The effect of prucalopride on gastric emptying in Parkinson’s disease patients, a pilot randomized, open-label study

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Abstract

Background: Gastrointestinal symptoms are common in patients with Parkinson’s disease (PD) and may precede the appearance of overt neurologic symptoms. Prucalopride was approved for treatment of chronic constipation in adults. Previous study showed prucalopride also accelerates gastric emptying in healthy subjects.

Objectives: Our study aimed to evaluate the efficacy of prucalopride on gastric emptying time and compare its effect with domperidone in patients with Parkinson’s disease.

Methods: A total of 10 patients with PD were enrolled in this randomized, open-label cross-over study. The patients were given prucalopride 1-2 mg daily, depending on patient’s age, or domperidone 30 mg daily. Scintigraphic gastric emptying for solid meal were performed to evaluate gastric emptying half time (GE T½) and percent meal retention at 120 min (%RA120). Gastrointestinal symptom score, spontaneous complete bowel movements (SCBMs) per week, neurologic outcomes, and adverse events were determined. We also performed testing of potential period and potential carry-over effect before analyzing the outcomes of this study.

Results: There were 5 patients in prucalopride group and 5 patients in domperidone group. Because carry-over effect of cross-over design was found, so only the outcomes measured at the first follow up period were analyzed. Prucalopride significantly improved mean gastric emptying T½ and %RA120 when compared with baseline (p = 0.020 and 0.002, respectively) and when compared with domperidone after adjusted for baseline (p = 0.004 and 0.008, respectively). Prucalopride also improved difficulty in relaxing anal sphincter and Bristol stool scale compared with baseline (p = 0.023 and 0.043, respectively). There were no significant differences between the two treatments in other gastrointestinal symptoms scores, SCBMs, neurologic outcomes and adverse events.

Conclusion: This pilot study demonstrated good efficacy of prucalopride in accelerating gastric emptying in PD patients. Further studies with more participants are highly warranted to evaluate the efficacy of prucalopride.
It also contributes significantly to response fluctuation in patients on antiparkinsonian drugs [8].

Domperidone, a peripheral dopamine D2-receptor antagonists, has shown to enhance gastric emptying and also increase the bioavailability of levodopa [9,10]. It is commonly used for treating gastrointestinal symptoms in patients with PD. However, domperidone is not available in every country. Recently, due to its potential cardiac side effects, especially in people older than 60 years old, domperidone is now restricted to short-term use only in relief of nausea and vomiting [11].

Prucalopride is a potent, selective and specific serotonin 5-HT4 receptor agonists with enterokinetic activities. Prucalopride has almost 300-fold higher affinity for the 5-HT4 receptor than the hERG channel [12]. At therapeutic concentration, prucalopride provides a large safety margin [13]. Without interaction with hERG channel, less unfavorable cardiovascular side effects is expected. From previous study on safety and tolerability, administration of prucalopride does not induce QT prolongation, ventricular arrhythmias or torsades de pointes [14].

The efficacy of prucalopride has been demonstrated to improve stool frequency and consistency among patients with chronic constipation [15,16]. It also accelerates gastric emptying, small bowel transit time and colonic transit time in both healthy and constipated patients [17-19]. Prucalopride was approved by European Medicine Agency (EMA) in 2009 for symptomatic treatment of chronic constipation in women whom laxatives fail to provide adequate relief at a dose of 2 mg per day. Recommended starting dose for older patients (older than 65 year-old) is 1 mg per day. Dosage of more than 2 mg per day does not provide additional benefit over 2-mg dose [15].

