Preliminary Study of Intravenous Amantadine Treatment for Ataxia Management in Patients with Probable Multiple System Atrophy with Predominant Cerebellar Ataxia

Jinyoung Youn[a]
Hyeeun Shin[b]
Ji Sun Kim[a]
Jin Whan Cho[a]

[a]Department of Neurology,
 Samsung Medical Center,
 Sungkyunkwan University
 School of Medicine, Seoul, Korea
[b]Department of Neurology,
 Eulji General Hospital,
 Eulji University School of Medicine,
 Seoul, Korea

Background and Purpose: Multiple system atrophy with predominant cerebellar ataxia is a disabling neurologic disease. However, effective management has not yet been established. We conducted a short-term, open-label preliminary study to assess the benefits of intravenous amantadine treatment in patients with probable multiple system atrophy with predominant cerebellar ataxia. **Methods:** Twenty patients (10 male, 10 female) with probable multiple system atrophy with predominant cerebellar ataxia received 400 mg of amantadine by intravenous per day for 5 days. Ataxia severity was evaluated by the International Cooperative Ataxia Rating Scale before and after intravenous amantadine therapy and all subjects reported subjective improvement after intravenous amantadine treatment using a patient global impression scale. We analyzed the total and subscale scores by the ataxia scale and patient global impression scale. **Results:** The mean age was 57.4 years (range: 47-72) and the mean disease duration was 30.8 months (range: 11-79). The ataxia severity significantly decreased after intravenous amantadine therapy from 42.5 to 37.3 ($p < 0.001$). The mean patient global impression scale for improvement was 2.9 and there were no side effects of intravenous amantadine treatment observed. When we assessed responders, the duration of intravenous amantadine effect was more than 1 month in 4 subjects of 7 responders. **Conclusions:** Our findings suggest that intravenous amantadine treatment can be a safe management option in cerebellar ataxia, although the mechanism is unclear. Thus, further double-blind, long-term studies with a larger sample size are needed.　**Journal of Movement Disorders 2012;5:1-4**

Key Words: Ataxia, Amantadine, Cerebellar, Multiple system atrophy, Intravenous, NMDA.

Corresponding author
Jin Whan Cho, MD, PhD
Department of Neurology,
Samsung Medical Center,
Sungkyunkwan University
School of Medicine,
50 Irwon-dong, Gangnam-gu,
Seoul 135-710, Korea
Tel　+82-2-3410-1279
Fax　+82-2-3410-0052
E-mail　praisecho@hanmail.net

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Multiple system atrophy with predominant cerebellar ataxia (MSA-C) is an adult-onset, sporadic, progressive neurodegenerative disease characterized by prominent cerebellar ataxia with varying severity of autonomic failure, urogenital dysfunction, parkinsonian features and corticospinal disorders.[1] MSA can reduce perceived quality of life,[2] but no cure or protection is currently available. Furthermore, even though somewhat effective symptomatic therapy is available to treat parkinsonism and dysautonomia in MSA, there is no symptomatic treatment for cerebellar ataxia, the main clinical feature of MSA-C.[3]

Because amantadine hydrochloride has been shown to antagonize N-methyl-D-aspartate (NMDA) receptors and stimulate dopamine release, amantadine has been used to treat many diseases involving the central nervous system. Because of the effect as a NMDA receptor antagonist, amantadine was regarded as one of possible agents for symptomatic ataxia management.[4-7] However, despite clinical trials on the effect of amantadine treatment on cerebellar ataxia, there are still controversies regarding the effect of amantadine on cerebellar ataxia.[4-7]

Orally administered amantadine might have some limitations because of different pharmacokinetics when administrated intravenously[8] and an interindividual variability of oral amantadine absorption.[9] However, to the best of our knowledge, there was no study focusing on the effect of intravenous (IV) amantadine on cerebellar ataxia. We conducted a short-term, open-label preliminary study to access the benefit of IV amantadine in patients with ataxia.

