Online ISSN: 2581-3935
Print ISSN: 2589-7837

International Journal of Medical Science and Diagnosis Research (IJMSDR)

Available Online at www.ijmsdr.com

Volume 2, Issue 4; July-August: 2018; Page No. 125-129

DIFFERENTIAL EFFECTS OF A CCB IN MES MODEL IN RATS

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ABSTRACT:

Objective: To study the anticonvulsant effect of nifedipine on maximal electroshock (MES) induced seizures in rats.

Materials and Methods: For this study, Sprague dawley albino rats (150-200g, 8-9 wks old, N=18) were used. Effects of nifedipine (2mg/kg and 5 mg/kg) via intraperitoneal injection were studied in MES seizure models. Reduction in duration of tonic hind limb extension (THLE) phase was taken as positive index of anticonvulsant activity in MES model. Statistical tests were applied to compare the effect in control and experimental groups of rats.

Results: The group of rats showed statistically significant difference with the control group (p less than 0.05) with nifedipine (2mg/kg) and (p less than 0.01) with nifedipine (5mg/kg) in MES Model

Conclusion: From our present study, we thus conclude that nifedipine possess some anticonvulsant property. It decreases duration of tonic hind limb extension phase in MES Model.

Key words: Nifedipine, Anti-convulsant, Hind limb extension, Seizures

INTRODUCTION:

A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is diagnosed when there are recurrent seizures due to a chronic underlying process (1)

Nifedipine,a commonly used Dihidropyridine group of CCB, exerts its effect in hypertension, as well as angina, by acting as an arterial vasodilator. Calcium ions regulate smooth muscle contractions contributing to inotropic and chronotropic activity in the heart(2).It binds to the L-type channel in arterial tissue, particularly coronary arteries, preventing the influx of calcium ions which allows for vasodilation, thus increasing myocardial oxygen supply(3,4)

The role of calcium ions in genetic epilepsy rat models was confirmed by **De Sarro *et al*** (1990) (5),who showed calcium channel opener **Bay K 8644** facilitates convulsions in sound induced epilepsy in genetically epilepsy prone rats**(GEPR).**Bay K 8644 is a dihydropyridine derived product which increases the opening probability of particular subclass of calcium channels, the L-type channel thereby promoting voltage dependent calcium influx(6)

Epilepsy is the second most common neurological disorder in India after stroke (CVA)(7,8).Despite many advances in epilepsy research, the pharmacotherapy of epilepsy remains largely empirical, owing to the lack of understanding of the underlying pathology. Moreover, approximately 30% of the people with epilepsy have seizures that do not respond satisfactorily to the conventional antiepileptic drugs (CAEDs) (9). These limitations with the CAEDs alone highlighted the need for exploring the drugs that could potentiate the action of CAEDs so as to make the treatment of epilepsy more effective.

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The presence of specific binding sites of calcium channel blockers (CCBs) that enable them to cross the blood brain barrier (BBB)(10) This gives an important evidence for the presence of central effects of CCBs. Hence, the present study was undertaken to determine whether CCBs ex-nifedipine could provide seizure control in maximal electroshock (MES)-induced convulsions.

MATERIALS AND METHODS

AIMS AND OBJECTIVES-To assess the anticonvulsant effects of nifedipine in Maximal Electroshock Seizues (MES) induced seizures models in rats.

The study was conducted in PG lab of Department of Pharmacology, M L N Medical College. Lab here is equipped with instruments, chemicals, drugs and medicines. Electroconvulsiometer is the commonly used instrument in the lab to study the anti-convulsant effects of drugs like Phenytoin, Phenobarbitone, Carbamazepine, Diazepam etc. In small animals for example-mice and rats. Out of number of CCBs we have used, commonly used agents are such as Diltiazem,Verapamil, Nifedipine. We as a part of regular lab practical work performed experiment on effect of Nifedipine on electrically induced seizures on rats. It was evaluated for its anticonvulsant effect on MES Model in rats using electro convulsiometer as per the guidelines of our registered Institutional Ethical Committee (IEC).

The experiments were performed on Sprague-Dawley albino rats of either sex (150-200 g; 8-9 weeks of age; N = 18) .The animals were housed in group of 6 per cage under controlled lighting conditions and room temperature at ~25°C and with food and water ad libitum. All efforts were made to avoid any unnecessary distress to the animals and all animal procedures were performed in accordance with institutional guidelines approved by the Institutional Ethics Committee, which are in accordance with the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals.

