The effect of cholinergic enhancement on brain activation in Parkinson*s disease patients with visual hallucinations using fMRI.

Published: 20-07-2009
Last updated: 05-05-2024

To investigate cerebral activation patterns after administration of an AChE-I (rivastigmine), compared to activation after placebo, in PD patients with VH.Secondly, to investigate whether cerebral activation changes after rivastigmine correlates...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON33228

Source
ToetsingOnline

Brief title
Cholinergic enhancement in PD patients with VH

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease, visual hallucinations

Research involving
Human

Sponsors and support

Primary sponsor: Neurologie

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cholinergic, fMRI, Parkinson's disease, visual hallucinations

Outcome measures

Primary outcome

Primary outcome: cerebral activation change after administration of

rivastigmine, compared to placebo, using fMRI

Secondary outcome

Secondary outcomes: Clinical effect of rivastigmine on cognition and extent of

VH. Correlation between clinical effect and cerebral activation effect of

rivastigmine.

Study description

Background summary

Visual hallucinations (VH) are common in Parkinson*s disease (PD) with a prevalence of approximately 30%. The exact etiology of VH in PD is unknown, however a combination of impaired visual processing and attention seems to be involved.
In our previous study, we used movies with images gradually revealed out of noise (pop-out movies) to investigate if PD patients with VH had a specific cerebral activation pattern before recognition of the image, compared to PD patients without VH and healthy controls. We found that PD patients with VH had decreased activation of the lateral occipito-temporal cortex (middle occipital and middle temporal gyri) before pop-out, compared to both PD patients without VH and healthy controls. We hypothesized that this impairment of the occipito-temporal cortex in PD patients with VH might predispose to VH via a *release* mechanism of higher order visual cortices.
Other studies have shown that apart from the dopaminergic neurotransmitter system, the cholinergic system seems to be involved in the pathogenesis of VH in PD. The cholinergic system plays an important role in conscious awareness. A decrease in the cortical acetylcholine (Ach) levels impairs the selection of subcortical information streams, causing unselected and chaotic cortical

activation, which may predispose to hallucinations.
Clinical evidence shows that visual hallucinations can be induced by anti-cholinergics, while acetylcholinesterase inhibitors (AChE-I) ameliorate cognitive dysfunction and VH in PD.
Cholinergic projections from the basal forebrain to the cortex include projections to primary and associative visual cortical regions. Non-demented PD patients have reduced cholinergic activity in occipital and temporal cortical regions while PD patients with dementia have a more extensive cholinergic loss, especially in the middle temporal gyrus, compared to healthy controls.
The previously found reduced activation of occipital and temporal cortex before visual pop-out in PD patients with VH, compared to PD patients without VH and healthy controls was independent of cognitive dysfunction. Possibly, this relative deactivation in PD patients with VH is due to reduced cholinergic innervation to the occipital and temporal cortex. This might, at least partly, explain beneficial effects of AChE-I on VH in PD and PD dementia.
Therefore, administration of AChE-I might *normalize* occipital and temporal cortex activation during a visual pop-out task in PD patients with VH.
Secondly, the extent of change in cerebral activation after administration of AChE-I might positively correlate with the clinical response of PD patients with VH on AChE-I.

Study objective

To investigate cerebral activation patterns after administration of an AChE-I (rivastigmine), compared to activation after placebo, in PD patients with VH.
Secondly, to investigate whether cerebral activation changes after rivastigmine correlates with individual clinical response on rivastigmine.

Study design

fMRI will be performed during a dynamic presentation of images popping out of noise after placebo and after administration of rivastigmine. Administration of placebo or rivastigmine will be single-blind (i.e. blind to the subject). The first intervention fMRI-session will take place at t=0 and the second intervention fMRI will take place after several days, up to one week (t=1). Intervention timing will be balanced, i.e. half of the subjects will receive placebo at t=0 and rivastigmine at t=1, while the other half will receive rivastigmine at t=0 and placebo at t=1.
After the last scanning session, PD patients with VH will be treated with a rivastigmine plaster according to a fixed titration schedule (4.6 mg/24 hours, after 1 month 9.5 mg/24 hours, highest tolerable dose). During the first session and after 2 months rivastigmine use, cognition and extent of VH will be assessed using the SCales for Outcomes in Parkinson's disease - part cognition (SCOPA-cog) and the University of Miami Parkinson*s disease Hallucinations Questionnaire (UM-PDHQ), respectively. Also after 2 months, the association between clinical response on rivastigmine (i.e. improvement on the SCOPA-cog

and the UM-PDHQ) and cerebral activation changes will be investigated.

Intervention

fMRI will be performed in two scanning sessions during which subjects watch a dynamic presentation of images popping out of noise either after placebo or after administration of rivastigmine. Several days before the first session, subjects will receive a transdermal patch with either rivastigmine (9.5 mg/24 hours) or placebo by post. They will be instructed to apply this patch the evening before the scan, before going to bed. It has been shown that rivastigmine concentration rises slowly after application of the patch and reached a plateau between 8 and 26 hours (median tmax 14.1 hours)12. The content of the plaster (rivastigmine or placebo) will be single-blind (i.e. blind to the patient).
The first intervention fMRI-session will take place at t=0 and the second intervention fMRI will take place after several days, up to one week (t=1). Intervention timing will be balanced, i.e. half of the subjects will receive placebo at t=0 and rivastigmine at t=1, while the other half will receive rivastigmine at t=0 and placebo at t=1.
After the last scanning session, PD patients with VH will be treated with a rivastigmine patch according to a fixed titration schedule (4.6 mg/24 hours, after 1 month 9.5 mg/24 hours, highest tolerable dose).

Study burden and risks

Local irritation patch (minor chance because of relatively short duration of patch application)
Adverse events of rivastigmine (less chance than with capsule, because of the slow rise of the blood concentration and absence of a dose peak)

Contacts

Public
Selecteer

Hanzeplein 1
9700 VB Groningen
NL
Scientific
Selecteer

Hanzeplein 1
9700 VB Groningen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- PD according to UK brain bank criteria
- At least weekly VH
- MMSE>24
- FAB>=12

Exclusion criteria

- Instable internal or psychiatric disease
- Visual acuity <0,5 (Snellen chart)
- Use of ChE-I

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Exelon
Generic name:	rivastigmine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	31-03-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2008-008728-34-NL

Register	ID
CCMO	NL26430.042.09