Tryptophan depletion in Parkinson*s disease patients treated with deep brain stimulation of the subthalamic nucleus: effects on mood and motor functions.

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

Summary

ID

NL-OMON41322

Source
ToetsingOnline

Brief title
Tryptophan depletion in PD patients treated with STN DBS.

Condition

- Movement disorders (incl parkinsonism)
- Mood disorders and disturbances NEC

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Prinses Beatrix Spierfonds

Intervention

Keyword: deep brain stimulation, Parkinson's disease, serotonin, tryptophan depletion

Outcome measures

Primary outcome

Our primary outcome measures are changes in mood scales (depression,

(hypo)mania).

Secondary outcome

Secondary outcome measures are

1) the motor scores as assessed through the Unified Parkinson Disease Rating

Scale and the motor component of the reaction time task;

2) impulsivity as assessed through the impulsivity component of the reaction

time task.

3) emotional responsiveness as assessed through the emotional responsiveness

task.

Study description

Background summary

Parkinsons* disease (PD) is a neurodegenerative disorder typically characterized by motor symptoms such as tremor, rigidity and bradykinesia (slowness of movement). These symptoms are classically attributed to a significant loss of the activity of the neurotransmitter dopamine in the nigrostriatal dopamine system. This system is part of the basal ganglia, a set of midbrain nuclei essential for movement. An important nucleus within this circuit is the subthalamic nucleus (STN).

PD patients are initially treated with dopaminergic drugs such as levodopa. However, long lasting levodopa treatment is associated with adverse effects like dyskinesias, motor fluctuations and other problems like hallucinations. In these cases, deep brain stimulation (DBS) of the STN offers the next therapeutic option.

STN DBS significantly improves motor symptoms. Additionally, post-operative dopaminergic medication can be greatly reduced. However, a substantial part of the patients experiences both cognitive and psychiatric side effects caused by the STN DBS. Cognitive decline, psychiatric adverse effects, such as increased impulsivity, depression and (hypo)mania, and even suicide attempts pose a great burden on both the patient and caretakers/family. Research has shown that up to 41% of patients undergoing STN DBS implantation show psychiatric and/or cognitive changes post-operatively.

Different psychiatric and cognitive disorders are generally associated with a dysfunction of the activity of the serotonin (5-hydroxytryptamine, or 5-HT) neurotransmitter system. Research in rats has shown that STN DBS significantly reduces the 5-HT release from the dorsal raphe, the major 5-HT production area in the brain. In humans, the same may occur upon STN DBS: diminished 5-HT levels may consequently lead to depression and other psychiatric disorders.

Additionally, it has been established that in the PD brain, not only the dopamine content is altered, but that 5-HT levels are also reduced. PD patients therefore suffer from a certain *5-HT vulnerability*: due to the diminished 5-HT levels, they are more susceptible to developing depression and other psychiatric and cognitive problems.

Our hypothesis is that STN DBS in PD patients can lead to psychiatric adverse effects through a further decrease in already lowered (vulnerable) 5-HT levels in the PD brain. To elucidate whether STN DBS is indeed the trigger for psychiatric and cognitive problems to arise in the PD patient, we will manipulate the 5-HT levels in PD patients implanted with STN DBS. In order to do this, we will make use of the tryptophan (TRP) depletion method, an established research paradigm. In TRP depletion, the brain is depleted of TRP, the precursor of 5-HT, which consequently leads to lowered 5-HT levels. In both the normal and 5-HT depleted condition, we would like to assess mood- and cognitive parameters of the PD patients both with the STN stimulation on (ON) and off (OFF). This way we can shed more light on the effect of STN stimulation on PD patients with a 5-HT vulnerability on 5-HT related mood and cognitive behavior.

Study objective

Our objective is to assess the effect of TRP depletion on mood and behavior in PD patients treated with STN DBS. By doing, this, we hope to be able to identify risk factors for and mechanisms underlying psychiatric side effects of

STN DBS. Ultimately, we would like to improve STN DBS management and treatment for future PD patients.

Study design

This study will be an intervention study with a placebo controlled, randomized cross-over design.

Intervention

1. Tryptophan depletion vs placebo condition (= no depletion)
2. In both conditions patients will be tested with their DBS stimulator on and off

Study burden and risks

In total, there will be 2 separate days of testing during which the subject will have to stay from 9:00am until 5:00pm. During a testing day the patients will drink an amino acid mixture to accomplish the TRP depletion or a control placebo drink. Blood samples will be taken to check serum TRP levels. The patient will be assessed at 3 time points with short questionnaires, non-invasive physical examination and a short reaction time task and emotional responsiveness task. Throughout the testing day the subjects are asked to minimize their activity and only under take light activities, e.g. reading, watching movies, taking a walk, etc.

No serious health risks are associated with participation in this study:
- Turning the STN DBS on and off: subjects will experience some degree of motor discomfort due to the temporarily returning PD motor symptoms, but this does not pose a health risk. Importantly, the normal STN DBS parameters are programmed again before finishing the testing day and patients returning home.
- Drinking the amino acid mixture to accomplish the TRP depleted condition has been reported to be safe. Nausea, headache and vomiting are reported in the literature in a very small number of cases (Booij et al., 2005). See also chapter 6, Non-investigational product.

Since the study objective is to assess the effect of TRP depletion on motor symptoms, mood and cognition in PD patients treated with STN DBS, only PD patients implanted with STN DBS can be included in this study. Other comorbidities (e.g. malignancy, infection) are regarded as an exclusion criterion.

Participation in this study does not directly yield any advantages for the subjects. In the long term, however, we hope that study participation will contribute to improving future DBS treatment and management.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must be mentally competent (*wilsbekwaam*)
Subjects must have undergone STN DBS surgery for Parkinson's disease symptomatology ;Age, duration and severity of disease, duration of DBS implantation do not play a role in the selection process.

Exclusion criteria

Head injury
Stroke
Neurological disorders other than PD
Psychoactive medication: antidepressants and antipsychotics (a stable dose of

benzodiazepines will be allowed).
Clinically relevant cognitive decline, operationalized as an Mini Mental State Examination score <24
Current psychiatric symptomatology, operationalized as a Hamilton Depression scale score >16 or a score >2 on any of the MDS-UPDRS section I items.
Current malignancy or infection;Age, duration and severity of disease, duration of DBS implantation do not play a role in the selection process.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-02-2016
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	06-10-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-12-2015
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL46543.068.13