Seizure associated with olanzapine

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ABSTRACT

Atypical antipsychotics are known to be associated with electroencephalogram abnormalities. Olanzapine can lower seizure threshold and induce epileptiform discharges. However, in patients on Olanzapine for the treatment of a primary psychiatric disorder, clinical seizure is a rare occurrence. We report the case of a 23-year-old female with mild mental retardation with schizophrenia and obsessive compulsive disorder who developed new-onset generalized tonic-clonic seizure probably due to Olanzapine. Electroencephalogram showed epileptiform discharges. The seizure risk associated with Olanzapine was reviewed.

Keywords: Adverse effects, drug-induced seizure, Olanzapine, seizure

Introduction

Olanzapine is one of the most commonly used antipsychotic agents. It is closely related to Clozapine chemically. The dose-related inducement of seizure by Clozapine though is well known, and that of Olanzapine is limited. Among the trials conducted for FDA approval of drugs, the incidence of seizure was significantly higher in the Clozapine and Olanzapine groups.¹

The premarketing trials have found incidence of seizures at 0.88%, which is comparable to other conventional antipsychotics.¹ Despite its proconvulsant liability, the literature reporting seizures are sparse. Few case reports of fatal status epilepticus and myoclonic status have attributed Olanzapine as the causative agent.²,³ Hereby we are reporting a case of seizure in a patient receiving Olanzapine with a brief review on seizure risk associated with Olanzapine use.

Case Report

A 23-year-old female diagnosed with mild mental retardation with schizophrenia and obsessive compulsive disorder under treatment from a psychiatrist. On treatment review it was noted that she had taken Olanzapine 20 mg with Fluoxetine 20 mg for nearly 4 years with good response. She discontinued her medicines finding a good improved period to relapse within a year of stopping. On re-emergence of symptoms she by herself on parents’ advice restarted Olanzapine 20 mg with Fluoxetine and within 3 months had an episode of seizures. She then visited a psychiatrist who shifted her from Fluoxetine to Escitalopram 10 mg. After 2 months of Olanzapine 20 mg with Escitalopram 10 mg she had a second episode of seizure with which she was brought to the hospital. Both the seizures were of similar manifestation, starting with a prodrome of dysphoric feeling and crying due to “unexplainable discomfort” lasting for around 90 minutes late in the evening and thereafter getting into sleep. Within an hour of sleep there was sudden awakening with right-sided twisting of head and jerky movements followed by loosening of awareness and then gradually spreading of jerky movements to whole of the body. Confusion prevailed for few minutes before gaining full consciousness.

On examination, tongue bite mark was noted without any focal neurological deficits. She had negative symptoms but no active positive psychotic symptoms, depressive or obsessive compulsive symptoms. Electroencephalogram (EEG) done after 12 hours of...
seizure revealed intermittent generalized frontal-dominant slow wave activities suggestive of postictal state. Magnetic resonance imaging brain showed diffuse atrophic changes.

Olanzapine was cross tapered with Risperidone. Carbamazepine was started with Lorazepam as anticonvulsant. Escitalopram was continued. Patient was discharged after 10 days with no subsequent seizures.

**Discussion**

The case suggests precipitation of seizures by Olanzapine which was restarted rapidly at the previously prescribed dose. Seizure occurred after the patient was on Olanzapine and did not have seizure in the brief follow-up period of stopping it. No other alternative explanation could be found for sudden appearance of seizures in our case although a high-risk state with mental retardation was present. The adverse event got repeated in our case but the trial for attribution by stopping and restarting the medicines could not be done owing to high fatal risk of the seizure. The objective evidence in the means of abnormal EEG was noted. Thus concluding according to Naranjo algorithm with a score of 5, the seizure occurring in our case was probably due to Olanzapine.[4]

**Olanzapine, seizure, and neurotransmitters**

Among second-generation antipsychotics, although Clozapine is a well-known agent inducing seizures, no drug is out of risk. Various mechanisms have been considered to cause seizures in persons on antipsychotics, reduction of GABA neurotransmission being a common final pathway. Dopamine D2 receptor antagonism, histaminergic H1 antagonism, and alpha-1 antagonism have been commonly attributed.[5] Chronic alpha-2 receptor and sigma-1 receptor changes have also been noted.

