Jaw-opening dystonia in Parkinson's disease improved by FOslevodopa-foscarbidopa Continuous Subcutaneous (FOCS) infusion

Motohiro Okumura
National Center Hospital, National Center of Neurology and Psychiatry
Yohei Mukai
ymukai@ncnp.go.jp

National Center Hospital, National Center of Neurology and Psychiatry
Jun Tanimura
National Center Hospital, National Center of Neurology and Psychiatry
Yuji Takahashi
National Center Hospital, National Center of Neurology and Psychiatry

Case Report

Keywords: Jaw-opening dystonia, Parkinson's disease, foslevodopa-foscarbidopa continuous subcutaneous infusion

Posted Date: March 5th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3997918/v1

Additional Declarations: Competing interest reported. YM declare that they have received lecture fees from AbbVie in the past. MO, JT, YU reports no disclosure.

Abstract

Background:

Jaw-opening dystonia (JOD) is an unusual manifestation of Parkinson's disease (PD) appearing in on-periods or off-periods. We present the case of a PD patient who presented with episodic JOD considered as off- and on-dystonia based on L-dopa concentration and improved by FOslevodopa-foscarbidopa Continuous Subcutaneous (FOCS) infusion.

Case presentation:

A 55-year-old man with a 14-year history of PD was hospitalized for induction of FOCS infusion therapy to control motor complications and wearing-off phenomena. The symptoms of JOD began with mild tightness in the lower jaw, followed by sudden involuntary JOD lasting for a few seconds at off-periods. After initiating the treatment by FOCS infusion, mild JOD appeared, coinciding with a relatively lower level of L-dopa concentration in the afternoon, despite the patient's relatively good movement symptoms. Optimizing the administration rates of FOCS infusion during the day and night by adding an additional dose resulted in near-complete relief of JOD.

Conclusions:

JOD can occur in both off-dystonia and on-dystonia in PD based on L-dopa concentration and is treatable with FOCS infusion, a new and minimally invasive device-aided therapy.

Background

Jaw-opening dystonia (JOD) is an unusual manifestation of Parkinson's disease (PD). Response to botulinum toxin or deep brain stimulation (DBS) has recently been reported in several cases of severe JOD that appeared in on-periods or off-periods.[1, 2] We report the case of a patient with a 14-year history of PD who presented with episodic JOD that could be considered off- and on-dystonia, that showed significant improvement following treatment by FOslevodopa-foscarbidopa Continuous Subcutaneous (FOCS) infusion.

Case presentation

A 55-year-old man with a 14-year history of PD was hospitalized for induction of FOCS infusion therapy to control motor complications and wearing-off phenomena that occurred when taking tablets. Regular medications for PD included a total of 4.5 tablets of levodopa/carbidopa (100/10 mg) divided into seven doses, cabergoline 2 mg/day, and rasagiline 1 mg/day. The symptoms of JOD began with mild tightness in the lower jaw, which he was aware signified initiation of an attack, followed by sudden involuntary JOD

lasting for a few seconds, accompanied by blepharospasm (Video 1). Using a previously described method, we employed high-performance liquid chromatography to measure L-dopa concentration in blood after taking oral levodopa/benserazide tablets, following an overnight fast and a medication-free period of at least 11 hours.[3] JOD occurred in the morning before and immediately after oral administration, and 3 hours after oral administration. The JOD could initially be considered as off-dystonia based on the lower concentration of L-dopa and findings of neurological examination conducted simultaneously at each time point (Fig. 1). The patient chewed gum constantly to alleviate the symptoms, which is considered a sensory trick. Additional motor complications included other types of dystonia such as toe-curling and foot inversion, wearing-off lasting for 3 hours, and non-troublesome dyskinesia immediately after taking tablets.

For relief of his motor complications, we initiated FOCS (Vyalev®, Abbvie, Tokyo, Japan) infusion, which was approved in Japan on July 26, 2023. In treatment by FOCS infusion, foslevodopa-foscarbidopa, which is a known levodopa/carbidopa phosphate prodrug, is delivered continuously for 24 hours/day via minimally invasive subcutaneous infusion.[4] Foslevodopa-foscarbidopa hydrate (240/12 mg/mL) contains the equivalent dose of oral levodopa/carbidopa (170/42.5 mg/mL). In terms of L-dopa concentration, we found that FOCS infusion maintained a higher level of L-dopa concentration compared with a single oral administration, leading to on-periods lasting most of the daytime. However, very mild JOD sometimes reappeared, coinciding with a lower level of L-dopa concentration in the afternoon, despite the patient's relatively good movement symptoms (Fig. 2). The daytime L-dopa measurements illustrated that episodic JOD might be considered to occur in on-periods as well as off-periods. Finally, optimizing the rate of administration (0.39 mL/h [levodopa/carbidopa 66.3/16.6 mg/h] during daytime and 0.25 mL/h [levodopa/carbidopa 42.5/10.6 mg/h] during nighttime) by adding an additional dose (0.25 mL [levodopa/carbidopa 42.5/10.6 mg]) resulted in near-complete relief of motor complications, including JOD (Video 2).

