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Case Report

The effect of lithium on clozapine-induced neutropenia reduction in refractory schizoaffective disorder

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Abstract
Resistant schizoaffective disorder has persistent psychotic symptoms and intermittent mood swings. A satisfying method for treating these patients is the use of the antipsychotic drug clozapine, but its use is limited due to significant side effects such as leukopenia and neutropenia. Lithium carbonate is another psychiatric drug that reduces these side effects. We hypothesized that lithium, along with clozapine, in addition to controlling side effects, could have a dual effect on mood episodes in schizoaffective disorder, and used it in a chronic case. The patient was a 48-year-old man with a 20-year history of the disease. Therefore, the use of lithium along with clozapine is recommended in refractory schizoaffective patients.
Keywords: Resistant schizoaffective, Clozapine, Leukopenia, Neutropenia, Lithium

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Introduction

Schizoaffective disorder is a mental disorder that includes general and persistent symptoms of psychosis with intermittent mood episodes (1).

The effect of antipsychotic drugs on this disorder can be understood according to the dopamine hypothesis of schizophrenia. However, the presence of serious side effects such as leukopenia and neutropenia due to the use of antipsychotic drugs is significant. Leukopenia is characterized by a decrease in the number of white blood cells (WBCs), which is often due to neutropenia. Neutropenia can be defined as the number of neutrophils $< 10^9 \times 1.5$/L (2). Similar side effects have been reported with risperidone (3), olanzapine (4), quetiapine (5), and paliperidone (6), but among these drugs, clozapine is strongly associated with such side effects; it requires regular biological monitoring, and clozapine treatment should be discontinued in the cases of secondary granulocytopenia for approximately 3% of patients (7). There are two known treatment strategies, including the adjuvant use of lithium and the granulocyte colony-stimulating factor (8). Lithium carbonate as the main mood stabilizer is effective in 80% of the cases of bipolar mania and in the treatment of patients with schizoaffective disorder (9). In addition, studies have shown that lithium carbonate increases neutrophil and total WBC counts as a side effect that may be useful in patients who develop neutropenia or leukopenia while being treated with clozapine (10).

However, few treatment teams have used lithium to reduce clozapine-induced granulocytopenia, and to the best of our knowledge, no study has so far focused on the effect of lithium carbonate on clozapine-induced leukopenia and neutropenia in similar conditions. Therefore, this report has discussed the effect of lithium carbonate on the treatment of clozapine-induced leukopenia and neutropenia in a male patient with schizoaffective disorder.

Case Presentation

The patient was a 48-year-old man who has been receiving medical treatment for schizoaffective disorder for about twenty years. Due to the lack of disease control, he has been kept in a boarding center for about ten years. It should be noted that the patient had a good job, education, and social function before the onset of the disease.

Different drugs have been used for the patient, but he has recurrent mania despite taking the drug. The patient's last medication was sodium valproate 500 mg every eight hours, risperidone 2 mg every eight hours, biperiden 2 mg every eight hours, and olanzapine 5 mg at night; while taking the drug, he experienced the symptoms of mania manifested in the form of insomnia, talkativeness, restlessness, aggression, hallucinations, and delusions.

Due to the frequent recurrences of mania, despite taking the drug, it was decided to start clozapine treatment for the patient. Clozapine 25 mg daily was started for the patient and increased to 200 mg/d within a week. In addition

Table 1. WBC Level During Hospitalization

Duration of hospitalization	The beginning of hospitalization	Seventh day	Eighth day	Second day after starting lithium	30th day (discharge time)
WBC	4540	3720	3450	5310	4760
Monocyte	10.8%	8%	9%	6%	8%
Neutrophil	61.2%	53%	66.1%	70%	62%
Lymphocyte	28%	39%	24.9%	24%	30%

Note. WBC: White blood cell.

to clozapine tablets at the time of admission, sodium valproate 500 mg every eight hours and olanzapine 5 mg every eight hours were continued for treatment.

At the beginning of hospitalization, the WBC of the patient was 4540 (monocyte 10.8%, neutrophil 61.2%, and lymphocyte 28%), and one week after hospitalization, the patient's WBC was 3720 (monocyte 8%, neutrophil 53%, and lymphocyte 39%). With repeated complete blood count (CBC), a decrease in WBC was evident the next day [3450 (monocyte 9%, neutrophil 66.1%, and lymphocyte 24.9%, (Table 1].

In this patient, it was decided not to discontinue clozapine as much as possible considering the drop in WBC and being on the neutropenic border, as well as the strong possibility of becoming neutropenic in the coming days and the rejection of other causes leading to the drop in WBC, including infections, malignancy, and the like. The other considered parameters were the strong possibility of the drop in WBC caused by clozapine and the fact that clozapine was a suitable drug for this patient. Thus, the dose of clozapine was reduced by 50 mg, and lithium tablets of 300 mg were started every eight hours for the patient whose CBC was checked daily.

Fortunately, the patient's WBC reached 5310 (monocyte 6%, neutrophil 70%, and lymphocyte 24%) two days after the start of lithium, and in the next weekly CBC checks, the patient's WBC was 4670 (monocyte 8%, neutrophil 62%, and lymphocyte 30%), which is equivalent to the same WBC on the first day of patient hospitalization. Moreover, by controlling the mania symptoms with clozapine 200 mg daily and lithium 300 mg every eight hours, as well as olanzapine and sodium valproate every eight hours, the patient was discharged after one month with the WBC of 4670 (monocyte 8%, neutrophil 62%, and lymphocyte 30%, Table 1).

Discussion

The risk of hematological side effects is still the major limitation of clozapine treatment (11). Potential mechanisms that may predispose to leukopenia and neutropenia include direct toxic effects upon the bone marrow, the formation of antibodies against hematopoietic precursors, or involvement in the peripheral destruction of cells (12). To reduce this risk, monitoring the number of WBC and treatment decisions, including early administration of growth factors or lithium, may be useful (13). This is because, unlike these drugs, lithium carbonate has the opposite effect, leading to leukocytosis and an improvement in neutropenia and leukopenia (14). Regarding neutropenia, the simultaneous administration of lithium is supported by published studies (13,15).

In the use of lithium, some limitations should be considered, including the fact that lithium may mask impending agranulocytosis and make this combination potentially dangerous and that the combination of lithium-clozapine may increase the risk of neurological symptoms, weight gain, and metabolic abnormalities. However, in most of the literature, this compound has been reported to be well-tolerated and effective when it is prescribed in the range of the optimal dose of lithium (300-900 mg/d) (15).

In our patient, leukopenia and neutropenia were observed after one week of starting clozapine, and then WBC levels returned to normal after two days of starting lithium carbonate.

Conclusion

It seems that in refractory schizoaffective patients who have to use clozapine, it is better that lithium tablets should be one of the additional drugs so that in addition to controlling mood symptoms in the case of a possible decrease in WBC, this effect can be prevented and the treatment-resistant schizoaffective patient is not deprived of taking clozapine. In this case, with the same strategy, the combination of clozapine and lithium was started for the patient and controlled the symptoms of the disease without the complications of WBC decrease. It may be appropriate to suggest a combination of clozapine and lithium in refractory schizoaffective patients.

Authors' Contribution

Conceptualization: Ahmad Karami.
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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

This report was published after obtaining the patient's consent. The protocol of this case report was approved by the Ethics Committee of Shahrekord University of Medical Sciences (Code: IR.SKUMS.REC.1401.071).

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