Research into the suitability of the NeuroKit test method in measuring drug effects

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Primary Objectives:Quantify the PD effects of CNS active compounds with distinct mechanisms of action (lorazepam, modafinil and S-ketamine) with NeuroKit and NeuroCart in healthy male and female participants. Estimate the ratio of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mental impairment disorders
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON57507

Source
Onderzoeksportaal

Brief title
Drug-response validation study of NeuroKit

Condition

- Mental impairment disorders
- Seizures (incl subtypes)

Synonym
central nervous system disorders

Research involving
Human

Sponsors and support

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

Intervention

- Other intervention

Explanation

N.a.

Outcome measures

Primary outcome

Primary endpoints: Saccadic eye movement (NeuroKit and NeuroCart)
Smooth pursuit eye movement (NeuroKit and NeuroCart)
Adaptive tracking (NeuroKit and NeuroCart)
Body sway
N-Back (NeuroKit and NeuroCart)
Finger Tapping (NeuroKit and NeuroCart)
VAS Bowdle (NeuroKit and NeuroCart)
VAS B&L (NeuroKit and NeuroCart)
The 90% confidence interval of the ratio of effect sizes of NeuroKit and NeuroCart, of each PD endpoint per treatment.

Secondary outcome

Secondary endpoints: Lorazepam, modafinil and S-ketamine concentration in plasma
Plasma PK endpoints
Proportion of fully executed VR measurements in %
CADSS questionnaire

Study description

Background summary

Central nervous system (CNS) function in humans can be assessed in groups of neurophysiological, neuroendocrine and neuropsychological effects. Drugs acting on the CNS will usually influence more than one of these groups and affect several different functional domains within each group. This offers numerous possibilities to measure drug-induced changes in CNS-activity. In general, several different complementary tests are applied in early CNS-drug research, with the aim of covering all relevant CNS-functional domains that can be responsive to drug effects such as sedation, stimulation or consciousness.

CHDR has developed a CNS test battery called NeuroCart, consisting of validated neurophysiological and neuropsychological assessments to quantify PD drug effects. The most sensitive assessments include (among others) saccadic eye movement as a measure of

arousal, adaptive tracking of visuomotor coordination and sustained attention, finger tapping of visuomotor coordination, smooth pursuit eye movements and body sway of motor coordination, visual analogue scales (VAS) for subjective drug effects, and N-Back for working memory. Additionally, several other tests can be included depending on the research question and study treatment.

In previous CHDR studies, NeuroCart has been shown to be sensitive to the acute effects of the sedative lorazepam, the stimulant modafinil, and the dissociative S-ketamine, with significant dose and concentration dependent effects on multiple NeuroCart endpoints. As such, NeuroCart represents a useful non-invasive tool to characterize the acute PD profile of several CNS active compounds with distinct mechanisms of action and to relate these to its respective PK profile. One limitation of the NeuroCart, however, is that the current set-up is confined to study execution at CHDR and specific study rooms.

NeuroKit has been developed by CHDR as a portable and scalable version of NeuroCart. It comprises a subset of eight NeuroCart tests, namely saccadic eye movements, smooth pursuit eye movements, adaptive tracking, body sway, N-Back, finger tapping, VAS Bond & Lader, and VAS Bowdle. To facilitate portability, NeuroKit's hardware setup has been adapted, with virtual reality goggles and a touchscreen tablet respectively replacing NeuroCart's computer screen and keyboard, and an accelerometer replacing the potentiometer in the implementation of body sway. Evaluation of the technical performance of individual NeuroKit measurements compared to NeuroCart has been concluded by CHDR, and preliminary analysis showed positive results that warrant the next step in the validation process. However, it remains uncertain whether and to what extent the implemented modifications could affect NeuroKit's performance compared to NeuroCart.

Study objective

Primary Objectives:

- Quantify the PD effects of CNS active compounds with distinct mechanisms of action (lorazepam, modafinil and S-ketamine) with NeuroKit and NeuroCart in healthy male and female participants.

