CASE REPORT

Attenuation of risperidone-induced hyperprolactinemia with the addition of aripiprazole

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SUMMARY

Hyperprolactinemia can be a complication of conventional neuroleptics as well as risperidone. We report the third case of attenuation of risperidone-induced hyperprolactinemia by aripiprazole.

Keywords: antipsychotic, aripiprazole, hyperprolactinemia, impulse-control disorder, mental retardation, risperidone

INTRODUCTION

Prolactin secretion is regulated by dopamine's inhibitory effect on lactotroph cells in the anterior pituitary (1–3). Agents that antagonize dopamine can induce hyperprolactinemia, which is a recognized complication of first-generation antipsychotics and risperidone (2–5). Hyperprolactinemia can lead to gynecomastia, galactorrhea, decreased bone mineral density, damage to cardiovascular endothelium and alterations in estrogen, progesterone, and testosterone levels (1, 2, 5). Treatment for drug-induced hyperprolactinemia consists of discontinuation of the offending agent or the addition of dopamine agonists (1, 2).

CLINICAL QUESTION

We questioned whether combining aripiprazole with risperidone would be beneficial in controlling impulse control disorder and correcting hyperprolactinemia in a mentally retarded patient who had previously responded well to risperidone only. This seemed a reasonable alternative to the addition of dopamine agonists, which can exacerbate psychosis and worsen impulsivity. We report the third case of attenuation of risperidone-induced hyperprolactinemia by aripiprazole (6, 7); however, this is the first case in a mentally retarded patient with impulse control disorder.

CASE

MH is a 48-year-old mentally retarded Native American male, diagnosed with impulse control disorder and obsessive-compulsive disorder. He became aggressive in 1995 or 1996 and stabilized in 1997. When we took over his care in 2001, he was psychiatrically stable on risperidone 8 mg daily, valproic acid 2000 mg daily, chlomipramine 150 mg daily, flurazepam 15 mg daily and trihexyphenidyl 2 mg twice daily. Trihexyphenidyl was withdrawn in October 2001 and flurazepam was discontinued in January 2002. He developed a tremor by October 2002. In February 2003, risperidone was decreased to 4 mg daily and the patient had a few behavioural outbreaks. Risperidone was then increased to 8 mg in August 2003 and symptoms of parkinsonism developed, including tremor and cog-wheeling, while improvement was seen from a psychiatric standpoint by March 2004. Later in 2004, levetiracetam and quetiapine were added. Amantadine was added for control of extrapyramidal symptoms in December 2004. At the same time, risperidone began to be tapered and was eventually withdrawn due to hyperprolactinemia and extrapyramidal symptoms. In September 2005, lamotrigine was added to the regimen. In October 2005, when risperidone was as low as 1 mg, serum
Prolactin was 25.07 ng/mL. After discontinuation of risperidone in January of 2006, serum prolactin was 19.41 ng/mL. As risperidone was decreased and discontinued, the patient developed increased behavioural outbursts including impulsivity, irritability, agitation, aggressiveness, hostility, swearing and talking to himself. Early in 2006, valproic acid was decreased and lamotrigine was increased.

Because the patient was previously stable on risperidone, he was rechallenged in June 2006. At 6 mg of risperidone, improvement was noted; however, serum prolactin was 45.93 ng/mL in August 2006. Aripiprazole 5 mg daily was then added and increased to 10 mg. In September 2006, at 10 mg of aripiprazole and 6 mg of risperidone, serum prolactin had decreased to 30.43 ng/mL. In October 2006, aripiprazole was increased to 15 mg daily, and serum prolactin was further decreased to 22.62 ng/mL. Serum prolactin levels continued to stabilize from November 2006 through August 2007 (see Table1). During this time the patient remained on valproic acid 500 mg, risperidone 6 mg, aripiprazole 15 mg, clomipramine 150 mg, lamotrigine 200 mg, quetiapine 700 mg, levetiracetam 3000 mg, amantadine 200 mg, bisacodyl 10 mg, and docusate 200 mg, which had been unchanged since early June 2006 (prior to the addition of risperidone). During this time there were a few situational difficulties at work but overall a dramatic psychiatric improvement was seen in functioning, behaviour and socialization.

