https://doi.org/10.14802/jmd.24114 / J Mov Disord 2024;17(4):453-455
pISSN 2005-940X / eISSN 2093-4939

LETTER TO THE EDITOR

Potential Psychosis Induced by a Sustained High Plasma Levodopa Concentration Due to Continuous Subcutaneous Foslevodopa/Foscarbidopa Infusion in a Patient With Parkinson's Disease: A Case Report

Toshiki Tezuka,[1,2] Tomonori Nukariya,[1,2] Yuta Kizuka,[1] Shohei Okusa,[1,2] Ryotaro Okochi,[1,2] Yuto Sakai,[1,2] Yoshihiro Nihei,[1,2] Jin Nakahara,[1,2] Morinobu Seki[1,2]✉

[1]Department of Neurology, Keio University School of Medicine, Tokyo, Japan
[2]Parkinson's Disease Center, Keio University Hospital, Tokyo, Japan

Dear Editor,

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons. Chronic dopamine (DA) replacement therapy remains the most effective method for treating the cardinal clinical symptoms of PD, including bradykinesia, tremor, and rigidity.[1] However, as PD progresses, the buffering capacity of striatal dopaminergic neurons decreases, and brain DA concentrations increasingly depend on plasma levodopa (LD) concentrations, resulting in "wearing-off" and dyskinesia.[2] Foslevodopa/foscarbidopa is a new soluble formulation of LD and carbidopa (CD) prodrugs delivered as a 24-h/day continuous subcutaneous infusion (CSCI) for the treatment of motor fluctuations in patients with advanced PD. In a previous clinical trial, treatment with foslevodopa/foscarbidopa resulted in a decrease in off-time (-3.5 hours) and an increase in on-time without troublesome dyskinesia (3.8 hours).[3] The most common adverse event leading to the discontinuation of CSCI was hallucination (n = 42, 17.2%).[3] Here, we report the case of a 75-year-old man with PD who exhibited psychosis while receiving CSCI and an unexpectedly high plasma LD concentration without a worsening of dyskinesia. The clinical characteristics and course of his PD are summarized in Figure 1.

The patient had been diagnosed with PD at the age of 61 years. His past medical history included mild cardiac hypertrophy without any symptoms. His first PD symptom was right-side-dominant bradykinesia in his upper limbs. Motor symptoms showed a good response to antiparkinsonian medications for 5 years, but the patient's disease slowly progressed. Wearing-off and dyskinesia emerged at the age of 66 years. He started taking LD five times a day at the age of 68 years. At the age of 75 years, diurnal fluctuations in symptoms and dyskinesia worsened with the emergence of delayed-on states, prompting the switch to device-aided therapies, including deep brain stimulation (DBS) and LD/CD continuous infusion gel (LCIG) therapy. His advanced age (>70 years) was a contraindication for DBS, and his camptocormia made it difficult to start LCIG therapy. Therefore, CSCI was initiated. At that time, tests scores were normal: Mini-Mental State Examination, 30; Montreal Cognitive Assessment (Japanese version), 28; and noise pareidolia test, negative. Neuropsychological tests, including Raven's colored progressive matrices, the digit span task, Ray Auditory Verbal Learning test, Stroop test, and word fluency test, revealed that his cognitive function abilities, including visuospatial cognitive ability and working memory, were retained except for word recall. On the LD chal-

Received: May 13, 2024 **Revised:** June 13, 2024 **Accepted:** June 28, 2024
✉ **Corresponding author:** Morinobu Seki, MD, PhD
Department of Neurology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan / **Tel:** +81-3-5363-3788 / **Fax:** +81-3-3353-1272 / **E-mail:** sekimori@keio.jp

