Ephedrine as add-on therapy for patients with myasthenia gravis

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON39601

Source
ToetsingOnline

Brief title
Ephedrine for MG

Condition

- Autoimmune disorders
- Neuromuscular disorders

Synonym
myasthenia, myasthenia gravis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: add-on therapy, ephedrine, myasthenia gravis, n-of-one trial

Outcome measures

Primary outcome

The efficacy of add-on therapy with ephedrine to treatment with pyridostigmine and / or low-dose prednisone for all patients enrolled in this study, based on an individual*s results on the multiple Quantitative Myasthenia Gravis (QMG) test during the multiple crossover phase of the trial.

Secondary outcome

a) The effect of add-on ephedrine as measured by QMG for individual patients enrolled in this study.

b) The feasibility of a larger series of n-of-one trials. We will conclude that a larger series of n-of-one trials is feasible under the current protocol if, on average, every patient in this pilot study completes two cycles of the multiple crossover phase.

c) Changes in secondary outcome parameters: MG Composite, MG ADL questionnaire. Subjective outcome measures include treatment preference and VAS score of muscle strength in a muscle group chosen by the patient.

d) After the cross-over part of the trial, patients who decide to continue ephedrine add-on treatment will be asked to participate in the open label extension study. We will study the long-term effect of ephedrine and compare outcome parameters with baseline and short-term effect.

e) The experiences of patients with n-of-one trials by means of semistructured interviews (by telephone) and to evaluate participating

professionals* (physicians*, pharmacists* and statisticians*) experiences.

f) Adverse events of ephedrine treatment as measured by ECG, laboratory tests (haematology, liver and renal function tests) and a questionnaire specifically developed for this purpose.

Study description

Background summary

Myasthenia gravis is a rare autoimmune neuromuscular condition which initially responds favourably to symptomatic treatment with acetylcholinesterase inhibitors (AChIs) that act on the neuromuscular junction (NMJ). The second line of treatment usually consists of high doses of immunomodulating or immunosuppressive drugs, which may have serious side effects. A potential alternative is the short-acting drug ephedrine which - together with AChIs or low-dose prednisone - may postpone (or even abolish) the need for high-dose immunomodulating or immunosuppressive therapies.

Study objective

The main objective of this pilot study of n-of-one trials is to determine the effect of add-on treatment with ephedrine for all participants enrolled in this small series of n-of-one trials. Secondary objectives include determining the effect in individual patients in the trial, feasibility of a larger series of n-of-one trials to investigate efficacy and adverse effects of oral add-on treatment for myasthenia gravis. We will also evaluate patients*, physicians* and pharmacists* experiences with this trial design and record adverse effects of add-on treatment with ephedrine.

Study design

The study consists of an inclusion phase and 4 n-of-one trials, followed by an evaluation phase and an optional open label extension phase. N-of-one trials are double-blind, multiple crossover single patient trials in which the order of treatment allocation is randomised over the cycles of the trial. Based on their individual results of the n-of-one trial, patients can decide whether to continue with ephedrine. In this case, they will be asked to participate in the open label extension phase to determine the long term efficacy of add-on treatment with ephedrine. Patients* experiences with (the burden of) n-of-one trials will be explored by interviews.

Intervention

During the randomised, double-blind multiple crossover phase, add-on treatment with 25 mg ephedrine 2 times daily will be compared to add-on treatment with placebo 2 times daily. Effect of treatment will be measured both objectively (Quantitative Myasthenia Gravis (QMG) score, MG Composite) and subjectively (Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile and VAS score of muscle strength). Adverse effects will be measured by a symptom questionnaire. Patients will continue to use their pre-study dose of pyridostigmine or low-dose prednisone throughout the n-of-one trial.

