Journal of Gastrointestinal & Digestive System

Abe, et al., J Gastroint Dig Syst 2014, 4:5
DOI: 10.4172/2161-069X.1000223

Research Article Open Access

Efficacy of Lubiprostone in Chronic Constipation: Clinical and Work Productivity Outcomes

Tatsuya Abe[1*], Yoshikazu Hachiro[1], Yoshiaki Ebisawa[1], Houhei Hishiyama[1], Masanori Murakami[2] and Masao Kunimoto[1]

[1]*Department of Proctology, Kunimoto Hospital, Asahikawa, Japan*

[2]*Department of Gastroenterology, Kunimoto Hospital, Asahikawa, Japan*

[*]**Corresponding author:** Tatsuya Abe, Kunimoto Hospital, 1-7-2-1 Akebono, Asahikawa 070-0061, Japan, Tel: +81-166-25-2241; Fax: +81-166-23-1726; E-mail: t-abe@cf6.so-net.ne.jp

Received date: July 23, 2014, **Accepted date:** Sep 25, 2014, **Published date:** Sep 30, 2014

Abstract

Objective: Chronic constipation is a common health problem that significantly affects the quality of life of patients and results in high economic burden. This clinical study was performed to assess the efficacy of lubiprostone in the treatment of chronic constipation using a validated constipation scoring system and the work productivity and activity impairment questionnaire.

Methods: We prospectively enrolled 35 patients who received lubiprostone. All the patients had chronic constipation as defined by the Rome III criteria. The patients were treated orally with a 24-μg lubiprostone capsule twice a day. Changes in the scores before and 2 weeks after the beginning of administration were recorded and analyzed.

Results: Of the 35 patients, 28 completed the study and were included in the efficacy analysis. The total constipation scoring system score was significantly improved from 11.3 ± 4.8 at baseline to 8.0 ± 4.0 after 2 weeks. Although the work activity subscale did not show a significant improvement, such an improvement was statistically significant in the case of non-work-related activities.

Conclusion: Our results demonstrate that lubiprostone is effective in improving many chronic constipation-related symptoms as well as the quality of life in patients with chronic constipation.

Keywords: Chronic constipation; Constipation scoring system; Laxatives; Lubiprostone; Work productivity; Activity impairment

Introduction

Chronic constipation (CC) is a common health problem that significantly affects the quality of life of patients and places a burden on the economy [1]. This impairment of quality of life is similar to or more severe than that experienced in several other chronic diseases (e.g., arthritis, asthma, or coronary artery disease) [2]. Both direct and indirect costs are associated with CC. Indirect costs include missing school or work (absenteeism) or being less productive (presenteeism), whereas direct costs of treating constipation include office visits, diagnostic tests, and medications [2]. Management of CC may involve an increased intake of dietary fiber, enemas, and stimulant or osmotic laxatives. Despite the availability of these therapies, approximately 50% of all patients with CC are not satisfied with their treatment, which is mostly attributed to the lack of efficacy [3]. Lubiprostone, a new medication designed for the treatment of CC in both men and women, was approved by the FDA in 2006. The efficacy of lubiprostone in the treatment of constipation has been established in phase III clinical trials [4,5]. The present clinical study was performed to assess the efficacy of lubiprostone in the treatment of CC using a validated constipation scoring system (CSS) [6] and the work productivity and activity impairment questionnaire (WPAI) [7].

Materials and Methods

We prospectively enrolled 35 patients who received lubiprostone from August 2013 to December 2013 at our institution. The research and ethics committee of Kunimoto Hospital approved this study, and all patients provided written informed consent before participation. Inclusion criteria were as follows: Japanese male and female patients aged >20 years with CC. All the patients had constipation as defined by the Rome III criteria [8], with decreased bowel frequency (less than three times per week), a sensation of incomplete emptying, hard stools, or a history of difficult evacuation on at least a quarter of occasions. To focus exclusively on the impact of CC and avoid the contribution from related gastrointestinal comorbidities, all patients with irritable bowel syndrome, frequent diarrhea, Crohn disease, or ulcerative colitis were excluded.

Each of the 35 patients was treated orally with a 24-μg lubiprostone capsule twice daily. The medication was taken with food and at least one glass of water. The patients were advised not to change their lifestyle or diet, including exercise and fiber intake during the study. The patients also took a prophylactic dose of itopride hydrochloride (one 50-mg tablet twice a day) together with lubiprostone to prevent nausea, because nausea was reported to be the most common drug-related adverse event, occurring in up to 31% of patients receiving lubiprostone [9].

