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CASE REPORT ON CLOZAPINE INDUCED SEIZURE

Greeshma Hanna Varghese*, Hanna Alexander, Swethalekshmi V., Neethu Ros Tom, T. R. Ashok Kumar, Dr. T. Sivakumar

Nandha College of Pharmacy and Research Institute, Erode-52.

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***Correspondence for Author**
Greeshma Hanna Varghese
Nandha College of Pharmacy and Research Institute, Erode-52.

ABSTRACT

Clozapine is a widely used atypical antipsychotic with a unique effectiveness in treatment-resistant schizophrenia. An important adverse effect is seizures, which have been observed at all stages of clozapine treatment. Compared with standard neuroleptics clozapine has minimal extra pyramidal side effects and poses a low risk for tardive dyskinesia. Most drug induced seizures resolve after discontinuation of the offending drugs, but some patients require supplementary treatment. Valproate has traditionally been considered the drug of choice for the prophylaxis of clozapine induced seizure.

KEYWORDS: clozapine, seizure, adverse drug reaction.

INTRODUCTION

Clozapine is a unique atypical antipsychotic which has an effect in the treatment of schizophrenia because of its binding to serotonergic and dopamine receptors.[1,2] It is distinguished from typical antipsychotics by its greater efficacy and reduced tendency to cause extra pyramidal movement disorders.[3,4] The literature varies on incidence rates of seizures, secondary to varying time frames in which each seizure occurred. Seizure is estimated to occur in association with clozapine with a cumulative 1 year risk of approximately 5 %.[5] The major adverse drug reaction is seizures, which have been observed at all stages of clozapine treatment. Other adverse effects include hypotension, fatigue, drug fever, pharmacogenic delirium, elevated troponin level and creatinine kinase level, cardiotoxicity and agranulocytosis.[6,7,3] In addition, clozapine causes epileptiform abnormalities in the EEG in up to 72% of patients.[8] Compared with standard neuroleptics clozapine has minimal extra pyramidal side effects and poses a low risk for tardive dyskinesia[3]. Most drug-induced seizures resolve after discontinuation of the offending drugs, but some patients require supplementary treatment. The antiepileptic of choice for the

prophylaxis and drug of choice of clozapine-induced seizures are valproate.[9] Here we are describing a case of paranoid schizophrenia that developed with clozapine.

CASE PRESENTATION

Mr. Z, a 30-year-old male with paranoid schizophrenia, was admitted in hospital on 16.1.2015 with a compliance of severe disruptive behaviours, severe aggression, auditory hallucinations and delusions. He often remained indoors, would not interact with family members and would become agitated when his privacy was intruded upon and patient claims of having relationship with filmstars.He was started on low dose of clozapine 25mg twice a day with concomitant administration of trihexiphenidyl.The dose of clozapine was gradually increased with close monitoring of the complete blood counts and ECG. An initial dose of 50 mg/day was increased to 100 mg twice daily. After 1 week again the dose of clozapine was increased to 900mg/day. On the 7th day of clozapine treatment, at a dose of 900 mg/day, the patient had symptoms of seizure. He complained of dizziness and his body became stiff and head turned to one side followed by rhythmic tonic and clonic convulsions of both upper limbs. There was frothing at mouth. There was no personal or family history of epilepsy or history of head injury; CT scan of head was normal. The clozapine plasma level reached above 700 mg/l. 15 to 30 minutes after the attack, the patient was controlled with intravenous administration of 1200 mg of phenytoin in 200 ml of normal saline over 30 minutes and clozapine was withheld. After 6 days of therapy, clozapine was reintroduced starting with low dose of 100 mg and increased and continued with the dose of 600mg along with sodium valporate 10mg twice daily.

DISCUSSION

We present this case since the management of this patient brought out a number of important points concerning clozapine-induced seizure. Clozapine is an atypical anti psychotic drug used for the treatment of schizophrenia. In this patient it was identified that the clozapine 900 mg is the major cause of seizure. Although, our patient was rechallenged with clozapine 600mg with concominent therapy of sodium valporate. In this case phenytoin was replaced with sodium valporate because of serious adverse effects additive to those of clozapine, which could potentially lead to clozapine cessation.

In this patient it was noticed that the patient plasma level of clozapine was above 700mg/l. The plasma level for acute response to clozapine is in the range 200 to 504 mg/l .In those not responding to clozapine, a plasma level of 350 to 500 mg/l has been suggested. When

initiating clozapine, the dose should be titrate slowly to 350 mg/l, because seizures are more common during the initiation phase .If there is no response, increase the dose to give a plasma level of 500 mg/l. Consideration should be given to introducing an AED if the clozapine plasma levels are above 500 mg/l. Antiepileptic therapy should also be considered at the beginning of clozapine treatment in patients using other epileptogenic medication, patients with pre-existing seizure disorder and in patients with neurological abnormalities.[8]

The antiepileptics of choice for the treatment and prophylaxis of clozapine-induced seizures are valproate and lamotrigine. Valproate has advantages over other AEDs: it has a broad spectrum of antiepileptic activity; it is effective in primary generalized seizures such as, tonic clonic, myoclonic and both simple and complex absence seizures. And also by using as a prophylaxis of sodium valporate it helps to continue clozapine 600mg /day without any alternative. Common adverse effects of valproate include dyspepsia, gastric irritation, nausea, increased appetite and weight gain. Valproate may not always be suitable for use in combination with clozapine because of certain adverse effects like weight gain and sedation.[8,7]

Other AED which is most preferable is Lamotrigine .It has a limited adverse effect and also there are only few pharmacodynamic interactions. In addition, its lack of effect on hepatic enzymes, there are also few pharmacokinetic interactions. It should be noted that lamotrigine concentrations are decreased by high estrogen levels in pregnancy and by estrogen-containing oral contraceptives.[8]

CONCLUSION

Physicians should consider about 4 factors before prescribing clozapine while treating psychiatric patients. Those are: I) dose shouldn't exceed above 600 mg/day; 2) slowly increase the daily doses; 3) therapeutic drug monitoring: plasma clozapine level shouldn't exceed 500mg/l and 4) add any antiepileptic drug as prophylaxis.

For seizure prophylaxis, AED should prescribe after the occurrence of myoclonus, stuttering or speech difficulties, any type of seizure, epileptiform changes on the EEG, and in those with risk factors such as pre-existing seizure disorder or those with relevant neurological abnormalities, and also once the clozapine plasma level reaches or exceeds 500 mg/l. The AEDs of choice appear to be valproate for a schizoaffective illness, topiramate or lamotrigine

for patients with clozapine- induced weight gain, and lamotrigine in clozapine induced refractory schizophrenia.

One of the other major factor is to avoid concomitant use of other medications which lower the seizure threshold. For example, lithium, neuroleptics and tricyclic antidepressants can lower the seizure threshold.

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