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Case study

3,4-Diaminopyridine for the treatment of myasthenia gravis with electrophysiological patterns of Lambert-Eaton myasthenic syndrome

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ABSTRACT

3,4-Diaminopyridine (34DAP) is a presynaptic transmission enhancer. Its efficacy for Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis (MG) was demonstrated. However, there are cases sharing the characteristics of both disease and the effect of 34DAP in "gray zone" patients is sparse. Recently, we prescribed 34DAP to five anti-acetylcholine receptor antibody-positive MG patients with electrophysiological LEMS patterns and three LEMS patients, and carefully monitored the responses. Sero-positive MG patients exhibited more favorable responses than LEMS patients. The combination of 34DAP and pyridostigmine resulted in the best outcomes. No significant side effects were recorded during the follow-up period. In conclusion, this study results provide evidence that 34DAP could be effective in sero-positive MG patients with pre-synaptic dysfunction.

1. Introduction

3,4-Diaminopyridine (34DAP) increases presynaptic acetylcholine (Ach) release by blocking pre-synaptic K^+ channels. It is used to treat patients with Lambert-Eaton myasthenic syndrome (LEMS) with demonstrated efficacy [1,2]. Its potential for the myasthenia gravis (MG) has been also suggested [3,4]. LEMS and MG are neuromuscular junction disorders distinguished by symptom presentations, responses to cholinesterase inhibitors, the presence of specific auto-antibodies, and repetitive nerve stimulation test (RNST) findings. However there are cases sharing the characteristics of both diseases and the literature concerning the symptomatic treatment in these "gray zone" patients is sparse due to its rarity. Recently, we prescribed 34DAP to sero-positive MG patients with LEMS patterns, and carefully monitored the clinical and electrophysiological responses. To share our clinical experience, this article describes the effect of 34DAP in our patient sample.

2. Material and methods

Eight patients who satisfied the electrophysiological criteria for LEMS in RNST (low resting compound muscle action potential (CMAP) in the intrinsic hand muscle [<5 mV]; decremental responses ≥10% at slow rates of stimulation (SRS); and incremental responses ≥100% at 50 Hz high rates of stimulation (HRS) or after maximal effort of voluntary contraction) were selected from the database. Informed consent for the use of oral 34DAP was obtained, and the Institutional Review Board of Severance Hospital (Seoul, South Korea) approved this study. Clinical status was assessed according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification and the quantitative MG score (QMG) [5,6]. The RNST was performed using the Toennies electromyography unit with Neuroscreen Plus software (Erich Jaeger GmbH, Hoechberg, Germany). The RNST was performed 10 min after QMG scoring. The CMAP was recorded using surface electrodes attached to the abductor digiti quinti (ADQ) muscle at supramaximal stimulation of the ulnar nerve at the elbow. First, the resting CMAP was verified, and maximal effort of isotonic muscle contraction (maximum 30 s) was performed to measure post-exercise CMAP. After 5 min of rest, serial SRS at 2 Hz, 3 Hz, and 5 Hz, with an inter-stimulation interval of 1 min were applied; 50 Hz HRS for 1 s was applied 10 min after SRS.

All patients underwent the same protocol as follows:

withdrawal of pyridostigmine (PDS) for 24 h;
baseline QMG scoring and RNST, then a second QMG scoring and RNST 30 min after intramuscular injection of 1.5 mg of neostigmine;
10 mg of 34 DAP taken four times per day for 48 h;
third QMG scoring and RNST;

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Table 1
Clinical profiles of the eight patients.

