ISRCTN03683971 https://doi.org/10.1186/ISRCTN03683971

The role of striatal serotonergic terminals in L-dopa induced-dyskinesia in Parkinson's disease patients: An in vivo Positron emission tomography (PET) study

Submission date
03/06/2012

Recruitment status
No longer recruiting

Registration date
31/07/2012

Overall study status
Completed

Last Edited
25/08/2016

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Levodopa (Sinemet or Madopar) is the main treatment for Parkinsons disease (PD). In the brain, levodopa is transformed into dopamine, the brain chemical whose levels are reduced in patients with PD. Unfortunately, after a few years of therapy patients develop troublesome involuntary movements known as dyskinesias. It is not clear what causes these involuntary movements and at present, there are few effective cures for treating them once they have developed. In this project we will explore a possible mechanism responsible for the Levodopa-induced dyskinesias. We believe that another brain chemical called serotonin may interfere with the transformation of levodopa into dopamine and this may cause or aggravate these involuntary movements.
At the Cyclotron Building, Hammersmith Hospital in London we perform special types of brain scans which can be used to measure chemical changes within the brain and consequently study the functions of the brain. These scans are called positron emission tomography (PET) scans. In this study we will use a PET scan to evaluate how serotonin affects the production of dopamine in the brain after a single administration of oral levodopa (namely a tablet of Sinemet). This information may help us to treat PD patients with dyskinesias better.

Who can participate?
In this project we are studying patients suffering from Parkinsons disease with and without dyskinesias.

What does the study involve?
In this study two groups of PD patients will be studied: PD patients suffering from dyskinesias and/or motor fluctuations and PD patients without dyskinesias and/or motor fluctuations.
The study will be conducted in two parts, and we will ask you to attend the Hammersmith Hospital for a total of 5-7 separate days. All visits will be on a weekday morning, and taxi transport will be provided. According to the type of anti-parkinsonian or other medication you are on, we will ask you NOT to take it overnight or on the morning of your visit.
In the first part, at the first visit we will enquire about the progression of your Parkinsons

disease and your medication history. We will perform a clinical examination to assess the severity of your symptoms (e.g. tremor and stiffness) when you are off medication. This clinical examination is very similar to those you have during Neurology clinic appointments. We will evaluate the presence of depression by asking you to fill in a questionnaire. We will ask you to take a tablet of levodopa and will observe for improvement in your symptoms and perform regular clinical exams (every 15-25 minutes), and note the presence and severity of dyskinesias. This visit will last about one and a half hours.
PD patients with dyskinesias and/or motor fluctuations will also attend a second visit, at which we will ask you to take a tablet of levodopa plus tablets of Buspirone. Buspirone is a medication currently licensed in UK for mild anxiety and has been shown in a previous research study to decrease the level and intensity of dyskinesias. We will observe with repeated clinical examinations (one every 15-25 minutes) how your symptoms and the severity of dyskinesias improve over the next one and a half hours. We expect that you will have less dyskinesia. Some of the results from part one will be compared with the PET scan findings to investigate their relationship with chemical changes within the brain.
In the second part of the research project, we will use PET scans to measure chemical changes within the brain areas known to play a role in PD and in the development of dyskinesias. You will undergo four different types of PET scans on four separate visits. In one of these visits, we will collect a blood sample (10 ml blood sample = two teaspoons) to investigate the presence of a gene related to depression and to serotonin. Each PET scan takes from 1 hour and 20 minutes up to 1 hour and 50 minutes (provided if there are no delays). During this time you will be asked to lie on your back on a couch with your head resting in the scanner. You may listen to music or the radio during the scan. Prior to the scan we will insert a small tube (cannula) into a vein in your arm. This is a simple procedure similar to a blood test. We will inject a small amount of radioactive compound (called a tracer), which is taken up by specific areas of the brain that we intend to investigate. One PET scan will be performed after you have taken a tablet of levodopa given at the hospital site. Another one will be performed after taking both Sinemet and Buspirone. The remaining two scans will be performed in an OFF medication state.
In addition, we will ask you to undergo a magnetic resonance scan (MRI). This provides a detailed structural picture of the brain and does not involve any additional radiation. This scan takes about 15 minutes. We will endeavour to perform this on the same day of one of the PET scans. If you are claustrophobic you may find MRI difficult to tolerate, if so please let us know in advance.

What are the possible benefits and risks of participating?
There will be no direct benefit for you taking part in this study. However, by conducting this study we hope to learn more about dyskinesias in PD and the role of Buspirone. In addition, this information may help us to improve the treatment of these common problems.
The placing of the cannula into a vein may cause some transient, mild discomfort and local bruising. The radiation dose you will receive by having this PET scan is about four times the background radiation dose to which we are all exposed every year simply by living in the UK. Along with other procedures involving radiation (including x-rays), PET scans can be hazardous to an unborn child. If you are a woman of child-bearing age you should not take part in the study unless you are on a reliable form of contraception, and even if this is the case a pregnancy test will be performed before the PET scan.
When you are off medication, your Parkinsonian symptoms, such as difficulty in movement, will be transiently worse. In particular, you may feel stiffer, especially if your Parkinsons disease is well established with stiffness rather than tremor being your main symptom. However, your symptoms will recover to their usual level as soon as you take your usual medication immediately after the PET scan.
You should be aware that there is a possibility that the methods used in this study may produce

an unexpected result that may have relevance for your health. In the unlikely event of this happening, we will discuss this with you and, if necessary, provide any support that you may require, such as arranging follow-up tests and/or treatment.

