

Hyperprolactinemia and Secondary Amenorrhea as Dose-Dependent Adverse Effects of Olanzapine in an Adolescent with Bipolar Affective Disorder

Bipolar Afektif Bozukluk Tanılı Bir Ergende Olanzapinin Doz Bağımlı Yan Etkisi Olarak Hiperprolaktinemi ve İkincil Amenore

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ABSTRACT

Olanzapine, a second-generation antipsychotic, can cause prolactin elevation due to its antidopaminergic effects. While considered to have a relatively low-risk of significant hyperprolactinemia among second-generation antipsychotics, some studies report prolactin increases with olanzapine, though clinical symptoms like amenorrhea and galactorrhea are rarely documented. In this case, a female adolescent on long-term olanzapine for bipolar disorder experienced worsening psychosis, leading to increased dosage. Ten weeks after escalating to 20 mg/day, she developed secondary amenorrhea and elevated prolactin at 38.7 µg/L. Reducing the dose to 10 mg/day normalized prolactin levels and resumed menstruation within four weeks. What makes this case noteworthy is that, while hyperprolactinemia related to olanzapine is rarely reported in adolescents, the occurrence of secondary amenorrhea as a clinical symptom appears to be, to our knowledge, undocumented in the literature.

Keywords: Hyperprolactinemia, secondary amenorrhea, olanzapine

ÖZ

Olanzapin, ikinci kuşak bir antipsikotiktir ve dopamin antagonizması nedeniyle prolaktin seviyelerinin yükselmesine neden olabilir. İkinci kuşak antipsikotiklerde belirgin hiperprolaktinemi riskinin görece düşük olduğu düşünülse de, bazı çalışmalar olanzapin ile olan prolaktin artışlarını bildirmektedir. Ancak olanzapin kullanımına bağlı klinik semptomlar olan amenore ve galaktore nadiren bildirilmiştir. Bu olguda, bipolar bozukluk tanısıyla uzun süredir olanzapin tedavisi alan bir kız ergenin, psikotik belirtileri nedeniyle olanzapin dozu 20 mg/gün'e yükseltildikten on hafta sonra, ikincil amenore gelişmiş ve prolaktin düzeyi 38,7 µg/L saptanmıştır. Olanzapin dozunun 10 mg/gün'e düşürüldükten dört hafta içinde prolaktin seviyeleri normale dönmüş ve menstruasyon yeniden başlamıştır. Bu olgunun dikkat çekici yönü, olanzapinle ilişkili hiperprolaktinemi olgularının adolesanlarda nadiren bildirilmesinin yanında, olanzapinle ilişkili ikincil amenorenin bildiğimiz kadarıyla literatürde ergenlerde daha önce bildirilmemiş olmasıdır.

Anahtar Kelimeler: Hiperprolaktinemi, ikincil amenore, olanzapin

Introduction

Olanzapine is a second-generation antipsychotic that also has mood-stabilizing effects, making it suitable for the treatment of bipolar affective disorder.¹ It is known that second-generation antipsychotics (except risperidone) generally cause less hyperprolactinemia compared to first-generation antipsychotics.² Antipsychotic-induced hyperprolactinemia is commonly observed in adolescents. It is also known that children and adolescents are more sensitive to hyperprolactinemia compared to adults.³

Several studies in the literature report that olanzapine induces moderate hyperprolactinemia.² Conversely, some studies, albeit a limited number, indicate that olanzapine may lead to a decrease in prolactin levels.⁴ There is a study indicating that olanzapine can cause hyperprolactinemia in children and adolescents, particularly during the first month of treatment, with tolerance developing thereafter. However, this study did not examine whether the hyperprolactinemia is dose-dependent.⁵ In another study, a correlation was found between plasma concentrations of olanzapine and prolactin levels in children with psychotic disorders, and galactorrhea was reported in girls experiencing

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olanzapine-induced hyperprolactinemia. However, although galactorrhea was reported as an adverse effect in this study, amenorrhea was not documented.⁶

Although few studies have identified a relationship between serum olanzapine and prolactin levels in children and adolescents,^{5,6} there is no evidence in the literature regarding secondary amenorrhea as a dose-dependent side effect of olanzapine in adolescents. We believe that this case report may be beneficial for clinicians in terms of dose adjustment and long-term side effect monitoring during olanzapine treatment in adolescents. The CARE guidelines were followed in this case report, and adherence to national ethical guidelines for case reports was also maintained.

