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A study to investigate the association between the acute response and long-term clinical response to galantamine in patients with mild to moderate Alzheimer's Disease

Submission date
21/08/2019

Recruitment status
No longer recruiting

Registration date
29/08/2019

Overall study status
Completed

Last Edited
31/10/2022

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Cholinesterase inhibitors (CEIs) have been shown to improve cognitive functioning in Alzheimer's Disease (AD) patients, but are associated with multiple side effects and only 20-40% of the patients clinically improve. In this study, we aim to investigate the acute pharmacodynamic effects of a single dose administration of galantamine on central nervous system function in patients with mild to moderate Alzheimer's Disease and its potential to predict long-term treatment response

Who can participate?
Patients with Alzheimer's disease

What does the study involve?
Participants will receive treatment with galantamine for six months. Participants will also take part in a number of mental health assessments at the start and end of the treatment.

What are the possible benefits and risks of participating?
There is a 10 per cent chance of side effects. Nausea and vomiting are the most prevalent side effects of galantamine. Application of the indwelling catheter to monitor the concentrations of galantamine can be painful. The treatment with galantamine is identical to the usual care that would be given if subjects did not participate in this study.

Where is the study run from?
Centre for Human Drug Research, Netherlands

When is the study starting and how long is it expected to run for?
June 2011 to October 2014

Who is funding the study?
The Netherlands Organisation for Health Research and Development (ZonMw)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2010-021152-25

Protocol serial number
NL33145.02910

Study information

Scientific Title
Study to investigate the association between the response to a cholinergic challenge with galantamine and the clinical response to subsequent treatment with galantamine in patients with mild to moderate Alzheimer’s Disease

Study objectives
1. There is a correlation between the pharmacodynamic effects of a single dose of galantamine and the clinical response to treatment with galantamine during a 6-month period in patients with mild to moderate Alzheimer's Disease
2. There is a difference in pharmacodynamic effects of a single dose of galantamine between responders and non-responders to treatment with galantamine during a 6-month period in patients with mild to moderate Alzheimer's Disease

Ethics approval required

Old ethics approval format

Ethics approval(s)
1. Approved 21/10/2010, Medical Ethics Committee of the VU University Medical Center (Medisch Ethische Toetsingscommissie VU Medisch Centrum, De Boelelaan 1117, 1081 HV Amsterdam; subcom-ethiek.org@vumc.nl; +3120-4443488), ref: NL33145.02910
2. Approved 23/05/2013, Medical Ethics Committee of the Clinicii de neurologie a Spitalului Universitar de Urgenta (Comisia Nitionali de Etici pentru Studiu Cllinica l Medicamettului, Adresa: S tr.A v. SanAtescnur .48, sect.1 , Bucurest, +40 314051076), ref: 35528C/04.02.2013

Primary study design
Interventional

Study design
Single-centre double-blind placebo-controlled two-period crossover intervention study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Alzheimer's Disease

Interventions
Single-centre double-blind placebo-controlled two-period crossover intervention study with a cholinergic challenge in patients with mild to moderate Alzheimer's Disease.

The challenge will consist of one daily dose of 16 mg galantamine or placebo. All patients are subsequently treated with open-label galantamine for a period of six months.

This study consisted of a challenge and treatment phase. In the challenge phase, a single dose of 16 mg galantamine was administered to 50 mild to moderate patients in a double-blind, placebo-controlled cross-over fashion. Acute effects were monitored up to 5 hours after administration with the use of the NeuroCart CNS test battery and safety and pharmacokinetics were assessed. In the treatment phase, patients were treated with open-label galantamine according to regular clinical care.

After 6 months of galantamine treatment, patients were categorized as either responder or non-responder based on their scores on cognitive tests (neuropsychiatric change). The correlations between the galantamine challenge effect on pharmacodynamic measures and the cognitive and neuropsychiatric change from baseline to month 6 will be determined. Also, responders and non-responders after 6 months of treatment will be defined based on the cognitive and neuropsychiatric outcome at month 6, and the difference in galantamine challenge effects on pharmacodynamic measures will be determined. It will be attempted to develop a PK/PD model for the effects of galantamine on pharmacodynamics in patients with mild to moderate Alzheimer's Disease.

