Korean J Gastroenterol Vol. 78 No. 4, 219-226
https://doi.org/10.4166/kjg.2021.099
pISSN 1598-9992 eISSN 2233-6869

ORIGINAL ARTICLE

KJG

한국인 만성 변비 환자에서 프루칼로프라이드의 안전성과 유효성: 시판 후 조사

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Safety/Efficacy of Prucalopride in Korean Patients with Chronic Constipation: Post-marketing Surveillance

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Background/Aims: Constipation is a common gastrointestinal disorder. Prucalopride is a dihydrobenzofurancarboxamide derivative with gastrointestinal prokinetic activities and is recommended as an appropriate choice in patients unresponsive to laxatives. This study assessed the safety and efficacy of prucalopride in Korean patients with chronic constipation, in whom laxatives were ineffective.
Methods: This prospective, non-interventional post-marketing surveillance of prucalopride was conducted from 2012 to 2018 at 28 hospitals in Korea. Adults who received prucalopride for the symptomatic treatment of chronic constipation were included. The patients received 2 mg of prucalopride once daily or 1 mg once daily in patients older than 65 years. The baseline characteristics, adverse events (AEs), and seven-point scale of Clinical Global Impression-Improvement were collected.
Results: Of 601 patients, 67.7% were female, and the mean age was 62.3 years. Three hundred patients (49.9%) were older than 65 years. At the baseline, 70.0% of patients reported less than two instances of spontaneous complete bowel movements per week. AEs were reported in 107 patients (17.7%), including headache (3.2%) and diarrhea (2.8%). Seven serious AEs (SAEs) were reported in five patients (0.8%). The SAEs were resolved without complications; there were no cases of death. All SAEs were assessed as 'unlikely' causality with prucalopride. In 72.7% of patients, chronic constipation was improved by the prucalopride treatment during the study period.
Conclusions: This study demonstrated the promising safety and efficacy profile of prucalopride in clinical practice. Thus, prucalopride should be considered in patients with chronic constipation when bowel symptoms are refractory to simple laxatives. **(Korean J Gastroenterol 2021;78:219-226)**

Key Words: Constipation; Prucalopride; Korea; Real clinical practice; Adverse events

Received June 30, 2021. **Revised** September 1, 2021. **Accepted** September 3, 2021.

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Financial support: This study was supported by Janssen Korea Ltd, Protocol no. PRUCOP4004.

Conflict of interest: Yeon SE and Kim SY are employees of Janssen Korea Ltd. Yeon SE and Kim SY were involved in the study design, protocol writing, study execution, data analysis, data interpretation, manuscript writing, and English editing and submission. Chung WC, Jeon SW, Park SJ, Choi CH, and Choi MG have no conflicts of interest to declare.

INTRODUCTION

Constipation is a common gastrointestinal disorder with a prevalence of approximately 11-18% in adults and children worldwide.[1-3] Owing to its high prevalence and chronicity, constipation adversely affects the quality of life and causes economic burden. Constipation occurs more frequently in women and the elderly.[4,5]

Prucalopride is a dihydrobenzofurancarboxamide derivative with gastrointestinal prokinetic activities, and it is a selective, high-affinity serotonin (5-hydroxytryptamine 4, 5-HT_4) receptor agonist. The drug directly affects bowel motility and a range of other constipation symptoms and has been recommended as an appropriate choice in patients unresponsive to laxatives.[6] The efficacy of prucalopride in chronic constipation has been established in three pivotal clinical trials (NCT00488137, NCT00483886,[7] and NCT00485940), which were designed as randomized, double-blind, placebo-controlled studies, in which prucalopride was administered once daily to the patients with chronic constipation.[8] Another clinical trial (NCT01147926) confirmed the efficacy and safety of prucalopride in male subjects.[9] These four clinical trials on chronic constipation were conducted in Western countries. The overall safety profile in a trial (NCT01116206) conducted in the Asia Pacific region was consistent with previous studies in Western countries.[10,11] The data on safety in Asian patients are limited compared with evidence from Western populations.

