Treatment of Japanese Restless Legs Syndrome Patients with Cabergoline: An Open Clinical Preliminary Trial

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Abstract

Objective To determine the effective dose of cabergoline in Japanese patients with restless legs syndrome (RLS).

Methods Six cases of idiopathic RLS and three of RLS with Parkinson disease (PD) participated in an open clinical preliminary trial. All cases were diagnosed based on the clinical criteria of the International RLS Study Group. Three RLS cases (1.3%) were detected out of 229 consecutive cases with PD. RLS severity was evaluated with International RLS Study Group (IRLSSG) Rating Scale Version 2.2 before and one year after the treatment with cabergoline.

Results For 6 idiopathic RLS patients, the IRLSSG questionnaire scores improved from 25.5±3.7 to 10.7±8.9 (p=0.028, Wilcoxon test) with 1 mg of daily cabergoline at the endpoint. For 3 RLS cases with PD, the score was 21.7±3.7 before the treatment, and RLS symptoms completely disappeared with 1 mg of cabergoline. One of RLS cases with PD required additional cabergoline later because of parkinsonism. No adverse event with cabergoline was reported in this study.

Conclusion One mg of daily cabergoline is effective in some Japanese patients of RLS.

Key words: restless legs syndrome, cabergoline, levodopa, dopamine agonist, Parkinson disease, clinical trial

Introduction

Restless legs syndrome (RLS) is characterized by an urge to move the legs, usually accompanied or caused by an uncomfortable sensation in the legs. The urge to move or unpleasant sensations begins or worsens during periods of rest or inactivity, such as lying down or sitting. The urge to move or unpleasant sensations are relieved by movement, and are worse in the evening or at night than during the day or only occur in the evening or at night (1). The sensory and motor symptoms of RLS often result in nocturnal insomnia and chronic sleep deprivation. Treatment with levodopa usually alleviates symptoms, however, many patients with RLS develop rebound or augmentation (2). The direct-acting dopamine agonists, with a longer duration of action, provide an alternative to levodopa. Bromocriptine (3), pergolide (4-7), pramipexole (8-10), ropinirole (11-13) and cabergoline (14-16) have shown good efficacy in RLS and also have reduced the frequency of augmentation and rebound. All of those reports are from Western countries. RLS occurs in about 5-20% of the adult population in Western countries (1, 17, 18). Although RLS is a common disorder in Western countries, the prevalence of RLS has been reported to be quite low (0.1-0.6%) in an Asian population (19). At least one-third of cases have a positive family history in Western countries, suggesting an autosomal-dominant pattern of inheritance (20-22). However, no familial RLS has been reported to date in Asian countries. Taken together, there may be an ethnic susceptibility to RLS and/or potential genetic predisposition. To examine the effectiveness of dopamine agonists for Japanese patients with RLS, we administered cabergoline, a long-acting dopamine agonist, to RLS patients.
Six idiopathic RLS patients and three RLS patients with Parkinson disease (PD) participated in this study. All patients gave informed consent and fulfilled the essential diagnostic criteria for RLS based on the International RLS Study Group (IRLSSG) (1).

Three RLS cases (1.3%) were detected out of 229 serial cases with PD. When two patients with PD (Nos. 7 and 8 in Table 1) first came to our hospital, they did not complain of PD symptoms (i.e., gait disturbance, bradykinesia, or tremor) but rather, RLS symptoms. On neurological examination, they had unilateral mild cogwheel rigidity of the wrist, mild bradykinesia and minimal hand tremor at rest. We diagnosed them with RLS with Parkinson disease (Hohen-Yahr stage I).

No patient had been treated with dopamine agonists, levodopa, benzodiazepines, opioids or other psychiatric drugs at least 4 weeks prior to this study. Because there has been no direct comparison among the agonists for the treatment of RLS, we selected cabergoline because it has the longest half-life among the available agonists. To prevent peripheral dopaminergic side-effects, cabergoline was started with a minimal dose (0.25 mg) in the evening. The dose was increased in steps of 0.25-1.0 mg up to 3 mg until RLS symptoms clearly improved.

We translated the questionnaire of the IRLSSG Rating Scale (IRLS) Version 2.2, which was developed by the IRLSSG to evaluate the effect of treatment (23), into Japanese. We used the abbreviated Japanese questionnaire for our clinical practice. RLS severity was evaluated with IRLS Version 2.2 before and one year after the treatment with cabergoline. Any adverse events, including augmentation, were monitored by phone or reported when the patients saw their doctor. Wilcoxon test was used for statistical analysis.

### Results

The data for all patients is summarized in Table 1. No adverse events were reported with cabergoline, and no patient withdrew from this study. The age was 74±8.3 (mean±SD) years, and the duration of RLS symptoms was 7.3±6.4 (mean±SD) years.

For 6 idiopathic RLS patients, the IRLSSG questionnaire scores improved from 25.5±3.7 to 10.7±8.9 (p=0.028, Wilcoxon test). Two idiopathic RLS patients (Nos. 2 and 5 in Table 1) reported that RLS disappeared within a week with the minimum daily dose of cabergoline (0.25 mg). These 2 patients later required an increase of dosage up to 1.0 mg of cabergoline to control RLS symptoms. There was no difference in effectiveness on RLS symptoms in the range of 1.0-3.0 mg of cabergoline for the other 4 idiopathic RLS patients (Nos. 1, 3, 4 and 6 in Table 1), 1.0 mg of cabergoline was selected as the endpoint.

For 3 RLS cases with PD, the score was 21.7±3.7 before the treatment with cabergoline, and RLS symptoms completely disappeared at the endpoint. The effective daily dosage of cabergoline for RLS symptoms at the endpoint was 1.0 mg. One of the RLS cases with PD (No. 9) required 3.0 mg of cabergoline later because of PD symptoms.

### Discussion

IRLSSG questionnaire scores improved significantly, indicating that cabergoline was effective for RLS symptoms in a patient population in Asia, where RLS is observed less frequently than in Western countries. Although there may be genetic/ethnic differences in RLS between Western countries and Asian countries, dopamine agonists would be one of the effective treatments for RLS patients across races. The use of standardized diagnostic criteria applied in this study will help to determine the effectiveness of treatments for RLS. Cabergoline has the longest mean elimination half-life (up to 65 hours) among the dopamine agonists (14, 16). Cabergoline needs to be given only once daily because of its long half-life. The long duration of action of cabergoline results in sustained stimulation of the dopamine receptors, mimicking normal physiological dopaminergic stimulation. Cabergoline has the beneficial effects of a sustained dopamine agonist on idiopathic and PD-related RLS, while levodopa-related augmentation is possibly due to the short half-life of levodopa (2).

The striatonigral dopaminergic system has been implicated in RLS, by neuropharmacological data including PET and SPECT studies. However, the pathogenesis remains unknown. Anticonvulsants including clonazepam, opioids and benzodiazepines are considered the drugs of choice as well.
as dopaminergic drugs (24). When dopaminergic drugs do not show a sufficient effect on RLS symptoms, other drugs, such as anticonvulsants, benzodiazepines or opioids, should be considered.

The prevalence and severity of RLS increase with aging, so that RLS is of importance particularly in geriatric patients. RLS may be underdiagnosed, probably because the initial symptoms are mild, without objective abnormality on neurological examination and are commonly thought to be psychogenic (25). We should pay more attention to the characteristic RLS symptoms because RLS usually leads to sleep disturbance and a decreased quality of life, especially for geriatric patients (26).

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