Onderzoek ter evaluatie van de test - retest variatie van [11C]fenytoine in gezonde vrijwilligers.

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Primary Objectives: 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...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON24061

Bron
NTR

Aandoening

- pharmacoresistant epilepsy
- Blood Brain Barrier (BBB)
- upregulation of multidrug efflux transporters (e.g. P-gp)
- brain pharmacokinetics

Ondersteuning

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Overige ondersteuning: Partly by EU:

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partly by Sponsor

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. Plasma kinetics of [11C]phenytoin in humans, including assessment of the presence of radioactive metabolites;
2. Brain kinetics of [11C]phenytoin in humans;
3. Determination of the most accurate tracer kinetic model for [11C]phenytoin in humans;
4. Determination of the most suitable parametric method for [11C]phenytoin in humans;
5. Assessment of inter- and intra-subject variation of [11C]phenytoin kinetics in humans.

Toelichting onderzoek

Achtergrond van het onderzoek

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, overexpression of P-gp in refractory patients has only been confirmed by examining brain tissue post-mortem or after surgical removal without resulting in direct information on P-gp functionality. Availability of non-invasive imaging methods that would allow for an in vivo assessment of distribution and function of P-gp in the brain is of vital importance.
At present only (R)-[11C]verapamil is routinely used for assessing P-gp function using PET. Verapamil is a substrate of P-gp and therefore cerebral concentrations are low. In case of upregulation of P-gp, it is likely that the signal will be reduced even further, but this is difficult to assess due to the low signal to noise ratio. The signal to noise ratio is even further reduced by cerebral uptake of radiolabelled metabolites of (R)-[11C]verapamil.

Consequently, (R)-[11C]verapamil is not an ideal ligand for assessing P-gp function. Therefore

novel PET probes, designed to specifically measure P-gp function, need to be developed.

It has been shown that phenytoin is a substrate of P-gp. Recently, phenytoin was labelled with carbon-11. PET studies in rats have shown that [11C]phenytoin has more favourable characteristics for measuring P-gp function than (R)-[11C]verapamil: First, [11C]phenytoin has a higher initial brain uptake in rats than (R)-[11C]verapamil, so an upregulation of P-gp would be easier to detect. Second, in animal experiments [11C]phenytoin has shown optimal brain kinetics, i.e. fast transport into the brain, reaching equilibrium well within the time span of a PET scan with an ideal rate of clearance (not too slow, not too fast) from the brain. Third, in rats, [11C]phenytoin is metabolically more stable than (R)-[11C]verapamil in both brain and plasma, causing less problems with labelled metabolites. Nevertheless, as the metabolite profile of (R)-[11C]verapamil in humans is completely different from that in rats, only direct studies in humans can determine whether [11C]phenytoin is indeed a more potent tracer to assess P-gp function in vivo. Furthermore, paired [11C]phenytoin scans are needed to determine inter- and intra-subject variation of [11C]phenytoin plasma and brain kinetics of [11C]phenytoin.

Volunteers will be recruited only in the Netherlands, mainly with some relation to the VU medical center.

Doel van het onderzoek

Primary Objectives:

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 inter- and intra-subject variation of [11C]phenytoin kinetics in humans.

Onderzoeksopzet

Positron Emmisson Tomography (PET) will be applied during after administration of the radiotracer [11C]phenytoin. This will be repeated on the same day.The complete procedure takes one day (9-17hr) per volunteer.

Data will be analysed off-line and final anlysis of the inter-and itra-individualvariability will take place after scanning all volunteers.

Onderzoeksproduct en/of interventie

This is a single-centre test-retest study in healthy humans. We will include (at least) 12 healthy subjects to obtain 12 evaluable test-retest [11C]phenytoin PET scans. These subjects

will receive paired [11C]phenytoin PET scans on one day at the Department of Nuclear Medicine & PET Research of the VUmc. All subjects will also undergo an MRI scan for localisation purposes that will be performed at the department of Radiology of the VUmc.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Age between 18-65 years;

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

3. Weight >50 kg;

4. For all females of childbearing potential a negative pregnancy test must be obtained within 48 hours before starting the study;

5. Written informed consent of each subject;

6. Hb must be >8 mmol \ litre at the time of the screening for males and >7 mmol \ litre for females.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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. Major psychiatric or neurological disorder;

4. History of alcohol and/or drug abuse (DSM-IV criteria);

5. History of coagulation problems;

6. Any sign of cardiovascular disease;

7. Claustrophobia;

8. Current use of any medication, other than contraceptive medication;

9. Breast feeding;

10. Pregnancy;

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

12. Need for elective surgery within two months;

13. Unable to understand or read the Dutch language;

14. Metal objects in or around the body (braces, pacemaker, metal fragments).

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-09-2012
Aantal proefpersonen:	12
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	01-08-2012
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 37882
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3410
NTR-old	NTR3553
CCMO	NL38803.029.11
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON37882

Resultaten

Samenvatting resultaten
N/A