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ANTICONVULSANT EFFECT OF NEBIVOLOL IN PENTYLENE TETRAZOLE INDUCED CONVULSIONS IN SWISS ALBINO MICE

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ABSTRACT

Aim & Objective

To evaluate the anticonvulsant activity of Nebivolol in Pentylentetrazole induced convulsions in mice.

Materials & Methods

All the 24 mice were randomly allocated into four groups of six animals each. Mice in group 1 served as control and received distilled water, group 2 as standard received phenobarbitone 30mg/kg intraperitoneally and group 3 & 4 received the test drug Nebivolol 0.25mg, 0.5mg/kg per oral respectively. After 30 minutes of drug treatment, convulsions were induced chemically with pentylentetrazole (PTZ) at a dose of 60mg/kg intraperitoneally. The latency to clonic jerks was observed immediately after PTZ injection for a period of 30min and it was tabulated.

Results

Nebivolol (0.25 and 0.5 mg/kg) significantly ($p < 0.01$) prolonged the latency to clonic jerks as compared with the control group.

Conclusion

β adrenoceptor antagonist nebivolol has an anticonvulsant effect against PTZ induced convulsions in mice. It may be advantageous in the treatment of epilepsy in hypertensive patients by improving their seizure control.

INTRODUCTION

Epilepsy is one of the commonest neurological diseases which represents an important public health problem. Stroke, oxidative stress and neurological dysfunction have been suggested to be contributing factors in the generation of epilepsy.^I Hypertension is the most prevalent modifiable risk factor for both ischemic and haemorrhagic stroke, which is often associated with epilepsy. Severe and uncontrolled hypertension might increase the risk of epilepsy in the absence of prior clinically detected stroke.^{II}

There is growing evidence of data that shows the activation of central β -adrenoceptors may also be involved in the development/progress of epilepsy. The contribution of nor-adrenergic neurotransmission to the seizure susceptibility and epileptogenesis is gaining more importance now a days. The high density of β -adrenoceptors occurs in all the subfields of the hippocampus known for its dominant role in the propagation of seizures.^{III} β agonists potentiated the epileptiform abnormalities occurring in slices of pyriform cortex obtained from kindled animals^{IV}. β receptor antagonists revealed anticonvulsant actions under experimental conditions.^V

Nebivolol is a new highly cardioselective β blocker which is devoid of intrinsic sympathomimetic activity but having vasodilator property which is not mediated through α_1 adrenergic receptors. It causes release of endothelial derived nitric oxide (NO) which is responsible for its vasodilatory effect. Nebivolol also has potent antioxidant property and is a high lipophilic drug.^{VI}

So, the aim of the study is to evaluate the protective effects of Nebivolol against PTZ induced convulsions.

MATERIALS

ANIMALS

Approval of Institutional Animal Ethics Committee was obtained (Dated 25.08.14 Ref. No. 6149/E1/5/2014).

A total of 24 male swiss albino mice (20–25g), bred locally in the central animal house of Madurai Medical College, were selected.

DRUGS

- Nebivolol (Nebistar, Lupin Ltd, Mumbai) 0.25mg, 0.5mg/kg^{VII}, suspended in 0.25% of carboxy methyl cellulose (CMC) in 0.9% saline solution.
- Pentylene tetrazole (Sigma, USA)
- Phenobarbitone (Gardenal, Abbott Healthcare Pvt Ltd, Himachal Pradesh).

STUDY DESIGN

The mice were randomly allocated into four groups of six animals each.

Table No: 1

GROUPS	STUDY	TREATMENT
1	CONTROL	Distilled Water 10ml/kg oral
2	STANDARD	Phenobarbitone 30 mg/kg i.p
3	TEST – 1	Nebivolol 0.25 mg/kg oral
4	TEST – 2	Nebivolol 0.5mg/kg oral

METHODOLOGY

PENTYLENE TETRAZOLE METHOD

All mice were given the respective treatments as shown in the table above. After 30 minutes of drug treatment, convulsions were induced chemically with PTZ at a dose of 60mg/kg intraperitoneally. The latency to clonic jerks was observed immediately after PTZ injection for a period of 30min.

Figure: No.:1



Figure: No.:2



Figure: No.:3



STATISTICAL ANALYSIS

The results were expressed as the mean \pm SD. Data were analysed by One way ANOVA, followed by Tukey's - test. P-value of <0.05 was considered as statistically significant.

