A randomized, double blind, placebo-controlled crossover study to investigate the effects of cholinergic and serotonergic challenges with galantamine and citalopram on resting state FMRI in aging and dementia.

Published: 27-02-2012
Last updated: 26-04-2024

We propose to conduct a study in healthy young and elderly subjects and patients diagnosed with mild to moderate AD, FTLD, or DLB where cholinergic and serotonergic challenges are given in a placebo-controlled, crossover fashion. Before each...

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

Summary

ID

NL-OMON37710

Source
ToetsingOnline

Brief title
Pharmacological resting state FMRI in aging and dementia.

Condition

- Other condition

Synonym
cognitive deterioration, Dementia

Health condition

neurodegeneratieve aandoeningen

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Aging, Challenge, Dementia, FMRI

Outcome measures

Primary outcome

Resting state network activity as measured with RS-FMRI.

Secondary outcome

1) Cognitive functioning as measured with different subtests of the Neurocart

(a validated multimodal CNS-test battery):

• Visual Analogue Scale (VAS) Bond & Lader (mood, alertness and calmness)

• VAS for nausea

• Adaptive tracking

• Simple reaction time

• Visual N-back test

• Stroop test

• Symbol-digit substitution test

• Visual Verbal Learning Test (VVLT; 15 words)

2) Pharmacokinetics of galantamine and citalopram:

• The time-course of the serum levels of galantamine and citalopram

Study description

Background summary

There is a strong need for early markers of dementia. Because brain function is more sensitive to early neurodegenerative changes than brain structure, functional MRI (FMRI) is widely studied for its potential as an early marker of brain dysfunction, and biomarker of treatment, in dementia. In pharmacological resting state FMRI (Ph-RS-FMRI) studies with healthy volunteers, specific drug-induced and concentration dependent changes are demonstrated in functional brain connectivity during rest after pharmacological challenges. Both normal aging and dementia are associated with overlapping and increased levels of pathology. In healthy aging, which is often accompanied by learning and memory problems, reduced functioning of several neurotransmitter systems, including cholinergic and serotonergic systems, has been demonstrated. These neurotransmitter systems are affected in several types of dementia as well. It is hypothesized that the Ph-RS-FMRI technique with specific pharmacological enhancement of the cholinergic and serotonergic systems in healthy young and elderly subjects, and patients diagnosed with mild to moderate Alzheimer*s disease (AD), frontotemporal lobe dementia (FTLD), or dementia with Lewy bodies (DLB) will lead to differential brain responses to these challenges and, as a consequence, to earlier and more accurate diagnosis of different types of dementia.

Study objective

We propose to conduct a study in healthy young and elderly subjects and patients diagnosed with mild to moderate AD, FTLD, or DLB where cholinergic and serotonergic challenges are given in a placebo-controlled, crossover fashion. Before each challenge, participants will be measured 2 times to define their baseline resting state networks (RSNs) and cognitive functioning. After each challenge, participants will be measured 4 times within 4 hrs to assess their RSNs and correlate these measures to the plasma PK samples of galantamine and citalopram. Additionally, the RSNs and plasma PK samples will be correlated to measures of cognition. The main goal of the research is to differentiate between young and elderly healthy subjects and dementia patients based on their RS-FMRI brain response. The study is divided in 4 parts:

Part A: Healthy young and elderly
The goal of this study (part A) is to investigate the sensitivity and specificity of the Ph-RS-FMRI technique to differentiate between young and elderly subjects without dementia.

Part B: Alzheimer*s disease
The goal of this study (part B) is to investigate the sensitivity and specificity of the Ph-RS-FMRI technique to differentiate between AD patients and age-matched controls. The elderly subjects of part A will serve as control group.

Part C: Frontotemporal lobe dementia
The goal of this study (part C) is to investigate the sensitivity and specificity of the Ph-RS-FMRI technique to differentiate between FTLD patients and age-matched controls. The elderly subjects of part A will serve as control group.

Part D: Dementia with Lewy bodies
The goal of this study (part D) is to investigate the sensitivity and specificity of the Ph-RS-FMRI technique to differentiate between DLB patients and age-matched controls. The elderly subjects of part A will serve as control group.

Study design

This single center, double-blind, placebo-controlled, 3-day crossover study with cholinergic and serotonergic challenges will be divided in 4 parts, pertaining to 4 different populations:

Part A: healthy young and elderly subjects
Part B: patients diagnosed with mild to moderate AD
Part C: patients diagnosed with mild to moderate FTLD
Part D: patients diagnosed with mild to moderate DLB

The healthy elderly group of part A will also function as the control group of part B-D. The challenge will consist of 1 daily dose of galantamine, citalopram or placebo.

