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Drug-induced parkinsonism: A case report

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Abstract

Drug-induced parkinsonism is defined as the appearance of parkinsonism on treatment with pharmaceutical agents. Symptoms typically manifest within a few days, and 90% of cases emerge within 3 months. The patient was a 68-year-old white man with a past psychiatric history significant for bipolar I versus cyclothymic disorder. The patient presented with pressured speech, flight of ideas, distractibility, delusions, and disorganized thinking. He was started on risperidone and, due to a subclinical response, was cross-tapered from risperidone to olanzapine, and divalproex was started. The patient was then given paliperidone 234 mg long-acting injection (LAI) and a second loading dose of 156 mg 1 week later. The patient's cognitive and functional status subsequently declined, all neuroleptics were discontinued, and he was diagnosed with drug-induced parkinsonism. After a complicated hospital course the patient died approximately 5 months after the administration of paliperidone LAI. Although there are several confounding factors, due to the temporal relationship of events it is likely that paliperidone LAI was a contributing factor for the development of severe parkinsonism. Practitioners should be cognizant of the potential long-term consequences of paliperidone LAI.

Keywords: parkinsonism, Parkinson disease, drug-induced parkinsonism, paliperidone, Invega Sustenna®, long-acting injection, divalproex, antipsychotic

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Background

Drug-induced parkinsonism (DIP) is defined as the appearance of parkinsonism on treatment with pharmaceutical agents. Drug-induced parkinsonism was first recognized in the early 1950s as a common complication of neuroleptic therapy. Symptoms are typically bilateral and symmetric without prominent tremor and may manifest within a few days; 90% of cases emerge within 3 months from the start of the offending agent. Histologically, marked substantia nigra neuronal loss is characteristic of Parkinson disease (PD). Although DIP shares clinical features with PD, there are no known histologic changes in the brain of person's who experience DIP. Positron emission tomography studies have shown that blockade of 75% to 80% of postsynaptic D_2 receptors results in motor features of parkinsonism. Alternatively, other drugs with no significant D_2 affinity also produce DIP, indicating that dopamine receptor blockade is not the sole mechanism.[1]

Case Report

The patient was a 68-year-old white man with a past medical history significant for bipolar I versus cyclothymic disorder, hypertension, hyperlipidemia, allergic rhinitis, coronary artery disease, and a positive purified protein derivative test for tuberculosis. He denied the use of alcohol, tobacco, or illicit substances and was homeless at the time of admission. He presented to a non-Veterans Affairs hospital for gastrointestinal upset, including severe diarrhea. Involuntary medical treatment was authorized through the Florida Mental Health Act of 1971, and the patient was transferred to a Veterans Affairs Medical