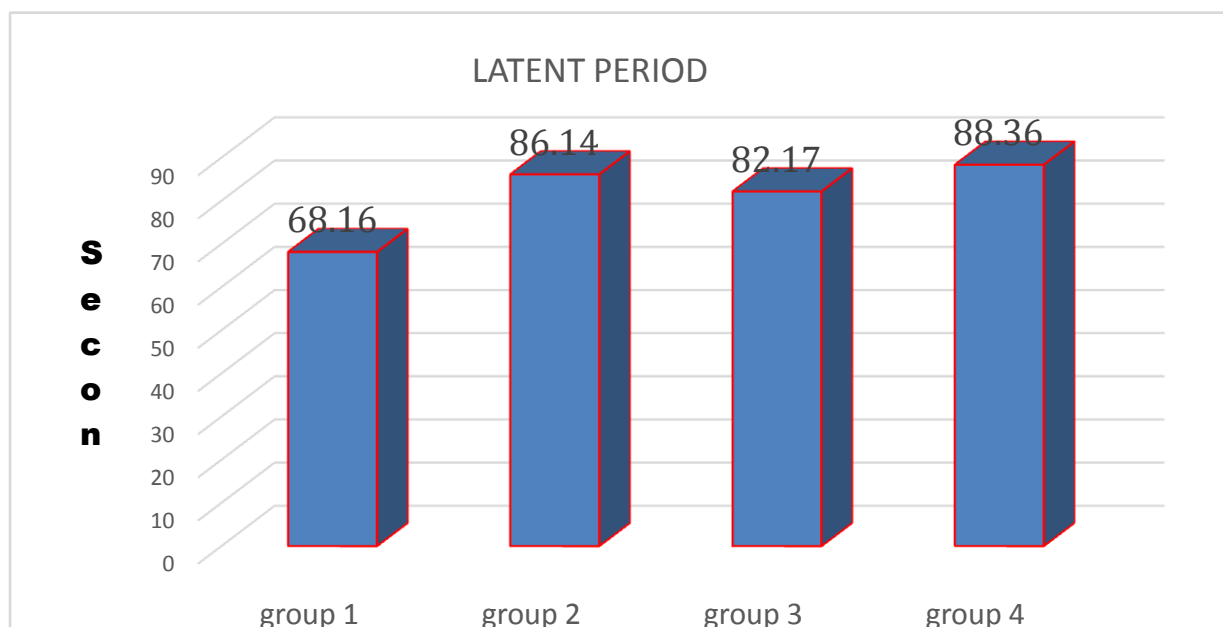
RESULTS

PENTYLENE TETRAZOLE METHOD

Table-1 Effect of nebivolol on pentylenetetrazole induced Convulsions in mice

Group	Treatment	Dose (p.o)	Latency Period (sec) (n=6)
Control	Distilled Water	10ml/kg	68.16 \pm 0.7491
Standard	Phenobarbitone	30mg/kg (i.p)	86.14 \pm 1.608
Test -1	Nebivolol	0.25 mg/kg	82.17 \pm 1.867
Test -2	Nebivolol	0.50 mg/kg	88.36 \pm 1.427

Figure: No.:4



Values are presented as mean \pm SD. n=6 (Number of animals in each group); p.o : per oral
(1 = Control , 2 = Standard, 3 = Test 1&4 = Test 2)

PTZ produced fore- and hind limb clonic jerks 60–70 seconds after injection in the control group. The standard drug phenobarbitone has prolonged the latency period for the development of clonic jerks. The test drug Nebivolol in graded doses (0.25 and 0.5 mg/kg) significantly ($p < 0.01$) prolonged the latency to clonic jerks as compared with the control group (Table-1). Moreover it was seen that nebivolol 0.5mg/kg showed equal to that of the effect produced by the standard drug

DISCUSSION

In the present study, nebivolol, a beta blocker drug, was evaluated with respect to its anticonvulsant activity against experimental models of epilepsy. It was shown that the protective effect of nebivolol against PTZ-induced convulsions is dose dependent.

NBV is highly lipophilic agent, easily penetrating the brain, and has antioxidant property. Increasing evidence suggests that apart from GABAergic and glutaminergic neurotransmission, central β -adrenergic neurotransmission might also play a modulatory role in epileptic phenomena.^{VIII} β -adrenoceptor activation increased the rate of spontaneous epileptiform discharges in hippocampal slices.^{IX} The involvement of central β -adrenoceptors in genetically programmed seizures has also been demonstrated.^X Moreover, β -adrenoceptor antagonists, especially propranolol display anticonvulsant effects, raising the threshold for electroconvulsions and protecting against pentylenetetrazol-induced convulsions.^{XI} Since β -adrenergic blockade leads to the reduced formation of cAMP, it might be hypothesized that β -adrenoceptor antagonists potentiate the activity of antiepileptic drugs that do not diminish the cAMP levels per se, such as Sodium valproate.^{XII}

Cognitive impairment is frequently associated with epilepsy.^{XIII} A better solution would be to use an Antiepileptic drug that provides not only seizure protection but also has a positive effect on memory. Nebivolol which acts through noradrenergic neurotransmission, may also display an important role in memory retrieval which is an area of interest for further studies.

CONCLUSION

β adrenoceptor antagonist nebivolol has an anticonvulsant effect against PTZ induced convulsions in mice. It may be advantageous in the treatment of epilepsy in hypertensive patients by improving their seizure control.

It is hoped that the outcome of this study will lead us to a safe approach to treat epilepsy associated with risk factors, especially for the elderly who are at great risk of epilepsy from hypertension; stroke and other cerebrovascular disease.

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