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EFFECT OF ATORVASTATIN, SIMVASTATIN AND LOVASTATIN ON ANIMAL MODELS OF EPILEPSY: A COMPARATIVE STUDY

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ABSTRACT

Introduction: Statins are the widely prescribed drugs for hyperlipidemia. Now it is well accepted that statins not only have hypolipidemic actions but also have a number of pleotropic effects.

Objective: To study the effect of atorvastatin, simvastatin and lovastatin on Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) induced seizures in Wistar rats. **Material and methods:** Atorvastatin, simvastatin and lovastatin in their therapeutically equivalent doses were administered to Wistar rats prior to induction of seizures by MES and PTZ. The abolition of hind limb extension (HLE) and duration of seizures in MES model and latency for onset of seizures as well as duration of seizures were observed in PTZ model. **Statistical analysis**: Data was analyzed using one way ANOVA followed by Dunnett's post hoc test. $p \leq 0.05$ was considered statistically significant. **Results:** None of the statins were able to abolish the HLE .Only simvastatin decreased the duration of seizures significantly in comparison to control group in MES model. In PTZ model simvastatin and lovastatin decreased the duration of seizures and also increased the latency for the onset of seizures in comparison to the control group. Atorvastatin increased the latency but had no effect on duration of seizures in PTZ model.

Key words: Statins, seizures, atorvastatin, simvastatin, lovastatin

INTRODUCTION

Statins are one of the most commonly prescribed drugs for cardiovascular diseases[1]. They are most effective and well tolerated drugs to treat dyslipidemia. They competitively inhibit HMG-CoA reductase enzyme which catalyzes the rate limiting step in cholesterol biosynthesis [2]. The benefits of statins appear to be greater than just lowering the lipid levels. These cholesterol-independent or pleiotropic effects of statins include improving endothelial function, enhancing stability of plaques, decreasing oxidative stress and inflammation and inhibiting thrombogenic response [3].Statins have also been shown to have neuroprotective effects in multiple sclerosis and spinal cord injury[4, 5]. A previous study has also reported that simvastatin reduced the number of inflammatory lesions in patients with multiple sclerosis [6]. In kainic acid model, a model for temporal lobe epilepsy, atorvastatin has shown to reduce kainic acid induced seizure activities, hippocampal neuron death and monocyte inflammation[7].

It has also been hypothesized that statins reduce the risk of developing epilepsy in the elderly. A cohort study also showed that statins reduced the hospitalization due to seizures. It was found that for every one gram increase in the dose of

atorvastatin, the risk of hospitalization for seizures decreased by 5%.[8]

However, the effects of statins on maximal electroshock (MES) model and pentylenetetrazole (PTZ) induced seizure model is lacking. Hence we planned to study the effect of various statins on MES and PTZ induced seizures.

Aim of the study - To study the effect of atorvastatin, simvastatin and lovastatin on Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) induced seizures in Wistar rats.

MATERIALS AND METHODS

Drugs and chemicals:

Atorvastatin (Zydus Cadila Healthcare Ltd) , simvastatin (Micro Labs Ltd), lovastatin (Dr. Reddy's Laboratories Ltd) ,carbamazepine (Novartis India Ltd, Mumbai), sodium valproate (Sun Pharmaceutical Industries Ltd, Mumbai) and pentylenetetrazole (Sigma – Aldrich, Mumbai) were used for the study. The doses selected were the therapeutically equivalent doses which were converted to rat dose according the table of Paget and Barnes[9].

Animals:

Albino rats weighing 150-200g were used for the study. They were maintained under standard conditions in Central animal house, Manipal University, Manipal approved by the CPCSEA. The rats were kept in polypropylene cages (U.N. Shah Manufacturers, Mumbai) and maintained on standard pellet diet (Amrut Lab Animal Feed, Pranav Agro industries Ltd, Sangli, Maharashtra) and water ad libitum. The rats were maintained at a room temperature 26 ± 20C, relative humidity 45-55% and light/ dark cycle of 12 h.

Study design:

The study was undertaken after obtaining permission from the Institutional Animal Ethics committee, Manipal. A total of 60 animals were used for the study. They were divided into two groups, the maximal electroshock group and the pentylenetetrazole group.

I Maximal electroshock model

Rats were divided into 5 groups (n=6). The groups I to V received gum acacia (1ml), carbamazepine(108mg/kg), atorvastatin(3.60mg/kg), simvastatin(1.80mg/kg) and lovastatin(3.60mg/kg) respectively 45 min before the electroshock. Maximal electroshock seizures were induced as described by Toman et al[10] with a current of 150 mA delivered through the ear clip electrode for 0.2 sec with the help of convulsiometer. Absence of hind limb extension (HLE) was taken as protection against seizures. Only those animals which showed hind limb extension during the screening procedure on the previous day were included in the study.

