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The potential use of ephedrine in Lambert-Eaton myasthenic syndrome

Clinical and electrophysiological evaluation

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Sirs: A Cochrane review on treatment of Lambert-Eaton myasthenic syndrome (LEMS) underscores the efficacy of 3,4-diaminopyridine (DAP) and of infusions of immunoglobulins (IvIg) [5]. The addition of pyridostigmine may enhance effects of DAP. Ephedrine, a controversial drug used in the past to treat myasthenia gravis without proven benefit [8], has recently been used to improve patients with synaptic congenital myasthenic syndrome [2]. Prompted by these observations, we evaluated the efficacy of ephedrine in one patient with idiopathic LEMS.

We describe a 60 year-old female who developed progressive proximal limb muscle weakness and generalized areflexia. A 300 % potentiation of the compound muscle action potential (CMAP) was demonstrated after a short exercise test (SET) and antibodies against the voltage gated Ca^{2+} channel were positive. Diagnostic works-up over the following 5 years did not uncover an underlying cancer. Pyridostigmine partially improved the patient for the first 2 years, and then DAP was introduced with efficacy over the following 12 months. After another phase of deterioration, two series of IvIg infusions were useful for 2 months. Then ephedrine sulfate was prescribed at a dose of 200 mg/d and the improvement was so impressive that we decided to quantify the clinical and electrophysiological (Edx) changes before proceeding with ephedrine.

The patient agreed to come for five consecutive days. Muscle testing and Hammersmith motor ability score (HMS) were performed after the Edx tests. Edx studies were carried out by recording CMAP from the abductor digiti minimi muscle (ADM). After a rest period, negative CMAP amplitude was evoked at rest and immediately after 15 s SET [4]. The clinical and Edx changes were recorded each day with 3 repetitions of the following 6 experimental conditions: no treatment, 90 minutes after taking 60 mg pyridostigmine, 25 mg 4-DAP, 100 mg ephedrine, pyridostigmine and DAP, ephedrine and DAP. The results are shown in Fig. 1. The highest HMS score correlates with the highest CMAP amplitude at rest obtained during the association of DAP and ephedrine. After obtaining these positive results, ephedrine (200 mg/d) and DAP (55 mg/d) were taken continuously. Benefits were observed after the patient was reviewed 1, 3 and 6 months after. A moderate increase in blood pressure was observed.

Ephedrine is a sympathomimetic drug with highly active adrenergic effects on the heart and vasculature [1], with untoward effects including hypertension and tachyphylaxis [9]. The precise mechanism of action in the muscle is only partially known. An *in vitro* Edx study has shown that ephedrine increases quantal release of acetylcholine (Ach) [10], and may cause an open-channel blockade of the Ach receptors [6], which cannot fully explain its beneficial effect. In a study using a rat model of myasthenia, the ephedrine effects were considered unrelated to neuromuscular transmission but to susceptibility to arousal [7]. In the reported Edx trial of ephedrine in synaptic congenital myasthenic syndrome it was concluded that ephedrine may exert a beneficial effect on muscle function at a remote level as a central effect [3]. In our patient we observed a relative mismatch between the good clinical benefit (HMS) and surprisingly low CMAP at rest during treatment with ephedrine alone (see Fig. 1, day 5), and this probably reflects the central beneficial effect. Based on this, we can only speculate on a synergic, but useful, effect of ephedrine with DAP. As a limiting factor it should be emphasised that (i) we do not know the safe and therapeutic optimum dose of ephedrine per kg body weight, and (ii) that patients should be monitored for potential cardiovascular side effects. Further trials are therefore needed to study the efficacy and tolerability of ephedrine in LEMS.

