The Lambert-Eaton myasthenic syndrome

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Chapter 12

Efficacy of 3,4-diaminopyridine and pyridostigmine in the Lambert-Eaton myasthenic syndrome

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Abstract

Background: Although 3,4-diaminopyridine (3,4-DAP) and pyridostigmine are widely used in the therapy of the Lambert-Eaton myasthenic syndrome (LEMS), either alone or in combination, no studies have compared their effects in patients with LEMS.

Methods: We performed a placebo-controlled, double-blind, randomized, cross-over study in nine patients with LEMS. Patients were treated intravenously with 3,4-DAP, pyridostigmine, both drugs, or placebo during four consecutive half-day sessions. 3,4-DAP (10 mg) was infused during one hour, and pyridostigmine in boli of 1 mg at 0 and 40 minutes. Drug effects were measured every 20 minutes by studying the change of isometric muscle strength of hip flexion, compound muscle action potential (CMAP) amplitude of hypothenar muscles, the CMAP decrement at 3 Hz stimulation, and the CMAP increment after maximum voluntary contraction.

Results: Compared to placebo, muscle strength and CMAP amplitude increased during treatment with 3,4-DAP (mean time-averaged difference 23 Newton; 95% CI, 12 to 34, and 0.9 mV; 95% CI, 0.4 to 1.4) and with both drugs combined (26 Newton; 95% CI, 15 to 38, and 1.1 mV; 95% CI, 0.5 to1.6), but not with pyridostigmine alone. Compared to 3,4-DAP, combination therapy showed slightly less decrement (-6%; 95% CI, -12% to -0.4%), but no other effects were observed.

Conclusions: 3,4-DAP is an effective drug in the treatment of LEMS. Pyridostigmine had no effects during treatment, and provided no additional benefits over 3,4-DAP alone.

Introduction

The Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder, clinically characterized by proximal muscle weakness and depressed tendon reflexes. In LEMS, antibodies against presynaptic voltage gated calcium channels inhibit influx of calcium in the nerve terminal and consequently the release of acetylcholine into the neuromuscular synapse. The diagnosis is reached on the basis of clinical findings and typical results of repetitive nerve stimulation (RNS). These are a low compound muscle action potential (CMAP) amplitude, that decreases at low-frequency RNS ("decrement") and increases following high-frequency RNS or maximum voluntary contraction ("increment").

3,4-Diaminopyridine (3,4-DAP) and pyridostigmine are both used in the treatment of LEMS. 3,4-DAP blocks neural potassium channels, resulting in prolongation of the nerve terminal action potential, which enhances influx of calcium ions, and consequently increases the acetylcholine release. Pyridostigmine is a potent reversible inhibitor of acetylcholinesterase, the enzyme responsible for clearance of acetylcholine from the neuromuscular synapse. Several studies have described a beneficial effect of 3,4-DAP in patients with LEMS, but only two studies were done in a prospective, double-blind and placebo-controlled manner.[1,2] Both studies described an additional clinical effect of pyridostigmine, although this effect was not quantified. No studies have investigated the therapeutic effect of an acetylcholinesterase inhibitor, alone or in combination with 3,4-DAP, in LEMS. The two drugs have different sites of action at the synapse, which could lead to a synergistic effect on neuromuscular transmission. Therefore, we compared the effects of 3,4-DAP, pyridostigmine, the combination of both drugs, and placebo on muscle strength and results of RNS in patients with LEMS.

Patients & methods

Patients

Patients with electrophysiologically confirmed LEMS were eligible for the study. Criteria for the diagnosis of LEMS were firstly, proximal muscle weakness of the legs and reduced or absent reflexes at neurological examination, and secondly, an increase in CMAP amplitude exceeding 100% following repetitive stimulation or maximum voluntary contraction of the tested muscle on RNS.[3] Exclusion criteria were hypersensitivity for 3,4-DAP or pyridostigmine, a significant (history of) polyneuropathy, myopathy, epilepsy, chronic obstructive pulmonary disease or

Table. Randomization scheme

Group	Occasion	Morning session	Afternoon session
A	1	all placebo	3,4-DAP and placebo
	2	pyridostigmine and placebo	3,4-DAP and pyridostigmine
B	1	all placebo	pyridostigmine and placebo
	2	3,4-DAP and placebo	3,4-DAP and pyridostigmine

