Randomized, Double-Blind, Double-Dummy, Placebo-Controlled 4-way Crossover Study to assess the Pharmacodynamics and Pharmacokinetics of Oral and Intravenous S-Ketamine in Healthy Volunteers

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Primary Objectives* To investigate the effects of PO and IV S-ketamine and its metabolite S-norketamine on functional CNS tests up to 6h (acute effects) and 24h (delayed effects) after administration using NeuroCart test battery in healthy subjects...

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

Summary

ID

NL-OMON55261

Source
ToetsingOnline

Brief title
PKPD of Oral vs IV S-Ketamine in HV

Condition

- Mood disorders and disturbances NEC

Synonym
Depression, depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Pharmacodynamics, Pharmacokinetics, S-Ketamine

Outcome measures

Primary outcome

Tolerability / safety endpoints

- treatment-emergent adverse events (AEs) and serious adverse events (SAEs)

- adverse events leading to premature discontinuation of study drug

- epileptic seizures as a result of TMS

- laboratory safety, vital signs and ECG

Pharmacokinetic endpoints

Pharmacokinetic variables (including but not limited to Cmax, AUC0-*, clearance (CL), Vss, terminal half-life (t*)) for the different compounds and metabolites will be evaluated if deemed appropriate. For analysis concentrations of S-ketamine, S-norketamine, and S-hydroxynorketamine will be obtained in plasma, according to the schedule specified in table 1. Data may be used for PK or PK-PD modelling.

Pharmacodynamic endpoints

NeuroCart

* Saccadic eye movements

* Smooth pursuit eye movements

* Body sway

* Adaptive tracking

* Visual Analog Scales (VAS) Bond and Lader

* Visual Analog Scale (VAS) Bowdle

* Digit Symbol Substitution Test (DSST)

TMS-EMG

* rMT measured with single pulse TMS

* Peak-to-peak amplitude of the motor evoked potential (MEP) measured with single pulse TMS (stimulation intensity: 120% rMT)

* Short intracortical inhibition (SICI) measured with paired pulse TMS at an interstimulus

* interval (ISI) of 2 ms (stimulation intensity: conditioning pulse 80% rMT, test pulse: 120% rMT)

* Long intracortical inhibition (LICI) measured with paired pulse TMS at ISIs 50, 100 and 300 ms (stimulation intensity: conditioning and test pulse 120% rMT).

TMS-EEG

* Amplitude of the TMS evoked potential (TEP) measured with single pulse TMS and paired pulse TMS at ISIs 2, 50, 100 and 300 ms

EEG

* Resting state EEG

* P300/ active auditory oddball

* 40Hz Auditory Steady State Response (ASSR)

* Auditory Sensory Gating (ASG)

Secondary outcome

Oxford ETB

* Facial Expression Recognition Task (FERT) - perception of social cues

* Emotional Categorisation Task (ECAT) - attention to affective information

* Faces Dot Probe Task (FDOT) - attention to affective information

* Emotional Recall Task (EREC) - memory for affective information

* Emotional Recognition Memory Task (EMEM) - memory for affective information

MEQ30

* scores on *mystical* (subdomain)

* scores on *positive mood* (subdomain)

* scores on *space/time* (subdomain)

* scores on *ineffability* (subdomain)

Study description

Background summary

Treatment resistant major depressive disorder (TR-MDD) is a serious and potentially lethal psychiatric illness with a lifetime prevalence of up to 2%.1 The non-competitive glutamate N-Methyl-D-aspartate receptor (NMDAR) antagonist ketamine demonstrates rapid antidepressant efficacy 24h after administration in

TR-MDD patients.2 It therefore is a unique compound in terms of onset of antidepressant effects compared to the conventional monoaminergic antidepressant drugs, and as a consequence, is currently being investigated as a potential treatment for TR-MDD in clinical practice.

