PRO-CONVULSANT EFFECT OF OLANZAPINE, AN ATYPICAL ANTIPSYCHOTIC ON MAXIMAL ELECTRO SHOCK INDUCED SEIZURES IN WISTAR ALBINO RATS

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ABSTRACT

Objectives: The aim of the study was to investigate the chronic effect of Olanzapine; an atypical antipsychotic drug on maximal electroshock (MES) induced seizures in Wistar albino rats.

Methods: Olanzapine (2mg/kg, 10 days orally) was used to study its effect on MES induced seizures in Wistar albino rats. Duration of the tonic hind limb extension was noted.

Results: Olanzapine (2mg/kg) significantly (p<0.001) increased the duration of hind limb extension induced by MES.

Conclusions: The data suggests that Olanzapine, the atypical antipsychotic drug has a proconvulsant action.

Key Words: Convulsion, Maximal electroshock, Olanzapine, Proconvulsant

INTRODUCTION

Mental disorders constitute a large part of the global burden of disease. Schizophrenia is an incapacitating mental disorder, with long term impact on a person’s life. This mentally devastating illness affects family relationships, social functioning and employment. This debilitating illness accounts for huge amount of health care cost all over the world. The symptoms of this complex disorder fall into two different categories, i.e. positive and negative symptoms. Multiple strategies are involved in the management of this psychiatric disability. Typical antipsychotics are good in alleviating the positive symptoms of this mental illness, whereas atypical antipsychotics are effective in reducing both the symptoms (Rene, 2009). Olanzapine is one among the atypical antipsychotic used as an oral formulation for treatment of schizophrenia and bipolar disorder. Olanzapine is high affinity antagonist at 5HT2A, 2C, 5HT6, D1-4 and adrenergic α1 receptors and moderate affinity antagonist at M1-5 & 5HT3 receptors. Being an atypical antipsychotic, the incidence of adverse effects with olanzapine are less on comparing with typical antipsychotics. Olanzapine is known to lower seizure threshold and induce epileptiform discharges in EEG. Still, clinical seizure is considered a rare occurrence, in patients on Olanzapine for the treatment of a primary psychiatric disorder. Seizures are not considered as known adverse effect (Behere, 2009; Martindale, 2009; Naim, 2007). However, there are quite a few case reports of generalized tonic clonic and myoclonic seizures in patients started on Olanzapine. Patients, who have no significant case history of seizures, had developed seizures after starting olanzapine. Interestingly, these episodes of seizures did not reoccur after switching the drug or adding an anticonvulsant with Olanzapine (Behere, 2009; Martindale, 2009; Naim, 2007). Hence, present study was carried out to evaluate the chronic effect of Olanzapine on Maximal Electroshock induced seizures in Wistar albino rats.

MATERIALS AND METHODS

Animals
The institutional animal ethical committee (IAEC) approval was obtained before conducting experiments. Adult Wistar Albino rats of both sexes, weighing 200-300g were used. They were kept under standard housing conditions.

Drugs
Phenytoin (standard) 25mg/kg (Manikkoth et al, 2011); Olanzapine (test drug) 2mg/kg (Alexa, 2008) were obtained from institutional pharmacy.
METHODOLOGY
Rats weighing 200-300g of either sex were divided into three groups of 6 animals each.  
Group I: Control (distilled water)  
Group II: Test drug (Olanzapine 2mg/kg)  
Group III: Standard drug (Phenytoin 25mg/kg)  
All the drugs were administered, orally for 10 days. On 10th day, after an hour of drug administration of test compounds, the animals were taken for maximal electroshock test.

Maximal electro shock (MES) test
Electrical stimulation was applied using ear electrodes. The electrodes were moistened with saline before application. All animals were stimulated with 150mA for 0.2 seconds, with constant voltage stimulators of 250 V. Suppression of tonic hind limb extension was taken as a measure of efficacy in this test (Manikkoth et al, 2011).

RESULTS
Animals treated with Olanzapine showed (Table-1) significant prolongation of duration of hind limb extension (P<0.001) than their control treated counterparts. Mortality rate in Olanzapine treated group was more than control group. This clearly suggests the pro-convulsant effect of this atypical antipsychotic.  

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drugs</th>
<th>Dose (mg/kg)</th>
<th>Duration of Hind Limb Extension in seconds on 10th day</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Distilled Water</td>
<td>-</td>
<td>6.41±0.02</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Olanzapine</td>
<td>2</td>
<td>14.32±0.643</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>Phenytoin</td>
<td>25</td>
<td>0.0±0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

N=6, Results are expressed as Mean ± SD. One Way ANOVA, followed by Tukey Kramer multiple comparison test a: p<0.01, considered significant, on comparing group II and III with group I

DISCUSSION
Ever Since 19th century, the relationship between epilepsy and Schizophrenia like psychosis has attracted and confused the psychiatric population. There are lot of clinical evidences to prove that there is an association between epilepsy and schizophrenia like psychosis. It is a known fact that all typical antipsychotic medications have the tendency to cause paroxysmal EEG irregularities and induce seizures, and the effect is connected to drug type and dose. The atypical antipsychotics are not free of this effect, clozapine being the most epileptogenic among the antipsychotics (Perminder Sachdev, 1998).

From this pre-clinical study it is evident that Olanzapine also has a potential to cause convulsions. One of the possible mechanisms may be 5HT antagonism. 5HT antagonists are known to lower epileptic threshold (Isaac, 2005). Mutant mice lacking 5-HTTc receptors have shown increased seizure activity and/or lower threshold (Bagdy, 2007). Other possible mechanism may be Glutamate potentiation. Studies have reported up regulation of AMPA and metabotropic glutamate receptors on chronic exposure to Olanzapine in rats (Tascedda, 2001). Another study has reported significant increased serum & cortical glutamate levels in patients of schizophrenia treated with Olanzapine (Donald, 2002). All the above facts underline that Olanzapine has a proconvulsant property. Considering the fact that psychosis is a direct consequence of the epileptic form disturbance Perminder Sachdev, 1998), the incidence of antipsychotic drug induced epilepsy will in turn derail the management of this awful psychiatric disorder. Hence, Olanzapine must be used cautiously in psychosis patients, with a history of generalized seizures, or who have conditions associated with seizures, or usage of concurrent medication that lowers seizure threshold or have a lowered seizure threshold.
CONCLUSION
Olanzapine has a potential to cause seizures. It’s better to do an EEG screening, before initiating olanzapine therapy in any psychiatric patient. This study also stresses the importance of a thorough pharmacovigilance.

REFERENCES