Based on the results of the above clinical trials, prucalopride was approved in the European Union in 2009 for the treatment of chronic constipation in adults. According to the treatment guidelines for chronic constipation, bulking agents, polyethylene glycol, and prucalopride are recommended for the treatment of chronic constipation with grade A evidence. In addition, new agents, such as lubiprostone, linaclotide, and plecanatide, have been used to treat chronic constipation.[6,7,12] On the other hand, there are serious cardiovascular safety concerns, including arrhythmias with QTc prolongation and ischemic events, associated with the use of first-generation nonselective 5-HT_4 receptor agonists, such as cisapride and tegaserod, which resulted in their withdrawal globally.[13,14]

After gaining regulatory approval of prucalopride for patients with chronic constipation, post-marketing surveillance has been conducted, as officially mandated by the Korean Ministry of Food and Drug Safety, to obtain further data on its safety profile and efficacy. This study examined the adverse events (AEs) associated with prucalopride and determined its efficacy in Korean patients with chronic constipation in whom laxatives failed to provide adequate relief.

SUBJECTS AND METHODS

1. Study design and patients

This prospective, multi-center, non-interventional post-marketing surveillance of prucalopride was conducted from October 2012 to October 2018 (Protocol no. PRUCOP4004). Institutional ethics approval was obtained from the institutional review board of each of the 28 participating hospitals.

All patients included in the study were adults who received prucalopride for the symptomatic treatment of chronic constipation, and laxatives failed to provide adequate relief. All patients provided written informed consent. The exclusion criteria were as follows: patients i) who had diseases, such as ischemic colitis, Crohn's disease, or ulcerative colitis; ii) with renal impairment requiring dialysis; iii) those who violated the dosage regimen, according to patient age; iv) those with missing safety or efficacy data; and v) those who received prucalopride before enrollment in the study. Patients were administered 2 mg of prucalopride once daily. In the geriatric population (older 65 years), 1 mg of prucalopride was administered once daily.

2. Measurements

The baseline characteristics included gender, age, duration of chronic constipation, comorbidities, daily dose of prucalopride at first administration, and the number of spontaneous complete bowel movements (SCBM). Information on concomitant laxatives, non-pharmacological therapies for chronic constipation, and concomitant medications were collected for the 6 months before study initiation and throughout the study period.

AEs were recorded and observed throughout the study. The investigator classified the causality between prucalopride and each AE into six grades: 'certain,' 'probable/likely,' 'possible,' 'unlikely,' 'conditional/unclassified,' and 'unassessable/unclassifiable'. Adverse drug reactions (ADRs), which were defined as AEs caused by prucalopride, were also evaluated. The AE was classified as an ADR if the causality between prucalopride and AE was considered 'certain,' 'probable/like-

ly,' 'possible,' 'conditional/unclassified,' or 'unassessable/unclassifiable'. Serious adverse events (SAEs) based on the International Conference on Harmonization and European Union guidelines on pharmacovigilance for medicinal products for human use are defined as any untoward medical occurrence at any dose that is life-threatening, results in persistent or significant disability/incapacity, results in hospitalization or prolonged hospitalization, may have caused a congenital anomaly/birth defect, may have been caused by the suspected transmission of any infectious agent via a medical product, is medically important, and results in death.

The number of SCBM per week was an inappropriate efficacy parameter because concomitant laxatives were permitted in the present study. Thus, the Clinical Global Impression-Improvement (CGI-I) scale was used to evaluate the improvements in the relief of constipation symptoms.[7,11] The CGI-I is a seven-point scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse) based on the investigators' assessment of the extent of improvement of the patient's condition since the initiation of prucalopride compared to the baseline.