Study objective

Primary Objectives
* To investigate the effects of PO and IV S-ketamine and its metabolite S-norketamine on functional CNS tests up to 6h (acute effects) and 24h (delayed effects) after administration using NeuroCart test battery in healthy subjects
* To investigate the effects of PO and IV S-ketamine and its metabolite S-norketamine on cortical excitability up to 6h (acute effects) and 24h (delayed effects) after administration using TMS-EEG and TMS-electromyography (EMG) in healthy subjects

Secondary Objectives
* To explore effects of PO and IV S-ketamine and its metabolite S-norketamine on emotional processing using ETB at 24h after administration (delayed effects) in healthy volunteers
* To explore effects of PO and IV S-ketamine and its metabolite S-norketamine on brain activity up to 6h (acute effects) and 24h (delayed effects) after administration using EEG in healthy subjects
* To further characterize the pharmacokinetics and pharmacodynamics of IV vs oral S-ketamine and its metabolite S-norketamine
* To characterize the subjective dissociative effects of S-ketamine and its metabolite S-norketamine retrospectively using the Mystical Experiences Questionnaire (MEQ30)

Exploratory Objective
* To assess the relationship between personality characteristics and individual response to S-ketamine using the Dutch Personality Questionnaire (DPQ)/Nederlandse Persoonlijkheidsvragenlijst(NPV), Cloninger Temperament and Character Inventory (TCI) and Spielberger State-Trait Anxiety Inventory*Trait inventory (STAI-DY).

Study design

Randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover study in 16 healthy subjects. The study consists of a medical screening (from 6 weeks prior to visit 1) and training period (from 3 weeks prior to visit 1) to ensure subjects meet eligibility criteria, followed by 4 in-clinic periods (of aproximately 2 days) separated with a wash-out period of 14 to 21 days, during which subjects will return for a short visit in which PD measurements will be done on Day 7 post-dose. A final follow-up visit takes place at least 14 days after last dose

Intervention

S-ketamine 0.2 mg/kg oral solution in single dose
S-ketamine 0.45 mg/kg oral solution in single dose
S-ketamine 0.4 mg/kg IV over 40 min
placebo: intravenous saline, oral matching solution (double-dummy)

Study burden and risks

Intranasal S-ketamine has been FDA-approved for the treatment of TR-MDD and intravenous S-ketamine has been approved for anaesthesia and/or pain treatment in several EU countries, including the Netherlands. However, S-ketamine will be administered in lower (antidepressant/subanaesthetic) dosages in the current study. S-ketamine has acute psychomimetic effects at the planned dose levels in this study which have been well-characterized previously.7 In higher dosages it is an anaesthetic drug with a favourable safety profile.91 Psychomimetic symptoms as described above, will wane off over time and disappear by 4 to 6h post-dose. Nonetheless, subjects will remain in the clinic for 30h post administration under supervision and will be discharged by a physician only if their medical condition allows. The subjects can be closely monitored for any adverse signs during the different treatments. In addition, subjects will not be allowed drive a car and should not engage in activities that require operating vehicles or dangerous machinery following administration of S-ketamine. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

Preclinical data may be of less importance as extensive clinical experience exists for racemic ketamine as well as S-ketamine. However, clinical use is often short-term. Therefore, long-term effects in humans have mostly been observed through reports of recreational abuse. In the current study, only single doses will be administered on each occasion.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy female or male subjects, 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 electrocardiogram (ECG), haematology, blood chemistry, and urinalysis.
2. Able to participate and willing to give written informed consent and to comply with the study restrictions.
3. 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.
4. Able to read and understand English at a sufficient level in order to participate in the ETB.

Exclusion criteria

1. Positive test for drugs of abuse at screening or pre-dose.
2. The subject has a positive pregnancy test.
3. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average.
4. History or symptoms of any significant disease including (but not limited to), neurological, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
5. The subject has a previous or current, or a family history of, a clinically significant psychiatric disorder, including substance use disorder.

6. A history or family history of epilepsy, seizures or convulsions.
7. Having metal objects in brain or skull.
8. The subject has a history of intracranial mass lesion, hydrocephalus and/or head injury or trauma.
8. Having a cochlear implant or implanted deep brain stimulator.
9. Abnormal sleeping pattern (e.g. working night shifts).
10. Resting motor threshold (rMT) of more than 75% of the maximum stimulator output, measured using TMS-EMG during screening.
11. Systolic blood pressure (SBP) greater than 140 mmHg during screening. The measurement may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
12. Use of any medications within 14 days of study drug administration, or less than 5 half-lives (whichever is longer).
13. Use of more than 5 cigarettes (or other tobacco or nicotine products with equivalent nicotine dose) daily within the previous month before the first dose administration, and/or unable or unwilling to not smoke during the in-house periods.
15. Regular recreational use of illicit drugs (notably ketamine) within 12 months of screening.

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):	13-08-2021
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketanest-S®
Generic name:	Esketamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2021
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

ID: 28424
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-002083-31-NL
CCMO	NL73916.056.20
OMON	NL-OMON28424