Biodistribution and dosimetry of the newly developed P-gp PET tracer [11C]laniquidar in healthy volunteers

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(1) To assess biodistribution of [11C]laniquidar in healthy volunteers; (2) To determine the actual effective radiation dose of [11C]laniquidar in humans; (3) To assess the metabolic profile of [11C]laniquidar in humans.

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

Summary

ID

NL-OMON35158

Source
ToetsingOnline

Brief title
Biodistribution of [11C]laniquidar 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: European FP7 grant - EURIPIDES (European Research initiative to develop Imaging Probes for early In-vivo Diagnosis and Evaluation of therapeutic Substances)

Intervention

Keyword: Biodistribution, Dosimetry, P-glycoprotein, Positron Emission Tomography

Outcome measures

Primary outcome

(1) Biodistribution of [11C]laniquidar in healthy humans;

(2) Effective radiation dose of [11C]laniquidar in humans;

Secondary outcome

Metabolic profile of [11C]laniquidar 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) seems to be involved in drug resistance. 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 overexpression of P-gp, it is likely that the

signal will be even further 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 expression, need to be developed.
Laniquidar is an antagonist of P-gp and therefore it should bind in a dose dependent manner. Recently, this compound was labelled with carbon-11, making it a potential tool for measuring P-gp expression. Initial results of brain uptake of [11C]laniquidar in rats were inconclusive. The rat biodistribution studies in peripheral organs showed the highest uptake in the spleen, heart, kidney and lung. This might be due to the formation of labelled metabolites. Based on these biodistribution studies, the expected dose for a standard 370 Mega Becquerel (MBq) injection would be 1.85mSv (0.005mSv/MBq), well below the accepted safety limit for human studies.
Nevertheless, as the metabolite profile of (R)-[11C]verapamil is expected to be completely different between humans and rats, only direct studies in humans can be used to determine the optimal (safe) dose of [11C]laniquidar. One condition for human use is that, in general, an injected dose of around 370 MBq is needed to allow for accurate measurements of plasma and tissue kinetics.

Study objective

(1) To assess biodistribution of [11C]laniquidar in healthy volunteers;
(2) To determine the actual effective radiation dose of [11C]laniquidar in humans;
(3) To assess the metabolic profile of [11C]laniquidar in humans.

Study design

Single-centre biodistribution and dosimetry study in humans.

Study burden and risks

1) Radiation exposure.
A PET-CT scan is a regular diagnostic imaging technique. Each study will be conducted in compliance with the radiation safety guidelines of the department. Based on results we obtained from biodistribution studies in rats, we calculated using Olinda software 26 that whole body radiation after intravenous injection of 370 MBq [11C]laniquidar is approximately 1.8mSv. In addition a low-dose CT scan performed during PET scanning has a radiation dose of 2-3 mSv depending on the required CT beam current. Therefore, the subject will receive a total radiation dose between 3.8 - 4.8 mSv. 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 is within an acceptable range. In case of previous exposure to radioactivity, subjects will be eligible if the yearly cumulative dose due to exposure to radiation remains below 10 mSv.

After scanning one evaluable subject the effective radiation dose will be calculated (using Olinda software26) based on the biodistribution data of this subject. If necessary, the dose of [11C]laniquidar will be adjusted in the next five subjects (see §3 Study design).

2) Idiosyncratic reaction to the tracer.
Due to the fact that only sub-pharmacological doses of [11C]laniquidar are administered in PET studies, no [11C]laniquidar-induced side-effects will be expected in this study. A physician will be present during PET scanning.

3) Intravenous cannulation.
There is a very small risk of infection and bleeding associated with intravenous catheters, which are prevented by proper techniques. The venous cannulas will be placed by qualified employees of the Department of Nuclear Medicine & PET Research. 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 100ml blood will be withdrawn during the total PET procedure and screening.

5) Discomfort during scanning.
It may be uncomfortable to lie motionless in the PET-CT camera 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
- 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):	26-10-2010
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[11C]laniquidar
Generic name:	[11C]laniquidar

Ethics review

Approved WMO Date:	09-09-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2010
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015380-13-NL
CCMO	NL29489.029.10