3,4-DAP = 3,4-diaminopyridine

cardiovascular disease, including recent myocardial infarction and cardiac arrhythmia, and intestinal or urinary obstruction. Any medication with a known influence on neuromuscular transmission or muscle strength except 3,4-DAP or pyridostigmine was disallowed for at least one week preceding and throughout the study period. An exception was made for stable dosages of corticosteroids. 3,4-DAP and pyridostigmine were discontinued for at least 10 hours before each study day. All patients gave written informed consent. The study was approved by the Medical Ethics Review Board of the Leiden University Medical Centre, and performed according to the principles of the Helsinki Declaration.

Study design and randomization

The study was a placebo-controlled, double-blind, double-dummy, partially randomized, cross-over study of 3,4-DAP, pyridostigmine, and their combination. Eligible subjects who complied with the inclusion and the exclusion criteria were randomized according to either treatment group A or group B, and subsequently according to the order of treatment occasions A and B. The randomization scheme is shown in the table.

Study medication

Study medication was administered intravenously to improve pharmacokinetic predictability and reproducibility. 3,4-DAP was infused over a 60 minute period in a dosage of 10 mg. This dose was chosen, because 3,4-DAP was effective in oral doses of 20-25 mg,[1,2] and the bioavailability of 3,4-DAP is approximately 30%.[4,5] Previously, intravenous boli of 6-9 mg 3,4-DAP were well tolerated.[5] Pyridostigmine was given over 1 min in two boli of 1 mg each at 0 and 40 minutes. Effective doses of pyridostigmine in myasthenia gravis and LEMS vary widely. The usual starting dose is 30 or 60 mg orally. The parental dose is approximately 1/30 of the oral dose. In the treatment of myasthenia gravis, pyridostigmine 1 mg intravenously is considered effective and safe.[6] In addition, double-dummy placebos for the infusions and boli were administered. To reduce autonomic side effects, atropine 0.5 mg was slowly injected intravenously 10 minutes before administration of trial medication.

Treatment protocol

The four treatment occasions were planned in the morning and afternoon of two consecutive study days, to reduce the burden for the patients. Patients were admitted to the Neurology Ward of the Leiden University Medical Centre on the night before the first study day. Patients were confined to bed for about four hours during each treatment occasion. On each occasion, three consecutive baseline measurement combinations of RNS and isometric muscle strength were performed before administration of study medication, with 20 minutes between each measurement combination (t=-50, -30, -10 minutes). Trial medication was administered according to the randomization schedule (at t=0 minutes). RNS and muscle strength were recorded every 20 minutes, from 10 to 170 minutes after the administration of the first dose of trial medication. During a break of 1.5 hours, patients had lunch and left the bed at will. Thereafter, the afternoon session was performed, using the same procedures (including baseline assessment) as with the morning session. One blinded assessor (PW) administered trial medication and performed measurements of muscle strength and RNS in all patients.

Endpoints

Primary study endpoints were isometric muscle strength and CMAP amplitude. CMAP amplitude was chosen as a primary endpoint because a study relating RNS measures with strength of hip flexors found it to be the best electrophysiological measure of weakness.[7]

Isometric strength of hip flexion was quantified using a dynamometer (CIT Technics, Groningen).[8] Before each study session, patients received the instruction to build up maximum strength during measurements. For measurements, the dynamometer was positioned at the anterior surface of the distal thigh, while the patient was in supine position with hip and knee 90° flexed and the ankle supported by the examiner. The meter was equipped with a maximum indicating pointer, which indicated force in Newton (N).

The CMAP amplitude (baseline to negative peak) was measured from the hypothenar muscles of the non-dominant hand. Supramaximal electrical stimuli were delivered with round self-adhesive stimulating electrodes over the ulnar nerve at the wrist (20 mm diameter, Nicolet Medical, Madison, WI). CMAPs were recorded with large self-adhesive recording electrodes (30 x 22 mm, Nicolet Medical, Madison, WI), having a beneficial effect on CMAP reproducibility.[9] All electrodes remained fixed on the skin throughout each study day, and the fingers and hand were immobilized with tape and a splint to ensure stable RNS procedures. Skin temperature was monitored throughout

the experiment, and a heating lamp was used when necessary to obtain skin temperatures of at least 32ºC.

