Therapeutic Response to Pramipexole in a Patient with Multiple System Atrophy with Predominant Parkinsonism: Positron Emission Tomography and Pharmacokinetic Assessments

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Abstract

Multiple system atrophy with predominant parkinsonism (MSA-P) usually shows poor responsiveness to dopaminergic medications. We herein describe a patient with MSA-P who exhibited a good response to pramipexole but not to an ordinary dose of L-dopa. Positron emission tomography (PET) displayed severely impaired presynaptic dopaminergic availability and relatively preserved postsynaptic D2 receptor binding capacity. The pharmacokinetic analyses demonstrated relatively low bioavailability for L-dopa and adequate plasma levels of pramipexole, even at baseline, on a stable daily dose. The PET features and pharmacokinetic differences between L-dopa and pramipexole indicate the presence of unique therapeutic responses to dopaminergic medications in the patient.

Key words: multiple system atrophy, pramipexole, positron emission tomography, pharmacokinetics


Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by cerebellar ataxia, parkinsonism and autonomic dysfunction or a combination of these manifestations (1). The disorder is classified into two clinical phenotypes based on the predominant symptoms of either parkinsonism (MSA-P) or cerebellar ataxia (1). An absent or poor response to antiparkinsonian drugs, such as L-dopa, usually combined with carbidopa or benserazide, and dopamine agonists, may suggest a clinical diagnosis of MSA-P in patients with akinetic-rigid syndrome, since most MSA-P patients exhibit poor responsiveness to dopaminergic medications (2). The present MSA-P patient, who demonstrated poor responsiveness to L-dopa, exhibited a good response to the non-ergot-derived dopamine agonist pramipexole. In this report, the patient’s unique therapeutic response to dopaminergic medications is discussed in relation to the features observed on positron emission tomography (PET) and the pharmacokinetic profiles of orally administered L-dopa and pramipexole.

Case Report

A 56-year-old man was admitted to our hospital due to a 3-year history of progressive parkinsonism. He had been treated with several antiparkinsonian medications, including L-dopa/carbidopa (L-dopa, 400 mg/day), pergolide (0.5 mg/day) and amantadine (150 mg/day); however, he complained of poor responsiveness to these medications. Indeed, his activities of daily living (ADLs) remained unchanged following a reduction in the daily dose of L-dopa/carbidopa (L-dopa, 200 mg/day). A neurological examination revealed saccadic ocular movement, left side predominant postural tremors and rigidity, bradykinesia, postural instability and mild cerebellar ataxia. The patient displayed asymptomatic orthostatic hypotension and severe constipation. Routine blood examinations were unremarkable. Although brain magnetic resonance imaging (MRI) showed obvious putami-
nal and equivocal pontine atrophy with no cerebellar atrophy on a previous examination conducted at 55 years of age (Fig. 1A), brain MRI performed on admission (at 56 years of age) disclosed mild degeneration in the middle cerebellar peduncle and pons in addition to atrophy of the posterolateral putamen (Fig. 1B). Serial PET studies were conducted at 56 years of age. PET with 18F-fluorodeoxyglucose (18F-FDG) displayed glucose hypometabolism in the cerebellum and putamen (Fig. 2A). PET with 11C-2-beta-carbomethoxy-3 beta-(4-fluorophenyl) tropane (11C-CFT) demonstrated severely reduced presynaptic dopamine transporter availability in the putamen (Fig. 2B), and PET with 11C-raclopride (11C-RAC) showed a right side predominant decrease in the postsynaptic D2 receptor binding capacity in the putamen (Fig. 2C). The relative binding potentials for 11C-CFT and 11C-RAC in the head of the caudate nucleus and the anterior/posterior putamen were semiquantitatively determined as ratios to those of the occipital cortex and compared to institutional normal data (Table). Although both the pre- and postsynaptic dopaminergic functions were affected in the patient, the postsynaptic function was relatively preserved compared to the presynaptic impairment. The clinical and neuroradiological features indicated a clinical diagnosis of MSA-P.

The Unified Parkinson’s Disease Rating Scale (UPDRS) scores were 33 for the ADL Score (Part-II) and 64 for the Motor Score (Part-III) on admission. The administration of antiparkinsonian drugs, including pramipexole (3.5 mg/day) combined with L-dopa/carbidopa (L-dopa, 200 mg/day), improved both the ADL and Motor Scores of the UPDRS (II: 19, III: 45). The scores were improved in the following categories: “speech,” “salivation,” “swallowing,” “handling utensils,” “dressing” and “turning in bed” for the ADL scores and “speech,” “rigidity,” “leg agility,” “arising from a chair,” “gait” and “postural stability” for the Motor scores. The patient was then transferred to another hospital for further rehabilitation. The antiparkinsonian treatment was modified to L-dopa/carbidopa (L-dopa, 600 mg/day) in combination with pergolide (0.75 mg/day) immediately after the transfer because pramipexole was not available in that hospital. This modification worsened the patient’s ADL performance. He was admitted to our hospital again, and the

![Figure 1. Initial and second MRI of the brain. T2-weighted MR images show obvious putaminal and equivocal pontine atrophy without cerebellar atrophy at 55 years of age (A) and mild degeneration in the middle cerebellar peduncle and pons in addition to atrophy of the posterolateral putamen at 56 years of age (B).](attachment:image1.png)
UPDRS scores on readmission (II: 34, III: 50) improved again following the readministration of the previous medications (II: 25, III: 35). The cerebellar ataxia remained unchanged throughout this period.

