Evaluation of [18F]MC225 to measure P-glycoprotein function in neurodegenerative disease

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This study has been transitioned to CTIS with ID 2024-518865-85-00 check the CTIS register for the current data. Primary objectiveEvaluation of [18F]MC225 to measure the P-glycoprotein function in Alzheimer*s disease, Mild Cognitive Impairment and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Dementia and amnestic conditions
Study type	Observational invasive

Summary

ID

NL-OMON50245

Source
ToetsingOnline

Brief title
[18F]MC225 in neurodegenerative disease

Condition

- Dementia and amnestic conditions

Synonym
neurodegenerative disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: - [18F]MC225, - neurodegenerative disease, - pharmacokinetic modeling

Outcome measures

Primary outcome

Tracer kinetics of [18F]MC225 reflect the BBB P-gp function and will be assessed as outcome measure for P-gp efflux function in different brain regions of interest (ROIs). Those will be compared in between groups of Alzheimer, Parkinson, MCI and healthy volunteers

Secondary outcome

1. [15O]H2O-PET influx curves will be added as variable in the kinetic analysis using PMOD, to assess possible influence of cerebral blood flow. The CBF measures obtained with [15O]H2O-PET will be compared with VT measures of the [18F]MC225 PET scan to see if uptake of [18F]MC225 is influenced by cerebral perfusion rate.

2. Since [15O]H2O-PET is the gold standard for quantitative imaging of cerebral perfusion, the results of [15O]H2O-PET will also be compared with the perfusion part of the MRI VAI sequence. In this way the perfusion MRI can be validated as less invasive method to measure cerebral perfusion and be used in future projects.

3. To compare venous blood samples with arterial bloodsamples, and to validate wheter pharmokinetic modeling with arterial samples could be replaced with less invasive venous samples.

Study description

Background summary

A decrease in P-glycoprotein (P-gp) function is associated with the onset of neurodegenerative disease (1,2). Development of new treatment strategies aim to restore the P-gp function. To measure effect of such therapies, measurement of the P-gp function is necessary. Up until now [11C]verapamil is considered to be the gold standard to measure P-gp function(3,4). However tracer uptake in the brain of [11C]verapamil is too low for adequate measurement of treatment effect, especially of restoring P-gp function. A novel PET tracer to measure P-gp function, [18F]MC225, has the potential advantage of higher brain uptake values at baseline and might therefore able to measure both up- and down regulation P-gp function. (5,6). [18F]MC225 was studied recently in healthy volunteers and showed promising results and a solid method to quantify P-gp function was developed (7). Since the study in healthy volunteers showed promising results, we would like to continue our research of [18F]MC225 under pathological conditions in neurodegenerative disease.

Study objective

This study has been transitioned to CTIS with ID 2024-518865-85-00 check the CTIS register for the current data.

Primary objective
Evaluation of [18F]MC225 to measure the P-glycoprotein function in Alzheimer*s disease, Mild Cognitive Impairment and Parkinson*s disease.

Secondary objectives
1. Evaluation of blood-brain barrier integrity using [18F]MC225 and MRI VAI sequence in Alzheimer*s disease, MCI and Parkinson*s disease.
2. Evaluation of perfusion measurements using both [15O]H2O PET and MRI (DSC, DCE) to simplify the scan protocol in further [18F]MC225 studies.

Study design

60 minute [18F]MC225 PET scans will be performed in 10 Alzheimer patients, 10 MCI patients and 10 Parkinson patients. Prior to the [18F]MC225 PET scan a 10 min dynamic [15O]H2O PET will be performed to measure the effect of cerebral blood flow on the uptake of [18F]MC225 in the brain. For both scansthe PET scans arterial blood sampling is needed to enable kinetic modeling of the [18f]MC225 PET tracer. In addition to the PET scans, every subject will undergo an MRI scan as anatomical reference to the PET scan. One week before the scans a neurological examination (assessment of sensory neuron and motor responses and reflexes) and a mini mental state examination (MMSE) will be performed by a

physician. [18F]MC225 brain uptake in the patient groups will be compared with the brain uptake of healthy volunteers obtained in our previous study.
For this study a duration of two years one year and six months is expected.

Study burden and risks

Participants will not have any direct benefit from the study, but this study will help to evaluate the reliability of [18F]MC225 as a measurement for P-gp function. Such a method aids the development of P-gp inducers, by being able to quantify increases in the function of P-gp.
[18F]MC225: A standard dose of 200 MBq [18F]MC225 with a molar activity > 25.000 GBq/mmol results in an injected mass > 4 µg. Since the total dose administered as a single dose or divided doses in any subject will be far less than 100 µg and is estimated to be <1/100th of the NOAEL and pharmalogically active dose, PET studies with [18F]MC225 can be considered as microdosing studies conform the European Medicines Agency IHC guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, Chapter 7 (EMA/CPMP/ICH/286/1995).
The injected mass of [18F]MC225 is negligible and idiosyncratic reactions are rare to occur for radio PET tracers. Nevertheless, a physician will be available during each injection of the tracer.
Preclinically, both acute toxicity as the Ames test and the cardiovascular safety evaluation were performed to study toxicity of [18F]MC225. Both tests concluded no acute toxicity and mutagenicity of MC225 or [18F]MC225 injection were observed. The methodology and the results of the complete toxicity tests are included in the IMPD, chapter Toxicology. In a recent study of [18f]MC225 in healthy volunteers no side effects were reported.
Dotarem - Dotarem is a gadolinium MRI contrast agent which is used in clinical routine. Adverse events occur in about 0.4% of cases, these events are feeling warmth, brief headache or dizziness. All these events are reversible and disappear immediately after injection.
Adverse effects - Adverse events in this study can be a bruise as a result of the arterial catheter or an allergic reaction to the PET-tracer or gadolinium.

