Symptomatic treatment of vascular cognitive impairment

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Primary Objective: To study the change on performance on executive function and memory function (as measured on Neurocart), after an active challenge with methylphenidate (monoaminergic) and galantamine (cholinergic), compared to placebo, in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44729

Source
ToetsingOnline

Brief title
STREAM-VCI

Condition

- Neurological disorders NEC

Synonym
memory complaints, post-stroke cognitive impairment

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Alzheimer Nederland

Intervention

Keyword: cognitive impairment, pharmacological, therapy, vascular dementia

Outcome measures

Primary outcome

Changes in the performance on the cognitive tests as measured with the

neurocart.

Secondary outcome

DTI and RS fMRI parameters integrity on white matter tracts and neuronal

networks

Study description

Background summary

Vascular Cognitive Impairment is an important cause of cognitive impairment and dementia. Up till now, there are no approved symptomatic treatments for Vascular Cognitive Impairment. Research on novel pharmacological treatments that may reduce clinical symptoms in these patients is needed. Evidence suggests that executive dysfunction and memory impairment in Vascular Cognitive Impairment are caused by damage to monoaminergic and cholinergic neurotransmitter-systems, respectively. However, patients with Vascular Cognitive Impairment form a clinically heterogeneous group, i.e. the extent to which fexecutive function and memory are affected differs from patient to patient. Previous intervention studies have not taken this inter-patient variability into account. Individually tailored pharmacological interventions, aimed at the affected neurotransmitter systems, may ameliorate cognitive symptoms in patients with Vascular Cognitive Impairment. Using a pharmacological challenge, it is possible to detect individual sensitivity to specific pharmacological interventions. Furthermore, with the use of novel MRI techniques, it is possible to correlate the location and severity of cerebrovascular lesions to impaired structural and functional connectivity in each subject.

Study objective

Primary Objective:

To study the change on performance on executive function and memory function (as measured on Neurocart), after an active challenge with methylphenidate (monoaminergic) and galantamine (cholinergic), compared to placebo, in patients with VCI.

Secondary objective:
To study the effect of cerebrovascular lesions on structural and functional connectivity with structural MRI, DTI *fiber tracking* and rs-fMRI in patients with VCI.

To correlate the location and severity of cerebrovascular lesions to impaired structural and functional connectivity in each subject. Based on this information we aim to develop a prediction model that estimates a positive response to a cholinergic and/or monoaminergic challenge in individual patients with VCI.

To investigate the relationship between the cognitive profile of individual subjects, i.e. executive dysfunction or memory impairment, and a positive response to a specific challenge.

Study design

We will recruit 30 patients with Vascular Cognitive Impairment (according to the criteria of the American Heart Association/American Stroke Association), at the Alzheimer Center of the VU University Medical Center and the Utrecht University Medical Center. Participants will receive a complete dementia screening, including a neuropsychological and neuropsychiatric examination. They will also undergo MRI at 3T, including DTI/*fiber tracking* and RS fMRI. In a double-blind, three-way, case cross over trial, we will study the effects of methylfenidate on executive function and of galantamine on episodic memory function. During three separate visits, patients will receive the pharmacological interventions (placebo, methylfenidate, and galantamine) at our Clinical Research Unit. Also, during a study day we will collect blood samples at different timepoints.

Intervention

Methylphenidate 10 mg
Galantamine 16 mg
Placebo

Study burden and risks

Patients will visit our clinical research unit four times on separate visits at least one week apart. The first visit is meant for screening study participation. During the study day patients will receive a single dose of

either medication or placebo. After the medication challenge they will perform several tests on the Neurocart on several timepoints.
Since there will be a single dose adminstration and the already registered medication in low dosage, the risk of adverse advents will be low.
During the study day blood samples will be taken via a canule. The canule might cause a haematoma, which might cause slight discomfort.
The MRI will be performed without any contrast, this keeps the MRI burden low.

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

Outpatients
Objective executive dysfunction and/or memory impairment and imaging evidence of cerebrovascular disease (white matter changes (Fazekas=/>2, lacunar infarcts)

MMSE =/>16
Clinical Dementia Rating Score (CDR of 0.5-1)
No contraindication for treatment with a cholinesterase inhibitor or methylphenidate
Assessed by the treating neurologist as mentally capable of understanding the implications of study participation
Presence of an informant,/caregiver at the information visit and the signing of the informed consent
Signed informed consent by patient

Exclusion criteria

Clinically relevant history of abnormal physical or mental health interfering with the study as determined by medical history taking and physical examinations obtained during the screening visit and/or at the study day as judged by the investigator;
Clinically relevant abnormal laboratory results, electrocardiogram (ECG) and vital signs, or physical findings at screening and/or at the start of the study day (as judged by the investigator);
Unwilling to or unable to stop smoking 12 hours before study day until 12 hours after the study day
Other causes that can explain cognitive symptoms
Use of doses of corticosteroids that in the opinion of the investigator may interfere pharmacodynamic measurements performed in the study.
Use of celiprolol or sotalol
Use of neuroleptics
Current use of centrally acting anticholinergics (e.g. oxybutinin, mebeverine, ipratropium(bromide)) Use of benzodiazepine within 48 hours before a study day
Current use of a CEI (rivastigmine, galantamine, donepezil)
Alcohol abuse (defined as use of alcohol despite significant areas of dysfunction, evidence of physical dependence, and/or related hardship due to alcohol)
Use of recreational drugs
Concomitant use of inhibitors of CYP2D6 (a/o kinidine, paroxetine, fluoxetine) or of CYP3A4 (a/o ketoconazole, ritonavir) unless on a stable dose and no expected upcoming changes in dosing.
Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject.
Any contra-indication for MRI

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-04-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Reminyl
Generic name:	Galantamine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ritalin
Generic name:	Methylphenidate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	07-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2016
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	EUCTR2013-003396-35-NL
CCMO	NL45933.029.13

Study results

Date completed:	01-09-2017
Actual enrolment:	30