (95% CI: -27.5, -13.3, $P < 0.001$) were observed after treatment with prucalopride 2 and 4 mg, respectively, compared with the 5-h reduction (95% CI: -10.7, 0.64; $P > 0.05$) seen with placebo (Figure 1b).

After treatment with placebo, a normal CTT was identified in 16% of the patients who had slow or very slow CTTs at baseline. Of the patients with slow or very slow CTTs at baseline, 36 and 38% achieved a normal CTT after treatment with prucalopride 2 and 4 mg, respectively. Of patients with a normal CTT at baseline, 58% had normal CTTs at the end of the trials in the placebo group compared with 68% in the prucalopride 2 mg group and 65% in

Table 1. Outline of symptoms assessed and how these were combined across the three trials

Symptoms as defined in this study	Symptoms as described in the original trial
Straining	Difficulty of stool passage/straining
Abdominal bloating/flatulence/distension	Abdominal bloating Abdominal distension Flatulence
Abdominal pain/cramps	Abdominal pain Abdominal cramps
Incomplete evacuation	Incomplete evacuation
Urgency	Urgency
Unproductive calls to stool	Unproductive calls
Tenesmus	Tenesmus
Nausea (with or without vomiting)	Nausea
Anorexia	Anorexia (loss of appetite)
Malaise	Malaise
Fatigue	Fatigue
Dysmenorrhea and/or irregular period	Irregular menstrual cycle period
Difficulty in starting micturition	Difficulty in starting urination

Table 2. Patient characteristics at baseline

	Total <i>n</i>	Women, <i>n</i> (%)	Age, years, mean (range)	Duration of constipation, years, mean (range)	CTT, hours, mean (range)	Patients with slow or very slow CTT (>48 h), <i>n</i> (%)	Patients with very slow CTT (>96 h), <i>n</i> (%)
All patients enrolled in the phase 2 trials	651	596 (92%)	42 (18–73)	18.3 (0.5–64)	—	—	—
Study population: patients CTT measurements both before and at the end of treatment	280	260 (93%)	43 (18–70)	19 (0.5–64)	66 (2–144)	196 (70%)	46 (16%)
Placebo	112	102 (91%)	43 (18–70)	19 (1.0–54)	66 (2–144)	79 (71%)	18 (16%)
Prucalopride, 2 mg	98	93 (95%)	43 (19–70)	18 (0.7–50)	65 (3–144)	67 (68%)	18 (18%)
Prucalopride, 4 mg	70	64 (91%)	41 (18–70)	21 (0.6–64)	67 (4–144)	50 (71%)	10 (14%)

CTT, colonic transit time.

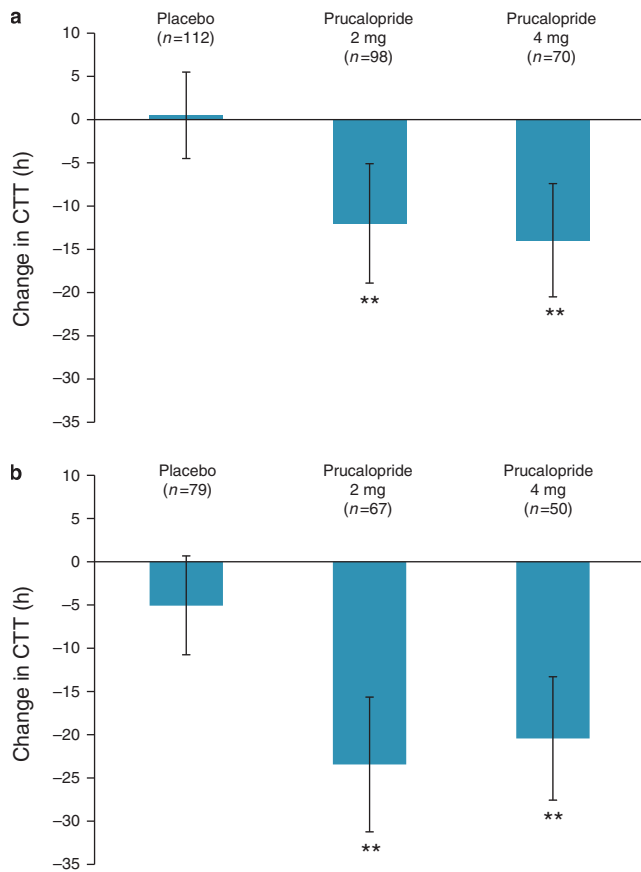


Figure 1. Change in CTT from before treatment to the end of treatment with placebo, prucalopride 2 mg, or prucalopride 4 mg in (a) all patients and (b) patients with slow or very slow CTTs (>48h) at baseline. ** $P < 0.001$ vs. baseline; two-sample t -test. Data are shown as mean \pm 95% confidence intervals. CTT, colonic transit time.

the prucalopride 4 mg group. Overall, at the end of the trials, the proportions of patients with normal CTTs were 29, 46, and 46% with placebo, prucalopride 2 mg, and prucalopride 4 mg, respectively.

