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LETTER TO THE EDITOR

Continuous 24-h Levodopa-Carbidopa Intestinal Gel Infusion After a Levodopa Holiday Suppressed Refractory Dyskinesia Despite Increasing Levodopa Dose

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Dear Editor,

Continuous delivery of levodopa–carbidopa intestinal gel (LCIG) to the jejunum can improve the symptoms of advanced levodopa-responsive Parkinson's disease (PD) by allowing continuous dopamine stimulation. However, even after LCIG treatment initiation, it may be difficult to control levodopa-induced dyskinesia (LID), especially in females.[1] Several studies have reported that 24-h LCIG improves disabling dyskinesia, freezing of gait, night-time akinesia, and sleep quality unresponsive to 16-h LCIG.[2,3] Herein, we report the case of a patient in whom disabling dyskinesia of the trunk and neck was completely ameliorated by 24-h LCIG treatment. Analyses of the levodopa blood concentration revealed that dyskinesia suppression was not caused by pharmacokinetic factors.

A 79-year-old female first presented with right lower limb resting tremor at age 63 (in 2005) and was diagnosed with PD. Levodopa treatment proved effective at first, while pramipexole and ropinirole induced camptocormia, camptocormia improved after drug discontinuation. By 2012, the wearing off phenomenon and LID of the neck and trunk emerged. Amantadine was administered to control dyskinesia but was discontinued due to hallucinations. Camptocormia reappeared due to strong abdominal contractions and thoracolumbar paraspinal muscle weakness in 2015. Although she received levodopa/carbidopa/entacapone 100/10/100 mg every 3 h 5 times a day, zonisamide 100 mg/day, and levodopa/carbidopa 50/10 mg before sleep, motor fluctuations became increasingly difficult to control, and the patient could not walk without assistance. Thus, continuous dopamine delivery was initiated using LCIG in 2017.

At first, LCIG was administered starting in the morning at 5 mL and then at 1.5 mL/h for 15 h to deliver a levodopa equivalent dose (LED) of 550 mg/day. The other anti-PD drug in addition to LCIG was zonisamide 100 mg for tremor symptoms. Under this regimen, the levodopa plasma concentration was 6.08 ± 0.30 nmol/mL (mean ± standard deviation) (Figure 1A). Measurement methods are described in the Supplementary Material (in the online-only Data Supplement). While the 15-h regimen reduced off-state symptoms, severe dyskinesia remained without improvement. This dyskinesia was characterized by forward bending and swaying from side to side in an athetosis-like pattern, which appeared all day and made it difficult to walk, even indoors, without aid (Supplementary Video 1 in the online-only Data Supplement).

The initial examination of the patient in the current case study revealed that LID occasionally overlapped with resting tremor. Resting tremor was also occasionally observed in the upper and lower limbs during the off state. Therefore, considering the possibility of diphasic dyskinesia when not fully in the on state, the continuous dose was increased to 2.5 mL/h. This dose increase resulted in a peak blood levodopa concentration of 9.5 nmol/mL

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(Figure 1A), generally considered a sufficient on-state therapeutic level. However, LID did not decrease.

Next, considering the possibility that dyskinesia appeared at the peak dose, the continuous dose was drastically reduced to 0.5 mL/h, but dyskinesia was not changed. Since dyskinesia appeared before the start of administration in the early morning, LCIG was discontinued, and dyskinesia disappeared completely within 48 h. After a 72-h washout period, LCIG was restarted at 0.1 mL/h for 24 h, and the dose was gradually increased to 1.3 mL/h over approximately 15 days. When the continuous administration rate was increased to 1.4 mL/h, mild dyskinesias re-emerged. Therefore, the rate was set to 1.3 mL/h (LED 624 mg/day), after which dyskinesia again disappeared, making it easier for the patient to stand up (Supplementary Video 2 in the online-only Data Supplement). At this time, the blood levodopa concentration was 6.5 nmol/mL (Figure 1A). Orthostatic hypotension was observed as an adverse event but was improved through the discontinuation of antihypertensive drugs. The patient experienced no hallucinations or delusions during dose adjustment.

