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Dual Antipsychotic Therapy and Hyperprolactinemia: A Case of Combined Amisulpride and Risperidone Use

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ABSTRACT

Hyperprolactinemia is a common but often underrecognized side effect of certain antipsychotics, especially those with strong dopamine D2 receptor antagonism such as risperidone and amisulpride. We present the case of a 34-year-old woman diagnosed with psychosis who developed significant hyperprolactinemia following combined treatment with amisulpride and risperidone. She reported symptoms including amenorrhea, galactorrhoea, and breast tenderness after several months of therapy. Laboratory investigations confirmed elevated serum prolactin levels. Gradual discontinuation of risperidone, followed by dose reduction of amisulpride, led to clinical improvement and normalization of prolactin levels. This case underscores the importance of considering and monitoring endocrine side effects during antipsychotic treatment, especially when using dual therapy involving prolactin-elevating agents

KEY WORDS: Hyperprolactinemia, Amisulpride, Risperidone, Psychosis, Antipsychotic-induced endocrine disorder

INTRODUCTION:

Hyperprolactinemia is a common but often underdiagnosed endocrine side effect associated with antipsychotic medications, particularly those that exert potent dopamine D2 receptor antagonism. Dopamine, through the tuberoinfundibular pathway, plays a key role in inhibiting prolactin secretion from the anterior pituitary gland. Antipsychotic-induced blockade of dopamine receptors disrupts this inhibition, leading to increased prolactin levels. The clinical manifestations of hyperprolactinemia include menstrual disturbances, galactorrhoea, sexual dysfunction, infertility, gynecomastia, and long-term risks such as osteopenia and osteoporosis due to hypogonadism.

Among the second-generation antipsychotics (SGAs), **risperidone** and **amisulpride** are particularly known for their high propensity to cause hyperprolactinemia. Risperidone has a strong affinity for D2 receptors and relatively poor penetration across the blood-brain barrier, leading to a higher concentration of the drug in the pituitary region, thus significantly raising prolactin levels. Amisulpride, though an atypical antipsychotic, exhibits pharmacological characteristics similar to typical antipsychotics. It selectively antagonizes dopamine D2 and D3 receptors, especially in the limbic system, and at therapeutic doses can cause significant prolactin elevation. The effect is dose-dependent and may appear even at lower doses used for negative symptom management.

Combination therapy with multiple antipsychotics is sometimes utilized in cases of partial response, treatment resistance, or when augmentation is deemed necessary. However, polypharmacy carries a greater risk for additive or synergistic side effects, including those related to hormonal imbalances. Concurrent use of two prolactin-elevating agents such as risperidone and amisulpride increases the likelihood of clinically significant hyperprolactinemia.

The impact of hyperprolactinemia extends beyond physical health and can impair adherence to treatment due to distressing symptoms such as galactorrhoea or menstrual irregularities. This is particularly important in premenopausal women, where reproductive and hormonal health may be significantly affected. In the absence of timely recognition, patients may be misdiagnosed or subjected to unnecessary investigations, such as brain imaging to rule out prolactinomas.

Although there is growing awareness about the endocrine effects of antipsychotics, clinical monitoring of prolactin levels is still not routine practice, unless overt symptoms prompt investigation. Endocrine side effects tend to be underreported and underemphasized in psychiatric management, especially when the primary focus is on symptom control. Hence, there is a critical need for a multidisciplinary approach that includes awareness, early identification, regular monitoring, and dose adjustment or switching to prolactin-sparing antipsychotics when appropriate.

This case report presents an example of antipsychotic-induced hyperprolactinemia resulting from the concurrent use of risperidone and amisulpride. The case highlights the importance of maintaining vigilance when prescribing antipsychotics known to raise prolactin levels, and supports the implementation of routine screening protocols, especially in patients receiving multiple dopamine antagonists. Clinicians must carefully weigh the benefits of symptom control against the potential for serious but avoidable adverse effects, aiming to deliver individualized care that minimizes long-term health risks.

CLINICAL PRESENTATION:

The patient presented with symptoms of psychosis, including persecutory delusions, auditory hallucinations, social withdrawal, and disorganized thought processes. Following psychiatric evaluation, a diagnosis of a psychotic disorder was made, and antipsychotic therapy was initiated. She was started on risperidone at a dose of 4 mg/day for acute symptom control, with gradual improvement in her psychotic symptoms over the

following weeks. Due to persistent negative symptoms and partial therapeutic response, amisulpride 20 mg/day was added as adjunct therapy.

