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Clinical Short Communication

Dalfampridine in Parkinson's disease related gait dysfunction: A randomized double blind trial

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ABSTRACT

Background: Disease-related gait dysfunction causes extensive disability for persons with Parkinson's disease (PD), with no effective therapies currently available. The potassium channel blocker dalfampridine has been used in multiple neurological conditions and improves walking in persons with multiple sclerosis. Objectives: We aimed to evaluate the effect of dalfampridine extended release (D-ER) 10 mg tablets twice daily on different domains of walking in participants with PD.

Methods: Twenty-two participants with PD and gait dysfunction were randomized to receive D-ER 10 mg twice daily or placebo for 4 weeks in a crossover design with a 2-week washout period. The primary outcomes were change in the gait velocity and stride length.

Results: At 4 weeks, gait velocity was not significantly different between D-ER (0.89 m/s ± 0.33) and placebo (0.93 m/s ± 0.27) conditions. The stride length was also similar between conditions: 0.96 m ± 0.38 for D-ER versus 1.06 m ± 0.33 for placebo. D-ER was generally well tolerated with the most frequent side effects being dizziness, nausea and balance problems.

Conclusions: D-ER is well tolerated in PD patients, however it did not show significant benefit for gait impairment.

1. Introduction

Gait dysfunction and postural instability represent major therapeutic challenges for persons with Parkinson's disease (PD). Axial symptoms such as freezing of gait and postural instability, are known to be dopamine resistant in PD, and as such, non-dopaminergic approaches are considered a viable alternative [1]. The pathogenesis of gait imbalance is not completely understood, but there is consensus that apart from substantia nigra degeneration, the loss of specific brainstem neuronal populations play a key role in gait dysfunction in PD [2]. These may include, among others, cholinergic neurons from pedunculo-pontine nucleus (PPN), noradrenergic neurons from locus coeruleus (LC) and serotoninergic raphe nuclei. Correlation between the severity of some parkinsonian symptoms and the reduction in

particular monoamines such as norepinephrine, glutamine and dopamine [3,4] suggest that in PD there is widespread neurodegeneration involving multiple neurotransmitters.

Efforts to enhance monoamines in order to improve gait have shown mixed results. Donepezil, a cholinesterase inhibitor, has been shown to decrease risk of falls in patients with PD. [5] Methylphenidate releases both dopamine and noradrenaline in the frontal cortex, but its use failed to result in a significant improvement in gait.in PD patients [6] while high doses seem to be effective for FOG post deep brain stimulation (DBS) [7] Droxidopa, a noradrenergic prodrug, has been approved for use in Japan since 1989 for treatment of freezing of gait (FOG) associated with PD [8], however atomoxetine, a central adrenergic agonist, did not show any effect on freezing of gait in subjects with PD. [9] Amantadine, an NMDA antagonist, was associated with reduced FOG in patients who had undergone deep brain stimulation (DBS) [10].

Dalfampridine (4-aminopyridine; 4-AP) is a K-channel blocker that has been shown to improve mobility in people with multiple sclerosis (MS). Two large double-blind, multicenter, randomized clinical trials in subjects with MS showed that the sustained-release 4-AP improved walking ability [11,12]. This improvement was associated with a reduction in patient-reported ambulatory disability, and was a clinically meaningful therapeutic benefit. 4-AP also improved walking, as shown by a higher proportion of subjects that had gait improvement in the 4-AP-treated group (42.9% versus the placebo-treated group 9.3%) [12].

Despite a limited understanding of its mechanism of action, 4-AP has been used for many years in humans with various neurological conditions such as multiple sclerosis, spinal cord injury (SCI), cerebellar ataxia, and Lambert Eaton syndrome. Experimental data suggest that 4AP has neuromodulatory properties; it increases neurotransmitter release at multiple levels in cortical and subcortical structures, and improves conduction velocity in gait-related networks [13]. A case report of 4-AP use in a subject with PD and severe FOG suggested that 4-AP could improve FOG, based on increased stride length and improved gait variability [14]. Based on its pharmacological profile, ability to enhance multiple neurotransmitter

release and promising clinical data in patients with multiple sclerosis [11,12] we hypothesized that D-ER will improve gait velocity, stride length and decrease FOG in PD patients with mild to moderate gait dysfunction To evaluate the efficacy of D-ER for the treatment of gait impairment in PD we carried out a randomized, double-blind, placebo-control, cross-over trial of extended release dalfampridine (D-ER) in a PD cohort with moderate gait impairment.

