NÖRO PSİKİYATRİ ARŞİVİ

Case Report / Olgu Sunumu

Arch Neuropsychiatr 2016; 53: 84-85 • DOI: 10.5152/npa.2015.9855

Leukocytosis after Clozapine Treatment in a Patient with Chronic Schizophrenia

Klozapin Tedavisi Sonrası Gelişen Lökositoz Olgusu

Aslıhan POLAT[1], Uğur ÇAKIR[2], Nermin GÜNDÜZ[1]

[1]Department of Psychiatry, Kocaeli University School of Medicine, Kocaeli, Turkey
[2]Department of Psychiatry, Abant İzzet Baysal University School of Medicine, Bolu, Turkey

ABSTRACT

Clozapine is an atypical antipsychotic drug that is approved by the US Food and Drug Administration (FDA) for the treatment of psychotic disorders. Agranulocytosis is a well-established side effect of clozapine; clozapine has also been associated with other blood dyscrasias like leukocytosis, albeit rarely. In this paper, we aim to report a case of possible clozapine-associated leukocytosis in a 41-year-old woman.

Keywords: Antipsychotics, hematological, clozapine, leukocytosis

ÖZ

Klozapin psikotik bozuklukların tedavisinde FDA (US Food and Drug Administration) onayına sahip bir antipsikotiktir. Klozapinin agranülositoza yol açabileceği çok iyi bilinmekle birlikte çok nadir olarak lökositoz gibi kan diskrazilerine de sebep olabilmektedir. Bu çalışmada yazarlar tarafından, klozapine bağlı geliştiği düşünülen lökositozu mevcut olan 41 yaşındaki bir olgunun paylaşılması amaçlanmıştır.

Anahtar kelimeler: Antipsikotik, hematolojik, klozapin, lökositoz

INTRODUCTION

Clozapine is an atypical antipsychotic drug that achieves therapeutic efficacy through serotonin-dopamine antagonism. It has been approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia, schizoaffective disorder, and for reducing the risk of suicidal behavior (1). Hematologic side effects, such as agranulocytosis and neutropenia, necessitate white blood cell (WBC) monitoring; this has been a long-standing barrier to the use of clozapine. Initially there was concern that clozapine caused leukopenia at a rate of 2.8% and agranulocytosis at a rate of 1–2% (2). In a registered study conducted amongst 99,502 patients between the years of 1990–1994, agranulocytosis and leukopenia incidence were reported as 0.38% (382 patients) and 2.95% (2931 patients), respectively (2). Following this study, the FDA decreased the frequency of monitoring WBC count to a biweekly schedule after six months of treatment. A few case reports have indicated that clozapine may be associated with blood dyscrasias other than leukocytosis and agranulocytosis, such as leukocytosis (3). This article aims to report a possible association between clozapine and leukocytosis, in the context of current literature.

CASE

Our patient is a 41-year-old woman with a diagnosis of paranoid type schizophrenia since the age of 12. She has a history of numerous hospitalizations and substantial treatment with conservative antipsychotics. Despite being treated with atypical antipsychotics, she has never achieved full remission. We assumed that she might have treatment-resistant schizophrenia and accordingly commenced treatment with clozapine. At that point, her WBC count was 8.6×10^9/L. Remission was achieved with 450 mg/day of clozapine. Following hospital discharge, the patient and her family were informed of routine hemogram controls, and a hemogram-monitoring calendar was planned. WBC count on the 8th and 16th day of treatment was 11.9×10^9/L and 14.100×10^9/L, respectively. At this point, the patient was referred to the Department of Hematology. Because the peripheral blood screening revealed normal cellular morphology, they did not recommend bone marrow aspiration. Urinary culture and pulmonary x-ray, which were performed following consultation with the Department of Infectious Diseases, did not reveal any pathology. The echocardiography and neurological examination results were also normal. Ultrasonographic examination (by a gynecologist) results were within the normal range. On the 25th day of treatment, WBC and thrombocyte counts were 24.3×10^9/L and 615×10^9/L, respectively. However, no general medical condition to explain the leukocytosis was found. Finally, the leukocytosis was linked to clozapine, and the treatment was stopped as per her family's request, despite there being no medical contraindication. After two weeks from starting haloperidol and zuclopenthixol decanoate, WBC count normalized. Unfortunately, consistent with her medical history, she was not very responsive to the new treatment; therefore, we decided to reinitiate clozapine treatment. After one week of starting clozapine, two different WBC counts were 11.9×10^9/L and 14×10^9/L. Repeated consultations and medical examinations found no explanation for the leukocytosis, so we assumed that the leukocytosis was linked to clozapine and stopped the treatment. Her new treatment plan was 450 mg/day of amisulprid. Like before, WBC count normalized and did not rise again. Because we decided to report the leukocytosis associated with the patient's treatment, informed consent was obtained from both the patient and her family.