Relationship between CTT and response to prucalopride

The proportions of patients in the present study with at least three SCBMs per week (responders) were significantly higher in both prucalopride 2 mg (42%, 41/98) and prucalopride 4 mg (44%, 31/70) groups than in the group receiving placebo (21%, 23/112; **Figure 2a**). The mean CTT across all groups at the end of the study was 43 h for responders and 61 h for nonresponders.

Overall, the mean CTT at the end of treatment was significantly shorter for responders than for nonresponders in all treatment groups (**Figure 2b**). Mean CTTs were 61.3, 60.0, and 69.9 h for nonresponders and 42.0, 44.6, and 50.6 h for responders in the prucalopride 2 mg, prucalopride 4 mg, and placebo groups, respectively (all $P < 0.05$). Therefore, the relationship between CTT and responder status was present irrespective of treatment group; however, CTTs were numerically shorter

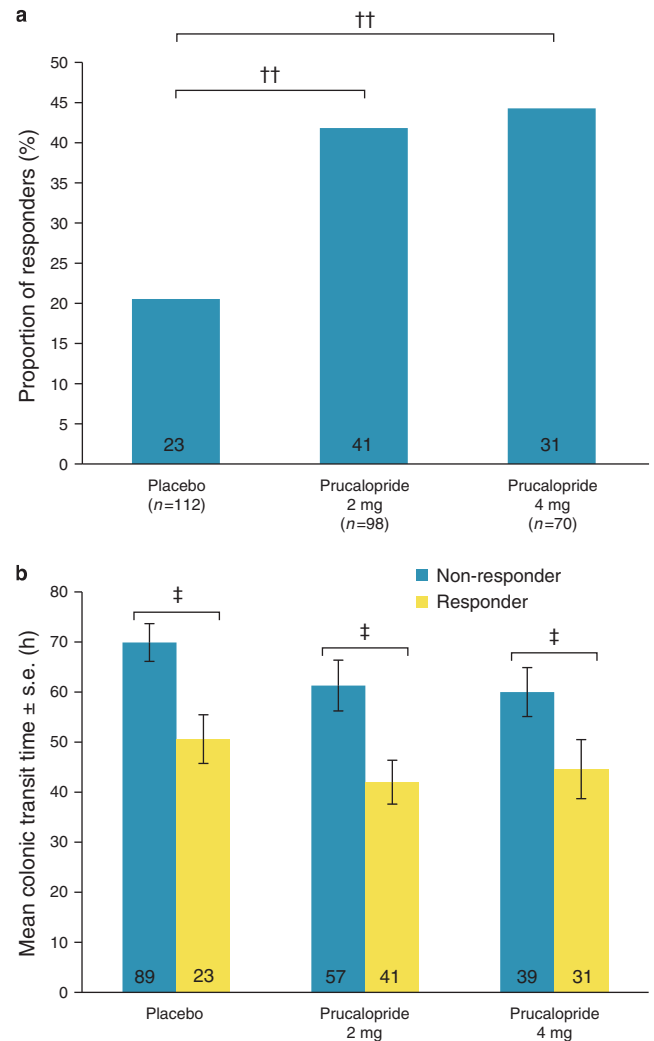


Figure 2. (a) Proportion of responders and (b) mean colonic transit times in responders and nonresponders after treatment with placebo, prucalopride 2 mg, or prucalopride 4 mg. †† $P < 0.001$ vs. placebo; † $P < 0.05$ vs. nonresponders calculated using the paired t -tests. Numbers in each bar indicate the number of patients in each group.

for patients treated with prucalopride than for those who received placebo.

Of patients with normal CTT at the end of treatment, 28% of the placebo group was responders compared with 51 and 59% of the prucalopride 2 mg and prucalopride 4 mg groups, respectively. Of the total patient population, the proportions of patients with normal CTT at the end of treatment were 39% in the placebo group and 56 and 61% in the prucalopride 2 mg and prucalopride 4 mg groups, respectively.

