SINEMET IN AMYOTROPHIC LATERAL SCLEROSIS AND PRIMARY LATERAL SCLEROSIS

Protocol Number: Sinemet-001

Sponsor: Washington University

Version 1.1, 03/13/2019

Project Title:

Carbidopa/levodopa for Spasticity in Amyotrophic Lateral Sclerosis and Primary Lateral Sclerosis Patients

Background

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting motor neurons. Clinically, ALS manifests with lower motor neuron signs (weakness, atrophy, fasciculation) and upper motor neuron signs (weakness and spasticity). Primary lateral sclerosis (PLS) is similar, however it has only upper motor neuron manifestations. ALS can present initially in any body segment, with asymmetric limb weakness being the most common presentation. From initial presentation, the disease continues to progress to affect other limbs or bulbar (facial) musculature in a pattern without remissions or exacerbations. ALS eventually progresses to effect the respiratory and bulbar musculature leading to life-threatening respiratory failure and dysphagia (difficulty swallowing). The median survival time from diagnosis is 3-5 years. PLS follows a similar progression affecting various body sites, but generally progresses more slowly. Current treatments for ALS are limited, with only riluzole being shown to have effect on survival. Edaravone has been shown to slow functional deterioration in some ALS patients.

There is also a lack of symptomatic treatments for ALS and PLS patients. Spasticity in particular can become severe enough in some patients to be debilitating causing chronic pain and reducing patient's functional capacity. These patients can have limited response to medications currently indicated to treat spasticity such as baclofen and tizanidine.

Anecdotally, there is evidence levodopa, a precursor to dopamine, can improve spasticity in some ALS/PLS patients with severe spasticity. Carbidopa-levodopa (Sinemet), a combination medication that improves the efficacy of levodopa, is a mainstay of treatment of Parkinson's disease making it interesting that it might have an effect in ALS and PLS patients. In Parkinson's disease patients, carbidopa-levodopa markedly improved patients' rigidity. At the extreme spasticity that can be seen in ALS and PLS, spasticity and rigidity are difficult to distinguish.

Motivated by the success of dopaminergic drugs in treating rigidity associated with Parkinson's disease, some neurologists have used carbidopa-levodopa to attempt to improve spasticity in ALS and PLS patients. However, data on the efficacy of carbidopa/levodopa is limited. In unpublished data at this institution (Table 1) carbidopa-levodopa reduced spasticity and improved function in about half of the ALS and PLS patients that received the drug. Given the limited data and potential to improve the quality of life of these patients, the effectiveness of carbidopa-levodopa in ALS and PLS patients with severe spasticity should be studied. Our hypothesis is that administration of carbidopa-levodopa will improve spasticity in ALS and PLS patients.

Objectives

1. Determine the effect of carbidopa-levodopa on spasticity in ALS and PLS patients by a patient reported outcome measure.
2. Determine the effect of carbidopa-levodopa on objective motor function in patients with ALS and PLS.

Significance

ALS and PLS are neurodegenerative diseases of the motor tract that markedly reduce patients' function. In addition to the lack of curative therapies, there is a lack of symptomatic treatments. Spasticity is a key symptom of ALS and PLS that causes pain and limits patient function. The potential for carbidopa-levodopa to improve spasticity in these patients is intriguing. If carbidopa/levodopa is effective in reducing spasticity in these patients, they could have improvement in their functional status.

Research Plan

Design: This study is an interventional, placebo-controlled, single site, double-blind randomized crossover clinical trial. Identified participants will be randomized to receive either placebo or carbidopa-levodopa for a period of three weeks before crossing over to the other arm of the study. The two periods will be separated by a one day washout period. Below is a schematic showing examples of the randomized treatment periods. Where A represents a 3 week treatment period with carbidopa-levodopa and B represents a 3 week treatment period with placebo.

Participant 1: A->washout day->B

Participant 2: B->washout day->A

Subjective data will be collected weekly via a instruments measuring spasticity, pain, and spasm.Objective data will be collected at enrollment and at the end of each three week period via a study visit. The Columbia Suicide Severity Rating Scale (CSSR-S) will also be performed at enrollment and at the end of each three week period during study visits, as suicidal ideation is a potential serious side effect of the drug. The study team will review the responses to the CSSR-S immediately during the study visit, and if a participant answers "yes" to any of the questions, the study PI will be notified immediately. Any adverse events or side effects will be discussed at each study visit. Additionally, participants will be contacted by the study coordinator by phone one week after the first visit and one week after the participants cross over to the other treatment group to assess for any side effects.

