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Case Report

Concurrent Hepatotoxicity and Neutropenia Induced by Clozapine

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Abstract

Clozapine is known as one of the atypical antipsychotics which is placed in the second line of medical treatment for schizophrenia due to its hematologic complications. It is used in cases of resistance to treatment. Some side effects of clozapine include leukopenia, granulocytopenia, fever, hepatotoxicity, sedation, dizziness, hypotension, weight gain, constipation, and seizure. Neutropenia and hepatotoxicity have been separately reported after taking atypical antipsychotics, including clozapine. However, simultaneous occurrence of these two complications is rare and has not been reported with clozapine use. This study reports a case of concurrent hepatotoxicity and neutropenia induced by clozapine. The patient was a 58-year-old man who started taking clozapine for the first time in March 2017, about seven weeks before his recent admission, because of a history of treatment-resistant schizophrenia. He had been referred to the emergency department of a general hospital with symptoms of weakness, lethargy, fever, and chills. The laboratory results showed neutropenia with a frequency of 352 × 10^3 (17.5%) and hepatotoxicity with alanine transferase (ALT) = 139 u/L, aspartate transferase (AST) = 214 u/L, total bilirubin = 11.5 mg/dL, and direct bilirubin = 9.3 mg/Dl, caused by taking clozapine. The symptoms were attenuated within eight days after discontinuation of clozapine. Moreover, the patient's para-clinical complications including neutropenia, and raised transaminases and bilirubin returned to normal. It was concluded that clozapine can simultaneously cause neutropenia and hepatotoxicity; physicians are recommended to be aware of this issue to prevent mortality through appropriate and timely diagnosis.

Keywords: Clozapine, Complications, Hepatotoxicity, Hyperbilirubinemia, Neutropenia

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Introduction

Clozapine is known as an atypical antipsychotic drug, reserved as the second line medication for resistant-to treatment schizophrenia because of its safety profile - mainly hematologic complications and need for continuous blood sampling, especially in the early stages of treatment. Some of the side effects of clozapine include sedation, dizziness, hypotension, weight gain, constipation, myocarditis and seizure. There are also other complications such as leukopenia, granulocytopenia, agranulocytosis, and fever. This lethal situation also occurs in approximately 0.3% of patients treated with clozapine during the first year of exposure to the drug, and this risk is gradually reduced.[1] One other side effect of clozapine is increased liver enzymes and sometimes hepatotoxicity. Indeed, neuroleptic drugs, especially the second generation or atypical antipsychotics, can commonly cause an asymptomatic rise in the liver enzymes and hyperbilirubinemia.[2,3] Nevertheless, clinical jaundice and severe hepatotoxicity have been reported in rare cases following the use of these medications.[3] Most of the case reports in this domain have also given details about this complication for atypical antipsychotic medications other than clozapine, such as quetiapine and olanzapine.[4,5] Clozapine-induced fatal fulminant hepatic failure is the most rare side effect and there are no guidelines for routine monitoring of such complications during its prescription.[6] Although the occurrence of neutropenia induced by antipsychotics and hepatotoxicity resulting from these drugs have been frequently presented in some other reports,[4,7,8] simultaneous occurrence of these two complications due to the use of clozapine has not been reported so far. The purpose of this study is to introduce a case of concurrent hepatotoxicity and neutropenia induced by clozapine in order to highlight the importance of preventing these complications via timely diagnosis and treatment.

Case Report

The patient was a 58-year-old man affected with schizophrenia living in a healthcare center for chronic psychiatric patients. Due to persistence of psychotic symptoms as well as the occurrence of tardive dyskinesia, clozapine was prescribed at the dose of 25 mg/day since March 2017 and about seven weeks before his recent

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admission, and then raised to 150 mg/day over the seven weeks dividedly. The patient started to develop fever (40°C) and experienced symptoms like weakness, lethargy, and chills about one week before admission, and referred to the emergency department of a teaching hospital in the city of Sari in northern Iran. His psychiatrist had stopped treatment with clozapine and had prescribed lithium carbonate after the onset of detection of neutropenia with the aim of inducing leukocytosis following clozapine-induced neutropenia. The patient was admitted to the gastroenterology ward due to hyperbilirubinemia. On admission, his white blood cell count was 2.1×10^3, with a neutrophil count of 17.5% (N = 352) and lymphocyte count of 85%. Before admission, his white blood cell count was reported by 0.9×10^3. The liver enzymes were alanine transferase (ALT) = 214 IU/L, aspartate transferase (AST) = 139 IU/L. Other laboratory tests were: direct bilirubin = 9.5 µmol/L, total bilirubin = 11.5 µmol/L, creatine phosphokinase = 230 U/L and lactate dehydrogenase = 363 U/L.

Various consultations were requested from specialists in toxicology, hematology, oncology, infectious diseases, and psychiatry. No pathologic findings were found on abdominal and pelvic ultrasound examination and computerized tomography (CT) scan. Moreover, no blastocyst was reported in peripheral blood smear, and the results were negative for substance screening in the urine. In addition, infectious agents of hepatitis including hepatitis A, B, and C were ruled out. The test results in the patient's medical records from admission to discharge are given in Table 1.

Clozapine was discontinued following consultation-liaison visit, necessary tests, history taking, as well as administration of risperidone 2 mg/d and trihexyphenidyl twice daily. In addition to these drugs, the Hematology and Oncology Services prescribed filgrastim to improve neutropenia. Thus, the clinical signs of the patient gradually decreased and his para-clinical abnormalities including neutropenia, elevated liver transaminases, as well as total and direct bilirubin, indicating hepatocellular damage, returned to normal values. The fever was resolved by day 2 after discontinuing clozapine. The neutrophil count also increased to $3.3 \times 10\%$ a day with white blood cell count = 7.8×10^3 (Table 1). Finally, the patient's alkaline phosphatase, alanine transaminase, direct bilirubin, indirect bilirubin, creatine phosphokinase, and lactate dehydrogenase returned to normal levels within one week. The discharge order was issued eight days after admission.