All data were collected and managed using electronic case report forms on the cubeCDMS® system (CRScube Inc., Seoul, Korea). Medical coding was performed for concomitant laxatives, concomitant medications, comorbidities, and AEs. The drugs were classified using the Anatomical Therapeutic Chemical Classification System 2018, with level 4 indicating concomitant laxatives and level 1 indicating concomitant medications. The comorbidities were classified into five categories, 'cardiovascular disorders,' 'hepatic disorder,' 'renal disorder,' 'allergies,' and 'others,' as judged by the investigators and then classified according to the System Organ Class of Medical Dictionary for Regulatory Activities version 21.0. All collected AEs were classified based on System Organ Class and preferred terms using Medical Dictionary for Regulatory Activities 21.0.

3. Statistical analysis

The dataset for analysis was obtained from the case report form collected from patients and classified as an evaluable set. The evaluable set was comprised of patients treated with at least one dose of prucalopride for chronic constipation and assessed at least once using the CGI-I scale.

The demographic and baseline characteristics were summarized in terms of descriptive statistics. For continuous variables, the data are presented as means with standard deviations and medians with ranges (minimum and maximum). For categorical variables, the data are presented as frequencies and their respective percentages. For safety assessment, the incidence rate of AEs and the number of patients are summarized descriptively.

For efficacy assessment, the number of patients and the percentage of CGI-I responses at each visit (weeks 4, 8, and 12) were determined. For the factors associated with efficacy, "very much improved," "much improved," and "minimally improved" were considered "effective" and the other responses were considered "ineffective." A Chi-square test, Cochran Armitage trend test, or logistic regression was used to analyze whether the baseline characteristics were effective or ineffective at the last visit for each patient.

All statistical analyses were performed using SAS ver. 9.2 (SAS Institute, Cary, NC, USA), and a p-value <0.05 was considered significant. For ORs, 95% CIs for the ratios were calculated.

RESULTS

1. Baseline characteristics

Seven hundred and thirty-one patients were enrolled in this study. Of these, 130 patients, including 109 patients who violated the dosage regimen, eight patients who received prucalopride before enrollment in the study, eight patients with contraindications, such as ischemic colitis, Crohn's disease, ulcerative colitis, and renal impairment requiring dialysis, and five patients with missing safety or efficacy data were excluded.

Table 1 lists the baseline demographics and clinical characteristics of the evaluable set. Of 601 patients in the evaluable set, the majority were females (67.7%), and the mean age was 62.3 years. Among the enrolled patients, one-third of patients had chronic constipation for more than 5 years. At least one comorbidity was observed in 89.0% of patients. The most common comorbidity was cardiovascular disorders in 248 patients (345 events), including hypertension and angina pectoris. Hepatic disorder (3.5%), renal disorder (2.5%), and allergies (1.0%) were rarely observed. There was no case of dose modification due to comorbidities. Four hundred and sixty patients (76.5%) were treated with concomitant laxatives.

One-hundred and five patients (17.5%) received non-pharmacological treatments for constipation, and lifestyle intervention was the most common non-pharmacological treatment (60.0%, 63/105). One patient received an enema. No patients received biofeedback therapy during the study period. Four hundred and fifty-seven patients (76.0%) used concomitant medications. The frequently used concomitant medication classes were alimentary tract and metabolism (n=383, 963 cases), nervous system (n=275, 690 cases), and cardiovascular system (n=203, 433 cases) drugs. Of the concomitant medications, opioids were used by 157 patients (26.1%, 238 cases), antidepressants by 66 patients (11.0%, 82 cases), calcium channel blockers by 56 patients (9.3%, 57 cases), and antineoplastic agents by 10 patients (1.7%, 14 cases). The daily dose of prucalopride at the initial administration was 1 mg daily in 49.9% of patients (n=300) and 2 mg daily in 50.1% of patients (n=301). These results indicate compliance with the daily doses assigned according to the age group (over 65 years or below). More than 70% of patients reported SCBM less than 2 times per week.

