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Propofol-induced Dyskinesias Controlled with Dexmedetomidine during Deep Brain Stimulation Surgery

Anupa Deogaonkar, M.D., M.Phil., Milind Deogaonkar, M.D.,† John Y. K. Lee, M.D.,† Zeyd Ebrahim, M.D.,‡ Armin Schubert, M.D., M.B.A.§*

DYSKINESIAS are the most common motor complication of drug therapy for Parkinson disease (PD).[1] Propofol may induce dyskinesias and choreoathetoid movements in patients with PD[2] and without PD.[3,4] We describe a patient with PD who developed propofol-induced dyskinesias during bilateral subthalamic nucleus deep brain stimulator (DBS) placement for PD. Dyskinesias were effectively controlled with dexmedetomidine, without adverse effect on microelectrode recordings.

Case Report

The patient is a 58-yr-old, right-handed man with a 10-yr history of PD that first presented as inability to control his left leg. His symptoms progressed to left arm tremor; hypophonia; intermittent dysphagia during "off" time; difficulty with handwriting, cutting food, dressing, and turning in bed; as well as occasional falling, freezing, dyskinesias, bradykinesia, and rigidity. The patient had tried several medications and was taking 100 mg/800 mg carbidopa–levodopa daily, 6 mg pramipexole daily, and 400 mg amantadine daily. Medication-related side effects included constipation and dyskinesias. Levodopa therapy had been started 10 yr ago when the patient was first diagnosed, initially with significant improvement of symptoms. During the past 2–3 yr, he noted worsening of symptoms, including more severe dyskinesias. The goal of surgery was to improve dyskinesias, bradykinesia, and freezing.

His preoperative neurologic examination revealed masked facies, severe dyskinesias of all extremities, bilateral moderate bradykinesia, and rigidity. His dyskinesias started 30 min after taking levodopa and continued for 3 h on a 6-hourly dosing schedule. Dyskinesias affected all extremities and were choreoathetoid in nature. A magnetic resonance imaging scan of the brain was normal.

On the night before surgery, all antiparkinsonian medications were stopped. On the morning of surgery, 1 mg midazolam was given for placement of the stereotactic frame. This induced severe dyskinesias that lasted for approximately 10 min and then subsided spontaneously. After placement of monitors in the operating room, propofol was started at the rate of 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Within minutes, the patient experienced violent dyskinesias of the whole body, so severe that the head frame needed to be released from the clamp affixing it to the operating table. Propofol was stopped, but the dyskinesias continued for the next 5 min. At this point, 1.5 μg/kg dexmedetomidine was administered as a loading dose over 20 min. The patient's dyskinesias subsided within 18–20 min of dexmedetomidine infusion. The dexmedetomidine infusion rate was then reduced to 1.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for another 10 min, after which it was continued at a rate of 0.2–0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. When the infusion was stopped just before the microelectrode recordings, dyskinesias recurred. The dexmedetomidine infusion was restarted with good control of dyskinetic movements and titrated to keep the patient sufficiently awake to answer questions. Specifically, during microstimulation at the end of microelectrode recording for each tract, the patient was asked whether he experienced paresthesias or pulling in the muscles of his face, arms, or legs. During macrostimulation at the time of placement of the DBS electrodes, he was asked to move his fingers or toes. This allowed satisfactory placement of bilateral subthalamic nucleus DBS electrodes. Approximately an hour after surgery, the patient had another brief episode of dyskinesias that subsided spontaneously while he was in the postoperative care unit. The patient was off dexmedetomidine infusion at this time. The patient did well postoperatively and was discharged home without further problems. During his follow-up visit at 5 weeks, he reported improvement of all symptoms, indicating satisfactory DBS function.

Discussion

This report highlights the clinical problem of dealing with sedative-induced dyskinesias in patients who must remain still but responsive for surgical DBS placement. In our patient, propofol-induced dyskinesias were controlled with dexmedetomidine, which allowed successful placement of bilateral subthalamic nucleus DBS electrodes. Midazolam-induced abnormal movements have been reported in nonparkinsonian individuals.[5,6] There are, however, no reports of midazolam-induced dyskinesias in patients with PD. Abnormal involuntary movements can be induced by a number of anesthetic agents, such as propofol, etomidate, thiopental, and methohexital in normal individuals.[7] Propofol is known to cause abnormal involuntary movements ranging from myoclonic movements[8] to dystonic[9] and violent choreoathetoid movements[10] in nonparkinsonian individuals that are not related to the dose or speed of administration.[11] Only one previous case report has documented propofol-induced dyskinesias in two PD patients that subsided without any specific treatment.[2]

Chronic levodopa therapy in PD patients commonly results in spontaneous, involuntary, abnormal movements called *dyskinesias*. The Parkinson Study Group has reported development of dyskinesias in 30% of PD patients after levodopa therapy for an average of 20.5 months.[12] The clinical pattern of these dyskinesias is variable. Most commonly, dyskinesias occur when

* Fellow, Division of Anesthesiology and Critical Care Medicine, † Clinical Fellow, Center for Neurological Restoration, ‡ Staff, Department of General Anesthesiology, § Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Department of General Anesthesiology.

