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Life-threatening citalopram induced hemolytic anemia in a patient with generalized anxiety disorder: A case report

Yaygın anksiyete bozukluğu olan bir hastada hayatı tehdit eden sitaloprama bağlı hemolitik anemi: Bir olgu sunumu

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Abstract

The hemolysis side effect of selective serotonin reuptake inhibitors is potentially lethal, although not much has been reported. We hereby report a 43-year-old male case of hemolytic anemia that developed after use of citalopram 40 mg/day and its improvement with discontinuation. Further studies should be conducted to provide a greater understanding of both its prevalence and etiology.

Keywords: Citalopram, hemolytic anemia, selective serotonin reuptake inhibitor.

Öz

Seçici serotonin geri alım inhibitörlerinin hemoliz yan etkisi potansiyel olarak ölümcüldür, ancak çok fazla bildirilmemiştir. Bu yazıda sitalopram 40 mg/gün kullanımı sonrası hemolitik anemi gelişen ve ilacın kesilmesi ile düzelen 43 yaşında erkek bir olguyu sunuyoruz. Hem prevalansı hem de etiyolojisi hakkında daha iyi bilgi sahibi olabilmek için daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: Sitalopram, hemolitik anemi, seçici serotonin geri alım inhibitörü.

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Introduction

Citalopram hydrobromide is a selective serotonin reuptake inhibitor (SSRI) that is used to treat symptoms of depression and anxiety. It has various adverse effects on gastrointestinal, autonomic nervous, central and peripheral nervous, musculoskeletal, urogenital, and cardiovascular system. Although manufacturer has listed hematologic adverse effects such as variants of anemia, no report is available in the literature [1].

Herein, we present a 43-year-old male who developed hemolytic anemia while using citalopram. We discuss the clinical features, etiology and significance of this clinical condition.

Case report

A 43-year-old male patient was referred to us by internal medicine with the possibility of drug side effects. It was learned that the patient had been treated intermittently for 10 years with anxiety complaints, that he had been using paroxetine 20 mg/day for the last one year but that paroxetine was discontinued due to inefficacy and citalopram 40 mg was started two months ago. Following citalopram 40 mg/day, fatigue, abdominal pain, and chills developed and these complaints increased day by day. Two weeks after citalopram was started, he admitted to internal medicine with these complaints. In the patient whose complete blood count (CBC) values were within normal limits prior to the present psychiatric treatment, some abnormalities were determined: Hemoglobin (HGB) 9.403 g/dL, hematocrit (HCT) 24.56%, red blood cell (RBC) 2.241 106/µL, mean corpuscular volume (MCV), 109.6 fL, mean corpuscular hemoglobin (MCH) 41.96 pg, mean corpuscular hemoglobin concentration (MCHC) 38.28 g/dL, red blood cell distribution width-coefficent of variation (RDW-CV) 18.69%. Total bilirubin was 2.3 mg/dl and indirect bilirubin was 1.6 mg/dl. Other CBC parameters, Infection markers, liver, kidney and thyroid functions, electrolytes, vitamin B-12, folate, iron, iron binding capacity, and ferritin were found to be normal. Reticulocyte count and percentage were increased and haptoglobulin was decreased. The reticulocyte production index indicated hemolysis with 2.7533. Peripheral smear showed basophilic stippling, polychromatic cells and physical examination revealed splenomegaly. Based on these results, he was diagnosed as acquired hemolytic anemia due to citalopram by internal medicine. Previously used drugs by patient were paroxetine, alprazolam, olanzapine, medazepam, and clomipramine. Family history was unremarkable. Mental status examination revealed an anxious affect. A diagnosis of generalized anxiety disorder was made according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) [2]. Citalopram was discontinued and the patient was started on sertraline 50 mg/day and increased to 100 mg/day. CBC values were regularly monitored by internal medicine during this period. The laboratory findings during the follow-up of the patient are shown in Table 1. Hemoglobin electrophoresis using high pressure liquid chromatography method to exclude beta thalassemia gave normal findings (A2= 3.1%; F= 1.1%). Immunocapture agglutination test to exclude brucellosis, Gruber-Widal test to exclude salmonellosis, direct and indirect coombs tests were negative. Endoscopic biopsy gave normal results. Four months after the drug was discontinued, HGB increased to normal limits, but MCV and MCH reached normal limits at the fifth month. In the sixth week of sertraline treatment, partial regression of anxiety symptoms was observed and the drug was continued at the same dose. No similar side effects were reported during the follow-up of the patient. The patient and his relatives were warned about anemia due to citalopram use and informed consent was obtained from them for their knowledges. Naranjo Adverse Dug Reaction Probability Scale (NADRPS) score of the patient was 7 [3].