Discussion and conclusions

JOD is a rare and refractory form of dystonia in Parkinson's syndrome that significantly impacts quality of life and can be life-threatening.[1, 2, 5] Previous studies have indicated improvement in JOD with botulinum toxin or DBS.[1, 2] However, botulinum toxin could not completely eliminate JOD and its excessive effectiveness in muscle relaxation risks impairing the ability to eat. DBS is a very invasive treatment that can cause secondary dystonia.[6] We propose FOCS infusion as a potential treatment option for JOD in patients with PD.

PD patients can experience several types of dystonia: at wearing-off, peak-dose, on-periods, or fluctuation periods.[6] The emergence of these motor complications is related to the narrowing therapeutic window of levodopa with disease progression.[7] Previous studies in PD patients have reported that JOD can manifest in off- or on-periods.[1, 2, 8] In our case, JOD had the distinctive features of jaw spasm and severe pain, and occurred in both wearing-off and on-periods depending on L-dopa concentration. Studies focusing on the association between L-dopa concentration and dystonia in PD patients are lacking.

Interestingly, in the present patient, the JOD also occurred at relatively lower levels of L-dopa concentration during on-periods, suggesting that maintaining a very narrow optimal range of L-dopa concentration even in on-periods might relieve JOD. Thus, continuous dopaminergic stimulation could help maintain an optimal level of L-dopa concentration and minimize fluctuations.

FOCS infusion is a breakthrough treatment for continuous subcutaneous delivery of foslevodopa-foscarbidopa (a formulation of levodopa/carbidopa prodrugs that has solubility) for relief of motor complications in patients with advanced PD.[9] FOCS infusion is minimally invasive, requires no surgical procedures, and can reduce various motor complications by maintaining an optimal level of L-dopa concentration equivalent to levodopa-carbidopa intestinal gel.[9, 10] FOCS infusion appears to be a suitable treatment option for complex and refractory dystonia, such as in the JOD that occurred in the present patient.

In summary, JOD is an unusual manifestation in PD patients that can occur in both off-dystonia and on-dystonia and is treatable with FOCS infusion, a new and minimally invasive device-aided therapy.

Abbreviations

DBS
deep brain stimulation
FOCS
FOslevodopa-foscarbidopa Continuous Subcutaneous
JOD
Jaw-opening dystonia
PD
Parkinson's disease

Declarations

Ethics approval and consent to participate: The authors confirm that the approval of an institutional review board was not required by our hospital for this work given its nature. The patient provided informed verbal and written consent for publication of this article. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent for publication: Verbal and written informed consent for the publication of clinical details and videos were obtained from the patient himself.

Availability of data and materials: The datasets and video clips without his voice are available from the corresponding author on reasonable request.

Conflicts of Interest: YM declare that they have received lecture fees from AbbVie in the past. MO, JT, YU reports no disclosure.

Funding: No specific funding was received for this work.

Authors' contributions

MO mainly participated in conceptualizing this work, collecting clinical data, and drafting the manuscript. YM designed this work and revised the manuscript. JT collected clinical data and revised the manuscript. YT helped revise the manuscript and supervised this work. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Agarwal PA. Severe Jaw-Opening Dystonia as an Unusual Manifestation of Levodopa-Related Wearing-Off in Parkinson's Disease, and Successful Treatment With Botulinum Toxin Injection. Mov Disord Clin Pr. 2019;6:500–1.
2. Bove F, Piano C, Fasano A, Romito LM, Contarino MF. Severe jaw-opening off-dystonia in Parkinson's disease masked by effective deep brain stimulation of the subthalamic nucleus. Neurol Sci. 2022;43:1449–50.
3. Shiraishi T, Nishikawa N, Mukai Y, Takahashi Y. High levodopa plasma concentration after oral administration predicts levodop a-induced dyskinesia in Parkinson's disease. Park Relat Disord. 2020;75:80–4.
4. Rosebraugh M, Voight EA, Moussa EM, Jameel F, Lou X, Zhang GGZ, et al. Foslevodopa/Foscarbidopa: A New Subcutaneous Treatment for Parkinson's Disease. Ann Neurol. 2021;90:52–61.
5. von Eckardstein KL, Sixel-Döring F, Kazmaier S, Trenkwalder C, Hoover JM, Rohde V. Asphyxia due to laryngeal spasm as a severe complication of awake deep brain stimulation for Parkinson's disease: a case report. BMC Neurol. 2016;16:216.
6. Shetty AS, Bhatia KP, Lang AE. Dystonia and Parkinson's disease: What is the relationship? Neurobiol Dis. 2019;132:104462.
7. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol. 2006;5:677–87.
8. Tee TY, Khoo CS, Norlinah MI. Prominent Oromandibular Dystonia as Levodopa-induced Dyskinesia in Idiopathic Parkinson's Disease. Mov Disord Clin Pr. 2019;6:330–1.

