Randomized, double-blind, placebo-controlled crossover study to validate finger tapping tasks for the quantification of levodopa/carbidopa effects in Parkinson*s Disease patients.

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Primary ObjectivesAssess whether the finger tapping task endpoints:• Differentiate between ON and OFF states in PD patients• Correlate with the MDS-UPDRS part III total score• Differentiate between placebo and levodopa/carbidopa treatmentSecondary...

Ethical review	Approved WMO
Status	Completed
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON49757

Source
ToetsingOnline

Brief title
Validation of finger tapping in PD patients

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR funded study

Intervention

Keyword: Finger Tapping Task, Parkinson's disease

Outcome measures

Primary outcome

Pharmacodynamic endpoints

1. AFTT

2. Repetitive finger tapping

3. MDS-UPDRS III

Secondary outcome

N.A.

Study description

Background summary

Prolonged dopamine (DA) replacement and DA agonist therapy for Parkinson*s disease (PD) is associated with unwanted motor fluctuations. These motor fluctuations tend to occur when DA medication is wearing off, referred to as ON and OFF states. ON state is characterized by stable motor functioning at the medication*s optimal efficacy level. OFF state is characterized by recurring parkinsonian symptoms [1]. These motor fluctuations have a sudden or slow onset [2]. Early in the treatment process, OFF states are predictably linked to decreased DA plasma concentrations, however they can become unpredictable when DA treatment is continued over the years [2].
Drawbacks of Current Clinical Endpoints. PD severity is assessed by the Unified Parkinson*s Disease Rating Scale (UPDRS) and its Movement Disorder Society (MDS-UPDRS)-revised version. Currently, the MDS-UPDRS is the *gold standard* in clinical studies on PD. The MDS-UPDRS is a four-part scale assessing (i) non-motor experiences of daily living, (ii) motor experiences of daily living, (iii) motor examination and (iv) motor complications. The

MDS-UPDRS part III is often used to monitor therapeutic efficacy by assessing motor function improvement in response to dopaminergic treatment or rate of progression of motor function decline over time. However, as motor symptom severity assessment occurs via observer ratings, the scale*s applicability poses certain disadvantages. First, MDS-UPDRS assessment can be subject to varying inter-rater reliability [3]-[5]. Second, patient visits and MDS-UPDRS' examinations are time consuming and costly. Lengthy assessments are not feasible when examining treatment effects of fast-acting dopaminergic agents. Third, clinician-based rating scales lack sensitivity to precisely monitor motor fluctuations throughout a day. Currently used patient reports and diaries can be subject to recall bias or faulty self-assessment [4]. Taken together, there is a need for a shorter and more reliable tool to assess dopaminergic treatment effects.

Touchscreen based Alternate Finger Tapping. The alternate finger tapping task (AFTT) is a short but sensitive test that differentiates between PD patients and healthy controls. Additionally, the test can be used to detect ON versus OFF states [6]-[11]. The test can be used to quantify symptoms of bradykinesia, which is most responsive to dopaminergic treatment. Commonly used aspects to quantify finger movement are the velocity, accuracy, total number of taps, and the inter-tap interval. These clinical endpoints are related to the medication state and the disease severity state. In addition, the variations of the AFTT show good correlations with the MDS-UPDRS part III [7], [8].

Initially, arcade buttons were used in AFTT study setup [12]. This method has been shown to detect ON/ OFF motor fluctuations [12]. However, an in-house validation attempt failed at replicating these results. The experiment*s failure is likely attributable to the configuration of the study. Arcade buttons were found to be difficult for PD patients to press and while the total number of taps can be measured, errors cannot be precisely assessed. One advantage of touchscreens is that they are more sensitive to tap accuracy, and are not dependent on the strength by which the subjects press the screen. In turn, the touchscreen based interface can more efficiently and reliably quantify PD upper limb motor movement and medication fluctuations than arcade button setups. Therefore, a touchscreen-based setup is more appropriate to use in future trials. As a future perspective, touchscreens are increasingly available and potentially remote patient monitoring will become more feasible. Taken together, there is a need for a validated, sensitive, and short test to assess dopaminergic treatment effects. Literature suggests that finger tapping tasks would be suitable for this purpose and would provide an additional pharmacodynamic measure, which is shorter in duration than the gold standard MDS-UPDRS part III. In this validation study, we chose a touchscreen based AFTT and a goniometer since this is likely able to provide sensitive data regarding tapping accuracy and speed and is not dependent on the strength by which the PD patients can press the screen. The current aim of the study is therefore, to assess whether the various finger tapping tasks is a sensitive measure in discriminating between ON/OFF states, is responsive to dopaminergic (i.e. levodopa/carbidopa) treatment and correlates with the MDS-UPDRS part III score.