Case Report

A 14-year-old adolescent girl with a history of dysthymia until one year prior was diagnosed with bipolar affective disorder following an evident manic episode. The patient's mood has become elevated, her self-esteem has increased excessively, her sleep duration has decreased, and her goal-directed activity has increased. She has also argued with friends and teachers at school in a manner completely unlike her usual behavior. According to DSM-5 criteria, she was diagnosed with bipolar disorder.⁷ She was started on olanzapine 5 mg/day, and her affective symptoms improved after treatment. The patient remained on this dose for 15 months without experiencing any new affective episodes.

Subsequently, the patient developed a contemplative affect, social withdrawal, and a stooped posture. Auditory hallucinations were reported, and her affect was characterized by mild blunting. There was no mood depression or elevation. During the catatonia assessment, no positive symptoms were observed except for ambitendency. Due to over a month of blunted mood, paranoid and nihilistic delusions, and auditory hallucinations, it was determined that the patient met the DSM-5 criteria for schizophreniform disorder, and a provisional diagnosis was made.⁷ The final diagnosis is planned to be based on the course of symptoms during follow-up. The olanzapine dose was increased to 10 mg/day.

One month later, her auditory hallucinations had improved, but her suspiciousness persisted, and the olanzapine dose was increased to 15 mg/day. Although treatment continued at this dose for two months, olanzapine dose was increased to 20 mg/day due to persistent symptoms including speaking in a hushed

voice, maintaining a stooped posture, and delusional beliefs such as thinking that a family member had died. At the one-month follow-up, it was observed that the patient no longer experienced auditory hallucinations at this medication dose, the affective blunting had diminished, suspiciousness had resolved, and she was able to attend school. However, she still continued to speak in a hushed voice and maintain a stooped posture.

Approximately two and a half months later, she presented with menstrual delay of one month. Blood serum prolactin level measured 12 hours after the last medication dose was found to be 38.7 µg/L. She exhibited no galactorrhea or other side effects aside from slight sedation during the day. Neurological examination showed only mild bradykinesia with no other positive findings. The olanzapine dose was reduced to 10 mg/day; after one month, she experienced no new affective or psychotic symptoms, her motor speed normalized, and serum prolactin level was rechecked at 13 µg/L. She reported that her menstrual cycle had resumed two days ago. The brief summary of the case is shown in Table 1. Written consent has been obtained from both the patient and the parent for the publication of the case report.

Discussion

Mechanistic Insights

This case report describes a dose-dependent development of hyperprolactinemia during olanzapine treatment, with clinical manifestation as secondary amenorrhea. Ten weeks after increasing the olanzapine dose to 20 mg/day, the patient experienced secondary amenorrhea and elevated prolactin levels. When the dosage was reduced to 10 mg/day, prolactin levels normalized within four weeks, and menstruation resumed.

Dopamine released from the hypothalamus reaches the anterior pituitary via portal vessels, where it binds to D2 receptors and inhibits prolactin secretion. Antipsychotics cause hyperprolactinemia by blocking dopamine. Potent D2 antagonism, as seen with typical antipsychotics, results in greater hyperprolactinemia. Additionally, differences in the duration of D2 receptor occupancy and the rate of receptor dissociation contribute to the variability among antipsychotics in causing hyperprolactinemia. Serotonin also plays an indirect role in inhibiting tuberoinfundibular dopaminergic neurons; antagonism of 5HT2 receptors in atypical antipsychotics generally leads to less hyperprolactinemia.^{8,9}

Table 1. Psychiatric symptoms, olanzapine doses, and prolactin levels

Age: 14	15 months later	1 month later	2 months later	1 month later	2.5 months later	1 month later
- BD diagnosed. - Olanzapine 5 mg/day.	- Psychotic symptoms added. - Olanzapine 10 mg/day.	- Hallucinations improving, delusions persist. - Olanzapine 15 mg/day.	- Delusions persist. - Olanzapine 20 mg/day.	- Psychotic symptoms decreasing. - Olanzapine 20 mg/day.	- Menstruation delayed. - Serum PRL: 38.7 µg/L. - Olanzapine reduced to 10 mg/day.	- Menstruation resumes. - Serum PRL: 13 µg/L. - No new psychotic/affective symptoms.

BD: Bipolar disorder, PRL: Prolactin

Comparison with Literature

The literature generally suggests that olanzapine causes moderate prolactin elevations, and while hyperprolactinemia has been reported in some cases, clinical adverse effects such as galactorrhea or amenorrhea are rarely documented.⁶ Some studies even indicate that olanzapine can decrease prolactin levels. Switching from other antipsychotics such as risperidone or haloperidol to olanzapine has been associated with reductions in prolactin.^{2,4} Additionally, research shows that hyperprolactinemia related to olanzapine tends to be more common in the initial months after starting treatment, with prolactin levels decreasing over the first year.⁵