Subsequently, the administration rate was increased to 1.5 mL/h (LED 720 mg/day), which further improved activities of daily living without the re-emergence of LID. The levodopa plasma concentration measured during 24-h LCIG at 1.5 mL/h was 7.67 ± 0.75 nmol/mL, high enough to be in the on state (Figure 1B). More than one year after the initiation of 24-h LCIG treatment, LID has not reappeared.

To summarize the course of this case, though the off-period was shortened by daytime LCIG treatment, dyskinesia remained a major impediment to activities of daily living. Dopamine agonists and amantadine could not be used due to tolerability problems and failed to suppress troublesome dyskinesia. Furthermore, neither an increased nor a decreased 15-h LCIG dose reduced dyskinesia severity. However, intractable dyskinesia resolved completely after a 72-h drug holiday followed by continuous 24-h LCIG treatment.

Waiting to start LCIG until the dyskinesia stopped created a 72-h dopaminergic drug interruption period. The presence of dyskinesia before levodopa was administered in the morning indicates abnormally high dopamine receptor sensitivity, and the drug holiday may have desensitized striatal dopamine receptors and contributed to the disappearance of dyskinesia.

Although drug holidays are reported to have no long-term effects,[4] in the case of the patient presented here, the dyskinesia has completely ceased for more than one year after the drug holiday. The strategy of starting a small dose of continuous levodopa for 24 h following a drug holiday was effective in suppressing dyskinesia.

In general, dyskinesia is more likely to occur when blood levels of levodopa are high. In the case of this patient, however, dyskinesia could be stopped even at the same blood concentration by altering the administration regimen from 15 to 24 h. This finding suggests that changes in pharmacokinetic parameters are not responsible for the suppression of dyskinesia.

Both accelerated dopamine release following levodopa administration and increased responsiveness to dopamine are required for the expression of dyskinesia.[5] As 24-h LCIG eliminated dys-

