LETTER TO THE EDITOR

To The Editor

Loss of Awareness after Continuous Apomorphine Infusion Withdrawal in Parkinson's Disease

Keywords: Parkinson's disease, Apomorphine withdrawal, Lethargic state

Apomorphine is a potent dopamine agonist which can be administered by intermittent injections or continuous infusion in patients with disabling motor fluctuations.[1] Continuous drug delivery imitates the physiological stimulation of striatal dopamine receptors, therefore reducing the duration and frequency of dyskinesia.[2] Suspension of dopamine agonists may result in a dopamine agonist withdrawal syndrome, which includes symptoms such as anxiety, fatigue, drug craving, and generalized pain.[3] However, lethargy is not usually described.

Here, we report a case of acute lethargy after apomorphine suspension. The patient is a 68-year-old man diagnosed with Parkinson's disease at 49 years of age. After around 5 years of treatment, he presented motor fluctuations and dyskinesias, which became severe in recent years. He also started presenting off dystonia and off non-motor symptoms, such as anxiety and pain. Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) was proposed, but the patient chose not to undergo surgery and try treatment with subcutaneous apomorphine infusion. This treatment was started and maintained for 14 months with positive response. At age 68, the patient became motivated for surgical treatment and STN-DBS surgery was performed. Preoperatively, he had been treated with 24-hour continuous subcutaneous apomorphine infusion (8.5 mg/h for 16 h/day; 5.5 mg/h for 8 h/day during night) and levodopa/carbidopa sustained-release (200/50 mg/day) at night, resulting in a L-dopa equivalent daily dose of 1940 mg. Apomorphine infusion was suspended at the beginning of the procedure. During surgery, after the second lead was placed, there was a brief period in which the patient became lethargic, with mild hypertension and a bradycardia of 40 beats per minute (bpm). Atropine was administered with partial recovery and, after a few minutes, he started to talk but was still somnolent. He was then put under general anesthesia and surgery was resumed. Apomorphine infusion was reintroduced 1 hour after the surgery at the previous rate. Postoperative computed tomography (CT) scan revealed correct lead positioning and no complications. The patient had a remarkable improvement after surgery, and apomorphine dosage was progressively reduced while increasing DBS stimulation amplitude. On the eighth postoperative day, apomorphine infusion was stopped, and within 5 hours, the patient presented a sudden lethargic state, not arousable by vocal or tactile stimuli (Video 1). All vital signs were normal with exception of a bradycardia of 40 bpm. Head CT was repeated and unremarkable. Electrocardiogram and blood tests, including cardiac enzymes, were also normal. Suspecting that the apomorphine suspension was the cause of the patient's lethargic state, apomorphine infusion was restarted at 3.5 mg/h (before suspension, the infusion rate was 2 mg/h). The patient completely recovered alertness in approximately 30 minutes and his heart rate normalized (Video 2). Afterwards, the infusion rate was reduced gradually and completely stopped 2 weeks later with no further episodes of decrease of consciousness.

Apomorphine has sedative and hypnotic properties.[4] Oral dopaminergic agonists, most of which are selective D2 receptors agonists, may also increase sleepiness and promote sleep attacks.[5] On the other hand, high dopaminomimetic doses have been shown to enhance wakefulness and suppress slow wave sleep, probably via D1-like postsynaptic receptors.[6] As apomorphine is a D1 and D2 dopamine agonist, its suspension could putatively result in excessive somnolence. This lethargy may happen by interference in the "mesocircuit model." In this model, a decrease in dopaminergic medium spiny neurons activity could lead to an inhibition of central thalamic neurons and in a failure to sustain thalamic projections to cortical areas, leading to a decreased activity in the anterior forebrain.[7] Apomorphine is also an agonist to serotonin and adrenergic receptors, and interference in the stimulation of these pathways (constituents of the ascending reticular activating system) could similarly influence consciousness.[8]

In our case, acute lethargy was likely related to the reduction of apomorphine, as no other modifications of medication had been done prior to these events. Apomorphine was being delivered in a continuous 24-hour infusion with high dosages, which may have contributed to the lethargic state of the patient when it was stopped. To the best of our knowledge, there has been only one previous report of acute lethargy after continuous subcutaneous apomorphine infusion suspension.[8] Neurologists should be aware of this disquieting complication. Continuous subcutaneous apomorphine infusion withdrawal should be done slowly and with attention to consciousness complications. These reports are important for daily clinical practice, as they support the need for maintaining apomorphine infusion intraoperatively in DBS surgery, particularly during periods when neurophysiological recordings or clinical evaluation with stimulation are not being performed.

Acknowledgements

The authors would like to thank the patient for allowing us to share this report.

Disclosures

VO: No conflicts of interest to report. GV: No conflicts of interest to report. AM: Consultancies: Abbvie. No other conflicts of interest to report.

Statement of Authorship

VO: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be submitted. GV: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be submitted. AM: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, and final approval of the version to be submitted.

https://doi.org/10.1017/cjn.2020.43 Published online by Cambridge University Press

Patient Consent

Permission for the publication of this article and associated video was obtained from the patient, via written informed consent, in compliance with laws regarding patient authorizations relating to the use or disclosure of protected health information.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2020.43.

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