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CASE REPORT

Late-onset clozapine-induced neutropenia treated with lithium

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ABSTRACT

Clozapine is a second-generation antipsychotic drug, proven to be effective in treatment-resistant schizophrenia. Among patients using clozapine; the incidence of neutropenia is approximately 3% and the incidence of agranulocytosis is approximately 1%. This side effect is diminishing after 18 weeks of drug initiation. Here, we present a case of clozapine-induced neutropenia in a schizophrenic patient seen after 7 years of clozapine use and its treatment with lithium supplementation.

Keywords: Clozapine, lithium, neutropenia.

INTRODUCTION

Clozapine is a second-generation antipsychotic drug proven to be effective in treatment-resistant schizophrenia. Among patients using clozapine, the incidence of neutropenia is approximately 3% and the incidence of agranulocytosis (neutrophils <500/mm^3 or white blood cells [WBC] <1000/mm^3) is approximately 1% (1). In a recent meta-analysis involving 108 studies, the incidence of clozapine-associated neutropenia was 3.8% and severe neutropenia was 0.9% (2). The period of greatest risk for both neutropenia and agranulocytosis is during the first 6-18 weeks of treatment (1). During the first 18 weeks of clozapine use, full blood count tests must be run weekly, later every month.

Clozapine therapy is recommended to be discontinued when WBC <2000/mm^3 or neutrophils <1000/mm^3. However, despite the development of neutropenia, it has been suggested that the use of clozapine may be continued with the addition of lithium or G-CSF in cases of resistant schizophrenia. The rechallenge choice should be made taking into consideration the benefits and damages of the treatment (3,4).

In this case report, clozapine-induced neutropenia in a schizophrenic patient after 7 years of clozapine use and its treatment with lithium supplementation will be presented.

CASE

A 45-year-old male patient with a 20-year schizophrenia diagnosis was admitted to hospital with irritability, aggression, disorganized speech, auditory and visual hallucinations. He had been using clozapine 600 mg/day for 7 years and his general condition had deteriorated for the last 3 months. One month ago, clozapine treatment was discontinued because of decreasing trends of neutrophils (neutrophils: 1140/mm^3) and the patient was admitted to the clinic on haloperidol 20 mg/day, quetiapine XR 300 mg/day, and biperiden 4 mg/day. Considering the extrapyramidal

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side effects associated with the current treatment, olanzapine 30 mg/day was started. There was no regression of the psychotic symptoms and catatonic features started to manifest in the patient (who did not benefit from antipsychotics other than clozapine). Given that the blood count values were found to be normal (WBC: 5010/mm^3 and neutrophils: 3030/mm^3), clozapine was increased to 450 mg/day.

On the 32nd day of clozapine treatment, WBC count was found to be 8680/mm^3, neutrophils 7080/mm^3 and CRP (C-reactive protein) 20.3 mg/dL. The patient was later diagnosed with pneumonia and was started on gemifloxacin 320 mg/day. On the 4th day of antibiotherapy, WBC, neutrophils, and CRP decreased to 2250/mm^3, 740/mm^3 and 4.74 mg/L, respectively. Blood count analysis on the same day revealed a leukocyte count of 1850/mm^3 and a neutrophil count of 670/mm^3. The patient was referred to hematology with an indication of G-CSF (Granulocyte Colony-stimulating Factor) administration, but there was no indication as the patient had no fever. Because of neutropenia, clozapine treatment was discontinued, but subsequently, psychotic symptoms increased. As a result, the olanzapine dose was increased to 40 mg/day, but there was no improvement in the psychotic symptoms. An increase in catatonia and disorganized speech and behavior were observed. The patient's leukocyte counts, specifically neutrophils, were seen to be normal. The patient was referred to hematology and was restarted on clozapine treatment because his health was deteriorating after the psychotic exacerbation; the condition was resistant to other antipsychotic treatments and the patient's next of kin did not consent to electroconvulsive therapy. The current treatment was strengthened with amisulpride 600 mg/day. We followed the patient, but the blood counts continued to decrease (WBC: 4580/mm^3 neutrophils: 2000/mm^3). The patient was referred to hematology again to determine a possible risk of agranulocytosis. Immediate treatment was not recommended, but continuation of the existing treatment and G-CSF was suggested in case the neutrophil count went below 1000/mm^3. With no indication of G-CSF treatment but a continuing decrease in neutrophils, we decided to add 900 mg/day of lithium to the clozapine. In the following 3 days, an increase in leukocyte and neutrophil values (WBC: 6000/mm^3 neutrophils: 3600/mm^3) was observed. While the patient was on 900 mg/day lithium, the blood count was monitored every day, and the clozapine dose was increased to 400 mg/day while olanzapine was tapered off. The patient showed a regression of psychotic symptoms. He had no disorganized speech or behavior. He was discharged on clozapine 400 mg/day, lithium 900 mg/day, amisulpride 600 mg/day, biperiden 2 mg/day, and weekly blood count monitoring was recommended. On the day of discharge, WBC count was 6010/mm^3, neutrophil count was 3290/mm^3, and serum lithium level was 0.423 mmol/L. The patient was seen 2.5 years later and no psychotic symptoms or disorganized speech or behavior were observed, with values of WBC: 8300/mm^3, neutrophils: 5400/mm^3, and serum lithium: 0.4 mmol/L.

