Original Research Paper

Volume-7 | Issue-11 | November-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Pharmacology

NEUROPHARMACOLOGICAL BENEFITS WITH ANTICONVULSANT EFFECT OF NEBIVOLOL IN SWISS ALBINO MICE

Dr. Muthukavitha.G — M.D, Assistant professor,Department of Pharmacology, Government Theni Medical College, Theni.

Dr. M. S. Ahil* — M.D DA, Assistant professor,Institute of Pharmacology, Madurai Medical College, Madurai. *Corresponding Author

ABSTRACT Aim & Objective: To evaluate the neuropharmacological benefits along with anticonvulsant activity of Nebivolol in Pentylenetetrazole induced seizure method in swiss albino mice.Materials & Methods:The mice were randomly allocated into four groups of six animals each.All mice in standard & test groups were given Phenobarbitone30 mg/kg i.p and the test drug Nebivolol (0.25 and 0.5 mg/kg) respectively. Effects on motor function were assessed using an Actophotometer. It was found that there was no impairment in the movement of the animals in both the test groups. After 30 minutes of drug treatment, seizures 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.The shortening of transfer latency was observed for the standard & test groups on the second day and it was tabulated. Results: Nebivolol (0.25 and 0.5 mg/kg) has no effect on memory when compared with the control group. No difference was observed in the locomotor activity with nebivolol (0.25 and 0.5 mg/kg) compared with the control group. 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 neuropharmacological benefits against PTZ induced seizures in mice with additional anticonvulsant effect . It may be advantageous in the treatment of epilepsy in hypertensive patients by improving their seizure control.

KEYWORDS : Anticonvulsant, Mice, Actophotometer, Nebivolol, Transfer latency

1.INTRODUCTION:

Epilepsy is the commonest neurological disorder [1] and the contributing factors have been suggested in the generation of epilepsy are stroke, oxidative stress and neurological dysfunction[2] 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[3].The contribution of nor-adrenergic neurotransmission to the seizure susceptibility and epileptogenesis is gaining more importance nowadays. The high density of β adrenoceptors in all the subfields of hippocampus play dominant role in the propagation of seizures[4]Epileptic patients are frequently reported to suffer from neurobehavioral problems such as memory impairment which may have a pathological and/or iatrogenic basis[5].A better solution would be to use an AntiEpileptic Drug (AED) with seizure protection as well as positive effect on memory.So the search for new drugs for epilepsy is ongoing.Nebivolol (NBV) is a relatively new highly cardio selective, β -adrenergic receptor antagonist that is devoid of intrinsic sympathomimetic activity but possesses vasodilator properties not attributed to blockade of α1- adrenergic receptors on smooth muscle cells[6].NBV has antioxidative effect and is a highly lipophilic drug[7] and is used as an antihypertensive agent nowadays. Hence, an attempt was made to study the protective effect of β blocker – Nebivolol, in experimental animal model which can be useful for the treatment of hypertension in patients with epilepsy.

2.AIM AND OBJECTIVE:

To evaluate the neuropharmacological benefits along with anticonvulsant activity of Nebivolol in Pentylenetetrazole induced seizure method in mice.

3.MATERIALS:

ANIMALS: Approval of Institutional Animal Ethics Committee obtained (Dated25.08.14 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[8] suspended in 0.25% of carboxy methyl cellulose (CMC) in 0.9% saline solution.

Pentylenetetrazole (Sigma, USA): Phenobarbitone (Gardenal, Abbott Healthcare Pvt Ltd, Himachal Pradesh).

STUDY DESIGN:

The mice were randomly allocated into four groups of six animals each.Group 1- control -Distilled Water 10ml/kg oral, Group -2 – standard -Phenobarbitone30 mg/kg i.p group 3- test 1 Nebivolol 0.25 mg/kg oral Group 4- test 2 -Nebivolol 0.5mg/kg oral

METHODOLOGY:

Neuropharmacological benefits:

- Transfer Latency - Elevated Plus Maze
- Locomotor Activity - Actophotometer

Figure 1: Elevated Plus Maze

Transfer Latency on Elevated PlusMaze[9]

The elevated plus maze is used to evaluate the spatial long term memory in mice. It consists of two open (16 × 5cm) and two closed arms (16× 5× 12cm) facing each other with an open roof. The entire maze is elevated at a height of 25cm. All the mice were placed at the end of either of the open arms and the time taken by the animal to move from open to closed arm (transfer latency) was noted on the first day. The shortening of transfer latency on the second day will be related to spatial long term memory. Transfer latency is the time in which the animal moves from the open arms to the closed arms. All the mice were allowed to move freely to explore the apparatus. Then the standard and test drugs were administered 30min after the first day trial. The transfer latency was again recorded 24h after first exposure. The transfer latency on the first day trial served as learning and the memory was examined 24h later. The shortening of transfer latency was observed for the standard & test groups on the second day and it was tabulated.