Secondary study endpoints were decrement of CMAP amplitude during 3 Hz RNS and its increment immediately after 10 seconds of maximum voluntary contraction. For determination of decrement, a train of 10 stimuli was given at 3 Hz. Decrement was quantified as the maximal percentage amplitude decrease during the train with regard to the first CMAP in the train. Increment was measured as the increase of CMAP amplitude after 10 seconds of maximal voluntary contraction of the hypothenar muscles. Increment is generally expressed as a percentage increase of initial CMAP amplitude, but this percentage depends excessively on the value of the often very low initial amplitude. As a result, it shows high variability and a skewed distribution. We expressed increment as the absolute increase in mV of the negative peak of the CMAP amplitude to avoid this problem, and because a voltage measure may be more closely related to muscle strength.

Assessment of safety and adverse events

For safety, electrocardiography was monitored for three hours during each treatment combination, and blood pressure was measured every hour. A 12-lead electrocardiogram was recorded before and after each treatment combination. All adverse events reported spontaneously by the subject or observed by the investigators were recorded. Checks for adverse events were made six times during each treatment by asking how the subject was feeling.

Statistical analysis

All repeatedly measured dynamic variables were characterized using the mean response over times > 0 minutes. An analysis of variance (ANOVA) with mean baseline value as co-variate and factors subject and treatment was performed. Mean baseline values were calculated over times -50, -30 and -10 minutes. Contrasts between placebo and the other treatments, between the pyridostigmine and the combination treatment, between 3,4-DAP and the combination treatment, and between pyridostigmine and 3,4-DAP treatment were calculated. A supra-additive interaction between 3,4-DAP and pyridostigmine, which compares the effect of the combination treatment with the sum of the separate 3,4-DAP and pyridostigmine treatments, was also assessed. All completed study sessions in all patients were analyzed, including withdrawals. Statistical analysis was performed using SAS Proc GLM (SAS version 8.1, SAS Institute Inc., Cary, NC).

Results

Patients

Nine patients (five men) participated in this study, who had LEMS for a mean of 10.5 years (range 1.5-39 years). Mean age was 54 years (range 33-73 years). Repeated search for an underlying malignancy had been negative in all patients. Four patients had an additional autoimmune disorder (two patients with type I diabetes mellitus, two with thyroid disorder). All patients had antibodies against P/Q-type voltage gated calcium channels. Eight patients were treated with 3,4-DAP, and six patients used pyridostigmine additionally. Two patients were on prednisone, one used azathioprine, and two were treated with both drugs. Seven patients completed all four treatment occasions. Two patients were withdrawn from the study after completing three study sessions, because of a study related side-effect.

Endpoints

The effects of the different treatments are shown in figure 1. Compared to placebo, isometric muscle strength (figure 1A) increased significantly during treatment with 3,4-DAP (mean difference 23 N; 95% CI, 12 to 34 N) and during the combination (26 N; 95% CI, 15 to 38 N), but not with pyridostigmine alone (1 N; 95% CI, -9 to 12 N). Treatment with the combination did not have a supra-additive effect (-2 N; 95% CI, -18 to 14 N), nor did treatment with the combination differ significantly from treatment with 3,4-DAP alone (3 N; 95% CI, -8 to 15 N).

CMAP amplitude (figure 1B) increased significantly during treatment with 3,4-DAP (mean difference 0.9 mV; 95% CI, 0.4 to 1.4 mV) and with the combination (1.1 mV; 95% CI, 0.5 to1.6 mV), but not with pyridostigmine alone (0.1 mV; 95% CI, -0.4 to 0.6 mV). Treatment with the combination did not have a supra-additive effect (-0.1 mV; 95% CI, -0.8 to 0.6mV), and did not differ significantly from treatment with 3,4-DAP alone (0.2 mV; 95% CI, -0.3 to 0.7 mV). The decrement at 3Hz stimulation (figure 1C) decreased significantly during treatment with 3,4-DAP (-9%; 95% CI, -14% to -3%) and with the combination (-15%; 95% CI, -21% to -9%), but not with pyridostigmine alone (0%; 95% CI, -6% to 6%). Treatment with the combination showed a slightly but significantly larger decrease of decrement, than 3,4-DAP alone (-6%; 95% CI, -12% to -0.4%), but this pyridostigmine effect was not supra-additive (6%; 95% CI, -2% to 14%). Increment after maximal voluntary contraction did not show any significant treatment effects (figure 1D).