Correspondence Address/Yazışma Adresi: Uğur Çakır, Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı, Bolu, Türkiye
E-mail: ugur_cakir@yahoo.com

Received/Geliş Tarihi: 02.07.2014 **Accepted/Kabul Tarihi:** 20.10.2014

DISCUSSION

The mechanism underlying how clozapine causes leukocytosis remains unknown (4). One possibility is that clozapine may stimulate the release of certain cytokines, including TNF, IL-2, IL-6, and G-CSF (5). Other possible risk factors may be smoking, being male, and the use of lithium (6). One study reported a case of a 50-year-old Caucasian male treated with clozapine for schizophrenia; the patient had a medical history of a head injury and a splenectomy. Prior to clozapine treatment, the patient had a normal WBC count of 5.2×10^9/L with a normal differential. After reaching a target dose of 350 mg/day of clozapine, WBC count fluctuated between 5.2×10^9/L and 12.2×10^9/L. A WBC count of 15.6×10^9/L was observed at week 16, without a sore throat, rash, or flu-like symptoms. From week 16 to week 23, the patient presented with intermittent leukocytosis; WBC count ranged from normal to significantly elevated (7). Another study reported a case of a 41-year-old Caucasian male treated with clozapine for the stabilization of paranoid schizophrenia. A medical record review indicated a normal WBC count prior to the initiation of clozapine treatment, with leukocytosis (15.4×10^9–24.4×10^9/L) that manifested shortly thereafter and lasted for a period of eight years. However, leukocytosis was not attributed solely to clozapine in this case, as the patient was simultaneously receiving lithium therapy (8). Madhusoodanan reported seven cases of chronic leukocytosis linked to clozapine (9). None of the seven patients had any evidence of infection or other potential general medical conditions (trauma, burns, etc.) that might have increased WBC count. The peak WBC count reported for these seven patients was 19.8×10^9/L; leukocytosis duration in these patients ranged from 2 to 5 years. The course for all patients was benign in nature, as there were no adverse effects associated with leukocytosis. Authors also considered chronic cigarette smoking and male gender as possible risk factors for leukocytosis (9). Sopko and Caley (10) reported a 37-year-old Caucasian patient treated for refractory schizophrenia. The patient also had a history of obsessive compulsive disorder and substance abuse. During the following two-year period, WBC count fluctuated between 10×10^9/L and 28×10^9/L with a dose of 225–300 mg/day. The authors found no medical condition to explain the leukocytosis (10). Our patient was female and had no history of lithium use. Despite being a heavy smoker, there was no chronological relation between her leukocytosis and smoking. However, several studies have shown that cigarette smoking induces the metabolism of clozapine by cytochrome P4501A2 (CYP1A2); therefore, a potential interaction between clozapine and nicotine might underlie the development of leukocytosis (11,12).

In this paper we have reported a patient who developed leukocytosis during clozapine treatment. It appears that clozapine-associated leukocytosis is a benign medical condition. The clozapine-associated risk of agranulocytosis is well established; however, clinicians should also be cautious of the risk for other blood dyscrasias, such as leukocytosis.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

REFERENCES

1. Marder SR, Hurford IM, van Kamen DP. Second-generation antipsychotics, Comprehensive Textbook of Psychiatry. Lippincott Williams and Wilkins, Philadelphia 2009.
2. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 1998; 59:3-7.
3. Gerson SL. Clozapine--deciphering the risks. N Engl J Med 1993; 329:204-205. [CrossRef]
4. Seifritz E, Hemmeter U, Holsboer-Trachsler, E, Pöldinger W. Chronic leukocytosis and neutrophilia caused by rehabilitation stress in a clozapine-treated patient. Pharmacopsychiatry 1993; 26:99. [CrossRef]
5. Fehsel K, Loeffler S, Krieger K, Henning U, Agelink M, Kolb-Bachofen V, Klimke A. Clozapine induces oxidative stress and proapoptotic gene expression in neutrophils of schizophrenic patients. J Clin Psychopharmacol 2005; 25:419-426. [CrossRef]
6. Lapierre G, Stewart RB. Lithium carbonate and leukocytosis. American Journal of Health-System Pharmacy 1980; 37:1525-1528.
7. Popli A, Pies R. Clozapine and leukocytosis. J Clin Psychopharmacol 1995; 15:286-287. [CrossRef]
8. Trinidad ED, Potti A, Mehdi SA. Clozapine-induced blood dyscrasias. Haematologica 2000; 85(E-letters): E02.
9. Madhusoodanan S, Cuni L, Brenner R, Sajatovic M, Palekar N, Amanbekova D. Chronic leukocytosis associated with clozapine: a case series. J Clin Psychiatry 2007; 68:484-488. [CrossRef]
10. Sopko MA, Caley CF. Chronic leukocytosis associated with clozapine treatment. Clin Schizophr Relat Psychoses 2010; 4:141-144. [CrossRef]
11. Bondolfi G, Morel F, Crettol S, Rachid F, Baumann P, Eap CB. Increased clozapine plasma concentrations and side effects induced by smoking cessation in 2 CYP1A2 genotyped patients. Ther Drug Monit 2005; 27:539-543. [CrossRef]
12. Carrillo JA, Herráiz AG, Ramos SI, Gervasini G, Vizcaíno S, Benítez J. Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. J Clin Psychopharmacol 2003; 23:119-127.[CrossRef]