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Case Report / Olgu Sunumu

Mania Possibly Induced by Clozapine: a Case Report

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ABSTRACT

Mania possibly induced by clozapine: a case report

Manic shift can be caused by the use of atypical antipsychotics. Hypomanic/manic episodes caused by olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, aripiprazole, zotepine, perospirone, and paliperidone have been frequently described in the literature. The proposed causes of mania/hypomania switching are due to blockages of 5HT2A and D2 receptors, enhancement of 5HT1A receptors, and dopamine release in the prefrontal/frontal regions. There have been no hypomanic/manic episodes described during clozapine use up to the present. A manic shift observed during clozapine use in a 30-year-old woman with schizoaffective disorder depressive type without any history of manic or mixed episodes was presented below.

Key words: Atypical antipsychotic, clozapine, manic episode, schizoaffective disorder

ÖZET

Olasılıkla klozapinin neden olduğu mani: Bir olgu sunumu

Atipik antipsikotiklerin kullanımı manik kaymaya neden olabilir. Literatürde olanzapin, risperidon, ketiyapin, ziprasidon, amisulpirid, aripiprazol, zotepin, perospiron ve paliperidonun yol açtığı hipomani/mani epizotları sıklıkla tanımlanmıştır. Hipomanik/manik kaymanın öne sürülen altta yatan mekanizmaları 5HT2A ve D2 reseptörlerinin blokajı, 5HT1A reseptörlerinin uyarılması ve prefrontal/frontal dopamin salımının artışıdır. Bugüne kadar klozapin kullanımı sırasında tanımlanmış bir mani epizodu yoktur. Aşağıda 30 yaşında şizoafektif bozukluk depresif tip tanısıyla izlenen ve hemen hiç yaşam boyu manik ya da karma epizodu olmayan bir bayan hastada klozapin kullanımı sırasında gözlenen manik bir kayma sunulmuştur.

Anahtar kelimeler: Atipik antipsikotik, klozapin, manik dönem, şizoafektif bozukluk

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INTRODUCTION

Schizoaffective disorder is typically treated by antipsychotics and mood stabilizers or antidepressants (1). Unfortunately, since the atypical antipsychotics have been widely prescribed, there have been many hypomania/mania episodes induced by olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, aripiprazole, zotepine, perospirone, and paliperidone reported (2,3).

Similarly, clozapine is a drug of choice for treating first and second generation antipsychotic drug resistant schizophrenia, recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder, treatment of resistant bipolar disorder and violence and aggression in patients with psychosis and other brain disorders not responsive to other treatments (4). Although, clozapine is a prototype of aforementioned atypical antipsychotics, there has been no hypomania/mania episodes addressed due to clozapine use. The definition of atypicality here comes from its affinity to $5HT_{2A}$ receptors, low affinity (fast dissociation) for the D_2 receptors, and antagonism at the D_4 receptors (5).

This case history focuses on a patient with schizoaffective disorder depressive type who experienced a manic episode after being treated with clozapine for the first time in literature.

CASE

A 30-year-old divorced woman with a daughter, who recently graduated from primary school was

brought to the psychiatry policlinic by her father because she had become withdrawn, tearful and was behaving in an unusual manner. The patient told her father that she heard female voices criticizing her and plotting to kill her. On admission, the patient said that she felt "very depressed" and that she wanted to "end it all". She reported that she felt "consumed by guilt" for the past few weeks. She also described difficulty in sleeping for two weeks prior to admission and had little desire to eat. The patient denied any alcohol or illicit drug use.

The patient has had this disorder for eight years. According to her medical records, she has been hospitalized due to schizoaffective disorder depressive type and experienced no manic or mixed episodes and had paranoid delusions even when there were no depressive symptoms at all. She has had eight previous hospitalizations for psychiatric illness. The first occurred when she was 27 years old. She was hospitalized in the general psychiatry unit for twenty days after reportedly displaying severe anxiety and she was treated with antidepressant and antipsychotic medications, which she discontinued on her own after discharge. She states that she was admitted to the psychiatry outpatient clinic for treatment of paranoid delusions eight years ago. She recalls feeling very depressed prior to these admissions, as feeling difficulty in coping with the divorce. The patient did not take psychotropic medications that were prescribed for her in the hospital.