The severity of constipation was quantified based on the CSS (range: 0–30 at increments of 1; no symptoms = 0) [6]. The following parameters were monitored on a daily basis for 1 week: the number of bowel movements; difficulty in evacuation; feeling of incomplete evacuation; abdominal pain; time in the lavatory; the use of laxatives, enemas, and digital assistance; failed attempts at bowel movement; and duration of constipation (Table 1). The total score was obtained by adding the scores of these 8 individual parameters. To assess work productivity, the WPAI for chronic constipation (WPAI-CC) [7] was used. As previously described for the WPAI-CC, the total work time missed or compromised because of constipation was calculated as a per-week percentage of presenteeism, absenteeism, and overall impairment (presenteeism plus absenteeism) for patients employed during the study. Additionally, the effect of constipation on non-work activities (such as housework, exercising, and studying) was calculated as percentage impairment [7]. The changes in the CSS and WPAI-CC scores before and 2 weeks after the administration were recorded and analyzed.

Chronic constipation patients (n=35)					
	Score	**n**		Score	n
Frequency of bowel movements			**Time: minutes in lavatory per attempt**		
1-2 times per 1-2 days	0	16	<5	0	10
2 times per week	1	4	5–10	1	16
Once per week	2	7	10–20	2	3
Less than once per week	3	7	20–30	3	4
Less than once per month	4	1	>30	4	2
Difficulty: painful evacuation effort			Assistance: type of assistance		
Never	0	13	Without assistance	0	6
Rarely	1	12	Stimulative laxatives	1	22
Sometimes	2	6	Digital assistance or enema	2	7
Usually	3	2			
Always	4	2			
Completeness: feeling incomplete evacuation			Failure: unsuccessful attempts for evacuation/24h		
Never	0	7	0	0	8
Rarely	1	5	1–3	1	18
Sometimes	2	6	3–6	2	7
Usually	3	8	6–9	3	1
Always	4	9	>9	4	1
Pain: abdominal pain			History: duration of constipation (years)		
Never	0	13	0	0	6
Rarely	1	9	1–5	1	9
Sometimes	2	7	5–10	2	3
Usually	3	2	10–20	3	6
Always	4	4	>20	4	11

Table 1: Symptom scores of Constipation Scoring System at baseline

Statistical analysis was performed using SPSS 16.0 for Windows XP (SPSS Inc., Chicago, IL, United States). Numeric variables are expressed as mean ± standard deviation. Data were compared using the Wilcoxon signed-rank test. A p-value <0.05 was considered statistically significant.

Results

The demographics of the enrolled patients are summarized in Table 2. Most patients were women (85.7%). The mean age was 59.8 (± 18.6) years with approximately 50% of patients aged ≥65 years. The total CSS score at baseline was 11.3 ± 4.8 and, of the 8 individual parameters, the feeling of incomplete evacuation and duration of constipation had higher scores than the other items (Table 3). Based on the CSS data, we divided the patients into 3 groups according to the constipation type: 2 cases of slow transit constipation (STC; defined as fewer than two defecations per week), 16 cases of obstructive defecation (OD; defined as feeling of incomplete evacuation or prolonged painful straining or frequent calls to defecate or excessive toilet time or digital assistance), and 17 combination of both (Mixed). Of the 35 patients who were enrolled, 6 did not visit our outpatient clinic after receiving lubiprostone and 1 discontinued the study because of drug-related nausea. Accordingly, 28 patients completed the study and were included in the efficacy analysis.

The changes in the CSS score from baseline to 2 weeks are shown in Table 3. The patients experienced statistically significant improvements, when compared with baseline, in the mean degree of difficulty ($p = 0.005$), completeness ($p = 0.012$), pain ($p = 0.009$), time ($p = 0.010$), and total score ($p < 0.001$). Frequency, assistance, and failure rates also improved but did not reach statistical significance. With respect to the constipation types, the total scores of the OD and Mixed groups showed significant decreases from 8.43 ± 3.11 and 13.7 ± 3.45 at baseline to 6.36 ± 2.41 and 10.0 ± 3.01 after 2 weeks, respectively ($p = 0.006$ and 0.002, respectively), whereas the number of patients with STC was too small to draw a conclusion.

None of the 11 patients (31.4%) who were employed at the time of the survey reported work time missed due to CC. The WPAI-CC results indicated no significant changes in absenteeism, presenteeism, and the combination of the two. However, improvement was statistically significant ($p = 0.002$) in the case of impairment of non-work activities, with alleviation of impairment reaching a mean magnitude of 14.3 ± 21.6% (Table 4).

