SHORT REPORT

ABSTRACT: To develop a symptomatic treatment for amyotrophic lateral sclerosis, we compared the effects of ultrahigh-dose and low-dose (25 and 0.5 mg/day, intramuscularly, for 14 days) methylcobalamin on averaged compound muscle action potential amplitudes (CMAPs) in a double-blind trial. No significant changes in CMAP amplitude were found in 12 patients who had the low-dose treatment at either 2 or 4 weeks after start of treatment. By contrast, 12 patients assigned to the ultrahigh-dose group demonstrated a significant increase at 4 weeks. This method may provide a clinically useful measure to improve or retard muscle wasting, if a larger extended trial fulfills its promise.

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EFFECT OF ULTRAHIGH-DOSE METHYLCOBALAMIN ON COMPOUND MUSCLE ACTION POTENTIALS IN AMYOTROPHIC LATERAL SCLEROSIS: A DOUBLE-BLIND CONTROLLED STUDY

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Amyotrophic lateral sclerosis (ALS) is a progressive disease without any treatment effective in improving clinical signs or parameters, although riluzole was shown to prolong life without tracheostomy.[4] Glutamate-induced neuronal death has been implicated in the pathogenesis of ALS. A recent study demonstrated that a vitamin B_{12} analog, methylcobalamin, has a protective effect on cultured neurons against glutamate-induced cytotoxicity.[1] Methylcobalamin, in ultrahigh doses (500 μg/kg per day), was also found to promote motor nerve regeneration from experimental acrylamide neuropathy.[5,7] ALS patients generally show reduced amplitudes of muscle potentials after peripheral nerve stimulation (compound muscle action potentials, or CMAPs), reflecting a decreased number of spinal motoneurons or limited capacity of motor nerve regeneration through sprouting.[2,3] We therefore tested the efficacy of ultrahigh-dose methylcobalamin in improving reduced CMAP amplitudes in ALS, using low-dose methylcobalamin as a control.

Abbreviations: ALS, amyotrophic lateral sclerosis; CMAP, compound muscle action potential

Key words: amyotrophic lateral sclerosis; methylcobalamin; compound muscle action potentials; therapy

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SUBJECTS AND METHODS

A total of 24 ALS patients without respiratory failure entered the study after giving an informed consent for the protocol approved by our institutional review board. Both upper and lower motor neuron signs were confirmed in all patients during the trial or follow-up observation period, and the diagnosis of ALS was based on El Escorial criteria.[8] Three patients showed only lower motor neuron signs at the time of the entry to this study.

Twelve patients (high-dose group; age 45–66 years, 5 men) were assigned ultrahigh doses (25 mg/day or 360–610 μg/kg per day, intramuscularly [IM]) of methylcobalamin, with the other 12 (low-dose group; age 41–66 years, 6 men) receiving the low dose (0.5 mg/day or 7–13 μg/kg per day, IM) as

control. Separation by age (below or above 50 years) before random assignment of the dose of methylcobalamin ensured that the two groups were matched for age. A retrospective analysis showed similar disease durations and initial averaged CMAP amplitudes between the groups (19.6 ± 4.1 vs. 21.7 ± 3.2 months and 5.27 ± 0.84 vs. 4.48 ± 0.91 mV). Clinical features of the patients are summarized in Table 1.

The patients were blinded as to the dose of methylcobalamin they received. One of the investigators, who was not informed of the dose, measured CMAPs immediately before starting methylcobalamin (day 1), at the end of 2 weeks of administration (day 14), and at 4 weeks after the start (day 28).

CMAPs were recorded bilaterally from the abductor pollicis brevis, abductor digiti minimi, and abductor hallucis muscles after stimulation of the median, ulnar, and tibial nerves at the wrist or ankle. Amplitudes were measured from the baseline to the negative peak. In each patient, the average amplitude from the six muscles (averaged CMAPs) served as an index of the number of muscle fibers innervated by spinal motoneurons.[2,3] Its normal range was defined as 7.30–12.82 mV (mean ± 2 SD) based on recordings from 10 normal subjects (31–53 years, 7 men).

RESULTS

The time course of averaged CMAP amplitudes in each patient is shown in Figure 1 and Table 1.

The low-dose group showed no significant changes in CMAP amplitude after treatment either at 2 or 4 weeks (Fig. 2A, $p = 0.60$, using repeated measures ANOVA). By contrast, the high-dose group demonstrated a significant increase at 4 weeks (day 28, $p = 0.017$, repeated measures ANOVA; $p = 0.038$, paired *t*-test, Fig. 2A), but not at 2 weeks (day 14, $p = 0.46$, paired *t*-test). The amplitude ratio between day 0 and day 28 was used to compare the effects of treatment between groups; the high-dose group had a significantly higher ratio than the low-dose group ($p = 0.030$, unpaired *t*-test, Fig. 2B). Two patients in the high-dose group (patients 14 and 23) noted an

Table 1. Clinical features of the patients and response to methylcobalamin.

Patient	Age/gender	Duration of disease	Average CMAP (mV)			Clinical signs*	Responder†
			Day 0	Day 14	Day 28		
Low-dose group							
1	41/M	24 mo	4.76	4.56	5.02	U = L	No
2	45/F	22 mo	6.39	5.80	5.21	U > L, B	No
3	45/M	18 mo	4.72	3.26	3.24	L	No
4	46/M	15 mo	5.49	6.30	5.51	U = L	No
5	58/F	19 mo	4.34	3.22	5.30	L > U	No
6	58/M	25 mo	5.78	5.22	5.48	U > L	No
7	64/M	17 mo	6.33	6.76	6.80	U = L	No
8	56/M	21 mo	6.45	6.51	5.71	U = L	No
9	58/F	23 mo	4.08	4.43	4.53	L	No
10	57/F	11 mo	4.35	3.48	3.73	U > L	No
11	54/F	22 mo	5.41	5.45	5.35	L > U, B	No
12	66/F	18 mo	5.25	5.73	6.11	L, B	No
High-dose group							
13	48/F	20 mo	4.62	4.98	7.66	U = L	Yes
14	49/F	23 mo	5.71	6.43	9.47	L > U	Yes
15	45/M	22 mo	3.24	4.87	4.76	L	Yes
16	47/M	18 mo	5.51	5.82	5.37	U > L, B	No
17	65/M	17 mo	4.77	4.09	4.31	U = L	No
18	56/M	19 mo	3.94	3.49	3.58	U = L	No
19	53/F	24 mo	3.96	3.65	5.76	L > U, B	Yes
20	58/F	26 mo	4.53	3.81	4.75	L > U	Yes
21	57/M	21 mo	3.73	3.43	3.27	U > L, B	No
22	55/F	27 mo	4.11	4.73	4.95	L > U	Yes
23	66/F	19 mo	6.11	7.04	7.65	L > U	Yes
24	64/F	24 mo	3.49	3.30	3.67	L > U	Yes

**Clinical signs were classified as follows: U = L, deep tendon reflexes (DTRs) were increased in the lower limbs, but were normal in the upper limbs; U > L, DTRs were increased both in the upper and lower limbs; L > U, DTRs were absent or decreased in the upper limbs, but were increased or normal in the lower limbs; L, DTRs were absent or decreased in both the upper and lower limbs; B, bulbar involvement.*
†Patients who showed increased CMAP amplitudes at day 28 (responders).

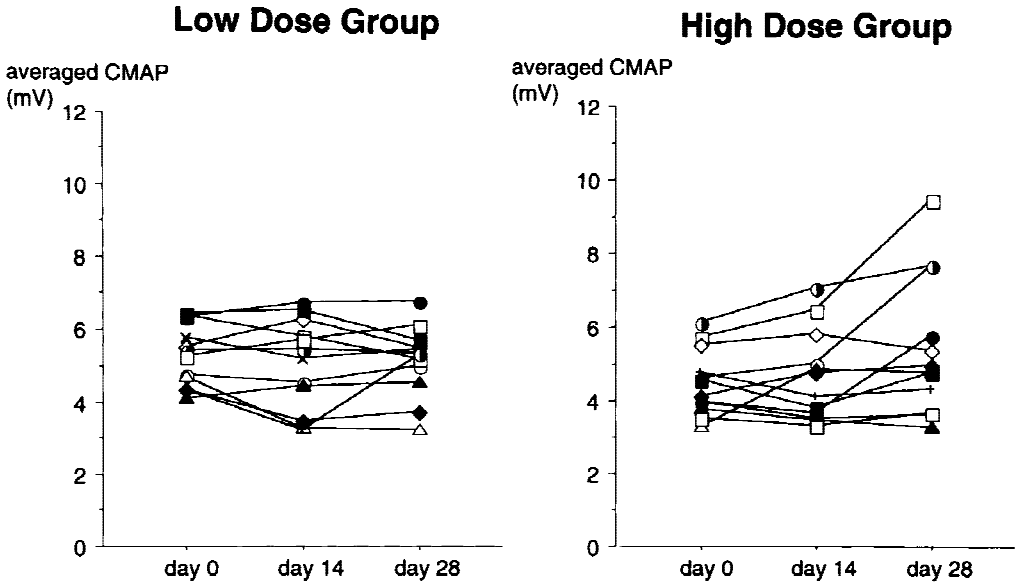

FIGURE 1. Time course of averaged CMAP amplitudes in each patient.

improvement in gait. These clinical benefits and improved CMAPs usually lasted for 1–3 months, but were followed by deterioration. Adverse reactions in the high-dose group included skin rash in 1 patient and mild elevation of serum GOT and GPT in another, both lasted for about a week.

In the high-dose group, 8 patients showed increased CMAP amplitudes at day 28 as compared with those at day 0 (responders), whereas 4 had decreased CMAP amplitudes (nonresponders). The age and the initial CMAP amplitude (day 0) were similar between responders and nonresponders (54.8 ± 7.6 vs. 56.3 ± 7.4 years and 4.47 ± 1.01 vs. 4.49 ± 0.82 mV), but the disease duration was longer in the responders than in the nonresponders (23.1 ± 2.7 vs. 18.8 ± 1.7 months; $P = 0.02$, Mann–Whitney U-test). This may imply that the responders had slower disease progression than the nonresponders.

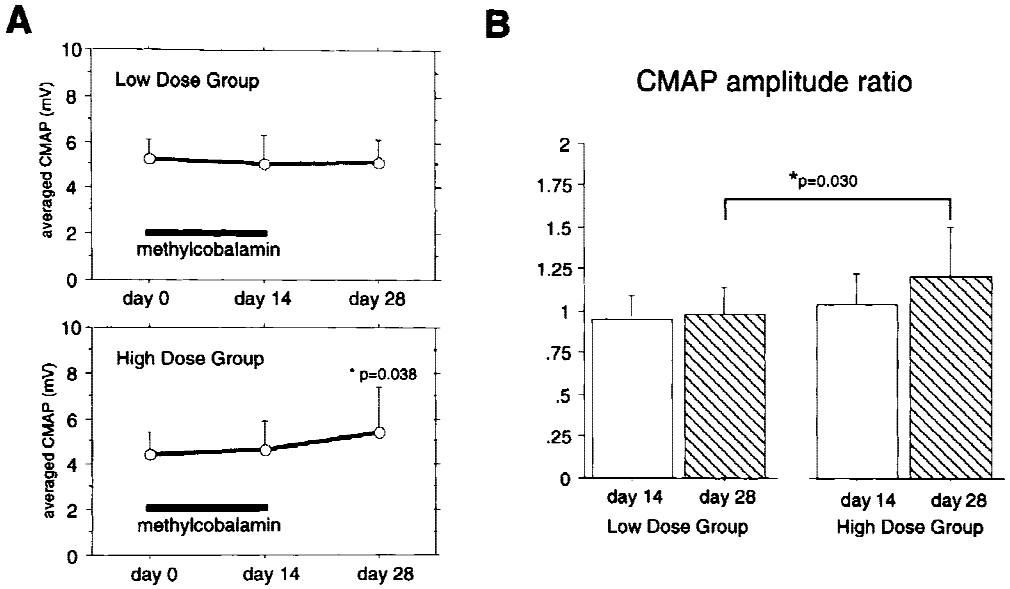

FIGURE 2. Summary of the analysis. **(A)** Serial changes of averaged CMAP amplitudes in the two groups. **(B)** Comparison of the ratio of averaged CMAP amplitude at day 14 (open bar) or at day 28 (hatched bar) to that at day 0 between the two groups. Vertical lines indicate standard deviations.

Another clinical feature of the responders was the predominant lower motor neuron involvement (Table 1); 6 of 8 had decreased deep tendon reflexes in the upper limbs, and 1 had exclusive lower motor neuron signs at the time of the entry into the study.

DISCUSSION

This preliminary double-blind study documented an increase in average CMAP amplitudes at day 28 in the group of patients receiving high-dose methylcobalamin, which suggests either nerve terminal sprouting or increased efficacy of neuromuscular transmission.[3] The time-lag before the improvement is possibly the period required for the soma of the motoneuron to upregulate DNA transcription for nerve sprouting and transmitter production.[5,6] The averaged CMAP tends to be more affected by the response elicited from the tibial nerves than the nerves in the upper limbs, because the tibial CMAP amplitude is almost twice as high as the others in normal subjects. This, however, is suited for representation of both upper and lower limbs equally, because two nerves are included for the former, but only one for the latter.

Responders showed longer disease duration than nonresponders, but they showed similar initial CMAP amplitudes. This finding may indicate that patients with slower disease progression respond better to the ultrahigh-dose methylcobalamin than those with faster progression, in whom the clinical benefit of the agent could not compensate for natural deterioration.

Nonresponders had more frequent upper motor neuron involvement than responders, who had predominant lower motor neuron signs. Because the degree of lower motor neuron involvement, as reflected in CMAP amplitude, was similar between the two groups, the presence of upper motor neuron signs may have an adverse effect on the action of high-dose methylcobalamin.

CMAP improvement, as demonstrated in this study, needs to be interpreted with caution, because it may not reflect clinical muscle wasting or weakness. Moreover, this transient effect does not necessarily lead to retardation of the disease process. Despite these limitations, ultrahigh-dose methylcobalamin is the first agent associated with improvement of an objective clinical measure in ALS patients. A larger clinical trial for extended use seems warranted.

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