

# Prolongation of Hyperprolactinemia by Clozapine: A Case Report

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## ÖZET:

Klozapinle uzamış hiperprolaktinemi: Bir olgu sunumu

Antipsikotik ilaçların mesolimbik yolaktaki dopamin blokajı antipsikotik etkilerinden sorumluyken, tuberoinfundibuler yolaktaki D<sub>2</sub> reseptör antagonizması ise hiperprolaktinemiye sebep olur. Atipik antipsikotikler belirgin şekilde tipik antipsikotiklere göre daha az düzeyde prolaktin artışına sebep olurlar. Bunun sebebi; 5-HT<sub>2A</sub> serotonin reseptörlerine ayrıcalıklı olarak yüksek, D<sub>2</sub> reseptörlerine görece düşük afiniteleri olmasıdır. Klozapinin nigrostriatal ve tuberoinfundibuler dopamin reseptörleri üzerinde zayıf etkisi vardır. Buna bağlı olarak düşük oranda ekstrapiramidal yan etki oluşturduğu, tardif diskineziye yol açmadığı ve serum prolaktin düzeyini minimal oranda etkilediği bildirilmiştir. Bu yazıda amisülpiride bağlı ekstrapiramidal sistem (EPS) yan etkileri ve galaktore gelişiminin ardından amisülpirid kesilip, klozapin tedavisine geçilen ancak, klozapin tedavisi sonrası da galaktore devam eden bir bayan hasta sunulmuştur. Hastada klozapin tedavisinin kesilmesinin ardından prolaktin değerleri normale dönmüş, ancak psikotik semptomları tekrar alevlenmiştir. Bunun üzerine klozapine tekrar başlanmış ve tedaviye literatürde antipsikotiklere bağlı olarak gelişen hiperprolaktinemiyenin düzelmesinde etkili olduğu vurgulanan, bir parsiyel D<sub>2</sub> agonisti olan aripiprazol eklenmiştir. Bu kombinasyonla hastanın hem kliniği düzelmiş, hem de prolaktin değerleri normal sınırlar içinde seyretmiştir.

**Anahtar sözcükler:** hiperprolaktinemi, klozapin, parsiyel D<sub>2</sub> agonizm

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## ABSTRACT:

Prolongation of hyperprolactinemia by clozapine: a case report

Dopamine antagonism by antipsychotic drugs in the mesolimbic pathway leads to their therapeutic effect, while their D<sub>2</sub> receptor antagonism in the tuberoinfundibular pathway causes hyperprolactinemia. Atypical (second generation) antipsychotics cause a significantly smaller increase in PRL levels than typical antipsychotics. The main reason for this is that atypical antipsychotics have more affinity for serotonin 2A (5-HT<sub>2A</sub>) receptors than D<sub>2</sub> receptors. Clozapine has weak affinity for D<sub>2</sub> receptors in the nigrostriatal and tuberoinfundibular pathways. Thus, clozapine is accepted to have minimal extrapyramidal side effects, to not cause tardive dyskinesia and have little effect on serum prolactin levels. This is the report of a patient who developed galactorrhea and extrapyramidal side effects (EPS) due to amisulpiride but galactorrhea continued even after amisulpiride was switched to clozapine. The serum prolactin level was normalized after stopping clozapine treatment but her psychotic symptoms relapsed. Clozapine was started again but this time it was combined with aripiprazole, a partial D<sub>2</sub> agonist agent, which has been emphasized in the literature as a treatment for antipsychotic induced hyperprolactinemia. The patient's psychiatric symptoms disappeared and her serum prolactin level returned to normal after this combination treatment.

**Keywords:** hyperprolactinemia, clozapine, partial D<sub>2</sub> agonist

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## INTRODUCTION

Prolactin (PRL) is a pituitary hormone synthesized by lactotroph cells located in the anterior pituitary gland, whose release is inhibited

by dopamine<sup>1</sup>. Hyperprolactinemia is a frequent side effect of antipsychotic drugs<sup>2</sup>. Dopamine pathways, which are related to the therapeutic effects and side effects of antipsychotic drugs in the brain are the mesolimbic, mesocortical,