**Critical Analysis and Discussion**

Risperidone exerts an acute and persistent effect on serum prolactin to a greater extent than the other atypical antipsychotics by blocking dopamine D_{2} receptors in the anterior pituitary (1, 2, 8). Striatal occupancy has been used as a marker for D_{2} receptor saturation on the pituitary as the D_{2} receptor affinities are similar (1). It has been reported that 50–72% occupancy of the D_{2} receptor in the striatum has resulted in hyperprolactinemia (1, 3). Prolactin levels are strongly correlated with risperidone dose (2, 5, 8). Risperidone has been shown to occupy the D_{2} receptor by 82% at 6 mg and 72% at 3 mg (9). 9-hydroxy-risperidone concentrations are strongly correlated with prolactin levels whereas risperidone concentrations are not (10). The blood–brain barrier is absent in the pituitary which allows neurosecretory products to pass into circulation. Both risperidone and its metabolite have been thought to cause marked elevations in prolactin compared to other atypicals as a result of poor penetration through the blood–brain barrier and greater effects in the periphery due to their low lipophilicity and high affinity for the D_{2} receptor (1, 10). 9-hydroxy-risperidone shares risperidone’s affinity for the D_{2} receptor but is even less lipophilic and has a greater half-

<table>
<thead>
<tr>
<th>Date</th>
<th>Prolactin level (ng/mL)</th>
<th>Risperidone dose (mg/day)</th>
<th>Aripiprazole dose (mg/day)</th>
<th>Quetiapine dose (mg/day)</th>
<th>Amantadine dose (mg/day)</th>
<th>Clomipramine dose (mg/day)</th>
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<td>1</td>
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<td>150</td>
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<tr>
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life than the parent compound and therefore may be mainly responsible for the sustained hyperprolactinemia (10).

Reversal of risperidone-, olanzapine-, and haloperidol-induced hyperprolactinemia and related symptoms has been reported after 15–30 mg of aripiprazole (6, 7, 11, 12). These cases are similar to the case presented here in that hyperprolactinemia was reversed while the patient was on the causative agent. A pilot study also evaluated the reversal of hyperprolactinemia and associated symptoms by switching from either amisulpride or risperidone to aripiprazole, in which all patients experienced reversal of hyperprolactinemia and its associated symptoms (13).

Aripiprazole is a partial agonist at D2, a partial agonist at serotonin 1A, and an antagonist at serotonin 2A receptors (1). It has a greater affinity for D2 than risperidone, with 90% occupancy at the D2 receptor at 15 mg (9). Because of aripiprazole’s partial agonist activity, it can act as an agonist in the presence of dopamine hypoactivity induced by risperidone, thus inhibiting lactotroph activity and reducing prolactin levels (9).

In addition to risperidone and aripiprazole, MH was treated with two other medications reported to increase prolactin secretion, clomipramine (14–18) and quetiapine; and amantadine (19, 20), which is reported to cause small decreases in prolactin levels. Doses of clomipramine and amantadine were constant since 2001 and 2004, respectively. MH was on 600 mg quetiapine with a prolactin level of 19–41 ng/mL, before rechallenging with risperidone. Prior to his next prolactin level at 45–93 ng/mL in August 2006, risperidone had been titrated to 6 mg and quetiapine had been increased to 700 mg. The hyperprolactinemia seen in our patient is believed to have been largely induced by the addition of risperidone. Although increasing quetiapine doses have been associated with higher prolactin levels (21), quetiapine has a higher Ki, and therefore less affinity, for the D2 receptor than risperidone (3, 22). Quetiapine has also been thought of as prolactin-sparing (3): It has been shown to elevate prolactin less than risperidone (21, 23); decrease prolactin levels (25); and reverse hyperprolactinemia when substituted for other neuroleptics (23, 24). Because doses of all other psychiatric medications were held constant during treatment with aripiprazole, the decrease in prolactin levels is attributed to the addition of aripiprazole.

**CONCLUSION**

This is the third case to report attenuation of risperidone-induced hyperprolactinemia by aripiprazole, without discontinuing risperidone, or adding a dopamine agonist. Our report clearly illustrates the time course of the effect of adding aripiprazole as well as demonstrates a sustained effect over 1 year. In addition, our report demonstrates psychiatric improvement on this combination with increased socialization in a mentally retarded individual with impulse control disorder. As this clinical conundrum is often encountered in the day-to-day care of the developmentally disabled, a controlled clinical trial would be of great benefit to the medical community.

**REFERENCES**


