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Ephedrine treatment for autoimmune myasthenia gravis

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Abstract

We studied the effect and safety of ephedrine as add-on treatment for patients with myasthenia gravis with acetylcholine receptor antibodies (AChR MG), who do not sufficiently respond to standard treatment. Four patients with AChR MG were included in a placebo-controlled, double-blind, and randomised, multiple crossover series of n-of-1 trials. Each n-of-1 trial consisted of 3 cycles, in which two 5-day intervention periods were followed by 2 days washout. In each cycle, ephedrine 50 mg daily in 2 doses was compared with placebo in the alternate treatment period. Primary outcome was a change in QMG score. Add-on treatment with ephedrine compared with placebo improved QMG score by 1.0 point (95% confidence interval 0.21–1.79), which was significant for the group of trial patients as well as for the population treatment effect. Ephedrine also showed a significant trial average treatment effect for all secondary outcomes, improving MG Composite by 2.7, MG-ADL by 1.0 and VAS score for muscle strength by 1.1. Adverse events were mild and included palpitations, tremor and restlessness. Although all ECGs were normal, ephedrine prolonged the corrected QT interval. Ephedrine as add-on treatment for myasthenia gravis resulted in a small but consistent reduction of symptoms and weakness in patients with moderate disease severity.

Keywords: Myasthenia gravis; Add-on therapy; Ephedrine; n-of-1 trial; Randomised controlled trial

1. Introduction

Myasthenia gravis (MG) is a rare autoimmune disease, characterised by fluctuating muscle weakness. Many patients initially respond favourably to symptomatic treatment with acetylcholinesterase inhibitors (AChIs) that act directly on the neuromuscular junction. The next step in treatment often consists of high doses of immunomodulating or immunosuppressive drugs, which may have serious side effects [1].

Anecdotal evidence suggests that some MG patients may benefit from ephedrine as add-on treatment to pyridostigmine [2,3]. Ephedrine might be an alternative, which, together with AChIs or low-dose prednisone, may reduce disease severity, while avoiding the often severe side-effects related to the use of aggressive immunomodulating or immunosuppressive therapies. Ephedrine is a sympathomimetic agent which mainly affects the adrenergic receptors [4,5]. Its mechanism of action in MG has been investigated, but is not well understood [6–11]. An increase in quantal content of the endplate potential and the probability of quantal release, as well as an antagonistic effect on acetylcholine receptor (AChR) conductance have been described, although these effects occurred at a much higher dose than is reached in patients [7,9,12]. Moreover, ephedrine could have a direct effect on fatigue, which is found in more than 40% of the MG patients and correlates poorly with muscle weakness [13].

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In contrast to congenital myasthenic syndromes, in which a maximal treatment effect of ephedrine is observed after weeks to months, the limited number of patients with autoimmune MG treated with ephedrine report an onset within hours to days [2,10,14]. Autoimmune MG is a rare disease with a low prevalence and moreover even consists of heterogeneous subgroups, due to differences related to age of onset, sex or associated thymic abnormalities. Therefore, a standard randomised controlled trial (RCT) is difficult to perform, as also highlighted by the limited success of therapeutic development in MG [15]. The likely short-acting nature and rapid onset of response to symptomatic treatment in MG in general permit a crossover design to test the effect of ephedrine. A series of n-of-1 trials has the advantage of using each patient as their own control in repeated crossover cycles, limiting the required sample size [16,17]. We studied the effect and safety of ephedrine as add-on treatment in a series of n-of-1 trials in patients with AChR MG who do not sufficiently respond to standard treatment.

2. Methods

For full details, we refer to the trial protocol, which has been previously published [18].

2.1. Patient population

Eligible subjects were adult patients with a diagnosis of generalised MG, based on clinical signs or symptoms and confirmed by presence of AChR antibodies. All screened subjects were being treated at the Leiden University Medical Center and enrolled between October and December 2014. Inclusion criteria were: treatment with pyridostigmine and/or low dose prednisone (max. 15 mg daily) and/or other steroid-sparing immunosuppressive drugs, all of which at a stable dose for at least 6 weeks. All patients had remaining symptoms of MG that were too mild to justify starting or increasing immunosuppressive drugs, but that were not adequately controlled by their current symptomatic treatment. Exclusion criteria were: regular or recent (<3 months) intravenous immunoglobulin or plasma exchange, recent (<3 months) myasthenic crisis, recent (<6 months) or planned thymectomy, any contraindication for ephedrine (myocardial ischaemia, any cardiac arrhythmia, prolonged QT interval, angle-closure glaucoma, current hypertension, poorly regulated diabetes mellitus, prostatic hypertrophy or thyrotoxicosis), relevant drug interactions, or inability to give informed consent or fill out the study questionnaires.

2.2. Intervention

During the n-of-1 trials, add-on treatment with ephedrine 50 mg daily in 2 doses was compared with placebo, which was similar in shape, colour and flavour to the ephedrine tablets. During the entire trial, pyridostigmine, low dose prednisone and steroid-sparing drugs such as azathioprine were continued as before, at the same dose and time schedule.

2.3. Design

Each patient was treated for three single weeks with ephedrine and three single weeks with placebo add-on treatment in a randomised, double-blind n-of-1 trial. Treatment was administered in three treatment cycles, each consisting of 2 periods during which either ephedrine 50 mg daily in 2 doses or placebo was administered for 5 days, followed by a 2-day washout period. This was followed by 5 days of the alternate treatment, again with a 2-day washout period. Treatment order within each cycle was block-randomised for each patient individually (example shown in Fig. 1). Randomisation was performed by the hospital pharmacy. Patients and investigators were blinded to the treatment sequence until completion of each n-of-1 trial, after which the individual results were discussed and patients were invited to participate in a 6-month open label extension phase.

2.4. Endpoints

The primary endpoint was the effect of add-on therapy with ephedrine compared with placebo on the Quantitative Myasthenia Gravis (QMG) score [19,20]. The QMG score is a severity score for muscle strength and fatigability consisting of 13 items, each scored from 0 (normal) to 3 (severe weakness). This endpoint was assessed for all patients enrolled to determine the trial average treatment effect. Only in case of significant improvement, the population treatment effect was also assessed to determine generalisability to other MG patients. Secondary outcome parameters were the MG Composite, MG-ADL scores and a VAS score for subjective assessment of muscle strength in a muscle group predefined by the patient [21,22]. Individual treatment effects were also assessed for all outcome measures. All tests were performed on day 5 of treatment periods, at a predefined time and interval after all medication.

Adverse events were monitored during each treatment period using questionnaires, which included a list of known side effects of ephedrine, as well as vital signs, screening blood tests and ECGs at the end of treatment periods. On the first day of both periods in the first treatment cycle, patients were admitted to the hospital to monitor vital signs and adverse events, as well as ECGs at the time of estimated maximum serum concentration (Tmax).

Treatment preference was recorded for each treatment cycle. Blinding was assessed by recording presumed randomisation sequence by patient and investigator after each treatment period.

2.5. Statistics

Based on our observations during clinical care, we estimated that the standard deviation of repeated measurements of QMG within a single person is 2.95. For our sample size calculation, we assumed a mean treatment effect of 3.5 with a standard deviation of 1. Power calculation by means of Monte Carlo simulation showed a sample size of 4 patients would yield