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Research Article

Anticonvulsant activity of nitrendipine in albino mice

M. S. Kishore[1]*, H. L. Kalabharathi[2], V. H. Pushpa[2], A. M. Satish[2], Syed Mohsin Ahmed[1], H. N. Nagesh[1]

[1]Department of Pharmacology, Mysore Medical College, Mysore, Karnataka, India, [2]Department of Pharmacology, JSS Medical College, JSS University, Mysore, Karnataka, India

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***Correspondence to:**
Dr. M. S. Kishore,
Email: drkishoregowda1972@gmail.com

ABSTRACT

Background: The objective is to evaluate the anticonvulsant activity of nitrendipine in seizure-induced mice.
Methods: Albino mice (25-30 g) of either sex were randomly selected and divided into four groups of six mice each. After overnight fasting, Group I received 0.25 ml of propylene glycol and served as the control, Group II received valproic acid (110 mg/kg orally) as standard, Groups III received 5 mg/kg of nitrendipine and 100 mg/kg of valproic acid, Group IV received 5 mg/kg of nitrendipine and 75 mg/kg of valproic acid, and Group V received 5 mg/kg of nitrendipine and 50 mg/kg of valproic acid all of which were administered orally 60 mins prior to the test in this acute study. The anticonvulsant activity was screened using maximal electroshock (MES) model and pentylenetetrazole (PTZ) model.
Results: The nitrendipine showed a considerable reduction in the duration of hindlimb extensor phase in MES model and also delayed the latency of seizures induced by PTZ when compared with control group. The probable mechanism of anticonvulsant action of nitrendipine could be due to its interference with the gamma amino butyric acid type aminergic mechanism, modulation of nicotinic, and N-methyl-D-aspartate receptors.
Conclusion: Nitrendipine possesses the anticonvulsant activity and has a beneficial role in epilepsy.

Keywords: Anticonvulsant, Nitrendipine, Maximal electroshock, Pentylenetetrazole

INTRODUCTION

Epilepsy is a common and disabling neurological disorder that can be gratifying to treat. It is a paroxysmal event due to abnormal, excessive, and hyperexcitable asynchronous discharges from an aggregate of central nervous system (CNS) neuron. Depending on the distribution of discharges, this abnormal CNS activity can have various manifestations, ranging from convulsions to electroencephalograph changes. The term epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of recurrent seizures.[1] The causes of epilepsy are many ranging from idiopathic to infection, neoplasm and trauma (head injury). Epilepsy is a major public issue in many nations with its frequency increased in early childhood and adulthood.[2,3] Despite the massive scale of the problem and much research, epilepsy remains poorly understood in terms of etiology and pathogenesis. Although several drugs are used in the treatment of epilepsy, the treatment for epilepsy is still far from adequate. Several attempts have been made in the past to screen anticonvulsant from plant origin, and these attempts will continue till a satisfactory treatment is available.[4]

In recent years, some investigators have reported that calcium channel blocker may prevent or suppress seizure induced by a variety of chemical or physical stimuli. Physiological studies have emphasized the possible role of calcium flux on the discharges associated with seizure activity.

In neurons showing intrinsic burst firing, signaling epileptic activity, there is a massive influx of calcium associated with

the paroxysmal depolarizing shift (PDS) and hence the influx of extracellular calcium into neurons is considered to be an important feature in triggering epileptic activity. Anticonvulsants such as phenytoin, barbiturates, and benzodiazepines may act in part by inhibition of calcium influx and thus alter PDS. Hence, Ca++ channel blockade may be important in preventing seizure spread. The above findings suggest that in refractory epilepsy, treatment with conventional antiepileptic drugs combined with agents which modify Ca++ modulation (*viz*. Ca++ antagonists), as add-on therapy, may provide better seizure control.[5]

The dihydropyridine (DHP) class of calcium channel antagonists provides a large group of structurally related compound with various levels of activity in which a structure activity relation can be determined. From cardiac and smooth muscle preparations, electrophysiological studies have shown that DHP analogs selectively attenuate the calcium ion flux to various degrees.[6] In the light of development cited above, an attempt has been made in this work to find out the effect of nitrendipine as an adjuvant along with the antiepileptic drugs in the prevention of experimentally induced seizures.