tuberoinfundibular, and nigrostriatal pathways<sup>5</sup>. Dopamine 2 (D<sub>2</sub>) receptor antagonism in the tuberoinfundibular pathway by antipsychotic drugs causes an increase in PRL levels<sup>3</sup>. It has been shown that PRL levels increase rapidly (minutes to hours) after usage of typical (first generation) antipsychotics<sup>4</sup>. Atypical (second generation) antipsychotics cause a significantly smaller increase in PRL levels than typical antipsychotics. The main reason for this is that atypical antipsychotics have more affinity for serotonin 2A (5-HT<sub>2A</sub>) receptors than D<sub>2</sub> receptors<sup>5</sup>. Among the atypical antipsychotics, those producing a greater increase in the levels of this hormone in blood are amisulpride, risperidone and its metabolite paliperidone<sup>4</sup>. Hyperprolactinemia (HP) may cause galactorrhea and menstrual disturbances in women, and gynecomastia and erectile dysfunction in men. Women are more sensitive to the HP effects of antipsychotics than men<sup>3,4</sup>. A total of 42-47% of men and 48-93% of premenopausal women diagnosed with schizophrenia who take conventional antipsychotic drugs will develop hyperprolactinemia<sup>2</sup>.

The only antipsychotic drug that does not cause HP is clozapine<sup>6</sup>. Clozapine has a mild effect on nigrostriatal and tuberoinfundibular D<sub>2</sub> receptors. Thus, it is reported that it has very low extrapyramidal side effects (EPS), it does not cause tardive dyskinesia, and its effect on serum PRL levels is minimal<sup>7</sup>. Clozapine attaches to D<sub>2</sub> receptors loosely and causes a transient low-level occupation of D<sub>2</sub> receptors, which has been proposed as the underlying mechanism for the low risk of HP and EPS caused by clozapine<sup>6</sup>.

In this case report, we present a schizophrenic female patient, with a history of HP after amisulpride treatment, whose HP was prolonged even after switching to clozapine, and whose PRL levels returned to normal after discontinuation of clozapine.

## CASE REPORT

The patient was a 29-year-old, high school graduate, divorced, mother of one child and

housewife. She was the first child of low income and poorly educated parents and had three siblings. She was married at the age of 18 and got pregnant after 7 months. The first symptoms of schizophrenia began during her pregnancy, including auditory hallucinations and disorganized speech and behavior related to these hallucinations. Despite these symptoms, neither the patient nor her family thought that this was a medical disease so she did not seek psychiatric treatment. After giving birth, she began to run away from home frequently, so she was unwillingly brought to a psychiatrist by her family. She was hospitalized in a psychiatric inpatient clinic for 45 days 3 years ago. She was given amisulpride 800mg/day and biperidene 4mg/day. After her discharge, she continued this treatment and did not have any positive symptoms of schizophrenia for almost 3 years. Negative symptoms (lack of interest, anhedonia, blunted affect) still continued during this time. Her galactorrhea began at this time, but she did not report this to her psychiatrist, since she thought it was normal. After three years, her auditory hallucinations returned. She had paranoid delusions that she was being followed by strangers who were trying to harm her. She was hospitalized for the second time. During this hospitalization, her galactorrhea was noticed by the treatment staff. They saw spots on her t-shirt and when she was asked about them, she reported that the spots were caused by the milk, which was coming out of her breast spontaneously. She thought this was normal since it had begun after giving birth. Her galactorrhea was confirmed by a physical examination. Her PRL level was found to be high (4640.68uIU/ml, normal range 102-496uIU/ml) and amisulpride was switched to clozapine. Despite this change in treatment regimen, her galactorrhea still continued.

The patient applied to our outpatient clinic at this time (almost 6 years after her schizophrenia had begun). She came with her mother, and her main complains were depressive symptoms such as anhedonia and depressive mood, as well as anxiety. She did not report any positive symptoms

of schizophrenia, but her affect was blunted and her speech was monotone. She reported that she had galactorrhea and menstrual disturbances, and she was hospitalized. Her blood screen was normal other than mild anemia (hemoglobin level 11.0g/dl, hematocrit level 33.7%) and mild elevation of alanine aminotransferase (36U/L). Her PRL level was 6117uIU/ml. A pituitary MRI (with contrast) was performed, which showed normal results. An endocrinology consultation was requested; it was thought that clozapine (she was receiving 300mg/day) was causing her HP, and it was recommended that clozapine be stopped. The clozapine dosage was decreased and finally it was stopped after 1 week. Her PRL level was checked again 3 days after clozapine was stopped (she was medication free during those 3 days), and it was normal (273.1uIU/ml). Clozapine was started at a very low dosage (100mg/day), and her PRL level increased again (647uIU/ml) after 5 days. It was decided that clozapine was causing prolongation of hyperprolactinemia in this patient, so it was switched to quetiapine. The dosage of quetiapine was slowly increased to 600mg/day. Her PRL level was checked twice after switching to quetiapine and it returned to almost normal levels (550.2uIU/ml), and her galactorrhea stopped.

