# Serotonin Syndrome In Parkinson Disease

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Parkinson disease is a progressively debilitating disease of the extrapyramidal motor system. Components of dementia, as well as depression, have been recently recognized as part of the syndrome. As psychopharmacology becomes more advanced in the treatment of clusters of symptoms, new pitfalls arise. The "serotonin syndrome" is a complication of the use of monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). The former are used as antiparkinson drugs, as well as antidepressants, and include phenelzine (Nardil), tranylcypromine (Parnate), and selegiline (Eldepryl). The latter make up the newer generation of antidepressants, such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). A case is presented that serves to illustrate the drug interactions and review the syndrome.

A 50-year-old man was found outside a nearby food outlet in a state of agitation with generalized spasms. Paramedics were called, and the patient was brought to the emergency department.

On arrival, his temperature was  $107^{\circ}$ F rectally, blood pressure 197/119 mmHg, heart rate 128/min, and respiratory rate 40/min. The patient was incoherent and had seizure-like muscle tremors of both upper and lower extremities. Neurologic examination was notable for rapid, dyskinetic movements mainly in the hands and feet bilaterally. He had moderate rigidity in both upper and lower extremities, his deep tendon reflexes were 2+ bilaterally, and his toes were downgoing.

Laboratory data were as follows: sodium 155 mEq/L, potassium 5.0 mEq/L, chloride 113 mEq/L, bicarbonate 24 mEq/L, blood urea nitrogen 21 mg/dL, creatinine 1.8 mg/dL, glucose 94 mg/dL. The creatinine kinase was 1029 U/L, with an MB fraction of 6.5 U/mL, and index 0.6 percent. The hemoglobin was 13.8 g/dL, hematocrit 40 per-

cent, white cell count 14,500 mm<sup>3</sup> with 78 percent segmented neutrophils, 17 percent lymphocytes, no band cells, and a platelet count of  $276 \times 10^3$ /mm<sup>3</sup>. Urinalysis was unremarkable as were results of a urine toxicology screening test. His ammonia level was 330 mg/dL.

An electrocardiogram showed sinus tachycardia, and findings on a chest radiograph were within normal limits. Computed tomography ( $C\Gamma$ ) of his head showed evidence of a right suboccipital craniotomy but no mass, midline shift, infarct, or hemorrhage. Findings from a lumbar puncture were unremarkable.

Meanwhile, further history was obtained from the patient's family, who said that the patient had had Parkinson disease for 16 years. Carbidopalevodopa (Sinemet) therapy began 3 years after the disease onset, and the medication improved his symptoms substantially. He denied any history of encephalitis or drug use. His surgical history was noteworthy for removal of a right cerebellar arteriovenous malformation that was incidentally discovered on CT of his head, which was performed for evaluation of the Parkinson disease 10 years prior to admission.

He was taking large doses of carbidopa-levodopa, 25/250 four times a day, and a sustainedrelease form (Sinemet CR), 50/200 two tablets each day. In addition, he was taking selegiline, 10 mg/d. The patient had been prescribed sertraline, 50 mg/d, for depression 2 weeks prior to admission. He had been forced to retire from his job as a chemical engineer at the California Institute of Technology because of his Parkinson disease and had become despondent about his physical deterioration. He had no recent history of exposure to an inhalational anesthetic or a neuroleptic medication.

The patient was thought to have the neuroleptic malignant syndrome despite no history of antipsychotic medication ingestion. He was admitted to the intensive care unit for further observation. Levodopa, bromocriptine, and supportive therapies were administered, and he improved overnight. The selegiline and sertraline were discontinued. Thirty-six hours after admission he

Submitted, revised, 12 May 1995.

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was transferred from the intensive care unit to a ward bed, never requiring intubation. He did suffer from a component of rhabdomyolysis with subsequent renal insufficiency. Total creatinine kinase reached a peak of 30,000 U/L. Renal function returned to normal with hydration and alkalinization of the urine. Two and one-half days after admission, the patient was released in stable condition. All blood, urine, and cerebrospinal fluid cultures remained negative.