Table 1. Demographics and Baseline Characteristics

Category	Value (n=601)
Sex	
Male	194 (32.3)
Female	407 (67.7)
Median age (years)	64 (19.0-92.0)
Age (years)	62.3±15.2
19 to <65	301 (50.1)
≥65	300 (49.9)
Duration of chronic constipation (years)	
<2	330 (54.9)
2-5	107 (17.8)
≥5	164 (27.3)
Comorbidities[a]	
Cardiovascular disorders	248 (41.3)
Hepatic disorder	21 (3.5)
Renal disorder	15 (2.5)
Allergies	6 (1.0)
Others	510 (84.9)
Concomitant laxatives[a]	
Osmotic laxatives	383 (83.3)
Bulk-forming laxatives	165 (35.9)
Stimulus laxatives	120 (26.1)
Probiotics	49 (26.1)
Others	17 (3.7)
Non-pharmacological therapies for chronic constipation	
Herbal laxatives	40 (38.1)
Enema	50 (47.6)
Lifestyle intervention	63 (60.0)
Daily dose of prucalopride at initial administration (mg/day)	
1	300 (49.9)
2	301 (50.1)
SCBM at Baseline[b] (number/week)	
≤1	76 (26.2)
2	129 (44.5)
3	61 (21.0)
>3	24 (8.3)

Values are presented number (%), number (min to max), or mean±standard deviation.
SD, standard deviation; Min, minimum; Max, maximum; SCBM, spontaneous complete bowel movement.
[a]Multiple counting; [b]Missing data on 311 patients.

2. Safety

Table 2 summarizes the AEs with more than 1.0% incidence. Overall, 144 AEs were reported in 107 patients (17.7%) from the evaluable set (n=601). The frequently reported AEs were headache in 3.2% of patients (19/601 patients, 19 cases), followed by diarrhea in 2.8% (17/601 patients, 17 cases), abdominal pain in 2.3% (14/601 patients, 14 cases), nausea in 1.5% (9/601 patients, nine cases), nasopharyngitis in 1.2% (7/601 patients, seven cases), and dyspepsia in 1.0% (6/601 patients, six cases). In total, 60 ADRs were reported in 46 patients.

Seven SAEs were reported in five patients (0.8%), including vertebral foraminal stenosis, diabetic neuropathy, inadequate

Table 2. Adverse Events

	Value	Event
Adverse event	107 (17.8)	144
Adverse drug reaction	46 (7.7)	60
Serious adverse event	5 (0.8)	7
Deaths	0 (0.0)	0
Adverse event ≥1%		
Headache	19 (3.2)	19
Diarrhea	17 (2.8)	17
Abdominal pain	14 (2.3)	14
Nausea	9 (1.5)	9
Nasopharyngitis	7 (1.2)	7
Dyspepsia	6 (1.0)	6

Values are presented as number (%).

control of diabetes mellitus, thermal burn, dyspepsia, chest discomfort, and ventricular extrasystoles. The SAEs in all five patients were resolved without complications, and there were no cases of death. All SAEs were assessed as 'unlikely' cau-

Table 3. CGI-I Response by Week

	Week 4	Week 8	Week 12
Very much improved	31 (5.2)	27 (6.5)	17 (5.1)
Much improved	192 (31.9)	132 (32.0)	104 (31.0)
Minimally improved	214 (35.6)	129 (31.2)	109 (32.4)
No change	148 (24.6)	111 (26.9)	92 (27.4)
Minimally worse	15 (2.5)	14 (3.4)	14 (4.2)
Much worse	1 (0.2)	0 (0.0)	0 (0.0)
Very much worse	0 (0.0)	0 (0.0)	0 (0.0)
Total	601 (100.0)	413 (100.0)	336 (100.0)

Values are presented as number (%).
CGI-I, clinical global impression-improvement.