II PTZ induced seizures

Rats were divided into 5 groups (n=10). The groups I to V received gum acacia (1ml,), sodium valproate (180mg/kg), atorvastatin (3.60mg/kg), simvastatin(1.80mg/kg) and lovastatin(3.60mg/kg) orally respectively 1hour before pentylenetetrazole (60mg/kg i.p.) [11]. Each animal was placed in an individual cage and observed for 30min. The onset of seizure with loss of righting reflex, number of seizures and duration of the seizures in each group was recorded.

Statistical analysis

All values are expressed as mean ± SEM. Data was analysed using one way ANOVA followed by Dunnett's post hoc test . $p \leq 0.05$ was considered statistically significant. All statistical analyses were carried out using SPSS software version 17.

RESULTS

Maximal electroshock induced seizures:

In this model all animals treated with carbamazepine showed 100% protection against

hind limb extension (HLE). None of the statins protected against HLE, however the duration of seizures was reduced significantly ($p<0.001$) in simvastatin treated group in comparison to the control group and was comparable to that of carbamazepine treated group (table 1).

Pentylenetetrazole induced seizures:

In this model sodium valproate significantly (p,0.001) increased the latency for seizure onset and decreased the duration of seizures when compared with the control group. Atorvastatin, simvastatin and lovastatin also significantly increased the latency ($p<0.001$) but a significant ($p<0.001$) decrease in the duration of seizure was observed only in simvastatin and lovastatin treated groups. There was no mortality in sodium valproate treated group. Among the statins least mortality was seen in lovastatin treated group. However there was no significant difference in the number of seizures among the different groups (Table 2).

DISCUSSION

Statins, the widely used hypolipidemic drugs are now found to have a number of pleotropic effects .Recently a cohort study concluded that taking a statin daily decreased the hospitalisation due to epilepsy. The authors suggested that statins may have a role in the treatment or prevention of seizures[8].

In kainic acid model, atorvastatin was shown to have decreased seizures, hippocampal neuron death, monocyte infiltration and proinflammatory gene expression. Also lovastatin decreased kainic acid excitotoxicity of cultured hippocampal neurons[7]. But there were no reports of effect of statins in generalised tonic clonic seizures and petit mal seizures. Hence we planned to study their role in maximal electroshock and pentylenetetrazole induced seizure models which have a close resemblance to generalised tonic clonic and petit mal seizures respectively.

In our study, simvastatin was comparable to carbamazepine in decreasing the duration of seizures, however none of the statins were effective in abolishing the hind limb extension . In PTZ model, simvastatin and lovastatin decreased the duration of seizures and also increased the latency for the onset of seizures in comparison to the control group. Atorvastatin increased the latency but had no effect on duration of seizures in PTZ model.

The difference in the effect of statins could be because of their difference in lipophilicity[3]. Lovastatin and simvastatin are highly lipophilic drugs whereas atorvastatin is less lipophilic. But in a previous study atorvastatin has shown to have antiepileptic effect in kainic acid induced seizures where it had been hypothesized that it is their antinflammatory action which is responsible for its benefit in seizures[7]. The lack of antiepileptic effect in our study with atorvastatin could be because of the lower dose used in our study. Hence, the authors plan to further study the effect of all these statins in a higher dose and on chronic administration in animal models of epilepsy.

CONCLUSION

In the present study , statins did have an antiepileptic effect , however the exact mechanism is not known. Further preclinical and clinical studies are required to study the role of statins and mechanism in epilepsy.

Table 1: Effect of various statins on Maximal Electroshock seizures

Group (n=6)	Duration of seizures (sec)
Control	23.5 ±1.18
Carbamazepine	19±1.03*
Atorvastatin	26.33±19
Simvastatin	17.67±1.14**
Lovastatin	26.5±1.87

Values are expressed as Mean ±SEM . ANOVA p=0.004. *p<0.01 and ** p<0.001 as compared to control group.

Table 2: Effect of various statins in PTZ model

Group (n=6)	Latency (min)	Duration of seizures (sec)	Number of seizures	% mortality
Control	0.78±0.13	383.17±80.04	2.66±0.42	66.7
Sodium valproate	1.33±0.81*	53.5±15.34*	2±0.51	0
Atorvastatin	1.33±0.21*	328±83±71.45	2.83±0.51	66.7
Simvastatin	1.08±0.27*	27.83±8.14*	2±0.73	33.3
Lovastatin	1.4±0.2*	26.5±4.16*	2.33±0.71	16.7

Values are expressed as Mean ±SEM . ANOVA p<0.05. *p<0.001 as compared to control group

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