Hyperprolactinemia in Antipsychotic Use

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Hyperprolactinemia is known to be caused by both typical and atypical antipsychotics, as these medications block dopamine 2 receptors in the tuberoinfundibular region of the brain. Atypical antipsychotics are known to cause less hyperprolactinemia as well as other common side effects caused by typical antipsychotic medications because of their serotonin antagonistic property of blocking 2A receptors in addition to dopamine receptors.

**CASE 1**

The patient is a 34-year-old, black female with a history of chronic paranoid schizophrenia, complicated by medication noncompliance. She had a history of doing well on haloperidol-decanoate. On admission, she was found to be acutely psychotic and extremely paranoid. Basic labs (complete blood count [CBC] with differential, comprehensive metabolic panel [CMP], thyroid-stimulating hormone [TSH], urinalysis [UA]) on admission were reported to be within normal limits.

A urine pregnancy test (human chorionic gonadotropin [HCG]) indicated she was not pregnant. The patient was restarted on a haloperidol-decanoate 150-mg monthly intramuscular dose. The day before her next injection, the patient complained of nipple discharge and breast tenderness, leading to a check of her prolactin level. Her fast...
ing serum prolactin was 56.8 ng/mL; the normal reading for nonpregnant females is 3 ng/mL to 30 ng/mL.

The patient exhibited symptoms of schizophrenia such as isolation and poor hygiene. After blood was drawn for her serum prolactin level, the patient was started on 10 mg of aripiprazole. After 1 week, the dose was increased from 10 mg to 20 mg daily to help mitigate symptoms. Her fasting serum prolactin level was again drawn the day before her next intramuscular injection and was 9.5 ng/mL. Her symptoms were notably improved.

**CASE 2**

The patient is a 27-year-old Native American female with a history of schizoaffective disorder and medication noncompliance. She was readmitted to the inpatient facility for acute psychotic symptoms. She did not have any medical problems except obesity. She had a baby more than 1 year before presentation; she had not breastfed her baby for more than 7 months. Basic labs (CBC with differential, CMP, TSH, UA) on admission were within normal limits. Her urine pregnancy test (HCG) ruled out the possibility of pregnancy at the time of presentation. The patient was started on 1 mg of risperidone twice daily with the plan to switch to long-acting injectable risperidone. In addition, the patient was also continued on her outpatient valproic acid dose of 250 mg in the morning and 1,000 mg at bedtime.

On day 4, the patient complained of galactorrhea. A test of her fasting serum prolactin level was 36 ng/mL. The normal range for a nonpregnant woman is 3 ng/mL to 30 ng/mL. During these 4 days, she also had received two 5 mg doses of haloperidol twice along with 2 mg of lorazepam for agitation. An internist was consulted about the galactorrhea and high serum prolactin level. He suggested repeating the serum prolactin test in 1 month because the patient could have galactorrhea even after 2 years of post-pregnancy. The patient was advised to avoid nipple stimulation and to support her breasts by wearing a bra.

After 1 week, the patient was started on 25-mg injections of risperidone. Her valproic acid level was 60 mg/L at that time (normal is 50 mg/L to 100 mg/L). She remained on oral risperidone, increased to 2 mg twice daily.

Her fasting serum prolactin level 1 month later was 129.5 ng/mL. During this period between fasting serum prolactin level tests, the patient was on 2 mg of risperidone twice daily for the first 15 days; received two doses of the 25-mg risperidone intramuscular injection; took clonazepam 0.5 mg twice daily; and took 500 mg of divalproex sodium in the morning, 250 mg in the afternoon, and 1,000 mg at bedtime (66 mg/L serum level).

After two doses of 25 mg of risperidone, the patient’s dosage was increased to 37.5 mg intramuscular injection every 2 weeks. The patient also started on 10 mg aripiprazole increased 2 days later to 20 mg daily to control frequent aggressive episodes.

Three days later, the patient no longer complained of galactorrhea. She received one 37.5-mg dose of risperidone before her prolactin level was reported at 39.2 ng/mL. Four days after the second dose of risperidone, her prolactin level was 34.7 ng/mL.

Although galactorrhea was no longer a complaint, the patient’s clinical symptoms worsened, leading to the discontinuation of aripiprazole. Risperidone was increased to 50 mg every 2 weeks. Her divalproex sodium was changed to a 500-mg morning dose; 500-mg afternoon dose, and 1,000-mg bedtime dose. The day before she received another risperidone 50-mg intramuscular dose and she had been off of aripiprazole for few weeks, her fasting serum prolactin showed raised level to 50.7 ng/mL. A few days later, serum prolactin was repeated, which showed the level as 98.4 ng/mL. All the serum prolactin levels were done the day before patient received risperidone except the 98.4 ng/mL level.