2. Methods

2.1. Study design

The study was a single-center double-blind, placebo-controlled cross-over study designed to assess the effect of D-ER on walking in people with PD and gait dysfunction. Based on previous trials in multiple sclerosis a dose of 10 mg twice daily was selected and each patient served as their own control in the crossover design. After screening, participants were randomized 1:1 to either placebo-D-ER arm or D-ER-placebo arm. Each treatment phase lasted 4 weeks, with a 2 week washout between the two treatment phases (see Fig. 1). Measurements were performed while ON levodopa at baseline, 1 h after drug administration (D-ER 1-h) and at 4 weeks (D-ER 4-wk). The study was approved by institutional board review (clinicaltrials.gov NCT01491022) of the University of Miami and all participants provided written informed consent prior to enrollment.

2.2. Study participants

Subjects were recruited from the University of Miami movement disorders clinic to participate in the trial. Inclusion criteria included: diagnosis of idiopathic PD with moderate to advanced PD Hoehn and Yahr Stage 2–3, stable dosage of a dopamine agonist and/or levodopa, able to walk at least 25 ft, and with presence of FOG despite levodopa treatment. All subjects underwent a preliminary assessment of their gait using the FOGQ and gait subscore from MDS-UPDRS and were included if they demonstrated mild to moderate gait

impairment. Exclusion criteria included: active or prior history of seizures, renal insufficiency, cardiac arrhythmia, diagnosis of dementia, treatment with DBS, severe arthritis, or women of childbearing potential.

2.3. Outcome measures

The primary outcome measure was change in gait velocity and stride length from baseline. Baseline measurements of the gait kinematics were performed while ON levodopa before study drug administration. All clinical assessments of motor function were performed by the PI(CCL) who was blinded to treatment phase. Gait kinematics were assessed pre and post treatment 1 h after intake of study drug and at 4 weeks, with three trials captured in each testing session, using wireless sensors (Mobility Lab, APDM Inc). Secondary outcome measures included: 3 m Timed Up and Go test (TUG), Timed 25 ft walk test (T25FW). Unified Parkinson Disease Rating Scale (UPDRS, part III), Freezing of Gait Questionnaire (FOGQ), and Postural Instability and Gait Dysfunction (PIGD) subscore. Safety and tolerability were assessed by monitoring adverse events (AE) reported at each visit and during a telephone follow up one week after treatment initiation.

2.4. Statistical analysis

A sample size of 22 PD subjects was calculated to achieve at least 80% power to uncover an effect size of 0.94 at a significance level of 0.05 for a two-sided test. This effect size corresponds to a mean difference of 14 cm in stride length given that the square root of the within-mean square error is 15. For the data analysis, we estimated frequencies of adverse events, central tendency and variability for demographic characteristics, T25FW, TUG, FOGQ and UPDRS score. Intent-to-treat (ITT) analysis was performed to evaluate the effect of D-ER on changes in T25FW, TUG, FOGQ and UPDRS score using mix-effects models that included both fixed and random subject-effects. All analyses were conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC).

3. Results

3.1. Study participants, demographics and baseline characteristics

A total of 39 subjects signed informed consent at our Movement Disorder Center, 22 subjects were randomized, 12 to placebo-D-ER arm, and 10 to D-ER-placebo arm. Eighteen subjects completed all study visits, 3 subjects discontinued the drug due to adverse events (2 while on D-ER, 1 while on placebo), one withdrew consent after randomization (Fig. 2). The data from 20 participants was included in the statistical analysis. Subject demographics are described in Table 1. The mean age was 67.5 years, average disease duration of 9.7 years and levodopa daily dose of 612 mg. Participants enrolled in the study had significant disability: mean UPDRS part 3 was 36.6 ± 14.1 with gait dysfunction PIGD subscore of 7.9(±4.7), mean FOGQ 14.1±5.3, TUG = 18.5 s (±9.5) and T25FW = 13.2 s (±6.9). No significant differences in baseline characteristics were seen between the 2 treatment arms.

