



# Reversible istradefylline-induced pleurothotonus in a patient with Parkinson's disease: A case report and literature review

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## ABSTRACT

Pleurothotonus, commonly known as Pisa syndrome (PS), is characterized by abnormal lateral flexion of the trunk. The precise mechanism of this disease is unknown. Istradefylline was administered to a 68-year-old male patient with Parkinson's disease (PD) to treat wearing-off; however, PS appeared 4 months after the first istradefylline treatment. Despite drug adjustments for 9 months, no improvement was observed. Finally, istradefylline was discontinued, and PS symptoms gradually improved over the subsequent 4 months and eventually disappeared. From 2005 to 2014, six studies appeared in the literature on dopaminergic therapy for PS patients with PD. The period between PS appearance after drug introduction until PS recovery with appropriate treatment differs among drugs. This study aimed to identify the drugs that initiate PS and assess the period between PS appearance and disappearance, respectively, after the drug is first administered and later discontinued.

## 1. Introduction

Pleurothotonus, commonly known as Pisa syndrome (PS), is characterized by abnormal posture created by sustained lateral bending of the trunk with or without spinal rotation. PS was initially reported as a side effect of neuroleptic drugs used for the treatment of dementia [1]; however, PS has also been reported in patients who have received other drugs, such as antiemetics and cholinesterase inhibitors, as well as in patients with neurodegenerative diseases, such as Alzheimer's disease [2] and multiple system atrophy [3].

PS has also been reported in patients with Parkinson's disease (PD) during treatment with pergolide [4,5], pramipexole [5,6], levodopa/carbidopa/entacapone [7], rasagiline [8], and ropinirole [9]. Most cases were cured with appropriate treatment. This is the first case report of PS that was reversed in a patient with PD who received istradefylline [10].

The objective of our study was to assess the period between PS appearance after drug introduction and PS recovery after the drug was discontinued. The drugs that might cause PS are identified.

## 2. Patients and methods

### 2.1. Patients

From 2005 to 2014, six studies [4–9] were published in the literature on PS in patients with PD who were given dopaminergic therapy. The studies comprised 14 recovery cases—2 after introducing levodopa/carbidopa/entacapone (STALEVO) [5,7], 1 after increasing levodopa/benserazide [5], 1 after increasing levodopa/carbidopa [5], 4 after introducing rasagiline [8], 4 after introducing pergolide [4,5], 1 after introducing pramipexole [5], and 1 after introducing ropinirole [9]. Because the present case also showed patient recovery, this study can be added to the 14 recovery cases. The literature cited only 1 case of no recovery after the introduction of pramipexole [6].

### 2.2. Present case

A 68-year-old man visited our clinic complaining of motor disturbance. His previous medical history revealed that at 58 years old, the patient experienced rigidity and motor slowness on his left side and subsequently developed gait disturbance. He presented with mild diabetes mellitus, which was treated with pioglitazone hydrochloride. Family history of was not absent. At 60 years old, a magnetic resonance image of the brain revealed no abnormality, and 123I-MIBG myocardial

*Abbreviations:* PS, Pisa syndrome; PD, Parkinson disease

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scintigraphy revealed a decrease in the ratio of Hoffmann reflexes to muscle responses (early, 1.71; delayed, 1.16) and increased clearance (49.4%). The patient was subsequently diagnosed with PD. Low doses of standard levodopa/carbidopa (200/20 mg daily) resulted in a marked improvement in PD; however, the disease slowly progressed over the subsequent 7 years, and other PD drugs were added to his treatment regimen. The dosage of levodopa/carbidopa was increased to 300/30 mg/d, and 300 mg entacapone, 1.5 mg pramipexole hydrochloride hydrate, 5 mg selegiline hydrochloride, 25 mg zonisamide, and 100 mg amantadine hydrochloride were administered daily, all of which improved motor control.

Four months before the onset of PS, 20 mg istradefylline was administered each day for severe wearing-off and freezing phenomena, after which motor disturbance improved. Three months after administering istradefylline, the patient experienced left lumbago, and 4 months later presented with marked tonic deviation on the right side of the trunk, with severe gait disturbance and postural instability. At this time, the patient received no neuroleptics, antidepressants, benzodiazepines, antiemetics, or cholinesterase inhibitors.

A neurological examination revealed marked truncal deviation to the right side with increased lumbar muscle tone that was evident while walking, standing, and sitting. This condition was compatible with the clinical characteristics necessary for the diagnosis of PS. While standing, the patient leaned toward the right foot at a 29° angle. This dystonic posture was slightly exacerbated during the off period, but complete disappearance was observed. Resting tremor, cogwheel rigidity, and bradykinesia were observed, all predominantly on the left side. No signs of pyramidal, cerebellar, autonomic, or cognitive impairments were noted. Unified Parkinson's Disease Rating motor scores of 36 for the on-period and 48 for the off period were obtained. Hematological and biochemical examinations revealed no abnormality. [123I]FP-CIT SPECT (DaTSCAN®) revealed a marked bilateral reduction in tracer uptake, primarily involving the putamen and more pronounced on the right side.

Pramipexole dihydrochloride (1.5 mg/day) administration was tapered off over 2 months, but PS did not improve. Moreover, carbidopa/levodopa/entacapone and amantadine hydrochloride were increased to 350/35/400 mg and 150 mg daily, respectively; however, PS did not improve after 2 months. Five months after PS appearance, 9 mg/d rotigotine was administered for 1 month without any improvement. Finally, 6 months after the onset of PS, 20 mg/d istradefylline was discontinued. One week after removing istradefylline from the treatment protocol, PS began to improve. At 1, 4, 8, and 12 weeks after removing istradefylline, trunk deviation continued to improve as follows: 25°, 20°, 15°, and 13°, respectively. Finally, 17 weeks after removing istradefylline, trunk deviation decreased to 12°. This deviation is nearly the same as that before istradefylline administration, and the deviation was most likely the result of a vertebral deformity related to the patient's lumbar spondylosis. Trunk deviation continued without aggravation over the following 2 years.