**HYPERPROLACTINEMIA AND ANTIPSYCHOTICS**

Hyperprolactinemia is a frequent and serious side effect of antipsychotic treatment. It has been reported that 48% to 93% of premenopausal women and 42% to 47% of men taking antipsychotic medications have hyperprolactinemia. Hyperprolactinemia may cause sexual dysfunction, amenorrhea, infertility, galactorrhea, and osteoporosis. Studies have reported that 25% to 65% of patients with schizophrenia have bone loss after taking antipsychotic drugs. Bone fractures in people with schizophrenia taking antipsychotics also occur more frequently than in the nonpsychiatric population.

Although the introduction of second-generation antipsychotics (SGAs) has reduced the prevalence and severity of hyperprolactinemia, it still commonly occurs in patients maintained with haloperidol and many other antipsychotic medications. Outside of the US, haloperidol is commonly used as a first-line agent to treat psychosis. Moreover, some SGAs also cause a marked and sustained increase in serum prolactin levels.

**TREATMENT OF HYPERPROLACTINEMIA**

Generally, three strategies have been recommended for the treatment of this condition: 1) reduction of antipsychotic dose; 2) administration of adjunctive dopamine agonists, such as amantadine or bromocriptine; and 3) discontinuation of current treatment with a switch to a different antipsychotic agent.
These strategies, however, can lead to the worsening of psychotic symptoms, which may put the patient at a greater risk for adverse consequences, possibly worse than experiencing hyperprolactinemia itself. Switching to prolactin-sparing SGAs such as olanzapine, quetiapine, or clozapine can be an effective solution; however, switching to these drugs is not always possible in clinical practice, especially if the patient has responded well to the antipsychotic that produced the hyperprolactinemia. Moreover, these antipsychotics may produce other adverse effects, such as weight gain, diabetes, and cardiac abnormalities.

**Adjunctive Treatment**

Aripiprazole is a potent (high-affinity) partial dopamine D2 agonist, serotonin 5-HT1A agonist, and 5-HT2A antagonist. It acts as a functional antagonist at D2 receptors under hyperdopaminergic conditions but exhibits functional agonist properties under hypodopaminergic conditions. Be- cause of these unique pharmacological profiles, aripiprazole monotherapy has little effect on and may actually lower prolactin levels in people with prior antipsychotic exposure. Moreover, aripiprazole is a safe and well-tolerated treatment for schizophrenia. Thus, based on the pharmacology of aripiprazole and its proven efficacy in schizophrenia, this medication may be an ideal adjunctive treatment for secondary hyperprolactinemia.

There is evidence that aripiprazole has a role in “iatrogenic hyperprolactinemia” but also has a role in “tumorogenic hyperprolactinemia.” Aripiprazole’s ability to decrease the prolactin level in patients with prolactinoma has also been described. Freeman and Levy describe a case report of a 23-year-old black woman who had been treated with ziprasidone for her schizophrenia. Her prolactin levels were > 170 ng/mL. An MRI revealed a pituitary tumor touching the optic chiasma. After switching to 30 mg monotherapy aripiprazole, her prolactin level was reduced to 4.79 ng/mL (97.1% reduction) after 2 weeks.17

Steinhagen reported a 40-year-old patient with recent onset of psychosis. Within 6 months of starting risperidal (0.75 mg 3 times daily), the patient complained of nipple discharge and frequent headaches. Prolactin was elevated (72.1 ng/mL) and an MRI revealed a pituitary mass. Aripiprazole at a dose of 15 mg/day was substituted for other antipsychotic drugs. Over the next 2 weeks, the patient reported resolution of her galactorrhea, and after 4 weeks the patient’s serum prolactin level was reduced to 1.8 ng/mL (97.5% reduction); 3 months later, she had no psychiatric symptoms.18

**Other Perspectives**

In the tuberoinfundibular dopamine pathway, the presence of dopamine causes the inhibition of prolactin release from the pituitary when conventional antipsychotics or some SGAs are given, the regulatory effects of dopamine in this pathway are blocked, leading to increases in prolactin secretion in areas of dopamine hypoactivity (such as tuberoinfundibular pathways). Aripiprazole acts as a functional agonist, thereby leading to decreases in prolactin levels.19

An alternative but related theory for the reduction of prolactin levels may be related to the density of dopamine D2 receptors in the tuberoinfundibular pathways in the brain. When a patient is administered a potent dopamine antagonist for an extended period of time, there is an increased density of dopamine D2 receptors present. This leads to hypersensitivity of the dopamine receptors that are left unbound. Aripiprazole may bind to the free receptors stabilizing dopamine response, which in turn, leads to decreased prolactin secretion.20

It also has been hypothesized that serotonin plays a role in regulation of prolactin secretion. Aripiprazole is an antagonist at serotonin 2A (5-HT2A) receptors that causes an increase in dopaminergic transmission in most dopamine pathways. This increase in dopamine is not sufficient to cause a decrease in efficacy, but it may mitigate any changes in prolactin secretion caused by conventional antipsychotic agents as a result of increasing dopaminergic transmission in the tuberoinfundibular pathways.21,22

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