Effect of selective COX-2 inhibition on neuroinflammation in Parkinson's disease.

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To measure in vivo effect on neuroinflammation of treatment with celecoxib, a selective COX-2 inhibitor, in PD using PK111-95 and PET.Celecoxib showed broad utility in animal models of neurodegeneration. Neurochemical effect of the treatment on...

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

Summary

ID

NL-OMON31350

Source
ToetsingOnline

Brief title
COX-2 inhibition in Parkinson's disease

Condition

- Movement disorders (incl parkinsonism)

Synonym
Paralysis agitans. Parkinson.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Int PD Foundation

Intervention

Keyword: Celecoxib, COX-2 inhibition, Neuroinflammation, Parkinson's disease

Outcome measures

Primary outcome

Analysis methods

[11C]-PK111-95 Binding Potential (BP) images will be generated based on a simplified reference tissue model4;13. Cluster analysis will be used to extract and identify a normal brain reference input function for individual PD cases. The reference tissue model will be compared to parametric analysis, using plasma input data and Logan analysis to generate distribution volume images. Pixel-by-pixel analysis will be done using Statistical Parametric Mapping program (SPM2)14. A coupled t-test will be applied to evaluate differences between the two scans. P-value of 0.001, uncorrected for multiple comparisons / 0.05 after correction will be taken for statistical significance.

Secondary outcome

nvt

Study description

Background summary

Local substantia nigra brain stem neuroinflammation mediated by microglial activation has been suggested to play a pivotal role in the pathogenesis of PD1-3. Animal studies have strongly suggested the relevance of microglia activation to the nigral cell death seen in PD patients; however the relation of microglia activation and PD progression in vivo in human PD patients remains unclear.

In vivo activated glial cells in the brain can be measured using the

radiotracer
[C-11]PK11195, a peripheral benzodiazepine ligand, and positron emission tomography (PET)4. Recently, in PD patients increased inflammation was found in the midbrain related to clinical asymmetry and inversely to the degree of striatal dopaminergic dysfunction1. Gerhard et al5 found apart from the mesencephalic increase of [11C]-PK11195 also cortical and basal ganglia regions with increased uptake. They did not find correlation with clinical severity or putamen [18F]-dopa uptake, nor longitudinal changes of microglial activation, suggesting that microglia are activated early in the disease process and levels then remain relatively static.
We recently studied neuroinflammation in PD patients with [11C]-PK11195 PET and found increased tracer uptake in basal ganglia, thalamus and mesencephalon in a pilot group of PD patients, compared to healthy control subjects (see protocol METc 2006.153)

The role of neuro-inflammation in the pathogenesis and clinical course of Parkinson*s disease needs to be further investigated. It may be possible to inhibit further progression of disease with treatment aimed at reducing neuro-inflammation.

Epidemiological data indicates that anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) have a protective effect on Parkinson*s disease 6. Regular intake of nonaspirin NSAIDs but also high doses of aspirin have been associated with a 45 % lower risk of PD in two large cohorts 7.
Increased expression of the enzyme cyclooxygenase-2 (COX-2) and elevated levels of prostaglandin E2 (PGE2) have been implicated in the cascade of deleterious effects leading to neurodegeneration 8. Teismann et al found that COX-2 expression is induced specifically within SNpc dopaminergic neurons in postmortem PD specimens and in the MPTP mouse model of PD during the destruction of the nigrostriatal pathway. A lack of COX-2 but not of COX-1 decreased MPTP neurotoxicity. The selective COX-2 inhibitor rofecoxib blocked ventral midbrain PGE2 production in MPTP injected mice and attenuated neuron and fiber loss, demonstrating the crucial enzymatic function of COX-2 to its neurotoxic effects on dopaminergic neurons8;9.
Until now, anti-inflammatory treatment has only been investigated in animal parkinsonian models. Increased expression of cyclooxygenase type 2 (COX-2) and production of prostaglandin E2 synthesis have been implicated in neurodegeneration in several parkinsonian animal models. Selective inhibition of cyclooxygenase (COX-2) by celecoxib remarkably reduced the microglial cell density in 6-OHDA lesioned parkinsonian rats. At later stages it also prevented further dopamine cell loss10.

Anti-inflammatory treatment with celecoxib showed promising results in rodent models for PD and can be studied safely in patient in vivo using [11C]-PK11195 PET. It will be important to investigate the effect of possible treatments neurochemically in vivo in PD patients and to study whether [11C]-PK11195 PET

provides a sensitive method for evaluation of response in humans.

Study objective

To measure in vivo effect on neuroinflammation of treatment with celecoxib, a selective COX-2 inhibitor, in PD using PK111-95 and PET.
Celecoxib showed broad utility in animal models of neurodegeneration. Neurochemical effect of the treatment on microglia activation in humans will be measured in vivo comparing the PET scans of 10 early stage PD patients before and after one month of treatment. An interim analysis will be perfomred after 5 patients have been investigated. If no effects of intervention are seen the study will be stopped.

