A randomized, double-blind, double-dummy, placebo-controlled, single dose, 4-way cross-over study of the reversibility of cognitive deficits induced by a nicotinic anti-cholinergic challenge with mecamylamine by a cholinesterase inhibitor and a nicotinic receptor agonist

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Primary Objectives • To demonstrate if the impairment of cognitive function caused by mecamylamine administration can be diminished by an nAChR agonist or CEI.• To evaluate to what extent a single dose of 30 mg mecamylamine may cause a more...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON42052

Source
ToetsingOnline

Brief title
Validation of the mecamylamine model

Condition

- Mental impairment disorders

Synonym
Alheimer's disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Study funded by CHDR

Intervention

Keyword: anti-cholinergic challenge, galantamine, mecamylamine, nicotine

Outcome measures

Primary outcome

Pharmacodynamic endpoints:

NeuroCart tests:

• Adaptive tracking

• Pharmaco-EEG

• Pupil size

• Finger tapping

• Simple reaction time task

• Milner Maze test

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

• N-back test

• Visual verbal learning test; immediate recall, delayed recall, recognition

(30 words)

Pharmacokinetic endpoints:

The concentration of mecamylamine in plasma will be used to construct a PK

model. If deemed appropriate a PK-PD model of mecamylamine will be developed.

Secondary outcome

Safety will be assessed through reporting of adverse events, physical

examinations, concomitant medication use, vital

signs, clinical laboratory evaluation, hematology and blood chemistry,

serology, drugs of abuse screening, routine

urinalysis, alcohol breath test, electrocardiograms.

Study description

Background summary

Anti-cholinergic pharmacological challenges have been used previously to induce cognitive disturbances reminiscent of Alzheimer*s Disease (AD), but their use is more appropriate for proof of pharmacology of cholinergic enhancing drugs. The most commonly used anti-cholinergic challenge is scopolamine, a muscarinic acetylcholine (ACh) receptor antagonist. However, using a muscarinic antagonist to prove nicotinic agonist pharmacology would seem pharmacologically inadequate. Furthermore, scopolamine exhibits a sedative effect following administration which could interfere with measurements of cognitive function. Due to increased activity in the development of selective nicotinic agonists it would seem appealing to establish an anti-cholinergic challenge model selective for the nicotinic receptor. Currently no model exists that allows the pharmacology of a nicotinic agonist to be determined based on a nicotinic antagonist. The aim of the present study is to validate a mecamylamine based anti-nicotinergic challenge model to prove pharmacology of nicotinic agonists. Mecamylamine is a nicotinic acetylcholine receptor antagonist, active in peripheral autonomic ganglia, but also binding to nicotinic ACh receptors (nAChR) present in the brain. The cholinergic system in the brain is known to play an important role in several cognitive processes such as attention, reaction time, and memory. A previous study confirmed that the administration of 10 and 20 mg mecamylamine in healthy volunteers leads to a temporary, reversible perturbation of these cognitive processes. This effect was however small when compared to a scopolamine challenge which was also examined in this study. In order to accurately characterize nicotinic agonist pharmacology it was decided that a higher effect was required. In the present study a dose of 30 mg mecamylamine will be used. This is predicted to cause an increased effect allowing for a more accurate pharmokinetic/pharmacodynamic (PK/PD) model to be

established, and allow improved characterization of the PD effects of nicotinic agonists. Furthermore by combining the data acquired from the previous study, it will allow a dose-effect relationship to be established (10 mg, 20 mg, 30 mg).
To validate the mecamylamine model as an effective anti-cholinergic challenge two nicotinic receptor agonists will be used. The first, galantamine, is a nicotinic acetylcholine receptor modulator and CEI and is used to treat patients with AD. The second, nicotine, is a full nAChR agonist, which acts on various nicotinic receptors which are believed to play a role in cognitive function.

Study objective

Primary Objectives
• To demonstrate if the impairment of cognitive function caused by mecamylamine administration can be diminished by an nAChR agonist or CEI.
• To evaluate to what extent a single dose of 30 mg mecamylamine may cause a more pronounced cognitive impairment than the lower dose levels of 10 and 20 mg that were previously tested.

Secondary Objectives
• To improve characterization of the mecamylamine-induced cognitive impairment (time course and additional parameters).
• To investigate the pharmacokinetics of mecamylamine following a 30 mg dose.
• To investigate the time course of the pharmacodynamic effect of mecamylamine and to explore the pharmacokinetic/pharmacodynamic relationship of mecamylamine on cognition, now including the data obtained at a 30 mg dose.
• To investigate the safety and tolerability of mecamylamine 30 mg compared with placebo.
• To investigate the safety and tolerability of a pharmacological challenge study with mecamylamine in conjunction with nicotinic receptor agonists.