Theoretically, using prucalopride in PD patients should be beneficial in accelerating gastric emptying which result in increased levodopa absorption and decreased motor fluctuation. Prucalopride can also improve gastrointestinal and colonic motility which leads to improving gastrointestinal symptoms especially constipation. In PD patients who already take a lot of medicine, once-daily administration of prucalopride can provide better compliance over three-times daily regimen of other prokinetic medications. However, the study about the effect of prucalopride on gastric emptying time in PD patients is still lacking. Therefore, we conducted this study aimed to evaluate the efficacy of prucalopride in comparison with domperidone and baseline in improving gastric emptying time in PD patients. We also evaluated the effects on gastrointestinal symptoms including sialorrhea, nausea, vomiting, dysphagia, bloating, sensation of incomplete evacuation, difficulty in relaxing anal sphincter were evaluated. Scores adapted from Talley bowel disease questionnaire [21] of the symptoms for each category will be determined by severity and frequency. Total score will be the sum of severity and frequency scores (minimum = 0 and maximum = 6) (Appendix 2).

Gastrointestinal symptoms including sialorrhea, nausea, vomiting, dysphagia, bloating, sensation of incomplete evacuation, difficulty in relaxing anal sphincter were evaluated. Scores adapted from Talley bowel disease questionnaire [21] of the symptoms for each category will be determined by severity and frequency. Total score will be the sum of severity and frequency scores (minimum = 0 and maximum = 6) (Appendix 2).

Neurologic outcomes, including Unified Parkinson’s Disease Rating Scale for motor functions (UPDRS part III) and on time which was expressed as a percentage of time while awake, were also evaluated by a neurologist who was blinded to study medications.

All subjects reported their adverse events during the study. Concomitant anti-PD medications were continued without

Study design

This study was initially designed as a randomized open-label crossover study.

Subjects

We performed a pilot study, including 10 subjects with Parkinson’s disease, who attended neurology clinic in Chiang Mai University hospital between August 2015 and November 2015, were randomized. All patients were 18-80 year of age, had fulfilled the UK Parkinson Disease Brain Bank criteria for PD and had been on stable anti-PD medications within the past 3 months. Patients were excluded if they had diabetes mellitus, chronic renal diseases, chronic liver diseases, thyroid diseases, connective tissue disorders, history of gastric surgery, prolactinoma, been pregnant, been during lactation, egg allergy, studied drug allergy or lactose intolerance.

The study was approved by Faculty of Medicine, Chiang Mai University ethical committee and accordance with Declaration of Helsinki. Patients voluntarily decided to participate in the study. We obtained written informed consent from all subjects.

Study protocol

This was initially designed as randomized open-label crossover study. Baseline data collection included clinical data and gastric emptying. The patients who took prokinetic medications were asked to stop taking that medications for at least one week prior to baseline data collection. Patients were randomized 1:1 (by using computer-generated randomization number) to receive 2 weeks of prucalopride (standard dose 2 mg/day or 1 mg/day if patients were older than 65 years) [20] and domperidone (10 mg oral three times a day). Gastric emptying time and clinical data were collected after each treatment period. The study consisted of two intervention periods of 2 weeks separated by a washout period of 1 week as in Figure 1. Because elimination half-life of prucalopride was 24-30 hours and biological half-life of domperidone was 7.5 hours so they should be totally eliminated from the body within 5 days.

Scintigraphic gastric emptying tests were performed using meal labeled Technetium-99m (99mTc)-phytate according to Thailand Adult solid meal gastric emptying scintigraphy protocol (Appendix 1). Patient were taken nothing by mouth for at least 6 hours before the study performed, except for the study medication in the morning of the study date, taken with small amount of water (30 ml). The results of gastric emptying half time (GE T%) and percent meal retention at 120 minutes (%RA120) were collected. In this study, a radiologist who interpreted gastric emptying was blinded to study medications.

Gastrointestinal symptoms including sialorrhea, nausea, vomiting, dysphagia, bloating, sensation of incomplete evacuation, difficulty in relaxing anal sphincter were evaluated. Scores adapted from Talley bowel disease questionnaire [21] of the symptoms for each category will be determined by severity and frequency. Total score will be the sum of severity and frequency scores (minimum = 0 and maximum = 6) (Appendix 2).