Relationship between CTT and symptom severity

The relationship between CTT and symptom severity is shown in **Figure 3**. Compared with patients with normal CTTs, a higher proportion of patients with slow or very slow CTTs at the end of treatment reported the following symptoms as severe or very

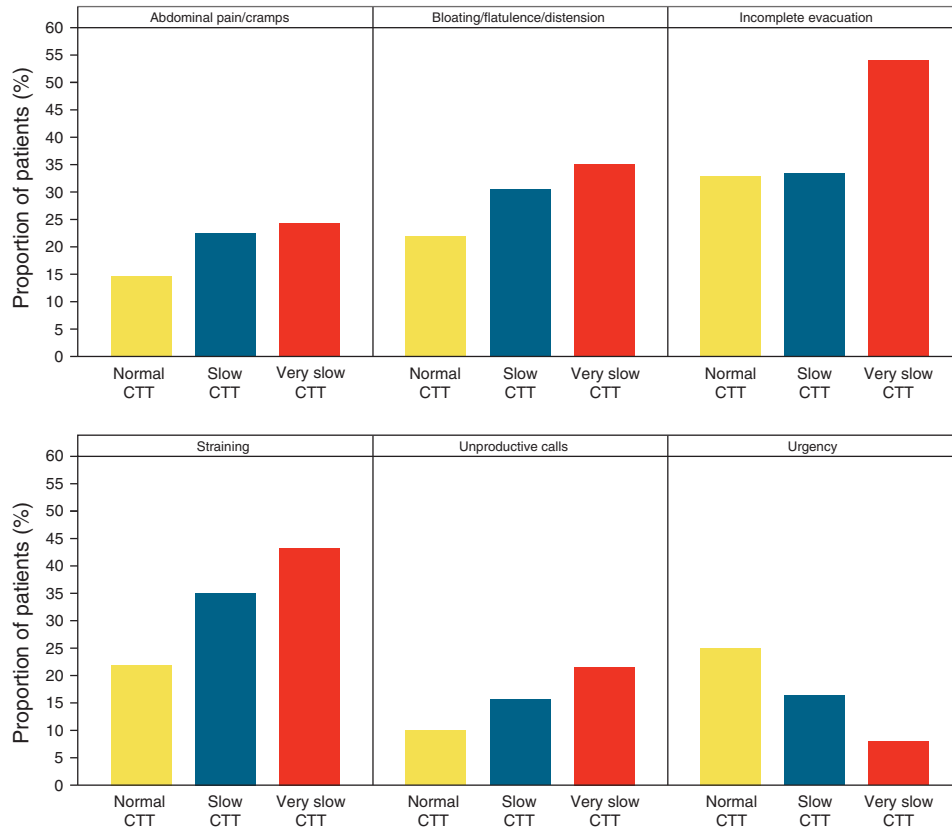


Figure 3. Relationship between CTTs at the end of treatment and the proportion of patients with severe or very severe constipation-related symptoms. Normal CTT $n=84$; slow CTT $n=150$; very slow CTT $n=46$. CTT, colonic transit time.

severe: abdominal bloating/flatulence/distension ($P=0.074$), straining ($P=0.006$), incomplete evacuation ($P=0.0664$), and unproductive calls to stool ($P=0.066$). A similar relationship was also seen for abdominal pain/cramps, but was less pronounced ($P=0.112$). Interestingly, severe or very severe urgency was reported more frequently among patients with normal CTTs than in those with slow or very slow CTTs ($P=0.014$).

Correlation between CTT and stool consistency

Regression analysis indicated a correlation between stool consistency and CTT (Pearson's correlation coefficient: 0.40). A 1-point increase in stool consistency in spontaneous bowel movements (representing harder stools) correlated with an 18-h increase in CTT.

Stool consistency was evaluated for all bowel movements in the last week of treatment. Stool consistency improved following prucalopride treatment compared with placebo in patients who had normal CTTs at the end of treatment (**Figure 4**). The mean proportion of bowel movements with stools of normal consistency in this patient subgroup was ~20% higher, and the mean proportion of bowel movements with hard/very hard stools was ~20% lower, in patients treated with prucalopride compared with those who received placebo.

Among patients with slow or very slow CTTs at the end of the trials, the consistency of stools in the last week of treatment

was similar across both prucalopride groups and the placebo group. The proportion of bowel movements with stools of normal consistency and the proportion of bowel movements with hard/very hard stools were both similar across the three groups (**Figure 4**).

DISCUSSION

This study demonstrates that there is a relationship between CTT and abdominal symptom severity, stool consistency, and frequency of bowel movements. It also demonstrates that CTT can be accelerated in some patients by treatment with prucalopride 2 mg, with mean CTT reduced by 12 h from baseline after 4–12 weeks of treatment. In fact, 36% patients with slow or very slow CTT had normalized transit times following treatment with prucalopride 2 mg. Such data have not previously been reported for laxatives or other prokinetics (24).