Where is the study run from?
Hammersmith Hospital, Imperial College London (UK).

When is study starting and how long is it expected to run for?
The study will run from January 2008 to January 2014.

Who is funding the study?
The Michael J Fox Foundation for Parkinson's Research.

Who is the main contact?
Dr Marios Politis
marios.politis@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Paola Piccini

Contact details
DuCane Road
Hammersmith Hospital
Imperial College London
London
United Kingdom
W12 0NN

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
The role of striatal serotonergic terminals in L-dopa induced-dyskinesia in Parkinson's disease patients: a proof of concept study

Study objectives
1. That dyskinetic PD patients will not show significant reduction in levels of integrity of serotonergic striatal terminals in comparison to non dyskinetic PD.
2. That the two groups of PD patients will show significant differences in levels of striatal DA after a single oral dose of L- dopa calculated as 11C-raclopride Δ BP.
3. That within the group of dyskinetic patients there will be a significant positive correlation between severity of dyskinesia, locomotor response and increases of levels of synaptic DA after single dose of L-dopa.
4. That in dyskinetic patients buspirone will attenuate synpatic levels of dopamine generated after administration of L-dopa and reduce dyskinesia severity but not increase parkinsonism.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Hammersmith and Queen Charlotte's & Chelsea Research Ethics Committee, Project Ethics approval: 14 December 2007, Major amendment to ethics approval: 7 November 2008, ref: 07 /H0707/133

Study design
Single center open-label proof of concept

Primary study design
Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please contact marios.politis@imperial.ac.uk to request a patient information sheet

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
Open label use of buspirone together with L-dopa in an aim to alleviate dyskinesias and to study the role of serotonergic terminals in L-dopa induced dyskinesia with PET.

Visit 1: Patients will take tablet of levodopa (Sinemet 275mg, provided at the hospital site). We will observe for improvement in your symptoms and perform regular clinical exams (every 15 - 25 minutes), and note the presence and severity of dyskinesias.

Visit 2: Patients will take tablet of levodopa (Sinemet 275mg, provided at the hospital site) plus tablets of Buspirone (total of 20 to 35 mg depending on your weight). We will observe with

repeated clinical examinations (one every 15 - 25 minutes) how the symptoms and the severity of dyskinesias improve over the next one and a half hours.

In the second part of the research project, PET scans are used to measure chemical changes within the brain areas known to play a role in PD and in the development of dyskinesias.One PET scan will be performed after the patients have taken a tablet of levodopa (Sinemet 275) given at the hospital site. Another one will be performed after taking both Sinemet 275mg and Buspirone. The remaining two scans will be performed in an off medication state.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. Dyskinesias assesments with Abnormal Involuntary Movement Scale (AIMS)
2. Reduction of abnormal dopamine release in the striatum of Parkinson's disease patients as measured with PET

Measured 150 minutes following administration of medication.

Secondary outcome measures
Changes in motor function as measured with Unified Parkinson's Disease Rating Scale (UPDRS) part III motor scale measured 150 minutes following administration of medication.

Overall study start date
01/01/2008

Completion date
01/01/2014

Eligibility

Key inclusion criteria
Parkinson's disease patients and healthy individuals

Parkinson's disease patients
1. Age between 50-80
2. Were diagnosed with PD according to the UK PD Society Brain Bank criteria (Hughes et al., 1992)
3. On L-dopa treatment during the time of the study
4. Responsive to L-dopa with more than 25% reductions in Unified PD Rating Scale (UPDRS) part III motor scores
5. More than 6 months on L-DOPA
6. Non-demented [minimental state examination (MMSE ≥ 26]
7. No psychiatric disorders as screened with a structured clinical interview for DSM-IV Axis I Disorders (SCID-I)
8. Do not fail screening for depression [Beck Depression Inventory - II (BDI-II) < 17; Hamilton Rating Scale for Depression (HRSD) < 14]
9. None of the subjects had received anti-depressant therapy in the past or any other medication

with known action on the serotonergic system
10. No more than 1.5 body mass index (BMI) units changes over the last 12 months

Healthy individuals
1. Age between 50-80
2. Non-demented (MMSE ≥ 26)
3. No psychiatric disorders as screened with a structured clinical interview for DSM-IV Axis I Disorders (SCID-I)
4. Do not fail screening for depression (BDI-II < 17; HRSD < 14)
5. None of the subjects had received anti-depressant therapy in the past or any other medication with known action on the serotonergic system
6. No more than 1.5 BMI units changes over the last 12 months
7. Were not on any medication
8. No previous history of neurological or psychiatric illness

Participant type(s)
Patient

Age group
Senior

Sex
Both

Target number of participants
Up to 200 Parkinson's patients to be screened - 36 Parkinson's patients to complete the study.
Up to 100 healthy individuals to be screened - 12 healthy individuals to complete the study.

Key exclusion criteria
Does not meet inclusion criteria

Date of first enrolment
01/01/2008

Date of final enrolment
01/01/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
DuCane Road
London
United Kingdom
W12 0NN

Sponsor information

Organisation
Imperial College London (UK)

Sponsor details
G02 Sir Alexander Fleming Building South Kensington Campus
London
England
United Kingdom
SW7 2AZ

Sponsor type
University/education

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
The Michael J. Fox Foundation for Parkinson's Research (USA)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration