Anti-epileptic effect of Rosuvastatin

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ABSTRACT

This study investigated the anti-seizure potential of Rosuvastatin, a known anti-hypertensive agent on Pentylenetetrazol-induced seizure in Wistar rats. 30 adult Wistar rats were used and divided into six (6) groups of five (5) rats per group. Group A, the negative control, was given just PTZ 110 mg/kg, intraperitonally. Groups B, C and D were exposed to oral Rosuvastatin 20, 40 and 60 mg, respectively preceding PTZ 110 mg/kg. Group E was treated with 10 mg diazepam and 110 mg/kg PTZ, while group F received diazepam 10 mg to Rosuvastatin 40 mg combined treatment 30 min prior to PTZ 110 mg/kg. The results obtained showed non-significant increase in latency to first minimal clonic seizure (FMCS), non-significant decrease in Post Ictal Sleep Period (PISP), whereas no effect was observed on the latency to first generalize tonic clonic seizure (FGTCS). The results of the combination of Rosuvastatin and diazepam however, revealed a potent synergistic effect. This study therefore concludes that Rosuvastatin can be used as an adjunct treatment to diazepam therapy for epilepsy as it has been found to have synergistic action when combined with diazepam.

Keywords: Rosuvastatin, anti-seizure potential, epilepsy, Wistar rats.

INTRODUCTION

Epilepsy is a non-contagious chronic brain abnormality evidenced by periodic and unpredictable manifestation of seizures, a transient alteration of behaviour due to disorganized, synchronous and rhythmic discharging of populations of brain neurons. It attacks people irrespective of age. Epilepsy has affected approximately fifty million people globally and is among the most ubiquitous neurological diseases worldwide (WHO, 2017). About 6.2% of Nigerian population in rural areas has epilepsy (Longe and Osungtokun, 1989).

The annual cost of anti-epileptic drugs used in Ahmadu Bello University Teaching Hospital Kaduna in Nigeria was thirty thousand nine hundred and eighty six naira sixty seven kobo (#30,986,67) in 2014 (Aduke, 2014). Besides this financial burden, victims of epilepsy and their family members across different countries are often stigmatized and discriminated because of the erroneous belief that epilepsy is contagious (Aduke, 2014; WHO, 2017). A single episode of seizure is not enough to confirm the patient epileptic nature. However, the patient is epileptic after manifestation of more than two episodes of convulsions (WHO, 2017). Interestingly, the lights of research have recently identified statins as one of the classes of drugs showing evidence of pleiotropism including anti-excitatory activity on neurons. This is an effort at drug repurposing where an existing drug used for other clinical conditions is being evaluated for efficacy on another clinical condition.

METHODOLOGY

A total of 30 adult Wistar rats weighing between 250 to 350 g were obtained from the Department of Pharmacology Animal House and used for this study. A 6-compartment cage was constructed of wood and wire-net at a portion allocated for this study. It was formed to permit adequate ventilation and natural illumination. The 6-compartment cage housed 5 rats per group.

Induction of experimental seizures

Pentylenetetrazol (PTZ) is a chemical used to induce epilepsy and evaluate the effectiveness of proposed anti-
Figure 1: Comparative effect of Rosuvastatin, Diazepam and diazepam-rosuvastatin combined therapy on the first minimal clonic seizure. ROS: Rosuvastatin; DZP: Diazepam.

Epileptic drugs (Hosseinzadeh and Sadeghnia, 2007; Mohammad et al., 2009). The study adopted the protocol and description pattern established by Hosseinzadeh and Sadeghnia (2007). Specific features were observed and documented. The Wistar rats were treated with the proposed anti-seizure agents 30 min before PTZ (110 mg/kg, i.p.). The animals were observed for 60 min after PTZ administration. Behavioral responses of the animals to PTZ administration were evaluated using these criteria: latency to first minimal clonic seizure (FMCS), which involves less-severe myclonic jerks, face and forelimbs clonus without loss of righting reflex, latency to the first generalized tonic-clonic seizures (FGTCS) (Figure 2), evidence by rigorous tonic extension of both forelimbs and hind limbs, Post Ictal Sleep Period (PISP) which reflects period from loss of righting reflex to resume of consciousness. Protection against mortality was also assessed (Hosseinzadeh and Sadeghnia, 2007).