3.2. Primary outcome measures: stride length and gait velocity

The changes in velocity and stride length from baseline are illustrated in Table 2. There was no significant difference between the 2 phases in change in gait velocity (−0.01 m/s, p = 0.63) or stride length (−0.06 m, p = 0.17) at 1-hour after drug administration or at 4 weeks. In the D-ER phase, gait velocity was 0.89 ± 0.33 m/s while in the placebo phase was 0.93 ± 0.27 m/s. The stride length was also similar between phases: 0.96 ± 0.38 m for D-ER versus 1.06 ± 0.33 m for placebo. There was a trend toward improvement in the motor UPDRS (−2.81, p = 0.16) and FOGQ (0.95 p = 0.16) after 4 weeks of D-ER treatment.

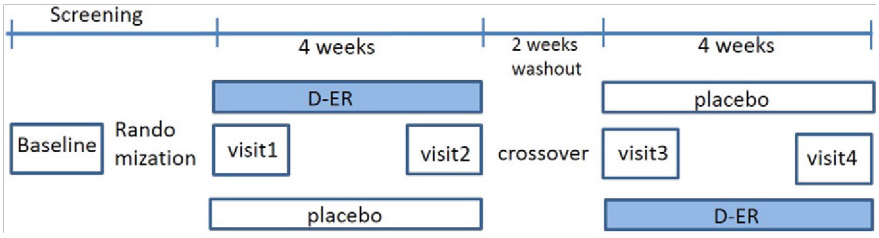

Fig. 1. Study timeline after screening, participants were randomized 1:1 to receive either placebo or D-ER for 4 weeks, with a 2 week washout.

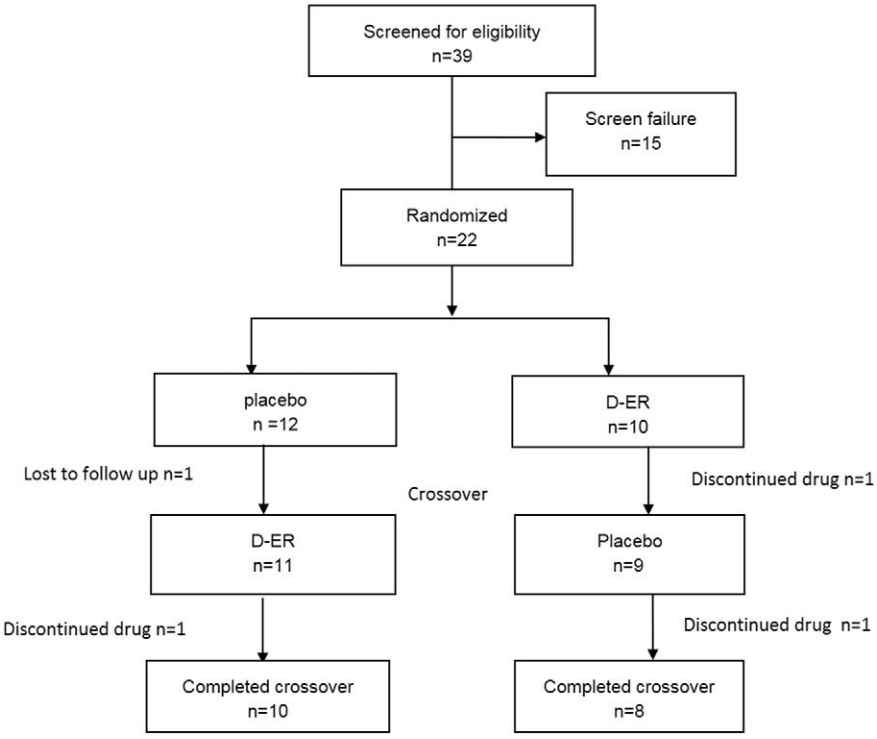

Fig. 2. Consort diagram.

3.3. Safety and tolerability

Dalfampridine–ER was well tolerated in the subjects with PD. The main concern from previous clinical experience with dalfampridine were seizures, in our cohort of PD patients no seizures were reported. Three subjects withdrew from the trial due to adverse effects, two while on drug and one while on placebo. The most frequent side effects were dizziness (18.1% in D-ER and 4.5% in placebo,), worsening of balance in D-ER group (9%) and urinary tract infections (D-ER −9%, placebo 4.5%). Infrequent (b5%) non-serious adverse events reported while on D-ER are: fatigue, peripheral edema, sleepiness, constipation, weakness, worsening tremors, asthenia.

Table 1

Sample characteristics at baseline.

