

# Hyperprolactinemia due to Paliperidone Palmitate and Treatment with Aripiprazole

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## ÖZET:

Paliperidon palmitat kullanımına bağlı hiperprolaktinemi ve aripiprazol ile tedavisi

Bütün tipik antipsikotikler güçlü D2 reseptör antagonizması yaptıkları için ve reseptöre uzun süre bağlı kaldıkları için prolaktin salgılanmasını artırırlar. İkinci jenerasyon antipsikotikler arasında risperidon ve amisülpirid prolaktin seviyesini tipik antipsikotikler gibi artırırken, klozapin, olanzapin, ketiapin, aripiprazol ve ziprasidon prolaktin seviyesini önemli derece artırmazlar. Ayrıca antipsikotiklerin aktif metabolitlerinin devam eden D2 reseptör blokaj etkisinin prolaktin seviyelerini artırabileceği ileri sürülmektedir. Bunlardan risperidon'un aktif metaboliti olan 9-OH risperidon'un (paliperidon); benzer reseptör profiline sahip olması, yarılanma ömrünün daha uzun olması ve daha az lipofilik olması nedeniyle prolaktin yüksekliğinde önemli role sahip olduğuna dair çalışmalar mevcuttur. Paliperidon palmitat kullanımına bağlı olarak hiperprolaktinemi görülebilir. Hiperprolaktinemi asemptomatik olabilir veya jinekoma, galaktore, oligomenore, amenore, cinsel işlev bozukluğu, akne, hirsütizm, infertilite ve kemik mineral dansitesinde azalmaya yol açabilir. Tedaviye aripiprazol eklenmesi prolaktin seviyelerini düşürüp yan etkileri azaltabilmektedir. Eğer hasta önemli derecede yarar görüyorsa tedaviye aripiprazol eklenerek antipsikotik kullanımına devam edilebilir. Biz de bu olgu sunumunda paliperidon palmitat uzun etkili antipsikotik tedavisinden ciddi fayda gören fakat takipleri sırasında hiperprolaktinemi gelişen ve tedaviye aripiprazol eklenmesi ile prolaktin seviyeleri normal düzeye dönen bir hastayı sunmayı amaçladık.

**Anahtar sözcükler:** paliperidon palmitat, şizoafektif bozukluk, aripiprazol, hiperprolaktinemi

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## ABSTRACT:

Hyperprolactinemia due to paliperidone palmitate and treatment with aripiprazole

For all typical antipsychotics, potent D2 receptor antagonism and prolonged connection to the receptor causes increased secretion of prolactin. Among second-generation antipsychotics, risperidone and amisulpride increase prolactin levels similar to typical antipsychotics whereas clozapine, olanzapine, quetiapine, aripiprazole and ziprasidone do not increase prolactin levels significantly. It has been claimed that the ongoing D2 receptor blockage by active metabolites of antipsychotic drugs might be responsible for elevated prolactin levels. There is clinical data about 9-OH risperidone (paliperidone), the active metabolite risperidone, suggesting that it may have a significant role in increased prolactin levels due to its similar receptor profile, longer half-life and less lipophilic structure. Hyperprolactinemia can be seen after the injection of paliperidone palmitate. Hyperprolactinemia may be asymptomatic or it may cause gynecomastia, galactorrhea, oligomenorrhea, amenorrhea, sexual dysfunction, acne, hirsutism, infertility and a decrease in bone mineral density. If the patient is receiving a significant treatment benefit from continued use of an antipsychotic, aripiprazole can be added to the treatment in order to reduce prolactin levels and the risk of side effects associated with it. In this case report, we present a schizoaffective disorder patient who significantly benefited from paliperidone palmitate long acting antipsychotic treatment but developed hyperprolactinemia and amenorrhea, which were resolved by adding aripiprazole.

**Keywords:** paliperidone palmitate, schizoaffective disorder, aripiprazole, hyperprolactinemia

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## INTRODUCTION

Antipsychotic medications are the basis of the treatment of psychosis<sup>1</sup>. There are some side effects of antipsychotic drugs such as sedation, hypotension, anticholinergic effects, extrapyramidal symptoms, arrhythmia,

agranulocytosis, sexual dysfunction, metabolic syndrome and hyperprolactinemia<sup>2</sup>. Hyperprolactinemia may be asymptomatic or it may cause gynecomastia, galactorrhea, oligomenorrhea, amenorrhea, sexual dysfunction, acne, hirsutism, infertility and a decrease in bone mineral density<sup>1,2</sup>. In a review, the prevalence of

hyperprolactinemia due to antipsychotics was found to be 42-93% for women and 18-72% for men<sup>3</sup>.