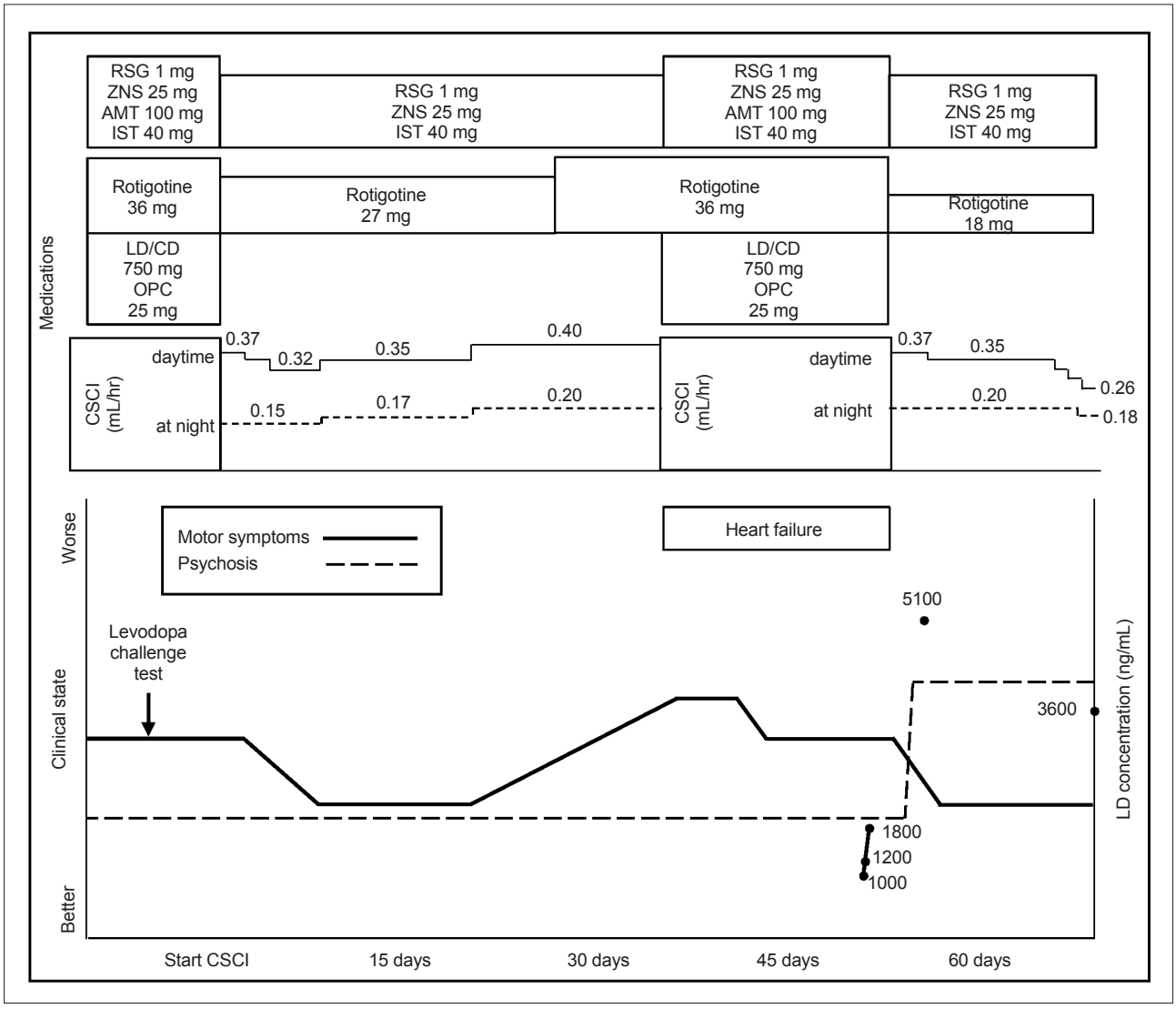

Figure 1. The clinical course of Parkinson's disease with the adjustment of foslevodopa/foscarbidopa and concomitant antiparkinsonism medications. Clinical course showing the degree of motor symptoms and psychosis, plasma levodopa concentrations (ng/mL), infusion rates of foslevodopa/foscarbidopa (mL/hr), and concomitant medications. Regarding foslevodopa/foscarbidopa, the solid line indicates the standard infusion rate, and the dotted line indicates the lower alternative infusion rate. AMT, amantadine; CD, carbidopa; CSCI, continuous subcutaneous infusion; IST, istradefylline; LD, levodopa; OPC, opicapone; RSG, rasagiline; ZNS, zonisamide.

lenge test, the improvement rate in the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III score was 33.3% (MDS-UPDRS Part III scores of 46 [on state] and 69 [off state]), which was less than expected, apparently because of his camptocormia, but revealed good the responsiveness of his bradykinesia and rigidity to CSCI. The daytime plasma LD concentration determined by high-performance liquid chromatography was 1,000 ng/mL immediately before LD/CD, 1,200 ng/mL one hour after LD/CD, and 1,800 ng/mL two hours after LD/CD. On the basis of the dose of LD/CD and a catechol-O-methyltransferase (COMT) inhibitor (opicapone; multiplying the sum of LD equivalents not by 1.33 but rather by 1.5), which corresponds to 1,125 mg as the levodopa equivalent daily dosage (LEDD), foslevodopa/foscarbidopa was introduced at an infusion rate of 0.37 mL/hr (62.9 mg/hr as LD/CD) and at the lower alternative infusion of 0.15 mL/hr according to previous data (Day 1).[4,5] The concomitant medications used were rotigotine transdermal patches (18 mg), rasagiline (1 mg), zonisamide (25 mg), and istradefylline (20 mg). One week after the initiation of CSCI, the off-time had decreased from 2 hours to 0.5 hours, with an MDS-UPDRS Part III score of 50 (Day 8). Afterward, the patient was hospitalized due to an acute exacerbation of chronic heart failure (Day 32); CSCI became less effective at that point, likely due to subcutaneous edema, with an MDS-UPDRS Part III score of 55. As his symptoms of heart failure were alleviated with medical treatment, the effect of CSCI improved. However,

as the effect of the CSCI became obvious, the patient appeared agitated, and visual hallucinations and delusions gradually developed (Day 52). The rate of CSCI was decreased from 0.37 mL/hr to 0.26 mL/hr over two weeks, but the psychiatric symptoms never improved. Interestingly, dyskinesia emerged only when the patient was moving or talking and was mild in that situation. Although the rate of CSCI can be adjusted in increments or decrements of 0.01 mL/hr to achieve more precise LD dosing,[4,6] the CSCI rate was adjusted based on the severity of motor and psychiatric symptoms and the dose of dopamine agonists (Figure 1). At the end of this period of tapering (Day 66), it became necessary to stop CSCI altogether because of the persistence of visual hallucinations and delusions. His plasma LD concentrations at the two infusion rates were unexpectedly high, at 5,100 ng/mL (0.37 mL/hr) and 3,600 ng/mL (0.26 mL/hr), respectively, and were likely the source of his psychiatric symptoms.

