Case Report

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A Case of Chronic Schizophrenia Who were Switched from Combined Treatment to Monotherapy and Achieved a Decrease in Positive Symptoms after Lowering the Clozapine Dose

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ABSTRACT:

A case of chronic schizophrenia who were switched from combined treatment to monotherapy and achieved a decrease in positive symptoms after lowering the clozapine dose

Despite the limited evidence to support the combination of antipsychotics in treatment resistant schizophrenia in the literature, this situation is common in clinical practice. Treatment guidelines recommend monotherapy for schizophrenia primarily. In this article, a chronic schizophrenic case whose treatment is changed from combination of clozapine with aripiprazole to clozapine monotherapy and whose positive symptoms decreased with the decrease of clozapine doses 900 mg/day to 625 mg/day is reported.

Keywords: clozapine, polypharmacy, schizophrenia

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INTRODUCTION

The clinical practice of using a combination of antipsychotics is common for schizophrenia and especially for treatment-resistant schizophrenia, although most treatment guides suggest monotherapy for schizophrenia[1]. Weinbrenner et al found that 42.5% of schizophrenic patients and 50% of institutionalized patients use two or more antipsychotics, while 70% of the patients used antipsychotics and other psychotropics simultaneously in a population-based cross-sectional study[2]. The rate of multiple antipsychotic use in inpatients with schizophrenia was 48.89% in a study conducted in our country[3] and 38.2% in another study[4].

There is little evidence supporting the combined use of antipsychotic drugs in treatment-resistant schizophrenia in the literature. It is recommended to increase the dose of any monotherapy until the maximum tolerated dose is reached and to use it at this dose for an adequate period, and also to try monotherapy with at least three different antipsychotic drugs, including clozapine, with different efficiency/ tolerability features before considering a combination[1].

Clozapine is the first effective drug to consider in the treatment of resistant schizophrenia,

schizoaffective disorder and bipolar disorder cases. However, there are patients in whom the desired response cannot be obtained despite adequate treatment duration and dose of clozapine. Clozapine cannot be increased to an effective dose in some patients due to emerging side effects. Case reports and studies indicate that various methods can be used to increase the medication effect in such cases[5]. However, there are no evidences that high-dose treatment would provide the best response.

Here, we present a case with decreased positive symptoms after switching from combined treatment to monotherapy and reducing the clozapine dose.

CASE

A 37-year-old elementary school graduate, single male patient was seen at our clinic. The patient had been attending various psychiatry clinics for the last 15 years for chronic schizophrenia and had used drugs such as trifluoperazine, biperiden, risperidone, olanzapine, quetiapine, haloperidol, zuclopentixol in unspecified doses and for unspecified periods. The patient was started clozapine, aripiprazole, and divalproex in 2008 for symptoms such as irritability, talking and laughing by himself (hallucinatory behavior), inability to go out of his house, and decrease in personal hygiene and self-care. Divalproex was stopped for a while but then started again at 500 mg/day upon the recommendation of the neurology specialist for the myoclonic seizures observed after the medication was discontinued. The patient was using clozapine 900 mg/day, aripiprazole 30 mg/day, divalproex 500 mg/day at the time of our admission to our clinic for his continuing and new symptoms such as hallucinatory behavior, swearing, irritability, and strange movements while walking.

The mental state examination revealed disrupted time orientation. The patient was restless, apathetic, and easily irritated. His personal care had decreased and the expression was in the form of questions and answers. His attitude towards the interviewer was defensive. He talked in a low voice in a way that could not be understood, and occasionally to himself. His talk sometimes did not serve his purpose and the associations were unrelated to the subject. The history revealed delusions of reference and persecution. His affect and mood were dysphoric. There was an increase in his expressions especially in the form of aggression. Attention and cognitive examination could not be performed due to lack of cooperation. Talking and laughing by himself indicated auditory and/ or visual hallucinations. The intelligence seemed to be below normal. The assessment of reality, judgment and abstract thinking were impaired.

The Positive and Negative Syndrome Scale (PANSS)total score was 124, positive scale score was 31, negative scale score was 33, and general psychopathology scale score was 60. A neurology consultation was requested due to the history of seizures in the patient who was diagnosed with undifferentiated schizophrenia. The divalproex was gradually increased to 1500 mg/day as the neurology examination revealed the presence of myoclonus and epileptiform spike wave on EEG. The blood valproic acid (VPA) level was 75.8 mg/ml at this dose and this dose was therefore continued. The lateral ventricles were symmetrical and wider than normal with deepened cortical sulci (atrophy) on cranial computed tomography (CT) scan. It was decided to decrease the clozapine dose gradually as the patient's history of seizures was related to clozapine. We also planned to discontinue aripiprazole due to the fact that polypharmacy was considered not to provide additional benefits. We continued clozapine due the patient's resistance to treatment.

It was observed that as the dose of the drugs decreases, the hallucinatory behaviors of the patient decreased, his self-care and communication effort increased, and his nervousness gradually decreased making him calmer. The PANSS total score decreased to 92 while the patient was on clozapine 700 mg/day, aripiprazole 10 mg/day, and divalproex 1000 mg/day. Aripiprazole was gradually discontinued and

changed the daily clozapine and divalproex dose to 575 mg/day and 1500 mg/day respectively. The hallucinatory behavior and hostility of the patient increased and the PANSS scores went up to 98 so we increased the clozapine dose to 625 mg/day. We discharged the patient with a PANSS total score of 89 (positive: 20, negative: 25, general psychopathology: 44) with divalproex 1500 mg/day and clozapine 625 mg/day. At the time of discharge, the hostility and irritability had decreased, self-care had somewhat increased, and the family stated that this was the patient's best period with this treatment so far.

