

## DOSE DEPENDENT EFFICACY OF LACOSAMIDE IN PROTECTION OF PENTYLENETETRAZOL INDUCED SEIZURE IN RATS.

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### ABSTRACT

Epilepsy is a common and frequently devastated disorder affecting 0.5 to 1% of the population with annual incidence rate of approximately 30 to 50 per 1, 00,000 per year. Lacosamide is a novel anti-epileptic drug, recently been licensed for adjunctive therapy of partial or secondary generalized seizures.

Objective: To evaluate dose dependent efficacy of lacosamide in protection of Pentylenetetrazol (PTZ) induced seizures in rats.

Method: The study was conducted in albino rats of either sex, weighing between 100-150 gm. The animals were grouped into 6 groups, each comprised of 8 animals. Group I was treated with requisite volume of normal saline, group II received pentylenetetrazol (80mg/kg, i.p). Animals in group III, IV, V and VI were pretreated with graded doses of lacosamide (3,10,30& 50mg/kg i.p),thirty minutes later, the lacosamide pretreated groups were treated with pentylenetetrazol (80mg/kg/i.p).

Results: It was found that animals in control group were normal, while the animals with PTZ treatment showed convulsions followed by mortality. However in group III 38%, group IV 60%, group V 88% & group VI 100% protection was observed with lacosamide against PTZ induced seizures.

Conclusion: So, in our study we observed that in the doses of 30 and 50mg/kg, ip, lacosamide increased the seizure threshold and showed protection against the minimal seizure.

**Keywords:** Lacosamide, Pentylenetetrazol, Convulsion.

### INTRODUCTION

Epilepsy is a common and frequently devastating disorder affecting 0.5 to 1% of the population with annual incidence rate of approximately 30 to 50 per 100000 persons. Despite wide range of old and new antiepileptic drugs (AED), approximately 30% of the patients are still not seizure free [1, 2]. Anything that disturbs the normal pattern of neuronal activity such as illness, brain damage, abnormal brain development can lead to seizure. It can be described as the repetitive occurrence of abnormal bioelectrical synchronization of a large number of neurons leading to temporary dysfunction of one or more brain areas.

Regardless of the agents used, a substantial proportion of patients still have inadequate seizure control and also suffer with adverse effects, on treatment with currently available AEDs [3]. Therefore, there is still a need for new AED with enhanced effectiveness, tolerability, and/or pharmacokinetic properties & less adverse effects, thus there is still a substantial need to develop newer antiepileptic drugs [4, 5].

Currently there are 20 medications approved by the Food and Drug Administration for the treatment of epileptic seizure that include, Carbamazepine, Clorazepate, Clonazepam, Ethosuximide, Felbamate, Fosphenytoin, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbital, Phenytoin, Pregabalin, Primidone, Tiagabine, Topiramate, Sodium Valproate and Zonisamide [6].

Among all the above, Lacosamide has shown a potent and neuro-protective effect in, in vitro and in vivo animal models making it a potential candidate for treatment of epilepsy. In comparison with classical sodium channel blocking agents which produce fast inactivation and or delayed recovery from inactivated state, lacosamide enhances slow inactivation of sodium channels and prolongs the inactivated state, stabilizes the membrane and reduces the hyperexcitability [7]. At resting potential, voltage gated sodium channels (VGSC) can be opened by depolarization of the membrane potential below a critical threshold [8]. Thus LCM reduces the ability of (epileptic) neurons to sustain prolonged firing bursts by regulating the long-term availability of VGSCs [7, 9].

In addition LCM inhibits collapsin-response mediated protein-2 (CRMP-2) mediated neurotrophins for down regulation of N-methyl-

D-aspartate (NMDA)-receptor subtype NR2B – a receptor subtype that seem to play a role in epileptogenesis [10,11].

The drug has been recently been licensed for adjunctive therapy of partial or secondary generalized seizures which was evident with various animal models. Therefore, the study was designed to find out dose dependent efficacy of lacosamide on pentylenetetrazol induced seizures in rats.

### MATERIALS AND METHODS

Albino rats of either sex, weighing between 100-150 g were used. They were allowed food and water ad libitum up to the time of experimentation. Each animal was used only once. All observations were made between 10-17 hr at 27° C in a noiseless, diffusely illuminated room. Each group consisted of 8 rats.

The drugs used were normal saline, pentylenetetrazol (80mg/kg, i.p) and lacosamide (3, 10, 30 & 50 mg /kg, i.p). The volume of injection was 2ml/kg, i.p. All drug solutions were prepared immediately before use and were injected intra-peritoneally. The animals were grouped into 6 groups, each consisting of 8 rats. Group I was treated with requisite volume of normal saline, group II received pentylenetetrazol (80mg/kg, i.p). Animals in group III, IV, V and VI were pretreated with graded doses of lacosamide (3, 10, 30 & 50 mg/kg i.p). Thirty minutes later, the lacosamide pretreated groups were treated with pentylenetetrazol (80mg/kg/i.p).

For observation, the animals were placed individually in open topped perspex cages (30x20x20cm) immediately after the injection of drugs. The animals were observed for the onset of seizure, duration of seizure, and mortality, if any. The study was undertaken at S.B.K.S, M.I & R.C. and all the procedures were performed in accordance with CPCSEA guidelines and was carried out after the approval of Institutional Animal Ethical Committee. The results were statistically analyzed by the unpaired t test with differences considered significant at p<0.05

### RESULTS

It was observed that in group I, animals treated with normal saline were seizure free, while in group II convulsion occurred in all the animals that lasted for 55-60 seconds , in group III, IV and V the animals suffered with

convulsions but the duration of seizure had reduced significantly as

compared to the pentylenetetrazol treated group (Table-1).