Parameter	Analyzed group (n =35)
Sex, n (%)	
Male	5 (14.3)
Female	30 (85.7)
Age, years n (%)	
20–44	11 (31.4)
45–64	7 (20.0)
≥65	17 (48.6)
Constipation type n (%)	
Slow transit constipation	2 (5.7)
Obstructive defecation	16 (45.7)
Combination of both	17 (48.6)

Table 2: Patient demographics

Constipation Scoring System	Baseline (n = 35)	After 2 weeks (n = 28)	p- Value
Total	11.3 ± 4.8	8.0 ± 4.0	<0.001
Frequency	1.2 ± 1.3	0.9 ± 1.1	0.092
Difficulty	1.1 ± 1.1	0.4 ± 0.6	0.005
Completeness	2.2 ± 1.5	1.6 ± 1.3	0.012
Pain	1.3 ± 1.3	0.6 ± 0.9	0.009
Time	1.3 ± 1.1	0.9 ± 1.0	0.010
Assistance	1.0 ± 0.6	0.9 ± 0.5	0.631
Failure	1.1 ± 0.7	0.9 ± 0.6	0.169
History	2.2 ± 1.5	2.2 ± 1.5	1.000

Table 3: Changes in Constipation Scoring System Questionnaire Score

Impairment due to constipation	n	Mean ± SD	p-value
Work activity			
Absenteeism, % of work time			
Baseline	14	0	p = 1
After 2 weeks with lubiprostone	11	0	
Change from baseline	11	0	
Presenteeism, % impairment			
Baseline	14	27.1 ± 33.5	p = 0.297
After 2 weeks with lubiprostone	11	17.3 ± 27.7	
Change from baseline	11	0.9 ± 5.1	
Overall productivity loss, %			
Baseline	14	27.1 ± 33.5	p = 0.297
After 2 weeks with lubiprostone	11	17.3 ± 27.7	
Change from baseline	11	0.9 ± 5.1	

Non-work activity, % impairment			
Baseline	35	38.6 ± 34.0	p = 0.002
After 2 weeks with lubiprostone	28	30.4 ± 29.3	
Change from baseline	28	14.3 ± 21.6	

Table 4: Results of the Work Productivity and Activity Impairment Questionnaire analyses

Although there were no serious adverse drug-related events during the study, 9 patients (31.0%) experienced at least one adverse effect (Table 5). They were able to tolerate the side effects (with the exception of one aforementioned patient), and lubiprostone was not discontinued. The most common treatment-related side effects were nausea (13.8%) and diarrhea (6.9%).

Parameter	**n (%)**
At least one adverse event	9 (31.0)
Adverse event	
Nausea	4 (13.8)
Diarrhea	2 (6.9)
Abdominal pain	1 (3.4)
Chest pain	1 (3.4)
Dyspepsia	1 (3.4)
Dyspnea	1 (3.4)
Flatulence	1 (3.4)
Vomiting	1 (3.4)

Table 5: Summary of adverse events

Discussion

The results of the CSS indicated that patient-reported improvements after treatment with lubiprostone were clinically and statistically significant. Patients taking lubiprostone also experienced significant improvements in health-related quality of life.

Currently, three types of constipation are differentiated: STC, OD, and a combination of the two [10]. Symptoms of OD (straining, hard and lumpy stools, or incomplete evacuation) are more frequent and bothersome than the infrequency of bowel movements [11]. Such patients are often unable to have spontaneous evacuations and generally experience better results with enemas, suppositories, and digitation than with laxatives [6]. Previous studies involving lubiprostone enrolled patients with CC defined as fewer than 3 spontaneous bowel movements per week, and the primary efficacy endpoints were the number of bowel movements, spontaneous bowel movements within 24 h of initiating therapy, or stool consistency [4,5]. In contrast, our patients mostly experienced OD rather than STC. Therefore, our CSS results are interesting; the difficulty, completeness, pain, and time parameters all improved significantly, yet the improvement of frequency was not significant. Overall, our data suggest that lubiprostone may be a useful agent in the management of patients with OD as well as STC.

No significant quality-of-life improvement was observed on the WPAI-CC work activity subscale, but <50% of the study participants were employed during the study, limiting the usefulness of that subscale. In contrast, the WPAI-CC subscale of non-work activity impairment showed significant improvement after treatment with lubiprostone, which may be related to less painful evacuation effort, less pronounced feeling of incomplete evacuation, reduction in abdominal pain, and reduction in time spent in the lavatory. The prevalence of constipation increases with age, especially in those aged >65 years [12]. Up to 50% of our study patients were aged >65 years, and most of them were already retired. Therefore, the improvement observed on the non-work activity impairment subscale is meaningful in terms of extending healthy life expectancy.