Methods

Subjects

This open-labeled preliminary study was conducted at the movement clinic in Samsung Medical Center, Seoul, Korea. We enrolled patients diagnosed with probable MSA-C according to the second consensus statement on the diagnosis of multiple system atrophy.[1] Information regarding age, gender and disease duration were collected as basic demographic data. Patients were excluded if they had 1) marked parkinsonism (resting tremor or rigidity of 2 or more score in one limb by unified Parkinson disease rating scale) to minimized the bias from improved parkinsonism after IV amantadine treatment; 2) history of psychiatric symptoms such as hallucination, delusion, or confusion; 3) cognitive dysfunction (Korean version mini-mental status examination ≤ 24); 4) history of epileptic seizure; 5) history of side effects associated with orally administrated amantadine; and finally; 6) renal or hepatic dysfunction as indicated by blood laboratory results on admission. All subjects were reviewed and provided informed consent before initiation of study procedures. The study received approval by an independent ethics review board, the Institutional Review Board of Samsung Medical Center.

Clinical trial design

We administered 200 mg in 500 cm³ of IV amantadine over a 3-hour period, twice per day (400 mg/day) for 5 days (Figure 1). The dose and duration of treatment were based on previous studies of IV amantadine.[10,11] For clinical rating, we evaluated cerebellar ataxia by the International Cooperative Ataxia Rating Scale (ICARS)[12] before and after IV amantadine treatment for 5 days. All subjects reported subjective improvement after IV amantadine treatment using the patient global impression of improvement (PGI-I).[13]

We designated 2 groups based on response to IV amantadine. Responders were defined as subjects who showed score improvement of 5 or more on the ICARS.[14] Non-responders were subjects showing score improvement of 2 or less on the ICARS. We compared demographic data, PGI-I and baseline ICARS score between the 2 groups. And we followed up responders 1 month after IV amantadine treatment to assess the duration of effect.

Statistical analysis

All data are presented as mean ± standard deviation. We compared the severity of cerebellar ataxia rated by ICARS before and after IV amantadine administration. Differences were evaluated using paired Student's t-tests or Wilcoxon's signed rank tests for continuous and ordinary variables, while Pearson's chi-square test or Fisher's exact test was used for categorical variables. The correlation between PGI-I score and the difference in ICARS scores after IV amantadine treatment was evaluated by Spearman's correlation analysis. p-values < 0.05 were considered statistically significant. All statistical analyses were conducted using commercially available software (SPSS for Windows, version 16.0; SPSS Inc., Chicago, IL, USA).

Results

Twenty subjects (10 males and 10 females) diagnosed as having probable MSA-C were enrolled from the movement disorder clinic. The mean age was 57.4 ± 8.2 years and disease duration was 30.8 ± 17.7 months. All subjects completed IV amantadine treatment for 5 days without any complications.

When the ICARS scores from baseline and post-IV amantadine treatment were compared, a significant reduction in score after IV amantadine treatment was observed. Especially, scores in subscales I (posture and gait disturbance), II (kinetic functions) and III (speech disorder) were significantly improved (Table 1). An improvement in total ICARS score of 5 or greater was observed in 8 subjects (responders), whereas 8 subjects (non-responders) had an improvement in total ICARS score of 2 or less, including one subject who demonstrated minimal worsening (from 22 to 24). When responders visit outpatients clinic 1 month after IV amantadine treatment, 4 (50%) notified that the effect of IV amantadine did not last for 1 month and their ICARS scores increased to the baseline ICARS score level (Figure 2). The mean ICARS score at 1 month after IV amantadine treatment was not significantly reduced when comparing with baseline ICARS score (47.8, and 42.8,
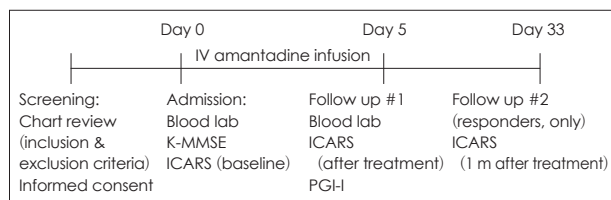
Figure 1. Flow chart of this study. IV: intravenous, K-MMSE: Korean version Mini-Mental Status Examination, ICARS: International Cooperative Ataxia Rating Scale, PGI-I: patient global impression of improvement.