			Treatment sequence				
	All (n = 20)		Placebo - D-ER (n = 11)		D-ER - Placebo (n = 9)		
	N	%	N	%	N	%	p-Value
Gender							0.094
Female	4	20.0	4	36.4	0	0	
Male	16	80.0	7	63.6	9	100.0	
	Mean	SD	Mean	SD	Mean	SD	
Age	67.5	8.7	67.4	10.8	67.6	5.9	0.962
Disease duration	9.7	5.2	9.2	4.5	10.2	6.1	0.667
UPDRS1	13.5	4.3	12.6	4.3	14.4	4.4	0.364
UPDRS2	20.7	6.3	20.9	7.1	20.3	5.4	0.844
UPDRS3	36.6	14.1	35.8	16.3	37.6	11.7	0.791
UPDRS4	5.1	3.1	5.4	3.7	4.8	2.2	0.681
TUG	18.5	9.5	18.2	8.8	18.9	11	0.87
T25_FW	13.2	6.9	12.3	4.6	14.5	9.1	0.487
FOGQ	14.1	5.3	13.2	6.4	15.2	3.8	0.408

3.4. Secondary analysis

A post-hoc analysis revealed a subgroup of participants (n = 10) that had significant improvement in their UPDRS (N3 points) at 4 weeks after D-ER treatment that was not associated with a change in gait kinematics. Analysis of the responder group (UPDRS increase of N3 points) demonstrated a concomitant improvement in the PIGD subscore (Table 3). Ten of 18 subjects that completed the study showed significant improvements with D-ER in motor UPDRS (5.9 ± 2.6, p = 0.03), PIGD sub-score (gait score; 2.8 ± 0.9, p = 0.006). In this group, freezing of gait was also significantly improved on the FOGQ (−2.1 ± 0.8, p = 0.01).

4. Discussion

Walking impairment and axial symptoms represent a therapeutic challenge in PD [14]. Previous studies have shown that non-dopaminergic pathways are likely involved in gait disturbances in PD and treatments addressing this aspect are lacking. Preclinical data of D-ER has suggested a potential to modulate the gait networks in a variety of neurological disorders, including PD, [13,14] with positive data in both multiple sclerosis and stroke [11,12,15]. This is the first randomized trial to aimed to determine the safety and tolerability of D-ER in a PD population as well as the effect on gait parameters in subjects with freezing of gait.

The primary outcomes of change in gait velocity and stride length did not show a difference in the treatment phase when compared with placebo. Contrary to open label studies [14] D-ER did not improved the gait velocity, stride or freezing 4 weeks after the treatment.

While gait kinematics were not improved by the D-ER, there was a tendency for UPDRS improvement in the treatment arm. We performed a responder analysis examining data from

subjects with a UPDRS improvement N3 points, and identified 10 subjects that showed a clinically significant improvement in motor UPDRS (5.9 ± 2.6, p = 0.03) after 4 weeks of D-ER treatment. While both placebo and D-ER showed improvement at 1 h after intake, only the D-ER maintained the benefit at 4 weeks. Interestingly the gait parameters, TUG, stride and velocity were not improved in this subgroup suggesting that D-ER may have effects on motor symptoms other than gait.

In the responder group the gait velocity and stride length did not change, however the PIGD sub-score improved with 2.8 ± 0.9 points (p = 0.006) and FOGQ decreased with 2.1 ± 0.8 points (p = 0.01).

Table 2

Mean changes in outcome measures from pre-treatment by follow-up time and treatment in whole sample (n = 20).

		Mean change from pre-treatment, multivariable-adjusted [a]			
		Placebo	D-ER	D-ER vs. Placebo	
Outcome	Follow-up time	estimate (se)	estimate (se)	estimate (se)	p
Change in velocity (m/s)	1 h	0.05 (0.03)	0.08 (0.03)	0.03 (0.03)	0.380
	4 weeks	0.05 (0.03)	0.03 (0.03)	−0.01 (0.03)	0.637
Change in stride_length	1 h	0.004 (0.04)	0.01 (0.04)	0.004 (0.04)	0.923
(meters)					
	4 weeks	0.05 (0.04)	−0.01(0.04)	−0.06 (0.04)	0.174
Change in UPDRS part3	1 h	−3.50 (1.58)	−3.07 (1.57)	0.42 (1.98)	0.831
	4 weeks	0.20 (1.58)	−2.61(1.64)	−2.81 (2.00)	0.167
Change in TUG	1 h	−2.64 (2.13)	−2.64 (2.13)	0.005 (2.38)	0.998
(seconds)					
	4 weeks	−2.42 (2.13)	0.43 (2.24)	2.85 (2.45)	0.250
Change in T25FW	1 h	−2.61 (1.60)	−0.14 (1.60)	2.47 (1.64)	0.139
(seconds)					
	4 weeks	−2.60 (1.60)	0.08 (1.67)	2.69 (1.69)	0.119
Change in FOG	1 h	−0.06 (0.57)	−0.01 (0.57)	0.05 (0.65)	0.939
	4 weeks	−0.96 (0.57)	−1.92 (0.60)	−0.95 (0.67)	0.162