Figure 1. Study protocol. The study consisted of two intervention periods of 2 weeks separated by a washout period of 1 week

The results of gastric emptying half time (GE T%) and percent meal retention at 120 minutes (%RA120) were collected. In this study, a radiologist who interpreted gastric emptying was blinded to study medications.
modification during study period. Use of any medications with a potential effect on gastrointestinal motility was prohibited. The patients were allowed to use senna or enema as a rescue medication if the patient did not have a bowel movement for more than 48 hours. The use of rescue medications were recorded.

Outcomes measurement

Primary outcome was the efficacy of prucalopride in decreasing gastric emptying time in patients with Parkinson’s disease and we compared this effect with domperidone. Secondary outcomes were gastrointestinal symptoms, using gastrointestinal symptoms score, frequency of spontaneous complete bowel movements (SCBMs) per week, proportion of patients with an increase of at least 1 SCBMs from baseline, Bristol stool scale (BSS), neurologic assessment, using UPDRS III and percent on time and treatment related adverse events.

Statistical analysis

We investigated potential period and carry-over effects of the crossover design. In the absence of these effects, the results from both periods will be combined. In the presence of these effects, the results will be analyzed as a randomized control trial where only the outcomes measured at the first follow up period will be analyzed. Baseline characteristics and clinical data were presented in percentages, mean + SD or median (IQR) as appropriate. Comparison of parameters between after treatment and baseline, paired t-test was used for analysis of GE T½ and %RA120. Comparison between treatment groups, t-test was used for analysis of gastric emptying half time, percent meal retention, on-time and UPDRS score. Gastrointestinal symptoms scores, frequency of SCBMs per week and proportion of patients with an increase of at least 1 SCBMs from baseline, BSS, adverse event rates and adherence rates were analyzed by McNemar’s or Chi-square test as appropriate.

Stata statistical software version 12.0 (Stata Statistical Software: Release 12.0, Stata Corporation, College Station, TX, 2011) were used for all statistical analysis. p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The clinical characteristics of the patients were shown in Table 1. Fifty percent of patients were female. The mean duration of PD was 11.2 ± 6.48 years. The median modified Hoehn and Yahr stage was 2.75 (IQR 2 to 4). All patients reported constipation. Median SCBMs per week was 1 (IQR 0 to 3). There were 2 and 3 patients in prucalopride group, who received 1 mg/day and 2 mg/day of prucalopride, respectively.

After we investigated the potential period and carry-over effects, we found carry-over effect in this study as shown in Table 2 and Figure 2. Therefore, the subsequent findings are results which were analyzed as a randomized control trial where only the outcomes measured at the first follow up period will be used.

At baseline, no statistical significant differences between prucalopride and domperidone group were noted, however, mean gastric emptying half time was lower in prucalopride group (63.9 ± 32.73) compared with domperidone group (88.0 ± 97.98), but this difference did not reach statistical significant (p = 0.616). There was one patient in domperidone group who had previously prescribed domperidone (20 mg/day). This patient discontinued domperidone for two weeks before baseline evaluation.