Discussion

In this case report, the patient was suffering from neutropenia and hepatotoxicity following seven-week prescription of clozapine without having a history of medical illness. Various investigations also ruled out other reasons for these two complications. Conclusively, consumption of clozapine was diagnosed as the cause of these two complications. This case shows that clozapine can result in concurrent hepatotoxicity and neutropenia. Some case reports had also explained multi-organ pathologies with clozapine; such as hepatitis, ascites, cholecystitis, pleural effusion, eosinophilia, and hematuria during clozapine consumption.[9] However, to the best of our knowledge, no case of concurrent hepatotoxicity and neutropenia induced by clozapine has been reported so far. However, there was a case report on simultaneous occurrence of these two complications using olanzapine,[10] probably resulting from either a metabolic idiosyncrasy or an immunoallergic reaction.

It should be noted that the most common etiologies of hepatotoxicity are viral or toxin-induced hepatitis,[6] immunoallergic reactions,[11] as well as drug overdose and idiosyncratic drug reactions.[12] The mechanism of hepatotoxicity induced by clozapine is the possible mediation of cytochromes P450 (CYPs); in particular, cytochrome P450,[6] CYP3A, and CYP2E1 in the metabolism of this medication.[13] Clozapine discontinuation also results in recovery from hepatitis in most patients.[8] However, fatalities have been reported.[6] Clinical jaundice and elevated liver enzymes disappeared in this patient within six days after cessation of clozapine. It was concluded that early discontinuation of clozapine due to the occurrence of agranulocytosis may have prevented the present patient from developing fatal fulminant hepatic failure. The resulting agranulocytosis, which is in fact idiosyncratic and non-dose dependent,

Table 1. Laboratory Results

	WBC	PMN	PLT	RBC	ALT	AST	ALP	Bili T	Bili D
1st Day	$2/1 \times 10^3$ mL	17/5 %	78×10^3	$3/8 \times 10^6$	139 u/L	214 u/L	215 u/L	11/5 mg/ dL	9/3 mg/dL
2nd Day	$1/4 \times 10^3$	8/4 %	266×10^3	$3/58 \times 10^6$	—	—	—	—	—
3rd Day	—	—	—	—	—	—	—	—	—
4th Day	$2/7 \times 10^3$	—	172×10^3	$3/28 \times 10^6$	39	25	202	2/8	2/2
5th Day	$7/8 \times 10^3$	41/8%	212×10^3	$3/07 \times 10^6$	—	—	—	—	—
6th Day	$12/5 \times 10^3$	68/6%	252×10^3	$3/01 \times 10^6$	39	34	177	2/7	1/5
7th Day	$16/5 \times 10^3$	58/1%	$32/8 \times 10^3$	$3/1 \times 10^6$	37	32	197	2/6	1/4
8th Day	$13/4 \times 10^3$	—	304×10^3	$3/14 \times 10^6$	19	22	153	1/3	0/3

WBC, white blood cells; PMN, polymorphonuclear leukocytosis; PLT, platelets; RBC, red blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Bili T, bilirubin total; Bili D, bilirubin direct.

is also considered as direct toxicity or immunoallergic adverse effects of clozapine metabolites.[14] Following the onset of some serious complications, including clozapine-induced agranulocytosis, re-administration of this medication should be avoided.[1] The Sandoz guidelines also suggest clozapine discontinuation in cases of jaundice and increased liver enzymes.[7] Furthermore, there are case reports of restarting clozapine after normalization of the enzymes,[15] although some patients have not been able to do so.[16]

Clozapine was discontinued based on a suspicion about the impact of clozapine on the development of both neutropenic and hepatotoxic effects, and then lithium carbonate was started to control the patient's psychiatric symptoms, especially psychotic ones, as well as clozapine-induced agranulocytosis. The patient fully recovered in terms of clinical and para-clinical symptoms after 10 days. Lithium has been also reported to treat the psychotic symptoms of schizophrenia.[17] Besides, lithium can cause benign koilocytosis, as a common side effect of benign leukocytosis,[18] and also plays a role in the improvement of clozapine-induced neutropenia.[19]

This experience should be of interest, because it seems that a rare complication (agranulocytosis leading to discontinuation of taking clozapine in the early stages of hepatitis) may have had a major role in preventing progression of another rare complication (fatal fulminant hepatitis). Although there is no consensus in the guidelines or recommendations for regular monitoring of liver enzymes during clozapine prescription, current guidelines in some countries support routine enzyme monitoring at the starting point and every 6 months following prescription.[8] As a result, clinicians should note that, despite the rarity of concurrent clozapine-induced hepatotoxicity and neutropenia, proper and timely diagnosis can prevent consequences.

Authors' Contribution

FE performed the psychiatric evaluation of the case following drug side effects, fulfilled the management of the case, contributed to the conception of the work, drafted the manuscript, and also edited the manuscript. MZ contributed to the conception of the study and editing of the manuscript as well as management of the psychiatric disorder in the patient before and after the side effects. SDH & FE wrote the primary manuscript and described the case. AK and FE contributed to the management of the case. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

The authors declared no conflict of interest.

Ethical Statement

This study was conducted along the Helsinki Declaration.

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