After two weeks of quetiapine use, her hallucinations, delusions, disorganized behavior and speech, as well as her negativism and hostility

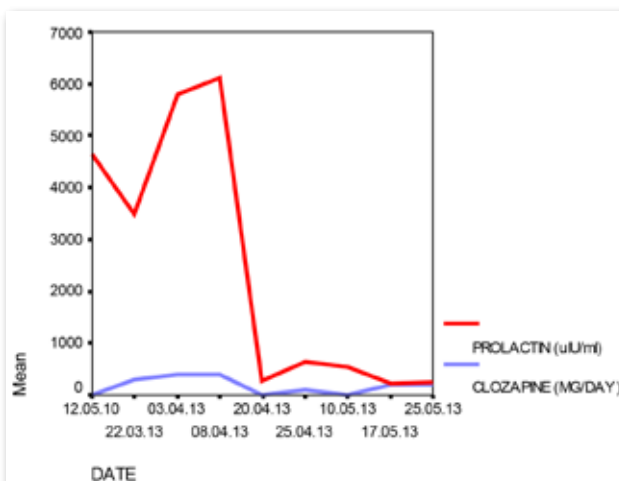
towards her family and clinical staff significantly increased. Because of this significant worsening of her symptoms, it was decided that quetiapine should be stopped. Clozapine was restarted (200mg/day) but this time, aripiprazole 10mg/day was added to her treatment regimen. Her PRL levels were checked twice and had returned to normal (212.8uIU/ml and 256.3uIU/ml respectively).

The fluctuations of PRL levels are shown in Figure 1.

## DISCUSSION

HP may cause many adverse events such as gynecomastia, galactorrhea, infertility, menstrual disturbances, oligomenorrhea, amenorrhea, decreased libido, sexual arousal difficulties, anorgasmia, hirsutism and acne. The risk for osteoporosis also increases. PRL also has immunomodulatory effects. It has also been proposed that HP may cause hostility, anxiety, and depression<sup>6</sup>.

Pharmacological HP is often under-diagnosed. This may be caused by the lack of externally observed symptoms, reluctance or shyness of the patients to talk about the symptoms, and/or lack of knowledge of the clinicians. Yet, pharmacological HP may be caused by many agents such as antipsychotics, antidepressants, buspirone, alprazolam, prokinetics, antihypertensive drugs, opioids, H<sub>2</sub> receptor antagonists, and chemotherapeutics<sup>3</sup>. Among these agents, antipsychotics are the most common drugs to cause HP, and most of the antipsychotics can cause it<sup>8</sup>. Antipsychotic induced HP is caused by the antagonism of D<sub>2</sub> receptors located in the anterior part of the pituitary gland<sup>9,10</sup>. HP effects of antipsychotics do not last long, since they can easily pass through the blood-brain barrier and their dissociation rate from the receptors is high<sup>11</sup>. Many of typical antipsychotics are potent antagonists of D<sub>2</sub> receptors, so they frequently cause HP. Atypical antipsychotics are generally low potency D<sub>2</sub> receptor antagonists, so an increase in PRL level during atypical antipsychotic usage is



**Figure 1: Fluctuations in patient's serum prolactin levels according to clozapine dosage. Aripiprazole 10 mg/day was added to clozapine treatment at 13.05.13**

usually mild and transient<sup>9</sup>. Among atypical antipsychotics, clozapine and quetiapine are the ones which have been reported to not to cause HP in therapeutic dosages<sup>12</sup>.

