A randomized, double-blind, two-way cross-over study to determine the effects of levetiracetam on corticospinal excitability in patients with treatment-controlled epilepsy, as measured by single and paired pulse TMS-EMG and TMS-EEG

Published: 11-12-2019
Last updated: 15-05-2024

- To evaluate effects of levetiracetam 2000 mg on single and paired pulse TMS-EMG and TMS-EEG in patients with epilepsy treated with mono-therapy levetiracetam, when compared to placebo (levetiracetam trough concentrations). - To evaluatethe effects...

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

Summary

ID

NL-OMON49353

Source
ToetsingOnline

Brief title
TMS to assess drug effects in epilepsy

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy

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. ,Centre for Human Drug Research (CRO)

Intervention

Keyword: EEG, Epilepsy, Levetiracetam, TMS

Outcome measures

Primary outcome

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

- Motor evoked potential (MEP)

o Resting motor threshold (rMT) - (percentage 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 a 50 and 100 ms

interval.

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 a 2 ms interval.

- TMS evoked potential (TEP) using single pulse, and paired pulse TMS at 3

different ISIs: 2, 50 and 100 ms:

o Amplitude of components - (µV)

N15

P30

N45

P55

N100

P180

Secondary outcome

NA

Study description

Background summary

Transcranial magnetic stimulation (TMS) combined with electromyography (EMG) or electroencephalography (EEG) offers a non-invasive opportunity to study corticospinal excitability. Excitability of the cortex is especially interesting in the pathophysiology of epilepsy, which is considered to be related to cortical hyperexcitability. Different anti-epileptic drugs (AEDs) are known to affect different TMS measures of motor cortical excitability, which makes TMS an interesting biomarker to assess the efficacy of current and new AEDs.

This study is the second part of the TRACE project (Tms-eeg as a biomaRker for phArmacological effects on Cortical Excitability). The aim of the TRACE project is the development of a biomarker for effects of AEDs on cortical excitability, which ideally could be used to measure and also predict treatment efficacy in epilepsy. The first study was performed to investigate the reproducibility of single and paired pulse TMS-EMG and TMS-EEG measures and to investigate the sensitivity of the measurement to detect effects of levetiracetam, valproic acid and lorazepam on cortical excitability in healthy volunteers. This study has been successfully completed, showing effects of all three study drugs on cortical excitability as measured by single and paired TMS-EMG and/or TMS-EEG. This follow-up study will evaluate the effects of levetiracetam on cortical excitability in epilepsy patients as this treatment showed the most pronounced effects on TMS-EMG and TMS-EEG in the previous study. The ultimate goal is to develop TMS-EMG and TMS-EEG as a biomarker that can assist in personalised treatment of patients with epilepsy. Unfortunately, it is practically and logistically not feasible to include treatment-naïve patients in this study. For this reason, two groups of patients that are stable on mono-therapy will be

included, one group on levetiracetam and one on valproic acid. These are common treatments for epilepsy in the Netherlands and based on the previous study we know the effect profile of these drugs, at least in healthy volunteers.

Study objective

- To evaluate effects of levetiracetam 2000 mg on single and paired pulse TMS-EMG and TMS-EEG in patients with epilepsy treated with mono-therapy levetiracetam, when compared to placebo (levetiracetam trough concentrations).
- To evaluatethe effects of levetiracetam 2000 mg on single and paired pulse TMS-EMG and TMS-EEG endpoints in levetiracetam-naïve epilepsy patients (using valproic acid), when compared to placebo (valproic acid trough concentrations)

Study design

This is a randomized, double-blind, two-way cross over study to determine the effects of levetiracetam on cortical excitability in patients with epilepsy, as measured by single and paired pulse TMS-EMG and TMS-EEG. Epilepsy patients will be recruited in two groups: patients using levetiracetam mono-therapy, and levetiracetam-naïve patients, who are using valproic acid mono-therapy.

Intervention

Group 1:
First dosing: levetiracetam 2000 mg or placebo
Second dosing after the last TMS measurement: placebo or levetiracetam 500 mg (subject*s regular dose of levetiracetam)

Group 2:
Levetiracetam 2000 mg or placebo

Study burden and risks

TMS is a non-invasive, safe, easy, and painless technique to stimulate the brain. A 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 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. When applied according to these guidelines TMS is generally well tolerated; however there are some possible side effects and risks.

