Combining N-of-1 trials to estimate population clinical effectiveness of drugs using Bayesian hierarchical modeling. The case of Mexilitin for patients with Non-Dystrophic Myotonia.

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(voor meer details zie CMO-protocol paragraaf 2: Objectives) Primary Objective: The objective of this project is to further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON34131

Source
ToetsingOnline

Brief title
Mex vs. placebo in NDMs

Condition

- Muscle disorders

Synonym
heritable muscle stiffness, Non-dystrophic myotonia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ZonMw subsidie thema HTA

Intervention

Keyword: Combined N-of-1 trials, Mexiletine, Non-dystrophic myotonia, Orphan disease

Outcome measures

Primary outcome

(voor meer details zie paragraaf 7: Methods)

Interactive Voice Response Diary (IVR):

The IVR is an automated centralized phone-system in rating scale ranking severity of symptoms and the frequency of symptoms (hours) for stiffness, pain, weakness, and fatigue. Using the telephone key pad participants will call in on a weekly or daily basis to rate their symptoms on an ordinal scale (1-9). The IVR used for this study will be developed by OrcaGroup communication solution (Heesch, the Netherlands).

Secondary outcome

(voor meer details zie paragraaf 7: Methods)

INQoL:

There are no quality of life studies examining the impact of NDM. NDM patients experience stiffness, pain, and weakness. The Individual Neuromuscular Quality of Life questionnaire (INQoL) is a quality of life instrument used to examine issues specific to patients with a neuromuscular disease. ,

SF36:

This is a generic questionnaire that is suitable for prospective assessment in NDM.

The Dutch Language version of the SF-36 has been shown to have a good validity and reliability.

Clinical Myotonia test:

Myotonia will be sought on physical examination.

Quantative grip myotonia:

Quantitative Grip Myotonia: Maximum Voluntary Isometric Contractions (MVIC*s) of the long finger flexors and the subsequent relaxation time (myotonia) will be measured using a technique developed at the University of Rochester.

Biceps force recording

Biceps force recording has been proved to be a successful technique to detect hyperexitability of the skeletal muscle cell membrane. Especially in isometric contractions at 60% of maximal voluntary contraction (MVC), disturbances of the skeletal muscle cell membrane can be seen by an irregular force pattern with intermittent decline in force.

Needle EMG

Concentric needle EMG will be performed in two muscles; the first dorsal

interosseous and the rectus femoris muscle.

Study description

Background summary

(voor meer details zie CMO-protocol paragraaf 1: Introduction and rationale)

Non-dystrophic myotonic syndromes are a heterogeneous group of rare diseases caused by mutations in genes encoding skeletal muscle ion channels. The key symptom is myotonia, a delayed relaxation after voluntary contraction. Despite the general notion that NDMs are benign diseases, symptoms do cause lifetime morbidity and a recent study demonstrated that the symptoms of these patients do greatly impact their self-reported health status. In our recent Cochrane review, we concluded that there is insufficient evidence of effectiveness and safety of drug treatment in myotonic syndromes.
Based on this review, the Healthcare Insurance Board (CVZ) decided to discontinue coverage of drugs for NDM patients. However, absence of evidence of effectiveness should not be confused with evidence of absence of effectiveness, and this decision might deprive NDM patients of substantial benefits. Indeed, CVZ has acknowledged that in the case of rare diseases, it is unreasonable to demand level 1 evidence (CVZ report 2007). As more than 7000 rare diseases in Europe and the USA suffer from this lack of treatment evidence, an innovative trial design is urgently needed.

The objective of our project is to further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient basis for coverage decisions on drugs for rare diseases. As reported in our Cochrane review, there is no level 1 evidence of classic RCTs available for treatment of myotonia in NDMs.3 However, evidence from single case reports and expert opinion point towards the class I antiarrhythmic agents with mexiletine as the (off-label) drug of choice in patients with NDMs. Drug efficacy of mexiletine will be tested in our study on NDM patients.

Study objective

(voor meer details zie CMO-protocol paragraaf 2: Objectives)

Primary Objective: The objective of this project is to further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient basis for coverage decisions on drugs for rare diseases.

The previously mentioned will be tested in combined N-of-1 trials using

mexiletine vs. placebo in NDM patients. The secondary objective of this proposal is to assess whether mexiletine improves myotonia measured (both quantitatively and qualitative) in patients with non-dystrophic myotonia.