9. Rosebraugh M, Liu W, Neenan M, Facheris MF. Foslevodopa/Foscarbidopa Is Well Tolerated and Maintains Stable Levodopa and Carbidopa Exposure Following Subcutaneous Infusion. J Park's Dis. 2021;11:1695–702.
10. 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;21:1099–109.

Figures

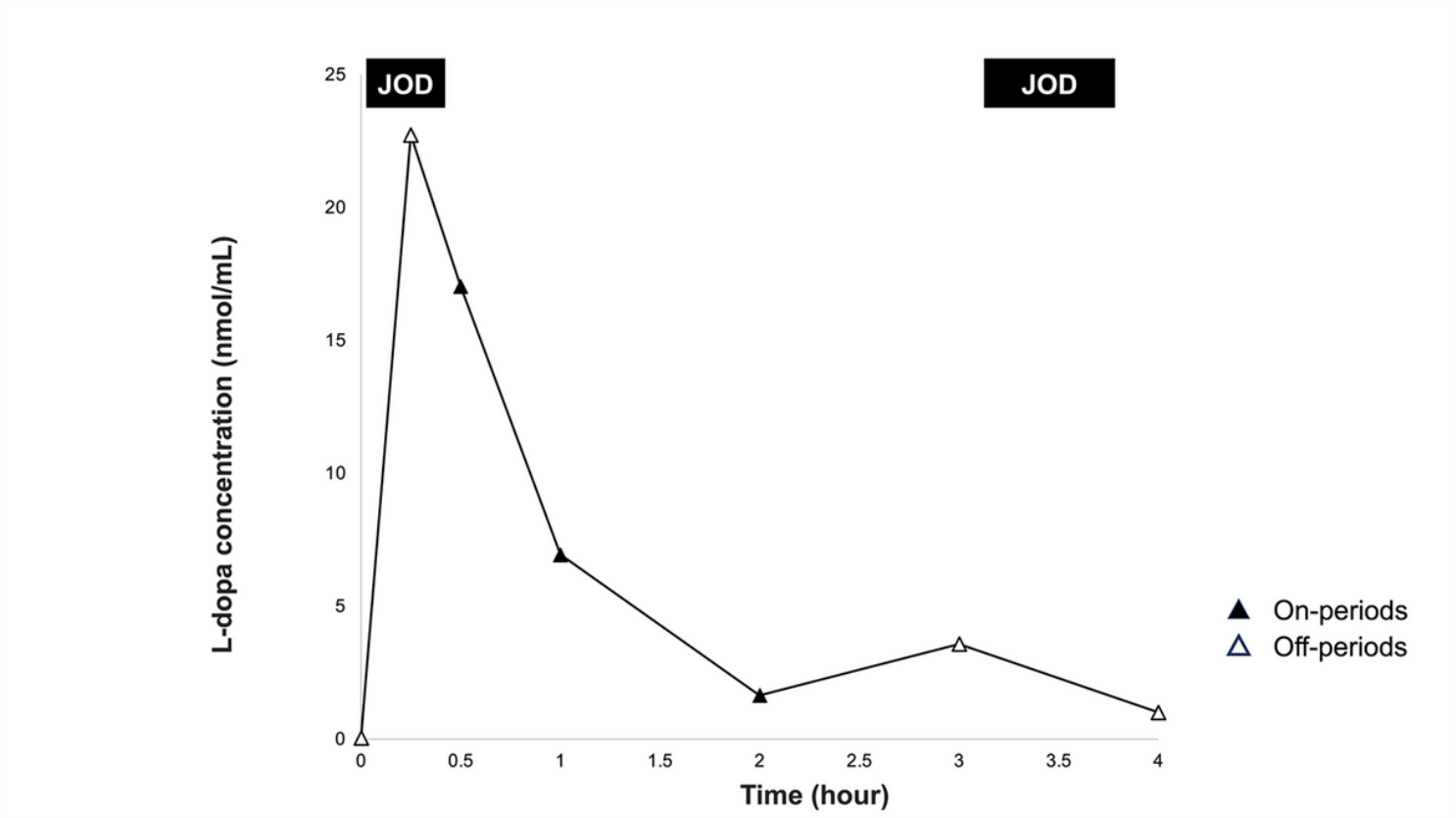

Figure 1

L-dopa concentration at oral intake

L-dopa concentration in blood according to time after oral intake of two levodopa/ benserazide tablets (100/25 mg). The concentration rose sharply immediately after administration, peaked after 15 minutes, and declined at 2 hours. The black triangles indicate on-periods, and the white triangles indicate off-periods. The on-periods showed a slight delay from peak blood concentration, approximately 30 minutes to 2 hours after oral administration. Jaw-opening dystonia (JOD) occurred in the off-periods.