Table 1. Total ICARS score and each subscale score before and after amantadine treatment

	Score before amantadine	Score after amantadine	p-value
ICARS, total	42.5 ± 13.3	37.3 ± 13.5	< 0.001*
I. Posture and gait disturbance	17.1 ± 6.0	15.2 ± 6.6	0.007*
II. Kinetic functions	20.1 ± 7.0	17.5 ± 6.4	< 0.001*
III. Speech disorders	3.4 ± 1.6	3.1 ± 1.6	0.034*
IV. Oculomotor disorders	1.5 ± 1.3	1.5 ± 1.4	0.564

p-value was calculated by paired t-test and Wilcoxon's signed rank test. *p-value < 0.05. ICARS: International Cooperative Ataxia Rating Scale.
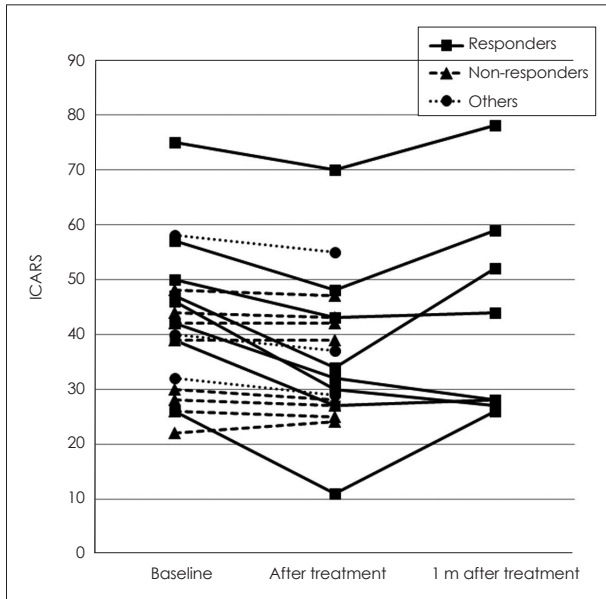
Figure 2. ICARS score of all subjects. ICARS: International Co-operative Ataxia Rating Scale.

Table 2. Demographic data, baseline ICARS score and clinical global impression-improvement scale by group (responders and non-responders)

	Responders (n = 7)	Non-responders (n = 8)	p-value
Age (years)	59.0 ± 7.7	58.1 ± 10.0	0.847
Sex (male/female)	5/3	3/5	0.619
Disease duration (month)	15.8 ± 11.2	34.4 ± 21.6	0.035*
PGI-I	1.8 ± 1.0	3.4 ± 0.5	0.006*
Baseline ICARS, total	47.8 ± 14.2	34.9 ± 9.6	0.061
I. Posture and gait disturbance	18.5 ± 5.3	14.6 ± 5.8	0.187
II. Kinetic functions	23.3 ± 8.3	15.9 ± 4.7	0.046*
III. Speech disorders	3.4 ± 1.8	2.9 ± 1.6	0.567
IV. Oculomotor disorders	2.0 ± 1.5	1.5 ± 1.3	0.552

PGI-I, clinical global impression-improvement scale. p-value was calculated by Mann-Whitney U test, unpaired Student t-test and Fisher's exact test. *p-value < 0.05. ICARS: International Cooperative Ataxia Rating Scale, PGI-I: patient global impression of improvement.

ICARS scores of baseline and 1 month after treatment, respectively). But decrease in ICARS scores were maintained in 4 responders (44.3, 33 and 31.8, ICARS scores of baseline, after treatment and 1 month after treatment, respectively).

Mean PGI-I was 2.85 ± 1.2 and 12 subjects (60%) felt their ataxia improved after IV amantadine treatment (4 patients felt very much improved, 3 felt much improved and 5 felt little improved). No subjects reported a worsened condition by the PGI-I after the IV amantadine treatment.

