Aripiprazole-Induced Hypoprolactinemia in an Adult Male with First-Episode Psychosis

Alanna J. Propst [1], G. Eric Jarvis [2], Howard C. Margolese [3]

Abstract

Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D2 receptors. Compared to other atypical antipsychotics, aripiprazole has less metabolic side effects and is less likely to increase prolactin. Moreover, it has been shown to have a unique prolactin lowering effect. While aripiprazole has been associated with subnormal prolactin levels in children, no documented cases of hypoprolactinemia in adults exist thus far. Here we report a case of aripiprazole-induced hypoprolactinemia in an adult male with first-episode psychosis, and the possible effects of abnormally low prolactin are discussed.

Key Words: Aripiprazole, Prolactin, Psychosis, Hypoprolactinemia

Introduction

Prolactin is a polypeptide hormone secreted by specialized lactotroph cells in the anterior pituitary gland. It is under tonic inhibitory control by dopamine from the hypothalamus (1, 2). It is involved in lactogenesis, maternal-infant bonding, and parental and sexual behavior in humans (1). Prolactin can be increased as a result of pituitary tumors and as a side effect of medications that decrease dopamine and, thus, remove the inhibitory effect on lactotroph cells. Antipsychotics are known to increase prolactin through this mechanism. Hyperprolactinemia is a common side effect of antipsychotic treatment and has been shown to cause menstrual disturbances, galactorrhea, infertility, and loss of libido in women; in men it has been associated with gynecomastia, loss of libido, erectile dysfunction, oligospermia, and infertility (2). Antipsychotics that are less likely to increase prolactin are often preferred due to these negative effects.

Aripiprazole is an atypical antipsychotic that exerts its effects via partial agonism at dopamine D2 receptors. It was first approved by the FDA in 2002 for schizophrenia in adults (3) and has since gained approval for use in bipolar maintenance, schizophrenia in adolescents, as an adjunct to depression treatment, acute manic and mixed episodes in patients ages 10 and older, and autism-related irritability in children ages 6 to 17 (4). It is known in part for its favorable metabolic side effect profile as well as for its low likelihood to increase prolactin. To our knowledge this is the first documented case of abnormally low prolactin levels in an adult treated with aripiprazole.

[1]Resident, Department of Psychiatry, McGill University
[2]Associate Professor of Psychiatry; Director, Cultural Consultation Service; Director, First Episode Psychosis Program; Research Associate, Lady Davis Institute; McGill University & Jewish General Hospital
[3]Medical Director, Early Psychosis and Schizophrenia Spectrum Program, McGill University Health Centre; Program Director, Clinical Pharmacology and Toxicology Residency Program, McGill University; Associate Professor, Department of Psychiatry, McGill University

Address for correspondence: Alanna Propst, MD
E-mail: alanna.propst@mail.mcgill.ca

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Case Report

Mr. A is a 27-year-old man who was hospitalized for one month in September 2012 with diagnoses of first-episode psychosis and schizoid personality traits. Symptoms included auditory hallucinations, anxiety, and somatic preoccupations. He was antipsychotic naive. Olanzapine 2.5 mg was given on presentation to hospital. This was increased to 2.5 mg twice daily after one day, at the same time that aripiprazole 2 mg was added. Over the next month aripiprazole was titrated to a dose of 15 mg, while olanzapine was tapered and discontinued due to sedation. Following discharge, his diagnosis was amended to Psychotic Disorder Not Otherwise Specified.

Our opposite finding (i.e., decreased prolactin coinciding with symptom improvement) highlights the nature of a partial dopamine agonist that likely acts as a dopamine agonist in the pituitary gland, thus decreasing prolactin while maintaining its dopamine antagonist activity and antipsychotic effects elsewhere.

Prolactin was mildly elevated at 27.4 μg/L (reference range 2.7–16.9) the day of aripiprazole initiation, tested as part of routine work-up before antipsychotic initiation in a first-episode psychosis program. Eight days later, repeat prolactin testing showed 1.5 μg/L, while the patient was taking aripiprazole 5 mg daily and olanzapine 2.5 mg twice daily. One month later, repeat prolactin was 0.6 μg/L on aripiprazole 15 mg monotherapy. Aripiprazole was subsequently tapered to 10 mg over four weeks; prolactin was consistently <0.5 μg/L for the next six months (i.e., so low as to be undetectable).

While Mr. A's initial mild hyperprolactinemia may have been secondary to olanzapine, removal of olanzapine may normalize prolactin but would not account for the subsequent subnormal levels. Endocrinological consultation did not reveal an underlying medical cause for hypoprolactinemia based on history, absence of symptoms associated with pituitary dysfunction (e.g., headaches, visual difficulties) and physical exam. Moreover, CT head on presentation to hospital was within normal limits. Mr. A's only other medication at the time of consultation, rosuvastatin for hypercholesterolemia, does not affect prolactin. Hence, we have discovered a patient in whom, to the best of our knowledge, aripiprazole dramatically reduced prolactin levels to subnormal levels.

Discussion

While aripiprazole has been shown to decrease prolactin levels in numerous studies of adults and children, it has never been shown to decrease levels to subthreshold values in adults. Aripiprazole's prolactin-lowering effect is likely due to its partial dopamine agonist properties in the pituitary gland; as mentioned above, dopamine is known to inhibit prolactin release from pituitary lactotroph cells (2, 3, 5). Indeed, aripiprazole has been found to occupy a significant portion of dopamine receptors in the pituitary gland as measured by PET scans in aripiprazole-treated patients with schizophrenia and schizoaffective disorder (6).

