Istradefylline is Recommended for Morning Use: A Report of 4 Cases

Keita Matsuura and Hidekazu Tomimoto

Abstract

We herein describe four cases of patients with Parkinson’s disease who were treated with istradefylline (ISD) in the evening and had severe daytime sleepiness. The time to onset of sleepiness varied between 2 weeks to 3 months. All patients recovered after changing the timing of the ISD dosage from evening to morning. ISD is an A2A receptor antagonist with a caffeine-like arousal effect that may worsen the quality of sleep and thus increase daytime sleepiness. This report provides the first evidence of daytime sleepiness induced by evening ISD treatment. We propose that ISD should therefore only be used in the morning, particularly if taken by professional drivers.

Key words: istradefylline, Parkinson’s disease, daytime sleepiness, A2A receptor antagonist

Introduction

Istradefylline (ISD) was introduced for the treatment of Parkinson’s disease (PD) in Japan in May 2013. A phase III clinical trial in Japan showed a one hour reduction of the off-time by oral administration of 20-40 mg ISD. In addition, there were side effects with rates of 0.8-4.0% for hallucination and 0.8-6.5% for somnolence (1, 2). Therefore, administration of ISD is recommended at a dose of 20-40 mg (orally, once daily) taken at any time of day. From May 2013 to January 2014, we prescribed 20 mg ISD for 8 PD patients. Six of the patients took ISD in the evening and 4 of these 6 patients exhibited severe daytime sleepiness. The timing of ISD prescription was determined by the patient. We herein describe the cases of the 4 patients who exhibited severe daytime sleepiness.

Case Reports

Case 1 was an 87-year-old man who developed right limb tremor at 80 years of age (Figure). He was classified as stage III on the Hoehn-Yahr scale (HY-S). At 84 years of age, he developed wearing-off symptoms and bradykinesia. Therefore, we prescribed 20 mg ISD to be taken in the evening. The patient was also receiving treatment with 600 mg levodopa/decarboxylase inhibitor (L-Dopa/DCI) and 1.5 mg pramipexole extended-release tablet. The patient’s Unified Parkinson’s Disease Rating Scale (UPDRS) part III scores at baseline, 1, and 3 months after the start of ISD treatment were 9, 9, and 11, respectively; the Parkinson’s Disease Questionnaire (PDQ-39) (3) (Best, 100%; Worst, 0%) scores were 42%, 78%, and 65%, respectively. However, the patient developed severe daytime sleepiness after 3 months without insomnia and had a score of 16 on the Epworth Sleepiness Scale (ESS). Therefore, we changed the timing of oral intake of ISD from evening to morning. One month later, the patient’s symptoms of daytime sleepiness markedly decreased and he had an ESS score of 2. The patient’s UPDRS part III score was 12 and the PDQ-39 was 63%.

Case 2 was a 75-year-old woman who developed right limb tremor at 55 years of age (Figure). She underwent bilateral subthalamic nucleus deep-brain stimulation (DBS) at 72 years of age because of severe wearing-off and dyskinesia. She was classified as HY-S stage III. The patient’s wearing-off periods transiently improved but then recurred. We were unable to control her symptoms except by tuning DBS. For this reason, we added 20 mg ISD to be taken in the evening. She was also receiving treatment with 125 mg L-Dopa/DCI and 100 mg zonisamide. At baseline, the pa-
Figure. Clinical courses of the 4 cases showing motor disability, daytime sleepiness, and treatment details

Case 1: 87-year-old man
- Motor disability
- Sleepiness
- Istradeffylane
- Other drugs for PD
- 600mg L-Dopa/DCI and 1.5mg pramipexole-extended released tablet
- 20mg in the evening
- 20mg in the morning
- 3 months

Case 2: 75-year-old woman
- Motor disability
- Sleepiness
- Istradeffylane
- Other drugs for PD
- 125mg L-Dopa/DCI and 100mg zonisamide with bilateral STN-EUS
- 20mg in the evening
- 20mg in the morning
- 4 months

Case 3: 77-year-old woman
- Motor disability
- Sleepiness
- Istradeffylane
- Rotigotine
- Other drugs for PD
- 400mg L-Dopa/DCI, 400mg entacapone, and 25mg zonisamide
- 20mg in the evening
- 2mg 24 hours
- 20mg in the morning
- 3 months

Case 4: 81-year-old man
- Motor disability
- Sleepiness
- Istradeffylane
- Zonisamide
- Other drugs for PD
- 250mg L-Dopa/DCI and 8mg ropinirole (prolonged-release tablet)
- 20mg in the evening
- 20mg in the morning
- 50mg
- 2 weeks
- 1 month
- 3 months

Discussion

Four of the six PD patients treated with ISD in the evening exhibited daytime sleepiness. The duration to onset of sleepiness varied between 2 weeks to 4 months. All patients recovered after altering the timing of ISD treatment from evening to morning. In the latest multicenter trial in Japan, somnolence occurred as a treatment-related adverse event in 3.2% of patients in the placebo group and 6.5% in the 20 mg/day ISD group (2). The frequency of daytime sleepiness
was much higher in our patients (4/6, 66.7%) which suggests that the administration of ISD in the evening may be responsible for daytime sleepiness.

Istradefylline is an A2A receptor (A2AR) antagonist that has an arousal effect similar to caffeine. This caffeine-like effect may worsen the patient’s quality of sleep and consequently increase sleepiness during the day. However, caffeine has many mechanisms in addition to A2AR antagonism (4), whereas ISD is a selective antagonist and its affinity for A2AR is much higher than that of caffeine (ISD, 12.4 nmol/L; caffeine, 23,400 nmol/L). Therefore, it is difficult to directly compare the effects of ISD and caffeine (5). A2ARs are expressed in striatopallidal neurons and the nucleus accumbens and are related to the mechanisms of wakefulness (4, 6). An arousal effect of an A2AR antagonist has been described in mice (4) but not in humans. This study is based on the clinical observation of elderly patients who were also taking other drugs, including zonisamide and a dopamine agonist. It is therefore possible that interactions and side effects of these drugs may have caused the symptoms of daytime sleepiness. However, we did not change the drugs prescribed throughout the observation period; only the timing of ISD administration was altered from evening to morning. Therefore, it is highly unlikely that the daytime sleepiness was attributable to the effects of other drugs. In these four cases, the effect of ISD was insufficient for altering the motor symptoms, and thus, the result was most likely affected by the symptoms of sleepiness. The reason for the delayed emergence of sleepiness may be partly due to iduronate 2-sulfatase (IDS)’s long half-life (over 50 hours); however, this is difficult to determine because sleepiness appeared latently after 3-4 months of ISD treatment in some patients. Conversely, the prompt recovery from sleepiness after altering the timing of ISD medication from evening to morning may be attributable to the peak concentration of ISD at daytime which seems to counteract daytime sleepiness. This is the first report to describe daytime sleepiness induced by ISD treatment in the evening. As a result, we strongly recommend the use of ISD in the morning, particularly for professional drivers.

Author’s disclosure of potential Conflicts of Interest (COI).
Hidekazu Tomimoto: Honoraria, Daiichi-Sankyo Pharma and Eisai Pharma.

References