Her physical and neurological examinations were normal. Complete blood tests, cranial MRI, and EEG were also within normal limits. Because of lack of detailed medical workup during her first episode in 8 years ago, cranial MRI and EEG were ordered for the first time to rule out any organic reason for her psychotic symptoms. Her first reference Positive and Negative Syndrome Scale (PANSS) value was 144 (6) and Hamilton Depression Rating Scale (HDRS) value was 45 (7). She had been treated with paliperidone, risperidone consta, quetiapine, amisulpride, carbamazepine, lithium, valproate, chlorpromazine, sertraline, venlafaxine, olanzapine, and lamotrigine for the past eight years. However, she had a relapse after a short period of treatment response with paliperidone, quetiapine, and valproate. The patient and her father acknowledged that she has not been taking her latest medications for nearly two weeks. So, she started clozapine at 25mg/day for this time to achieve stable and long-term remission. The starting dose was 12.5mg twice daily. The total daily dose was increased in increments of 25mg to 50mg per day, if well-tolerated, to achieve a target dose of 300mg per day (administered in divided doses) by the end of 2 weeks. On the 15th day, after her dosage was increased to 300mg/day and she presented with pressured speech, logorrhea, hypermotility, aggression, insomnia, and increased libido suddenly. Her score on Young Mania Rating Scale (YMRS) was 34 at that time (8). Subsequently, clozapine dose was increased once weekly or twice weekly, in increments of up to 100mg until a total daily dose of 500mg/day over a 2-week period to suppress her mania. But her YMRS score increased to 51. The patient became irritable and grandiose. There was not any concomitant medication use during the clozapine titration. Thereafter, the dose of clozapine was gradually reduced to 300mg/day over a 10-day period. The manic symptoms subsided following the clozapine reduction (YMRS=23 and PANSS=88). The patient was given amisulpride, which she had responded partly well to before. The dose of amisulpride was slowly increased to 800mg/day, while the dose of clozapine was reduced to 200mg/day. The manic symptoms further settled down one week later (YMRS=8, PANSS=65). Within a few days, clozapine treatment was discontinued.

DISCUSSION

Mania and hypomania cases induced by olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, aripiprazole, zotepine, perospirone, and paliperidone have been described in the literature previously (3,9). The causes of mania/hypomania switching are thought to be the result of the blockage of $5HT_{2A}$ and D_2 receptors, enhancement of $5HT_{1A}$ receptors, and prefrontal/frontal dopamine release (10,11).

There are 8 guidelines for the evaluation of drug-associated events: symptomatology and diagnosis

before the onset, diagnostic evaluation at the time of side effect onset, interval between onsets of side effects, dose, medication until introduction of suspected treatment, co-medication, outcome, and rechallenge (9,12). Taking all these aspects into consideration, the patient had no manic episodes during her 8 years suffering from schizoaffective disorder depressive type and during her first year after hospitalization. Psychotic symptoms without any depressive complaints were observed for at least 1 month. Major depressive episode were present for a substantial portion of the total 8 years of the active and residual periods of the illness. Also, mood episodes could be seen in schizophrenia but schizoaffective disorder patients have more severe depressive and manic symptoms (13). Therefore, schizophrenia is not considered in differential diagnosis, according to DSM-IV-TR. The induction of manic symptoms after 15 days following prescription of clozapine (YMRS 34) and the increase of manic symptoms coincided with the increase of clozapine to 500mg/day (YMRS 51), the rapid remission of symptoms with dose reduction by tapering off and the introduction of amisulpride point to a link between clozapine and mood switching. According to algorithm of Naranjo et al. (14), there are no manic episodes described previously due to clozapine use; manic episode appeared after clozapine was administered; manic episode improved after clozapine was discontinued; mania was more severe when the clozapine dose was increased and mania was less severe when the clozapine dose was decreased; manic episode induced by clozapine confirmed by YMRS and PANSS values. Score of 5 according to Naranjo et al. (14) rates the likelihood of mania induced by clozapine as probable. Of course, the other possible explanation in this particular case is that the onset of mania might be coincidental due to a natural course of the disorder rather than the drug use.

Clozapine is classified as an atypical antipsychotic drug because of its profile of binding to serotonin as well as dopamine receptors (15). The $5HT_{2A}$ receptor blockage causes dopamine release in the neocortex. The $5HT_{2A}$ receptor is associated with the cognitive processes of working memory. The $5HT_{2C}$ receptor is found in the hippocampal formation, amygdala, prefrontal cortex, striatum, hypothalamus, and choroid plexus. Stimulation of $5HT_{2C}$ receptors has been proposed to produce anxiogenic and anorectic effects (16). By blocking $5HT_{2C}$ receptors, clozapine may cause an increase in appetite, as well as antidepressant and anxiolytic effects. $5HT_2$ antagonistic action through disinhibition of the dopaminergic system may enhance dopaminergic activity in the forebrain. In this way, it can influence mood. Clozapine is also a partial agonist at the $5HT_{1A}$ receptor, putatively improving depression, anxiety, and negative cognitive symptoms.

Dopaminergic system might also be important in the etiology. In particular, clozapine interferes to a lesser extent with the binding of dopamine at D_1, D_2, D_3, and D_5 receptors; has a fast dissociation from the D_2 receptors and a high affinity for the D_4 receptors (16). The highest levels of D_4 receptors are found in the frontal cortex, midbrain, amygdala, hippocampus, and medulla. The D_4 receptor has long been thought to play a role in expression of novelty seeking behavior. The D_1 receptor mRNA is found in the dorsal striatum, nucleus accumbens and amygdala and has been associated with locomotor stimulation and cognitive functions of dopamine, such as control of working memory and attention (17). The affinity of clozapine for limbic dopamine receptors, especially at D_4 and D_1 and sensitization of the dopaminergic system by fast dissociation at molecular level could explain the mood switching that we observed in our patient.

CONCLUSION

In conclusion, our case report suggests that clozapine may induce mania, similar to other atypical antipsychotic drugs. However, although the exact reasons for this remain unclear, understanding of treatment effects of clozapine on the receptor systems may be important to explain the possible differential mechanisms underlying its clinical and side effect, including mood switching profiles.

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