METHODS

Animals

Albino mice (25-30 g) of either sex were randomly selected from central animal facility, JSS Medical College, Mysore. Animals were housed in groups of 6-8 per cage at a temperature of 25°±1° and relative humidity of 45-55%. Animals had free access to food and water. The Institutional Animal Ethical Committee approved the protocol of this study.

Drugs and chemicals

Valproic acid 110 mg/kg body weight (Cadila Laboratories, India), pentylenetetrazole (PTZ) 80 mg/kg[7] (Sigma, USA), nitrendipine 5 mg/kg body weight, propylene glycol, and distilled water.

Methodology

Animals were divided into five groups (with six mice each group) for both the models, i.e., maximal electroshock (MES) induced and PTZ induced seizure models. After overnight fasting, Group I received 0.25 ml of propylene glycol and served as the control, Group II received valproic acid (110 mg/kg orally) as standard, Group III received 5 mg/kg of nitrendipine and 100 mg/kg of valproic acid, Group IV received 5 mg/kg of nitrendipine and 75 mg/kg of valproic acid and Group V received 5 mg/kg of nitrendipine and 50 mg/kg of valproic acid all of which were administered orally 60 mins prior to the test in this acute study.

Assessment of anticonvulsant activity

MES induced seizures (MES MODEL)

Swiss albino mice weighing 25-30 g were used. The animals were pre-screened for their ability to develop full tonic extension in the MES test and only those which showed good response were included in the test. Electrical stimulation causes seizures, which passes through phases of tonic limb extension, tonic limb flexion, and clonus period. Suppression of tonic hind limb extension was taken as a measure of efficacy in this test. *Calotropis gigantea* along with control and standard drugs were administered to respective groups of mice 30 mins before application of electroshock (50 A, 0.2 sec) using ear electrodes. The duration of tonic extension of hind limbs was noted.[8]

PTZ induced seizures (PTZ model)

PTZ is a CNS stimulant. The convulsive effect is analogous to petit mal type of convulsions in man. Seizures were induced in mice with PTZ at a dose of 80 mg/kg body weight intraperitoneally. The experiment was assessed by its ability to delay the onset of myoclonic spasm and clonic convulsions. The test compound and standard drug was administered to respective groups of mice 30 mins prior to PTZ. The animals were observed for onset of myoclonic spasm and clonic convulsions.[9,10] The onset of convulsions were observed until 30 mins after administering PTZ.

RESULTS

MES model

The hind limb extensor phase in nitrendipine-treated group was 3.10±0.17 sec, and that of control group was 15.31±2.0 sec. The aqueous root extract of nitrendipine 200 mg/kg showed a reduction in duration of hindlimb extensor phase in MES model. It was noted that the clonus period was also reduced in calotropis treated groups to 2.20±0.09 sec when compared to 3.72±0.10 sec of control groups as shown in Table 1. The combination of nitrendipine and sodium valproate (T_2) reduced the duration of hindlimb extensor phase when compared to both test (T_1) and control groups.

PTZ model

The delay in onset of seizures in nitrendipine-treated group was 92.6±4.31 sec when compared to 80.03±5.95 sec in control treated group. The aqueous root extract of nitrendipine 200 mg/kg showed a delay in the latency of seizures induced by PTZ when compared with control group as shown in Table 2 whereas the combination of nitrendipine and sodium valproate (T_2) showed a delay in onset of seizures by113.6±5.94 sec when compared to both the standard treated and control groups.

Table 1: Duration of hind limb extensor phase (sec) in MES model.

Groups	Hind limb tonic flexion (sec)	Hind limb tonic extension (sec)	Clonus (sec)	Post-ictal depression (sec)	Recovery (R)/ death (D)
Control	1.5±0.55	12.83±1.47	10.5±1.05	94.67±48.61	R
Standard	-	1.83±4.49	2.67±0.82	-	R
T1	-	3.10±4.69*	1.5±1.76*	16.67±40.82	R
T2	-	0.83±2.04*	1.83±2.86*	-	R
T3	-	7.86±3.91	0.83±2.04	-	R

*p<0.05 when compared with control and drug-treated groups, MES: Maximal electroshock

Table 2: Latency and duration of convulsions in PTZ model.