DISCUSSION

Although the discovery of the new generation of antipsychotics started a new era in the treatment of schizophrenia, the use of antipsychotics are considered again due to the unresponsive cases and problems with the efficacy of the new drugs. A tendency to use combinations of antipsychotic drugs has emerged due to the chronic course of schizophrenia and the limited results obtained from drug treatment due to drug resistance. A few studies have found that the multiple antipsychotic use has advantages in the treatment of the schizophrenia[6]. Our case was using clozapine 900 mg/day, aripiprazole 30 mg/day, and divalproex 500 mg/day. The most important reason for multiple antipsychotic use in treatment is to increase the efficiency of the antipsychotics[7]. However, 5-25% of schizophrenia patients are considered to have no or very little response to this treatment and it is therefore obvious that this aim cannot always be achieved. A study comparing cases receiving multiple antipsychotic drugs and those who received treatment with a single antipsychotic showed that polypharmacy led to a higher dose of drugs, more side effects, and longer hospitalization durations while the clinical scale values were similar between the groups[8]. Certain open studies and case reports show that the clozapine-aripiprazole combination has a positive effect on the general psychopathology and negative symptoms. On the other hand, the psychopathology-related results of randomized controlled studies are less optimistic[9]. The clozapine-aripiprazole combination has been shown to decrease metabolic risk factors related to clozapine treatment but not to make a significant change in the scores of the positive and negative symptom scale in a multi-centered, double-blind placebo-controlled randomized study[10]. We planned to reduce and discontinue aripiprazole in our case.

We went on to monotherapy as polypharmacy had not been as successful as desired and we also reviewed the clozapine dosage as regards efficacy and side effects. The history of the patient revealed clozapine-related myoclonic seizures. Seizures are reported to be an important side effect of clozapine treatment and their occurrence is thought to be related to the clozapine dose[11]. It is reported that clozapine-related seizures tend to be seen at low doses (<300 mg/day) in the titration phase and high doses (>or=600 mg/day) in maintenance phase[12]. Most are tonic-clonic but myoclonic seizures can also be seen and it is possible to continue clozapine by decreasing its dose or adding an antiepileptic to the treatment[11].

Changes in the GABAergic and glutamatergic systems are linked to some neuropsychiatric disorders such as epilepsy, schizophrenia, and depression[13]. According to the NMDA glutamate receptor hypofunction hypothesis in schizophrenia, such hypofunction causes GABAergic inhibition loss, eliminating the inhibition on the excitatory pathway that plays a role in the development of psychotic symptoms and schizophrenia development[14]. Neurophysiological studies suggest that clozapine facilitates GABAergic neurotransmission[15]. On the other hand, there is abnormal and excessive firing of glutamatergic neuronal pathways and the loss or blockage of GABA inhibition in epileptic seizures[16]. Many cortical cells receive both GABAergic and glutamatergic stimulation at the same postsynaptic region and the balance between these two systems is complicated and important[17].

The myoclonus and EEG epileptiform activity of our patient were considered to be due to high

doses of clozapine and we tried to slowly decrease this dose in addition to antiepileptic treatment. We decreased the clozapine dose to 625 mg/day, aiming to return to the therapeutic window that was currently exceeded. We had to stay at the 625 mg/day dose when the psychotic symptoms increased with further dose reduction.

Studies report that D2/3 receptor occupancy above a certain threshold is necessary for a response to antipsychotic treatment and the side effects are seen with very high occupancy levels. This indicates the presence of an optimal therapeutic window related to D2/3 receptor occupancy and the potential difficulties of high-dose antipsychotic treatment in clinical practice. Although adequate D2/3 blockage with antipsychotic drugs is necessary for a response, it is not always enough[18].

Clinical studies indicate that there is a therapeutic window for clozapine serum levels during the acute treatment of schizophrenia and schizoaffective patients who do not respond to typical antipsychotics. Serum clozapine levels have been reported to be 198±211 ng/ml in patients with relapse, 1969±705 ng/ml in patients with intoxication, and 384±255 ng/ml in patients with a good response[19]. We were unfortunately unable to check the plasma clozapine level in our case.

The hallucinatory behaviors in our case decreased and his communication increased with a clozapine dose of 625 mg/day. The mean clozapine dose used was 283 mg/day in Europe and 444 mg/day in the USA in a study comparing the mean values in Europe and the USA[20]. Our case was using much higher doses of clozapine. The use of high doses of aripiprazole plus clozapine or just clozapine in our patient did not provide an improvement in the psychopathology of the patient and also caused epileptic seizures. Clozapine-induced side effects such as seizure and confusion would increase as the clozapine concentration or dose increases. Seizure-induced psychotic symptoms can also be seen.

In conclusion, we wanted to emphasize in this article that monotherapy should be preferred for psychiatric patients, the clozapine dose decreased in patients who develop epileptic seizures with clozapine and antiepileptic therapy should be regulated, the optimum therapeutic window should be adhered to during drug use, since higher doses create a risk of side effects and toxicity.

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