

## NIMODIPINE HAS NO EFFECTS ON CEFTRIAXONE - INDUCED EPILEPTOGENIC FOCUS IN RABBITS \*

(Received 2 March, 1994)

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### SUMMARY

In this study antiepileptic effects of nimodipine (ND) on ceftriaxone - induced epileptogenic focus in twenty rabbits were analysed. After base - line EEG was recorded 3% ceftriaxone was administered topically under dura mater of left sensori-motor area. EEG recording was made at least for twenty minutes. ND was given intravenously in doses of 0.1 mg/kg for three minutes and EEG recording was continued for thirty minutes. The parameters used in EEG analysis were the number of spikes, spike and wave bursts per second and EEG scores evaluated in both the ipsilateral and contralateral focus. The number of spikes, spike and wave bursts per second decreased after ND in four rabbits (20%), but increased in four rabbits (20%). No changes were observed in the others (60%). The EEG scores showed no difference before and after ND. In the second step, diazepam was administered intravenously in dose of 0.5 mg/kg to twelve rabbits receiving ND. EEG findings and foci absolutely disappeared in four rabbits (33.3%) but in the others (66.7%) showed general depressing activity with minimal epileptic activity. The EEG scores of diazepam receiving group after ND decreased significantly ( $p < 0.01$ ). We conclude that ND is not effective on ceftriaxone - induced epileptogenic focus in rabbits.

**Key Words :** Nimodipine, Ca<sup>++</sup> channel blocker, experimental focal epilepsy.

### INTRODUCTION

Current research suggests that Ca<sup>2+</sup> flux into the neuron may be a critical factor in the genesis of seizures and neuronal hyperexcitability (1-3). Ca<sup>2+</sup> channels modulated by dihydropyridines play a facilitating role in experimental seizures (1). In addition the dihydropyridine agonist BAY K 8644 has been shown to induce seizure like behavior in mice and dogs (3,4). Previous investigations have demonstrated that the dihydropyridine Ca<sup>2+</sup> antagonist nimodipine (ND) has anticonvulsant properties in seizures induced through bicuculline, pentylenetetrazol, electrocortical shock and ischemia

(5-7). Some experimental studies have shown anticonvulsive properties in both flunarizine and verapamil (8,9).

Cephalosporins and penicillin - induced epilepsy has been widely used as an animal model of focal or generalized epileptic seizures. Cephalosporin administered in high doses intraventricularly was capable of producing a behavioral and electrophysiological pattern of epilepsy in rats (10).

In this study we investigated antiepileptic effects of nimodipine, a calcium antagonist capable of crossing the blood-brain barrier, on experimental model of epilepsy induced by topical cortical application of 3% ceftriaxone in rabbits.

### MATERIALS AND METHODS

In this study we used twenty white New Zealand rabbits weighing between 2.5 and 3.5 kg. In this experimental model, after general anesthesia, four burr holes of 2 mm were made bilaterally to the sagittal suture in fronto - parietal region. One day later, triclofos Sodium PB has been given in doses of 30 mg/kg to rabbits by nasogastric catheter for sedation. Then four needle electrodes were placed to the dura mater and base-line EEG was recorded. Consequently as a convulsant substance 3% ceftriaxone was administered topically under dura mater of left sensori-motor area. EEG recording was made for twenty minutes. ND was given intravenously in doses of 0.1 mg/kg for three minutes and EEG recording was continued for thirty minutes.

The parameters used in EEG analysis were the number of spikes, spike and wave burst per second and EEG scores (10) (Table I) evaluated in both the ipsilateral and contralateral focus. In the second step, ND was compared with diazepam as potential anticonvulsant. Immediately after Diazepam was administered intravenously in doses of 0.5 mg/kg to twelve rabbits and no change in epileptic activities with ND were observed. Statistical analyses were made by using the Wilcoxon rank pair test.

**Table I-** Scoring system used for estimation of seizure intensity

Score	EEG
0	No change
1	Spike
2	Occasional appearance of spike and wave complex
3	Burst of spike and wave complex with short duration appearing no more than twice
4	Uninterrupted burst of spike and wave complex with high amplitude and high frequency

**RESULTS**

Epileptic seizures were observed as tonic rotation of the head contralateral to the focus, chewing and clonic movements of the face in some rabbits.

Epileptic activity and focal discharge on EEG have appeared in about 6.4 minutes after ceftriaxone application (Fig. 1). The number of spikes, spike and wave bursts per second decreased after ND in four

rabbits (20%) but increased in four rabbits (20%). No changes were observed in the others (60%). The EEG scores showed no difference before and after ND ( $p>0.05$ ) (Table II).