Table 4. Factors Associated with the CGI-I Scale for Efficacy by Univariate Analysis

Variable	Effective	Ineffective	Total (n=601)	p-value
Sex				0.8160[a]
Male	135 (69.6)	59 (30.4)	194	
Female	287 (70.5)	120 (29.5)	407	
Age				0.4069[a]
19 to <65 years	216 (71.8)	85 (28.2)	301	
≥65 years	206 (68.7)	94 (31.3)	300	
Duration of chronic constipation				0.0005[a,d] 0.0002[b,d]
<2 year	249 (75.5)	81 (24.5)	330	
2-5 years	77 (72.0)	30 (28.0)	107	
≥5 years	96 (58.5)	68 (41.5)	164	
Comorbidity				0.4484[a]
Yes	373 (69.7)	162 (30.3)	535	
No	49 (74.2)	17 (25.8)	66	
Concomitant laxatives				0.0583[a]
Yes	314 (68.3)	146 (31.7)	460	
No	108 (76.6)	33 (23.4)	141	
Non-pharmacological therapies for chronic constipation				0.0404[a,d]
Yes	65 (61.9)	40 (38.1)	105	
No	357 (72.0)	139 (28.0)	496	
Concomitant medications				0.0388[a,d]
Yes	311 (68.1)	146 (31.9)	457	
No	111 (77.1)	33 (22.9)	144	
Daily dose at initial administration (mg)				0.2595[a]
1	119 (71.3)	48 (28.7)	167	
2	80 (65.0)	43 (35.0)	123	
SCBM/week at baseline[c]				0.0795[a]
≤1	52 (68.4)	24 (31.6)	76	
2	96 (74.4)	33 (25.6)	129	
3	34 (55.7)	27 (44.3)	61	
>3	17 (70.8)	7 (29.2)	24	

Values are presented as number (%).
CGI-I, clinical global impression-improvement; SCBM, spontaneous complete bowel movement.
[a]Chi-square test; [b]Cochran Armitage trend test; [c]Missing data on 311 patients; [d]Statistically significant difference.

Table 5. Factors associated with the CGI-I scale for efficacy by multivariate logistic regression analysis

Variable	OR	95% CI		p-value
Duration of chronic constipation				
<2 year	Ref			
2-5 years	0.850	0.517	1.397	0.3534
≥5 years	0.463	0.303	0.708	0.0011[a]
Non-pharmacological therapies for chronic constipation				
Yes	0.799	0.499	1.280	0.3504
No	Ref			
Concomitant medications				
Yes	0.576	0.369	0.899	0.0151[a]
No	Ref			

CGI-I, clinical global impression-improvement; OR, odds ratio; CI, confidence interval.
[a]Statistically significant difference.

sality with prucalopride. In all except for one patient, prucalopride administration was maintained despite the SAE. Among the SAEs, vertebral foraminal stenosis, diabetic neuropathy, inadequate control of diabetes mellitus, and dyspepsia were assessed as severe, whereas chest discomfort and ventricular extrasystoles were assessed as mild.

Two cardiac AEs, palpitation and ventricular extrasystoles, were reported infrequently (0.2%). Mild palpitation was assessed as an ADR, resulting in the discontinuation of prucalopride in that patient, but it was resolved according to the investigator's judgment. This patient had a medical history of angina pectoris, arrhythmias, hypertension, and hyperlipidemia. The patient in whom ventricular extrasystoles were reported had a previous history of hypertension, angina pectoris, hyperlipidemia, and chest discomfort.

Fifteen patients had an impaired renal function, but only one AE occurred; a moderate headache was reported in one patient with severe chronic kidney disease who had received 1 mg of prucalopride.

3. Efficacy

Table 3 lists the CGI-I responses. In the evaluation set with 601 patients, the proportion of patients with efficacious improvement was 72.7% (437/601), 69.7% (288/413), and 68.5% (230/336) at weeks four, eight, and 12, respectively. There were no patients with the response 'very much worse' and few patients reported 'minimally worse' and 'much worse' responses throughout the study.

