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Case Report

Zuclopenthixol-related Perioral Dermatitis: Treatment Challenges in the Triad of Autism Spectrum Disorder, Attention Deficit/Hyperactivity Disorder, and Conduct Disorder

Zuklopentiksol Kullanımı Sonrası Perioral Dermatit: Otizm Spektrum Bozukluğu, Dikkat Eksikliği/Hiperaktivite Bozukluğu ve Davranım Bozukluğu Üçgeninde Tedavi Zorlukları

Elif Gözde YÜCE ANTEPÜZÜMÜ, Dilek ALTUN VARMIŞ, Serkan GÜNEŞ

Clinic of of Child and Adolescent Psychiatry, University of Health Sciences Türkiye, Adana City Training and Research Hospital, Adana, Türkiye

ABSTRACT

A 12-year-old boy with autism spectrum disorder, attention deficit/hyperactivity disorder, and conduct disorder developed perioral rash after zuclopenthixol injection in addition to olanzapine and guanfacine treatment. The onset of rash within 48 hours after the injection may suggest a clear relationship in terms of timing. Also, the Naranjo score of 6 may support that zuclopenthixol is the probable reason for this adverse reaction. The rapid regression after discontinuation of the drug may further reinforce the specificity of this relation.

Keywords: Zuclopenthixol, perioral dermatitis, antipsychotic side effects, autism spectrum disorder, adverse drug reaction, pharmacovigilance

ÖZ

Bu olgu sunumunda otizm spektrum bozukluğu, dikkat eksikliği/hiperaktivite bozukluğu ve davranım bozukluğu tanılarıyla takip edilen 12 yaşındaki erkek hastada olanzapin ve guanfasin tedavisine ek olarak uygulanan zuklopentiksol dekanoat enjeksiyonu sonrası gelişen perioral dermatit olgusu ele alınmaktadır. Enjeksiyondan sonraki 48 saat içinde döküntülerin başlaması, zamanlama açısından belirgin bir ilişkiyi düşündürmektedir. Ayrıca, uygulanan Naranjo skorunun 6 olması, zuklopentiksolün bu reaksiyona neden olma olasılığını güçlü bir şekilde desteklemektedir. İlacın kesilmesiyle döküntünün hızla gerilemesi ise bu ilişkinin spesifikliğini daha da pekiştirmektedir.

Anahtar Kelimeler: Zuklopentiksol, perioral dermatit, antipsikotik yan etkileri, otizm spektrum bozukluğu, advers ilaç reaksiyonu, farmakovijilans

INTRODUCTION

Autism spectrum disorder (ASD) is a complex, lifelong neurodevelopmental disorder characterized by persistent deficits in social communication and repetitive behavioral patterns (1). Current epidemiological data report that one in every 31 children has ASD (2). ASD frequently coexists with various psychiatric conditions, such as attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), intellectual disability, and anxiety disorders (3).

Although the basic treatment approach for ASD is individualized special education, pharmacotherapy is frequently employed in the presence of comorbid disorders, especially ADHD and CD. In clinical practice, methylphenidate, atomoxetine, and guanfacine are commonly used to manage ADHD symptoms. For comorbid CD or pronounced behavioral dysregulation, second-generation and typical antipsychotics, including risperidone, aripiprazole, olanzapine, and haloperidol, may be introduced. Combined pharmacotherapy may also be considered in complex cases (4-6).

Olanzapine is an atypical antipsychotic that exerts antagonistic effects on dopamine (D2) and serotonin (5HT2A, 5HT2C) receptors (5). It has demonstrated clinical efficacy in managing symptoms associated with

Address for Correspondence: Elif Gözde Yüce Antepüzümü, Clinic of of Child and Adolescent Psychiatry, University of Health Sciences Türkiye, Adana City Training and Research Hospital, Adana, Türkiye
E-mail: elifntpzm@gmail.com **ORCID ID:** orcid.org/0009-0008-3204-5568
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non-schizophrenic psychotic disorders, impulse control disorders, CD, and ASD.

Guanfacine acts by stimulating presynaptic alpha-2 adrenergic receptors in the central nervous system (6). This effect contributes to the relief of behavioral symptoms such as hyperactivity and aggression by increasing attention and impulse control and can be used alone or in combination treatments (4-6).