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Address correspondence to Dr. Schubert: Department of General Anesthesiology, E-31, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. schubea@ccf.org.

plasma levels of levodopa are the highest and are referred to as *peak dose dyskinesias*.[13] Dyskinesias that occur when the levodopa plasma levels are low are called *diphasic dyskinesias*.[14]

The molecular and biochemical alterations in basal ganglia that are responsible for dyskinesias are not yet completely understood.[1] A possible role of neurotransmitters such as γ-aminobutyric acid (GABA) has been proposed.[15,16] The γ-aminobutyric acid–mediated (GABAergic) neurons located in the globus pallidus internus that project to the thalamic nuclei are supersensitive to GABAergic input from the striatum in dyskinetic subjects.[15] Therefore, striatal increase in GABA may induce dyskinesias in PD patients. The anesthetic effects of propofol are mediated by potentiation of GABAergic transmission.[17–19] Propofol potentiates GABAergic responses in postsynaptic neurons hippocampal CA1 region[20] and the cortex.[21] Dopaminergic and nondopaminergic neurons in the substantia nigra pars reticulata are similarly affected by propofol,[22] which also potentiates GABAergic transmission in thalamocortical circuits *via* GABA type A receptor–mediated presynaptic blockade of the reticular thalamic nucleus.[23] Direct modulation of important neural output from basal ganglia regions such as the substantia nigra pars reticulata and potentiation of GABAergic transmission in thalamocortical outflow may thus be among the mechanisms responsible for propofol-induced dyskinesias. Propofol's effect on glutaminergic neurotransmission is less clear but may also play a role.[17] Although propofol inhibits glutaminergic neurotransmission,[17,18] recent reports have demonstrated increased levels of glutamate in the cerebrospinal fluid of patients during propofol anesthesia.[24] However, the lipid emulsion used as a carrier for propofol activates *N*-methyl-D-aspartate receptor channels,[25] which is strongly implicated in the pathogenesis of dyskinesias in PD.[26]

Our patient's dyskinesias stopped completely when the dexmedetomidine loading dose was completed. Dexmedetomidine, a recently introduced α_2-adrenergic agonist, is increasingly being used for sedation of neurosurgical patients who need to be awake and cooperative during the procedure.[27–30] Preservation of cortical somatosensory evoked potentials[31–33] at clinical doses of dexmedetomidine have been reported. Furthermore, it does not seem to affect cortical mapping.[27,30,29] The effectiveness of dexmedetomidine in relieving propofol-induced dyskinesias may be a result of its action on neuronal α_2-adrenergic receptors.[34] α_2-Adrenergic receptors participate in the regulation of dopamine release in the striatum. An abnormal intermittent increase in striatal concentration of dopamine has been implicated in the pathogenesis of dyskinesias in PD.[13] It has been proposed that α_2-adrenoceptor agonists reduce the striatal dopamine concentration.[34] Moreover, postsynaptic α_2-adrenoceptors located downstream from nigrostriatal dopaminergic neurons modulate motor functions[34] and hence could also control the dyskinesias. Moreover, dexmedetomidine pretreatment of hemiparkinsonian rats reduces levodopa-induced turning behavior that is analogous to dyskinesias in PD.[35] Both of these studies point to a significant role of dexmedetomidine in controlling dyskinesias through its action at various points in the striatonigral pathway.

It should be noted that, although dexmedetomidine fulfilled a useful need in our patient, DBS electrode placement can be accomplished without the use of propofol, which precipitated the dyskinesias. Furthermore, it is conceivable that the violent dyskinetic movements experienced by our patient, which necessitated immediate removal of the head frame, may eventually have resolved on their own without pharmacologic intervention.

In summary, we report the occurrence of midazolam- and propofol-induced dyskinesias during DBS placement for PD and their treatment with dexmedetomidine. Because dexmedetomidine was effective in controlling dyskinesias while allowing successful DBS placement, its use should be considered to abolish refractory dyskinetic movements, which interfere with the surgical procedure.

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