Muscle velocity recovery cycles as a biomarker for drugs targeting muscle excitability

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

Samenvatting

ID

NL-OMON20195

Bron
NTR

Verkorte titel
CHDR1918

Aandoening

Method development for testing medication that is in development for muscular diseases.

Ondersteuning

Primaire sponsor: CHDR
Overige ondersteuning: Sponsor or CHDR

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

At a minimum, following endpoints will be derived from the MVRC measurement. Other exploratory endpoints may be derived.
Recovery cycles with 1+2+5 conditioning stimuli
From MVRCs with one conditioning stimulus:
- Relative refractory period in ms (RRP)
- Early supernormality (ESN)
- Late supernormality (LSN)

From recordings with two conditioning stimuli:
- Extra late supernormality due to the second conditioning stimulus (XLSN)
From recordings with five conditioning stimuli:
- Extra late supernormality due to 5 conditioning stimuli (5XLSN)

Frequency ramp
- Lat(15Hz)first; Lat(15Hz)last; Lat(30Hz)first; Lat(30Hz)last: the latency of the negative peak of the muscle action potential,
expressed as a percentage of baseline latency recorded at 15Hz. Responses will be indicated with “First” and “Last”, because
latency chances are different for the first and last responses in each train of action potentials.
- Peak(15Hz)first; Peak(15Hz)last; Peak(30Hz)first; Peak(30Hz)last: peaks of action potential amplitudes, recorded as
percentages of baseline values.
- FLatMinfirst; FLatMinlast: the frequency at which the latency is minimal, determined by fitting a quadratic to each 6 adjacent
points.
15-pt recovery cycles
These are repeated recovery cycles in which the following endpoints are calculated every 30 seconds before, during and after 5
minutes of ischemia:
- Relative refractory period
- Peak supernormality

Toelichting onderzoek

Achtergrond van het onderzoek

Muscle velocity recovery cycles (MVRCs) is a method to obtain information on muscle membrane potential in vivo. To our knowledge, MVRCs have not been used to assess acute pharmacological effects. The ultimate goal is to introduce this method as a pharmacodynamic biomarker of drugs targeting muscle excitability. As a proof of concept, the sensitivity of MVRCs to detect effects of a sodium channel blocker will be assessed.

Doel van het onderzoek

As a proof of concept, the sensitivity of MVRCs to detect effects of a sodium channel blocker will be assessed. Sodium channels account for the propagation of action potentials in muscle cells and are therefore largely responsible for membrane excitability. Mexiletine blocks the voltage-gated sodium channel Nav1.4, which is present in skeletal muscles. In a previous study, effects of mexiletine on membrane depolarization in patients with myotonia congenita were detected, as measured by MVRCs. Additionally, blockade of Nav1.4 results in decreased muscle excitability in animal models of myotonia congenita. We hypothesise that effects of Nav1.4
blockade by mexiletine will have effects on muscle excitability in healthy volunteers as well. Sodium channel blockers have a state-dependent affinity, the affinity for open and inactivated sodium channels is greater than for closed channels. The drugs will therefore block the sodium channels in a voltage dependent manner, with greater affinity to depolarized cells. The pharmacodynamic effect of mexiletine may thereby be revealed by ischemia-induced membrane depolarization. Furthermore,
the channel blocking is dependent on frequency of stimulation. Therefore, the results of repeated stimulation using MVRCs may exhibit effects.
Part B of the study will investigate a group of patients with myasthenia gravis, to assess whether effects of myasthenia gravis on muscle membrane potential can be detected when compared to healthy volunteers. By performing MVRCs in patients with myasthenia gravis, we can study their muscle membrane potential, independent of the neuromuscular transmission. Thereby, this study would allow us to clinically test the hypothesis that the loss of sodium channels in the muscle cells of myasthenia gravis patients leads to decreased muscle excitability.

Onderzoeksopzet

Day 1 treatment period 1 and 2

Onderzoeksproduct en/of interventie

Mexiletine (Namuscla) 333 mg or placebo
MVRC measurement

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Part A
1. Signed informed consent prior to any study-mandated procedure
2. Healthy male subjects, 18 to 45 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. All subjects 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.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the
study restrictions.

