PKPD of Oral vs IV S-Ketamine in HV

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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...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28424

Bron
Nationaal Trial Register

Verkorte titel
CHDR2004

Aandoening

Depressive Disorder

Ondersteuning

Primaire sponsor: CHDR
Overige ondersteuning: CHDR

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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 (t½)) 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 75 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 50 paired pulse TMS at an interstimulus interval (ISI) of 2 ms (stimulation intensity: conditioning pulse 80% rMT, test pulse: 120% rMT)

TMS-EEG
- Amplitude of the TMS evoked potential (TEP) measured with 75 single pulse TMS and 50 paired pulse TMS at ISIs 2, 50, 100 and 300ms

EEG
- Resting state EEG
- P300/ active auditory oddball
- 40Hz Auditory Steady State Response (ASSR)
- Auditory Sensory Gating (ASG)

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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) and24h (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 afteradministration (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).

Onderzoeksopzet

Day -42 (Screening) till EOS

Onderzoeksproduct en/of interventie

S-ketamine
Placebo

Contactpersonen

Publiek

Centre for Human Drug Research
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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	15-08-2021
Aantal proefpersonen:	16
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Toelichting
N.A.

Ethische beoordeling

Positief advies

Datum:	06-09-2021
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 55261
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9717
CCMO	NL73916.056.20
OMON	NL-OMON55261

Resultaten

Samenvatting resultaten
N.A.