JOD; jaw-opening dystonia

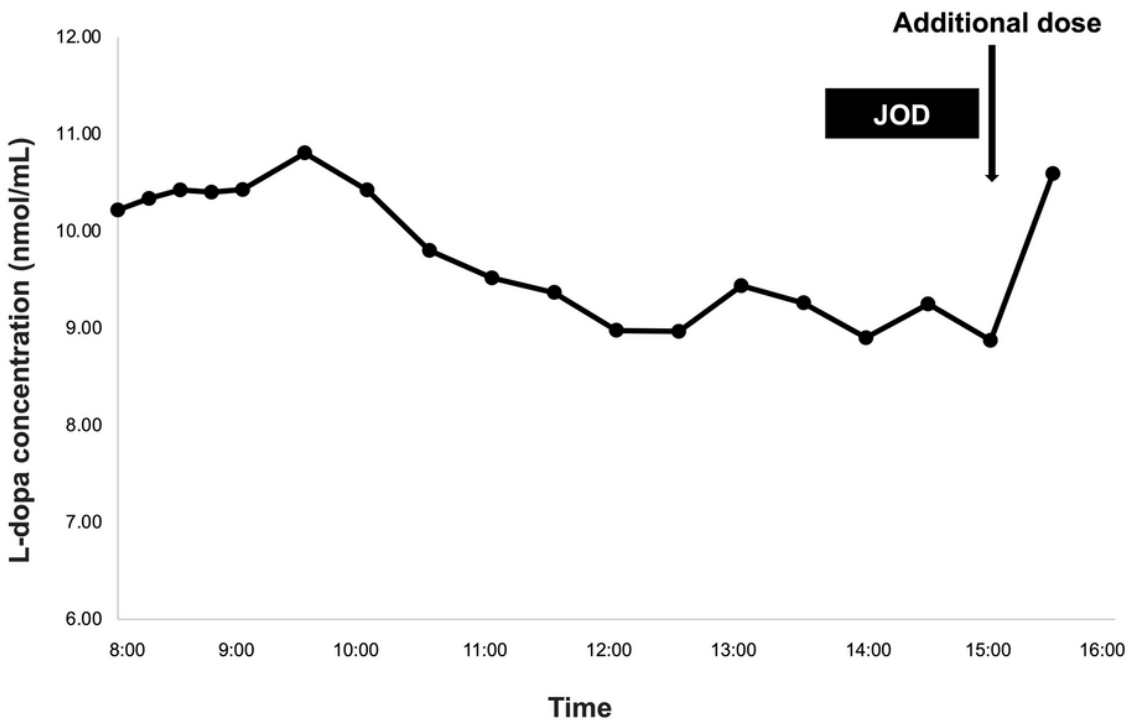

Figure 2

-dopa concentration at FOslevodopa-foscarbidopa Continuous Subcutaneous (FOCS) infusion

L-dopa concentration was measured between 8:00 and 16:00, during FOCS infusion therapy. The dose rate was switched from 0.37 mL/h during sleep to 0.39 mL/h at 8:00. Compared to the rapid steep and decline by oral intake, FOCS infusion maintained a high L-dopa concentration of around 10 nmol/mL. However, mild jaw-opening dystonia (JOD) reappeared during on-periods. Following an additional dose of FOCS infusion (arrow), disappearance of JOD correlated with the increase in L-dopa concentration.

JOD; jaw-opening dystonia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Video1image.mp4
- Video2image.mp4