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Letter to the Editor

Acute lethargy after abrupt apomorphine withdrawal in Parkinson's disease

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Dear Editor,

Continuous subcutaneous apomorphine infusion represents an established treatment for motor complications in Parkinson's disease (PD). Its main advantage is to overcome the pulsatile dopaminergic stimulation [1]. Apomorphine infusion can be delivered over 12–16 h a day up to 24 h a day and abrupt interruptions of apomorphine infusion may occur, mainly related to technical issues (pump malfunction), and result in quick worsening of motor condition [1]. Interestingly, we have observed acute lethargic states following abrupt apomorphine withdrawal. Here, we documented the case of a patient repeatedly presenting acute lethargic state after abrupt apomorphine interruption.

A 55-year-old man, diagnosed with PD since his 40s, underwent bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) because of severe motor and non-motor fluctuations. At time of surgery, his treatment consisted of 24-hour continuous subcutaneous apomorphine infusion (6.5 mg/h), oral levodopa/carbidopa/entacapone (525 mg/day) and oral rasagiline (1 mg/day), for a L-dopa equivalent daily dose (LEDD) of 2.358 mg. Since his motor and non-motor fluctuations were disabling, it was decided to keep the apomorphine infusion during awake DBS surgery, and to stop the infusion one hour before intraoperative microrecordings and microstimulation. A progressive reduction of arousal with drowsiness and subsequent lethargia was observed in the operating room one hour after apomorphine withdrawal (Video S1, segment 1). Resuming apomorphine infusion allowed recovering of arousal within one hour. Postoperative CT scan and brain MRI were normal and showed a correct lead positioning. When apomorphine was stopped again in order to perform the programming of STN stimulation, the patient presented again a progressive reduction of arousal within one hour (Video S1, segment 2). Resuming apomorphine allowed again, one hour later, a full recovery of arousal (Video S1, segment 3). Reduced arousal was not associated to severe akinesia or rigidity, or hallucinations, psychiatric or autonomic symptoms neither during surgery nor during programming. In the following days, apomorphine treatment was gradually reduced while increasing the stimulation amplitude and discontinued within 14 days, without any other arousal change. The patient had a very good improvement after surgery, which allowed to reduce the treatment to oral levodopa/carbidopa/entacapone 600 mg/day and ropinirole prolonged release 10 mg/day (LEDD 998 mg). Unfortunately, one month after surgery, the patient developed an infection of the neurostimulator, which was removed. Antibiotic therapy was started and dopaminergic treatment was increased, resuming 24-hour continuous apomorphine progressively up to 7.5 mg/h, due to the worsening of motor conditions. A new stimulator was implanted 6 months later. When resuming stimulation (right STN: 2 −/1.0 V/60 μs/130 Hz, left STN: 10 −/1.0 V/60 μs/130 Hz), although keeping oral dopaminergic medication unchanged, a new abrupt withdrawal of apomorphine infusion provoked again a progressive alteration of consciousness within one hour. This episode was characterized by initial fatigue followed by psychomotor slowing and somnolence culminating in lethargy (Video S1, segment 4). After resuming apomorphine the patient again recovered alertness in 1–2 h (Video S1, segment 5).

This is the first description of relapsing lethargy after abrupt apomorphine withdrawal. We have previously observed lethargy in PD patients, following abrupt apomorphine withdrawal, related to technical issues or to dopaminergic medication withdrawal during DBS surgery. In this patient, lethargy was consistently reproduced each time that apomorphine was abruptly interrupted. Worsening of akinesia and rigidity did not precede or associate with reduced vigilance in our patient, as it can happen in acute akinetic crises in PD. [2] Neither dopaminergic medication state nor DBS activation influenced the development and the course of the withdrawal symptoms in our patient, highlighting the key role of apomorphine in lethargy. It is well known that in the setting of dopamine agonist (DA) tapering, PD patients could develop dopamine agonist withdrawal syndrome (DAWS) characterized by prominent psychiatric manifestations, ranging from anxiety or panic attacks to dysphoria, depression, apathy and irritability, autonomic dysfunctions, diaphoresis, generalized pain, and drug cravings [3,4]. In our case the progressive reduction of arousal was not preceded or followed by the highly stereotyped prominent psychiatric manifestations or by the autonomic dysfunctions seen in DAWS [3]. The profound lethargy in our patient appears as the extreme spectrum of the dopaminergic withdrawal syndrome. In other words, the lethargic state might be the most severe DAWS. We might speculate that the clinical difference between the “classical DAWS” and lethargy might be related to a different receptor affinity, to the more rapid onset of apomorphine compared to the other DA and to the high doses of apomorphine used.

