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Case Report Open Access

A Case Study of Partial Seizure with Secondary Generalization Induced by Clozapine in Patient with Treatment Resistant Schizophrenia

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Abstract

Background: A patient with schizophrenia, who was resistant to treatment by several typical and atypical antipsychotic medications, was prescribed clozapine. After receiving clozapine at a high dose, he experienced two seizure episodes.

Objectives: To highlight serious side effects, such as seizure, that can emerge with administration of psychotropic agents, as well as recommend approaches to intervene in these cases.

Conclusion: Clinical knowledge of potential severe side effects of antipsychotic medications (e.g Clozapine) is essential and detailed clinical evaluation may help to avoid serious harm to patients as well as treatment failure.

Keywords: Clozapine; Schizophrenia; Seizure

Introduction

Schizophrenia is a mental disorder that generally appears in adolescence or early adulthood; although, it can emerge at any time in life. Schizophrenia patients may have different symptoms like; delusions, abnormal affect, disorganized speech, hallucination, agitation, social withdrawal, and bizarre behaviors.

The primary treatment of schizophrenia is antipsychotic medications, preferably combined with psychological and social support (National Collaborating Centre for Mental Health UK). Hospitalization may be required for some patients, either voluntarily or involuntarily; if needed. The first-line intervention for schizophrenia is antipsychotic medication [1] which can reduce the positive symptoms of psychosis. However, these medications may not significantly improve the negative symptoms of schizophrenia and cognitive dysfunction [2]. Among antipsychotic medications, clozapine has some negative side effects in the treatment of resistant schizophrenia.

Different substances, including medications and illegal drugs, increase the risk of epileptic seizures [3,4] Reports related to antidepressants and antipsychotics show seizures are more often related to these medications than other neuroactive drugs [4]. Almost all antipsychotic medications have been associated with a risk of decrease seizure threshold. Among the typical antipsychotics; chlorpromazine appears to be associated with the greatest risk of seizures while Clozapine is highly suspected of causing convulsions among the atypical antipsychotics [5].

Clozapine is a dibenzodiazepine derivative which has receptor blocking activity at dopamine D1 and D4 as well as seroto-nin 5-HT1A and 5-HT2 receptors [6]. Clozapine is a widely used atypical antipsychotic for treatment-resistant schizophrenia that can cause other medical problems [7].

In the available published data, there is no case report in literature of Clozapine induced seizure reported from Saudi Arabia which is a common prescribed medication in our local psychiatric hospital, and there is paucity of local data to emphasize the importance of this issue, although there are hundreds of publications worldwide. One of the main reasons for this case report is to highlight the importance of the unusual adverse effects of clozapine that may encounter in patient with psychiatric disorder by general practitioners and psychiatrists

Case Presentation

A 32-year-old male, who smokes and is a well-known to Al-Amal Complex for Mental Health-Dammam as having schizophrenia for about 14 years, was admitted to the inpatient unit with a history of exacerbation of his psychotic symptoms, as well as deterioration in his mental condition. Upon admission the patient exhibited: grandiose delusions, auditory hallucinations, self-talking, irritability, lack of sleep and disruptive behaviors. Routine assessment as well as a drug screen was requested upon admission. All results were within normal range; there was no evidence of drug abuse. Clinical data were reviewed as well as farther history was obtained from the family. This showed the patient has been prescribed various antipsychotic medications (both typical and atypical) with no improvement. Patient was diagnosed as having treatment resistant schizophrenia and was started on clozapine at a dose of 25 mg at night, titrated up gradually. This had never tried with this patient. After reaching 900 mg of clozapine per day on a divided dose, the patient lost consciousness while in the bathroom, fell and was unconscious for 2 minutes, but was not injured. Upon examination his vital signs were within normal range. The second day after his loss of consciousness, the patient again lost consciousness in

the washroom, although not witnessed by nursing staff. After the ictal phase of the seizure, he was drowsy with a bleeding wound on his face. On examination vital signs were: blood pressure (BP) 128/83, respiratory rate (RR) 19, pulse rate (PR) 118, temperature 36.8°C, O2 saturation 98%. Patient was semiconscious, and disoriented to time and place. He was in distress, lying on the bed with a 5 cm wound on his face, which received stitches. Pupils were reactive bilaterally. Tongue was central and no signs of lower cranial nerve palsy. Chest and air entry were clear, with no wheezes or crackles. Cardiovascular examination was normal. Central nervous system examination was significant for up-going plantar response bilaterally with no focal or lateralizing signs. His electrocardiogram showed tachycardia and right bundle branch block. Echocardiogram was normal (Figure 1).

