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EFFICACY OF A NOVEL AND POTENT ANTIEPILEPTIC IN INFLAMMATORY AND ACUTE PAIN MODEL IN RODENTS

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ABSTRACT

Pain is one of the most common presentations of many disorders and needs immediate appropriate attention of treating physician. Some antiepileptics are established drugs for neuropathic pain while the analgesic effect of these drugs in acute and prolonged inflammatory pain needs to be evaluated. The present study was planned to observe the effect of lamotrigine [a newer anticonvulsant] in formalin test which is a model of acute and prolonged inflammatory pain and to compare it with conventional opioid analgesic tramadol. Per oral administration of lamotrigine produced no marked effect on first phase response of formalin test but significantly suppressed the second phase response. As lamotrigine produced significant effect in prolonged inflammatory pain in second phase of formalin induced paw oedema test, so it could be effective in various clinical conditions associated with prolonged inflammatory pain.

KEYWORDS : Lamotrigine, Nociception, Formalin Induced Paw Oedema, Tramadol

The principal objective of the treatment of pain is to remove or abolish the cause of pain. But it is not always possible to do so, analgesics are used for the symptomatic treatment of pain. Pain could be acute, inflammatory or neuropathic. Inflammatory pain is due to chronic inflammation that is increased by pressure, but neuropathic pain occurs due to involvement of nervous system and are non adaptable.

Pain is an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. NSAIDs and opioids are the most potent and commonly used group of established analgesic drugs in treatment of pain, but their use is associated with a greater degree of adverse drug reactions and abuse liability.

Gabapentin and Carbamazepine like drugs are being widely used for postoperative pain and trigeminal neuralgia (Arguelles et al., 2002). Other antiepileptics are also being tried as newer nonconventional analgesic drugs that are expanding day by day.

There is no comparable data available, whereby these drugs could be compared with analgesic effect of conventional opoids for their analgesic activity in suitable animal models of acute and chronic pain, although there is some consistency in their effects as far as neuropathic animal pain models are concerned.

Thus we examined the antinociceptive effects of lamotrigine in animal models of pain and compared its antinociceptive effects with conventional opioid analgesic tramadol. So the aim of this study is to verify the effects of lamotrigine in formalin induce paw oedema which is a common animal model of showing effects of drugs on both acute and prolonged inflammatory pain.

MATERIALS AND METHODS

This study has been done in postgraduate lab of pharmacology department, Himalayan Institute of Medical Sciences[HIMS], Dehradun over a period of six months for testing analgesic effects of certain anticonvulsants in animal models of pain after clearance from IAEC.

Animal Used

Adult albino rats of either sex, wt 150-200gm have been utilized for these experiments.

Drugs

The following drugs have been used to evaluate their antinociceptive effects in each group of 6 animals, given per oral [p.o] 1 hr before the experimentations. There has been a control group of 6

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animals, run simultaneously, and given saline/vehicle p.o. as per the experiment. All the experiment was done at the same time in the morning hours on all days of experimentation (Assi et al., 1996; Carrie and Jones, 2005; Chen et al., 2002 and Craig & Follenfant, 1995).

Lamotrigine 50mg/kg

Tramadol 10mg/kg

Commercial preparations of these drugs have been used. Lamotrigine [Consern Pharma Pvt. Ltd., Ludhiana, Punjab] and control drug tramadol [Lupin Ltd. Santacruz Mumbai] has been dissolved in saline as they are water soluble. Both drugs were administered p.o. by gavage in a volume of 1.0ml/kg in rats (Dickenson and Sullivan, 1987).

Procedure for antinociceptive evaluation

Formalin Test

The formalin test was used as the model of chronic inflammatory pain. Formalin has been characterized by the occurrence of two characteristic phases of increased pain sensitivity in rats. The first phase was of 0-15 minutes and phase second phase was of 45-75 minutes. Rat was administered 0.05ml of 10% formalin into the dorsal portion of the front paw. The test drugs was administered orally and scored according to a pain scale. Pain has been quantified by counting the incidence of spontaneous flinches, shakes and jerks of the formalin injected paw. Number of leg raising[LR], licking and biting [LB] were measured for the two phases as end points. Analgesic response or protection has been indicated if both paws are resting on floor with no obvious favoring of injected paw. Treatment group was compared with appropriate control groups using "student t test".