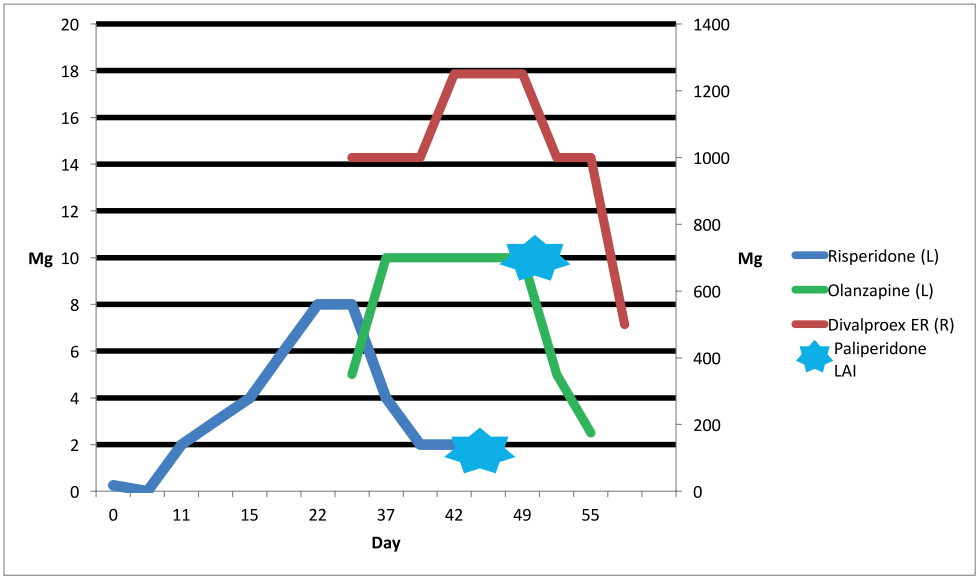

Figure: Administration of psychiatric medications; abbreviations: Mg = milligram; L = left Y-axis of graph; R = right Y-axis of graph; LAI = long-acting injection

Center with pressured speech, flight of ideas, distractibility, delusions, and disorganized thinking.

The patient's gastrointestinal upset was self limiting and resolved with supportive care. He was admitted to the psychiatry unit and started on risperidone 0.25 mg daily and titrated to a maximum daily dose of 8 mg with periods of nonadherence. The formulation of risperidone was converted from tablets to orally disintegrating tablets to encourage adherence. During this time, oral benztropine 0.5 mg once daily was started for extrapyramidal symptom prophylaxis and possible parkinsonism symptoms, which included stooped posture and shuffling gait.

Due to a subclinical response, on day 34, the patient was cross-tapered from risperidone to oral olanzapine, reaching up to 10 mg daily; divalproex ER was started, reaching up to 1250 mg daily; and benztropine was discontinued (Figure). The patient was given paliperidone 234 mg long-acting injection (LAI) (Invega Sustenna®, Janssen Pharmaceuticals Inc, Titusville, NJ) in the gluteal muscle and a second loading dose of 156 mg in the deltoid 7 days later.

Following the first injection, the patient was increasingly sedated. After the second injection, the patient's cognitive and functional status started to decline. He developed a shuffling gait, slowed movements and speech, hypophonia, hypomimia, sedation, sialorrhea, and cogwheeling. Magnetic resonance imaging showed no acute intracranial abnormalities. All neuroleptics were discontinued, and the patient was transferred to the medicine floor and diagnosed with neuroleptic-induced parkinsonism approximately 1 month after the initial injection. At the time of the injection his basic metabolic panel was not significant, and creatinine clearance (CrCl) was approximately 60 mL/min.

For symptom management he was intermittently treated with diphenhydramine; total daily doses reached up to 275 mg, which led to excessive sedation and delirium. He was also treated with benztropine up to 4 mg per day to which he developed a severe allergic reaction causing respiratory distress. Oral diphenhydramine and benztropine were primarily used and were administered parenterally when the patient was unable to swallow. He was also treated with carbidopa/levodopa and titrated to a dose of carbidopa/levodopa 50/200 mg twice daily and carbidopa/levodopa extended release 50/200 mg at bedtime. Use of carbidopa/levodopa became complicated, however, and was later discontinued when the patient was no longer able to swallow and his Dobhoff nasogastric feeding tube was frequently clogged. The patient was then treated with amantadine 200 mg twice daily and was given onabotulinumtoxinA injections for cervical dystonia.

Approximately 2.5 months from the time of the paliperidone LAI administration, a gastrostomy tube was placed due to poor oral intake. Approximately 4 months from the time of injection a tracheostomy was placed due to prolonged respiratory failure. The patient's hospital course was complicated by recurrent urinary tract infections, deep vein thrombosis, gastrointestinal bleeding, pneumothorax, heart failure, acute hypoxic respiratory failure, acute renal failure, and ventilator-associated pneumonia. Approximately 5 months after the administration of paliperidone LAI the patient died of cardiorespiratory failure.

Discussion

The initiation regimen for paliperidone LAI was designed to rapidly attain steady-state concentrations without the use of oral supplementation. In general, with the initiation of paliperidone LAI the patient's plasma levels were in the exposure range observed with 6 to 12 mg extended-release oral paliperidone.[2] Prior to the initiation of paliperidone LAI, the patient had taken up to 8 mg of oral risperidone. Data suggest that 6 to 12 mg of extended-release oral paliperidone produces similar efficacy to 4 to 6 mg of oral risperidone.[3] Despite a previous subclinical response and possible parkinsonism symptoms with oral risperidone, concerns about long-term adherence led to the choice of paliperidone LAI as the most appropriate treatment.