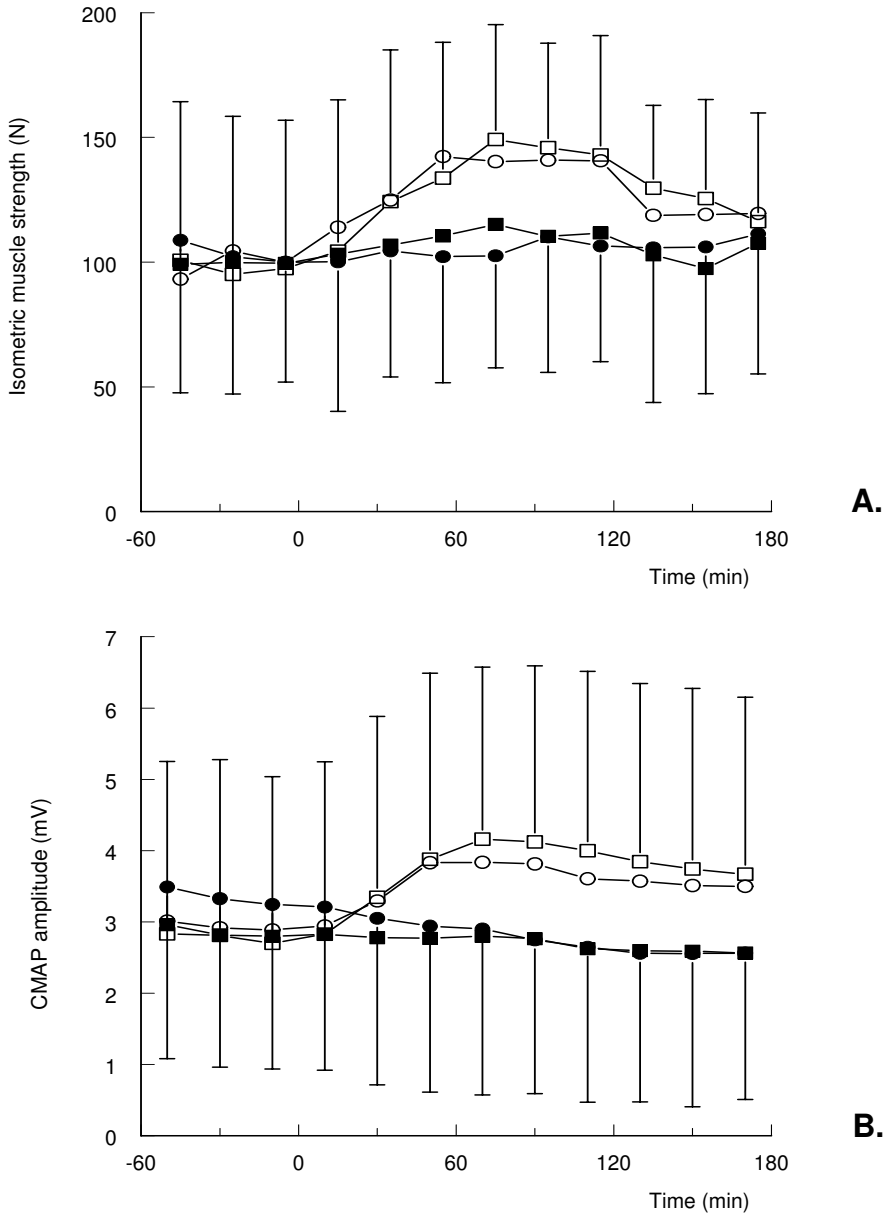

Figure 1. Isometric muscle strength (A), CMAP amplitude (B), decrement at 3 Hz (C) and increment after 10 seconds of maximum voluntary contraction (D) (mean + SD) for the four treatment occasions: for the treatment with 3,4-diaminopyridine (open circles), pyridostigmine (solid squares), the combination of both drugs (open squares), and placebo (solid circles).

