A randomized, double blind, placebo-controlled crossover study to investigate the effects of a selective serotonergic reuptake inhibitor on resting state fMRI in heathy volunteers.

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

Summary

ID

NL-OMON38858

Source
ToetsingOnline

Brief title
Pharmacological resting state fMRI with an SSRI.

Condition

- Mental impairment disorders

Synonym
Depressie, stemming

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Challenge, FMRI, SSRI

Outcome measures

Primary outcome

Resting state network activity as measured with RS-fMRI.

Secondary outcome

1) Cognitive functioning as measured with different subtests of the Neurocart

(a validated multimodal CNS-test battery):

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

• VAS for nausea

• Adaptive tracking

• Simple reaction time

• Visual N-back test

• Stroop test

• Symbol-digit substitution test

• Face encoding and recognition task

2) Pharmacokinetics of sertraline:

• The time-course of the serum levels of sertraline

Study description

Background summary

Over the past years CHDR has collaborated with the Leiden Institute for Brain and Cognition (LIBC) at the Leiden University Medical Centre (LUMC) to develop a novel method of drug characterization using resting state functional magnetic resonance imaging (RS-fMRI). This method uses the principles of a pharmacokinetic study with dosing of a drug, followed by a series of measurements. Measurements taken are RS-fMRI scans, a selection of Neurocart tasks, neuroendocrine parameters and plasma drug levels, at intervals deemed relevant for the particular drug under study.

It is well known that central nervous system (CNS) functions depend on large-scale network interactions of brain regions. Such interactions can be studied with RS-fMRI. Previous pharmaco-rs-fMRI studies (Ph-RS-fMRI) in healthy volunteers demonstrated specific, dose-dependent changes in functional connectivity of different brain regions after administration of alcohol, morphine or THC. These findings were associated with changes in cognition.

In the most recent, ongoing study (CHDR1203/P12.042) the Ph-RS-fMRI method is used to gain more insight into changes with normal aging and in various types of dementia. The hypothesis of CHDR1203 is that the Ph-RS-fMRI technique with specific pharmacological intervention in the cholinergic (galantamine) and serotonergic (citalopram) system will lead to a different response both in functional connectivity and on cognitive tests between the study groups (healthy young adults; age 18-30, healthy elderly; age 50-75, patients with Alzheimer*s disease, dementia with Lewy bodies, or frontotemporal dementia). In the future, this technique may provide more certainty in early diagnosis of the different types of dementia.

The control group of the CHDR1203 study, consisting of 12 healthy young adults and 12 healthy elderly, has been completed in the first week of February 2013. These data will be analyzed in April/May 2013. The aim of the study proposed here is to confirm the expected differences found in the CHDR1203 study with another drug in the same class as citalopram (a selective serotonergic reuptake inhibitor (SSRI)). If these show qualitatively similar results, this strengthens the confidence in this technique as a highly sensitive and specific method of drug investigation.

Study objective

We propose to conduct a study in healthy subjects where a serotonergic challenge is given in a placebo-controlled, crossover fashion. Before each challenge, participants will be measured 1 time to define their baseline resting state networks (RSNs) and cognitive functioning. After each challenge, participants will be measured 4 times within 9 hrs to assess their RSNs and correlate these measures to the plasma PK samples of sertraline. Additionally, the RSNs and plasma PK samples will be correlated to measures of cognition. The main goal of the research is to investigate whether the Ph-RS-fMRI technique is sensitive as a measure of pharmacokinetics and to compare the results to the

effects of citalopram in the ongoing Ph-RS-FMRI study (CHDR1203/P12.042).

Study design

• Randomized, double blind, placebo-controlled crossover study
• Treatment arms
• Sertraline 75 mg
• Placebo
• Wash-out of at least 10 days

Intervention

During 2 study days, the effect of a single dose of sertraline 75 mg will be measured in a double-blind, randomized, placebo-controlled design. On each study day, one of the 2 agents (sertraline or placebo) will be administered. Washout periods between study days will be at least 10 days. On each study administration will be combined with administration of granisetron and a snack, to prevent for nausea and vomiting:
• Sertraline study day: 75 mg
• Placebo study day: placebo

Study burden and risks

Not applicable

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

• Have a body-mass index (BMI) between 18 and 30 kg/m2.
• Each subject is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent.
• Age subjects: age 18-30.

Exclusion criteria

• Contra-indication to MRI scanning (pacemaker and defibrillator, intraorbital or intraocular metallic fragments, cochlear implants, one or more metal eartubes, intracranial clips, a non-removable insulin pump, a non-removable neurostimulator, a mechanical cardiac valve, an hydrocephalus pump, ferromagnetic implants, intra-uterine device, permanent make-up, tattoos above the shoulders, pregnancy, operation in 6 weeks preceding the MRI, claustrophobia, inability to lie still for a period of 20 minutes in the MRI scanner, Fear or problems during the RS-FMRI scan).
• Relatives of study personnel directly involved with the conduct of the study, study investigators or sub-investigators.
• Clinically relevant abnormal history of physical and mental health as determined by medical history taking and physical examinations obtained during the screening visit (as judged by the investigator).
• Clinically relevant abnormal laboratory results, ECG and vital signs, or physical findings at screening (as judged by the investigator).
• Positive test for hepatitis B, C or HIV.
• Subjects using, on average, more than 4 units of alcohol per day, and unable to refrain from alcohol use during the study days.
• Subjects smoking, on average, more than 5 cigarettes per day, and unable to refrain from smoking during the study days.
• Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at the time of the study and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, black tea, cola, chocolate) during study days.
• Positive drug or alcohol test at screening and/or study days.
• 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 drug.
• Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug or more than 4 times per year.
• Donation or loss of blood (> 500 mL) within 3 months prior to screening.
• Inadequate venous accessibility as judged by the physician or nurse.
• Use of benzodiazepine within 48 hours before a study day.
• Pregnancy or breast feeding.
• Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject.
• Use of medication in the 2 weeks prior to the first study day that is, in the opinion of the investigator, interfering with the study or the study medication.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-04-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Granisetron
Generic name:	Granisetron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zoloft

Generic name:	Sertraline
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2013
Application type:	First submission
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	EUCTR2013-000426-62-NL
CCMO	NL43446.058.13