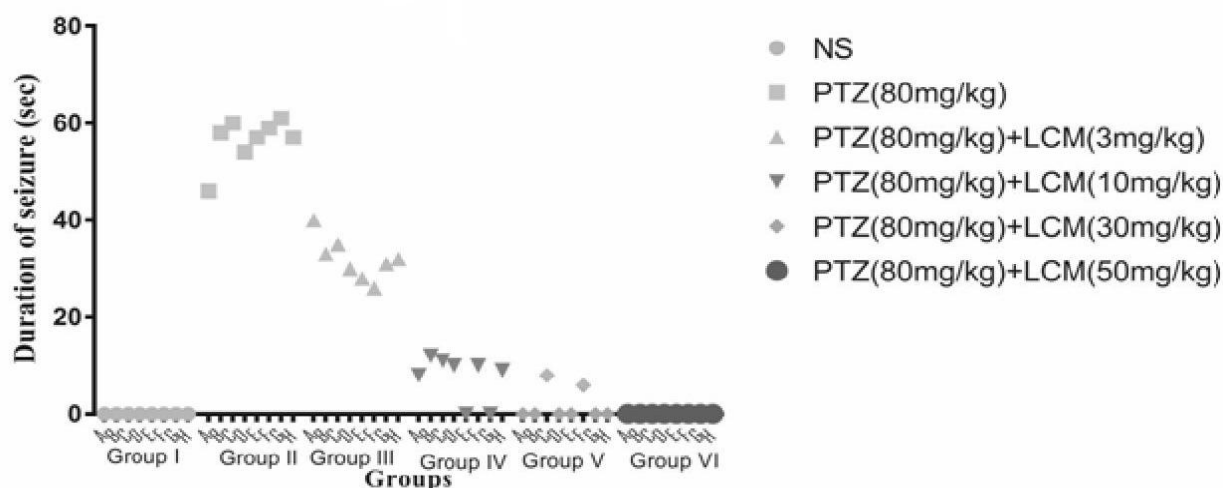
**Table 1: Dose dependent effect of Lacosamide (LCM) on Pentylenetetrazol (PTZ) induced seizures in rats (n=8).**

Study Group	Drug & Dose in mg/kg, i.p	Myoclonic spasms		% Protection from seizure
		(Duration in seconds)	Mean $\pm$ SEM	
I	NS	00	0.00	-
II	PTZ(80)	55-60	56.50 $\pm$ 1.68	-
III	PTZ(80) + LCM (3)	22-40	31.88 $\pm$ 1.53*	38
IV	PTZ(80) + LCM (10)	0-12	7.50 $\pm$ 1.69*	60
V	PTZ(80) + LCM (30)	0-8	1.75 $\pm$ 1.16**	88
VI	PTZ(80) + LCM (50)	00	0.00***	100

\*p<0.05,\*\*p<0.01,\*\*\*p<0.001, NS=Normal Saline.

In group III that was treated with lacosamide (3mg/kg) we observed that duration of convulsions had reduced significantly but also resulted in mortality (25%). Hence, only 38% of protection against chemically induced seizures was obtained in group III. However, a significant reduction in seizure duration was observed in groups IV & V, with 68% & 88% of protection from seizure in respective groups.

Later, it was further observed that in group VI the animals treated with lacosamide (50mg/kg) showed 100% protection against chemically induced seizures with no mortality. Hence, the study reveals that animals which were pretreated with lacosamide showed a dose dependent protection against PTZ induced seizures (Figure-1).



**Fig. 1: Dose dependent effect of Lacosamide (LCM) on Pentylenetetrazol (PTZ) induced seizures in rats (n=8).**

Minimum protection was seen in group III (3mg/kg,i.p) with 25% mortality. However, in the remaining groups no mortality was observed but 100% protection was obtained in group VI (50mg/kg, i.p).

## DISCUSSION

Pentylenetetrazol, a chemoconvulsant that was used to induce seizures in our study induced myoclonic jerks in all the 8 animals, which lasted for 55-60 seconds, followed by mortality. Lacosamide in dose dependent manner by its dual mechanism of action showed protection in animals against pentylenetetrazol induced seizures.

Lacosamide, a newer antiepileptic drug has the dual mechanism of action. The available experimental data suggest it to be synergistic in combination with other antiepileptic drugs. It has mild, unspecific side effects that are dose dependent and makes it an acceptable drug for adjuvant therapy in various seizure models. Various seizure models have proved the drug to be effective for generalized, complex partial seizure and status epilepticus [11]. In our study we have found the drug to be effective against chemically induced seizures, which suggests it to be beneficial in absence seizure.

## CONCLUSION

With our observations, we conclude that lacosamide (30 mg & 50 mg/kg, i.p) is protective against pentylenetetrazol induced seizures in rats. Hence, apart from its use as an adjuvant in partial seizures it could also be beneficial in absence seizures.

However, extensive studies are needed to evaluate the drug for its use in absence seizures and other condition such as diabetic neuropathy, osteoarthritis, cancer pain etc.

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