Aripiprazole has been shown to decrease prolactin levels when initiated as antipsychotic monotherapy in adults with schizophrenia spectrum disorders (7, 8) and in children and adolescents with autism spectrum disorders being treated for irritability (9, 10). These studies, however, may be confounded by the fact that many patients received other antipsychotics prior to aripiprazole. As such, despite medication washout periods, prolactin decreases may be due to removal of the antipsychotic that initially caused hyperprolactinemia. This phenomenon is also seen when patients are cross-tapered from another antipsychotic to aripiprazole: decreases in prolactin levels have been demonstrated with aripiprazole cross-tapering in women with schizophrenia and schizoaffective disorder with symptomatic hyperprolactinemia taking risperidone or sulpiride (5), men with chronic schizophrenia and sexual dysfunction treated with risperidone, amisulpride, or olanzapine (11), and adults with schizophrenia and schizoaffective disorder receiving risperidone or olanzapine (12). Of note, in contrast to our patient, prolactin levels in these studies were never reported to be in the subnormal range.

Contributing to the notion that aripiprazole exerts a unique prolactin-lowering effect is the fact that prolactin levels decrease when aripiprazole is used in conjunction with other antipsychotics; in these cases, decreases in prolactin cannot be attributed to removal of the offending agent. Aripiprazole has been associated with a decrease in prolactin levels when used as an adjunct to risperidone long-acting injection in adults with psychosis (2), to oral risperidone in adult females with schizophrenia (13), to oral risperidone in adolescents with bipolar disorder, schizoaffective disorder, psychotic depression, and posttraumatic stress disorder (14), to oral haloperidol in adults with schizophrenia (15), and to clozapine in adults with schizophrenia (16). Aripiprazole has also been used as treatment for psychosis in patients with prolactinomas, with positive outcomes on both psychotic symptoms and hyperprolactinemia (17). Once again, none of these studies in adults reported subnormal prolactin levels.

On the other hand, subnormal prolactin levels have been found in children and adolescents treated with aripiprazole. A 2013 literature review indicates that 60% of children under the age of 13 developed subnormal prolactin levels when treated with aripiprazole compared to 8.3% of untreated children. Subnormal levels were also found in 30–32% of treated adolescents. No adults treated with aripiprazole had levels reported below the normal range (3).

As risk factors for medication-induced hypoprolactinemia have not yet been identified, routine monitoring of prolactin in aripiprazole-treated patients may be useful in minimizing these negative outcomes.

Children and adolescents have higher mean peak steady state concentrations than adults for equivalent aripiprazole doses and reach maximum serum concentrations more rapidly than adults, leading to the hypothesis that children and adolescents may be more susceptible to dose-dependent side effects of aripiprazole (18) and this may account for the observed subnormal prolactin levels. Alternatively, while some studies clearly indicate that prolactin levels of adult subjects taking aripiprazole remain within the normal range, many do not comment on the presence or absence of subnormal levels and do not include actual values, perhaps leading to an under reporting of aripiprazole-induced hypoprolactinemia in adults.

Hypoprolactinemia has medical consequences, including decreased sperm motility (19) and decreased sperm count and abnormal sperm morphology in men (20). In women, aripiprazole has been associated with failure to lactate after delivery when used during pregnancy (3). Prolactin has also been implicated in immune function. Low or absent levels cause immune dysfunction in mice and in rats, while elevated levels are associated with autoimmune disorders in humans (21); the effects of hypoprolactinemia on immune function in humans have yet to be elucidated.

Interestingly, Mr. A's decreasing prolactin levels coincided with symptomatic improvement of psychosis. However, increased prolactin levels have been inconsistently observed to correlate with symptomatic improvement in patients treated with dopamine antagonist antipsychotics. As dopamine blockade is the mechanism that increases prolactin, one explanation is that prolactin increase may be viewed as a marker of dopamine blockade and indirectly of antipsychotic efficacy (1). Our opposite finding (i.e., decreased prolactin coinciding with symptom improvement) highlights the nature of a partial dopamine agonist that likely acts as a dopamine agonist in the pituitary gland, thus decreasing prolactin while maintaining its dopamine antagonist activity and antipsychotic effects elsewhere.

Prolactin disturbances are often considered secondary to medications in patients with psychosis; however, both elevated and decreased levels have been shown in unmedicated patients. While low prolactin levels have been inconsistently associated with positive symptoms (1), elevated levels of prolactin have been found in patients with first-episode psychosis (1, 22). Moreover, one study found higher levels of a genetic polymorphism of the prolactin gene in patients with schizophrenia compared to controls; this polymorphism has been associated with higher promoter activity of the prolactin gene and with increased prolactin mRNA (22).

Nonetheless, these findings do not explain the subnormal prolactin values observed in Mr. A. First, while low prolactin levels have been associated with the presence of positive symptoms, Mr. A's symptoms diminished as his prolactin level decreased. Second, the abovementioned gene polymorphism would likely confer hyperprolactinemia and not hypoprolactinemia.

As in this case report, dramatically reduced prolactin levels may be a quiet side effect of aripiprazole that goes unnoticed, but that has the potential to negatively impact the lives of affected patients. As risk factors for medication-induced hypoprolactinemia have not yet been identified, routine monitoring of prolactin in aripiprazole-treated patients may be useful in minimizing these negative outcomes. Moreover, the potential for hypoprolactinemia and associated effects should be discussed with patients, particularly those of childbearing age and those with immune deficiencies.

Conflicts of Interest

Alanna J. Propst—no conflicts; G. Eric Jarvis—no conflicts; Howard C. Margolese—Dr. Margolese is a consultant/paid speaker for and/or grant recipient from Amgen, BMS, Janssen, Lundbeck, Novartis, Otsuka, Roche, and Sunovion.

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