Amisulpride-Induced High Elevation in Prolactin Levels

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Drug-induced hyperprolactinemia is a common adverse effect of most antipsychotics. It can cause several consequences, including galactorrhea, amenorrhea, sexual dysfunction, infertility, and bone density loss. The increase in prolactin levels is usually less than 100 ng/mL and rarely exceeds 250 ng/mL, which warrants evaluation for prolactinomas.[1] We present a case of amisulpride-induced high increase in prolactin levels to a range usually seen in patients with pituitary prolactinomas.

Case Report

Ms A was a 41-year-old married woman suffering from schizophrenia (based on *DSM-5* criteria) for the last 4 months. She presented to the psychiatry outpatient department with extrapyramidal symptoms (Naranjo Adverse Drug Reaction Probability Scale[2] score of 9 and Simpson Angus Scale [SAS][3] score of 8), including bilateral resting tremors and rigidity of both upper limbs, while on the combination of amisulpride 900 mg/d, chlorpromazine 100 mg/d, trihexiphenidyl 4 mg/d, and long-acting injection (LAI) haloperidol decanoate 50 mg intramuscular (IM) once every 15 days for the last 3 months. At presentation, Ms A's positive psychotic symptoms were in remission. LAI haloperidol decanoate was stopped, and LAI flupenthixol decanoate 20 mg IM once every 15 days was initiated. During subsequent visits, chlorpromazine was stopped, and amisulpride was decreased to 600 mg. Due to persisting extrapyramidal symptoms, LAI flupenthixol was stopped 3 months after initiation, and the extrapyramidal symptoms improved but persisted with mild severity (SAS score of 4).

Ms A was also noted to have amenorrhea, which persisted despite the changes in medications. Her serum prolactin level was 301.6 ng/mL 8 weeks after stopping flupenthixol. A diagnosis of drug-induced hyperprolactinemia (Naranjo scale score of 8) was made. We considered the possibility of a pituitary prolactinoma and requested a visual field evaluation and brain magnetic resonance imaging (MRI) to evaluate for the same. An endocrinologist's opinion was sought, who advised the addition of tablet cabergoline 0.25 mg twice daily. Visual fields were within normal limits, and the MRI revealed no evidence of a microadenoma or any other structural abnormality. As the patient continued to have amenorrhea, the dose of amisulpride was further decreased to 400 mg/d. After discussing with the patient and her caregiver, cabergoline was stopped, and tablet aripiprazole 2 mg/d was added. Following this change, a repeat serum prolactin test showed that levels had decreased to 211.3 ng/mL. Amisulpride was gradually decreased and stopped over 4 months, and aripiprazole was increased to 15 mg. This led to the resolution of amenorrhea after approximately 8 months since its onset, and a repeat serum prolactin test showed a level of 23 ng/mL. Currently, the patient is maintaining remission on aripiprazole 15 mg/d with no significant adverse effects (SAS score of 0).

Discussion

Hyperprolactinemia is a common adverse effect of antipsychotics with dopamine receptor–blocking actions and is shown to occur in up to 70% of individuals.[4] Risperidone, paliperidone, amisulpride, sulpiride, chlorpromazine, and haloperidol have all been shown to cause significant hyperprolactinemia as per a recent network meta-analysis.[5] Although hyperprolactinemia secondary to antipsychotics is highly variable, most cases do not show elevation >100 ng/mL. Elevations >250 ng/mL are rare and usually should warrant an evaluation for pituitary causes.[1] There have been a few cases of prolactin elevation as high as 380 ng/mL with risperidone and first-generation antipsychotics in various studies[6] but not with amisulpride.

Amisulpride penetrates the blood-brain barrier very poorly due to its hydrophilicity. As a result, at a given dose of amisulpride, the concentration in the brain is lower than outside. The dose of amisulpride required to achieve a sufficient concentration in the brain to act on mesolimbic/mesocortical dopamine-2 receptors (D_2) exposes lactotrophs in the anterior pituitary to extremely high levels of amisulpride.[7] This is reflected by the very high ratio of central to peripheral potency in animal studies for amisulpride compared to other antipsychotics (amisulpride: 21,764, risperidone: 14, quetiapine: 10, and olanzapine: 1.7).[8] P-glycoprotein has high affinity for amisulpride and selectively removes amisulpride from the brain into the blood draining into the hypothalamus.[9] Due to these reasons, even at a lower dose, given its D_2-blocking property, amisulpride blocks dopamine transmission on the anterior pituitary's lactotroph cells, leading to increased prolactin levels in up to 90% of patients.[10] Our patient showed a very

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high elevation of prolactin at therapeutic doses. Prolactin levels in the range seen in our patient usually lead to a suspicion of a prolactinoma. However, imaging and visual field analysis evaluation failed to find any evidence of the same in our patient.

Our patient's prolactin levels did not improve with the initial amisulpride dose reduction. The prolactin levels decreased with the addition of low-dose aripiprazole; however, they continued to be >200 ng/mL. Only after stopping amisulpride and increasing aripiprazole did the levels return to normal. Amisulpride-induced hyperprolactinemia occurs over the whole range of therapeutic doses. Several studies[11–13] have shown that low-dose amisulpride, even doses as low as 50 mg/d, can cause hyperprolactinemia. As a result, in a large majority of patients, dose reduction alone is not helpful, and alternate treatment should be considered.[14] A recent network meta-analysis[15] has shown aripiprazole at low doses (< 5 mg) to be the most effective agent for treating antipsychotic-induced hyperprolactinemia. Metformin, PGD (Peony-glycyrrhiza decoction), and higher dose aripiprazole were also effective in treating hyperprolactinemia. However, some studies[16] show that while aripiprazole is effective in treating hyperprolactinemia due to risperidone, it is ineffective in hyperprolactinemia caused by benzamide antipsychotics like sulpiride and amisulpride.

Our case illustrates that very high prolactin levels can occur secondary to amisulpride. Relevant principles underlying the management of the same have been discussed.

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