Study burden and risks

Each n-of-one trial lasts 10 weeks. In week 1 and 2 of every n-of-one trial, each patient will visit the hospital for a full day to establish whether the treatment is safe for that patient. VAS score of muscle strength, all adverse effects (questionnaire) and vital signs are measured 30, 60 and 120 minutes after ephedrine administration, an ECG will additionally be performed 60 minutes after administration.
During the 6-week blinded multiple crossover phase, patients will receive 3 weeks of ephedrine and 3 weeks of placebo add-on treatment (week 1-6). The order of treatment will be randomised over each of the 3 crossover cycles (e.g. AB-BA-BA). Patients will fill out adverse event questionnaires twice a week (+ baseline; 13 adverse event questionnaires in total), visit their neurologist once a week (+ baseline; 7 hospital visits), answer an ADL questionnaire once a week (+ baseline: 7) and give a VAS score once a week (+ baseline: 7).
In week 8, patients will have a follow-up consultation with their neurologist to discuss the results of the n-of-one trial. Based on the results and experience in the multiple crossover phase, patients can decide whether they want to continue ephedrine after the trial. During the qualitative evaluation phase (week 9 or 10), patients will be interviewed by telephone by one of the researchers to explore their experiences with the n-of-one trial.
If a patient has decided to continue treatment with ephedrine after the n-of-one trial, we will ask them to participate in the open label extension phase. This will consist of three outpatient visits at 2, 4 and 6 months afterwards. An n-of-one trial directly assesses benefits and risks of treatment for individual patients. This means that treatment decisions can be made based on the results of an individual patient*s results of the n-of-one trial. If ephedrine treatment is effective in a patient, his or her functional status and quality of life may improve.
Adverse effects of ephedrine treatment include palpitations, anxiety, nausea, restlessness and insomnia. These will be recorded and monitored throughout the trial.

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. Adult patient with a diagnosis of generalised MG based on
a) Clinical signs or symptoms suggestive of generalised myasthenia gravis (for example, slowly progressive fluctuating muscle weakness in specific muscle groups); and
b) A positive serologic test for acetylcholine receptor (AChR) antibodies ;2. Treatment with pyridostigmine, and / or low dose (max. 15 mg/day) prednisone and / or other immunosuppressive drugs does not (or no longer) adequately improve myasthenic symptoms.
The dosage of pyridostigmine, prednisone and other immunosuppressive drugs need to have been stable for at least 6 weeks prior to the trial.

Exclusion criteria

1. Purely ocular myasthenia (i.e. myasthenic symptoms that are limited to the extraocular muscles, such as ptosis and diplopia)
2. Treatment with ephedrine is contraindicated or was not tolerated in the past. Contraindications include myocardial ischemia (angina pectoris and / or myocardial infarction), any cardiac arrhythmia, angle-closure glaucoma, current treatment by a psychologist or psychiatrist, current hypertension (defined as 2 measurements >= 140 / 90 mm Hg), poorly regulated diabetes mellitus, inherited QT syndrome or a prolonged QT interval (as indicated by ECG), prostatic hypertrophy and thyrotoxicosis. Patients with relevant drug interactions (MAO inhibitors, alpha and beta blockers) are also excluded.
3. Reliance upon medium-high dose prednisone (> 15 mg/day) and recent (< 3 months) or regular intravenous immunoglobulin (ivIG) or plasma exchange therapy. This excludes steroid-sparing therapy such as azathioprine and excludes supportive therapy such as any form of physical therapy.
These treatments are not exclusion criteria for the open label extension phase.
4. Myasthenic crisis in the past 3 months
5. Thymectomy in the past 6 months, or thymectomy (expected) to take place during the trial
6. The patient is unable to fill out the study questionnaires or be interviewed in Dutch, or is unable to undergo the tests needed for the study, or is unable to give informed consent for participation in the study.
7. The investigator can exclude patients for this trial which are deemed not suitable for any reason.

Study design

Design

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

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	07-10-2014
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ephedrine
Generic name:	ephedrine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-05-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-08-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-001355-23-NL
CCMO	NL40960.058.14