Intervention

During 3 study days, the effect of a single dose of galantamine 8 mg and citalopram 20 mg (increased to 30 mg after 1 hr when well tolerated) will be measured in a double-blind, randomized, placebo-controlled design. On each study day, one of the 3 agents (galantamine, citalopram or placebo) will be administered. Washout periods between different study days will be at least 1 week. On each study day there are two or three moments of administration. The second administration on each day will only take place when subjects tolerate the first dose well (do not vomit or feel too nauseous). Furthermore, to correct for different time point of maximum concentration (Tmax) of the two agents (galantamine: 1-2 hrs, citalopram: 2-4 hrs), oral administration of the agents will be combined with administration of a placebo separated by 1 and/or

2 hrs (depending on whether a second dosage is administered). This way the Tmax of both agents will be reached at around the same time of the day:
• Galantamine study day: 1) placebo 2) placebo 3) galantamine 8 mg
• Citalopram study day: 1) citalopram 20 mg 2) citalopram 10 mg 3) placebo
• Placebo study day: 1) placebo 2) placebo 3) placebo

Study burden and risks

Not applicable

Contacts

Public
Centre for Human Drug Research

Zernikedreef 10
Leiden 2333 CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 10
Leiden 2333 CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Part A: Healthy subjects;• Have a body-mass index (BMI) between 18 and 34 kg/m2.
• All subjects participating in this study are absent on cognitive deficits with a Mini Mental State Examination (MMSE) score between 28 and 30.
• Each subject is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent.
• Healthy young subjects: age 18-30.
• Healthy elderly subjects: age 55-75.;Part B-D: Dementia patients
• A body-mass index (BMI) between 18 and 34 kg/m2.
• All patients participating in this study only have mild cognitive deficits with a Mini Mental State Examination (MMSE) score between 21 and 27.
• Patients will be assessed by the treating neurologist as mentally capable of understanding the implications of study participation.
• Each patient is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent. ;Part B: patients with Alzheimer's disease
• The clinical diagnosis AD will be established according to the revised NINCDS-ADRDA criteria for diagnosing probable AD.
• Age 55-75.;Part C: patients with frontotemporal lobe dementia
• The clinical diagnosis possible FTLD will be established according the revised International Consensus Criteria for frontotemporal lobar degeneration, and supported by neuropsychological deficits and frontal and/or temporal atrophy (MRI) or hypoperfusion (ASL, SPECT). All patients will undergo extensive history taking and neurological examination in order to exclude other causes of frontal dysfunction.
• Age 50-70.;Part D: patients with dementia with Lewy bodies
• The diagnosis DLB will be made according to clinical criteria for probable DLB.
• Age 55-75.

Exclusion criteria

• Contra-indication to MRI scanning (pacemaker and defibrillator, intraorbital or intraocular metallic fragments, cochlear implants, one or more metal eartubes, intracranial clips, a non-removable insulin pump, a non-removable neurostimulator, a mechanical cardiac valve, an hydrocephalus pump, ferromagnetic implants, intra-uterine device, permanent make-up, tattoos above the shoulders, pregnancy, operation in 6 weeks preceding the MRI, claustrophobia, inability to lie still for a period of 20 minutes in the MRI scanner, Fear or problems during the RS-FMRI scan).
• Clinically relevant abnormal history of physical and mental health as determined by medical history taking and physical examinations obtained during the screening visit (as judged by the investigator).
• Other causes that can explain cognitive symptoms.
• Clinically relevant abnormal laboratory results, ECG and vital signs, or physical findings at screening (as judged by the investigator).
• Positive test for hepatitis B, C or HIV.
• Subjects using, on average, more than 4 units of alcohol per day, and unable to refrain from alcohol use during the study days.

• Subjects smoking, on average, more than 5 cigarettes per day, and unable to refrain from smoking during the study days.
• Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at the time of the study and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) during study days.
• Positive drug or alcohol test at screening and/or study days.
• History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion of the study drug.
• Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug or more than 4 times per year.
• Donation or loss of blood (> 500 mL) within 3 months prior to screening.
• Inadequate venous accessibility as judged by the physician or nurse.
• Use of benzodiazepine within 48 hours before a study day.
• Use of monoamine oxidase inhibitors (MAOIs) from 14 days prior to the first study day until 7 days after the last study day (incl. linezolid).
• Severe asthma or obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).
• Pregnancy or breast feeding.
• Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject.
• Use of medication in the 2 weeks prior to the first study day that is, in the opinion of the investigator, interfering with the study or the study medication.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-07-2012
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Citalopram
Generic name:	Citalopram
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Granisetron
Generic name:	Granisetron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Reminyl
Generic name:	Galantamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-02-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-04-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-06-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-07-2012

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2012-000732-26-NL
CCMO	NL39864.058.12