Zuclopenthixol is a typical antipsychotic with high affinity for dopamine D1 and D2 receptors. Although it carries the risk of extrapyramidal side effects like other typical antipsychotics, it can be preferred in some cases due to its long-acting decanoate formulation. The intramuscular decanoate formulation reaches peak plasma concentrations within 3 to 7 days and has an elimination half-life of approximately 19 days. It is commonly utilized in the management of severe aggression, particularly in individuals with CD (7).

In this paper, we present a rare adverse event that has not been previously reported in the current literature: a perioral dermatitis, which developed after the administration of zuclopenthixol decanoate on ongoing olanzapine and guanfacine treatment.

CASE REPORT

The focus of this presentation is a 12-year-old boy who was followed up in our outpatient clinic with the diagnoses of ASD, ADHD, and CD. The patient's anamnesis indicated that despite receiving risperidone and atomoxetine treatment for seven years, his behavioral problems and hyperactivity continued. He tended toward aggressive behaviors directed at family members, special education staff, and peers. The childhood autism rating scale score was 51, and the problem behavior checklist score was 107. Guanfacine and olanzapine treatments were gradually started. The patient used guanfacine 3 mg/day and olanzapine 10 mg/day for the last two months and had no side effects. However, the treatment dose was increased to guanfacine 4 mg/day and olanzapine 15 mg/day due to the continuation of behaviors like not obeying the rules at school, being constantly on the move, and harming everything and everyone around him. Since the dose increment was not very beneficial, an intramuscular injection of 200 mg zuclopenthixol decanoate was applied in addition to the current treatment.

Forty-eight hours after the injection, the patient came to our clinic with rashes around the mouth (Figure 1. A). Physical examination revealed elevated, crusted, and painless skin lesions localized around the mouth. The child did not have habits such as putting foreign objects in the mouth or touching/licking the oral area. There was no previous history of a similar lesion, and no similar condition was observed in any other family members that would suggest a contagious infection. Additionally, there was no use of a different medication and no change in the patient's diet or daily life routine.

The patient was referred to the pediatrics and dermatology departments for detailed examination and evaluation. The dermatology clinic diagnosed the rashes as perioral dermatitis, with no evidence of infectious or systemic etiology, suggesting a possible drug-related reaction (Figure 1. B). In laboratory tests, hemogram and biochemical parameters were found to be within normal limits. Local cortisone treatment was started for the lesions.

The patient continued to use guanfacine 4 mg/day and olanzapine 15 mg/day since he benefited from these doses during the regression of perioral dermatitis. The local cortisone treatment was applied for two weeks, and the lesions around the mouth completely resolved (Figure 1. C). Due to complaints of insomnia and agitation reported during clinical interviews, the olanzapine dosage was increased to 20 mg/day, and perioral dermatitis did not recur during the follow-up.

DISCUSSION

Antipsychotic medications can lead to various adverse cutaneous reactions. These reactions may range a wide spectrum from benign lesions, such as eczema, erythema, pigmentation, photosensitivity, urticaria, and pruritus, to serious conditions like life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis (8). Possible mechanisms of these dermatological reactions include immunomodulation, accumulation of toxic metabolites, and photosensitization (8). Also, the increase in prolactin levels may stimulate sebum production and exacerbate cutaneous reactions (9,10). On the other hand, thioxanthene-based antipsychotics, especially zuclopenthixol, have the potential to predispose to phototoxic reactions (11).

In the present case, erythematous, scaly lesions were observed in the perioral region, and the lesions were accompanied by subjective symptoms such as itching. Although the pathogenesis of this reaction has not been fully elucidated, the immunomodulatory effects of antipsychotics may play an important role. Antipsychotics can trigger inflammatory

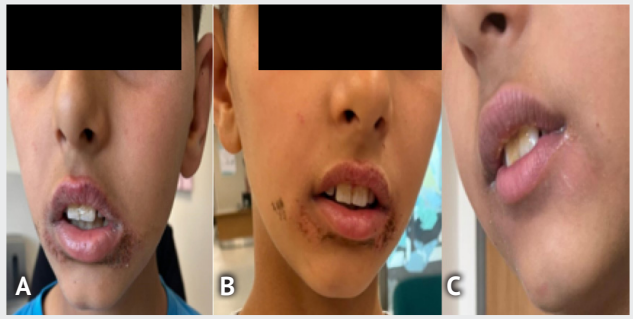

Figure 1. The occurrence and regression of perioral dermatitis after zuclopenthixol decanoate injection in a 12-year-old boy A) 2 days after the injection, B) 5 days after the injection, C) Lessions resolved in 2 weeks