Study Participants: Participants will be identified by chart review of patients with a diagnosis of ALS or PLS with spasticity who are currently participating or have participated in clinical research at this institution. These patients will be contacted at the phone number recorded in the electronic medical record and asked about their interest in participating in the study. A study visit will then be scheduled where consent for enrollment will be obtained.

Inclusion Criteria: Criteria for inclusion in this study include diagnosis of ALS or PLS, age greater than 18 years, and clinically significant spasticity.

Exclusion Criteria: Participants currently taking carbidopa-levodopa or with known hypersensitivity of any component of carbidopa-levodopa, narrow-angle glaucoma, current use of a non-selective monoamine oxidase inhibitor (MAOI), a history of malignant melanoma or suspicious skin lesions, depression, suicidal ideation, psychosis, myocardial infarction, ventricular arrhythmia, severe cardiopulmonary disease, uncontrolled hypertension, asthma, renal disease, hepatic disease, endocrine disease, history of peptic ulcer, or who are pregnant and/or breastfeeding will be excluded due to risk of administration of carbidopa-levodopa. Current participation in another interventional study will also exclude participants from enrolling in this study.

Randomization: The randomization of intervention sequence will be predetermined at the onset of the study and maintained by the study coordinator. At the time of consent, each participant will be assigned the randomly generated sequence of interventions.

Intervention: The study medication of carbidopa-levodopa and placebo will be prepared at the time of study initiation according to the randomization schedule. The intervention medication will be identified as drug 1-1, 1-2, 2-1, 2-2, 3-1, etc. according to the participant number and time period. The study medication and placebo will be obtained from the research pharmacy at Washington University in St. Louis. Each capsule of carbidopa-levodopa in this study will be equivalent to half of a standard carbidopa-levodopa 25/100mg tablet. Participants will take one capsule three times a day for the first week of the study period, increasing to two capsules three times a day for the remainder of the study period. Placebo capsules will be administered in the same way.

Measurement: The outcome measurements for this trial will be of subjective and objective measures of spasticity, pain, spasm, and functional capacity. The primary outcome of this study will be patient-reported symptoms on a numerical rating scale assessing spasticity severity . This scale will be administered at enrollment and weekly during the study.

Secondary outcomes measures of this study will be subjective and objective measures of pain, spasm, patient motor function, and spasticity. Participant symptoms of pain and spasm will be assessed via weekly administration of a numerical rating scale of pain and spasm. Patient strength and spasticity will be assessed on the MRC and Ashworth scale. Lower extremity function will be assessed by the Timed Up and Go (TUG) and 10 meter walk tests. These assays will be repeated twice at each study visit. Upper extremity function will be assessed by the 9 Hole Peg Test. This test will be repeated twice per arm at each visit. The Columbia Suicide Severity Rating Scale will be performed at enrollment, and repeated at each visit.

Blinding: As described above, the intervention sequence for each patient will be known only to the study coordinator. The participants and those evaluating the participants at each study visit will be blinded to the identity of the drug the participant has been taking.

Participant Schedule Summary: Participation in this study will last for 6 weeks from the initial study visit. At the initial study visit, the participant's vital signs will be taken and the participant will undergo a neurological exam. Following this, the participant will complete the outcome measures as described above. The participant will leave with three weeks of the assigned study medication or placebo. At the end of each week, the participant will complete the spasticity, pain, and spasm numerical rating scales at home. At the end of the third week, the participant will return for a research visit where the exam and outcome measures will be repeated. The participant will cross over to the other treatment arm, and the above process will be repeated. After the second three week period, the participant will come in for a final assessment. At that point the participant's role in the study will be concluded. At each visit, potential side effects will be discussed. Over the course of the study, participants will be called by phone one week after the first visit and one week after the second visit to assess for side effects

