Assessment of blood-brain barrier passage of flumazenil in patients with epilepsy.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29646

Source
NTR

Health condition

epilepsy
P-glycoprotein
flumazenil
pharmacoresistance

epilepsie
P-glycoproteine
flumazenil
farmacoresistentie

Sponsors and support

Primary sponsor: VU University Medical Center and Stichting Epilepsie Instellingen Nederland (SEIN
Source(s) of monetary or material Support: FP7 grant (EURIPIDES project)

Intervention

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. 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-gp is an efflux transporter, which is located at the 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.
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

Flumazenil is a substrate of P-glycoprotein at the blood-brain barrier.

Study design

N/A

Intervention

2x [11C]flumazenil- and 2x [15O]water PET scan with one gift of Tariquidar in between.

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Eligibility criteria

Inclusion criteria

Investigational group:

1. Diagnosis of pharmacoresistant TLE, based on clinical evaluation and (video-) EEG;

2. Age between 18-60 years;

3. Normal liver function tests;

4. Normal full blood count;

5. Weight >50 kg;

6. All subjects have to be willing and able to give informed consent (written).

If necessary, healthy volunteers will be included:

1. Age between 18-50 years;

2. Good physical health evaluated by medical history, physical (including neurological) examination and screening
laboratory tests;

3. Weight >50 kg;

4. RDC (Research Diagnostic Criteria) diagnosis never mentally ill;

5. Written informed consent of each subject.

Exclusion criteria

1. Any clinical significant abnormality of any clinical laboratory test;

2. 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;

3. Any subject who has been prescribed a benzodiazepine preparation within 1 month prior to the start of this study;

4. Major psychiatric or neurological disorder other than TLE with or without a known substrate;

5. History of alcohol and/or drug abuse;

6. History of coagulation problems;

7. Use of non-steroid anti-inflammatory drugs or drugs known to interfere with the P-gp, other than AEDs;

8. Abnormalities on MRI other than temporal localised pathology, 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;

9. Blood donation or substantial blood loss within 3 months before the scan day;

10. Metal objects in or around the body.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2010
Enrollment:	24
Type:	Anticipated

Ethics review

Positive opinion

Date:	26-01-2010
Application type:	First submission

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
NTR-new	NL2067
NTR-old	NTR2184
Other	METC VUmc : 09052
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A