

## Low-dose Clozapine-induced Seizure: A Case Report

Abdullah Bolu<sup>1</sup>, Süleyman Akarsu<sup>2</sup>, Erdal Pan<sup>1</sup>, Emre Aydemir<sup>3</sup>, Taner Oznur<sup>4</sup>

<sup>1</sup>Aircrew's Health Research and Training Center, Eskişehir, <sup>2</sup>Department of Psychiatry, Iskenderun Military Hospital, Hatay, <sup>3</sup>Department of Psychiatry, Beytepe Military Hospital, Ankara, <sup>4</sup>Department of Psychiatry, Gülhane Military Medical Faculty, Ankara, Turkey

Seizures are believed to be a dose-dependent side effect of clozapine. In this case report, we describe a patient who had tonic-clonic seizures after using a low dose clozapine who did not have any seizure risk. The 29-year-old male patient had been followed-up with a diagnosis of schizophrenia for about 5 years. When using clozapine 200 mg/day he had a tonic-clonic seizure with bilateral diffuse epileptic activity in electroencephalography (EEG). In the literature, there are a few case reports about low-dose clozapine-induced seizure. Seizures were observed in our case with a low dose of clozapine (200 mg/day) making this case remarkable. EEG monitoring at regular intervals and examination of plasma levels of clozapine could be useful in preventing the development of seizures.

**KEY WORDS:** Clozapine; Adverse effects; Seizures; Safety.

### INTRODUCTION

Clozapine is a serotonin-dopamine (5HT<sub>2A</sub>-D<sub>2</sub>) receptor antagonist and an atypical antipsychotics that is used successfully in the treatment of schizophrenia. Although clozapine is one of the most effective antipsychotics, it has life-threatening side effects. Agranulocytosis, bowel infarction, myocarditis, diabetes, sialorrhea, weight gain are common side effects of clozapine.<sup>1)</sup> It can induce epileptic seizures and changes in electroencephalography (EEG)-patterns, and the incidence of seizures during treatment is 1.3% to 10%, depending on dose. The incidence of EEG abnormalities induced by clozapine treatment range from 16% to 74%.<sup>2-9)</sup> The risk of epileptic seizures at low doses is very low, but is associated with dosage escalation and rapid dose titration.<sup>7)</sup> Preexisting seizure disorders, neurological abnormalities, and the combination with epileptogenic medications are the other risk factors.<sup>10)</sup> In this case report, a patient had tonic-clonic seizures after using low dose clozapine. The patient did not have any seizure risk. Physical or neurological disease was not presented.

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**Address for correspondence:** Süleyman Akarsu, MD  
Department of Psychiatry, Iskenderun Military Hospital, Mustafa Kemal District, İbrahim Karaoğlanoğlu Street, 31200, Iskenderun, Hatay, Turkey  
Tel: +90-538-3283032, Fax: +90-326-6182143  
E-mail: sakarsu82@gmail.com

### CASE

The 29-year-old male patient had been followed-up for schizophrenia for about 5 years. He had several symptoms including introversion, impaired social functioning, and unwillingness. He had used olanzapine and risperidone at standard doses and for an adequate period of time. In the process, auditory hallucinations and suicidal thoughts had occurred, and he had been hospitalized twice.

He was admitted to our department with positive symptoms two years ago. On the first hospital day, common blood cell count, routine biochemical tests, electrocardiogram and EEG were done. All test results were within normal limits. Clozapine (25 mg/day) was started and showed inadequate response. Low dose titration up to 200 mg/day was done within 4 weeks. Remission was achieved with 200 mg/day clozapine.