Study design

(voor meer details zie CMO-protocol paragraaf 3: study design)

Study design: Bayesian hierarchical approach of N of 1 trials
N-of-1 trials have initially been developed to optimize individual patient management. More recently, results of multiple N-of-1 trials have been used to produce an evidence base for drug effectiveness at group level, using Bayesian hierarchical modeling. , Bayesian methodology is highly appropriate for this, since it allows for an estimate of the probability that wrong inferences are made on the basis of available data (e.g., concluding that a drug is effective, whereas in reality it is not, or vice versa). For this, we will test robustness of the method, by comparing results when using noninformative or informative priors. Furthermore we will compare the results of our study with the results of the worldwide multi-center trial *Phase II therapeutic trial of mexiletine in Non-Dystrophic myotonia* of the consortium of Clinical Investigation of Neurological Channelopathies (CINCH) with dr. Robert Griggs (University of Rochester) and dr. Richard Barohn (University of Kansas Medical Center) as the principal investigators. NDM provides an excellent model, since prior probability estimates can be based on the detailed knowledge of the pathophysiology of the disease and mechanism of action of the various drugs

Each N-of-1 trial consists of a minimum of one, and a maximum of 4 treatment sets, each comprising a 4-week period of active treatment (Mexiletine) and a 4-week period of treatment with placebo, in random order, with one week for wash-out in between (see Figure 1). Total study enrolment will be maximally 44 weeks per patient and minimally 11 weeks. Patients will be enrolled in two cohorts, each consisting of ten patients. Patients in one cohort will be treated and followed up in parallel. Thus, all N-of-1 trials can be conducted within 88 weeks.

Intervention

Mexiletine intervention:
Three times a day 200 mg tablet.

Placebo intervention:
Three times a day a placebo tablet.

Study burden and risks

(voor meer details zie CMO-protocol 10.4: Benefits and risks assessment, group

relatedness)

Benefits and risks assessment, group relatedness
Testing Related Risk:
EMG testing may be painful. It may be uncomfortable for some participants. The patient may feel some pain or discomfort when the needles are inserted, but most people are able to complete the test without significant difficulty. Afterward, the muscle may feel tender or bruised for a few days. The risks associated with blood drawing include discomfort from the needle stick, bruising, and rarely, an infection from the needle stick.
Other measurements are non-invasive and are not associated with any risks.

Pregnancy Related Risk:
It is not known how Mexiletine will affect an unborn or nursing child. There may be risks to an unborn or nursing child that have not yet been identified. There are no adequate and well-controlled studies in pregnant women. Because the drug(s) in this research study may affect an unborn child, pregnant patients will be excluded from this study. If a patient becomes pregnant during the study the patient must immediately inform the primary investigator and visit a doctor. If female patients have not been surgically sterilized, or have not undergone menopause at least 1 year ago, they must practice a method of birth control during the trial. Examples of birth control include: birth control pills, implant, intrauterine device, (IUD), or a barrier method such as a diaphragm with intravaginal spermicide, cervical cap, male or female condom

Possibility of Unknown Risks
There may be other risks that have not yet been identified and unexpected side effects that have not been previously observed may occur

New findings statement:
You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate in this study.

Benefits
Because of the proposed design of combined N-of-1 trials, each patient is treated with several treatment periods with mexiletine and placebo. Thereby, patients could directly benefit from participation in this study. Information on adverse events from therapy can already be registered and if therapy significantly decreases complaints of myotonia, the trial could be preliminary ended and treatment with mexiletine could be started.

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

Inclusion criteria
1. At least 18 years of age
2. Genetically confirmed diagnosis of NDMs
3. Participation in the *Genetical variability of the Non-dystrophic Myotonia* study of J. Trip or a new patient with genetically confirmed NDM.

Exclusion criteria

Exclusion criteria
1. Inability or unwillingness to provide informed consent.
2. Other neurological conditions that might affect the assessment of the study measurements.
3. Genetic confirmed DM1 (CTG > 50 repeats), or DM2.
4. Patients with existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbances

(such as second degree AV block, third degree AV block, or prolonged QT interval >500 ms or QRS duration > 150 msec).
5. Current use of the following antiarrhythmic medication for a cardiac disorder: lecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine.
6. Women who are pregnant or lactating.
7. Patients currently on medications for myotonia such as phenytoin and flecainide acetate within 5 days of enrollment, carbamazepine and mexiletine within 3 days of enrollment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrollment.
8. Patients with an existing permanent pacemaker.
9. Patients with renal or hepatic disease, heart failure, or seizure disorders.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-01-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mexiletine
Generic name:	Mexitil

Ethics review

Approved WMO Date:	17-02-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2010-024026-38-NL
CCMO	NL34801.091.10