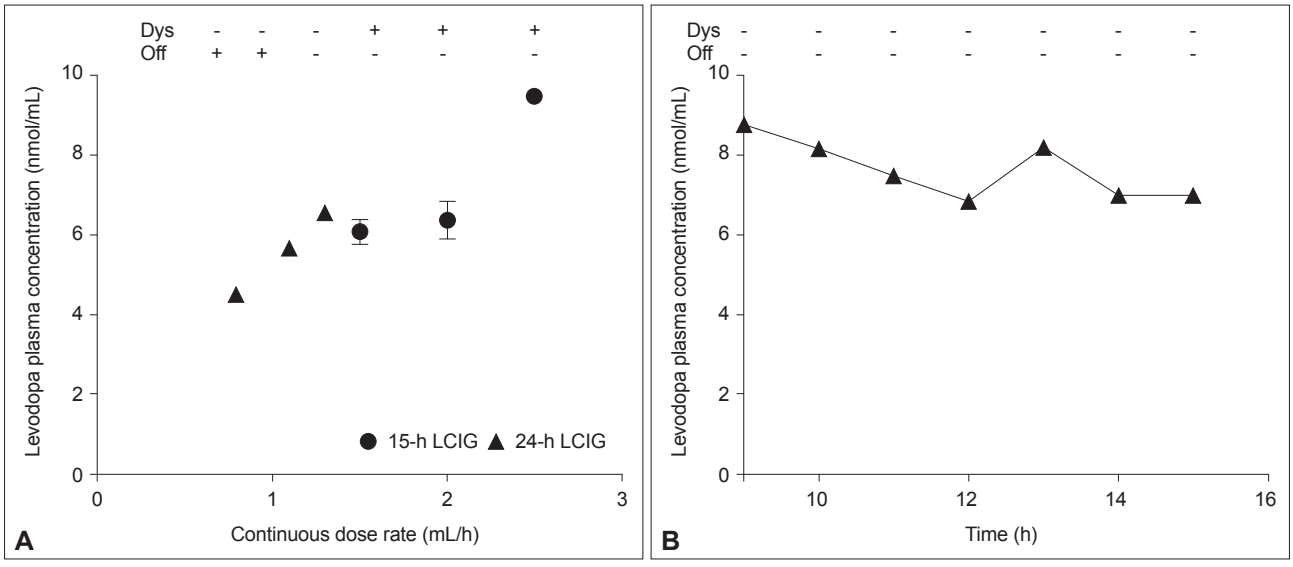

Figure 1. Levodopa plasma concentration during LCIG. A: Levodopa plasma concentration of 15-h LCIG. The plasma was collected 2 hours or more after the administration rate was changed. The circles indicate the blood concentration of 15-h LCIG, and the triangles indicate the blood concentration of 24-h LCIG. Data for 1.5 mL/h and 2 mL/h, where multiple samplings were performed, are shown as the mean ± standard deviation. For the other dose rates, only one sampling was performed. B: Levodopa plasma concentration during the administration of LCIG 1.5 mL/h from 9:00 AM to 15:00 PM, one year after the start of 24-h LCIG treatment. LCIG, levodopa–carbidopa intestinal gel; Dys, dyskinesia.

kinesia without reducing blood levodopa concentration, it is speculated that this treatment regimen induced a more sustained striatal dopamine release level.

In addition to higher peak levels, decreased trough levels of dopamine contribute to the expression of dyskinesia.[5] We suggest that the sustained delivery of dopamine provides a higher trough level than 15-h delivery and modifies postsynaptic dopaminergic plasticity,[6] which may in turn alter the threshold for LID appearance and expand the therapeutic window.[6,7]

In summary, 24-hour continuous LCIG successfully ameliorated severe dyskinesia that was resistant to 15-hour LCIG in a patient with advanced PD. The presence of dyskinesia was unrelated to peripheral blood levodopa levels, suggesting that sustained 24-h dopamine stimulation can suppress the central neural mechanisms underlying dyskinesia.

Ethics Statement

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient provided written informed consent for the publication of the details of the medical case and any accompanying images. The study protocol for measuring levodopa blood levels was reviewed and approved by the Ethics Committee of Juntendo University School of Medicine (approval number 2018095).

Supplementary Video Legends

Video 1. Dyskinesia that constantly twists the neck and trunk from side to side with daytime LCIG treatment.

Video 2. Dyskinesia remains absent 10 weeks after the start of 24-h LCIG treatment. The forward bending position also improved.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22021.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

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SUPPLEMENTARY MATERIAL

Measurement of levodopa concentration

Levodopa concentration was measured in blood plasma by high-performance liquid chromatography (UltiMate™ 3000 HPLC system; Thermo Scientific, Waltham, MA, USA). Briefly, plasma was obtained by centrifugation of blood collected in EDTA-2Na tubes (3,000 rpm, 10 min, 4°C). A 500 μL plasma sample was then mixed with 50 μL of 60% perchloric acid and centrifuged (14,000 rpm, 40 min, 4°C). The supernatant was further centrifuged in an ultrafree tube, and the new supernatant (25 μL) was injected into an HPLC system equipped with an Acclaim™ 120 C18 column (Φ4.6 × 150 mm), an ECD-3000RS detector, and a WPS-3000 TRS autosampler with a cooling device. The mobile phase buffer was prepared by adding 27.6 g sodium phosphate, 680 μL of 0.2 mg/mL nitrilotriacetic acid, and 100 μL tetrahydrofuran to 2 L distilled water and then mixing in 400 μL 5% SDS, 200 μL ProClin150, and 728 μL phosphoric acid. Levodopa was separated at a flow rate of 1.0 mL/min and column temperature of 31°C. Chromatographs were analyzed using Chromeleon 7.2. The limit of detection and limit of quantification were 2.1 pmol/mL and 7.0 pmol/mL, respectively.