The tuberoinfundibular pathway, which starts from the arcuate nucleus of the medial basal hypothalamus, plays a major role in the regulation of prolactin secretion<sup>4</sup>. Dopamine released from the hypothalamus directly inhibits prolactin secretion by binding to the D2 receptors on lactotrope cell membranes<sup>5</sup>.

For all typical antipsychotics, potent D2 receptor antagonism and prolonged connection to the receptor causes increased secretion of prolactin<sup>5,6</sup>. Among second-generation antipsychotics, risperidone and amisulpride increase prolactin levels similar to typical antipsychotics whereas clozapine, olanzapine, quetiapine, aripiprazole and ziprasidone do not increase prolactin levels significantly<sup>5,6</sup>. In the past, it has been claimed that the 5-HT<sub>2A</sub> receptor affinity of atypical antipsychotics prevents them from increasing prolactin levels significantly<sup>6</sup>. However risperidone, although it has a high affinity for 5-HT<sub>2A</sub> receptors, increases prolactin levels like typical antipsychotics. One of the reasons for this has been thought to be that risperidone might directly affect the anterior pituitary gland, which resides outside the blood brain barrier<sup>5,6</sup>. In addition, it has been claimed that the ongoing D2 receptor blockage effect of active metabolites of antipsychotic drugs might be responsible for elevated prolactin levels. There is clinical data about 9-OH risperidone (paliperidone), the active metabolite risperidone, suggesting that it may have a significant role in increased prolactin levels due to its similar receptor profile, longer half-life and less lipophilic structure. In one study, blood prolactin levels were found to correlate with blood levels paliperidone rather than risperidone<sup>7</sup>.

The receptor profile of paliperidone palmitate is similar to that of risperidone. It has dopamine D2 and serotonin 5HT<sub>2A</sub> receptor antagonism effects. In recent studies, its effectiveness has been shown in the acute treatment of schizophrenia<sup>8</sup> and the prevention of relapse<sup>9</sup>. In

studies with paliperidone palmitate, the most common side effects were found to be headache, vomiting, limb pain or pain at the injection site<sup>8</sup>, insomnia and akathisia<sup>10</sup>. Hyperprolactinemia was also reported after paliperidone palmitate injection but most cases seemed to be asymptomatic<sup>8</sup>.

In this case report we present a schizoaffective disorder patient who significantly benefited from paliperidone palmitate long acting antipsychotic treatment but developed hyperprolactinemia and amenorrhea which were resolved by the addition of aripiprazole.

## CASE

E.G. is a 25 year old, single woman, who dropped out of college and is unemployed. She is the second of two siblings and lives with her mother. Her parents are divorced.

The patient was brought to our clinic by her relatives with complaints of temper tantrums, talking to herself and bizarre behaviors.

She had shown social withdrawal for the last 1 year with occasional irritability, screaming and cursing. She had cut the curtains in order to make handbags. Her self-care was extremely diminished and she was cutting her hair by herself. Just before being admitted to our clinic her speech was increased, she was cursing and irritable, her sleep was decreased and she had psychomotor activation.

She had a history of psychiatric complaints for 10 years. She was studying all night long with just a couple of hours sleep. Despite this, she was feeling energetic and irritable and her speech was increased. She was hearing voices that commanded her and told her that she was special. She thought that programs at television and radio were about her and she was being followed by a camera, which also read her thoughts. She was hospitalized with the diagnosis of bipolar disorder manic episode with psychotic features and she was treated with olanzapine 15 mg/day and lithium 900 mg/day. She used her drugs regularly until the last year when her parents got divorced.

She had hypomanic episodes almost every year but never had to be hospitalized again.

In her family history we learnt that her brother had been diagnosed with schizoaffective disorder and being treated effectively with risperidone 4mg/day, 37.5 mg of risperidone long-acting injection every 15 days and lamotrigine 100 mg/day.

There was no specific information about her self-history of other diseases.

