A Randomized, Double-Blind, Placebo-Controlled, 2-Period, 2- Treatment Cross-Over Study to Evaluate the Effects of Ketamine on Resting State Functional Brain Connectivity in Major Depressive Disorder Patients who fail to respond to a Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Noradrenaline Reuptake Inhibitor (SNRI)

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Primary objectiveTo evaluate the CNS effects of a single intravenous dose of ketamine on functional brain networks by performing resting state functional magnetic resonance imaging (fMRI) in major depressive disorder (MDD) patients who fail to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON43144

Source
ToetsingOnline

Brief title
A study to assess the effect of ketamine on depression using fMRI

Condition

- Mood disorders and disturbances NEC

Synonym
depression, Major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Sumitomo Dainippon Pharma
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Depression, fMRI, Ketamine

Outcome measures

Primary outcome

1. Resting state fMRI whole brain analysis:

Changes in functional connectivity in the 10 standard template resting state brain networks as described by (Smith et al. 2009), as measured using independent component analysis (ICA) and dual regression. These networks comprise three visual networks (consisting of medial, occipital pole, and lateral visual areas), the default mode network (DMN, medial parietal, bilateral inferior*lateral*parietal and ventromedial frontal cortex), cerebellar network, sensorimotor network (supplementary motor area, sensorimotor cortex, and secondary somatosensory cortex), auditory network (superior temporal gyrus, Heschl's gyrus, and posterior insular), executive control network (medial*frontal areas, including anterior cingulate and paracingulate) and two frontoparietal networks (frontoparietal areas left and

right).

2. Altered functional connectivity by a single intravenous dose of ketamine using a seed-based approach:

a. functional connectivity from amygdala

b. functional connectivity from dorsal nexus (dorsomedial prefrontal cortex)

3. Effects of baseline cerebral blood flow on changes in the MRI signal by performing arterial spin labeling (ASL)

4. Effect on depressive symptoms using the MADRS

5. Dissociative symptoms using the CADSS.

6. Bond-Lader Visual Analogue Scale (VAS) and Bowdle VAS assessment scores.

Secondary outcome

Pharmacokinetic endpoints

* Individual and mean Cmax, Tmax, AUC0-t (t to be determined) for plasma ketamine, norketamine and (2S,6S;2R,6R)- hydroxynorketamine

* The ratio ketamine: norketamine and (2S,6S;2R,6R)- hydroxynorketamine for Cmax and AUC0-t.

* The primary pharmacokinetic parameters for ketamine, norketamine and (2S,6S;2R,6R)- hydroxynorketamine will be estimated by means of compartmental analysis. All pharmacokinetic parameters will be summarized descriptively including mean, geometric mean, median, range, standard deviation and coefficient of variation. Individual plasma concentrations at each sampling point for ketamine and its metabolites will be presented by listing and descriptive summary statistics including means, geometric means, ranges, standard deviation and coefficient of variation. Individual and mean

concentration versus time will be plotted on linear or semi- logarithmic scale

as appropriate.

Tolerability / safety endpoints

The safety and tolerability of ketamine will be assessed in patients with MDD,

with special attention for:

* Suicidal ideation/behaviour as measured with the Columbia Suicide Severity

Rating Scale (C-SSRS).

* The frequency and severity of adverse events

* Questionnaire Psychotic Experiences (QPE)

* Laboratory safety, blood pressure, pulse rate, ECG

Study description

Background summary

Ketamine can be conceived of as a pharmacological probe to investigate the role of glutamatergic system in MDD by modulating central NMDAR*s. Since the administration of ketamine in untreated MDD patients may raise ethical concerns, the current study aims to evaluate the effects of a single intravenous dose of ketamine on functional brain networks in a MDD population who fails to respond to a first trial with a SSRI or serotonin noradrenaline reuptake inhibitor (SNRI). To our knowledge this will be the first study to investigate the CNS PD effects of ketamine by performing resting state functional magnetic resonance imaging (fMRI) in a non-therapy resistant MDD population.

Study objective

Primary objective
To evaluate the CNS effects of a single intravenous dose of ketamine on functional brain networks by performing resting state functional magnetic resonance imaging (fMRI) in major depressive disorder (MDD) patients who fail to respond to a selective serotonin reuptake inhibitor (SSRI) or serotonin

noradrenaline reuptake inhibitor (SNRI).