As none of these mono-neurotransmitters can explain the differential seizurogenic potential of psychotropic drugs, dual neurotransmitter/receptor imbalances have been hypothesized. Drugs with higher dopamine:acetylcholine imbalance, serotonin:acetylcholine imbalance, D1:D2 antagonism, alpha 1:alpha 2 antagonism, and alpha 1:D2 receptor affinities are observed with higher rate of convulsions. Drugs with more affinity on dopamine receptors in cortical compared to subcortical (hippocampal/nigrostriatal) areas have also been noted to increase seizure liability.[6]

Neurosteroids have also been commonly implicated. Progesterone, allopregnanolone, and dehydroepiandrosterenedione protect against seizures by modulating GABA-A, NMDA, and acetylcholine receptors. Their secretion and metabolism are often altered by Olanzapine and triggers kindling. Testosterone, adrenocorticotropic hormone, and desoxycorticosterone also may get affected, thereby increasing the risk of seizures. Estradiol, cortisol, and thyroid hormones are by themselves proconvulsants and on elevation during treatment with antipsychotics may precipitate seizures.[7]

Although Olanzapine and Clozapine are structurally similar, they differ in few of the receptor affinities. Olanzapine is having higher D1, D2 and lower D4 dopamine receptor affinity compared to Clozapine. It has only half the affinity to alpha-1 in comparison to D2 receptor, whereas Clozapine has 18 times higher affinity. More 5HT6 serotonergic action and lesser muscarinic anticholinergic action with increasing neurosteroids are observed in Olanzapine. All these have been hypothesized to be the cause of lower risk of Olanzapine in decreasing seizure threshold.[8] Hence we hypothesize that those with mutations in genes encoding these receptors or their messenger systems may have an elevated risk for seizure with Olanzapine.

**Olanzapine and risk for seizures**

Olanzapine is known to cause highest EEG changes, in 35-45% of cases,[6-9] among the non-Clozapine newer antipsychotics.[5] Atypicals have high propensity to cause EEG changes compared to typical antipsychotics.[9] Generalized/focal symmetrical theta and delta waves are more commonly found abnormal activities followed by asymmetrical slow waves, sharp waves with phase reversals, and spike-and-slow wave patterns. The later severe epileptic changes were noted in up to 11-15% of cases on Olanzapine.[8,9] EEG changes were noted at around 4-7 months of starting Olanzapine in most of the literature.[1,2,8]

As normal EEG could be seen in most of the reported cases including our case, it would be seen beneficial to monitor EEG as a seizure preventive strategy in high-risk patients after the cost effectiveness being evaluated. Few of the high-risk groups as discussed below would benefit from it.

No prospective data regarding mean duration of appearance of changes have been done. But dose and duration both were not found to be correlating with the EEG changes. As in our case, the patient had long-term Olanzapine use, but had discontinued and restarted which led to seizures. Abrupt changes in doses are noted to increase the risk.[11] An acute stimulation of Olanzapine-sensitive/kindled neurons could be elevating the risk. A U-shaped relation of dose—seizure frequency was established for conventional antipsychotics like Chlorpromazine.[12] Similar mechanism of seizurogenic potential at a dose lower than therapeutic level might be inducing seizures with Olanzapine. The presensitized patients having developed tolerance would be at a lower therapeutic range in synapses even at the prior doses. Thus, the prior dose could be precipitating a seizure as a co-occurrence which is lower than the therapeutic level.

Old age, organicity, epilepsy, hypertension, bipolar disorders, and comorbid OCD are few known factors associated with Olanzapine-induced seizures.[13] Multiple psychotropic drugs except Benzodiazepines[7,13-15] change from typical to atypical antipsychotic,[11,16] and addition of another serotonin–dopamine inhibitor (Quetiapine) to Olanzapine is seen in reported cases of Olanzapine-induced seizures.[13] As in our case, the presence of mental retardation, obsessive compulsive disorder, and SSRI would have increased the risk of seizure with Olanzapine.
No expert reviews exist regarding the suitable way of managing these seizures. Stopping Olanzapine though could be recommended, the risk of cholinergic rebound effects on abrupt cessation of Olanzapine should be monitored. Olanzapine might take few weeks to completely wane off from the body even after stopping. With the report of fatal status epilepticus and persistence of abnormal EEG, the need of anticonvulsants at least until normalization of EEG could be considered.

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Conflicts of interest
There are no conflicts of interest.

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