Locomotor Activity Test: Effects on motor function were assessed using an Actophotometer.All the mice were individually placed in the Actophotometer for 2 minutes and their motor activity before and after drug treatment were noted by counting the movements. It was found that there was no impairment in the movement of the animals in both the test groups.

Pentylene Tetrazole Method: All mice were given the respective treatments as shown in the table above. After 30 minutes of drug treatment, seizures were induced chemically with PTZ at a dose of 60mg/kg intraperitoneally[10]. The latency to clonic jerks was observed immediately after PTZ injection for a period of 30min.

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

4.RESULT: Effect Of Nebivolol On Memory

Table-1 Effect Of Nebivolol On Spatial Long Term Memory In Mice

GROUP	TREATMENT	DOSE	TRANSFER LATENCY (SEC)
CONTROL	DISTILLED WATER	10ML/KG	28±1.154
STANDARD	PHENOBARBITONE	30 MG/KG	60.83±1.343
TEST1	NEBIVOLOL	0.25 MG/KG	29.33±1.490
TEST 2	NEBIVOLOL	0.50 MG/KG	26.83±1.343

Data Are Presented As The Mean ± Sd ; N= 6 (number Of Animals In Each Group); P.o: Per Oral; (anova Followed By Tukey's-test).the Effect Of Nebivolol Treatment On Transfer Latency In A Plus Maze Is Summarized In Table 1. Nebivolol (0.25 And 0.5 Mg/kg) Has No Effect On Memory When Compared With The Control Group.

Table 2: Effect Of Nebivolol On Locomotor Activity

GROUP	TREATMENT	DOSE	LOCOMOTOR ACTIVITY (SEC)
CONTROL	DISTILLED WATER	10ML/KG	214 ± 3.21455
STANDARD	PHENOBARBITONE	30 MG/KG	194 ± 4.219663
TEST1	NEBIVOLOL	0.25 MG/KG	204 ± 6.448514
TEST 2	NEBIVOLOL	0.50 MG/KG	212 ± 3.184162

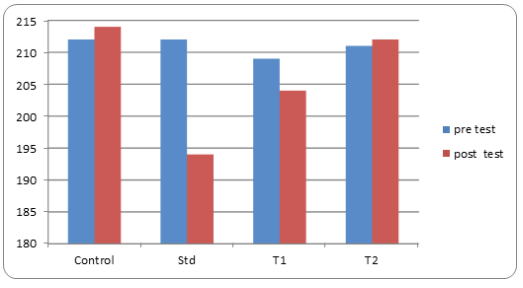

Figure 2: Comparision Of Pre And Post Test –locomotor Activity

No Difference Was Observed In The Locomotor Activity With Nebivolol (0.25 And 0.5 Mg/kg) When Compared With The Control Group (table 2).

Pentylene Tetrazole Method:

Table-3 Effect Of Nebivolol On Pentylenetetrazole Induced Seizures In Mice

GROUP	TREATMENT	DOSE	LATENCY PERIOD (SEC)
CONTROL	DISTILLED WATER	10ML/KG	68.16 ± 0.7491
STANDARD	PHENOBARBITONE	30 MG/KG	86.14 ± 1.608
TEST1	NEBIVOLOL	0.25 MG/KG	82.17 ± 1.867
TEST 2	NEBIVOLOL	0.50 MG/KG	88.36 ± 1.427

PTZ produced fore- and hind limb clonic jerks 60–70 seconds after injection in the control group.Nebivolol (0.25 and 0.5 mg/kg) significantly ($p < 0.01$) prolonged the latency to clonic jerks as compared with the control group (Table-3).