Some studies report that the hyperprolactinemic effect of olanzapine is dose-dependent, whereas others find no such relationship.^{10,11} In this case, the onset of amenorrhea and hyperprolactinemia ten weeks after dose escalation, followed by symptom resolution upon dose reduction and normalization of prolactin levels, aligns with existing literature regarding dose and duration effects. While olanzapine generally causes less prolactin increase compared to other second-generation antipsychotics like risperidone and ziprasidone,^{2,12} it still can induce hyperprolactinemia—albeit less frequently than some agents, but more than aripiprazole.¹³

Regarding the use of atypical antipsychotics in children and adolescents, guidelines vary: some do not recommend routine prolactin screening unless symptoms are present,¹⁴ while others suggest measuring PRL levels before treatment, at the third month, and then every six months thereafter.¹⁵ Based on this case, especially when olanzapine is used at high doses in adolescents, it would be beneficial for the patient's care to include clinical assessments for signs such as galactorrhea and amenorrhea during routine examinations. Additionally, monitoring prolactin levels at specified intervals can help in early detection and management of hyperprolactinemia.

The patient's psychiatric symptoms were initially diagnosed as bipolar disorder according to DSM-5 criteria, followed by the emergence of schizophrenia symptoms without affective episodes, which were then classified as schizophreniform disorder. However, the definitive diagnosis will be established after long-term follow-up. It is also important to note that because the primary focus of this case was olanzapine-induced amenorrhea, the differential diagnosis for psychiatric conditions was kept brief, which can be considered a limitation. Additionally, the absence of blood tests for other hormones such as follicle-stimulating hormone, luteinizing hormone, and estradiol—which could be related to prolactin levels—represents another limitation of this case report.

Olanzapine, although generally prolactin-sparing, may cause clinically significant, dose-dependent hyperprolactinemia and secondary amenorrhea in adolescents. Further research is needed to better understand the short- and long-term effects of olanzapine on sexual function and reproductive health.

Ethics

Informed Consent: Written consent has been obtained from both the patient and the parent for the publication of the case report.

Footnotes

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References

1. Narasimhan M, Bruce TO, Masand P. Review of olanzapine in the management of bipolar disorders. *Neuropsychiatr Dis Treat*. 2007;3:579-587.
2. David SR, Taylor CC, Kinon BJ, Breier A. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clin Ther*. 2000;22:1085-1096.
3. Krøigaard SM, Clemmensen L, Tarp S, Pagsberg AK. A meta-analysis of antipsychotic-induced hypo- and hyperprolactinemia in children and adolescents. *J Child Adolesc Psychopharmacol*. 2022;32:374-389.
4. Volavka J, Czobor P, Cooper TB, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Lieberman JA. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiatry*. 2004;65:57-61.
5. Migliardi G, Spina E, D'Arrigo C, Gagliano A, Germanò E, Siracusano R, Diaz FJ, de Leon J. Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:1496-1501.
6. Alfaro CL, Wudarsky M, Nicolson R, Gochman P, Sporn A, Lenane M, Rapoport JL. Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. *J Child Adolesc Psychopharmacol*. 2002;12:83-91.
7. APA (American Psychiatric Association). *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
8. Stojkovic M, Radmanovic B, Jovanovic M, Janjic V, Muric N, Ristic DI. Risperidone induced hyperprolactinemia: from basic to clinical studies. *Front Psychiatry*. 2022;13:874705.
9. Tewksbury A, Olander A. Management of antipsychotic-induced hyperprolactinemia. *Ment Health Clin*. 2016;6:185-190.
10. Karagianis JL, Baksh A. High-dose olanzapine and prolactin levels. *J Clin Psychiatry*. 2003;64:1192-1194.
11. Citrome L, Stauffer VL, Chen L, Kinon BJ, Kurtz DL, Jacobson JG, Bergstrom RE. Olanzapine plasma concentrations after treatment with 10, 20, and 40 mg/d in patients with schizophrenia: an analysis of correlations with efficacy, weight gain, and prolactin concentration. *J Clin Psychopharmacol*. 2009;29:278-283.
12. Wu XL, Wang JH, Hu SH, Tao J. Serum prolactin levels and the acute-phase efficacy in drug-naïve schizophrenia treated with ziprasidone and olanzapine (translated version). *East Asian Arch Psychiatry*. 2012;22:7-11.
13. Byerly MJ, Marcus RN, Tran QV, Eudicone JM, Whitehead R, Baker RA. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomized, open-label study. *Schizophr Res*. 2009;107:218-222.
14. American Academy of Child and Adolescent Psychiatry. Practice parameter for the use of atypical antipsychotic medications in children and adolescents. 2011.
15. National Collaborating Centre for Mental Health (Great Britain). *Psychosis and schizophrenia in children and young people: recognition and management*. London: National Institute for Health and Care Excellence; 2013.