## Discussion

#### Parkinson Disease

Paralysis agitans, or Parkinson disease, was first described in 1817.<sup>1</sup> Occurring sporadically in the general population, it is a progressive, debilitating disorder with its first onset in mid to late life. Despite extended research the cause is not well understood. Two related conditions resulting in similar symptoms are postencephalitis parkinsonism and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication (a drug of abuse) providing evidence for an environmental insult.

#### Clinical Syndrome

Symptoms of the full-blown syndrome are unmistakable — stooped posture; stiff, slow movements; impassive facies; and rhythmic tremor at rest. Symptoms generally begin asymmetrically and progress to symmetric involvement. There is no paralysis, but the progressive tremor and stiffness make activities of daily living nearly impossible in the end stages of disease. Deep tendon reflexes, as well as sensory perception, remain intact. Nearly one-half of patients suffer from depressive symptoms.

## Treatment

The mainstay of treatment has been to provide an exogenous source of dopamine. The timing of this intervention is critical, because dopamine replacement is not without side effects, including precipitation of dyskinesias, the on-off phenomenon (sudden variation in response), mental confusion, and loss of efficacy.

More recently, the selective monoamine oxidase B (MAO-B) inhibitor selegiline<sup>2</sup> has been found to delay by 1 year the need for levodopa therapy.<sup>3,4</sup> The most intriguing hypothesized mode of action is the inhibited production of free radicals that cause lipid membrane degradation in neurons.<sup>5</sup> Some drawbacks observed with selegiline are that it irreversibly inhibits MAO-B, it tends to be nonselective for MAO-B at higher doses (thereby creating risk for the "tyramine cheese" effect), and it has somewhat weak amphetamine metabolites. Newer drugs are being actively investigated to overcome these problems.<sup>6</sup>

## The Serotonin Syndrome

Clinical depression is now recognized as occurring in nearly 50 percent of patients with Parkinson disease. To treat these patients fully, antidepressants are being prescribed in ever-growing numbers. Clinicians are becoming increasingly familiar with the third-generation antidepressants as a result of their circumscribed side-effect profile,<sup>7</sup> and it is common to find patients on fluoxetine and sertraline as opposed to the older tricyclic antidepressants.

As a result a new syndrome known as the serotonin syndrome has come to be recognized.<sup>8-16</sup> It results from a combination of MAOIs with selective serotonin reuptake inhibitors (SSRIs), such as L-tryptophan, clomipramine, fluoxetine, and sertraline. Clinically, the serotonin syndrome is similar to the neuroleptic malignant syndrome that occurs when antipsychotic medications are combined with dopamine receptor blockers.<sup>17</sup>

Signs and symptoms include the acute onset of fever, confusion, myoclonus, hyperreflexia, diaphoresis, tremor, diarrhea, and incoordination. Resolution is usually equally rapid, in contrast to the neuroleptic malignant syndrome, which can take up to 1 to 2 weeks to resolve fully.

The syndrome occurs in both sexes and in adults of all ages. There have been 38 cases reported during the past 12 years. The typical scenario is one in which medications are being altered for a variety of reasons — efficacy, side effects — and an overlap between the serotonin reuptake inhibitors and the MAOIs causes hyperstimulation of brain-stem and spinal-cord serotonin receptors. It is now recommended that a full 5 weeks lapse after discontinuing fluoxetine and before starting MAOI treatment.

In the case described, a selective MAO-B inhibitor was taken with sertraline. Although MAO-A rather than MAO-B is specific for serotonin metabolism, there have been reports implicating MAO-B inhibition in a nonspecific reaction with serotonin reuptake inhibitors. It is currently not advised to prescribe selegiline with any of the selective serotonin reuptake inhibitors.

Treatment consists of removing the offending agents and providing supportive therapy. Active serotonin antagonism using methysergide or propranolol is still under investigation.

### Conclusion

This case shows the hazard of polypharmacy in the patient with the diagnoses of Parkinson disease and depression. To treat patients in this specialized group, it might be necessary to rely on the older generation of antidepressants. If those medications are not tolerated, then careful consideration of the most efficacious drug regimen must be made to avoid life-threatening complications.

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