- Estimate the ratio of PD effects of NeuroKit and NeuroCart for CNS active compounds with distinct mechanisms of action (lorazepam, modafinil and S-ketamine) in healthy male and female participants.

Secondary Objectives:

- Quantify the pharmacokinetic profiles of lorazepam, modafinil and S-ketamine during PD measurements on NeuroKit and NeuroCart in healthy male and female participants.

- Evaluate the feasibility of Virtual Reality (VR) to perform NeuroKit saccadic eye movements, smooth pursuit eye movements and adaptive tracking assessment under influence of a compound with dissociative effects (S-ketamine) in healthy male and female participants.

Study design

This is a single centre, randomized, double blind, double-dummy, placebo-controlled, four-way crossover pharmacological validation study to investigate the ability of the newly developed CNS test battery NeuroKit to reliably quantify the pharmacodynamic effects (PD) of CNS-penetrant drugs by comparing PD effects of drugs with distinctly different mechanisms of actions to NeuroCart in healthy male and female volunteers.

The study consists of a medical screening period (from 42 days prior to visit 1) to ensure subjects meet eligibility criteria, including a training on NeuroCart and NeuroKit in a period up to 21 days before first drug administration, followed by four occasions of three days in-clinic each, separated by a wash-out period of 7 to 10 days. A final follow-up visit takes place 7-10 days after last dose, resulting in a total study duration of 82 – 94 days for each subject. This study design will allow for adequate PD assessments of both CNS test batteries.

Intervention

Three study drugs or placebo will be administered to the subjects. S-ketamine 0.475 mg/kg for 75 min + 0.275 mg/kg for 75 min IV, modafinil 200 mg PO, and lorazepam 2 mg PO will be prepared with matching placebo formulations, including capsules and a NaCl 0.9% solution. For modafinil, two 100 mg tablets will be encapsulated for blinding, resulting in two administered capsules for the total dose of 200 mg. For lorazepam, two 1 mg tablets will be encapsulated for blinding, resulting in two administered capsules for the total dose of 2 mg. Administration will occur in a double-dummy fashion, thus, subjects will each time receive four capsules PO and one IV administration. IV S-ketamine or placebo will be administered for 150 minutes at two different infusion rates. Subjects will rinse and swallow all orally administered capsules with a total of 240 mL of water.

Matching placebo will consist of a saline solution or encapsulated placebo capsule. S-ketamine dosing will be individually prepared based on the subject weight at screening. Prior to each dosing the subject will be weighed again. If the change in weight is 15% or more

relative to the weight at screening, the dose must be adjusted to the new weight.

Study burden and risks

Lorazepam, modafinil and S-ketamine are registered drugs with well-characterized pharmacological and safety profiles in humans. Nonetheless since side effects might occur, the study drug administrations will be performed under medical supervision during admission to CHDR's clinic research unit. Subjects will be closely monitored and will only be discharged from the unit if their medical condition allows this. Furthermore, single doses of lorazepam 2 mg, modafinil 200 mg and S-ketamine reaching plasma exposures similar to those targeted in the current study (~ 150 ng/mL) administered in previous CHDR studies, were safe as no serious adverse effects occurred, and those that did occur, were anticipated based on the respective drugs' pharmacological profiles. NeuroCart is a validated CNS-battery that quantifies various pharmacodynamic drug effects including CNS suppression (sedation), stimulation and changes in consciousness and perception. Previously, Neurocart has previously been shown to be sensitive to single doses of lorazepam 2 mg, modafinil 200 mg and S-ketamine reaching plasma exposures similar to those targeted in the current study (~ 150 ng/mL). The key objective of this study is to validate the ability of NeuroKit, as a portable and scalable version of NeuroCart, to reliably quantify the PD effects of CNS-penetrant drugs by comparing the effects of drugs with distinctly different mechanisms of action on NeuroKit to NeuroCart in healthy male and female volunteers. Together therefore, the potential risks to participants are considered minimal and weigh up to the scientific objectives of the study.