The drug used in the study was Nifedipine dicarboxylate in dose of 2 and 5 mg/kg which was used as intraperitoneal injection (i.p)in a volume of 5ml/kg of body weight. Fresh drug solution was taken during study and were given intraperitonially 45 minutes before conducting experiment. The reduction in hind limb extension phase in experimental group as compared to control was taken as positive criteria in MES model.

MES seizure method

This method was originally described by **Merritt and Putnam (1938**) which has been modified by many investigators. (11) The electro shock test in Rats has been proven as important tool in detection of anticonvulsant effects. This model is useful for screening of drugs effective against primary and secondary generalized tonic –clonic seizures.(12)

PROCEDURE:

Anticonvulsant activity was tested for MES seizure by inducing convulsions with an electro convulsiometer. In this method, electrical stimulation was applied via ear-clip electrodes (moistened with saline solution before each application) with an electro convulsiometer, which delivered alternating current of 150 mA for 0.2 seconds at 60 Hz. Abolition of hind limb tonic extension(180 degree to the plane of body axis) was taken as an index of anticonvulsant activity(13,14).Drugs were given 45 min prior to the induction of convulsions.

In this study 3 groups of 6 rats each were taken:

Group 1-control animals: received distilled water

Group 2-test animals: received nifedipine 2mg/kg

Group 3-test animals: received nifedipine 5mg/kg

STATISTICAL ANALYSIS:

Student’s t-test was used for analysis. Student’s t test is used to compare the means of two small samples. If samples are collected from two different populations or from randomly selected individuals from same population at different times, student t test (unpaired) should be used.

OBSERVATION AND RESULTS:

We divided rats into 3 groups, first control group,second group receiving nifedipine 2mg and third group receiving nifedipine 5mg.After 45 mins of test drug administration convulsions

were induced via electroconvulsiometer and then noted.Results obtained are as follows: duration of tonic hind limb extension was

TABLE 1: Duration of Tonic Hind Limb Extension Phase(seconds)in control group of rats and group receiving Nifedipine (2mg/kg) to electrical stimulation by MES model.

	CONTROL	NIFEDIPINE(2mg/kg)
1	9.11	8.00
2	7.97	7.30
3	8.32	8.02
4	9.50	8.29
5	10.00	7.48
6	8.14	7.46
MEAN	8.85	7.76
S.D.	0.83	0.39

After following same procedure, results obtained in group receiving Nifedipine 5mg/kg:

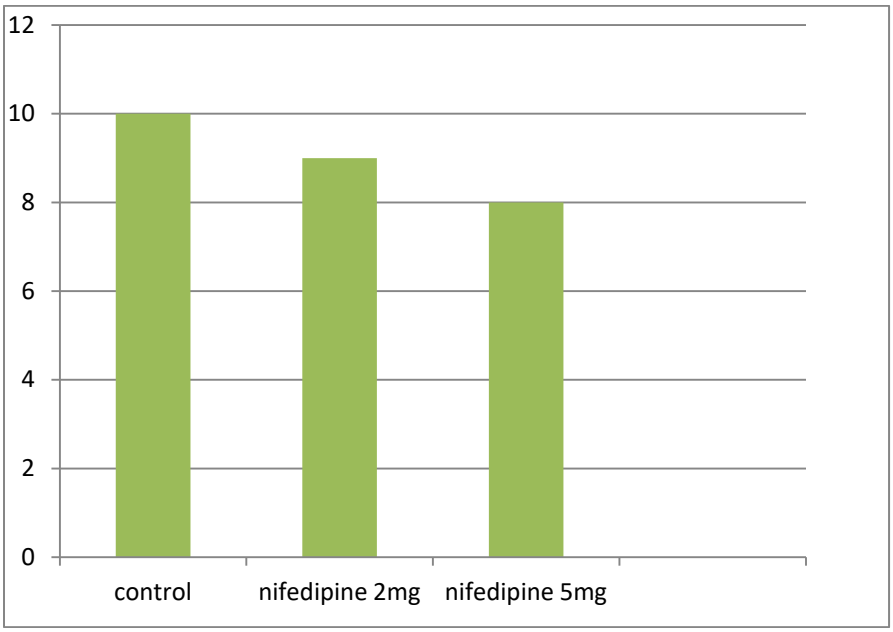
TABLE 2: Duration of Tonic Hind Limb Extension Phase (seconds)in control group of rats and group receiving Nifedipine (5mg/kg) to electrical stimulation by MES model.