Clinical follow-up: She was in the state of psychomotor excitation without any possibility of cooperation. She was having pointless conversations and inappropriate laughter which gave the impression of auditory hallucinations. Her mood was irritable and her affect was limited. Her associations were incoherent and her self-care diminished. Her CGI score was 7, PANNS score was 149 and YMRS score was 18. On the 2<sup>nd</sup> day of hospitalization electroconvulsive therapy was started and her psychomotor excitation and psychotic features were ongoing with lorazepam 5 mg/day and quetiapine 300 mg/day. On the 6<sup>th</sup> day, her excitation was less and her PANNS score had decreased to 117. Lorazepam was stopped on 12<sup>th</sup> day. On the 22<sup>nd</sup> day, her CGI, PANSS and YMRS scores were decreased to 4, 89 and 4 respectively after administration of eight sessions of ECT. On the 23<sup>th</sup> day, her mood elevated, her sleep decreased and her speech increased again with a CGI score 5 and YMRS score 20. We stopped ECT administration and added lorazepam 5 mg/day again, increased quetiapine dosage to 600 mg/day and added oral paliperidone 12 mg/day. On the 30<sup>th</sup> day, her CGI, PANNS and YMRS scores decreased to 4, 82 and 7 respectively. Her menstruation was delayed and blood prolactin level was measured as 94 ng/ml. There was no organic pathology reported after the consultation with obstetrics and gynecology department. We started 150 mg paliperidone palmitate long acting injection, which was administered to her deltoid region and gave 100 mg paliperidone palmitate after 8 days and decided to keep on administering 100 mg injections once every month as maintenance

treatment. Her prolactin level increased to 125 ng/ml after the first two injections. On the 60<sup>th</sup> day of hospitalization, she was discharged with YMRS score 2 and PANNS score 60. Her mood was euthymic and her affect was compliant and reactive. Her emotional involvement with others improved dramatically and she was expressing herself easily. Her associations were improved and there was no disorganized behavior. There were no hallucinations and her delusions were decreased significantly. She still had amenorrhea and her prolactin level was 105 ng/ml at the time of discharge.

The history of the patient's illness revealed that her psychotic symptoms continued without affective symptoms and her mood episodes constitute approximately 30% of a 10 year period. In light of this data her diagnosis was changed to schizoaffective disorder bipolar type and she was discharged with paliperidone palmitate 100 mg per month treatment. After 2 months of discharge at the outpatient follow-up, her prolactin level was measured as 74 ng/ml and she still had no menstruation. Aripiprazole 5 mg/day added to her discharge treatment. After 1 month of aripiprazole treatment, her prolactin level decreased to 38 ng/ml and after 2 months aripiprazole treatment she started to have menstruation. Her prolactin level was 31 ng/ml after 6 months. During the follow-up visits the patient did not have any affective and/or psychotic episodes.

## DISCUSSION

In this case, we have summarized the hyperprolactinemia observed after the use of a new drug, paliperidone palmitate and decrease in prolactin levels after adding aripiprazole to the treatment.

Hyperprolactinemia could impair compliance to treatment especially in young female patients therefore these patients should be closely monitored in this respect. Even though most cases of hyperprolactinemia due to paliperidone palmitate have been reported to be

asymptomatic<sup>8</sup>, there may be long-term side effects and patients should be informed about possible side effects of hyperprolactinemia.

It has been claimed that the prolactin lowering effect of aripiprazole comes from its partial D2 receptor agonist effect<sup>1</sup>. Aripiprazole has been shown to decrease high prolactin levels induced by risperidone long-acting injection and relieve menstrual disorders in previous cases<sup>11</sup>. There is a case report, which has been reported that aripiprazole addition lowers prolactin levels in symptomatic hyperprolactinemia associated with the use of oral paliperidone<sup>12</sup>. If the patient has significant benefits from antipsychotic treatment, it is suggested to continue the treatment by adding aripiprazole<sup>1</sup>. Our patient had treatment adherence issues and benefited significantly from paliperidone palmitate but hyperprolactinemia

and amenorrhea occurred, therefore we added aripiprazole 5 mg/day rather than decreasing or stopping the antipsychotic treatment based upon the data from literature. After adding aripiprazole to the treatment, prolactin levels decreased and the patient started to have menstruation again. To our knowledge, this is the first case which shows that aripiprazole can be used in treatment of paliperidone palmitate induced hyperprolactinemia and amenorrhea.

As a result, paliperidone palmitate can cause hyperprolactinemia and related side effects and this can decrease treatment compliance. If hyperprolactinemia occurs together with some symptoms like menstrual irregularity, clinicians should consider decreasing the dosage of paliperidone palmitate or adding aripiprazole to the treatment.

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