This study is meant to be a pilot study which tries to deliver a proof of principle, namely whether neuroinflammation of the brain can be blocked by available medication and whether this can be monitored by the applied radiotracer scans. If a positive result is achieved then a larger study is warranted to investigate longitudinally whether long-term treatment has a positive clinical effect.

Study design

Synthesis of [11C]-PK111-95
[11C]-PK111-95 will be prepared through a reaction of [11C]-methyliodide with (R)-desmethyl-PK11195 with potassiumhydroxide as a base (see Cremers J.E. et al, Nucl.Med.Biol 1992) The product is purified by semi-preparative reversed phase HPLC and meets the requirements of the responsible hospital pharmacist.

Toxicity of PK11195
PK11195 has been used in a clinical trial in daily doses of 200 to 400 mg during 2 weeks, without toxic effect11. With the [11C]-labeled (R)-PK11195 tracer, many studies have been done in humans. The amount of labeled tracer, using 400 MBq with a specific activity of 4000 GBq per mmole, will be 100 nmole, corresponding with 35 microgram of PK11195. Toxic effects of this amount of tracer, being 1/10.000 of the amount used in the clinical trial, have never been demonstrated.

Scanning methods
PET scans using [11C]-PK111-95 will be carried out at the dept. of Nuclear Medicine and Molecular Imaging of the UMCG, University of Groningen.
The subject will be positioned with the head in the centre of the PET camera. To improve the signal-to-noise ratio, a neuroshield will be applied. This consists of a lead protective shield, which will be placed at the level of the shoulders of the subject, to prevent detection of radiation from other body

parts (e.g. the bladder) by the camera. First, a 5 minutes transmission scan will be performed to measure normal tissue absorption of the radiation. Then a dose of 400 (minimum dose of 200) MBq [11C]-(R)-PK11195 will be injected in a bolus followed by 3D dynamic emission scanning during 60 minutes. During the emission scan, blood samples will be taken from a canula in the radial artery using a blood monitor system, for measurement of radioactivity in the blood. Extra blood samples will be taken by hand at 10, 20, 30, 45 and 60 minutes after injection of the tracer, for analysis of tracer metabolites. With the data of the emission scan and blood samples, the binding potential of the tracer to the peripheral benzodiazepine receptor (PBR) in activated microglia can be calculated on a pixel-by-pixel basis.
The tracer is cleared rapidly via the bladder. After the scan, the subject will be asked to empty the bladder to minimize radiation dose.
After one month of treatment, the same PET scanning procedure will be repeated.

Radiation dose
In this study, the R-enantiomer of [11C]-(R)-PK11195 will be used, because this tracer has better affinity for the peripheral benzodiazepine receptor (PBR) in activated microglia than the racemic PK1119512. Radiation dose is calculated using a model in which activity spreads homogenously over the body and no activity is excreted. From the calculation according to the *Formules Shapiro in Radiation Protection* (1992), radiation load for a 75 kilogram subject will be 3,37 *10-3 mSv/MBq. Radiation load of a scan with 400 MBq [11C]-PK111-95 is 1,35 mSv, which is 0.8 times the annual radiation load of natural background radiation (1.7 mSv in the Netherlands). For two PET scans, subjects are exposed to a radiation load of 2,70 mSv. According to the standards of the International Commission on Radiological Protection (ICRP62), the amount of radiation reaches category 2b, minor to intermediate level of risk, 1-10 mSv.

MRI scan
Anatomical T1-weighted MRI scans of the brain will be obtained, for co-registration with the analysis of the PET scan data. MR scans will be made using the 1,5 Tesla machine at the department of Radiology of the UMCG.

Intervention

Treatment
Patients are informed about the possible side effects of the treatment by celecoxib as listed in the *Farmacotherapeutisch kompas 2005* and asked to contact the investigators if any effect is experienced during the treatment. If the drug is not tolerated, treatment will be stopped and the second PET scan will be canceled. Treatment with celecoxib will start the day after the first PET scan and will be stopped the night before the second PET scan.
Regular dosage of celecoxib in clinical practice is 100 to 200 mg twice a day. We will use a dose of 100 mg twice a day. Most common side effects include gastro-intestinal complaints as stomachache, nausea, diarrhea, dyspepsia and

flatulence, and fluid retention with edema. When mild gastro-intestinal complaints occur, patients can receive treatment for stomach protection (the proton-pump inhibitor omeprazol, 20 mg daily during the treatment with celecoxib).

Study burden and risks

Twice half a day for preparation and performance of the radiotracer PET scans. Half an hour for the accompanying MRI scan (once).

The scans do not pose any particular risk.

One month taking of 100mg celecoxib. Possibly unwanted effects like gastrointestinal sigsn and symptoms may occur.

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

Age over 40 yr
No cognitive disturbances
Probable PD according to criteria by Gelb
Early stage Hoehn and Yahr 1-2

Exclusion criteria

Cardiovascular brain diseases
Usage of antiinflammatory drugs
Gastrointestinal ulcers or bleeding

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2007
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine

Brand name:	Celebrex
Generic name:	celecoxib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-03-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
Other	CCT-NAPN-16254
EudraCT	EUCTR2007-001206-24-NL
CCMO	NL16901.042.07