Study design

A randomized, double-blind, double-dummy, placebo-controlled, single dose, 4-way cross-over study of the reversibility of cognitive deficits induced by a nicotinic anti-cholinergic challenge with mecamylamine by a cholinesterase inhibitor and a nicotinic receptor agonist

Intervention

Acethylcholine receptor antagonist
• Mecamylamine hydrochloride (HCl) 30 mg (hard gelatin capsules containing 12.2 mg mecamylamine HCl (equivalent to 10 mg mecamylamine free base) and microcrystalline cellulose as filling agent). Thirty mg are 3 capsules, oral dose

Nicotinic receptor agonist
•Nicotine-containing patch of 21 mg nicotine, patch.

Cholinesterase inhibitor
Galantamine hydrobromide, 4 capsules of 4 gr galantamine HBR, oral.

Placebo
Matching placebos (oral and transdermal)

Study burden and risks

Blood sampling: possible pain and bruising(transient)

Study drugs:
mecamylamine: This drug was a registered antihypertensive for over 50 years and was removed from the market for economical reasons. A side effect likely to occur is orthostatic hypotension. When using as pharmacological challenge, mild and transient adverse have been reported: sedation (7%), *feeling fuzzy*. Other anticholinergic adverse effects had not been reported in these studies, but in the postmarket surveillance as anti-hypertensive drug following AE were described: dry mouth, constipation, vomiting, urinary retention, and mydriasis. All are mild in severity and transient. The most commonly reported adverse events following dosing with mecamylamine 20 mg were somnolence (64%), fatigue (36%), nausea (36%) and dizziness (29%), and were all mild in intensity. Galantamine and nicotine are registered drug and widely used in smoking cessation therapy (nicotine0 and improvement of cognitive function (galantamine HBR). The adverse event most commonly reported of galantamine was nausea. The general toxicity of nicotine is well known. Application site reactions are the most frequent adverse reaction associated with patches. Excessive use of nicotine patches by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

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

1.Healthy male subjects, 18 to 45 years of age, inclusive. Healthy status is defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;;2.Body Mass Index (BMI) between 18 kg/m2 and 32 kg/m2;;3.Incidental smokers (defined as smoking tobacco at least once a month and no more than 5 cigarettes per day);;4.Able to participate and willing to provide written informed consent and to comply with the study restrictions.

Exclusion criteria

1.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 as judged by the investigator;;2.Any disease associated with cognitive impairment, including schizophrenia and dementia;;3.Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), electrocardiogram (ECG) and vital signs, or physical findings at screening (as judged by the investigator);;4.Presence of orthostatic hypotension as defined by a decrease of blood pressure >= 20 mmHg systolic or >= 10 mmHg diastolic, measured 2 min after standing up; ;5.Evidence of elevated blood pressure at screening of >140 mmHg systolic or >90 mmHg diastolic;;6.Positive Hepatitis B surface antigen (HBsAG), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;;7.History of alcoholism or substance abuse within three years prior to screening;;8.Subject is unable to refrain from alcohol consumption during study confinement and at least 24 hours before screening, before dosing, and before each scheduled visit;;9.Subject is a habitual and heavy

consumer of caffeinated beverages (more than 8 cups of coffee or equivalent/day) and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) from 24 hours prior to dosing until discharge from the CRU for each study period;;10.Positive urine drug screen (UDS) or alcohol test at screening and/or Day 1 of each period;;11.Subject is unable to refrain from the use of concomitant medication which, in the opinion of the investigator, interferes with their ability to participate in the study, from 7 days prior to dosing on Day 1 Period 1 until end of study;;12.Subject has a history of severe allergies, or has had an anaphylactic reaction to prescription or non-prescription drugs or food;;13.Known hypersensitivity to the investigational drug or comparative drug or drugs of the same class, or any of their excipients. ;14.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 drugs;;15.Currently using any nicotine replacement therapy, smoking cessation medications or remedies, including varenicline (Chantix ®) or have used any nicotinic products for smoking cessation within 3 months of screening; ;16.History of allergic reaction to nicotine-containing products ;17.Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug (Day 1 Period 1) or more than 4 times per year;;18.Donation or loss of more than 500 mL blood within three months prior to screening;;19.Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-07-2015
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Inversine
Generic name:	mecamylamine hydrochloride
Product type:	Medicine
Brand name:	NiQuitin
Generic name:	Nicotin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Reminyl
Generic name:	Galantamine hydrobromide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-07-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-09-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-09-2015
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-09-2015
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	EUCTR2014-001358-41-NL
CCMO	NL49296.058.14