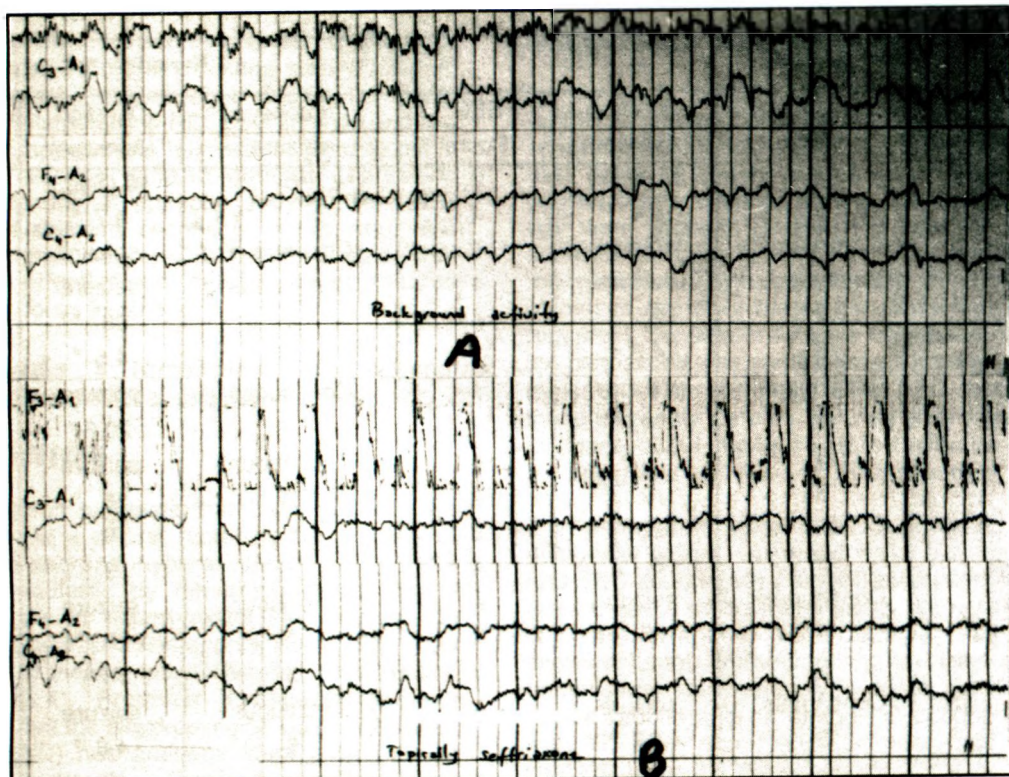
In the second step, EEG findings and foci absolutely disappeared in four rabbits (33.3%) (Fig.2). But the others (66.7%) showed general decreasing activity with minimal epileptic activity. The EEG scores of diazepam receiving group after ND decreased significantly ( $p<0.01$ ) (Table III).

**Table II-** Results of Nimodipine

Focal epilepsy				Nimodipine		
Number of animals	Frequency of seizure	Duration (Average)	EEG Score	Frequency of seizure	Duration (Average)	EEG Score
1	7	23 (Sec.)	2	6	10 (Sec.)	2
2	5	8.4 "	4	7	9.7 "	4
3	Continuous	seizure	4	Continuous	seizure	4
4	Continuous	seizure	4	Continuous	seizure	4
5	9	28 "	4	3	28 "	4
6	6	4.8 "	1	7	4.5 "	1
7	Continuous	seizure	4	Continuous	seizure	4
8	5	14.9 "	3	5	20.6 "	3
9	6	70.9 "	4	Continuous	seizure	4
10	5	70 "	4	2	55 "	4
11	6	22 "	2	5	9	2
12	5	8 "	4	7	9	4
13	Continuous	seizure	4	Continuous	seizure	4
14	4	28 "	4	4	28 "	4
15	5	12 "	3	5	13 "	3
16	Continuous	seizure	4	Continuous	seizure	4
17	6	4.7 "	1	6	4.8 "	1
18	Continuous	seizure	4	Continuous	seizure	4
19	5	60 "	4	2	45 "	4
20	6	70 "	4	Continuous	seizure	4
Total			68	68		