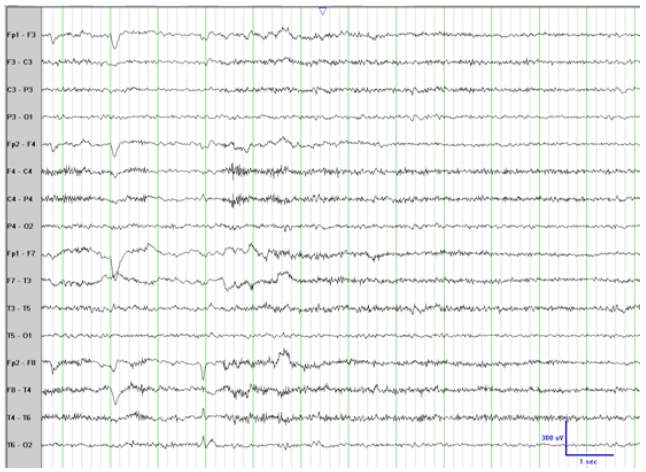

Figure 1: Interictal scalp EEG recording during wakefulness; showed right anterior temporal sharp wave over F8 - T4 electrodes with prominent muscle artifact.

Patient was evaluated by cardiologist, neurologist and ear nose and throat specialist. Patient had an Electroencephalogram (EEG) which showed infrequent spikes over left fronto-temporal area with moderate generalized theta and delta activity. The clozapine was withheld and then restarted at a reduced dose; 400 mg twice daily. Valproic acid was introduced and titrated up gradually to the therapeutic dose of 500 mg twice daily. Patient did not develop any more seizure and was discharged from the hospital in stable medical and mental condition. 6 month post discharge in the follow up visit to the outpatient clinic patient report no recurrence of seizure or attacks of loss of consciousness and no side effect from the medications.

Discussion

Seizures have been reported with different psychotropic medications including antidepressants and antipsychotics [3-5,8]. Clozapine is one of the atypical antipsychotic medications with limited use for treatment of resistant schizophrenia [9]. One serious side effect is seizures, which have been observed at different doses. Reported incidence rates for seizures during clozapine treatment is 2.8% [10], 1.3% [11] and more recently as 4% [2] Some studies also showed a strong relationship between clozapine dose and plasma level and EEG abnormalities [7,12] Lower dosages and slower titration may reduce the risk of seizure.

There is no agreement yet about when to use antiepileptic medications with clozapine treatment [2] Valproic acid is considered sometimes as prophylaxis for clozapine-induced seizures [7] in our patint we started valproic acide at a low dose 200 mg twice a day then increase the dose gradually. valproic acid may be a better choice for the treatment and prophylaxis of clozapine-induced seizures if there is a mood disturbance, but it might not be beneficial for all patients. In some cases where they are resistant to clozapine treatment, lamotrigine may be a better option [7]. In this patient the EEG was abnormal and Clozapine has a significant tendency to induce electroencephalogram (EEG) changes, ranging from 53% [13] to 74% [14]. The abnormality including the presence of generalized slow activity of theta and delta frequency which is a prominent finding in similar studies [15] other EEG abnormality is the presence of focal spikes which is reported in 16% [13].

Smoking cessation has been associated with seizures, since it reduces metabolism of clozapine via CYP1A2, which leads to increased clozapine levels [16] Clozapine levels in the blood should be monitored closely and dosage reduced if necessary [17]. In our facility, smoking is prohibited in the inpatient unit. A thorough assessment [18] upon admission will determine a patient's health habits; medications then can be adjusted to avoid any metabolism issues.

Conclusion

Clozapine is an effective treatment for Schizophrenia, Serious side effects can occur with the use of clozapine including seizure, which can occur with different doses. Clinicians should be aware of these side effect since they can be life threatening particularly with the use of high dose of clozapine. Comprehensive clinical evaluation with the appropriate lab test and electroencephalogram are essential to establish the diagnosis of seizures in patients treated with clozapine. If seizure occurs it is recommended to withhold clozapine for 1 day, and then restart clozapine at a reduced dose, while also initiating anticonvulsant medication (Taylor D et al.). Close observation to other factors should be considered that might influence the plasma level of clozapine, such as drug-to-drug interaction, as well as smoking. Farther studies are needed to quantify the true risk of seizures with clozapine use.

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