Clozapine has both dopaminergic and serotonergic antagonistic properties. It has been proposed that clozapine modulates HP at a supra-pituitary level, by regulating pre- and post-synaptic dopaminergic effects via its selective interactions with D<sub>1</sub>, D<sub>2</sub>, D<sub>4</sub> and 5-HT<sub>2A</sub> receptors. The lack of PRL increase following clozapine administration could be due to both the sparing of dopamine-mediated inhibition of PRL release and the direct stimulatory effect on tuberoinfundibular dopamine neurons<sup>3</sup>. It has even been reported that clozapine usage for 6 weeks decreased the risk of HP by 16-80%<sup>13</sup>.

We think that HP in our case was primarily caused by amisulpride. Amisulpride is one of the most HP-causing agents among atypical antipsychotics. It has even been shown that amisulpride causes significantly more HP than haloperidol in schizophrenic patients<sup>14</sup>. When a classification according to D<sub>2</sub> receptor blockage is made, haloperidol, risperidone, and amisulpride are "prolactin-raising" drugs, while olanzapine, clozapine, quetiapine, ziprasidone, and aripiprazole are called "prolactin-sparing" drugs<sup>4</sup>. This is the reason why we cannot assume that HP in this patient was caused by clozapine; however, we may say that HP and galactorrhea were prolonged by clozapine.

To our knowledge, this is the first reported case of prolongation of HP by clozapine in the literature. We think the possible reason for HP prolongation in this patient is clozapine since (1) we excluded pituitary adenoma as a possible cause of HP and galactorrhea (her pituitary MR was normal); (2) her PRL levels returned to normal 3 days after stopping clozapine; (3) PRL levels increased again after re-challenging with clozapine twice. It has been reported that in drug induced HP, PRL levels return to normal after 2-4 days of drug cessation. It would have been helpful to determine clozapine blood levels and /or if she is a slow metabolizer (i.e.CYP450 1A2 or CYP450 3A4)

but these blood tests can not be performed in our hospital (or any hospital nearby).

There are different management strategies of antipsychotic induced HP, including (a) decreasing the dosage of antipsychotic; (b) switching to a "prolactin-sparing" antipsychotic; (c) adding a partial dopamine agonist to the regimen; (d) estrogen replacement treatment for women with hypoestrogenemia<sup>4</sup>. Switching to clozapine among other "prolactin-sparing" antipsychotics is usually recommended after antipsychotic induced HP<sup>15</sup>. Adding or starting aripiprazole can be another management strategy, since it is the first potent D<sub>2</sub> partial agonist among antipsychotics. Aripiprazole is called a "dopamine regulator" since it acts as a D<sub>2</sub> antagonist in hyperdopaminergic, but as an agonist in hypodopaminergic conditions<sup>16</sup>. In relation to its partial agonism, it has been reported that this drug not only increases the serum levels of prolactin, but also corrects the hyperprolactinemia caused by other antipsychotics when added to them<sup>10</sup>. Recent case series report that aripiprazole could reverse the PRL increase and secondary galactorrhea caused by atypical antipsychotics<sup>17,18</sup>. In a meta-analysis of 639 patients with antipsychotic induced HP (326 patients received aripiprazole as an add-on therapy, while 313 patients received placebo), it was reported that 79.1% of the patients' prolactin levels have returned to normal after adding aripiprazole. In the same meta-analysis, aripiprazole and placebo patients did not show any significant differences with regard to side effects such as insomnia, headache, sedation, extrapyramidal symptoms, dry mouth, and fatigue. It was concluded that adding aripiprazole to patients with antipsychotic induced hyperprolactinemia is both effective and safe<sup>19</sup>. The prolactin-lowering effect of aripiprazole is likely due to its unique pharmacology as a D<sub>2</sub> receptor partial agonist. With haloperidol or risperidone treatment, antagonist activity at D<sub>2</sub> receptors at the tuberoinfundibular system region reduces dopamine activity, increasing the risk of hyperprolactinemia. In contrast, aripiprazole may act as a dopamine agonist in conditions of low

endogenous dopamine activity, which prevents the development of hypodopaminergia in the tuberoinfundibular system region, thereby decreasing the serum prolactin level<sup>20</sup>.

Our case report adds further evidence to the positive effect of adding aripiprazole to patients with antipsychotic induced HP, since her prolactin

levels returned to normal after adding aripiprazole to clozapine treatment. We believe that this case report reminds us to be aware of the possibility of HP even with the so called “prolactin-sparing” antipsychotic drugs, and to ask the patients about HP symptoms even if they do not report them spontaneously.

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