| Table 1. Baseline characteristics |
|----------------------------------|
|                                | All patients  | Prucalopride group | Domperidone group | P-value |
| Age (yr)                         | 63.1 ± 7.72   | 64.4 ± 6.18         | 63.8 ± 4.28       | 0.624   |
| Sex (Female)                     | 5 (50%)       | 2 (40%)             | 3 (60%)           | 0.500   |
| Disease duration (yr)            | 11.2 ± 6.48   | 12.4 ± 8.01         | 10 ± 5.47         | 0.595   |
| MHY scale                        | 2.75 (2.4)    | 3 (2.3)             | 2.5 (2.5.4)       | 0.749   |
| Gastric emptying study           |               |                     |                   |         |
| - T ½ (min)                      | 75.9 ± 70.03  | 63.9 ± 32.73        | 88.0 ± 97.98      | 0.616   |
| - %RA120 (%)                     | 25.95 ± 21.95 | 24.92 ± 15.33       | 26.98 ± 29.09     | 0.892   |
| GI symptoms scores               |               |                     |                   |         |
| - Diarrhea                       | 3 (0.4)       | 4 (0.4)             | 3 (0.3)           | 0.443   |
| - Nausea                         | 0 (0.0)       | 0 (0.0)             | 0 (0.0)           | 1.000   |
| - Vomiting                       | 0 (0.0)       | 0 (0.0)             | 0 (0.0)           | 0.882   |
| - Dysphagia                      | 0 (0.0)       | 0 (0.0)             | 0 (0.0)           | 1.000   |
| - Blunting                       | 3 (2.4)       | 2 (2.3)             | 4 (3.0)           | 0.455   |
| - Incomplete evacuation          | 4.5 (4.5)     | 4 (4.5)             | 5 (4.5)           | 0.829   |
| - Difficulty in relaxing anal sphincter | 5 (5.6) | 6 (5.6) | 5 (5.5) | 0.371 |
| SCBMs / week                     | 1 (0.3)       | 2 (0.3)             | 0 (0.3)           | 0.572   |
| BSS                              | 1.5 (1.2)     | 1 (1.1)             | 2 (2.3)           | 0.054   |
| Neurological status              |               |                     |                   |         |
| On time (%)                      | 84.14 ± 9.40  | 77.33 ± 5.13        | 89.25 ± 8.84      | 0.094   |
| UPDRS                            | 9.7 ± 5.61    | 11.2 ± 6.94         | 8.2 ± 4.14        | 0.430   |
| MHY, Modified Hoehn and Yahr scale; T/2, gastric emptying half time; %RA120, percent meal retention at 120 min; SCBMs, Spontaneous complete bowel movements; BSS, Bristol stool scale; UPDRS, Unified Parkinson’s Disease Rating scale

Table 2. Gastric emptying half time outcomes from a two-treatment, two period crossover trial

| Treatment sequence | Treatment period | Within-individual difference |
|--------------------|------------------|----------------------------|
|                    |                  | 1                          |
| prucalopride then domperidone | 41.5 ± 21.14 | 36.48 ± 11.60 | 5.02 ± 10.59 |
| Sample size        | 5                | 5                          |                  |
| domperidone then prucalopride | 88.06 ± 82.45 | 63.94 ± 23.11 | -24.12 ± 34.47 |
| Sample size        | 5                | 5                          |                  |
| Treatment effect   | Mean (SD)        |                             |
| Mean (SD)          | 9.55 ± 28.52    |                             |
| Sample size        | 10               |                             |
| T-test for paired samples | 0.317      |

Gastric emptying scintigraphy

Comparing to baseline, GE T½ and %RA120 significantly decreased during treatment with prucalopride (p = 0.020 and 0.002, respectively) (Figure 3A and 3B). These parameters were not significantly decrease during treatment with domperidone (p = 0.994 and 0.955, respectively) (Figure 3C and 3D). After adjusted for baseline, mean GE T½ and %RA120 statistically significant decreased during prucalopride treatment compared with domperidone treatment (p = 0.004 and 0.008, respectively) (Table 3).

Gastrointestinal symptoms

Median baseline symptom score for difficulty in relaxing anal sphincter was 6 (IQR 5 to 6) and was significantly decreased to 4 (IQR 3 to 4) during prucalopride treatment, p = 0.023 (Table 4). Improvement
Table 3. Gastric emptying time

| Gastric emptying | Prucalopride (n=5) | Domperidone (n=5) | Differences (95% CI) | P value | Adjusted mean difference | Adjusted P-value |
|------------------|---------------------|-------------------|----------------------|---------|-------------------------|-----------------|
| T 1/2 (min)      | 41.5 ± 21.14        | 88.06 ± 82.45     | -46.56 (-134.34, 41.22) | 0.256   | -46.56 (-134.34, 41.22) | 0.004           |
| % RA 120 (%)     | 13.46 ± 12.58       | 26.72 ± 22.46     | -13.26 (-39.81, 13.29) | 0.282   | -13.26 (-39.81, 13.29)  | 0.008           |