At the third month of treatment, he had a tonic-clonic seizure witnessed by his mother. It lasted 30-40 seconds with a loss of consciousness, deadlock in the chin and urinary incontinence. The patient was in a state of confusion when he arrived the emergency room of our hospital. He had no epileptic seizures before and there was no history of epilepsy in first-degree relatives. There was no history of alcohol use, drug use or head trauma. His body weight was 71 kg, waist circumference was 84 and body mass index was 23.2 kg/m<sup>2</sup>. Blood biochemistry test results (fasting blood glucose levels of serum electrolytes, and re-

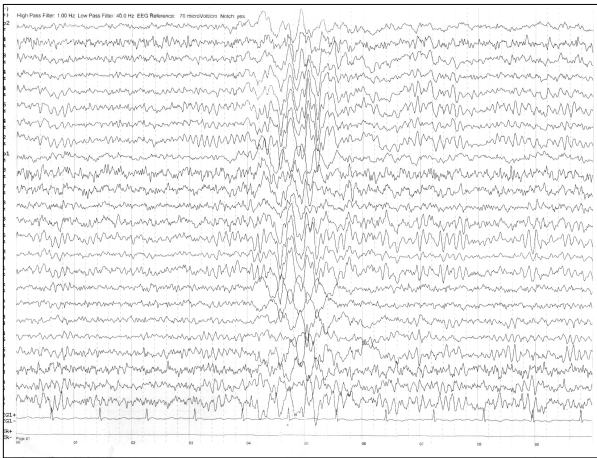


Fig. 1. Bilateral diffuse epileptic activity with 200 mg/day clozapine use.

nal and liver function tests) were normal. Bilateral diffuse epileptic activity was detected at EEG (Fig. 1). The results of the investigations that were performed to rule out other causes of seizures (brain computerized tomography scan, brain magnetic resonance imaging) were normal. The seizure was considered to be triggered by clozapine, according to neurological consultation. Clozapine was reduced to 100 mg/day, and valproic acid 1,000 mg/day was started. EEG performed at 2 weeks, and 4 months after the seizures showed no abnormality (Fig. 2). There was no change in the patient's weight. Seizures did not recur in the patient's follow-up and psychotic symptoms were under control. The patient has taken the same treatment until now and is in remission.

## DISCUSSION

The mechanism lowering seizure threshold of clozapine is not clearly known. Different mechanisms are considered to be effective. According to the prominent hypothesis; mesolimbic structures are closely associated with seizure onset areas and clozapine inhibits D4 receptors on mesolimbic system and cortex.<sup>11</sup> It is thought that this situation causes high epileptogenicity of clozapine.<sup>7</sup> Other possible mechanisms are anticholinergic efficacy of clozapine (H1, Ach-Mus receptor blockade) and its effects on other receptor types such as gamma-aminobutyric acid A, nicotinic acetylcholine, glutamate N-methyl-D-aspartate, serotonin 5-HT<sub>2A</sub>, and strychnine-sensitive glycine.<sup>4,12-16</sup> Increasing seizure threshold of clozapine is dose-dependent. High-dose therapy (greater than or equal to 600 mg/day) was associated with a greater risk of seizures (5% to 14%) than medium (300 to 600 mg/day; 2.7% to

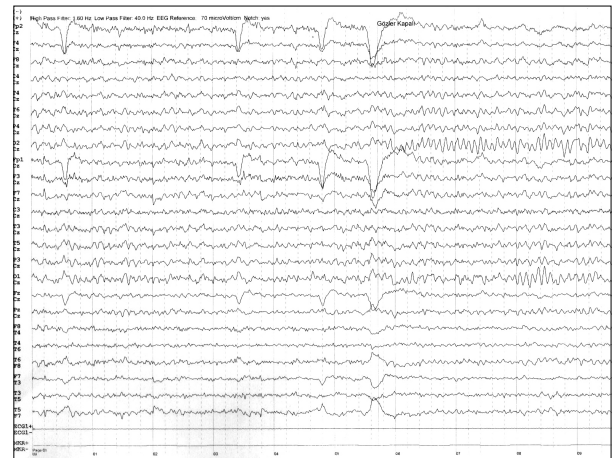


Fig. 2. No abnormality at the electroencephalography performed at 4 months after the seizures with 100 mg/day clozapine and 1,000 mg/day valproic acid use.