Foslevodopa/foscarbidopa has been shown to alleviate motor fluctuations, with benefits in both on-time without troublesome dyskinesias and off-time.[5] A previous study characterizing the LD pharmacokinetics of CSCI in PD patients revealed that average steady-state LD concentrations ranged from 747 ng/mL to 4,660 ng/mL across groups receiving four different infusion rates.[6] Although the optimal LD concentration varies widely, this concentration was higher in our patient than in previous LD concentration profiles regarding therapeutic and dyskinetic concentrations.[7] The initial infusion rate calculated via the LEDD corresponding to the LD/CD and COMT inhibitors and increases of more than 0.01 mL/hr can also lead to an unexpectedly high LD concentration. In addition, the difference in the drug delivery route (i.e., subcutaneous infusion rather than oral intake) may lead to unexpectedly elevated LD concentrations even in terms of the LEDD. In the adjustment of the CSCI rate, neurologists should detect dopamine overload by screening patients for symptoms, including headache, insomnia, agitation, hypomania and distractibility, even in the absence of peak-dose dyskinesia. Although there are no reports about heart failure induced by CSCI, LD treatment increases serum homocysteine levels,[8] and CSCI may aggravate any comorbid cardiac conditions in advanced-stage PD patients, such as our patient.

In summary, we report the case of a PD patient who exhibited psychosis without a worsening of dyskinesia while on CSCI, accompanied by unexpectedly high plasma LD concentrations. In advanced-stage PD patients, it is safest to start foslevodopa/foscarbidopa at a low infusion rate and adjust the infusion rate carefully.

Ethics Statement

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We confirmed informed consent from the patient.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

None

Acknowledgments

None

Author Contributions

Conceptualization: Toshiki Tezuka, Tomonori Nukariya, Morinobu Seki. Data curation: Toshiki Tezuka, Tomonori Nukariya, Shohei Okusa. Project administration: Toshiki Tezuka, Tomonori Nukariya, Morinobu Seki. Resources: Toshiki Tezuka, Yuta Kizuka, Shohei Okusa, Ryotaro Okochi, Yuto Sakai. Supervision: Yoshihiro Nihei, Jin Nakahara, Morinobu Seki. Visualization: Toshiki Tezuka, Tomonori Nukariya, Shohei Okusa, Ryotaro Okochi, Yuto Sakai, Morinobu Seki. Writing—original draft: Toshiki Tezuka, Tomonori Nukariya, Morinobu Seki. Writing—review & editing: Toshiki Tezuka, Yoshihiro Nihei, Jin Nakahara, Morinobu Seki.

ORCID iDs

Toshiki Tezuka	https://orcid.org/0000-0001-9380-6756
Shohei Okusa	https://orcid.org/0000-0001-6962-6640
Yoshihiro Nihei	https://orcid.org/0000-0002-3171-9080
Jin Nakahara	https://orcid.org/0000-0002-5858-0998
Morinobu Seki	https://orcid.org/0000-0002-6726-6781

REFERENCES

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA 2020;323:548-560.
2. Hauser RA. Levodopa: past, present, and future. Eur Neurol 2009;62:1-8.
3. Aldred J, Freire-Alvarez E, Amelin AV, Antonini A, Bergmans B, Bergquist F, et al. Continuous subcutaneous foslevodopa/foscarbidopa in Parkinson's disease: safety and efficacy results from a 12-month, single-arm, open-label, phase 3 study. Neurol Ther 2023;12:1937-1958.
4. Fung VSC, Aldred J, Arroyo MP, Bergquist F, Boon AJW, Bouchard M, et al. Continuous subcutaneous foslevodopa/foscarbidopa infusion for the treatment of motor fluctuations in Parkinson's disease: considerations for initiation and maintenance. Clin Park Relat Disord 2024;10:100239.
5. Soileau MJ, Aldred J, Budur K, Fisseha N, Fung VS, Jeong A, et al. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial. Lancet Neurol 2022;21:1099-1109.
6. Rosebraugh M, Liu W, Neenan M, Facheris MF. Foslevodopa/foscarbidopa is well tolerated and maintains stable levodopa and carbidopa exposure following subcutaneous infusion. J Parkinsons Dis 2021;11:1695-1702.
7. Contin M, Martinelli P. Pharmacokinetics of levodopa. J Neurol 2010; 257(Suppl 2):S253-S261.
8. Rogers JD, Sanchez-Saffon A, Frol AB, Diaz-Arrastia R. Elevated plasma homocysteine levels in patients treated with levodopa: association with vascular disease. Arch Neurol 2003;60:59-64.