• 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 during or after TMS. In a study on the risk of seizures in epilepsy patients, the crude risk of a TMS-associated seizure in TMS in epilepsy patients was 0 to 3.6%. A recent study has published the number of reported TMS induced seizures between 2012 and 2016. A total of 24 seizures was reported, in the 318.560 reported sessions. This is 0.08 seizures per 1000 sessions. The risk of seizures during TMS was largely influenced by risk factors: only 4 out of 24 seizures occurred in subjects without risk factors. Out of the 24 reported seizures, 7 occurred in epilepsy patients.
Overall, the risk of an epileptic seizure in TMS is extremely low in healthy subjects and low in epilepsy patients, especially when these guidelines are followed. Personnel skilled in the management of syncope and seizure will be present in the clinical research unit. The patients in this study will have been seizure free for at least 1 year. They will be on a stable dose of antiepileptic treatment for at least 3 months. Subjects are asked to refrain from their regular dose of AEDs until 4 hours after t=0h, which might increase the risk of seizures in the placebo arm. However, the risk is small and considered to be outweighed by the scientific benefit.
Levetiracetam is a registered drug. The safety profile of this compound is known, however, side effects might occur. Therefore, study drug administrations will be done in the clinical research unit 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 a single dose of levetiracetam, the risk is small and considered to be outweighed by the scientific benefit.

Risk of SARS-CoV2 infection during pandemic.

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. Signed informed consent prior to any study-mandated procedure
2. Male or female subjects, 18 to 54 years of age, inclusive at screening, with generalized epileptic seizures.
3. Study participant is currently treated for epilepsy with stable doses of the following for at least 3 months:
a. Group 1: levetiracetam mono-therapy (1000 mg daily)
b. Group 2: valproic acid mono-therapy (up to and including 1000 mg daily)
4. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
5. All women of child bearing potential must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
6. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Evidence of any active or chronic disease or condition, apart from epilepsy, that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (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.
2. 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.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Abnormal findings in the resting ECG at screening defined as:
a. QTcF> 450 msec for males, or >470 for females; or < 300 msec
b. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
5. Use of concomitant medications (prescription or over-the-counter [OTC]) that could interfere with the study drug or the TMS measurements, within 14 days of study drug administration, or less than 5 half-lives (whichever is longer), as judged by the investigator. This does not include the permitted medication as listed in chapter 4.4 of this protocol.
6. Participation in an investigational drug or device study within 3 months prior to first dosing.
7. History of abuse of addictive substances (alcohol, illegal substances) or current (within the last 6 months) use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent
8. Positive test for drugs of abuse at screening or pre-dose.
9. Alcohol will not be allowed from at least 24 hours before screening or pre-dose.
10. Use of tobacco or nicotine products within 24 before the dose administration.
11. A previous significant allergic reaction (urticaria or anaphylaxis) to levetiracetam
12. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study, or plasma donation within 2 weeks of screening.
13. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
14. Any known factor, condition, or disease that might interfere with treatment

compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
15. The subject has a history of intracranial mass lesion, hydrocephalus and/or clinically significant head injury or trauma that could increase the risk of applying TMS
16. The subject has metal objects in brain or skull.
17. The subject has a cochlear implant or deep brain stimulation device.
18. The subject has abnormal sleeping patterns (eg, working night shifts).
19. The subject has an rMT of more than 83% of the maximum stimulator output, measured using TMS-EMG during screening.
20. History of side effects related to levetiracetam administration that would pose an unacceptable risk to the subject in the opinion of the investigator, such as suicidality.
21. Study participant has a history of seizures during a year before dosing.
22. Study participant has epilepsy with a clear focal onset.
23. Any comorbidity known as a risk factor for COVID-19, including cardiovascular, pulmonary or immune system diseases.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-07-2020
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keppra

Generic name:	Levetiracetam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-12-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2020
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: 25822
Source: NTR

Title:

In other registers

Register	ID
EudraCT	EUCTR2019-004320-38-NL
CCMO	NL71944.056.19
OMON	NL-OMON25822