### 2.3. The period between PS appearance after drug introduction until PS recovery

To determine the drugs that were likely to cause PS, the period between PS appearance after drug introduction until PS recovery with appropriate treatment was investigated in the above 15 recovery cases.

## 3. Results

The periods between PS appearance after the introduction of different drugs until PS recovery with the appropriate treatment are summarized in Table 1. The period between appearance and disappearance of PS caused by replacing levodopa/benserazide with levodopa/carbidopa/entacapone (STALEVO) and vice versa was approximately 2 weeks to 1 month and a few days to 10 d, respectively

**Table 1**

Period until PS appearance after introduction of the drug and until PS recovery after appropriate treatment.

Drug(ref)	Period until PS appearance after introduction of the drug	Period until PS recovery (with appropriate treatment)
Pergolide(4,5)	2–3 months	3 months(susp. or redu.)
Pramipexole(5)	2 months	40 days(susp.)
Ropinirole(9)	within 1 year	3 months(susp.)
STALEVO(5,7)	2w–1 month	a few days–10 days(LDL)
Levodopa/Ben.(5)	15 days	20 days(LDL)
Levodopa/Car.(5)	2 months	2 months(LDL)
Rasagiline(8)	3–4 weeks	2–4 weeks(susp.)
Istradefylline(PC)	4 months	4 months(susp.)

STALEVO: levodopa/carbidopa/entacapone, Ben.: benserazide, Car.: carbidopa, PS: Pisa syndrome, ref.: reference, susp.: suspension, redu.: reduction, LDL: changed to low-dose levodopa, PC: present case.

[5,7]. The period between the increase and decrease in levodopa/benserazide was 15 and 20 d, respectively [5], and between the increase and decrease in levodopa/carbidopa was 2 months and 2 months [5], respectively. After the introduction of high-dose levodopa and an increase in PS, PS disappeared by switching to low-dose levodopa, and the period between PS appearance and disappearance was relatively short. The period of PS appearance induced by rasagiline was 3–4 weeks and that of PS disappearance after suspension of the drug was 2–4 weeks [8], both of which were considered to be relatively short.

On the contrary, the period of PS appearance induced by a dopamine agonist and that of PS disappearance by suspending or reducing the drugs were 2–3 months and 3 months with pergolide, respectively [4,5]; 2 months and 40 d with pramipexole, respectively [5]; and within 1 year and 3 months with ropinirole, respectively [9], all of which were longer compared with periods for high-dose levodopa and rasagiline.

After introducing pramipexole, 1 case showed no recovery [6].

## 4. Discussion

The dopaminergic dysfunction and imbalance of the dopaminergic–cholinergic systems are implicated in PS pathogenesis [5,7], but the precise mechanism underlying PS remains unclear. Several cases of PS have been reported in patients with PD who were treated with various anti-PD drugs. These cases showed an acute course, and most were cured with appropriate treatment. These acute PS cases were reported with the introduction of pergolide [4,5], pramipexole [5,6], high-dose levodopa [5,7], rasagiline [8], or ropinirole [9]. This is the first case report of an acute course of reversible PS after istradefylline introduction, and the mechanism of reversible PS with PD is discussed.

Istradefylline is a new adenosine A2A receptor antagonist. Adenosine A2A receptors are mainly situated on the GABA- and enkephalin-containing medium spiny neurons (indirect pathway), which project from the striatum to the external globus pallidus and are collocated with D2 receptors. Adenosine A2A and D2 receptors regulate GABAergic neurons through reciprocal antagonistic interactions. Istradefylline is effective against PS by suppressing the upregulation of A2A receptor in the indirect pathway [10].

PS in our case was induced by istradefylline, and the period between PS appearance and disappearance after the introduction and suspension, respectively, of the drug was 4 months each, which nearly coincides with the period related to the introduction and suspension of a dopamine agonist.

The period between PS appearance and disappearance caused by the switch from high-dose levodopa to low-dose levodopa and vice versa, and the period between PS appearance and disappearance caused by the introduction and suspension of an MAO-B inhibitor is shorter than that caused by the introduction and suspension of a dopamine agonist

and istradefylline.

The administration of high-dose levodopa or an MAO-B inhibitor might exert a direct effect on dopamine receptors by rapidly increasing dopamine levels in the synapse, causing PS to appear as a result of these rapid effects, and PS recovery by switching to low-dose levodopa and suspending an MAO-B inhibitor might cause a rapid decrease in dopamine levels in the synapse, causing PS to rapidly disappear within a short period of time.

On the other hand, administration of a dopamine agonist and istradefylline might indirectly exert a mild effect on dopamine receptors, which might lead to the later onset of PS, and PS recovery after reducing or suspending these drugs might require more time because of their indirect effect on the dopamine receptors.

Three milligrams per day of pramipexole and 300 mg/d levodopa were administered in the case studied by Gambarian et al. [6], and PS appeared 4 months after pramipexole administration for the wearing-off. All drugs were discontinued for only 1 week and then readministered, after which PS did not improve over the subsequent 4 years. If pramipexole had been suspended for another 4 months, PS might have improved.

## 5. Conclusion

The causative new drug or drugs for which doses were altered over 4 months should be identified when PS first appears in patients with PD. Because recovery is expected with appropriate treatment within 4 months (i.e., the suspension or reduction of the causative drug), a

minimum of 4 months of follow-up is warranted.

## Declaration of interest

None.

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