The study has a 2-way cross-over randomized design, i.e. 50% of the subject received placebo and galantamine and 50% received galantamine and placebo in reversed order. The randomization was created by an independent statistician at the Centre for Human Drug Research using SAS software.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Galantamine

Primary outcome(s)
Long-term clinical response to galantamine assed using pharmacodynamic parameters measured by the NeuroCart test battery, including:
1. The N-back tests evaluated working memory
2. Adaptive tracking measured sustained attention
3. Eye-hand coordination
4. Simple Reaction Time task measured the attention and speed of information processing
5. Visual analogue scale according to Bond and Lader assessed changes in subjective states
6. Facial encoding and recognition task episodic memory
7. Visual verbal learning test (VVLT) covered the scope of learning behaviour (i.e., acquisition, consolidation, storage and retrieval
8. Pharmaco-electroencephalography
9. Eye movements and pupil size were used to determine drug effects on neurophysiological and autonomous system function.
Pupil size, eye movements, adaptive tracking, simple reaction time, visual analogue scales and N-back tests were performed twice at baseline, and at 1, 2, 4, and 5 hours following galantamine or placebo administration. The VVLT was executed 1.5 hours after drug-administration (immediate recall) and 3.0 hours following drug-administration (delayed recall and recognition). The facial recognition task was performed at baseline and 2.5 hours after dosage. Pharmaco-EEG measurements were performed at baseline and 0,5, 1, 1,5, 2, 4 and 5 hours post galantamine administration.

Key secondary outcome(s)
1. Pharmacokinetic parameters:
1.1 Plasma galantamine concentrations via an indwelling catheter at baseline and at 0,25, 0,5, 1, 1,5, 2, 2,5, 3,5 and 5 hours following drug administration.

2. Safety assessments by blood sampling:
2.1 Vital signs measurements
2.2 12-lead ECG
2.3 Urinalysis
2.4 Urinary drug screen
2.5 Haematology
2.6 Biochemistry
All safety assessments were performed at baseline and additionally at 0.5, 1.5 and 5.0 hours post- drug administration.

3. Clinical outcomes assessments:
3.1 The Alzheimer's Disease Assessment (ADAS)-cog subscale was used to evaluate the severity of cognitive and non-cognitive behavioral dysfunction characteristic for AD patients
3.2 Cognitive performance of subjects was assessed by the Clinical Dementia Rating Scale (CDR) in which statements related to the following 6 domains are scored: memory, orientation,

judgment and problem solving, community affairs, home and hobbies, and personal care
3.3 The Disability Assessment in Dementia (DAD) scale was used to evaluate basic and instrumental activities of daily living (ADL)
3.4 The Mini Mental State Examination (MMSE) is a brief 30-point questionnaire test which was used to screen for cognitive impairment
3.5 With the Neuropsychiatric Inventory (NPI) diverse behavioural and psychological symptoms of dementia were measured
3.6 The ADAS-cog, CDR, DAD, MMSE and NPI were carried out after two and 6 months of treatment

Completion date
18/06/2015

Eligibility

Key inclusion criteria
1. Clinical diagnosis of AD
2. Mini Mental State Examination (MMSE) score ranging from 18 to 26
3. Clinical Dementia Rating (CDR) score between 0.5 and 2.0

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
50

Key exclusion criteria
1. Previous or current use of CEIs, anticholinergic drugs or neuroleptics
2. Contraindications for the use of CEIs
3. Use of benzodiazepines 48 hours prior to the study days
4. History of psychiatric disorders

Date of first enrolment
20/06/2011

Date of final enrolment
14/10/2014

Locations

Countries of recruitment
Netherlands

Romania

Study participating centre
Centre for Human Drug Research
Zernikedreef 8
Leiden
Netherlands
2333 CL

Study participating centre
Amsterdam UMC
De Boelelaan
Amsterdam
Netherlands
1081 HV

Study participating centre
Spaarne Gasthuis
Boerhaavelaan 22
Haarlem
Netherlands
2000 AK

Study participating centre
Tangent data research unit at University hospital of Bucharest
Sector 5,
B-Dul Independentei Nr. 169
Bucharest
Romania
050098

Sponsor information

Organisation

Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Research organisation

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/06/2022	31/10/2022	Yes	No