Lethargic state as a result of abrupt apomorphine withdrawal in Parkinson's disease patients.

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Introduction: Continuous apomorphine subcutaneous infusion represents an established treatment for motor complications in Parkinson's disease (PD), allowing to reduce pulsatile dopaminergic stimulation. Abrupt interruption of apomorphine infusion in PD patients can be observed in relation to technical issues preventing apomorphine delivery, or to dopaminergic medication withdrawal during deep brain stimulation (DBS) surgery and programming. In these conditions leading to abrupt apomorphine withdrawal, we repeatedly observed an acute lethargic state.

- A 55-year-old man, with PD since his 40s, was started on 24-hour continuous apomorphine infusion because of severe motor and non-motor fluctuations.
- 2 years later the patient underwent bilateral STN DBS.
- During awake surgery, apomorphine (6.5 mg/h) was discontinued a few hours before intraoperative microrecordings and microstimulation.
- A progressive reduction of arousal with drowsiness and lethargia was observed one hour after apomorphine withdrawal.
- Resuming apomorphine infusion allowed recovering of arousal.
- During STN DBS programming, dopaminergic medication withdrawal led to progressive reduction of arousal with subsequent lethargia (Figure, A).
- Resuming apomorphine again allowed recovering of arousal (Figure, B).

- One month after the surgery, the patient developed an infection of the internal pulse generator (IPG), with subsequent removal of the IPG and the extension wires. 24-hour continuous apomorphine infusion was resumed (7.5 mg/h) and IPG and extensions wires were repositioned 6 months later.
- When resuming stimulation although keeping oral dopaminergic medication (LEDD: 2449 mg/day), the abrupt withdrawal of apomorphine infusion provoked again after one hour a progressive alteration of consciousness (Figure, C).
- After resuming apomorphine the patient gradual recovered alertness in 1-2 hours (Figure, D).

Discussion: This is the first description of a lethargic state after abrupt apomorphine withdrawal. In our patient, lethargia was consistently reproduced each time apomorphine was abruptly interrupted, confirming our previous unreported observations.

Since its first applications, dopaminergic medication has been described to increase arousal in never treated PD patients, as nicely reported by O. Sacks in Awakenings. One of the first sign of apomorphine kick-in is yawning, representing an increased arousal. Moreover, apomorphine is used as treatment for severe disorders of consciousness. As such, the abrupt interruption of chronic 24-hour continuous apomorphine infusion induces a withdrawal state, resulting in a lethargic state in severe cases. Similarly, addicts to amphetamine, a strong and rapid inhibitor of dopamine re-uptake, might fall into a profound lethargic state after amphetamine withdrawal. The occurrence of a lethargic state as a result from abrupt apomorphine withdrawal should be taken into account in the management of PD patients.

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