After approximately three months of combination therapy, the patient began experiencing menstrual irregularities, including amenorrhea, along with breast tenderness and spontaneous galactorrhoea. She denied any history of pregnancy, thyroid dysfunction, or use of other medications known to elevate prolactin levels. There were no visual disturbances or signs suggestive of pituitary pathology.

On physical examination, galactorrhoea was evident upon gentle breast expression. No masses or abnormalities were detected on breast palpation. Neurological examination was unremarkable. A hormonal work-up was conducted, revealing a markedly elevated serum prolactin level of 283 ng/mL (reference range: <25 ng/mL). Other endocrine parameters, including thyroid function tests, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and oestradiol levels, were within normal limits.

To rule out intracranial pathology such as a prolactinoma, magnetic resonance imaging (MRI) of the brain and pituitary region was performed, which showed no abnormalities. The clinical and laboratory findings, along with the absence of other contributing factors, suggested a diagnosis of antipsychotic-induced hyperprolactinemia, likely due to the combined effect of risperidone and amisulpride.

After consultation with the psychiatric team, risperidone was tapered and discontinued. The dose of amisulpride was gradually reduced while monitoring the patient's psychiatric status. Within six weeks, the patient reported resolution of galactorrhoea and the return of regular menstrual cycles. A repeat prolactin level showed normalization to 22 ng/mL, confirming reversal of hyperprolactinemia following modification of the antipsychotic regimen.

DISCUSSION:

Hyperprolactinemia is a well-established adverse effect of antipsychotic therapy, particularly with agents that exhibit strong dopamine D2 receptor antagonism. Dopamine physiologically inhibits prolactin secretion from lactotroph cells in the anterior pituitary. When this inhibition is blocked—especially by antipsychotics that poorly cross the blood-brain barrier or have strong pituitary affinity—serum prolactin levels rise, often leading to symptomatic hormonal disturbances. The two drugs implicated in this case, risperidone and amisulpride, are among the most potent antipsychotics in terms of prolactin elevation.

Risperidone is unique among second-generation antipsychotics (SGAs) in that it behaves similarly to first-generation agents with respect to prolactin elevation. It exerts high D2 receptor affinity and has a low serum-to-cerebrospinal fluid ratio, which results in significant pituitary dopamine blockade. Clinical studies have consistently shown that risperidone is associated with high rates of hyperprolactinemia—affecting up to 70% of premenopausal women treated with standard doses. Amisulpride, although an atypical antipsychotic, also has high selectivity for D2/D3 receptors and a strong tendency to elevate prolactin levels, even at lower doses used for negative symptoms or mood stabilization.

The combination of risperidone and amisulpride, though sometimes used in treatment-resistant psychosis, significantly increases the risk of prolactin-related side effects. In this case, the patient developed classic symptoms of hyperprolactinemia, including galactorrhoea and amenorrhea, within a few months of dual therapy. Importantly, neuroimaging ruled out prolactin-secreting pituitary adenoma, reinforcing the diagnosis of drug-induced hyperprolactinemia. The marked improvement following discontinuation of risperidone and dose reduction of amisulpride further supported a causal relationship.

Hyperprolactinemia may have both short- and long-term consequences, particularly in women of reproductive age. Beyond reproductive dysfunction, prolonged elevation of prolactin can lead to bone mineral density loss, mood disturbances, and reduced treatment adherence. Despite these risks, prolactin is not routinely monitored in clinical practice unless symptoms arise. This case illustrates the importance of proactive endocrine surveillance in patients prescribed prolactin-elevating antipsychotics—particularly when combination therapy is considered.

Management of antipsychotic-induced hyperprolactinemia involves several strategies, including dose reduction, switching to prolactin-sparing agents such as aripiprazole or quetiapine, or the use of adjunctive dopamine agonists. In this case, conservative management with antipsychotic tapering proved sufficient. However, such adjustments must always be balanced against the risk of psychotic relapse, necessitating close collaboration between psychiatry and endocrinology.

CONCLUSION:

Antipsychotic-induced hyperprolactinemia is a clinically significant but often underappreciated complication, especially in women receiving dopamine D2 receptor antagonists such as risperidone and amisulpride. This case emphasizes the importance of recognizing the endocrine side effects of antipsychotic therapy, particularly when combining agents known to elevate prolactin levels. Regular monitoring for clinical symptoms and serum prolactin levels should be considered part of routine care when initiating or continuing such medications. Early identification and appropriate dose adjustments can effectively reverse symptoms and normalize prolactin levels, improving patient safety and treatment adherence. Clinicians should adopt a multidisciplinary approach, balancing psychiatric stability with long-term hormonal health, especially in premenopausal women and other high-risk groups.

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