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.

Published: 26-07-2017
Last updated: 19-03-2025

Primary Objective- To investigate the ability of TMS-EEG measures to detect effects on cortical excitability of valproic acid, levetiracetam and lorazepam in healthy subjects- To investigate the ability of TMS-EMG measures to detect effects on...

Ethical review	Approved WMO
Status	Completed
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON44198

Source
ToetsingOnline

Brief title
Cortical excitability study in healthy volunteers

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy, epileptic seizures

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Health Holland;Stichting Life Sciences - TKI,Clinical Reserach Organization

Intervention

Keyword: Anti-epileptic drugs, EEG, Excitability, Transcranial magnetic stimulation

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 (*z) with the respective half-life

(t*).

- 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 techniques are currently in use to measure changes in cortical excitability, where it is presently unclear which is best. The ultimate goal is to develop techniques that can assist in personalised treatment of patients with epilepsy and other disorders where cortical excitability is changed.

We propose to map concentration effect relationship of the cortical excitability for several anticonvulsants and a benzodiazepine in a single dose

setting with multiple measurements over time using various readouts and to evaluate test-retest reliability.

Study objective

Primary Objective
- To investigate the ability of TMS-EEG measures to detect effects on cortical excitability of valproic acid, levetiracetam and lorazepam in healthy subjects
- To investigate the ability of TMS-EMG measures to detect effects on cortical excitability of valproic acid, levetiracetam and lorazepam in healthy subjects.

Secondary Objectives
- To evaluate the test-retest reliability of TMS-EEG.
- To determine the plasma concentration - effect relation of valproic acid, levetiracetam and lorazepam on TMS-EEG as a measure for cortical excitability in healthy subjects.
- To evaluate the test-retest reliability of TMS-EMG.
- To determine the plasma concentration - effect relation of valproic acid, levetiracetam and lorazepam on TMS-EMG as a measure for cortical excitability in healthy subjects.

Study design

This is a 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.

Intervention

-Valproic acid oral solution 1000 mg single oral dose
-Levetiracetam oral solution 2000 mg single oral dose
-Lorazepam capsule 2 mg single oral dose
- Placebo

Study burden and risks

Benefit and risk assessment
Valproic acid, levetiracetam and lorazepam are registered drugs. The safety profiles of these compounds are known. However, side effects might occur. Therefore, study drug administrations will be done in the clinic under medical supervision. Subjects will be closely monitored and will only be discharged from the unit if their medical condition allows this. As subjects will receive single doses of the three registered drugs, the risk is small and therefore acceptable compared to the scientific benefit.

Valproic acid
Valproic acid is registered as therapy for the treatment of generalised, partial or other epilepsy. Dosage for adults should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day i.e. 20-30 mg/kg body weight daily. Where adequate control is not achieved within this range the dose may be further increased to a maximum of 2500 mg per day. The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/L. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. Valproic acid was given in healthy volunteers in single doses up to 3000 mg, and a single dose of 1000 mg will lead to a Cmax within the therapeutic range.(25) Therefore a 1000 mg single dose is considered safe in this study.

Levetiracetam
Levetiracetam is registered as monotherapy for the treatment of partial onset seizures. The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily. Levetiracetam was given in healthy volunteers in single doses up to 5000 mg.(26, 27) In a previous study, 15 healthy male volunteers tolerated a single dose of 3000 mg levetiracetam relatively well.(6) Therefore a 2000 mg single dose is considered safe in this study.

Lorazepam
Lorazepam is registered as treatment for symptomatic relief of anxiety and insomnia at doses of 1-4 mg. With the proposed 2 mg dose therapeutic blood levels are expected to be reached, and therefore some somnolence, dizziness and drowsiness are expected. This dose has been regularly used at CHDR (when effects of a benzodiazepine are tested) and is considered safe and well tolerated.

TMS
Paired pulse TMS is a non-invasive, safe, easy, and painless technique to stimulate the brain.(7-12) Through a coil which is kept on the head of the subject, a magnetic pulse is applied to the brain (12) to assess cortical excitability.(8) MagPro R30 with MagOption stimulator (MagVenture GmbH, Hückelhoven, Germany) and a MCF-B65 butterfly coil (2x75mm) (MagVenture GmbH, Hückelhoven, Germany) are used to apply the paired pulse TMS.
Both the TMS stimulator and coil are developed and manufactured in accordance with the standard ISO 13485:2012 and are approved as medical devices in Europe.
In 2009 Rossi and colleagues published the *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research*. This article is based on a consensus conference (Siena, Italy; 2008), intended to update the previous safety guidelines for the application of TMS in research and clinical settings.(14)

According to these guidelines paired pulse TMS is generally well tolerated; however there are some possible side effects and risks:(14)
* Temporary hearing problems.
* Syncope: When a subject reports nausea, dizziness or feelings of (almost) fainting, the experiment is stopped and will not be continued. During the experiment, the subject will be asked frequently if he/she experiences any of these feelings. Syncope is not related to direct brain effects of paired pulse TMS.
* Headache, local pain or discomfort on the day of the TMS session: Most participants experience paired pulse TMS as painless, however we will warn subjects that TMS may not be pleasant and may cause some discomfort. This is probably caused by stimulation of the trigeminus nerve. If subjects do not tolerate paired pulse TMS, the experiment is stopped and will not be continued.
* Seizures: Rarely, there have been reports of seizures in healthy subjects during or after TMS. However, using TMS, seizures only occurred when subjects were taking pro-epileptogenic medication. This is not the case in our study. In epilepsy patients, there were no TMS-linked seizures in weekly rTMS applications at frequencies of * 1 Hz.(14) The crude risk of a TMS-associated seizure in paired pulse TMS in epilepsy patients is 0 to 3.6%.(28)
Overall, the risk of an epileptic seizure in paired pulse TMS is extremely low in healthy subjects and low in epilepsy patients, especially when these guidelines are followed.(14) Therefore, the risk of TMS is low. The TMS session may be intense, but during previous TMS studies performed at the University of Twente and Medisch Spectrum Twente (Enschede) was well tolerated by the vast majority of the subjects.

Personnel skilled in the management of syncope and seizure will be present in the clinical research unit when subjects are first measured.

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

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 mmHg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mmHg.
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 (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
18. Use of tobacco or nicotine products within the previous month before the first dose administration.
19. Clinically significant abnormalities in ECG, as judged by the Investigator, including evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
20. Any confirmed significant allergic reactions (urticaria 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
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-09-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Depakene
Generic name:	valproic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keppra
Generic name:	levetiracetam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lorazepam
Generic name:	Lorazepam
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	26-07-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	15-08-2017
Application type:	First submission
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: 28239
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-002367-18-NL
CCMO	NL62207.056.17
OMON	NL-OMON28239

Study results

Date completed: 13-02-2018

Results posted: 15-06-2022

First publication
12-01-2022