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Effect of L- type Calcium Channel BlockerNimodipine and T-type Calcium Channel Blocker Flunarizineon Motor Control in Mice

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Abstract
Objective: To study the effect of L-type of Calcium channel blocker nimodipine and T-type of calcium channel blocker funarizine on locomotor activity in mice without pretreatment by any other drug.
Materials and method: The study was carried out following permission from the Institutional animal ethics committee. Healthy Swiss albino mice of either sex were selected by the strict inclusion and exclusion criteria and the grouping is done. Group A is control treated with normal saline, Group B and C received two titrated doses of nimodipine while Group D and E received two titrated doses of flunarizine. The animals were then observed for motor control on inclined plane and the Statistical analysis was done by using unpaired't' test.
Results: L-type calcium channel blocker nimodipine has dose dependent effect on motor control on inclined plane while the T- type calcium channel blocker flunarizine has no effect on motor control.
Conclusion: Nimodipine has significant dose dependent depressant action on motor control on inclined plane while flunarizine has no effect on the above mentioned parameter.
Keywords: Nimodipine, Flunarizine, motor activity.

1. Introduction

Calcium ions play an essential role in regulating skeletal and smooth muscle contractility.Pathological changes in calcium channel expression have been shown to occur in several disease states including neuropathic pain, epilepsy and congestive cardiac failure. The use of drugs targeting calcium channels now extends far beyond the original discoveries of Fleckenstein.[1] Nimodipine has been approved for use in patients with neurological deficits.The effects of one calcium antagonist should not be extrapolated to another of a different subtype because drugs belonging to different subtypes have different pharmacological effects.[2]

It was found that only L-type channels were sensitive to calcium channel-inhibiting drugs. Since the distribution of channel subtypes differs in various tissues, drug sensitivity of the tissues is also different. In addition, even the L-type calcium channels are different in various tissues with respect to their affinities for calcium antagonists. CCBs bind to the receptors with higher affinity under depolarized rather than polarized conditions. The effects of one calcium antagonist should not be extrapolated to another of a different subtype because drugs belonging to different subtypes have different pharmacological effects.

2. Materials and methods

The study was carried out at Research Laboratory, Department of Pharmacology, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha between 1st January 2010 to 30th June 2011.

The research protocol was approved by I. A. E. C. in the meeting held on 23.12.2009.(Ref. No. DMIMSU/ JNMC/ IAEC/ 2009-10/ 39; Date: 30.12.2009)

2.1. Materials

Experimental Animals: Healthy Swiss albino mice of either sex weighing between 20-30 gms were selected and maintained in identical conditions. They were housed in colony cages with free access to food and water except just before and during experimentation.All the experiments were performed between 10 am to 4 pm at room temperature in noiseless, well ventilated and illuminated room.

2.2 Test Samples

Table 2: Dose selection of drugs

Drugs	Manufacturer	Doses (mg/kg)
Nimodipine (Tab.Nimodip)	USV Ltd (Corvette).	3.9 7.8
Flunarizine (Powder)	Cipla Ltd, Mumbai.	1.3 2.6

The drugs were dissolved in distilled water. The solutions were freshly prepared just before the experiments. All the drugs were injected orally. All aseptic precautions were taken while administering the drugs to the animals.

2.3 Equipments

1. Inclined plane
2. Feeding syringe

2.4 Methodology

2.4.1 Acclimatization

Animals were housed in polypropylene cages maintained at controlled temperature, light cycle and humidity. Animals were allowed to take rest for a period of one week, so that they were adapted to the new surrounding before experimentation.They were fed with the food provided by animal house and with water ad libitum.

2.4.2 Screening of Animals

2.4.2.1Inclusion Criteria

1. Weight between 20 to 30 grams
2. Healthy mice

2.4.2.2Exclusion Criteria

1. Weight less than 20 grams or more than 30 grams
2. Pregnant mice
3. Diseased mice
4. Newborn mice

2.4.3 Grouping of Animals: Each group consisted 10 mice of either sex.

Group A: Control group, treated with normal saline.

Group B&**Group C**: Treated with Flunarizine in 2 titrated doses respectively.

Group D&**Group E**: Treated with Nimodipine in 2 titrated doses respectively.

2.4.4 Study of motor control on inclined plane

It was used to determine impairment of motor co-ordination due to drugs. Following the dose of drug, the mice were placed on the plane, which was raised slowly until the mice slide down. The angle at which the mice slide down is noted.