Univariate and multivariate logistic regression analyses were performed to observe any clinical factors that may have resulted in a negative CGI-I response to the prucalopride treatment at the last visit of each patient. Univariate analysis showed that a longer duration of chronic constipation, use of non-pharmacological therapies for chronic constipation, and use of concomitant medications had a significant negative effect on the CGI-I response (p=0.0002, p=0.0404, and p=0.0388, respectively) (Table 4). Multivariate logistic regression analysis showed that the CGI-I response deteriorated in those with a longer duration of chronic constipation (OR 0.463; 95% CI 0.303, 0.708; p=0.0011) and use of concomitant medications (OR 0.576; 95% CI 0.369, 0.899; p=0.0151) (Table 5).

DISCUSSION

This post-marketing surveillance study assessed the safety and efficacy profile of a prucalopride treatment for chronic constipation in real clinical practice in Korean adults. Prucalopride showed a favorable safety and efficacy profile.

In the present study, the incidence of AEs and ADRs were 17.7% and 7.6%, respectively. The common AEs of prucalopride were nausea, headache, abdominal pain, and diarrhea, similar to that observed in this study. The safety profile of prucalopride in this study was confirmed as safe when used in an established regimen in real clinical practice in Korea. Previous studies conducted in the United States (U.S.) and Europe also reported similar results in safety.[7,9] An Asian study showed that the incidence of AEs was 57.0%, with diarrhea, headache, nausea, and abdominal pain reported in more than 5.0% of patients.[11] The incidence rate of AEs in

the above studies differed due to differences in study design, study period, and region. Prucalopride was found to be safe in patients with renal function impairment, even though the main route of prucalopride elimination is renal excretion.[15] Regarding cardiotoxicity, only two AEs, palpitations and ventricular extrasystoles, occurred in the 601 patients in this study. In this post-marketing surveillance study, electrocardiograms were not checked before and after administration of prucalopride. The inability to identify asymptomatic cardiac events was a limitation of this study. An observational population-based cohort study conducted in 5,715 European patients with chronic constipation showed no risk of major adverse cardiovascular events associated with prucalopride treatment.[16] Overall, prucalopride was tolerable and safe without the occurrence of cardiovascular adverse events.

The excellent clinical response of prucalopride was observed consistently throughout the study period. The investigators assessed the improvement in the patient's condition, and more than 70% of patients reported that their chronic constipation was improved by a prucalopride treatment. This finding is also consistent with the observation of previous prucalopride trials. In a 2017 systematic review including multiple randomized controlled trials, prucalopride successfully increased the number of bowel movements per week in adults with chronic constipation.[17] The reason for the high clinical response in this study compared to previous pivotal trials of prucalopride may be due to the concomitant laxative use permitted in this study.

In this study, the clinical response to prucalopride was consistent across age, gender, and comorbidities in routine clinical practice. On the other hand, a longer duration of chronic constipation and the use of concomitant medications reduced the efficacy of prucalopride. One hundred and sixty-seven patients (27.8%) discontinued treatment because of the economic burden, AEs, and sufficient or insufficient efficacy. These results are in agreement with those of a survey in the US, which reported that approximately half of the patients with chronic constipation were unsatisfied with their treatments for the following reasons: ineffective (39%); inconsistent results (25%); adverse effect concerns (16%); and price and cost issues or still requiring laxative use (3%).[5]

This study had some limitations. First, the safety and efficacy results should be considered without control groups owing to the nature of post-marketing surveillance. Second, there was missing information because of the early completion of the study, which may have induced bias.

In conclusion, this study examined the favorable safety and efficacy profile of prucalopride in 601 Korean patients with chronic constipation in real clinical practice. This study confirmed the safety of prucalopride and demonstrated that prucalopride is effective in improving chronic constipation, with a positive response in more than 70% of patients in a real clinical setting. Thus, prucalopride should be considered in patients with chronic constipation when bowel symptoms are refractory to simple laxatives.

ACKNOWLEDGEMENTS

We show our deep appreciation to the physicians of the medical institution who participated in this study and YoungJa Lee of Janssen Korea Ltd. who advised on the manuscript. We would like to thank Editage (www.editage.co.kr) for English language editing. This study was funded by Janssen Korea Ltd, Republic of Korea.

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