Groups	Seizure latency (sec)	Mild myoclonic jerks (sec)	Generalized clonic seizures with loss of righting reflex (sec)	Post-ictal depression (sec)	Recovery/ death (sec)
Control	46.67±15.67	5.5±1.87	11.83±2.04	185.33±15.88	2D
Standard	53.05±129.82	1.91±2.45	-	29.33±71.85	R
T1	65.6±101.4*	5.33±8.64*	1.67±4.08*	23.5±52.56*	R
T2	25.6±61.23*	1.67±4.08*	1.6±2.45*	13.33±32.66*	R
T3	50.6±122.47	1.6±2.45	0.33±0.82	10.6±24.49	R

Values are in mean±SD and the data was analyzed by one-way ANOVA followed by Dunnett's test. *p<0.05 when compared with control and treated groups. SD: Standard deviation, PTZ: Pentylenetetrazole, ANOVA: Analysis of variance

Table 3: Percentage inhibition of hind limb extensor phase and onset of convulsions.

Groups	Percentage inhibition of hind limb extensor phase	Percentage inhibition of onset of convulsions
Control	0	0
Standard	85.79	13.67
T1	75.93	40.56
T2	93.55	45.14
T3	38.73	8.42

Statistical analysis

The effects of different drugs under study were calculated by taking the mean and standard deviation of the outcome parameters. Analysis of variance (ANOVA) was applied to compare the effects of drugs under the study. The data were analyzed using ANOVA followed by Dunnett's test. Differences were considered significant at 5% level (*p<0.05).

DISCUSSION

Epilepsy is a very common disorder affecting 0.5-1% of world's population. Its incidence in India is around 20-50 cases per lakh population.[3] Although newer and selective agents are currently used, there is still a drawback due to their side effect profile and also few cases being refractory to conventional treatment. The current study was undertaken to evaluate the anticonvulsant activity of aqueous root extract of nitrendipine (200 mg/kg) in MES and PTZ seizure induced mice.

MES predicts activity against generalized tonic-clonic and cortical focal seizures while PTZ tests activity against petit mal epilepsy or absence seizures. The reduction in duration of hindlimb extensor phase and delay in the latency of seizures are considered as the important parameters to assess the efficacy of anticonvulsant agents. MES model is useful for screening of drugs against primary and secondary generalized tonic-clonic seizures, but do not give any clue regarding the mechanism of action of the compound. Since PTZ acts as convulsant by antagonizing the inhibitory gamma amino butyric acid (GABA)ergic neurotransmission, any drug effective against PTZ model is said to possibly exert its anticonvulsant action through GABA receptor.[11]

MES induced seizure can be prevented either by drugs that inhibit voltage-dependent Na+ channels such as phenytoin, sodium valproate, felbamate, and lamotrigine or by drugs that block glutamatergic receptor such as felbamate. On the other hand, drugs that reduce T-type Ca+± currents such as ethosuximide can prevent seizures induced by PTZ. Drugs that enhance GABA Type A receptor-mediated inhibitory neurotransmission such as benzodiazepines and phenobarbital and perhaps valproate and felbamate can prevent this type of seizure.[12]

The test drug 5 mg/kg of nitrendipine and 100 mg/kg of valproic acid brought about a reduction in duration of hindlimb extensor phase in MES model and showed a delay in the latency of seizures induced by PTZ when compared with control group. In this study, T1 was more effective than T2 and T3 in both MES and PTZ induced seizure models when compared to control group.

Therefore, the probable anticonvulsant action of nitrendipine could be due to its interference with the GABA aminergic

mechanism, modulation of nicotic and N-methyl-D-aspartate receptors.[13]

Thus nitrendipine was observed to have anticonvulsant activity against MES and PTZ induced models of seizure. The study explores the complementary nature of nitrendipine with conventional treatment making it comparatively safer, economical, easily available and well-tolerated therapy.

CONCLUSION

We conclude from the study that nitrendipine has a beneficial role as an anticonvulsant. Further studies are indicated to identify the adverse effects, optimal treatment routes, and dosage.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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