DISCUSSION

We have presented a case of clozapine-induced neutropenia. Interestingly, neutropenia emerged very late, in the 7th year of the treatment. Clozapine was restarted after the psychiatric condition worsened as a result of the termination of clozapine treatment. During the second course of clozapine, neutropenia was treated with lithium. Within the first 6 months, agranulocytosis associated with the use of clozapine emerges in 90% of patients (5). Over time, the risk of developing agranulocytosis decreases (6). After 1 year of treatment with clozapine, the risk of developing neutropenia or agranulocytosis was found to be less than 1% (7). There are other cases in the literature with clozapine-induced late-onset agranulocytosis/neutropenia (8-10). It is not recommended to start patients who previously experienced clozapine-induced neutropenia on clozapine treatment again because of a serious risk for developing neutropenia again, found to be 38% (6). Clozapine treatment is only recommended to be restarted in schizophrenic patients who are resistant to other antipsychotics in combination with lithium (11-13) or G-CSF (14-16).

G-CSF is a cytokine that directly stimulates the proliferation of hematopoietic precursors and terminal granulocytic differentiation, with the most commonly reported rechallenge strategy being three times per week with 150 to 480 μg of filgrastim per day. In a study analyzing 17 articles based on case reports of G-CSF rechallenge, there were no drug-specific side effects except for one reported case of euphoria (17). However, another study reported bone pain, rare instances of splenic rupture, allergic reactions exacerbation of autoimmune disorders, lung injury, and vascular events as potential side effects of G-CSF (18).

We chose augmentation with lithium for the recurrence of clozapine-induced neutropenia because G-CSF treatment was not recommended as the

neutrophil counts were found to be low but not below 1000/mm^3 and there was no fever. In the first 3 days of treatment with 900 mg/day lithium, leukocyte and neutrophil counts were rising. The mechanism of lithium is not fully understood; however, a direct stimulation of the stem cells, GM-CSF, cytokine and demargination are believed to play a role (19).

Studies on the combination of clozapine and lithium are not sufficient. There are potential serious side effects like weight gain and metabolic abnormalities (11). An increased risk for epileptic seizures with the combination of lithium and clozapine should be monitored. The risk of developing neurotoxicity in patients treated with the combination of lithium and clozapine is approximately 20% (20). There is one case of a patient who benefited from clozapine rechallenge with lithium for 14 months, but eventually developed neurotoxicity. As a result, lithium was discontinued (21).

Although serum lithium levels do not appear to have a correlation with neutrophil levels (22), there are studies suggesting that the minimum lithium levels should be 0.4 mmol/L (23). The combination of clozapine and lithium is effective when administered within an optimal lithium dose range of 300-900 mg/day with serum lithium levels between 0.4 and 0.9 mmol/L (24, 25). We also administered 900 mg/day of lithium and kept the serum lithium level in our patient around 0.4 mmol/L. More studies on the combination of clozapine with lithium or G-CSF are recommended.

We found this case to be worth presenting because it shows a patient whose schizophrenia is resistant to antipsychotics other than clozapine who developed recurrent clozapine-induced neutropenia and showed remission on hematologic and psychiatric parameters with lithium treatment.

Contribution Categories		Author Initials
Category 1	Concept/Design	P.T.D.
	Literature review	M.B.S., R.K.Ç.
	Data analysis/Interpretation	P.T.D., Y.G.
	Case follow-up (if applicable)	P.T.D., Y.G.
Category 2	Drafting manuscript	P.T.D., Y.G.
	Critical revision of manuscript	P.T.D., Y.G.
Category 3	Final approval and accountability	P.T.D., Y.G., M.B.S., R.K.Ç.
Other	Technical or material support	P.T.D.
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