Randomized, Double-Blind, Placebo-Controlled Trial of Lubiprostone in the Treatment of Constipation Associated with Parkinson's Disease

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ABSTRACT

Object: To evaluate the efficacy and tolerability of lubiprostone (Amitiza®) for constipation in Parkinson's disease in a double-blind, randomized, controlled study.
Background: Constipation is a commonly encountered non-motor symptom in Parkinson's disease (PD), and may be caused by peripheral autonomic degeneration. It often precedes the development of cardial PD motor features. There is relatively little data regarding treatment of constipation in PD.
Methods: Patients with PD and clinically meaningful constipation (Constipation Rating Scale score >10, (0-28)) were recruited from two academic movement disorder centers to participate in the study. After enrollment, patients were initially followed for two weeks, and then randomized 1:1 to lubiprostone, and titrated up to 48 micrograms per day. They returned 4 weeks later for a final assessment. Data included diaries and global impressions (co-primary endpoints), demographics, UPDRS, constipation scales, visual analogue scales (VAS), a stool diary, and adverse events.
Results: Fifty-four subjects, 39 male, age 67.0± 10.1 years, duration of PD 8.3± 5.4 years, began drug or placebo. One patient in the drug group discontinued the study due to logistics, and one patient in the placebo group discontinued the study due to "lack of efficacy". A "marked" or "very marked" clinical global improvement was reported by 16/25 (64.0%) on drug vs. 5/27 (18.5%) on placebo, p=0.001. The constipation rating scale (p<0.05), VAS (p=0.001), and stools/day on the diary (p<0.001) all improved on drug compared to placebo. Adverse events on drug were mild, most commonly loose stools.
Conclusion: In this randomized controlled trial, lubiprostone appears to be safe and effective for the short term treatment of constipation in PD.

INTRODUCTION

PD is common neurodegenerative disease that has been traditionally thought to affect predominantly the motor system and result from substantia nigral dopamine cell loss. More recently, a broader view of PD has emerged, incorporating non-dopaminergic symptoms and wide spread pathology. Among the most common of these non-motor features is gastrointestinal (GI) dysfunction, which was noted by James Parkinson in 1817 in his original monograph. [1] Constipation is reported much more commonly in PD than controls. [2-4] In fact, constipation predicts the onset of PD motor features and is thus thought to occur in PD long before meaningful substantia nigral dopamine cell loss. [5]

Decreased bowel movement frequency in PD probably results from prolonged colon transit time. [6-8] Gastric emptying time and small intestine transit time is also prolonged in PD, but in normal physiology passage of food through the esophagus, stomach and small intestine takes 4-6 hours, whereas colon passage takes about 24 hours. [9] PD patients also have difficulties with the volitional defecation process. This is most commonly caused by dyssynergy between sphincter / puborectalis muscles, which normally relax during defecation, and contraction of the muscles that increase intraabdominal pressure to propel the stool from the sigmoid colon to the rectum. [8, 10, 11]

PD patients demonstrate marked neuropathology throughout the GI system. The majority of parasympathetic innervation that normally increases GI motility derives from the dorsal motor nucleus, a region of the brain heavily damaged early in PD. [12, 13] The peripheral enteric nervous system, including the Myenteric plexus, also show marked abnormalities in PD, including Lewy body deposition, alpha-synuclein deposition, and dopaminergic neuronal loss. [14-18] In fact it is now speculated that this may represent the initial pathology in PD.

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum that is approved for the treatment of chronic constipation. [19] Lubiprostone acts by specifically activating the chloride channel-type 2 (ClC-2), which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. Systemic absorption of the drug is negligeble. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. [20] Lubiprostone has not been formally studied in constipation associated with PD.

METHODS

We conducted a parallel-group, double-blind, placebo-controlled (1:1) study at two academic centers (Baylor College of Medicine and University of South Florida) to determine the safety and efficacy of lubiprostone in the treatment of constipation for PD patients. The protocol was approved by the respective Institutional Review Boards and registered on ClinicalTrials.gov. Recruitment began December 2008 and ended October 2010. Inclusion criteria were patients standardly diagnosed with PD, age 35-85 years, who met ROME II criteria [21] for constipation and scored at least 10 on the ROME II constipation assessment. Patients were excluded if they had any other identifiable cause of constipation, including any history of GI surgery, any use of opioids, anti-cholinergic, or antacids containing magnesium or aluminum salts. Other medication that could possibly affect GI function, including PD medications, anti-depressants, and calcium channel blockers, were at stable doses for a month prior to entry, and throughout the study. If over age 50, subjects were required to have had a colonoscopy within the past 5 years. Patients were not allowed to take any scheduled anti-constipation medications except fiber. Any rescue laxative use was recorded.

At visit 1, patients signed informed consent, were randomized via a computer generated randomization program to drug or placebo, completed demographic assessments, medical histories, a Unified Parkinson's Disease Rating Scale (UPDRS) while on medications, and the constipation scale. [21] They were trained to keep a diary of bowel movements, marking those requiring rescue laxatives. After 2 weeks of diary entries, they returned for similar assessments (baseline) and began taking drug or matching placebo started at 24µg/day for 7 days in the morning, then was increased to 24 µg/ twice daily. Patients were allowed to reduce the medication back to once daily if the higher dose was not tolerated. They continued their diaries, were called for a safety visit at week 2 and seen for a similar final assessment at week 4, which also included clinical global impressions of change, a visual analogue scale of efficacy, and adverse events.