The results indicate that there is an improvement in CTT for patients treated with prucalopride (mean reductions in CTT of ~12–14 h) and not for those receiving placebo (mean increase in CTT of ~0.5 h). Patients who responded to treatment (i.e., who achieved at least three SCBMs per week) decreased their CTTs more than nonresponders in all three treatment groups, with a mean posttreatment CTT of 43 vs. 61 h, respectively. A higher

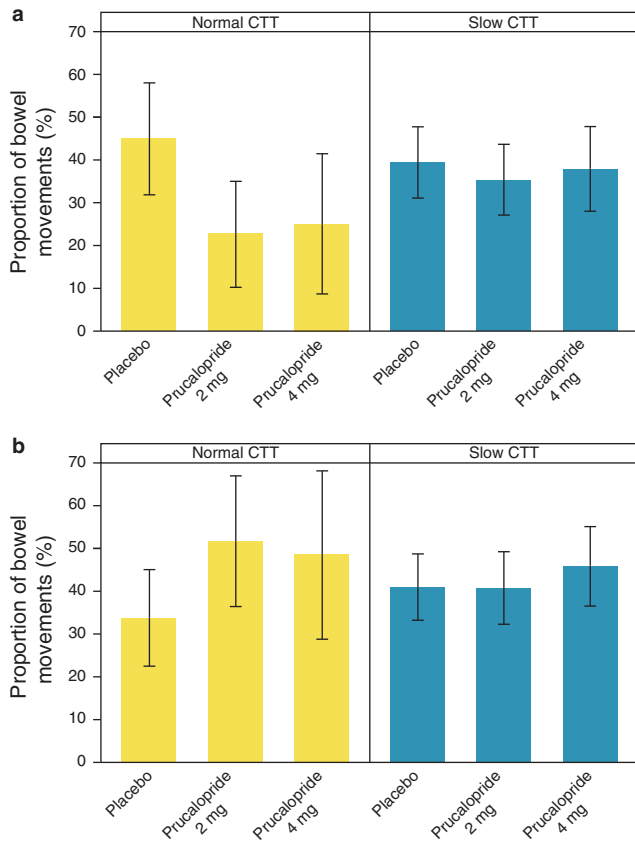


Figure 4. Proportion of bowel movements with (a) hard/very hard consistency or (b) normal consistency in patients with normal and slow CTTs at the end of treatment. Data are shown as mean \pm 95% confidence intervals. CTT, colonic transit time.

proportion of patients treated with prucalopride were responders than those who received placebo.

Three phase 3 pivotal trials have previously demonstrated that prucalopride is effective at treating constipation compared with placebo (9–11). Integrated analyses of these trials have confirmed the positive impact of prucalopride on clinical end points, including stool frequency, stool consistency, and reduction in the need for rescue medication, as well as in the results of the patient assessment of constipation symptoms questionnaire (12,25). The demographics of the patients in the phase 2 trials were similar to those of patients in the phase 3 pivotal trials of prucalopride (9–11). In the phase 3 trials, there was a higher proportion of responders among patients treated with prucalopride (range: 20–27%) than among those who received placebo (range: 8–12%) (9–11). The proportion of responders is also higher in the prucalopride than in the placebo group in the present study (42% for prucalopride 2 mg and 21% for placebo) but, interestingly, is almost twice as high for both placebo and prucalopride groups than in the phase 3 trials. Patients included in the present study were demographically representative of the whole population included in the phase 2 trials in which they took part, which also had a higher proportion of respond-

ers than the phase 3 trials. This suggests that the differences in response rate between the present study and the phase 3 trials are not due to selection of a responsive patient population for the current analysis, but may be explained by other differences between the patients or methodologies included in the phase 2 and phase 3 trials.

Chronic constipation is a largely symptomatic disorder, with the exact symptoms varying extensively among patients. The Rome III criteria provide the most widely used definition of chronic constipation, but in clinical practice patients do not always meet these criteria. This may partly be due to the different etiologies of the condition (e.g., slow transit) and it has been suggested that differences in the types of symptoms and symptom severity could be good indicators of the underlying pathophysiology (26).

