A randomized, double-blind, double-dummy, single dose, 4-way cross-over study to develop an anti-cholinergic pharmacological challenge with mecamylamine in comparison to scopolamine

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

Summary

ID

NL-OMON37435

Source
ToetsingOnline

Brief title
Mecamylamine challenge in healthy volunteers

Condition

- Neurological disorders NEC

Synonym
Alzheimer, mental deterioration

Research involving

Human

Sponsors and support

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

Intervention

Keyword: attention, mecamylamine, memory, nicotinic ACh receptor antagonist

Outcome measures

Primary outcome

Main Parameters:

Pharmacokinetics: Levels of mecamylamine and scopolamine will be determined in blood samples collected at the time points depicted in the Time and Events schedule. The following parameters will be calculated: cmax, tmax, t1/2el. Additional exploratory analyses of PK parameters may be performed as necessary. Also, a PK/PD-model will be created. To this end, the PK samples will be taken within a 20 minute window to match PD measurements.

Pharmacodynamics: The following PD criteria will be evaluated (see the Time and Events Schedule for the exact time of PD measurements):

• Adaptive tracking

• Neuro-endocrine parameters (LH, prolactin, cortisol)

• Pharmaco-EEG

• Pupil size

• Saccadic eye movements

• Smooth pursuit eye movement

• Body sway

• Finger tapping

• Simple reaction time task

• Stroop test

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

• Visual n-back test

• Visual verbal learning test (30 words).

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 pro-cholinergic drugs. The most well known anti-cholinergic challenge method is with scopolamine, a muscarinic acetylcholine (ACh) receptor antagonist, and has been used amongst others to prove pharmacology of cholinesterase inhibitors (CEI). Currently, few new CEI*s are being developed, but there is more activity in the development of selective nicotinic receptor agonists. Using a muscarinic antagonist to prove pharmacology of a nicotinic agonist would seem pharmacologically inadequate (even though some reversal of scopolamine induced cognitive deficits has been shown to occur due to nicotinic agonists). The aim of the present study is to set up an anti-nicotinergic challenge method in order to better prove pharmacology of nicotinic agonists. Mecamylamine is a nicotinic ACh receptor antagonist, active in peripheral autonomic ganglia, but also binding to nicotinic ACh receptors present in the brain. The cholinergic system in the brain is hypothesized to play an important role in several cognitive processes

such as attention, reaction time, and memory. Administration of mecamylamine to healthy volunteers has been shown to lead to a temporary, reversible perturbation of these cognitive processes. An anti-nicotinic pharmacological challenge using mecamylamine has been described previously, but with the current study we aim to gain more and time-dependent information on pharmacodynamic (PD) effects of mecamylamine. Simultaneously, pharmacokinetic (PK) characterization will be performed in order to confirm and extent non-compartmental PK data. Moreover, the PK/PD relationships of mecamylamine have not been addressed yet. Assessing simultaneously PD effects of scopolamine and mecamylamine using the Neurocart test battery, a computerized system for psychological and cognitive measurements including cognitive test performance, will allow comparison of anti-cholinergic challenges without the limitations of post hoc analysis.

Study objective

The specific goals of the study are:
- To identify which dose(s) of mecamylamine cause cognitive and memory impairment as demonstrated using the NeuroCart CNS test battery
- To investigate the safety and tolerability of mecamylamine by comparison with placebo.
- To determine the pharmacokinetic (PK) profile of mecamylamine after oral administration.
- To investigate the time course of the pharmacodynamic (PD) effects of mecamylamine as well as the PK/PD relationships in healthy volunteers
- Compare the effects of mecamylamine, a nicotinergic ACh receptor antagonist, on cognitive function and memory with the effects of scopolamine, a muscarinic ACh receptor antagonist

Study design

Single center, double-blind, double-dummy, placebo-controlled, randomized 4-period way crossover study with mecamylamine (nicotinergic antagonist) and scopolamine (muscarinergic antagonist) in healthy volunteers.

Intervention

Drugs and Dosages:

Active Compound: Mecamylamine hydrochloride
Dosage form: Hard gelatin caspsules containing 12.2 mg mecamylamine HCl (equivalent to 10 mg mecamylamine free base) and microcrystalline cellulose as filling agent
Strength: 10 mg (1 capsule + placebo), 20 mg (2 capsules)
Placebo: Gelatin capsule containing microcrystalline cellulose

Active Compound: Scopolamine Hydrobromide
Dosage form: Solution for intravenous (i.v.) administration
Strength: 0.1 mg/mL
Placebo: saline
Scopolamine hydrobromide (5 mL) will be administered as a 15-minute i.v. infusion (i.e. 0.33 mL/min). The total dose will be 0.5 mg scopolamine hydrobromide that is equivalent to 0.35 mg scopolamine as free base.

Study burden and risks

Mecamylamine:
Mecamylamine has been more than 50 year on the market in the US. 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 have not been reported in these studies.

Scopolamine:
Scopolamine is well known to block postganglionic autonomic sites, producing an array of anticholinergic symptoms. Less known CNS symptoms, such as hallucinations, are mentioned only sparingly or anecdotally. Because of its shorter half-life, and far better defined PK properties and the experience of CHDR in scopolamine challenges using this dosage and form of dosage, the chance of risks is considered minimal. Following adverse effects have been reported in a previous CHDR study: anticholinergic symptoms (97%), nausea (8%), dizziness (7%) and palpitations (6%). In general, the scopolamine treatment was well tolerated by all other subjects. All symptoms were mild and transient.

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. Signed informed consent document
2. Healthy, male volunteers aged between 18 and 45 years
3. Body Mass Index between 18 kg/m2 and 32 kg/m2
4. Non-smokers for at least 1 year
5. Willingness to comply with study procedures and 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. Clinically relevant abnormal laboratory results, electrocardiogram (ECG) and vital signs, or physical findings at screening (as judged by the investigator);
3. Presence of orthostatic hypotension as defined by a decrease of blood pressure >=10 mmHg systolic or >= 20 mmHg diastolic measured 2 min after standing up
4. Positive test for hepatitis B, C or HIV;
5. History of alcoholism or substance abuse within three years prior to screening;
6. Subjects unable to refrain from alcohol use from 24hours prior to dosing on Day 1 Periods 1-5 until discharge from the CRU for each study period;
7. Used tobacco and/or nicotine-containing products within one year of dosing on Day 1 Period 1;
8. Evidence of elevated blood pressure at screening of >140 mmHg systolic or >90 mmHg diastolic;
9. Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at screening and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) from 12 hours prior to dosing until discharge from the CRU for each study period;

10. Positive urine drug screen (UDS) or alcohol or cotinine 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 trial, from 7 days prior to dosing on Day 1 Period 1 until the follow-up study visit;
12. Subject has a history of severe allergies, or has had an anaphylactic reaction to prescription or non-prescription drugs or food;
13. 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 (mecamylamine or scopolamine);
14. 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; history of allergic reaction to nicotine-containing products
15. 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;
16. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines of approximately 500 mL or significant blood loss;
17. Have a history of an allergic reaction to nicotine containing products;
18. Subject does not have veins suitable for canula placement on both arms;
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:	Pending
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Inversine
Generic name:	Mecamylamine hydrochloride
Product type:	Medicine
Brand name:	Scopolamine Cooper
Generic name:	Scopolamine hydrobromide

Ethics review

Approved WMO Date:	17-04-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-05-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-06-2012
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)

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	EUCTR2012-001392-36-NL
CCMO	NL40218.058.12