a Adjusted for age, sex, disease duration, treatment period and baseline score if applicable.

The study has several limitations. The small sample size may have limited the ability to detect small but clinically significant changes in the stride and velocity Subjects with PD experience FOG episodes that are unpredictable, highly variable, and dependent on external factors such as levodopa dosage, concomitant medication, stress, fatigue and cognitive status. FOG is a heterogeneous condition and some patients may have been pseudo ON freezer if levodopa was not titrated high enough. Another important limitation is the absence of a dose-finding study for patients with PD - we have relied on the dose considered safe and efficacious in MS population.

Also, our study did not take into consideration the cognitive aspects to further differentiate the freezing episodes.

In spite of these limitations the study is important since it demonstrated that D-ER is safe to administer in an older PD population. No serious adverse events such as seizures were seen during the trial. The most common side effects were dizziness, balance loss, fatigue and nausea. Even though no significant changes in the velocity and stride length were seen, in a subgroup of patients a change was detected in the UPDRS wherein the effect size was significant. Interestingly this was accompanied by a significant improvement in PIGD subscore and FOG. Due to the limited sample size, we cannot determine the profile of patients with PD who will respond to D-ER. Larger studies that test higher dosages will better address this question.

Table 3

Mean changes in outcome measures from pre-treatment by follow-up time and treatment in responders (n = 10).

		Mean change from pre-treatment, multivariable-adjusted			
		Placebo	D-ER	D-ER vs. Placebo	
Outcome	Follow-up time	estimate (se)	estimate (se)	estimate (se)	p
Change in velocity	1 h	−0.007 (0.07)	0.02 (0.07)	0.03 (0.04)	0.455
	4 weeks	−0.003 (0.07)	0.004 (0.07)	0.007 (0.04)	0.875
Change in stride length	1 h	−0.03 (0.09)	−0.01 (0.09)	0.02 (0.053)	0.658
	4 weeks	−0.01 (0.09)	−0.01 (0.09)	0.002 (0.053)	0.976
Change in UPDRS part 3	1 h	−7.03 (3.16)	−6.17 (3.16)	0.85 (2.67)	0.751
	4 weeks	−3.13 (3.16)	−9.07 (3.16)	−5.94[a] (2.67)	0.035
Change in PIGD	1 h	−0.57 (1.00)	−2.65 (1.00)	−2.07[a] (0.95)	0.039

	4 weeks	−0.17 (1.00)	−3.05 (1.00)	−2.87[a] (0.95)	0.006
Change in TUG	1 h	−4.43 (4.13)	−4.54 (4.13)	−0.11 (2.00)	0.955
	4 weeks	−2.31 (4.13)	−1.45 (4.13)	0.85 (2.00)	0.674
Change in T25FW	1 h	0.16 (1.61)	−1.31 (1.61)	−1.48 (1.43)	0.311
	4 weeks	−0.93 (1.61)	−0.27 (1.61)	0.65 (1.43)	0.655
Change in FOG	1 h	−1.64 (0.99)	−1.42 (0.99)	0.22 (0.82)	0.791
	4 weeks	−2.54 (0.99)	−4.72 (0.99)	−2.17[a] (0.82)	0.014

a Adjusted for age, sex, disease duration, treatment period and baseline score if applicable.

Authors' roles

1) Research project: A. Conception: CCL, FBN, CS; B. Organization: CCL, FBN, EFF, CS; C. Execution: CCL, GN, EFF, CS;

2) Statistical Analysis: A. Design CD, CCL, CS; B. Execution: CD; C. Review and Critique: EFF, CD;

3) Manuscript: A. Writing of the first draft: CCL; B. Review and Critique:

GN, CD, FBN, EFF, CS;

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