Since its first applications, dopaminergic medication has been described to increase arousal in never treated PD patients, as described by

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O. Sacks in Awakenings [5]. Nocturnal hyperactivity can develop as a side effect of dopaminergic stimulation, among other hyperdopaminergic behavioral issues [6]. On the other side, lethargy, stupor and bradyphrenia can appear as extreme hypodopaminergic symptoms [6,7]. Cases of stupor following dopaminergic medication withdrawal were described already in the '70s [7]. DA use can cause somnolence and may be responsible for irresistible episodes of uncontrolled sleep [8,9]. However, very frequently DA-related diurnal somnolence indirectly reflects excessive nocturnal activities leading to chronic lack of sleep explaining a narcolepsy-like clinical picture [10].

The lethargy induced by apomorphine withdrawal reminds that of addicts to amphetamine, a potent inhibitor of dopamine transporter (DAT), after drug withdrawal [11]. In amphetamine abusers, withdrawal symptoms typically present acutely within 24 h of the last use of the drug and hypersomnia represents one of the main withdrawal symptoms [12]. Apomorphine has also been used as a treatment in severe disorders of consciousness, as well as other dopaminergic medication, like bromocriptine [13]. The neurobehavioral effect of dopaminergic agents in disorders of consciousness seems related to the modulation of activity in the dopaminergic mesolimbic, mesostriatal, mesocortical, and thalamic pathways [14]. These findings are consistent with the theory of a "mesocircuit model" in which the medium spiny neurons (MSN) of the striatum play a key role in maintaining activity of the anterior forebrain, in particular the central thalamus, that sends diffuse excitatory inputs to the cerebral cortex and strongly innervates the frontal and prefrontal cortex, maintaining a stable state of wakefulness [14]. This patient did not undergo EEG. However, in similar previous cases EEG was performed and was unremarkable.

Due to its pharmacodynamics properties, apomorphine acts as an agonist of both D1 and D2 dopamine subtype receptors leading to an increased central dopaminergic activity. In addition, it presents a moderate affinity for adrenergic (1D, 2B, 2C) and serotonergic (5HT1A, 5HT2A, 5HT2B, 5HT2C) receptors [15]. The action of apomorphine on adrenergic receptors could also play a role in wakefulness. Although continuous apomorphine infusion is a well-established treatment, to our knowledge there are no previous descriptions of lethargy after apomorphine withdrawal. In all our patients presenting this complication, apomorphine was administered 24 h a day and the withdrawal was abrupt. The continuous stimulation of dopaminergic system over 24 h might resetting down the "mesocircuit system", in order to maintain a "correct and nor excessive wakefulness". The abrupt interruption of continuous 24 h apomorphine infusion might therefore suddenly deprive of his dopaminergic stimuli the "mesocircuit system", provoking reduced arousal. This might explain why this side effect has been reported only with 24-hour apomorphine infusion. In conclusion, the occurrence of lethargy as a result from abrupt apomorphine withdrawal should be taken into account in the management of PD patients and abrupt interruption of continuous apomorphine infusion should be avoided.

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Authorship

Dr. F. Cavallieri: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

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All authors have approved the final article.

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V. Fraix received reimbursement of travel expenses from Merz, honoraria for scientific counselling from AbbVie, and from UCB for lecturing.

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Ethical standards

Written informed consent was obtained from the patient to be videoed for publication.

Declaration of Competing Interest

None.

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