T1/2, gastric emptying half time; %RA 120, percent meal retention at 120 min

Table 4. Gastrointestinal symptom score

| Symptoms                          | Prucalopride (n=5) | Domperidone (n=5) | P-value |
|-----------------------------------|--------------------|-------------------|---------|
| - Sialorrhea                       | 0 (0,3)            | 2 (0,3)           | 0.823   |
| - Nausea                           | 0 (0,0)            | 0 (0,0)           | 0.317   |
| - Vomiting                         | 0 (0,0)            | 0 (0,0)           | 0.317   |
| - Dysphagia                        | 0 (0,0)            | 0 (0,0)           | 0.317   |
| - Bloating                         | 2 (2,3)            | 3 (2,4)           | 0.076   |
| - Difficultly in relaxing anal sphincter | 3 (3,4) *     | 5 (4,5)           | 0.268   |
| SCBM/s/week                       | 3 (2,4)            | 3 (2,3)           | 0.513   |
| Changes of No of SCBM/s/week      | 0 (0,1)            | 0 (0,2)           | 0.654   |
| Increase of ≥1 SCBM/s/week (No %) | 2 (40%)            | 2 (40%)           | 1.000   |
| BSS                               | 3 (2,3) †          | 3 (2,4)           | 0.519   |
| BSS Changes                       | 1 (1,2)            | 0 (0,1)           | 0.228   |

SCBM, Spontaneous complete bowel movements; BSS, Bristol stool scale
* P-value 0.023 compared to baseline
† P-value 0.043 compared to baseline

Figure 2. Gastric emptying half time of two intervention group

in median BSS was also observed in prucalopride group compared with baseline (from 1.5 (IQR 1 to 2) at baseline to 3 (IQR 2 to 3), p = 0.043). Other symptom scores and SCBMs per week were not different comparing with baseline and another treatment.

Neurological symptoms

There were no differences in percent on time and UPDRS motor function comparing with baseline and another treatment (Table 5).

Table 5. Neurologic outcomes

| Outcomes | Prucalopride (n=5) | Domperidone (n=5) | Difference (95% CI) | P-value | Adjusted P-value |
|----------|--------------------|-------------------|---------------------|---------|-----------------|
| Percent On time (n=7) | 80.33 ± 5.85 (n=3) | 91.25 ± 10.11 (n=4) | -10.91 (-27.92, 6.10) | 0.160 | 0.813 |
| UPDRS III | 9.4 ± 8.53 | 7 ± 4.24 | 2.4 (-7.42, 12.22) | 0.588 | 0.847 |

UPDRS, Unified Parkinson's Disease Rating scale

Figure 3A. Gastric emptying time compared to baseline in prucalopride and domperidone group
(A) GE T1/2 in Prucalopride group

Figure 3B. Gastric emptying time compared to baseline in prucalopride and domperidone group
(B) %RA 120 in Prucalopride group
Adverse events and medication adherence

The adverse events experienced during the study were reported in table 6. Five patients reported side effects during treatment with prucalopride and two reported side effects during treatment with domperidone. Three patients who received prucalopride had abnormal bowel sound and one had abdominal pain. We did not find these side effects in domperidone group. These adverse events were mild and required no medical intervention. No serious adverse event was reported and there was no discontinuation due to adverse events. All patients in this study reported more than 90% adherence to study medications.

Discussion

This study demonstrates decreased GE T½ and %RA120 after 2 weeks of standard dose (1-2 mg) prucalopride in patients with PD. In addition, gastric emptying time was significantly lower in prucalopride group than domperidone group. From previous studies on healthy subjects, prucalopride showed significant improvement of gastric emptying time [18]. Despite lower dosage of prucalopride was used in our study (1-2 mg/day and 4 mg/day in the previous study) and abnormalities of ENS in PD patients, the results of this study showed that prucalopride also provided good efficacy in reducing gastric emptying time in PD patients.