2.5 Statistical Analysis

Statistical analysis was done by using SPSS 17.0 version and results were analyzed by using descriptive statistics and inferential statistics, using unpaired 't' test.

3. Results

3.1 Study of Motor Control

3.1.1 Effect of Nimodipine on Motor Control on an Inclined Plane:

Nimodipine had significant dose dependent depressant action on motor control on an inclined plane at both, 3.9 mg/kg and 7.8 mg/kg doses, at 15, 30 and 45 minutes.

Table 2: Effect of Nimodipine on Motor Control on an Inclined Plane

Drug dose (Nimodipine)	Motor control on an inclined plane (Mean ±SEM)		
	15 min	30min	45min
Control	87.50±1.11	87.50±1.11	87.50±11.84
3.9 mg/kg	80.00±1.29*	77.50±14.74*	85.50±0.89*
7.8 mg/kg	82.50±0.83*	79.00±1.24*	79.00±1.00*

*p<0.05 compared to control group

Figure 1: Effect of nimodipine (3.90 mg/kg) on motor control on an inclined plane

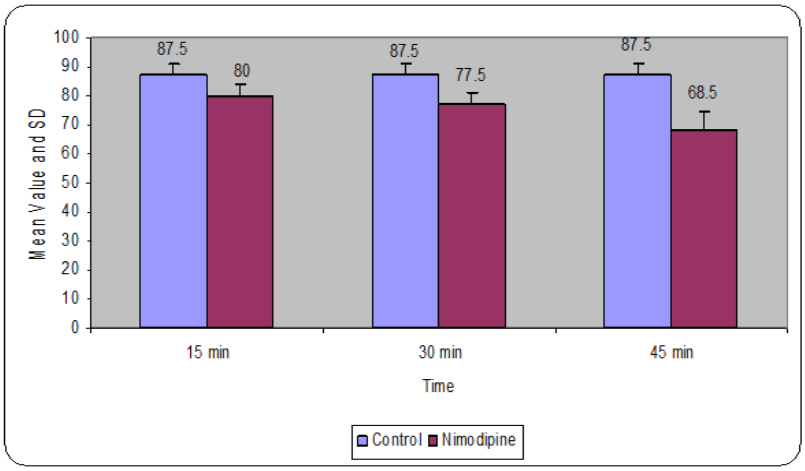
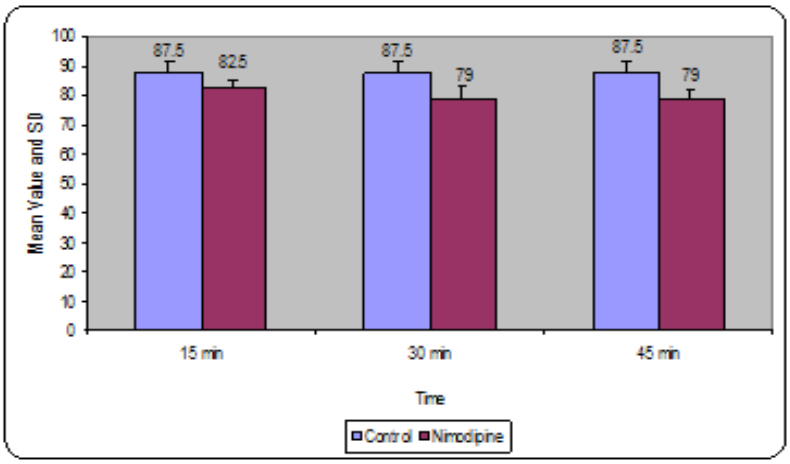


Figure 2: Effect of nimodipine (7.80 mg/kg) on motor control on an inclined plane



3.1.2 Effect of Flunarizine on Motor Control on an Inclined Plane:

Flunarizine did not produce any action on motor control on an inclined plane at both, 1.30 mg/kg and 2.60 mg/kg doses, at 15, 30 and 45 minutes.