Despite perceived associations between CTT and the symptoms of constipation, there has been little direct evidence of this relationship to date (2). In a comparison of women with and without functional bowel disorders, Bharucha *et al.* (27) identified a relationship between stool consistency and symptom severity. For example, hard stools were associated with increased straining, and straining was experienced more frequently by patients with constipation than by participants without constipation. Increased CTT in healthy patients has been demonstrated to result in harder stools than when CTT is in the normal range (28), suggesting a link between increased CTT and increased straining. Consistent with this, there was a correlation between increasing CTT and harder stool consistency in the present study.

The present study provides the first example of a correlation between idiopathic slow CTT and severity of symptoms. Previous studies have shown that loperamide-induced constipation (which slows colonic transit) in healthy volunteers induces bloating and colonic pain, consistent with the idea that constipation symptoms and slow transit are linked (29). In patients with irritable bowel syndrome, a relationship has been suggested between transit time and bloating, but both delayed and accelerated intestinal transit have been associated with this symptom (30). In the present study, a slower CTT was linked to harder stools, a greater need to strain, increased frequency of unproductive calls to stool, increased bloating, increased incomplete evacuation and abdominal pain/cramps, as well as with reduced urgency compared with a normal CTT. These results can be explained by the hypothesis that a slow CTT reduces the volume of intestinal contents delivered to the rectum, which results in evacuation difficulty and associated symptoms.

If this hypothesis was correct, a constipation therapy targeted at reducing CTT might have a direct impact on alleviating symptoms in patients with slow CTT. Recent studies on the effect of pelvic floor biofeedback as a therapy for chronic constipation have demonstrated improvements in constipation symptoms (31). However, despite early studies indicating the efficacy of this treatment for the majority of patients with chronic constipation (32,33), recent evidence suggests that the technique works preferentially for patients with pelvic floor in coordination, with negligible effect

in those with slow-transit constipation (34). This supports the idea that transit and evacuation difficulty are intimately linked, both in terms of underlying pathophysiology and the resulting symptoms. The present study provides evidence that prucalopride reduces CTT and stool hardness, suggesting a mechanism through which this drug reduces the symptoms of constipation.

The suggested relationship between slow transit and hard stools discussed above (28) can be explained by increased water reabsorption during the prolonged time in the gut. In the present study, there was a reduction in the proportion of bowel movements with hard/very hard stools following prucalopride treatment, but this was seen only in patients who achieved normal CTT at the end of the trials. This suggests that the prucalopride-induced reduction in CTT is the mechanism resulting in stool softening. If transit remains slow following treatment, this improvement in stool consistency does not occur.

Limitations

A limitation of the present study is that these pooled results were part of a retrospective analysis using data collected after 4 weeks of treatment for two of the trials (INT-1 and USA-3) and after 12 weeks for the third trial (INT-2). Second, there are some inconsistencies among the pooled trials: notably, the terminology used to assess symptoms was different across the three trials. Although similar terms were pooled, the differences identified in our integrated analysis may relate to variability in symptom definition across the trials. However, we feel that the symptom profiles we have used reflect clinical practice in a way that is recognizable to health-care professionals treating patients with constipation, and that these profiles are therefore clinically relevant.

Conclusions

This study is the first to show a clear relationship between increased CTT and the severity of symptoms of constipation, including abdominal cramps, bloating, hard stools, decreased bowel movement frequency, straining, and an increased number of unproductive calls to defecate. Consistent with results from previous studies, patients with slow or very slow CTT at baseline treated with prucalopride were more likely than those receiving placebo to return to normal CTT by the end of the study. These patients had an accelerated CTT during the course of the trials and fewer hard stools, suggesting the efficacy of the mechanism through which prucalopride leads to improved symptoms in patients with chronic constipation.

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CONFLICT OF INTEREST

Guarantor of the article: Anton Emmanuel, MD.

Specific author contributions: All authors were involved in the conception and design of the study, as well as in the interpretation of the

data. René Kerstens also carried out the statistical analyses. All authors reviewed each draft and approved the final version of the manuscript.

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Potential competing interests: Anton Emmanuel has served on advisory boards for Shire. René Kerstens, Marina Cools, and Lieve Vandeplasseche were employees of Shire at the time during which this analysis was conducted.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Chronic constipation is characterized by symptoms such as bloating and straining.
- ✓ Constipation has been linked to slow colonic transit, but a relationship between symptoms and colonic transit time (CTT) has not been shown.
- ✓ Prucalopride stimulates gastrointestinal motility.
- ✓ Prucalopride is indicated for the treatment of chronic constipation in patients in whom laxatives have failed.

WHAT IS NEW HERE

- ✓ Prucalopride reduces CTT in patients with chronic constipation.
- ✓ Increased CTT is associated with increased severity of constipation symptoms.

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