Table 1. Naranjo adverse drug reaction scale

No.	Question	Response	Score
1.	Are there previous conclusive reports on this reaction?	Not known or not done	0
2.	Did adverse event appear after the suspected drug was given?	Yes	2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	1
4.	Did the adverse reaction appear when the drug was readministered?	Not known or not done	0
5.	Are there alternative causes that could have caused the reaction?	No	2
6.	Did the reaction reappear when a placebo was given?	Not known or not done	0
7.	Was the drug detected in any body fluid in toxic concentrations?	Not known or not done	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Not known or not done	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Not known or not done	0
10.	Was the adverse event confirmed by any objective evidence?	Yes	1
	Total score		**6**

Scoring: >9 = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR; 0 = doubtful ADR
ADR: Adverse drug reactions

responses by changing the cytokine balance (12). Similar mechanisms have been described, particularly with beta-lactam antibiotics and some anticonvulsants, suggesting that non-drug-specific immune-mediated dermatological side effects may occur (13). Additionally, zuclopenthixol may contribute to the pathophysiological process by disrupting epidermal barrier function or increasing neurogenic inflammation through dopaminergic effects (14,15).

In our case, the dermatitis occurred only two days after the zuclopenthixol injection, suggesting a drug-induced hypersensitivity reaction. The naranjo scale was 6 for zuclopenthixol, supporting the probability of drug-relatedness (Table 1). The patient was using olanzapine and guanfacine simultaneously, and drug interactions might also trigger this dermatological side effect. The potent M3 muscarinic antagonism of olanzapine (5) may impair stratum corneum hydration in the perioral region by suppressing sweat and sebum production. This pharmacological effect may predispose to the development of perioral dermatitis, which is particularly prone to transepidermal water loss (16). Moreover, the weakening of the skin barrier may be further enhanced by guanfacine's reduction of local tissue perfusion via α2A adrenergic receptors (17).

In this case, perioral dermatitis completely regressed after zuclopenthixol was discontinued, and the findings did not recur despite the olanzapine dose being increased. This may show that the dermatitis was primarily due to zuclopenthixol. On the other hand, dermatitis associated with olanzapine has been reported in the literature (18); it is seen that olanzapine alone did not cause a similar side effect in this patient. There are examples that synergistic adverse effects can occur, especially in the combination of antipsychotics with other psychotropic drugs (19). This may support that the dermatitis in our case may be due to a possible synergistic effect between olanzapine and zuclopenthixol. The combination of D2 receptor blockade by zuclopenthixol and the anticholinergic properties of olanzapine may have triggered a localized skin inflammation (5,7). The metabolism of both drugs via the CYP2D6 enzyme system may also bring an interaction at the pharmacokinetic level to the agenda (7).

While olanzapine has been frequently associated with cutaneous adverse drug reactions, including serious manifestations such as DRESS syndrome (20), dermatological complications from zuclopenthixol are infrequently described.

CONCLUSION

We present a rare case of perioral dermatitis related to zuclopenthixol decanoate injection. In clinical practice, when similar dermatological findings are encountered, possible side effects related to antipsychotic drugs should be taken into consideration, and the treatment plan should be revised if necessary. It should be remembered that drug interactions may pose a risk in combination treatments. New case reports and comprehensive pharmacovigilance studies are needed for a better understanding and management of such reactions.

Ethics

Informed Consent: Written assent from the patient and consent from his parents/guardians were received for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: E.G.Y.A., D.A.V., S.G., Concept: D.A.V., Design: D.A.V., S.G., Data Collection or Processing: E.G.Y.A., Analysis or Interpretation: S.G., Literature Search: E.G.Y.A., Writing: E.G.Y.A.