**Determination of anti-seizure potential of rosuvastatin**

This was performed using a total of thirty (30) adult Wistar rats. The rats were randomly allocated into six groups with five rats per group. Group A, the negative control, were given just pentylentetrazol 110 mg/kg, i.p. Groups B, C and D were treated with oral Rosuvastatin 20, 40 and 60 mg and pentylentetrazol 110 mg/kg, respectively. Group E were treated with 10 mg diazepam and 110 mg/kg pentylentetrazol, while group F received Rosuvastatin 40 mg-diazepam 10 mg combined treatment 30 min prior to pentylentetrazol 110 mg/kg (Table 1).

**Special considerations**

In this research the time limit for observation of the Wistar rats for experimental seizure manifestation was one hour. Therefore, any Wistar rat whose seizure manifestation was delayed beyond an hour was considered atypical and replaced with another rat. More so, any rat whose experimental seizure manifestation was so abrupt as a result of unidentified factor was also replaced with another rat.

A substance with potential activity against PTZ induced seizure should be able to prolong the latencies to First Minimal Clonic Seizure (FMCS) and First Generalized Tonic Clonic Seizure (FGTCS) and reduce the Post Ictal Sleep Period (PISP).

**Statistical analysis**

This was done by application of SPSS version 20. A statistical tool, ANOVA was employed for comparing the mean of the various groups. The means and standard
Table 1: Potential anti-seizure activity of rosuvastatin against pentylenetetrazol induced seizure in Wistar rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>FMCS (min) M±SEM</th>
<th>FGTCS (min) M±SEM</th>
<th>PISP (min) M±SEM</th>
<th>%Protection</th>
<th>%Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTZ. 110 mg/kg</td>
<td>4.6±0.17</td>
<td>9.4±0.51</td>
<td>6.2±0.58</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>ROS. 20 mg</td>
<td>4.2±0.23</td>
<td>9.4±0.58</td>
<td>5.0±0.32</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>ROS. 40 mg</td>
<td>4.8±0.33</td>
<td>9.5±0.45</td>
<td>8.0±0.95</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>ROS. 60 mg</td>
<td>4.6±0.51</td>
<td>9.5±0.45</td>
<td>6.4±1.36</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>DZP. 10 mg</td>
<td>12.8±1.49</td>
<td>25.2±1.02</td>
<td>4.9±0.56</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>DZP. 10 mg + ROS.40 mg</td>
<td>14.7±0.83</td>
<td>24.3±1.28</td>
<td>3.4±0.10</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Evaluation of the effects of Diazepam, Rosuvastatin and Diazepam + Rosuvastatin regimen on FMCS, FGTCS and PISP on PTZ model of seizure using simple statistic. **TNA:** Total number of animal per group; **FMCS:** First minimal clonic seizure; **FGTCS:** First generalized tonic clonic seizure; **PISP:** Post ictal sleep period; **DZP + ROS:** Diazepam + Rosuvastatin.

![Figure 2](image_url)

**Figure 2:** Comparative effect of Rosuvastatin, Diazepam and Diazepam-Rosuvastatin combined therapy on the first generalized tonic clonic seizure.

Errors of mean were calculated and test groups result compared with that of the control group. The P-values less than 0.05 were deemed significant.

**RESULTS AND DISCUSSION**

This study showed that the increase in the latency to FMCS and reduction in PISP caused by Rosuvastatin treatment in pentylenetetrazol induced seizure model in Wistar rats were not significant (Figures 1 and 3). Rosuvastatin in this study has offered some protection against mortality following pentylenetetrazol induced seizure. Furthermore, there is existence of synergism when Rosuvastatin was combined with diazepam. These findings are in conformity with former reports by Julian et al. (2005); Jovita et al. (2008) and Ashwini et al. (2017), that treatment with statins does not have statistically significant anti-seizure potential. It has been reported that PTZ elicits its anti-seizure potential through interaction with GABA<sub>4</sub> receptor.
complex. However, while several GABA<sub>A</sub> ligands exhibit potential anti-seizure activities, PTZ has opposite effect on GABA<sub>A</sub> receptor (Squires et al., 1984).

In addition, Papp (1987) reported that pentylenetetrazol enhances calcium and sodium ions entry, both of which induce excitability. Therefore, it is likely that statins’ anti-seizure activity is the consequence of their potential to antagonize the excitatory effect of pentylenetetrazol at GABA<sub>A</sub> receptor complex. This is also suggested by their augmentation effect with other AEDS, for instance diazepam, against seizure.

Conclusion

Rosuvastatin in doses of 20, 40 and 60 mg/day does not have statistically significant anti-seizure potential but there was synergistic anti-epileptic effect in the Diazepam-Rosuvastatin combined therapy, respectively.

REFERENCES


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