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Trial sites

Trial sites in the Netherlands

Centre for Human Drug Research
Target size: 16

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Healthy female or male participants, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical, surgical and psychiatric history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.

- Body mass index (BMI) between 18 and 32 kg/m^2, inclusive, with a minimum weight of 50 kg.

- A self-reported normal or corrected vision.

- Use of any form of birth control is required for heterosexual subjects of childbearing potential who are sexually active during the study, either used by the subject or their sexual partner.

- Female subjects of childbearing potential are required to have a negative urine β-hCG test at screening and pre-dose.

- Participants are willing to give a written informed consent (ICF) in Dutch and adhere to the lifestyle restrictions.

Exclusion criteria

- Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis).

- Clinically significant abnormalities on ECG, as judged by the investigator, including evidence of atrial fibrillation, cardiac arrythmia, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.

- Untreated hypertension defined as SBP greater than 140 mmHg or DBP greater than 90 mmHg at screening. The measurement may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.

- Clinically significant respiratory insufficiency, problems with free airway (as sleep apnea) or muscle conditions limiting breathing (such as myasthenia gravis).

- (History of) increased intracranial pressure.

- History of active malignancy within the last 5 years before screening, with the exception of localized or in situ carcinoma (e.g., skin basal or squamous cell carcinoma).

- Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.

- Current diagnosis, personal history or family history of a clinically significant psychiatric disorder, including substance use disorder or suicidality, at screening.

- A self-reported history of symptoms indicative of any clinically significant disorder including neurological, cognitive or psychiatric diseases at screening.

- History of abuse of alcohol or current use of more than 21 units alcohol per week. Consumption of alcoholic beverages within 24 hours prior to screening or pre-dose. Positive alcohol breath test at screening or pre-dose.

- History of abuse of addictive substances or current abuse, regular user of sedatives, hypnotics, tranquilizers, or any other addictive agent; and/or recreational use of ketamine on 2 or more occasions within 12 months of screening.

- Consumption of illegal drugs within 7 days (within 6 weeks for cannabis or THC) before screening or pre-dose. Positive urine test for drugs of abuse (e.g barbiturates, phencyclidine, cocaine, opiates or amphetamines) at screening or pre-dose.

- Use of any medication (prescription including psychoactive compounds, or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary supplements within 14 days, or less than 5 half-lives (whichever is longer), of study drug administration.

- Smoking more than 5 cigarettes per day within 3 months prior to screening or inability to refrain from using nicotine products from 24 hours pre-dose until discharge from the clinic.

- Performing strenuous physical exercise within 48 hours prior to each admission to the clinical research unit.

- Excessive caffeine consumption, defined as >800 mg per day from 7 days prior to the first dose of the study drug until 24 hours prior to dosing and during wash-out periods in between occasions, in addition to any caffeine consumption from 24 hours prior to the start of dosing until discharge from the study unit. Caffeine quantities defined as: one cup of coffee contains 100 mg of caffeine; one cup of tea, or one glass of cola, or potion of chocolate (dark:100 g, milk 200 g) contains approximately 40 mg of caffeine; one bottle of Red Bull contains

approximately 80 mg of caffeine.

- Confirmed significant previous allergic reaction (urticaria or anaphylaxis) to any (prescription) drug, or multiple drug allergies (non-active hay fever is acceptable).

- Any blood donation or other loss of blood greater than 500 mL within 3 months of screening or plasma donation within 2 weeks of screening.

- Participation in an investigational drug or device study, more than four times per year, and last dosing of previous study was within 90 days, or 5 half-lives (whichever is longest) prior to first dosing of this study

- Unwillingness or inability to understand or comply with the study protocol and lifestyle restrictions.

- Legal incapacity or inability to provide written informed consent.

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-04-2025
Enrollment:	16
Duration:	3 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Yes

Plan description
N.a.

Ethics review

Approved WMO Date:	11-04-2025
Application type:	First submission
Review commission:	METC Stg BEBO

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
Research portal	NL-009162