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REFERENCES

1. American Psychiatric Association Diagnostic and statistical manual of mental disorders, (DSM 5). American Psychiatric Association. 2013.
2. Shaw KA, Williams S, Patrick ME, Lee LC, Maenner MJ, Dietz PM, et al. Prevalence and early identification of autism spectrum disorder among children aged 4 and 8 years - autism and developmental disabilities monitoring network, 16 sites, United States, 2022. MMWR Surveill Summ. 2025;74(2):1-22.
3. Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet. 2014;383(9920):896-910. doi: 10.1016/S0140-6736(13)61539-1. Epub 2013 Sep 26.
4. Iffland M, Livingstone N, Jorgensen M, Hazell P, Gillies D. Pharmacological intervention for irritability, aggression, and self-injury in autism spectrum disorder (ASD). Cochrane Database Syst Rev. 2023;10(10):CD01176.
5. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F, Di Pace C, et al. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 2014;13:1163-91.
6. Mechler K, Banaschewski T, Hohmann S, Häge A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. Pharmacol Ther. 2022;230:107940. doi: 10.1016/j.pharmthera.2021.107940. Epub 2021 Jun 23.
7. Correll CU, Kim E, Sliwa JK, Hamm W, Gopal S, Mathews M, et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. CNS Drugs. 2021;35(1):39-59. doi: 10.1007/s40263-020-00779-5. Epub 2021 Jan 28. Erratum in: CNS Drugs. 2025;39(1):111-2. doi: 10.1007/s40263-024-01138-4.
8. Mitkov MV, Trowbridge RM, Lockshin BN, Caplan JP. Dermatologic side effects of psychotropic medications. Psychosomatics. 2014;55(1):1-20. doi: 10.1016/j.psym.2013.07.003.
9. Kim S, Jeong JH, Um YH, Kim TW, Seo HJ, Hong SC. Prolactin level changes according to atypical antipsychotics use: a study based on clinical data warehouse. Clin Psychopharmacol Neurosci. 2023;21(4):769-77. doi:10.9758/cpn.23.1057.
10. Langan EA, Hinde E, Paus R. Prolactin as a candidate sebotrop(h)ic hormone? Exp Dermatol. 2018;27(7):729-36. doi: 10.1111/exd.13545.
11. Eberlein-König B, Bindl A, Przybilla B. Phototoxic properties of neuroleptic drugs. Dermatology. 1997;194(2):131-5. doi: 10.1159/000246080.
12. Marcinowicz P, Więdłocha M, Zborowska N, Dębowska W, Podwalski P, Misiak B, et al. A meta-analysis of the influence of antipsychotics on cytokines levels in first episode psychosis. J Clin Med. 2021;10(11):2488. doi: 10.3390/jcm10112488.
13. Kaplan AP. Drug-induced skin disease. J Allergy Clin Immunol. 1984;74(4 Pt 2):573-9. doi: 10.1016/0091-6749(84)90109-x.
14. Fuziwara S, Suzuki A, Inoue K, Denda M. Dopamine D2-like receptor agonists accelerate barrier repair and inhibit the epidermal hyperplasia induced by barrier disruption. J Invest Dermatol. 2005;125(4):783-9. doi: 10.1111/j.0022-202X.2005.23873.x.
15. Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. J Invest Dermatol. 2006;126(8):1697-704. doi: 10.1038/sj.jid.5700104.
16. Elias PM, Wakefield JS, Man MQ. Moisturizers versus current and next-generation barrier repair therapy for the management of atopic dermatitis. Skin Pharmacol Physiol. 2019;32(1):1-7. doi: 10.1159/000493641.
17. Honda M, Suzuki M, Nakayama K, Ishikawa T. Role of alpha2C-adrenoceptors in the reduction of skin blood flow induced by local cooling in mice. Br J Pharmacol. 2007;152(1):91-100. doi: 10.1038/sj.bjp.0707380. Epub 2007 Jul 9.
18. Shenefelt PD. Psychodermatological disorders: recognition and treatment. Int J Dermatol. 2011;50(11):1309-322. doi: 10.1111/j.1365-4632.2011.05096.x.
19. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2014;10(5):721-46. doi: 10.1517/17425255.2014.885504.
20. Stirton H, Shear NH, Dodiuk-Gad RP. Drug reaction with eosinophilia and systemic symptoms (DReSS)/drug-induced hypersensitivity syndrome (DiHS)-readdressing the dress. Biomedicines. 2022;10(5):999. doi: 10.3390/biomedicines10050999.