

New Observations Letters

Istradefylline for Restless Legs Syndrome Associated with Parkinson's Disease

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Introduction

Restless legs syndrome (RLS) is the most common movement disorder and is characterized by the feeling of an urgent need to move the legs while lying down or resting. RLS worsens during the evening and at night and is relieved by leg movement.^{1,2} It is also known that RLS is commonly comorbid with Parkinson's disease (PD).³ Although the exact pathological mechanism of RLS is unknown, dopaminergic medications for PD, such as levodopa and other dopamine agonists, symptomatically improve RLS as well.⁴

Istradefylline is a highly selective adenosine A2A receptor antagonist that is thought to modulate the overactivated striatopallidal pathway (indirect pathway) in PD,⁴ reducing the duration of the "off" state and extending the "on" state without inducing dyskinesia.⁵ Istradefylline has been recently approved in Japan for the treatment of PD, but, to date, there are no data on the effect of istradefylline on RLS in PD.

Here we report the cases of three patients with RLS comorbid with PD who were treated with istradefylline.

Case reports

Case 1

A 73-year-old right-handed male had developed a tremor in his right lower limb at the age of 61 years. He began taking selegiline 5 mg/day at the age of 62 years but experienced only mild improvement and subsequently began taking pramipexole 1 mg/day. As wearing-off developed, and he found it difficult to work when in the "off" state at the age of 70, he began taking istradefylline 20 mg/day, which improved his gait. After a while, as wearing-off got severe, he also started to feel discomfort at night. This discomfort led to an urge to walk around, and the patient experienced relief after walking; his istradefylline was increased to 40 mg/day for his parkinsonism.

Table 1. Patient Characteristics of the Three Presented Cases

	Case 1	Case 2	Case 3
Age/sex	73/M	65/M	52/M
Parkinson's disease duration (years)	12	11	5
Dosage of istradefylline	20 mg	40 mg	20 mg
L-dopa	+	+	+
Dopamine agonist	+	+	+
Follow-up	30 months	5 months	17 months
Augmentation	–	–	–

His parkinsonism improved, and his Unified Parkinson's Disease Rating Scale part 3 (UPDRS-III) score improved from 40 to 30. The increased istradefylline subsequently improved his RLS symptoms, and resulted in complete remission. The discomfort in his legs that made him feel the need to move his legs disappeared. His score on the International RLS Study Group RLS Severity Scale⁶ improved from 18 to 0 points. This improvement lasted at least 30 months without augmentation.

Case 2

A 65-year-old right-handed male had developed a resting tremor in his right hand at the age of 54 years and was subsequently diagnosed with PD. He began taking pramipexole extended release (2 mg/day), but development of gait disturbance required an increase in dosage to 3 mg/day; however, the dosage increase resulted in hypersexuality. His medication was then changed from pramipexole extended release to ropinirole controlled release, and he was started on levodopa/carbidopa (150 mg/day) at the age of 62 years. After a while, he began to feel the urgency to walk around when he was resting, particularly in the evening and at night. He was started on istradefylline (20 mg/day), and his RLS symptoms improved and almost disappeared, and resulted in an improvement in his sleep. The improvement lasted 5 months until he stopped taking istradefylline due to the initiation of levodopa/carbidopa infusion gel therapy because of a wearing-off and dyskinesia.

Case 3

A 49-year-old right-handed male noted slowness in his left leg and difficulty in using his left hand at the age of 44 years. He began to take pramipexole (up to 3.75 mg/day), which effectively improved the PD symptoms. At the age of 46 years, he was prescribed selegiline 2.5 mg/day in addition because of wearing-off. His left leg began dragging at the age of 47 years, and he started falling down occasionally. He also reported sleep disturbance and an urgency to move his legs at age 49 years. Istradefylline (20 mg/day) was started, and the feelings of urgently needing to move his legs diminished and his quality of sleep improved remarkably. This effect lasted at least 17 months.

Discussion

Summaries of the outcomes of the three cases are presented in Table 1. In all three cases, introducing or increasing istradefylline produced a favorable response to both RLS and PD symptoms. Patients in all three cases reported feeling the urgent need to move their legs when resting or lying in bed. The symptoms worsened in the evening and at night, leading to sleep disturbance in at least one case. Starting or increasing istradefylline subjectively improved the RLS symptoms in all three cases. To the best of our knowledge, this is the first report that notes that istradefylline improves RLS that is comorbid with PD.

One of the hypothesized mechanisms suggests that istradefylline improved the “hidden” RLS that became unmasked in the “off” state of PD. Improving parkinsonism may subsequently improve the underlying RLS in PD. In fact, RLS is thought to occur in up to 50% of patients with PD,³ but the symptoms of RLS may be masked by anti-PD dopaminergic treatment.⁷ Undertreatment of PD can unmask RLS. In addition, there are reports indicating that the motor symptoms of PD improved as expected after subthalamic deep brain stimulation but that reducing dopaminergic medication led to unmasking of RLS.⁸

It is also possible that istradefylline directly improves RLS. One suggested pathogenetic mechanism of RLS is brain iron deficiency.¹ Current studies have indicated that adenosine receptors play a significant role in both brain iron deficiency and sleep disorders in RLS.¹ One study demonstrated a significant downregulation of adenosine A1 receptors and upregulation of adenosine A2A receptors in RLS.¹ Thus, inhibiting adenosine A2A receptors may directly improve RLS, although this hypothesis remains speculative.

A third hypothesis suggests that the improvement in dopamine agonist-induced daytime somnolence upon administration of istradefylline could improve RLS at night. Istradefylline is an analog of the stimulant caffeine, and it is known to be anti-somnogenic.⁴ However, the extent of these potential interactions is still unknown.

In conclusion, istradefylline may be efficacious against RLS that is comorbid with PD. Further prospective studies are needed to confirm our observations.

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