Lubiprostone selectively stimulates type 2 chloride channels in the cells of the epithelium, which leads to an efflux of chloride into the intestinal lumen. As a result, fluid secretion into the gastrointestinal lumen initiates a bolus effect that softens stool, enhances intestinal transit, and alleviates symptoms of constipation. Importantly, the action of lubiprostone is limited to the intestinal tract. Furthermore, this drug is rapidly metabolized and has very low systemic bioavailability [9]. It has been demonstrated that lubiprostone is both effective and safe in the treatment of constipation even in the elderly [13].

Gastrointestinal adverse events were the most often encountered tolerability issues in patients receiving lubiprostone in clinical trials. In previous studies, nausea was the most frequent adverse event, affecting up to 31% of patients receiving lubiprostone [9]. Nausea was mild to moderate in severity in the clinical trials and resulted in treatment discontinuation in 8.7–20% of these patients [9,14]. The mechanism underlying the development of nausea in patients treated with lubiprostone is unknown. Theories include an exaggerated pharmacodynamic effect from secreted fluids in the small intestine or a direct gastric effect. In the current study, the prevalence of nausea and the frequency of treatment discontinuation were lower than those in previous investigations [13]. Accordingly, our results suggest that prophylactic administration of itopride hydrochloride can decrease the risk of nausea and consequently reduce the risk of discontinuation of lubiprostone.

The most common side effects of itopride include abdominal pain and diarrhea [15]. Therefore, we were concerned that these adverse events would be exacerbated by administration of itopride. However, in our earlier study, the incidence of both abdominal pain and diarrhea showed a slightly decreasing trend in patients who received itopride [16].

In conclusion, our results demonstrate that lubiprostone is effective in improving many constipation-related symptoms and non-work activities in patients with CC. Compared with younger patients, the elderly report more frequent symptoms of OD such as straining, self-digitation, and feelings of anal blockage [17]. Thus, with the

population aging rapidly becoming a global phenomenon, lubiprostone may find wider clinical application in the future. This study is limited by its small sample size and lack of control group. Further refinement of study design and additional cases in the future will be needed to confirm our conclusions.

References

1. Lembo A, Camilleri M (2003) Chronic constipation. N Engl J Med 349: 1360-1368.
2. Irvine EJ, Ferrazzi S, Pare P, Thompson WG, Rance L (2002) Health-related quality of life in functional GI disorders: focus on constipation and resource utilization. Am J Gastroenterol 97: 1986-1993.
3. Johanson JF, Kralstein J (2007) Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther 25: 599-608.
4. Johanson JF, Morton D, Geenen J, Ueno R (2008) Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol 103: 170-177.
5. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R (2014) Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol 12: [Epub ahead of print].
6. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD (1996) A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum 39: 681-685.
7. Sun SX, Dibonaventura M, Purayidathil FW, Wagner JS, Dabbous O, et al. (2011) Impact of chronic constipation on health-related quality of life, work productivity, and healthcare resource use: an analysis of the National Health and Wellness Survey. Dig Dis Sci 56: 2688-2695.
8. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, et al. (2006) Functional bowel disorders. Gastroenterology 130: 1480-1491.
9. McKeage K, Plosker GL, Siddiqui MA (2006) Lubiprostone. Drugs 66: 873-879.
10. Alame AM, Bahna H (2012) Evaluation of constipation. Clin Colon Rectal Surg 25: 5-11.
11. Pare P, Ferrazzi S, Thompson WG, Irvine EJ, Rance L (2001) An epidemiological survey of constipation in canada: definitions, rates, demographics, and predictors of health care seeking. Am J Gastroenterol 96: 3130-3137.
12. Bouras EP, Tangalos EG (2009) Chronic constipation in the elderly. Gastroenterol Clin North Am 38: 463-480.
13. Gras-Miralles B, Cremonini F (2013) A critical appraisal of lubiprostone in the treatment of chronic constipation in the elderly. Clin Interv Aging 8: 191-200.
14. Barish CF, Drossman D, Johanson JF, Ueno R (2010) Efficacy and safety of lubiprostone in patients with chronic constipation. Dig Dis Sci 55: 1090-1097.
15. Huang X, Lv B, Zhang S, Fan YH, Meng LN (2012) Itopride therapy for functional dyspepsia: a meta-analysis. World J Gastroenterol 18: 7371-7377.
16. Abe T, Hachiro Y, Ebisawa Y, Hishiyama H, Murakami M, et al. (2014) Efficacy of itopride in the prevention of lubiprostone-induced nausea. Open J Gastroenterol 4: 305-309.
17. Rao SS (2007) Constipation: evaluation and treatment of colonic and anorectal motility disorders. Gastroenterol Clin North Am 36: 687-711, x.