Pt	Sex/Age	PHx	Onset age	Age at Dx	Initial Sx	Symptom	Thymectomy (age)	Pathology	Ach Ab (nmol/L)	Knee jerk	MGFA class	Previous meds (mg)	Final daily dose of 34DAP & PDS
1	F/46	None	37	38	Generalized weakness	L, B, O	Y (38)	hyperplasia	14.98	NL	IIIa	AZA 50, PL 60 PDS 660	34DAP 40, PDS 660
2	F/32	None	18	22	lower leg weakness	L, B, O	Y (26)	N/A	7.775	NL	IIa	PL 15/5, PDS 360	34DAP 40, PDS 360
3	F/35	None	29	30	Generalized weakness	L, B, O	Y (30)	NL	15.488	↓	IIa	AZA 100, PL 15/0, PDS 180	34DAP 30, PDS 180
4	F/45	Hyperthyroidism	42	42	Diplopia	L, B, O	Y (42)	hyperplasia	16.32	NL	IIIa	PL 20, PDS 480	34DAP 55, PDS 480
5	F/56	Myoma	46	56	Generalized weakness	L, B	N		10.8	↓	IIIa	PDS 180	34DAP 40, PDS 240
6	F/61	None	55	56	lower leg weakness	L, B	Y (57)	NL	(−)	↓	IIIa	AZA 150, PL 15/5, PDS 480	34DAP 40, PDS 480
7	M/38	Rheumatic fever	37	38	Diplopia	L, B, O	N		(−)	↓	IIa	PL 40, PDS 180	34DAP 80, PDS 480
8	M/68	Lung cancer	67	68	lower leg weakness	L, B, O	N		(−)	↓	IIIa	PDS 480	34DAP 80, PDS 480

Pt: patient, F: female, M: male, PHx: past medical histories, Dx: diagnosis, Sx: symptom, L: limb weakness, B: bulbar weakness, O: ocular weakness, Y: yes, N: no, N/A: not available, NL: normal, ↓: decreased, AZA: azathioprine, PL: prednisolone.

tolerable dose of 34DAP and PDS three or four times per day for 48 h; and
fourth QMG scoring and RNST.

3. Results

3.1. Clinical profiles

Six patients were female. The ages at disease onset ranged from 18 to 67 years. Five patients (1, 2, 3, 4, and 5) were sero-positive for anti-Ach receptor antibody (anti-AchR Ab); the other patients (6, 7, and 8) were sero-negative. Anti-P/Q type voltage-gated calcium channel antibody (VGCC Ab) was tested in only one patient (patient 1) and the result was negative. All patients exhibited limited improvement in response to conventional treatments including immunosuppressants, plasma exchange, thymectomy, or PDS. Three patients (2, 3, and 7) were in MGFA class IIa and the others were MGFA class IIIa. Patients were classified as group A (sero-positive for anti-AchR Ab) and B (sero-negative). Clinical profiles are summarized in Table 1.

3.2. QMG and RNST results

3.2.1. QMG scores

The mean QMG scores were 12 points at baseline, 8.3 at neostigmine trial, 8.1 at 34DAP trial, and 5.9 at combined trial of PDS and 34DAP. The best results were achieved in the 34DAP mono trial in one individual (patient 5), and the combined trial in five patients (1, 3, 4, 6, and 7). QMG scores did not change in two patients (2 and 8) throughout the trial sessions. The QMG scores are summarized in Table 2.

3.2.2. Responses to slow rates of stimulation

The SRS responses were normalized in one individual (patient 3) during the neostigmine trial, and two patients (2 and 3) in the combined trial. The best results were produced by 34DAP or combined trials in all patients. The SRS responses are summarized in Fig. 1.

3.2.3. The post-exercise facilitation responses

The PEF responses were normalized by 34DAP (difference < 40%) in two patients (1 and 5) during 34DAP mono trial, and all patients in the combined trial in group A. In group B, none of the patients was normalized by 34 DAP mono trial, and two patients (7 and 8) were normalized by combined trial. To visualize the changes of the resting and post-exercise CMAPs, the percent value of CMAP of the ADQ muscle was calculated using the formula:

$$\text{Percent value } (\%) = \text{resting or post-exercise CMAP of each session} / \text{baseline resting CMAP} \times 100$$

Fig. 2 report the changes of resting and post-exercise CMAPs in each treatment session.

3.3. Follow up

Loss to follow up occurred in one individual (patient 7, [unknown cause]). Seven patients took combined treatment of 34DAP and PDS. They were followed-up for three years with active dose adjustment. 34DAP markedly improved daily living function in five out of seven patients (1, 4, 5, 6, and 8). Patient 2 felt a mild improvement in quality of life. The functional status of patient 3 was not changed. These two individuals discontinued 34DAP early due to paresthesia (patient 2) or low efficacy (patient 3). Two patients (4 and 5) were treated for one year and

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