Part B
1. Signed informed consent prior to any study-mandated procedure
2. Male and female subjects, above 18 years of age, inclusive at screening.
3. Diagnosis of generalized myasthenia gravis, MGFA class II-IV, based on characteristic muscle weakness and
with a positive AChR antibody test.
4. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the
study restrictions.
5. Must be able to cease the use of pyridostigmine as per study requirements, if applicable.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Part A
1. Evidence of any active or chronic disease or condition 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). Subjects with pre-dose findings of clinically
significant changes in electrolytes should be excluded. 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. 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 at screening.
5. Abnormal findings in the resting ECG at screening or baseline defined as:
a. QTcF> 450 or < 300 msec
b. Notable resting bradycardia (HR < 50 bpm) or tachycardia (HR > 100 bpm)
c. Personal or family history of congenital long QT syndrome or sudden death;
d. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac
pacemaker
e. Ventricular tachyarrhythmia
f. Atrial tachyarrhythmia, fibrillation or flutter
g. Complete heart block (i.e. third-degree atrioventricular block) or any heart block susceptible to evolve to
complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 240 ms) and/or
wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and
trifascicular block),
h. Sinus node dysfunction (sinus rate < 50 bpm, sinus arrest of >3.5 sec)
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or
less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to
1g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less
than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the

investigator.
8. Participation in an investigational drug or device study within 3 months prior to first dosing, or for more than 4
times a year.
9. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units
alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent
10. Positive test for drugs of abuse at screening or pre-dose.
11. Alcohol will not be allowed from at least 24 hours before screening or pre-dose.
12. Current use of tobacco or nicotine products and unable to abstain from use of these products within the
previous month before the first dose administration.
13. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day).
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug
allergies (non-active hay fever is acceptable).
15. Hypersensitivity to the active substance, mexiletine hydrochloride, or other ingredients (maize starch, colloidal
anhydrous silica, magnesium stearate, gelatin, iron oxide [E 172], titanium dioxide [E 171])
16. Hypersensitivity to any local anaesthetic.
17. Loss or donation of blood over 500 mL within three months prior to screening, or plasma donation within 2
weeks of screening, or intention to donate blood or blood products during the study.
18. 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.
19. History of trauma to the lower extremities or other conditions (most importantly neurological or muscle
diseases) that, in the opinion of the investigator, could affect the electrophysiological measurements.
20. Clinically significant abnormalities in coagulation, personal or family history of bleeding disorders.
21. Excessive exercise within 72 hours before study drug administration.
22. Diameter of the upper leg of more than 65 cm, to allow for the induction of ischemia by the blood pressure cuff.

Part B
1. Evidence of any active or chronic disease or condition 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, analysis of coagulation). Minor deviations from the normal
range may be accepted, if judged by the Investigator to have no clinical relevance.
2. History of or current conditions that, in the opinion of the investigator, could affect the

electrophysiological
measurements, such as trauma to the upper extremity, renal failure, or neuromuscular diseases, including but not
limited to critical illness neuropathy, Anderson Tawil syndrome, channelopathies, erythromelalgia, myotonic
dystrophies, sodium channel myotonias and myotonica congenetica.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus
antibody (HIV Ab) at screening.
4. Use of any medications (prescription or over-the-counter [OTC]) that could influence the MVRC measurements
(apart from pyridostigmine), within 14 days of study drug administration, or less than 5 half-lives (whichever is
longer), including use of anti-coagulants, sodium channel blockers, dantrolene, anti-epileptic drugs.
5. Participation in an investigational drug or device study within 3 months prior to the study day, or for more than 4
times a year.
6. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units
alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent
7. Positive test for drugs of abuse at screening or the study period. Retesting is allowed at the discretion of the
Investigator.
8. Alcohol will not be allowed from at least 24 hours before the study period.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	N.v.t. / één studie arm
Blindering:	Enkelblind
Controle:	Placebo

Deelname

Nederland
Status: Werving nog niet gestart

(Verwachte) startdatum:	20-01-2020
Aantal proefpersonen:	22
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Toelichting
NA

Ethische beoordeling

Positief advies

Datum:	14-10-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 49444
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8084
CCMO	NL70723.056.19
OMON	NL-OMON49444

Resultaten

Samenvatting resultaten
NA