Table 3:Effect of Flunarizine on Motor Control on an Inclined Plane

Drug dose (Flunarizine)	Motor Control on an Inclined Plane (Mean ±SEM)		
	15 min	30min	45min
Control	87.50±1.11	87.50±1.11	87.5±1.11
1.30 mg/kg	87.00±0.81*	84.50±1.16*	85.50±0.89*
2.60 mg/kg	87.00±0.81*	86.50±1.06*	87.50±0.83*

*p>0.05 compared to control group

Figure 3: Effect of flunarizine (1.30 mg/kg) on motor control on an inclined plane

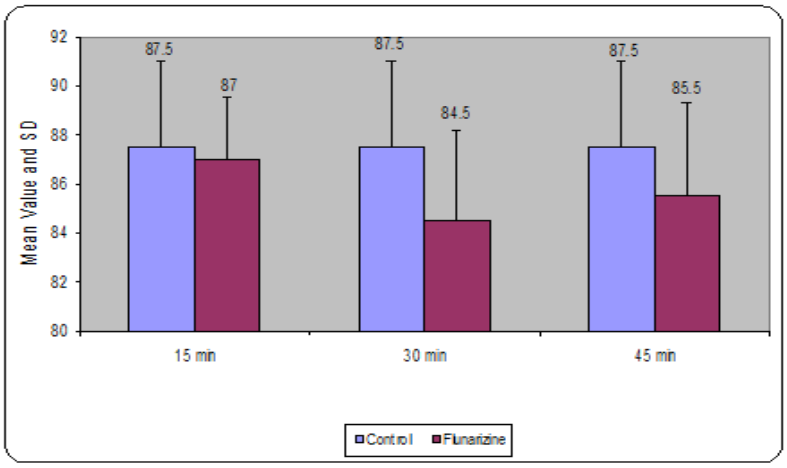
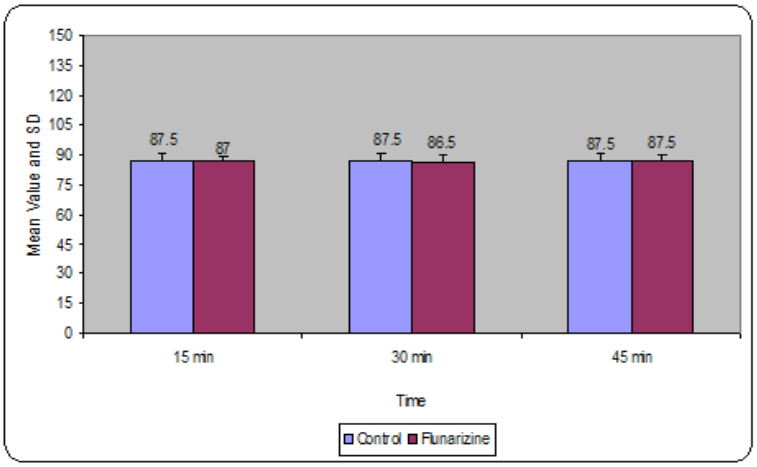


Figure 4: Effect of flunarizine (2.60 mg/kg) on motor control on an inclined plane



4. Discussion

Voltage-gated calcium channels play a major role in the normal functioning and also in various pathological processes that occur in neuronal, neurosecretory and muscle cells.[3]

Central nervous system diseases, including pain, epilepsy, seizure, anxiety, depression, dementia, and stroke, are characterized by an altered balance between excitatory and inhibitory neuronal functions. An efficient way of controlling such diseases is to block or modulate voltage dependent calcium channel (VDCC) function.[4]

Calcium dependent release of dopamine from the nerve terminal is thought to occur in response to invasion of nerve terminal by action potential. The extent of dopamine release appears to be function of rate and pattern of firing. The opening of calcium channel upon depolarization allows calcium to enter into presynaptic nerve terminal, leading to increase in the calcium concentration inside the nerve terminal. Activation of calcium sensors leads to activation of fusion machinery in the nerve terminal. The main mode responsible for synaptic neurotransmission is quantal release. Activation of the fusion machinery causes the fusion of synaptic vesicles which stores the neurotransmitter with the surface membrane which leads to quantal release of dopamine.[5]

Beninger RJ stated that changes in overall level activity of dopamine neurons appear to produce parallel changes in locomotor activity.[6]

In certain studies, it was found that nifedipine, flunarizine and diltiazem inhibited the drug induced locomotor activity. This may be correlated to the observations of Jack A Grebb who reported that Nifedipine, flunarizine and possibly PY 108-068 were effective in blocking amphetamine-induced locomotor stimulation.[7]

Nimodipine was found to have significant dose dependant depressant effect on locomotor activity by Digital photo-actometer, while flunarizine has no effect on locomotor activity when compared with the control group.

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