Test-retest of the newly developed P-gp PET tracer [11C]phenytoin in healthy volunteers

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(1) To assess [11C]phenytoin plasma and brain kinetics in healthy volunteer(s), including assessment of the presence of radioactive metabolites in plasma. (2) To develop a tracer kinetic model for [11C]phenytoin in humans. (3) To determine intra-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37882

Source
ToetsingOnline

Brief title
Test-retest of [11C]phenytoin in healthy volunteers

Condition

- Other condition

Synonym
not applicable

Health condition

geen (nu nog in gezonde mensen)

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: EURIPIDES (European Research initiative to develop Imaging Probes for early In-vivo Diagnosis and Evaluation of response to therapeutic Substances).

Intervention

Keyword: Healthy volunteers, P-glycoprotein, Positron Emission Tomography, Test-retest

Outcome measures

Primary outcome

(1) To assess [11C]phenytoin plasma and brain kinetics in healthy volunteer(s),

including assessment of the presence of radioactive metabolites in plasma. (2)

To determine intra-subject variation of [11C]phenytoin kinetics in humans.

Secondary outcome

To develop a tracer kinetic model for [11C]phenytoin in humans.

Study description

Background summary

Resistance to current drug therapy is an issue for approximately 30% of all people who develop epilepsy. Consequently, there is a pressing need to develop new and more effective treatments. P-glycoprotein (P-gp) is an efflux transporter (member of the multi-drug resistance (MDR) family), which is located at the blood-brain barrier (BBB) and transports substrates (including multiple CNS drugs) from brain to blood and cerebrospinal fluid. Overexpression of P-gp is thought to be an important mechanism of pharmacoresistance in epilepsy. Various invasive techniques used in animal studies of epilepsy showed upregulation of P-gp. At present upregulation of P-gp in refractory patients can only be confirmed by examining brain tissue post-mortem or after surgical removal. Therefore availability of non-invasive imaging methods that would allow for an assessment of distribution and function of P-gp in the brain is of vital importance. At present only (R)-[11C]verapamil is available for assessing P-gp function using PET. Verapamil is a substrate of P-gp and therefore cerebral concentration is low. In case of upregulation of P-gp, it is likely

that the signal will be reduced, but this is difficult to assess due to the low signal to noise ratio. Consequently, (R)-[11C]verapamil is not an ideal ligand for assessing P-gp (over)expression. Therefore novel PET probes, designed to specifically measure P-gp upregulation, need to be developed. Phenytoin is a P-gp substrate. Recently, this compound was labelled with carbon-11, making it a potential tool for measuring P-gp function. The first step to evaluate this tracer is a test-retest brain-PET study in healthy volunteers.

Study objective

(1) To assess [11C]phenytoin plasma and brain kinetics in healthy volunteer(s), including assessment of the presence of radioactive metabolites in plasma. (2) To develop a tracer kinetic model for [11C]phenytoin in humans. (3) To determine intra-subject variation of [11C]phenytoin kinetics in humans.

Study design

Test-retest study of [11C]phenytoin in humans.

Study burden and risks

1) Radiation exposure. The exact radiation exposure of [11C]phenytoin is not yet known. The expected radiation burden is primarily determined by the half-life of C-11. Based on experience with 20 other C-11 labelled ligands, it is known that the radiation exposure for a standard 370 MBq injection is between 0.4 and 4.1 mSv (0.001-0.011 mSv/MBq), with an average of 2 .5mSv, which is well below the accepted safety limit for human studies. The radiation exposure of a low-dose CT of the head is 0.25mSv. For comparison, the natural background radiation dose in the Netherlands gives annual dose of 2 * 2.5 mSv. Thus, the total radiation exposure of the total PET procedure, based on experience with other C-11 labelled ligands is expected to be within an acceptable range. 2) Idiosyncratic reaction to the tracer. Due to the fact that only sub-pharmacological doses of [11C]phenytoin are administered in PET studies, no [11C]phenytoin-induced side-effects will be expected in this study. A physician or physician-assistant will be present during PET scanning. 3) Intravenous and intra-arterial cannulation There is a very small risk of infection and bleeding associated with intravenous and intra-arterial catheters, which are prevented by proper techniques. The venous cannulas will be placed by qualified employees of the Department of Nuclear Medicine & PET Research and/or employees of the department of Anesthesiology. However, occasionally these cannulas may cause a haematoma. 4) Blood sampling. Adverse effects of blood sampling will be minimised by exclusion of subjects with low haemoglobin levels No more than 500 ml blood will be withdrawn during the total PET procedure and screening. Subjects are excluded if 3 months before the PET procedure substantial blood loss or a blood donation has occurred. Subjects are advised not to give blood until 3 months after the scan has been completed. 5)

Discomfort during scanning. It may be uncomfortable to lie motionless in the cameras (both PET and MRI) and it may cause some subjects to feel anxious. Subjects will be made acquainted with the surroundings beforehand. Our staff will be available to provide support, reduce anxiety, optimise the comfort of the subject and remove the subject from the scanner if requested.

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 between 18-65 years - Good physical health evaluated by medical history, physical (including neurological) examination and screening laboratory tests - Weight >50 kg - RDC diagnosis never mentally ill - Written informed consent of each subject

Exclusion criteria

- Any clinical significant abnormality of any clinical laboratory test - Any subject who has received any investigational medication within 30 days prior to the start of this study, or who is scheduled to receive an investigational drug - Major psychiatric or neurological disorder - History of alcohol and/or drug abuse (DSM-IV criteria) - History of coagulation problems - Any sign of cardiovascular disease - Current use of any medication, other than contraceptive medication - Breast feeding - Pregnancy - Unable to understand or read the Dutch language

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-09-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	[11C]phenytoin

Ethics review

Approved WMO

Date:	04-06-2012
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 24061
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-006217-34-NL
CCMO	NL38803.029.11
OMON	NL-OMON24061