Statistical analysis: The primary outcome data will be assessed for normality. If the data is normally distributed, analysis will be performed using ANOVA to compare the baseline and two treatment groups. Further testing for differences between groups will be carried out using the Paired-samples T-test. If the data is not normal, the non-parametric Kruskal-Wallis one way analysis of variance followed by the

Mann-Whitney U test will be used. As to the secondary variables, the data from the pain and spasm numerical rating scales will be analyzed like the spasticity data described above. The time data collected by the TUG, 10 meter walk, and 9 Hole Peg Tests will be analyzed via ANOVA, with further testing between groups performed by the Paired-samples T-test. The Ashworth scale and MRC will be compared between groups using Kruskal-Wallis one way analysis of variance followed by the Mann-Whitney U test as indicated. These non-parametric tests will be used as the Ashworth and MRC data will likely not be normally distributed.

As for sample size, given the preliminary data, we expect the intervention to have a moderate to moderate-high effect. Thus with α=0.05, power=0.07, and expected effect size of 0.7, the required sample size is 15 participants. This number is total given this is a paired analysis with the patients serving as controls for themselves.

Data Management:

Each participant will be given a coded ID number, and the spreadsheet containing the code correlating the patient's name with their study number will be kept on an encrypted, password-protected document (known only by members of the research team), which is behind the Washington University Department of Neurology firewall (accessible only by those with a department of Neurology account). Data collected during this study will be stored in RedCap.

Potential Benefits: In a case series of patients with ALS or PLS who have received carbidopa-levodopa at the Washington University School of Medicine Neuromuscle clinic, about one half have reported improvement in their symptoms of spasticity. These improvements have ranged from feeling less tightness, to improved gait and manual dexterity. Given the limitations of this data and the apparent ineffectiveness in some patients, no benefit is certain. Participants will be provided with a $50 gift card for their time and effort. Parking validation will also be provided for study visits.

Potential Risks: The side effects most commonly associated with carbidopa-levodopa are diarrhea, orthostatic hypotension, and somnolence. Other rare adverse effects include hallucinations and dyskinesias. The dose of carbidopa-levodopa to be used in this study is commonly used in the Parksinon's disease patient population and is well tolerated. Additionally, the titration from the equivalent of one half of a 25/100mg tab to the equivalent of a full tab over a week should reduce the incidence of side effects.

Adverse Events: Participants in this study will be informed of the possible adverse effects of the medication and instructed to call the study coordinator if they begin to exhibit any of these symptoms. In particular, at each study visit and during the phone calls after the first and second study visits, the participants will be asked about symptoms of suicidal ideation, dyskinesia, and neuroleptic malignant syndrome among other possible side effects..All adverse events will be reviewed monthly by the study PI.

Patient	Age	Sex	Duration of Dz (years)	Diagnosis	Site of onset	Symmetry	Parkinsonism	Sinemet Response/Dose	Response Grade
1	69	F	8	PLS	RLE->RUE	symmetric	No	Yes, 25/100 TID	1, improvement in spasticity
2	51	F	20	PLS	BLE->bulbar	symmetric	No	Yes, 25/250 TID	2, improvement in spasticity, decreased fall frequency
3	63	M	4	PLS	RLE->bulbar	symmetric	No	No, 25/100 TID	0
4	63	M	21	PLS	Diffuse	symmetric	No	No, 25/100 TID	0
5	75	M	20	ALS with Parkinsonism	BLE	symmetric	Yes (B, Mf)	Yes, 25/100 TID	2, Improved manual dexterity and overall movement
6	69	M	4	ALS	LLE	asymmetric	No	Yes, 25/100 TID	2, Improved gait
7	83	F	6	ALS	RLE->RUE	asymmetric	yes (R)	No, 25/100 TID	0
8	74	F	8	ALS	bulbar	Symmetric	No	Yes, 25/100 BID	2, improved dexterity in upper limbs

Table 1. Preliminary data of the use of carbidopa-levodopa in patients with ALS or PLS

Site of onset key: RLE-right lower extremity, RUE-right upper extremity, etc.

Parkinsonism Key: R=rigidity, B=bradykinesia, Mf=masked facies

Response Grade Key: 0=no response, 1=mild subjective or objective improvement, 2=moderate subjective or objective improvement, 3=marked subjective or objective improvemt