The normal recommended washout period was 5 times of elimination half-life. Elimination half-life of prucalopride was 24-30 hours so the washout period of 7 days should be long enough to eliminate prucalopride. However, this study showed significant carry-over effect in prucalopride then domperidone group, which indicated inadequate washout time for prucalopride. This might be related to the high affinity binding of prucalopride to 5-HT₄ receptors. Therefore, longer washout period should be considered for the future study.

Previous study by Soykan et al. [10] showed that domperidone (20 mg, four times daily) significantly improved gastric emptying in PD patients and also improved upper gastrointestinal symptoms, including nausea, vomiting, anorexia, bloating, heartburn and regurgitation [10]. In contrast, domperidone failed to showed this effect in our study. In the previous study, domperidone dosage was higher (80 mg per day) and longer (more than 4 months) than our study. For these reasons, the difference between two trial results might be due to difference in drug dose and duration of treatment. Our results suggested that 30 mg of domperidone per day might not be enough to improve gastric emptying in PD patients. Reasons for requiring higher dosage likely due to the degeneration of autonomic nerves and the suppression of cholinergic transmission by antiparkinsonian drugs.

In our study, the patients also reported improvement in difficulty in relaxing anal sphincter and BSS during prucalopride treatment. Improvement of BSS indicated improvement in stool consistency, however, prucalopride failed to demonstrate increase in SCBMs which was a significant endpoint of improvement of constipation. This result differed from other previous studies which showed improvement in both stool consistency and frequency in individuals taking prucalopride [15,16]. Because there were limited participants, this effect may occur by chance.

Although a standard dose of prucalopride significantly shortened gastric emptying half-time, this study did not show any beneficial effect of prucalopride on percent on time and UPDRS motor function score. Asai et al. [22] reported increased gastric motility and reduced gastric retention of anti-PD drugs during treatment with mosapride and prolonged on time and decreased UPDRS score were also found in this study. Our study could not show these beneficial effects might be from higher percent on time at baseline, which was 77% in our study and 69% in Asai’s study, and lower UPDRS score during on period at baseline (11 in our study and 44 in Asai’s study). Better motor control is attributed to medical care including better medical treatment.

Our study had some limitations. First, there was carry-over effect so the analysis had to be changed. Second, the relatively small numbers

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**Table 6. Adverse events**

|                      | Prucalopride (n=5) | Domperidone (n=5) |
|----------------------|--------------------|-------------------|
| Abnormal bowel sound | 3 (60%)            | 0                 |
| Tiredness            | 1 (20%)            | 1 (20%)           |
| Abdominal pain       | 1 (20%)            | 0                 |
| Loss of appetite     | 0                  | 1 (20%)           |
| Headache             | 0                  | 0                 |
| Galactorrhea         | 0                  | 0                 |

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**Figure 3C.** Gastric emptying time compared to baseline in prucalopride and domperidone group (C) GE T1/2 in Domperidone group

**Figure 3D.** Gastric emptying time compared to baseline in prucalopride and domperidone group (D) %RA120 in Domperidone group

**Figure 3E.** Gastric emptying time compared to baseline in prucalopride and domperidone group.

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of participants limited the study power. Finally, there were missing on-time data in 3 participants, which further limited the data for analysis.

Conclusions
This study demonstrated good efficacy of prucalopride in accelerating gastric emptying in PD patients. Further study with more participants appears highly warranted to evaluate the efficacy of prucalopride in advanced PD patients with motor fluctuation.

Authors’ contribution
KP, PK, ST were responsible for the conception of the study and design. KP, AS, WT were responsible for acquisition of data. KP and CA analyzed the data. KP wrote the first draft of the manuscript. All authors contributed to interpretation of the data, revised the manuscript and approved the final manuscript.

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Competing interests
The Authors declare that there is no conflict of interest.

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