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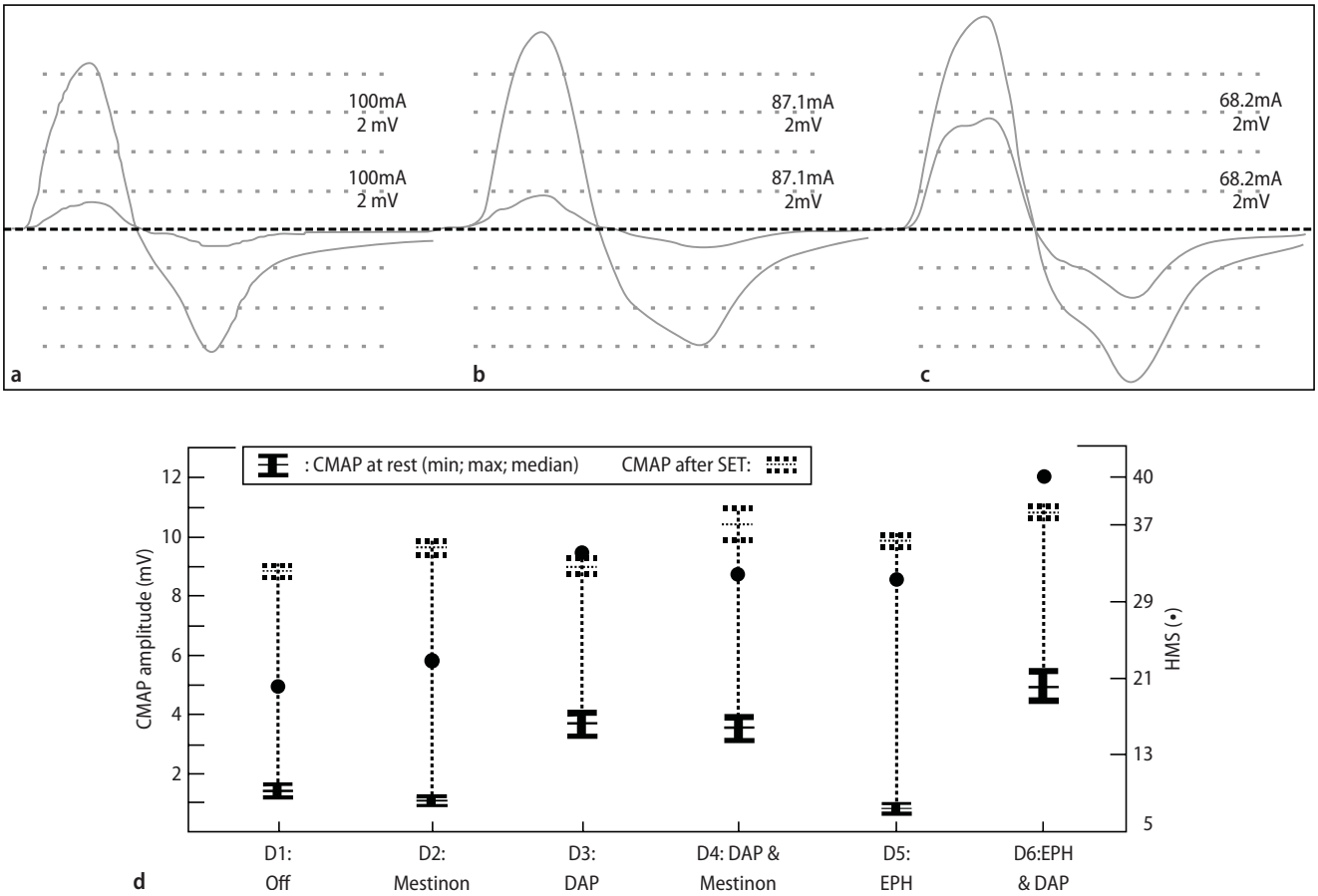

Fig. 1 **A** to **C** shows examples of raw data of two superimposed traces, the smallest corresponding to the CMAPs evoked at rest and the largest those evoked immediately after a 15 s of maximal voluntary exercise test. Data with no treatment or OFF (**A**); 90 min after taking ephedrine (**B**), and after taking ephedrine and DAP (**C**). Note the huge potentiation obtained in **B**, as well as the synergic effect of the combined treatment with ephedrine and DAP on the CMAP obtained at rest in **C**. **D** Diagram showing the relationship between Hammersmith motor score (HMS), and CMAP amplitude. CMAPs obtained at rest (solid lines) and after exercise (dashed lines) were repeated 3 times. Amplitude is expressed as minimal and maximal, and median values, in the following experimental conditions during 5 different days (D): no treatment (OFF), 90 min after taking (i) 60 mg pyridostigmine (Mestinon), (ii) 25 mg 3,4-diaminopyridine (DAP), (iii) 100 mg ephedrine (EPH), (iv) DAP and pyridostigmine (DAP+ Mestinon) and (v) ephedrine and DAP (EPH+DAP). The CMAPs obtained after exercise are quite similar in amplitude. The highest CMAP amplitude at rest was obtained at D6 (5.2 mV, DAP+ EPH), and correlates with the highest HMS score. The lowest CMAP amplitude obtained at rest was seen at D1 (Off), D2 (Mestinon) and D5 (EPH) (1.4 mV; 1.0 mV; 0.7 mV, respectively). Controversially, the HMS score under ephedrine is relatively high at day 5, probably reflecting the central effect of the drug

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