Assessment of blood-brain barrier passage of flumazenil in pharmacoresistant patients with temporal lobe epilepsy

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(1) To asses the influence of P-gp function at the BBB on flumazenil binding to the GABAA-receptor in pharmacoresistant patients with temporal lobe epilepsy (TLE), using PET and [11C]flumazenil as a ligand and tariquidar as P-gp blocker. (2) If we...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Seizures (incl subtypes)
Study type	Observational invasive

Summary

ID

NL-OMON37282

Source
ToetsingOnline

Brief title
Blood-brain barrier passage of flumazenil in epilepsy patients

Condition

- Seizures (incl subtypes)

Synonym
temporal lobe epilepsy (TLE)/ epilepsy with the focus in one particular part of the brain

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: Epilepsy, Flumazenil, P-glycoprotein, Positron-Emission Tomography

Outcome measures

Primary outcome

The influence of P-gp function at the BBB on flumazenil binding to the

GABAA-receptor in pharmacoresistant patients with TLE.

Secondary outcome

(1) The effect of tariquidar on the cerebral blood flow (CBF).

If there is an effect of tariquidar on CBF:

(2) The effect of blood flow in the brain on [11C]flumazenil uptake. 1) Effect

of blood flow in the brain on [11C]flumazenil uptake.

If flumazenil is a substrate for P-gp:

(3) Quantification of the upregulation of P-gp by TLE, by comparing

pharmacoresistant patients with TLE with healthy volunteers.

Study description

Background summary

Resistance to current drug therapy is an issue for approximately 30% for 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 the 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 have shown upregulation of P-gp. At present upregulation of P-gp in refractory patients can only be confirmed by examining post-mortem or surgically removed brain tissue. Therefore the availability of non-invasive imaging methods that would allow the assessment of the distribution and function of P-gp in the brain is of vital importance. Currently only [11C]verapamil is available to assess P-gp function by using positron emission tomography (PET), but is not an ideal ligand to assess P-gp expression. Novel imaging probes, which are markers for the function of P-gp need to be evaluated. Such a probe could then be used to establish a non-invasive molecular imaging-based tool which will allow evaluation of the role of P-gp for pathophysiology and treatment response in epilepsy and other major CNS diseases, using the established imaging techniques.
This project concerns a sub-project of EURIPIDES (European Research initiative to develop Imaging Probes for early In-vivo Diagnosis and Evaluation of response to therapeutic Substances). One of the important goals of the project is to quantify to what extent P-gp upregulation affects the binding of an established PET ligand known to be a P-gp substrate, namely [11C]-flumazenil. Flumazenil is a ligand that binds to the GABAA-receptor, but has no agonistic or antagonistic actions on this receptor. Labeled with [11C], flumazenil is frequently used for PET scanning in epilepsy patients to assess changes in GABAA-receptor density and to determine focus localization prior to resective surgery. There is circumstantial evidence from animal and in vitro studies that flumazenil is a substrate for P-gp. If this is indeed the case, changes in P-gp expression or functionality would compromise the interpretation of GABAA-receptor binding data.

Study objective

(1) To asses the influence of P-gp function at the BBB on flumazenil binding to the GABAA-receptor in pharmacoresistant patients with temporal lobe epilepsy (TLE), using PET and [11C]flumazenil as a ligand and tariquidar as P-gp blocker.

(2) If we conclude, after analysing the data of these twelve patients, that flumazenil is a substrate for P-gp, twelve healthy volunteers will be recruited to asses the influence of P-gp function at the BBB on flumazenil binding to the GABAA-receptor in this group, to allow quantification of the upregulation of P-gp by TLE.

(3) To study the effect of tariquidar on CBF.

(4) If there is an effect of tariquidar on CBF, we will study the relation

between changes in CBF and [11C]flumazenil uptake in the brain.

Study design

Multi-centre proof of concept study in humans.

Study burden and risks

Risks associated with participation in this study are related to

1) Radiation exposure
The radiation exposure of 1100MBq [15O]water and 370 MBq of [11C]flumazenil is 0.5 milliSievert (mSv) and approximately 2.5mSv respectively. Therefore, each patient will receive a total radiation dose of 6mSv. For comparison, the natural background radiation dose in the Netherlands gives an 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.

2) Idiosyncratic reaction to the tracer or to the P-gp blocker
The injected mass of [11C]flumazenil in this study is negligible. [11C]flumazenil is a radiotracer that has routinely been used in humans (patient care). Side effects have never been reported at the tracer doses used in PET studies. Tariquidar will be given at a dose of 2 mg/kg, equivalent to what has been given in clinical trials. Tariquidar may, at high doses, transiently cause a decrease in blood pressure. Furthermore it may cause haemolysis and change in transaminase activity. For this reason a physician will constantly be present during and after each injection of the radiotracer and the injection of tariquidar. Blood pressure and heart rate will be measured (each 15 minutes) during tariquidar administration and during the subsequent PET scan.A physician will be present during each injection of the radiotracer and the injection of tariquidar. Blood pressure and heart rate will be measured (each 15 minutes) during tariquidar administration and during the second PET scan.

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.

4) Blood sampling.
Adverse effects of blood sampling will be minimised by exclusion of subjects with low haemoglobin levels (Hb must be > 8 mmol / litre at the time of the scan for males and be > 7 mmol / litre for females). No more than 500ml 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

Investigational group:
- Diagnosis of pharmacoresistant temporal lobe epilepsy (TLE), based on clinical evaluation and (video-) EEG (electro-encephalography)
- Age between 18-60 years
- Normal liver function tests
- Normal full blood count
- Weight >50 kg
- All subjects have to be willing and able to give informed consent (written);If necessary, healthy volunteers will be included:
- Age between 18-50 years
- Good physical health evaluated by medical history, physical (including neurological) examination and screening laboratory tests
- Weight >50 kg
- RDC (Research Diagnostic Criteria) 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
- Any subject who has been prescribed a benzodiazepine preparation within 1 month prior to the start of this study
- Major psychiatric or neurological disorder other than temporal lobe epilepsy (TLE) with or without a known substrate
- History of alcohol and/or drug abuse (DSM-IV criteria)
- History of coagulation problems
- Any sign of cardiovascular disease including new abnormalities on ECG
- Use of non-steroid anti-inflammatory drugs or drugs known to interfere with the P-gp, other than anti epileptic drugs (AEDs)
- Abnormalities on MRI other than temporal localised pathology (i.e. mesial temporal sclerosis, tumor) that is the cause and/or effect of the TLE, and/or abnormalities on MRI other than white matter changes or an incidental small lacunar lesion without clinical diagnosis
- Blood donation or substantial blood loss within 3 months before the scan day
- Metal objects in or around the body (braces, pacemaker, metal fragments)
- Use of antithrombotics and acetylsalicylacid (ASA)
- Unable to understand or read the Dutch language

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2010
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	11C-flumazenil
Generic name:	11C-flumazenil
Product type:	Medicine
Brand name:	Tariquidar
Generic name:	tariquidar

Ethics review

Approved WMO Date:	26-11-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	09-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2011
Application type:	Amendment
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	EUCTR2009-013026-17-NL
CCMO	NL26248.029.09