[18F]MC225-PET: Assessment of the blood-brain barrier integrity and P-glycoprotein function in healthy volunteers,a pilot study

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Translation of [18F]-MC22518 to the clinic to measure P-gp function in healthy volunteers.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON49215

Source
ToetsingOnline

Brief title
[18F]-MC225-PET to assess blood-brain barrier P-glycoprotein function

Condition

- Neurological disorders NEC

Synonym
Alzheimer's dementia, Alzheimer's disease, blood brain barrier dysfunction which is involved in Alzheimer's disease

Research involving
Human

Sponsors and support

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

Siemens;UMCG Healthy Aging Pilot Funding

Intervention

Keyword: Alzheimer, Blood-brain barrier, PET, P-glycoprotein

Outcome measures

Primary outcome

Tracer uptake values in several brain regions of interest (ROIs), representing local BBB P-gp efflux function with and without inhibition of the P-gp function by Cyclosporin-A, to validate the tracer as specific P-gp substrate.

Secondary outcome

1. Arterial sampling will be assessed, and based on advanced kinetic modelling approaches the most suitable scan analysis model with least necessary blood sampling will be chosen for further studies in Alzheimer*s patients and patients diagnosed with MCI.

2. In five subjects a test-retest study will be performed, in order to correct for scan variability

3. A [15O]H2O-PET scan will be performed to measure the effect of cerebral blood flow on the brain uptake of [18F]MC225. If [18F]MC225 uptake proves to be independent of blood flow measures, this extra scan can be left out in further studies.

4. MRI VAI measures of blood-brain barrier integrity will be compared to BBB dynamic P-gp function, to evaluate the influence of microvascular disturbances on tracer uptake

Study description

Background summary

Accumulation of neurotoxic amyloid (Aβ) in the brain is a pathological hallmark of Alzheimer*s disease (AD). Development of new treatment strategies aims to reduce Aβ load in the brain. Transporters at the blood-brain barrier (BBB) are involved in the efflux of neurotoxic substances, and more specifically the transport pump P-glycoprotein (P-gp) has been shown to be involved in Aβ efflux. Up until now [11C]verapamil is considered to be the gold standard to measure P-gp function and it showed decreased P-gp function in AD patients. 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 new developed PET tracer to measure P-gp function, [18F]-MC225, has the potential advantage of higher brain uptake values at baseline and is therefore able to measure both up- and down regulation P-gp function, which is important in measuring the effect of p-gp inducers in future research studies.

Study objective

Translation of [18F]-MC22518 to the clinic to measure P-gp function in healthy volunteers.

Study design

Intervention study in which ten healthy volunteers aged 50-80 will undergo two dynamic [18F]-MC225-PET scans with arterial plasma sampling. Prior to the scan a H2O PET scan will be performed to estimate the cerebral perfusion rate. A MRI with gadolinium contrast as anatomical reference and BBB integrity assessment will be performed. Five of these healthy volunteers will undergo the second dynamic PET scan after administration of Cyclosporin to reach a blocked P-gp state. The remaining five volunteers will undergo a second [18F]MC225 in test-retest setting, in order to correct the validation of [18F]MC225 for variability.

Intervention

1. Administration of radiopharmacon [18F]MC225
2. Arterial and venous plasma sampling
3. Administration of one gift Cyclosporin (registered pharmaceutical) to cause inhibition of p-gp function in five volunteers

Study burden and risks

This study will include healthy adult volunteers. Ten subjects will undergo two

dynamic PET scans in three visits to the department of nuclear medicine and molecular imaging. The visits will take approximately 3-4 hours. During this visit a blood sample will be obtained to measure the renal function (eGFR), since an impaired renal function is a contra-indication for Cyclosporin and gadolinium contrast. Also, a neurological examination will be performed and a mini mental state examination will be scored. Before the PET scans a radial arterial line will be placed by an anaesthesiologist for blood sampling at several predetermined time intervals during the PET scans. [18F]-MC225 will be administered through a line placed intravenously in the elbow. Since for PET tracer studies microdoses of the investigational products are used, no toxicological effects are expected (microdoses are far below the toxicological value of 1.5 µg a day). The subjectis will be exposed at a radiation dose of a maximum of 6.6 mSv in total (minor-intermediate risk classification according to the International Commission on Radiological Protection (ICRP). During the second visit, the healthy subjects will also undergo a gadolinium contrast-enhanced MRI, which is used as anatomical reference and for measurement of blood-brain barrier integrity with MRI-VAI sequence. Five out of these ten subjects will undergo a second [18F]MC225-PET scan after inhibition of the p-gp function using Cyclosporin to validate the tracer specificity.
Since cyclosporin is a registered pharmaceutical with extensive use in clinical practice and side effects of cyclosporin normally only occur in longterm use in high dosages there are no harmful effects expected of the administration of one gift CyclosporinThe remaining five subjects will undergo a second [18F]MC225 PET scan without Cyclosporin, in a test-retest setting.

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

Healthy volunteers aged 50-80.

Exclusion criteria

- Past history of neuropsychiatric disorders such as epilepsy, major depression, or schizophrenia
- Subjects who are currently taking prescription drugs with an influence on P-gp function, general pharmaceuticals
- Exhibition to a radiation dose for other reasons, exceeding the maximum annual dose.
- Contra-indication for MRI-scanning (metal parts in the body, insuline pump, pacemaker, claustrophobia)
- Disturbed kidney function with eGFR<60

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-11-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

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-tetra

Ethics review

Approved WMO Date:	02-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	14-07-2021
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
EudraCT	EUCTR2020-001564-28-NL
CCMO	NL70620.042.20