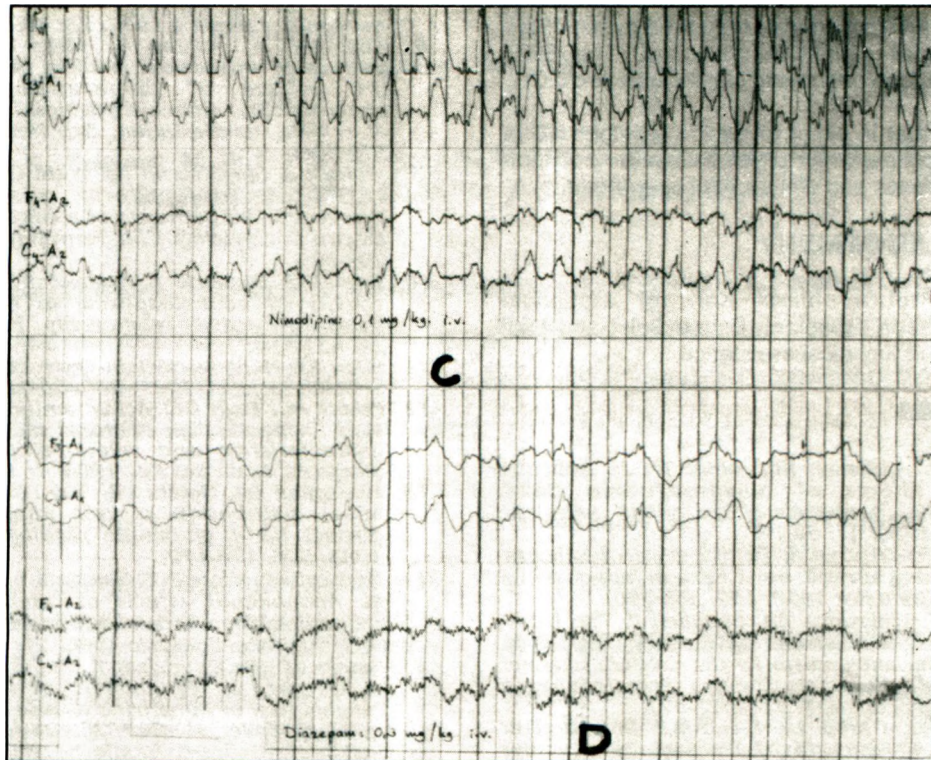
**Table III-** The Results of Diazepam

Nimodipine group				Diazepam group		
Number of animals	Frequency of seizure	Duration (Average)	EEG Score	Frequency of seizure	Duration (Average)	EEG Score
1	3	28 (Sec.)	4	1	10 (Sec.)	1
2	7	4.5 "	1	2	2.5 "	1
3	Continuous seizure		4	No seizure		0
4	5	20.6 "	3	2	15 "	1
5	Continuous seizure		4	2	5 "	2
6	2	55 "	4	No seizure		0
7	3	26 "	4	1	10 "	1
8	6	5 "	1	1	2 "	1
9	Continuous seizure		4	No seizure		0
10	5	18 "	3	2	14 "	1
11	Continuous seizure		4	2	6 "	2
12	2	40 "	4	No seizure		0
Total			40			10



**Fig 1.** A : Background activity  
 B : Focal epilepsy induced by ceftriaxone





**Fig 2.** C : There is no change by Nimodipine  
D : Epileptic activity disappeared by Diazepam

## DISCUSSION

Neuronal calcium channels have been generally classified into two major types : voltage - dependent channels sensitive to membrane potential alterations caused by electrical or chemical stimulus and receptor - operated channels sensitive to chemical stimulus. Three subtype voltage dependent  $Ca^{2+}$  channels have been identified as T, N, and L channels. Only the L channel of these three different calcium channels is modulated by dihydropyridine agonists and antagonist (11). Therefore the anticonvulsant effects of dihydropyridines may be due to antagonism of calcium influx through the L - channel. In addition dihydropyridine binding is voltage dependent which might explain the observation that seizure discharge was suppressed but not prevented (1).

Three major receptors have been identified for the excitatory aminoacids on the basis of selectivity by kainic acid (K), quisqualate (Q) and NMDA (12). The NMDA receptor has its highest concentration in the hippocampus (13). Glutamate stimulation of K/Q receptors still leads to  $Na^{+}$  influx and depolarization which may trigger some calcium influx by alternative routes. When glutamate interacts at the NMDA receptor, however a  $Ca^{2+}$  channel is opened. Activation of NMDA receptors leads to the opening of a channel that allows a large amount of  $Ca^{++}$  to pass in to the cell. No evidence indicates that this receptor - operated  $Ca^{2+}$  channel is blocked by organic

calcium antagonists. Therefore, if the NMDA-gated  $Ca^{2+}$  channel is critical for seizure induction dihydropyridine calcium antagonists may not be effective in clinical epilepsy (1).

Intraventricular verapamil administration produces an amplitude and frequency reduction of the interictal epileptic discharges in penicillin induced epileptic foci in rats (9).

Morocutti et al showed that ND administration at the dose of 0.1 mg/kg produced significant changes in the 2% cefazolin - induced epileptic activity but did not in the 4% cefazolin - induced epileptic activity (14).

Flunarizine and nifedipine, two calcium channel antagonists have been reported as useful drugs in the management of patients with intractable epilepsy (15-17). But Larkin reported that their study did not support important anticonvulsant efficacy for nifedipine as adjuvant therapy for refractory epilepsy at doses appropriate for the treatment of angina or hypertension (18). Treatment with I.V. nimodipine abolished continuous focal epileptic seizures in two patients in whom conventional therapy was unsuccessful (19).

The results of our ND study on topically 3% ceftriaxone - induced epileptogenic foci in rabbits did not show any significant changes. EEG scores showed no difference between before, and after ND.

But diazepam application after ND at the doses of 0.5 mg/kg produced significant changes. The EEG scores of this group decreased significantly ( $p < 0.01$ ).

We conclude that in order to decide whether ND is effective in epilepsy, more research must be done with different doses and different epilepsy models.

## ACKNOWLEDGEMENT

We thank Prof.Dr. İsmet Kan for statistical assistance, Mehmet Sağlam, Emine Bulut and Lütfi Özgür for expert technical assistance.

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