f. Pharmacokinetic considerations
The use of radioactive isotopes in PET imaging implies exposure of patients or healthy volunteers to radiation. The estimated radiation-absorbed doses were calculated by a radiation expert and the total effective dose is 3.3 mSv, which is below the effective annual radiation dose limit of 20 mSv/y. The radiation dosimetry of [18F]MC225 is comparable to that of other regularly used PET tracers. According to international commission of radiological protection (ICRP) Publication 62, the radiation burden of [18F]MC225 belongs to risk category IIb (1-10 mSv, minor to intermediate risk). It can be concluded that [18F]MC225 has a favorable radiation dose profile in humans, allowing multiple PET examinations per year to be performed on the same subject.

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

1. Alzheimer's disease (n=10)
Patients who meet the criteria for Alzheimer*s disease and are mentally competent to give informed consent:
I. Documented cognitive decline
II. Progressive course of cognitive decline
III.Complaints in the following areas
a. memory
b. language
c. visuospatial functions
d. executive functions
IV. Absence of cerebrovascular disease or signs of other neurodegenerative disease except for Alzheimer*s disease.

and show biomarkers positive for AD:
I. amyloid-depositions in the brain showed by low Aβ42 in CSF and/or positive amyloid imaging at a PIB-PET
II. Neuronal damages showed by increased tau/ptau in CSF or;
decreased FDG uptake at the parietotemporal lobe or;
disproportional atrophy of the medial, basal and lateral temporallobes, generalised atrophy and/or biparietal atrophy.

2. Mild Cognitive Impairment (n=10)
Patient is not meeting the criteria for Alzheimers disease, but shows:
- Decline in one or more cognitive domains (showed by a neuropsychological examination)
- No interference of symptoms with daily life
The diagnosis Alzheimer*s disease is made by a multidisciplinary team consisting of psychiatrists, neurologists, psychologists and internists.
- Absence of cerebrovascular disease or signs of other neurodegenerative disease except for MCI
The diagnosis MCI is made by a multidisciplinary team consisting of neurologists, psychologists and internists

3. Parkinson's disease
Symptoms of bradykinesia and one of the following symptoms (25):
- rigidity
- rest tremor
- instability (not related to visual, cerebellar or proprioceptive disorders)
- no other explanation for abovementioned symptoms at MRI
- The diagnosis Parkinson*s disease is made by a neurologist
- Absence of cerebrovascular disease or signs of other neurodegenerative disease except for Parkinson*s disease
The diagnosis Parkinson*s disease is made by a neurologist.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- History of neuropsychiatric disorders such as epilepsy, major depression, or schizophrenia
- Claustrophobia

Use of medication with known P-gp influence, according to the Farmacotherapeutisch Kompas:
- Digoxine
- Dabigatran
- Everolimus
- Verapamil

- Tacrolimus
- Rosuvastatin
- Lercanidipin
- Repaglinide
- Aliskiren
- Aminoglycosides
- Vancomycine
- NSAIDs
- Acyclovir
- Trimethoprim
- Amfotericine B
- Ciprofloxacine
- H2 receptor antagonists
- Methotrexate
- St. John*s Wort
- Loperamide
- Rifampicine
- Carbamazepine
- Fenobarbital
- Fenytoine
- Hypericum
- Primidon

The list contains pharmaceuticals with P-gp influence mentioned in the FK, for other pharmaceuticals, the influence on P-gp will be checked using kennisbank KNMP or Pubmed)

Exclusion Criteria contrast-enhanced MRI:
- Metallic objects or fragments placed in the body
- Artificial metal joints or implants
- Pacemaker
- Clips/Stents in blood vessel
- Claustrophobia
- a history of mastocytosis
- Pregnancy or breastfeeding
- Kidney failure (< 45 ml/min)
- Allergy to MR contrast or dye
- Tattoo (>20cm)

Study design

Design

Study phase: 2

Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2021
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	[18F]MC225
Generic name:	5-(1-(2-[18F] fluoroethoxy))-[3-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propyl]-5,6,7,8-tetr
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Brand name:	[18F]MC225
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Ethics review

Approved WMO Date:	19-01-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-11-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2024
Application type:	Amendment
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
EU-CTR	CTIS2024-518865-85-00
EudraCT	EUCTR2021-005024-37-NL
ClinicalTrials.gov	NCT202100647
CCMO	NL79155.042.21