Secondary Objectives
1. To explore altered functional connectivity by administration of a single intravenous dose of ketamine in patients with SSRI/SNRI-treatment resistant MDD.
2. To explore the changes of functional brain networks and functional connectivity associated with the pharmacokinetics of ketamine and its metabolites by PK/PD correlation analysis following a single intravenous dose of ketamine administration in MDD patients who fail to respond to a SSRI or SNRI
3. To evaluate the effect of single intravenous dose of ketamine on the course of depressive symptoms using the The Montgomery-Asberg Depression Rating Scale (MADRS) in MDD patients who fail to respond to a selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI).
4. To evaluate the psychomimetic effects of a single intravenous dose of ketamine) using the The Clinician Administered Dissociative States Scale (CADSS) and Questionnaire Psychotic Experiences (QPE) in MDD patients who fail to respond to a selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI).
5. To evaluate the safety (ECG, blood and urine analysis, CSSRS) of administration of a single intravenous dose of ketamine in MDD patients who fail to respond to a selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI).

Study design

A Randomized, Double-Blind, Placebo-Controlled, 2-Period, 2-Treatment Cross-Over Study

Intervention

The glutamatergic NMDAR antagonist ketamine is a racemate of R-(-)-ketamine and S-(+)-ketamine. It is registered in Europe as an anesthetic agent and it is frequently applied as an off-label treatment to help manage chronic pain. In addition, both single and multiple subanaesthetic intravenous (IV) administrations of ketamine have demonstrated robust antidepressant effects in patients suffering from major depressive disorder (MDD).

Study burden and risks

The administration of a subanaesthetic dose of ketamine was generally well tolerated in previous studies performed at the CHDR (data on file, manuscript in preparation) and in literature. However, subjects who have no/limited experiences with the effects of recreational psychoactive substances such as alcohol may have a higher risk of intolerability to ketamine effects. Psychotomimetic reactions include anxiety, chest pain, palpitations, agitation, flashbacks, delirium, dystonia, psychosis and schizophrenia-like symptoms. The

psychomimetic reactions seem related to the infusion of ketamine and disappear soon after the discontinuation of the infusion. None of the cited studies reports a rebound effect (increased depressive experience) after termination of the infusion.
Potential adverse effects of ketamine administration include hypersalivation, hyperreflexia, muscle hypertonicity, transient clonus, increased intraocular pressure, emesis, transient rash, agitation dizziness and seizures.
Hypertension, tachycardia, increase pulmonary pressures, increased intra-ocular pressure and pulmonary edema can also be seen as an effect of sympathomimetic stimulation by ketamine.
Laryngospasm (during infusion) is frequently cited as an adverse effect of ketamine, but it is rarely observed. At the dose used during treatment for treatment resistant depression (TRD) (0.5 mg/kg of ketamine) no laryngospasm has been observed in literature.

Ketamine has a potential for abuse and abuse may lead to moderate or low physical dependence or high psychological dependence. Subjects should not drive a car and should not engage in activities that require operating vehicles or dangerous machinery following administration of ketamine. Thus, the subjects will remain in the clinic under supervision and will be discharged by a physician only if their medical condition allows. No specific antidotes are available/are necessary. Supportive measures will be used in case of adverse events. Careful observation and medical management will minimize any associated risk in this study.
No beneficial effect for the patient is expected from a single subanaesthetic IV dose of ketamine.

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

Eligible subjects must meet all of the following inclusion criteria at screening:
- Men or women, 18 to 65 years of age, inclusive.
- Meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for depression, without psychotic features based upon clinical assessment at screening and confirmed by the Mini-International Neuropsychiatric Interview (MINI). Comorbid anxiety disorders with the exception of Post-Traumatic Stress Disorder (PTSD) are allowed, provided these are not the primary psychiatric diagnosis.
- Confirmation of the psychiatric diagnosis by the attending general practitioner and/or psychiatrist.
- Be medically stable on the basis of physical examination, 12-lead ECG, and vital signs, performed at Screening. If there are abnormalities, they must be consistent with the underlying illness in the study population.
- Be medically stable on the basis of clinical laboratory tests performed at screening.
- Has a Hamilton questionnaire score of * 18, at screening and randomization
- Partial or no response to a first trial with a SSRI or SNRI despite a therapeutic dose for at least 4 weeks of treatment.

Exclusion criteria

- Current DSM-IV-TR diagnosis made by attending GP or psychiatrist, or established with the MINI of a comorbid psychotic disorder or MDD with psychotic features, bipolar or related disorders, obsessive compulsive disorder, intellectual disability, borderline personality disorder, antisocial personality disorder, histrionic personality disorder or narcissistic personality disorder
- Patient has a history of drug or alcohol abuse or dependence according to DSM-IV criteria, except nicotine or caffeine, within 6 months before Screening.

- Has been involuntarily committed to psychiatric hospital (current episode)

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):	01-12-2016
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ketamin Rotexmedica
Generic name:	Ketamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-11-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	13-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-003999-51-NL
CCMO	NL59430.056.16