The written consent was taken from the patient.

Table 1. The Patient's Follow-up Laboratory Data

	B	B + Week 1	B + Week 5	B + Week 7	B + Week 12	B + Week 16	B + Week 20
HGB (g/dL)	9.403	9.960	10.83	10.93	11.85	13.24	13.66
HTC (%)	24.56	26.09	29.86	30.07	36.37	37.51	37.17
RBC (10^6/µL)	2.241	2.367	2.886	3.068	3.255	3.727	3.999
MCV (fL)	109.6	110.2	103.5	98.02	111.7	100.64	92.96
MCH (pg)	41.96	42.07	37.52	35.62	36.39	35.53	33.98
MCHC (g/dL)	38.28	38.18	36.26	36.34	32.58	35.39	35.52
RDW-CV (%)	18.69	16.84	15.11	14.84	18.74	15.43	13.80
Total bilirubin (mg/dl)	2.3	2.1	2.0	2.0	2.5	1.4	1.1
Indirect bilirubin (mg/dl)	1.6	1.4	1.3	1.2	1.7	0.7	0.5
Reticulocyte count (10^3/µL)	-	-	-	-	161	173	140
Percentage of reticulocyte (%)	-	-	-	-	5.11	4.63	4.28
Haptoglobulin (g/L)	-	-	-	-	0.01	0.01	-

B:Beginning (two weeks after starting citalopram); HGB: Hemoglobin, HTC: Hematocrit, RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW-CV: Red blood cell distribution width-coefficient of variation.

Discussion

This case report was evaluated as a case of hemolytic anemia due to citalopram. Because there was a temporal relationship between them, the side effect began with the addition of the drug and completely cured after discontinuation of the drug. Other causes of anemia, such as beta thalassemia and gastrointestinal system bleeding were excluded. The NADRPS score indicates a probable association between drug use and side effect [3]. World Health Organization (WHO) defines 'probable' as an event or laboratory test abnormality, with reasonable time relationship to drug intake. WHO also says this relationship cannot be explained by disease or other drugs, response to withdrawal clinically reasonable, re-challenge (not necessary) [4].

The mechanism by which citalopram could cause hemolytic anemia has not been fully elucidated. Possible mechanisms in drug-induced hemolytic anemia may be related to RBC coating, drug-membrane interaction true autoimmune. While RBC coating is characterized by extravascular hemolysis, steroid treatment may be required in autoimmune conditions. The mechanism of hemolytic anemia in our patient was associated with drug-membrane interaction. In drug-membrane interaction, drug covalently or non-covalently bond to RBC, creating neo-antigen, and in this type of reaction, fatalities are more common [5]. According to our best knowledge, this is the first case of citalopram-induced hemolytic anemia. The

mechanism by which citalopram causes this side effect is not fully understood. Clinical reports and researches of hemolysis side effects of SSRIs other than citalopram are also insufficient and provide no explanation. Jilani et al. [6] reported in an in vitro study that fluoxetine stimulates eryptosis, the suicidal erythrocyte death, which may result in anemia.

Clinical presentation may be rapid in hemolytic anemia. Pallor, jaundice, fever, tachycardia, splenomegaly are physical findings that can be detected in almost all patients with hemolytic anemia. The increase in indirect bilirubin in patients with hemolytic anemia is a valuable finding since it shows hem catabolism above the conjugating capacity of the liver. In all hemolytic anemias, reticulocytosis is the most important laboratory finding in the initial evaluation of the case and shows the response of bone marrow to hemolysis. Hemoglobin released in intravenous hemolysis is bound to haptoglobin, an alpha 2 glycoprotein made in the liver, and this complex is destroyed in phagocytic cells in the liver. Therefore, the haptoglobin level in the serum decreases to 0 [7]. Considering all these information, it is clear that the condition in our patient is a hemolysis. The fragmented erythrocytes suggested intravascular hemolysis. Discontinuation of the drug was sufficient in the treatment of case.

As a result, this case report suggests that physicians and relatives should be aware that citalopram may induce hemolytic anemia with a fatality risk, a low quality of life and low compliance. Further systemic research should be conducted with respect to citalopram-associated hemolytic anemia to provide a greater understanding of both its prevalence and etiology.

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