4%) or low doses (less than 300 mg/day; 0.6% to 2%).<sup>17-20</sup> Rapid upward titration may also increase seizure risk.

A seizure at 200 mg/day is remarkable. In the literature, there are a few case reports with inaccessible content about low-dose clozapine-induced seizure.<sup>21,22</sup> A case of tonic-clonic seizures after using 300 mg/day of clozapine has been reported.<sup>23</sup> In a study of 26 patients, EEG abnormalities were observed with average  $305.0 \pm 131.7$  mg dose in 10 patients. Clozapine dose was 200 mg/day in 3 of these 10 patients.<sup>4</sup> Having seizures despite low dose clozapine suggests that there may be other risk factors than dose and titration rate for seizures. Some factors such as high doses of antipsychotic drugs, rapid dose changes, abrupt discontinuation of medication, sedative properties of drugs, the presence of organic mental disorders, the presence of previous epilepsy or EEG abnormalities, a history of head trauma, family history of epilepsy and alcohol withdrawal have been reported to increase the risk of seizures.<sup>9,24</sup> An epileptic seizure had developed in our case although he had no these risk factors.

Welch *et al.*<sup>2</sup> suggested that the EEG is a sensitive indicator of clozapine toxicity. EEG abnormalities such as spikes and sharp waves indicate a increased risk of convulsions. Other studies show that EEG abnormalities may be present without any association with clinical seizures.<sup>25-27</sup> In this case, while EEG pathology was not detected before starting clozapine, no EEG monitoring was performed while using the drug. The relationship between incidence of seizure and EEG abnormalities developed after starting clozapine use needs to be examined with more extensive prospective studies.

Plasma clozapine levels were not measured here. A

strong relationship between clozapine dose and plasma level and clozapine-induced EEG abnormalities were described. However, no statistically significant relationship between dose and incidence of seizures has been detected,<sup>27,28)</sup> and plasma levels of clozapine in some patients may be low despite the high-dose clozapine use. Clozapine plasma levels may be excessively reduced with smoking. After quitting smoking, a sudden rise in plasma clozapine level can be seen. Also, drugs interfering with cytochrome P450 1A2 may increase or decrease the plasma levels of clozapine. Thus, therapeutic drug monitoring of clozapine has been suggested to predict the onset of seizures.<sup>27,29)</sup> In case of developing epileptic seizures during clozapine treatment, clozapine dose reduction, changing clozapine with another antipsychotic drug or adding antiepileptics to the treatment are recommended.<sup>30)</sup> We did not change the clozapine treatment of our case because of previously insufficient response to the antipsychotic treatment except clozapine. We thought it was more appropriate to make seizure prophylaxis with antiepileptic treatment. We started sodium valproate as standard dose level for the prevention of seizures occurring due to the use of clozapine.<sup>7)</sup> Antiepileptic prophylaxis in patients using clozapine without clinical seizures can be performed in such cases at a certain clozapine dose or plasma level (> 500 µg/L) or the appearance of clear epileptiform discharges on EEG.<sup>27,28)</sup>

Clozapine has serious side effects and to monitor patients on clozapine is advisable.<sup>31)</sup> EEG monitoring at regular intervals and examining plasma levels of clozapine would be useful for preventing the development of seizures. However, plasma level of clozapine or electroencephalogram findings may be insufficient to predict the incidence of seizures.<sup>32,33)</sup> Epileptic seizures can be seen even in very low risk situations such as our patient. Using drugs to reduce the epileptic threshold with clozapine should be avoided. Also raising awareness in the families of patients using clozapine is important. When a first seizure occurs, reducing the dosage of clozapine or employing an alternative antipsychotic agent should be preferred. If a second seizure occurs, an anticonvulsant drug should be started.<sup>32)</sup>

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