Based on non-PD constipation trials data provided by Takeda Pharmaceuticals, we calculate that, for a double-blind, placebo-controlled trial using a two-sided α value of .95 (for a p value of 0.05), and for a power of 0.8, 68 total patients (1:1) would be required to show a frequency difference of 3.87 ± 4.62 SBMs for cases versus 1.33 ± 2.52 SBMs for controls based on stool diaries. An interim analysis of 52 completers showed robust statistical improvement and the study so recruitment was stopped. Data were entered into a database and checked for accuracy and logical consistency. Analysis datasets were generated, and imported into Stata IC, version 11.1. for analyses. Student's t-tests were performed assuming unequal variances; Fisher's exact method was used for calculations of Chi-square statistics. Wilcoxon rank sum test was used in comparison of ordinal subjective assessments, assuming independence of groups.

RESULTS

Patient demographics were similar in the randomized groups and summarized in Table 1. Disposition throughout the study is summarized in figure 1. Compared to placebo, the drug group had improved global impression of change (p=0.001), increased stools/day by diary (p=0.001), improved VAS score (p<0.001), and improved constipation questionnaires (p<0.05). [Table 2] There was no change in UPDRS scores. Loose stools and diarrhea were common but usually mild, self limiting, and caused no withdrawals after starting the medication. [Table 3]

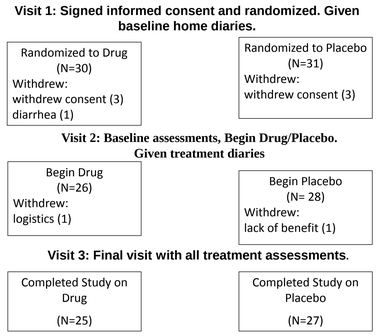

Table 3: Adverse Events

	Drug Group	Placebo Group
any loose stool	12	1
persistent diarrhea	1	0
abdominal pain	2	5
stool discoloration	1	0
indigestion	0	1
daytime sleepiness	1	1
fatigue	1	0
fever	0	1
rash	1	0
bladder incontinence	0	1
hallucinations	0	2

Table 1: Patient Demographics

Item	Lubiprostone (N= 30)	Placebo (N= 31)	P value
Sex (M/F)	22/8	24/7	0.772
Age (mean ±SD)	68.8± 8.7	65.9± 10.9	0.267
Age Onset (mean ±SD)	59.9± 8.5	56.5± 12.5	0.223
Duration PD (mean ±SD)	8.9± 6.3	9.5± 6.3	0.741
Weight (lbs)	181.1± 43.5	172.1± 35.4	0.401
Fluctuators	12	11	.079
UPDRS (Section III "on")	20.7± 8.4	21.0± 9.6	0.93

Table 2: Patient Outcomes

Item	Lubiprostone (N=25)	Placebo (N=27)	P value
Patient subjective assessment of change	Mildly worse 1 No change 3 Mildly improved 6 Much improved 9 Very much improved 7	Mildly worse 4 No change 12 Mildly improved 6 Much improved 3 Very much improved 2	0.001 Z = 3.188
Visual analog scale score (change in constipation) visit 2 to visit 3	51.4± 8.5 to 71.2± 16.6	50.7± 5.9 to 56.8± 13.0	0.001
BM review questionnaire, visit 2 to visit 3	13.3± 4.91 to 6.6± 1.11	13.4± 4.8 to 10.2± 6.5	0.033
BM Diaries BMs / day for period before to after drug	0.75± 0.80 to 0.97± 0.88	0.84± 0.76 to 0.83± 0.76	0.001
Weight change: change visit 2 to visit 3 (lbs.)	-0.32± 2.39	-1.01± 3.56	0.440
UPDRS part II, "on": change visit 2 to visit 3	-0.48± 3.31	0.54± 4.26	0.352
UPDRS part II "off": change visit 2 to visit 3	0.04± 0.45	1.13± 5.41	0.323
UPDRS part III, on meds: change visit 2 to visit 3	-0.16± 5.70	1.58± 6.31	0.315

CONCLUSIONS

In this multi-center, controlled trial lubiprostone significantly improved all assessments of constipation associated with PD without effecting PD motor features. Although loose stools were common on drug, they were seldom felt to be problematic. Interestingly, no patient reported nausea, which is the most common adverse event in non-PD trial populations. [19]

There is remarkably little formal data regarding the management of constipation in PD. Dopaminergic medications do not improve, and may worsen constipation. [22] Polyethylene glycol improved constipation in one controlled trial. [23] Other osmotic agents such as lactulose, glycerin and sorbitol have not been formally assessd in PD. In a small trial, the fiber supplement psyllium increased stool frequency and weight. [24] Other fiber supplements have not been assessed in PD but one trial found methylcellulose mostly superior to psyllium in a chronic constipation population. [25] Open label series report benefit of the serotonin-4 (5HT-4) antagonists cisapride [26, 27] and tegaserod [28] in PD patients, but a controlled trial of tegaserod was negative [29], and both drugs have been removed from the market due to cardiac toxicity. An anecdotal report suggested that pyridostigmine, a cholinergic agent, may improve constipation in PD. [30] Botulinum toxin into the puborectalis muscle to reduce outflow resistance has been advocated in some cases. [31-33] Other treatments such as stool softeners, increased water intake, increased physical activity, herbal remedies, and enemas are mostly anecdotal.

The treatment duration in this study was only 4 weeks so longer term results could not be discussed. However, Phase III trials for chronic constipation were also only 4 week duration. Anecdotally many subjects have maintained a good clinical response for months to years. Overall our results support the safety and efficacy of lubiprostone for treatment of constipation in patients with PD.

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