Randomized, double-blind, double-dummy, placebo-controlled, four-way crossover single dose study to determine the test-retest reliability of, and the effect of oral valproic acid, levetiracetam and lorazepam on, cortical excitability measurements in healthy volunteers as measured by TMS-EEG and TMS-EMG

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28239

Source
Nationaal Trial Register

Brief title
Cortical excitability study in healthy volunteers

Health condition

Epilepsy, epileptic seizures

Sponsors and support

Primary sponsor: Centre for human drug research

Source(s) of monetary or material Support: Centre for human drug research

Intervention

Outcome measures

Primary outcome

TMS-EMG (MEP) and TMS-EEG (TEP) response measured by:

- Motor evoked potential (MEP):

o Resting motor threshold (rMT) – (% of maximal output)

o Peak-to-peak amplitude (µV)

o Long intracortical inhibition (LICI) – (percentage ratio of the mean peak-to-peak amplitude of the response to the second pulse (TR) and the first conditioning pulse (CR) at each ISI (TR/CR%)), measured at 50, 100, 150, 200, 250 and 300 ms intervals

o Short intracortical inhibition (SICI) – (percentage ratio of the mean peak-to-peak amplitude of the response to the second pulse (TR) and an unconditioned pulse (MEP) at each ISI (TR/MEP%)), measured at 2 and 5 ms intervals.

- TMS evoked potential (TEP), measured on the Cz electrode with single pulse and paired pulse TMS at 8 different ISIs: 2, 5, 50, 100, 150, 200, 250 and 300 ms.

o Amplitude of components - (µV)

- N15

- P30

- N45

- P55

- N100

- P180

Secondary outcome

Safety and tolerability endpoints

- Treatment-emergent (serious) adverse events ((S)AEs).

- Concomitant medication

Pharmacokinetic endpoints

The following endpoints will be determined for levetiracetam, valproic acid and lorazepam following each treatment. They will be derived by non-compartmental analysis of the plasma concentration-time data:

- The area under the plasma concentration-time curve from zero to infinity(AUC0-inf);

- The maximum plasma concentration (Cmax);

- The area under the plasma concentration-time curve from zero to t of the last measured concentration above the limit of quantification (AUC0-last);

- The time to reach maximum plasma concentration (tmax);

- The terminal disposition rate constant (λz) with the respective half-life (t½).

- Other parameters, including Vz/F, CL/F, and other parameters as appropriate, as well as dose adjusted parameters, may be determined.

Study description

Background summary

Non-invasive brain stimulation techniques like transcranial magnetic stimulation (TMS) offer an opportunity to study mechanisms of cortical physiology at the systems level of the human brain. The combination of brain stimulation with central nervous system (CNS) active drugs might help to explore the effects of these drugs on brain physiology. Combined with electroencephalography (EEG) or
electromyography (EMG), cortical excitability can be measured, as well as effects of CNS active drugs there upon. Excitability of the cortex is especially interesting in the setting of epilepsy, which is considered to be related to cortical hyperexcitability. Different anticonvulsants are known to affect different TMS measures of motor cortical excitability, which would therefore be an interesting biomarker for the efficacy of current and new treatments. Similarly, benzodiazepines have been shown to affect TMS-EEG and TMS-EMG in a few studies. However, so far few studies have investigated the dose effect relationship on cortical excitability. Additionally, such a biomarker must be measured reliably in order to be able to determine drug effects. Thus far no detailed studies exploring concentration-effects relationships in relation to cortical excitability exist. Further, various

Study objective

The key objective of this study is to investigate if cortical excitability can be reliably measured with TMS-EEG and TMS-EEG. And if so, whether modulation of this excitability could serve as a proof-of-biology biomarker to track the effect of therapeutic interventions aimed at modifying cortical excitability in response to pharmacological treatment, for example in treatments of epilepsy and amyotrophic lateral sclerosis (ALS), in which cortical hyper excitability plays an important role.

Study design

Screening (up to 30 days before study start); physical examination / blood sampling / vital signs / TMS training and questionnaires.

Days 1, 8, 15 and 22 ; dosing, blood sampling, vital signs, TMS at different time points during the day.

Follow up visit ; 7-10 after last dosing ; physical examination, blood sampling, vital signs.

Intervention

Keppra (levetiracetam), Lorazepam, Depakine (valproinezuur), placebo.

Contacts

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Eligibility criteria

Inclusion criteria

1. Healthy 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 and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.

2. Body mass index (BMI) between 18 and 32 kg/m2, inclusive, and with a minimum weight of 50 kg.

3. Able to participate and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

1. Legal incapacity or inability to understand or comply with the requirements of the study.

2. Positive test for drugs of abuse at screening or pre-dose.

3. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol). Alcohol consumption will be prohibited during study confinement and at least 24 hours before screening, before dosing, and before each scheduled visit.

4. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric,
endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.

5. A history of epilepsy or febrile seizures.

6. Having metal objects in brain or skull.

7. Having a cochlear implant or implanted deep brain stimulator.

8. Abnormal sleeping pattern (e.g. working night shifts)

9. Resting motor threshold (rMT) of more than 83% of the maximum stimulator output, measured using TMS-EMG during screening.

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

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

12. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.

13. Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary
supplements within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is discussed and clearly documented by the Investigator.

14. Clinically significant abnormalities, as judged by the Investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.

15. Participation in an investigational drug or device study within 3 months prior to screening.

16. 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.

17. Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.

18. Use of tobacco or nicotine products within the previous month before the first dose administration;

19. Clinically significant abnormalities, as judged by the Investigator, in ECG.

20. Any confirmed significant allergic reactions (urticarial or anaphylaxis) against any drug, or multiple drug
allergies (non-active hay fever is acceptable).

21. Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-09-2017
Enrollment:	16
Type:	Anticipated

Ethics review

Positive opinion

Date:	15-11-2017
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 44198
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL6638
NTR-old	NTR6824
CCMO	NL62207.056.17
OMON	NL-OMON44198

Study results

Summary results
NA