A study on peripheral motor nerve excitability in patients with ALS

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25730

Source
NTR

Brief title
Peripheral motor nerve excitability study in patients with

Health condition

ALS ;Amyotrofische Laterale Sclerose

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

To evaluate the test-retest reliability of nerve excitability threshold tracking in patients with ALS.

Secondary outcome

• To investigate the ability of Strength Duration Time Constant (SDTC) to detect effects of retigabine and riluzole in patients with ALS.

• To investigate the ability of Refractoriness at 2 ms to detect effects of retigabine and riluzole in patients with ALS.

• To investigate the ability of Superexcitability to detect effects of retigabine and riluzole in patients with ALS.

• To investigate the ability of depolarizing Threshold Electrotonus (40-60 ms)to detect effects of retigabine and riluzole in patients with ALS.

• To investigate the ability of depolarizing Threshold Electrotonus (90-100 ms) to detect effects of retigabine and riluzole in patients with ALS.

• To determine if there is a correlation between ALSFRS-R score at baseline and at 3 months and motor nerve excitability measures refractoriness at 2 ms, superexcitability, depolarizing Threshold Electrotonus (40-60 ms), depolarizing Threshold Electrotonus (90-100 ms) or Strength Duration time Constant at baseline on day 0.

• To assess the intra-individual (day-to-day) variability of POWERjar measurements (patients with neurological disorder only)

• To assess the ability of the POWERjar to measure muscle fatigue in patients with ALS.

Study description

Background summary

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease characterized by ongoing loss of motor neurons throughout the neuraxis. In ALS unique "positive" phenomena of hyper excitability of the peripheral and central motor neuronal system can be observed, specifically fasciculations, muscle cramps, hyperreflexia, and spasticity. At the peripheral nervous system level, hyper excitability of nerves has been shown in ALS in several studies that indicated involvement of sodium and potassium conductance with a technique called peripheral excitability threshold tracking. Remarkably, the degree of this abnormal hyper excitability appeared to correlate with patient survival. Regardless of the underlying mechanism, the alteration of membrane excitability may therefore be a relevant component of the disease pathophysiology. All these findings suggest that hyper excitability
(as a pathophysiological insult) may precede the structural damage to the motor neuronal system in ALS. This may suggest that early identification of a hyper excitable motor system may help in the prediction of the development of ALS and as such, may provide a chance to initiate a "neuroprotective" intervention early in the disease process. In an in vitro cell culture

model of ALS, the use of the potassium channel Kv7 activator retigabine was shown to reduce the abnormal membrane excitability and improve cell survival. Interestingly riluzole, the only registered drug for the treatment of ALS, has also shown to partially normalize some hyper excitability parameters (both peripheral and cortical) in patients with ALS. Therefore, if this phenotype can be reliably measured in patients with ALS, modulation of hyper excitability could serve as a proof-of-biology biomarker to track the effect of therapeutic interventions aimed at modifying the genetic mutations underpinning the disease. Subjects recruited in the Netherlands.

Study objective

Patients with ALS are routinely prescribed riluzole, the only registered drug for the treatment of ALS. This study will evaluate the concentration-effect relationship of riluzole (100 mg) and retigabine (300 mg) on axonal excitability measures. In this study, test-retest reliability of axonal excitability measures of the motor axons of the median nerve (to abductor pollicis brevis, APB) will also be evaluated in patients with ALS. Lastly, muscle strength and fatigue of the hands will be measured with the POWERjar.

Study design

Medical screening (1x), 3 visits of +/- 1.5 hours with multiple measurement such as blood pressure, ECGs blood sampling, and 2 follow up calls (questionnaires).

Intervention

Retigabine (300 mg)

Riluzole (100 mg)

Placebo

Contacts

Public
NA

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Eligibility criteria

Inclusion criteria

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.

2. Aged 18 to 80 years old, inclusive, at the time of informed consent.

3. Women of childbearing potential must practice effective contraception for the duration of the study.

4. Willing to limit the intake of alcohol to no more than 2 units per day from the screening visit to the the last scheduled visit and to refrain from alcohol intake 48 hours prior to each study visit until their stay in the clinical research unit. One unit of alcohol is defined as 1 pint of beer (350 mL), 1 glass of wine (150 mL) or 1 shot of liquor (30 mL).

5. Willing to refrain from marijuana use throughout the study.

6. Willing to refrain from vigorous exercise within 48 hours prior to each study visit.

7. Must have a diagnosis of “definite”, “probable”, or “probable laboratory-supported”, ALS according to the World Federation of Neurology El Escorial criteria (revised according to the Airlie House Conference 1998 [Brooks 1999]).

8. Fasciculations in the arms observed by the treating neurologist

Exclusion criteria

1. History of diabetes or neuropathy.

2. History of neuromuscular disorders (other than ALS) including but not limited to ALS mimic syndromes, myopathy, myasthenia gravis, and other motor neuron diseases.

3. Median nerve CMAP less than 1 mV.

4. Unstable cardiac, pulmonary, renal, hepatic disease or active malignancy.

5. Clinically significant abnormalities in laboratory test results as judged by the investigator. In the case of uncertain or questionable results, laboratory tests performed during the screening visit may be repeated 1 time before participation in the study to confirm eligibility or may be judged to be clinically irrelevant.

6. History or symptoms of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and ophthalmologic or other major disease, as determined by the investigator (with the exception of the neurological syndrome listed in the inclusion criteria section).

7. 12-lead ECG demonstrating QTcB >450 msec at Screening.

8. Concomitant disease or condition that can interfere with the conduct of the study, or that in the opinion of the investigator, would pose an unacceptable risk to the subject in this study.

9. History of trauma to the upper extremities or other orthopaedic conditions that, in the opinion of the investigator, could affect the electrophysiological measurements.

10. Use of medications including but not limited to anticholinergics and muscle relaxants that, in the opinion of the investigator, could affect the electrophysiological measurements within 2 weeks prior to first dosing or within 6 times the elimination half-life of the medication prior to first dosing (whichever is longer).

11. Current enrolment in any interventional clinical study in which treatment with an investigational drug or approved therapy for investigational use is administered within 30 days prior to the screening or participation in an interventional study for an investigational drug or device within 3 months prior to Screening.

12. Pregnant, breastfeeding, or a positive pregnancy test result at Screening.

13. A positive urine test for drugs of abuse at Screening.

14. Unwillingness or inability to comply with study requirements.

15. Unspecified reasons that, in the opinion of the Investigator, make the subject unsuitable for enrolment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2015
Enrollment:	18
Type:	Actual

Ethics review

Positive opinion

Date:	07-04-2017
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
NTR-new	NL6139

Register	ID
NTR-old	NTR6278
Other	NL53042.056.15 / 2015-001431-20 : CHDR1417

Study results