According to the package insert, the recommended administration site for paliperidone LAI is the deltoid muscle for the first 2 injections.[2] Data show that administration of a single dose of paliperidone in the deltoid muscle produces, on average, a 28% higher peak concentration compared with injection in the gluteal muscle.[4] This patient was given the first injection in the gluteal muscle and the second injection in the deltoid muscle. Based on this information, it is possible that the patient had a lower plasma concentration than expected with a deltoid injection. However, the patient had a CrCl of approximately 60 mL/min. Per the package insert, with a CrCl between 50 and 79 mL/min the loading dose of paliperidone LAI should be reduced to 156 mg on day 1 and 117 mg 1 week later, both administered in the deltoid muscle.[2] In this case, the patient was given 234 mg followed by 156 mg 1 week later. This increased dose likely led to higher serum drug levels.

Pharmacokinetic studies with extended-release oral paliperidone 12 mg and divalproex extended release 1000 mg resulted in a 50% increase in the maximum serum concentration and area under the plasma drug concentration versus time curve of extended-release oral paliperidone. This interaction has not been studied specifically with paliperidone LAI; however, per the package insert this interaction is not expected to be clinically significant with paliperidone LAI.[2] The difference in clinical significance of divalproex ER with oral paliperidone and paliperidone LAI is likely due to the absence of first-pass metabolism with the LAI.[5] Nevertheless, a drug interaction between paliperidone LAI and divalproex cannot be ruled out.

The use of paliperidone LAI has been associated with the development of parkinsonism, although the authors identified no case reports describing parkinsonism symptoms to the extent identified in this patient. In a 23-week open-label trial with paliperidone LAI in those with schizoaffective disorder, the incidence of parkinsonism was 8.7%. During a 15-month double-blind treatment study the incidence of parkinsonism was 3% with paliperidone LAI versus 1.8% with placebo.[2] In addition, numerous case reports have identified valproic acid–induced parkinsonism in the elderly. The mechanism by which valproic acid induces parkinsonism remains unclear, and only a small number of case reports showed the efficacy of carbidopa/levodopa in treating symptoms.[6] The Naranjo probability score suggests that the adverse drug reaction was possibly related to the use of paliperidone LAI.[7] Due to the time course of the patient's symptoms and the long duration of action with paliperidone LAI, it is believed that paliperidone LAI was the precipitating factor for this severe case of parkinsonism. This cannot be definitively determined, however, as the patient was also exposed to risperidone, divalproex, and olanzapine, all of which are associated with parkinsonism.

Although the patient did not display any symptoms of PD prior to admission, it is possible that he had an early or undiagnosed case of PD. While not performed for this patient, a dopamine transporter single photon emission computed tomography scan would have helped to determine if this was a case of functional parkinsonism or DIP.[8] The use of this scan was considered but deferred because of the cost and because the results would not have affected the treatment plan.

Conclusion

Although there are several confounding factors, due to the temporal relationship of events it is likely that paliperidone LAI was a contributing factor in the development of severe prolonged parkinsonism, which ultimately contributed to this patient's death. This was possibly a result of supratherapeutic levels of paliperidone due to altered pharmacokinetics with a CrCl of 60 mL/min. It is unclear if divalproex had a role in increasing the risk for the development of parkinsonism. Although olanzapine was being tapered off after the initiation of paliperidone LAI, this may also have increased the risk for the development of DIP.

Providers and pharmacists should be vigilant about the necessary dose adjustments with paliperidone LAI. Adding a warning message into the drug file for both the provider and pharmacist highlighting the necessity for dosage adjustments with estimated CrCl less than 80 mL/min is recommended. Additionally, careful consideration should be used when administering oral antipsychotics and divalproex in combination with a long-acting injectable antipsychotic. Practitioners should be cognizant of the potential long-term consequences of paliperidone LAI.

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