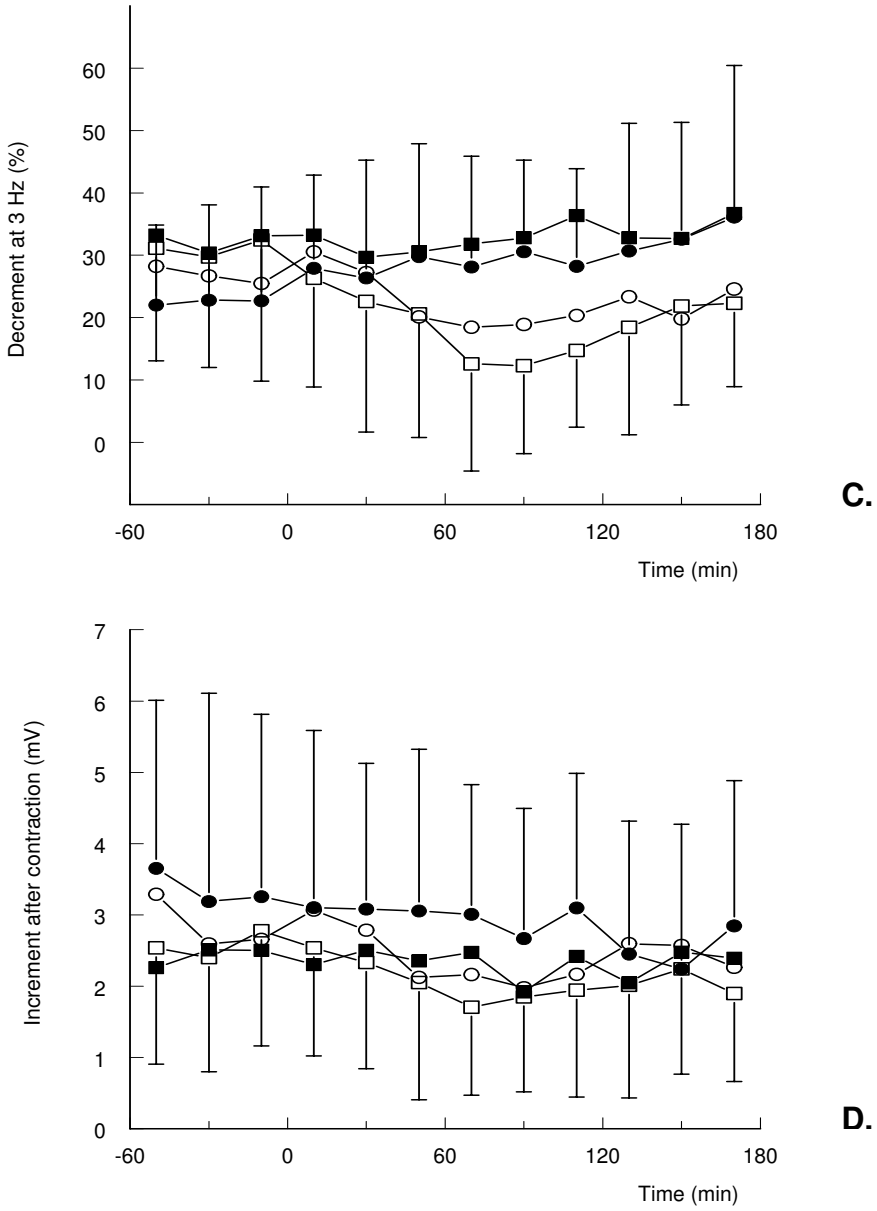

Figure 1 (continued).

Adverse events

Three patients reported perioral and lingual paresthesias after starting the administration of 3,4-DAP or the combination, lasting 1-2 hours. All patients but one reported pain in the upper arm in which study medication was administered, lasting 2-3 hours in total, during the study sessions of treatment with 3,4-DAP or the combination. In two patients, severe pain occurred during the morning session of the second study day, so it was decided not to continue with the last occasion. No other study-related side effects were found.