The plasma L-dopa concentration following the oral administration of a L-dopa/carbidopa tablet (100 mg/10 mg) was assessed up to 180 minutes according to a previously described protocol (3). The pharmacokinetic profile of orally administered L-dopa/carbidopa demonstrated relatively low bioavailability associated with delayed absorption in the patient (area under the blood concentration time curve (AUC): 799 ng·hr/mL, Cmax: 410 ng/mL, Tmax: 180 minutes), based on our previous data obtained in patients with Parkinson’s disease (low bioavailability; AUC ≤2,500 ng·hr/mL) (3). The plasma pramipexole concentration at baseline and at 15, 30, 60, 120 and 180 minutes following the oral administration of pramipexole (1 mg) on a stable daily dose of pramipexole (3.5 mg/day) was similarly determined, and each value was 5.20, 4.95, 4.96, 4.70, 6.22 and 6.71 ng/mL, respectively.
Eventually, the patient developed recurrent syncopal attacks associated with severe orthostatic hypotension, despite the treatment with droxidopa (600-900 mg/day). The syncopal attacks worsened his ADL performance; however, the dopaminergic medications remained essentially effective. Brain MRI performed at 57 years of age revealed progressive degeneration in the middle cerebellar peduncle and cerebellum, pontine atrophy with the cross sign and putaminal involvement (Fig. 3).

**Discussion**

The present patient fulfilled the consensus criteria (1) for probable MSA-P, although postmortem confirmation was not available. In addition, the longitudinal MRI studies disclosed progressive pontine atrophy associated with the cross sign, progressive atrophy in the middle cerebellar peduncle and cerebellum and marked atrophy of the posterolateral putamen on T2-weighted images. These MRI characteristics also supported the clinical diagnosis, based on an algorithm for the MRI diagnosis of MSA-P (4).

The present MSA-P patient exhibited good responsiveness to pramipexole, regardless of the poor response to L-dopa. Wenning et al. summarized the clinical features observed in 100 patients with pathologically-confirmed MSA and found an initial good response to L-dopa (subjective improvement ≥50%) in 20% of the MSA-P patients, with a retained good response at the latest follow-up in 13% of these cases (2). Furthermore, a good response to dopamine agonists was observed in 10% of the MSA-P patients, and a therapeutic benefit of dopamine agonists despite a poor response to L-dopa was noted in only 7% of the patients (2). These data indicate a generally poor response to antiparkinsonian medications in MSA-P patients. Previous 18F-dopa and 11C-RAC PET studies have reported presynaptic and postsynaptic dopaminergic dysfunction in patients with MSA-P (5, 6), providing a biochemical basis for poor responsiveness to dopaminergic medications. In contrast, the present observations revealed severely impaired presynaptic dopaminergic availability on 11C-CFT PET with relatively preserved postsynaptic D2 receptor binding, especially on the left side, on 11C-RAC PET, indicating the potential effectiveness of dopaminergic medications. However, the antiparkinsonian medications, which primarily consisted of L-dopa/carbidopa, administered after transfer, resulted in severely disabled conditions. The equivalent dose of 1 mg of pramipexole is considered to be 1 mg of pergolide (7), and 0.5-1.0 mg of pergolide reportedly corresponds to 100 mg of L-dopa combined with carbidopa (8). Therefore, the daily doses of antiparkinsonian medications transformed into L-dopa equivalents before transfer (500-800 mg) may be theoretically similar to those observed after transfer (675-750 mg). The pharmacokinetic profile of L-dopa involving relatively low bioavailability and delayed absorption observed in the present case may explain the patient’s poor responsiveness to orally administered L-dopa. Although the efficacy of a higher dose of L-dopa (e.g. a daily dose of ≥1,000 mg) should be tested based on the consensus criteria (1), the patient’s maximum daily L-dopa dose was 600 mg because clinical improvement was noted following the administration of pramipexole. However, the high dose of L-dopa (if administered) may have potentially improved the patient’s symptoms, since his postsynaptic D2 receptors were relatively preserved on 11C-RAC PET. In contrast, the temporal profile of the plasma concentration for orally administered pramipexole disclosed an adequate level, even at baseline (5.20 ng/mL for a daily dose of 3.5 mg/day), based on the previously described data (the mean minimum concentration for a daily dose of 3.0 mg/day and 4.5 mg/day in male volunteers was 1.85 and 3.03 ng/mL, respectively) (9). Pramipexole is known to exhibit good oral bioavailability (≥90%) compared to other dopamine agonists (10). In contrast, the pharmacokinetics of oral L-dopa largely depends on various factors, such as gastric emptying, which is

![Figure 3. Third MRI of the brain. T2-weighted MR images obtained at 57 years of age show progressive degeneration in the middle cerebellar peduncle, cerebellum and pons associated with the cross sign in addition to putaminal atrophy.](image-url)
known to be slow in MSA patients (11). This results in considerable variability among patients (12). Furthermore, the plasma half-life is also different between L-dopa and pramipexole. The reported elimination half-life of L-dopa/carbidopa is 2.1 hours (13), while that of pramipexole is 12.9 hours (9). Such pharmacokinetic differences between L-dopa and pramipexole may explain why pramipexole, but not L-dopa, improved the patient’s symptoms.

The present observations confirmed the presence of presynaptic impairment and postsynaptic relative preservation in the dopaminergic function, which indicated the potential effectiveness of dopaminergic medications, in the present MSA-P patient. In addition, the high bioavailability of pramipexole together with the relatively low bioavailability of L-dopa provided a biochemical basis for a good response to pramipexole, but not to L-dopa, in the present patient. Treatment with dopamine agonists, including pramipexole, as well as higher doses of L-dopa should be considered in MSA-P patients who exhibit a poor response to the ordinary dose of L-dopa.

The authors state that they have no Conflict of Interest (COI).

References