5. DISCUSSION:
In the present study, nebivolol (NBV), a beta blocker, was evaluated with respect to its neuro protective effect along with anticonvulsant activity against experimental chemical model (PTZ) of epilepsy. It was evidenced that the anticonvulsant effect of nebivolol against PTZ-induced seizures is dose dependent.There are increasing evidences to prove that central β-adrenergic neurotransmission might also play a modulatory role in epileptic phenomena[11]. The involvement of central β-adrenoceptors in genetically programmed seizures has also been demonstrated[12]. β -adrenoceptor activation increased the rate of spontaneous epileptiform discharges in hippocampal slices[13] Nor adrenergic neurotransmission with increased cAMP level plays a role in epileptogenesis. β -adrenergic blockers with reduced formation of cAMP, might be beneficial if combined with antiepileptic drugs that do not diminish the cAMP levels per se, such as Sodium Valproate[14].β -adrenoceptor antagonists, especially propranolol display anticonvulsant effects, raising the threshold for electroconvulsions and protectingagainstpentylenetetrazol-induced convulsions[15]. NBV being a highly lipophilic agent, easily penetrates the brain, with additional antioxidant property showed prolongation of latent period for clonic jerks in PTZ-induced convulsions.Nebivolol which acts through noradrenergic neurotransmission, may also display an important role in memory retrieval which is an area of interest for further studies. The present study demonstrated the shortening of transfer latency in Elevated PlusMaze which was observed for the control & test groups on the second day. This is to demonstrate the spatial long term memory in mice and there is no effect of the test drug (Nebivolol) on memory. The neurological deficits are almost invariably the manifestation of the toxicity of anti- epileptic agents. Minimal neurological deficits, such as impaired motor function, can be assessed by standardized tests such as the actophotometer test. In the present study, nebivolol had no effect on motor parameters which was demonstrated by actophotometer. Thus, nebivolo appears to be devoid of adverse neurological effects.

6.CONCLUSION:
Nebivolol, a β adrenoceptor blocker has neuropharmacological benefits with an additional anticonvulsant effect against PTZ induced seizures in mice. It may be advantageous in the treatment of epilepsy in hypertensive patients by improving their seizure control.It is hoped 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. However, our results are preliminary and further studies are warranted to extrapolate animal data to human situations.

7. REFERENCES:

1. Berg AT, Shinnar S. The contributions of epidemiology to the understanding ofchildhood seizures and epilepsy.J child Neurol 1994; 9 (suppl): S19-S26.
2. Waldbaum S, Patel M. Mitochondria: oxidative stress and temporal lobe epilepsy. EpilpesyRes 2010; 88: 23-45.
3. Hesdorffer DC, Hause WA, Annegers JF, and Rocca WA. Severe, uncontrolled hypertension and adult-onset Seizures: A case-control study in Rochester. Minnesota.Epilepsia 1996; 37: 736-741.
4. McNamara JO. Cellular and molecular basis of epilepsy. J Neurosci 1994; 14: 3413-3425.
5. Ali A, Pillai KK, Pal SN. Effects of folic acid and lamotrigine therapy in some rodentmodels of epilepsy and behavior. J Pharm Pharmacol 2003; 55: 387-391.
6. Janssens WJ, Xhonneux R, Janssen PA. Animal pharmacology of nebivolol. Eur JPharmacol 1991; 159: 89–95.
7. Cheymol G, Wostenborghs R, Snoeck E. Pharmacokinetic study and Cardiovascularmonitoring of nebivolol in normal and obese subjects. Eur J Clin Pharmacol 1997; 51:493-498.
8. Goel R, Goel A, Maoncha A, Pllai KK. Influence of nebivolol on anticonvulsanteffects of lamotrigine.Indian J Pharmacol 2009; 41: 41-46.
9. Kulkarni S.K , Handbook of Experimental Pharmacology. 2012; 4: p. 67-69.
10. Vohora D, Pal SN, Pillai KK. Thioperamide, a selective histamine H3 receptor antagonist, protects against PTZ-induced seizures in mice. Life Sci 2000; 66: 297-301.
11. Rutecki PA. Noradrenergic modulation of epileptiform activity in the hioppocampus.Epilepsy Res 1995; 20: 125-136.
12. Khanna N, Ray A, Alkondon M, Sen P. Effect of β -adrenoceptor antagonists and some related drugs on maximal electroshock seizures in mice. Indian J Exp Biol 1989;27: 128–130.
13. Mueller AL, Dunwiddie TV. Anticonvulsant and proconvulsant of alpha-and betaadrenergic antagonists on epileptiform activity in rat hippocampus. Epilepsia 1983; 24:57-64.
14. Moriwaki A, Hattori Y, Yasuhara H, et al. Lateral differences in responsiveness ofnorepinephrine-sensitive cyclic AMP-generating systems of rat cerebral cortex withironinduced epileptic activity. Brain Res 1988; 461: 190-193.
15. Fischer W, Lasek R, Muller M. Anticonvulsant effects of propranolol and theirpharmacological modulation. Pol J Pharmacol Pharm 1985; 37: 883–896.