When the demographic data of responders and non-responders were compared, the more severe kinetic dysfunction (subscale II in ICARS) and shorter disease duration were observed in responders (Table 2). A correlation between PGI-I score and the difference in ICARS scores was also observed ($p = 0.001$, ρ = -0.677).

Discussion

The study presented here is the first to assess the effect of IV amantadine on cerebellar ataxia in MSA-C. Because few previous studies have explored the use of IV amantadine in other diseases,[10,11] we chose a daily dose and duration of treatment that was as high and long as practical based on those previous assessments. In this study, IV amantadine treatment improved ataxia in MSA-C patients and 60% of subjects reported improvement. Additionally, there were no side effects observed of IV amantadine treatment or worsening of PGI-I, although 2 points on the total ICARS score in one subject were worse after treatment. Based on these results, we propose that IV amantadine treatment can be an effective and safe management option for ataxia in MSA-C patients in spite of short duration of the effect.

Although the exact mechanism by which amantadine works in the central nervous system is not known, the drug is considered to have two major actions: a dopaminergic effect and an NMDA receptor antagonistic effect. Due to the dopaminergic effect of amantadine, effects on the bradykinesia and rigidity can appear to improve ataxia.[15] But first of all, we excluded MSA-C patients with marked parkinsonism such as resting tremor and rigidity. And in subscale analysis, there was significant improvement in not only subscale II (kinetic functions) but also subscale I (posture and gait disturbance) which is not regarded as indicative of dopaminergic dysfunction. NMDA receptors are important in neuronal signaling in the cerebellum, especially in the climbing fibers, mossy fibers and granule cells.[16] Additionally, some study assessing memantine, a potent blocker of NMDA receptors was effective in mitigating ataxia.[17] These points suggest that NMDA receptors play an important role in ataxia, and may indicate why amantadine was effective in improving cerebellar ataxia.

A previous study in humans assessing the effectiveness of up to 600 mg/day of orally administered amantadine reported no improvement in ICARS scores after amantadine treatment.[7] But there was limitation due to the large interindivisual variability of oral amantadine absorption.[9] And in animal studies, IV amantadine treatment resulted in different pharmacokinetics than those observed after orally administrated amantadine.[8] Two-compartment model best describes the deposition of amantadine after IV administration, while a one-compartment model best describes the deposition of oral amantadine. When similar dose of amantadine was administrated by IV and orally, the maximum concentration was much higher after IV treatment.[8] It is possible that a similar difference exists

when the drug is applied in humans and based on these features of IV amantadine treatment, it may be more effective than oral amantadine.

Although our results demonstrated an effect of IV amantadine on ataxia, there were 8 non-responders. Thus, it is very important to select patients that will likely respond to treatment with IV amantadine. Responders had more severe limb ataxia (subscale II, kinetic function) and shorter disease duration. Although there was significant improvement in both subscale I and II of ICARS, MSA-C patients with severe limb ataxia may be responders of IV amantadine treatment. And responders showed shorter disease duration although there was no difference in total ICARS score. Considering this result, responders could be regarded as having a more progressive clinical course. Therefore we suggest that MSA-C patients with more severe limb ataxia and progression would more likely benefit from IV amantadine treatment than others, and that these can be the predictors for the effect to IV amantadine medication.

When we compared PGI-I scores between responders and non-responders, responders had significantly higher PGI-I scores. There was also a correlation between PGI-I score and the difference between the pre- and post-treatment ICARS scores. These results suggest that IV amantadine treatment is an effective management option from the perspective of both patients and clinicians.

This study had some limitations. First of all, the present study was also limited in that it was open-label, short-term and of an uncontrolled design, making the results susceptible to the placebo effect. To overcome these limitations, further studies that are double-blinded with a placebo-controlled design are needed. Second, although ICARS is a useful tool for ataxia, ICARS can be contaminated by parkinsonism.[15] Thus, we excluded the patients with marked parkinsonism. Moreover, the clinical improvement was seen in posture and gait disturbance scores in ICARS, which is not only dependent on dopaminergic function. Finally, although there were some studies suggesting the different effect of oral and IV amantadine, more studies are needed to confirm the usefulness of IV amantadine.[9,18,19]

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