Discussion

This is the first study to systematically investigate the effects of 3,4-DAP, pyridostigmine, and their combination on neuromuscular function in LEMS. We found that intravenous administration of 3,4-DAP in patients with LEMS produced a significant increase in muscle strength and CMAP amplitude, whereas pyridostigmine had no significant effects on these measures as monotherapy, nor as additional therapy with 3,4-DAP.

In our study, intravenous treatment with 3,4-DAP resulted in a mean increase of muscle strength from 99 N to 129 N, with a maximum of 142 N (figure 1A). Mean CMAP amplitude increased from 2.9 mV to a maximum of 3.8 mV during treatment with 3,4-DAP (figure 1B). The effectiveness of 3,4-DAP administered orally in the treatment of LEMS was shown in two previous placebo-controlled studies.[1,2] In the first of these, 3,4-DAP was given in doses up to 100 mg per day to 12 patients.[1] Muscle strength in the legs increased from 45% to 65% of normal, and CMAP amplitudes nearly doubled. The second study showed an improvement of a quantitative muscle function score, and of the summated CMAP amplitude recorded from three muscles, during treatment with 20 mg of 3,4-DAP three times daily.[2] Both studies described an additional benefit of pyridostigmine, but this effect was not quantified. We did not find any significant effect of pyridostigmine on muscle strength or CMAP amplitude. Given the clearly significant effects of 3,4-DAP and the absence of any effect of pyridostigmine, it is unlikely that this is due to the small size of the patient group. We administered medication intravenously, to ascertain adequate drug exposure. Comparable doses of intravenous pyridostigmine are given effectively in myasthenia gravis.[6] The only pyridostigmine effect we found, consisted of a small reduction of the CMAP decrement during 3 Hz stimulation, during the combination of pyridostigmine and 3,4-DAP. This suggests that pyridostigmine facilitates neuromuscular transmission only when 3,4-DAP is acting as well, and only at low frequency stimulation. Although this was a small and isolated effect, it is in line with

our understanding of neuromuscular transmission. Pyridostigmine can only have an effect when a sufficient amount of acetylcholine is available in the neuromuscular cleft. In LEMS, defective acetylcholine release improves in the presence of 3,4-DAP. It is unclear why this observed additive effect is limited to the decrement at low frequency stimulation. Under physiological circumstances, muscles are stimulated at higher frequencies, and the functional correlate of the CMAP decrement in LEMS is unknown.

3,4-DAP has been given intravenously in LEMS patients previously.[4,5] The effective oral dose of 3,4-DAP was approximately three times the dose given intravenously,[4] indicating that the dose we gave equals an oral dose of about 30 mg. Administered orally, the daily dose is limited to 80 mg/day due to possibility of developing seizures at higher doses.[2] Perioral and acral paresthesias are a known side effect of 3,4-DAP and were common in this study.[4] Pain in the arm above the site of infusion of 3,4-DAP was seen in almost all of the patients in our study and was sometimes severe, resulting in withdrawal of two patients. In all patients, the pain disappeared within two hours after stopping the infusion, without residual effects. The pain to some extent unblinded the study, although it was unknown which of the study treatments (3,4-DAP, pyridostigmine or the combination) caused it. Moreover, the objective nature of the assessments and the clear effects of one drug but not the other make it extremely unlikely that the results can be explained through observer or patient bias. Transient pain at the site of intravenous administration of 3,4-DAP was previously described in 4 of 5 treated patients.[5] No injurious side effects were encountered. Thus, in the dosage we used, 3,4-DAP can be administered intravenously safely and effectively, although pain at the administration site may be an annoying side effect.

In conclusion, this study shows that 3,4-DAP, but not pyridostigmine, in LEMS patients produces significant improvement in muscle strength and CMAP amplitude. Moreover, the combination of the two drugs has no additional effect on these measures. The small effect of pyridostigmine, in combination with 3,4-DAP, may reflect a facilitating effect on neuromuscular transmission, but the effect is minimal and the therapeutic relevance is unclear. The results of this study provide no further support for the use of pyridostigmine in LEMS. 3,4-DAP on the other hand, causes significant improvements in the neurophysiological and clinical characteristics of LEMS, and is the mainstay for the symptomatic treatment of this condition.

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