	CONTROL	NIFEDIPINE(5mg/kg)
1	9.11	6.20
2	7.97	7.39
3	8.32	6.25
4	9.50	7.60
5	10.09	6.00
6	8.14	6.11
MEAN	8.85	6.5
S.D.	0.83	0.67

It is clearly seen in above table,there is statistical significant difference between group of rats receiving:

1) Nifedipine (2mg/kg) and control group (p less than 0.05) , T VALUE= 2.94

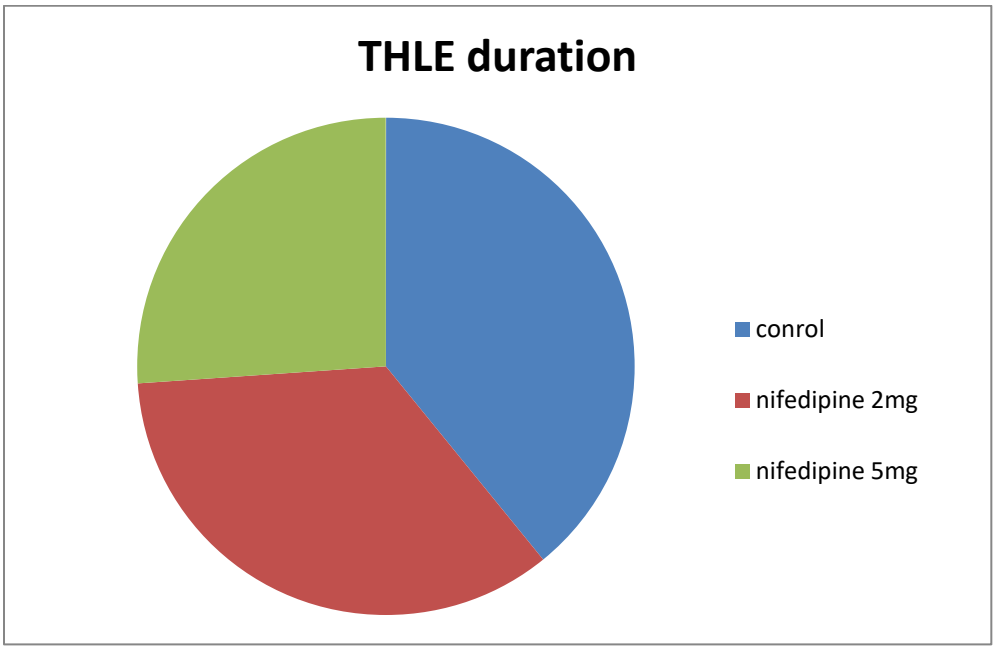
2) Nifedipine(5mg/kg) and control group (p less than 0.01) , T VALUE=5.964



Graph showing severity of seizures in Sprague dawley albino rats

X-AXIS-Rats with control and experimental group

Y-AXIS-Duration of tonic hind limb extension



As per analysis,it was observed that nifedipine have an anticonvulsant action.It prolongs the latent period and reduce the duration of tonic extensor phase of MES(15). The anticonvulsant activity elicited by nifedipine observed in our study is in keeping with previous studies.Clinical data, as well as experimental studies have demonstrated that nifedipine reduces the severity of convulsions(16-20).The results obtained provide a lead for the possible potential benefit of CCBs like Nifedipine in the treatment of epilepsy, which needs to be further evaluated.

CONCLUSION:

The following conclusion was obtained after completion of experiment:

1) Nifedipine was found to decrease duration of tonic hind himb extension phase in MES Model.

2) The group of rats showed statistically significant difference with the control group (p less than 0.05) with nifedipine (2mg/kg) and (p less than 0.01) with nifedipine (5mg/kg) in MES Model

3) From our present study,we thus conclude that nifedipine possess some anticonvulsant property. Further studies are required to establish the exact mechanism of action of CCBs in epilepsy with respect to extended range of doses 5,10,20,30 and comparison with other CCBs.In addition clinical studies should be done to establish their use in human population.

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