Study objective

Primary Objectives
Assess whether the finger tapping task endpoints:
• Differentiate between ON and OFF states in PD patients
• Correlate with the MDS-UPDRS part III total score
• Differentiate between placebo and levodopa/carbidopa treatment
Secondary Objectives
• Evaluate inter- and intra-subject variability of each endpoint of the finger tapping tasks
• Evaluate user satisfaction of the AFT task and the goniometer

Study design

This is a randomized, double-blind, placebo-controlled, two-way crossover study in PD patients with recognizable OFF episodes. Patients come to CHDR for two treatment periods, each consisting of 2 days with 1 overnight stay. Between treatment periods there is at least a one-week washout period. A maximum washout of 3 weeks is allowed. Subjects are randomized 1:1 to one of the two treatment sequences (either levodopa/carbidopa, followed by placebo or the other way around). Subjects should withhold their own antiparkinsonian medication in the evening prior to treatment in both treatment periods. Several times prior and after dosing, finger tapping tasks and the MDS-UPDRS part III will be performed.

Intervention

Levodopa/carbidopa 100/25 mg, over-encapsulated oral tablets or placebo.

Study burden and risks

Levodopa/carbidopa 100/25 mg is a registered product and its side effects are known. The most common side effects of are: dyskinesia, lack of appetite; headache, paresthesia, muscle cramps, psychological disorders such as hallucinations, confusion, daytime sleepiness, sudden sleep attacks, dizziness, nightmares, insomnia and depression; chest pain, asthenia, heart palpitations, orthostatic hypotension (especially when initiating treatment); dyspnea, gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, dry mouth, dyspepsia). Patients that already use levodopa, or have used it in the past, are included in this study, so side effects are expected to be limited and/or known.
Even though the goal is to provide patients with a levodopa/carbidopa dose that most closely matches their usual morning dose of Parkinson*s medication, there is a risk of slightly under- or overdosing. This can lead to a prolonged OFF or partial ON state, or dyskinesia. This is uncomfortable, but transient and harmless.

On Day -1 of both treatment periods, patients are asked to withhold their usual anti-Parkinson medication overnight. In the morning of Day 1 they will receive the study treatment (placebo or levodopa/carbidopa). Due to withholding of the medication, patients are expected to be OFF in the morning of Day 1. This is characterized by increased Parkinson*s symptoms and generally perceived as uncomfortable. Moreover, patients can experience some difficulty in returning back to their normal disease state in the days thereafter.
There are no expected benefits for patients by participating in this study.

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Aged 20-69 years, inclusive at screening.
2. Clinical diagnosis (confirmed by a neurologist) of PD and classified by the

investigator as Hoehn & Yahr stage I-III in the ON state.
3. Subject has self-described motor fluctuations and recognizable OFF periods.
4. Taking oral anti-Parkinson medication and willing to withhold medication overnight for study purposes.
5. Known to be levodopa responsive, either by current use or historical use of levodopa.
6. Willing and able to maintain stable doses and regimens for all medications, herbal treatments and dietary supplements from the screening visit through the last study visit.
7. Negative urine tests for selected drugs of abuse. However, positive urine drug screen for Parkinson*s disease related medication is allowed at the discretion of the PI.
8. Willing and able to abstain from alcohol 24 hours prior to each CHDR visit. Negative alcohol breath test at screening and pre-dose.
9. Must be capable to communicate in the Dutch language.
10. Signed informed consent prior to any study-mandated procedure.

Exclusion criteria

1. History, signs or symptoms suggesting the diagnosis of secondary or atypical parkinsonism.
2. Previous intolerance, potentially relevant interaction of co-medication with or contraindication to levodopa and/or carbidopa.
3. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
4. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
5. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
6. Last dosing in a previous investigational drug study within 3 months prior to first dosing of this study.
7. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
8. Female patients who are pregnant, trying to become pregnant, or nursing

(lactating) an infant.
9. Having a levodopa equivalent dose of the morning medication that exceeds 500 mg.
10. Subjects that test positive for a SARS-CoV-2 infection
11. Subjects with a BMI > 30 and/or cardiovascular, respiratory or immune system disorders

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-07-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SINEMET 125, tabletten
Generic name:	Levodopa/Carbidopa 100/25 mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	09-03-2020

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26165
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000686-16-NL
CCMO	NL73068.056.20

Study results

Date completed:	05-11-2020
Results posted:	06-10-2022

First publication

14-08-2022