RESULTS

Formalin test [Table 1 & Figure 1, 2]: In the first phase of leg raising [LR] formalin test, tramadol produced significant decrease in leg raising [$p<0.05$], of experimental antiepileptic drug produced no any significant effect on leg raising in comparison to control values.

In the first phase of licking and biting [LB], positive control tramadol again produced significant decrease [$p<0.02$] than control values while lamotrigine had no effect.

In the second phase of leg raising [LR] tramadol and lamotrigine produced significant decrease [$p<0.05$] as compared to control. In the licking and biting episodes of second phase also tramadol and lamotrigine exert significant effect [$p<0.02$] in comparison to control in licking & biting and leg raising response. Decrease observed in licking and biting [LB] with tramadol was more [$p=0.001$] as compared to control values than with experimental antiepileptic drug [$p<0.02$] versus control values.

Table 1 : Time effects of experimental drug and positive controls [tramadol] administered p.o 1 hr before on number of raising foot (LR) and licking and biting (LB) responses of albino rats in formalin induced paw oedema

Group	No of Albino Rats	Dose and Route of Administration of drugs	Leg Raising (LR) [Mean±SE]		Licking & Biting(LB) [Mean±SE]	
			First Phase	Second Phase	First Phase	Second Phase
Control	6	0.09% p.o.	15.8±3.7	6.3±2.1	28.1±3.5	15.3±2.0
Tramadol	6	5 mg/kg p.o.	7.2±1.2*	4.0±0.2**	8.2±1.5**	5.9±0.6***
Lamotrigine	6	50 mg/kg p.o.	13.0±3.1	4.9±0.3*	24.1±2.9	6.8±1.1**

Observation measured in 2 phases, 1st is 0-15 min and 2nd is 45-75 min

*$p < 0.05$ vs control values **$p < 0.02$ vs control values ***$p = 0.001$ vs control values

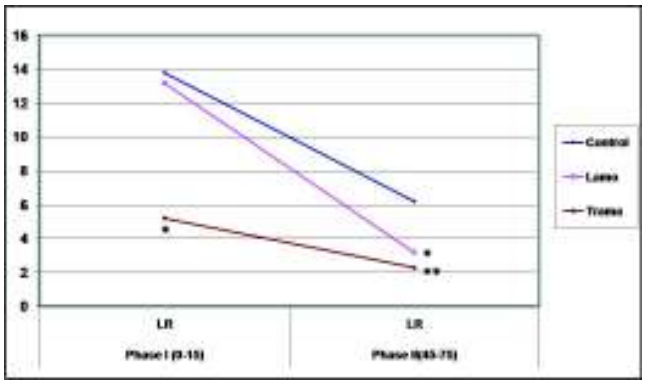

Figure 1 : Time effects of experimental drug &positive control(tramadol) administered p.o 1 hr before on number of raising foot responses (LR) of albino rats in formalin induced paw oedema

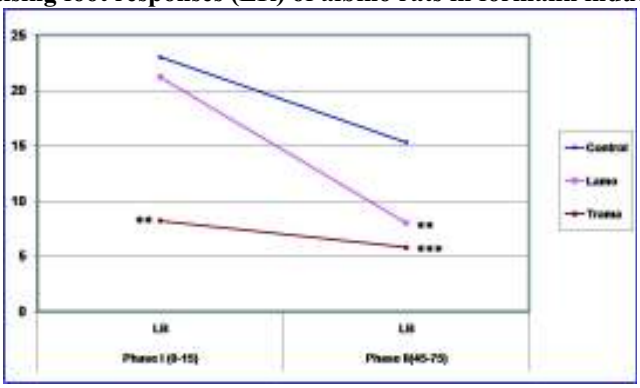

Figure 2 : Time effects of experimental drug and positive control [tramadol] administered p.o 1 hr before on number of licking and biting (LB) responses of albino rats in formalin induced paw oedema

As we have taken test drug lamotrigine and observed its antinociceptive effect on formalin induced paw oedema in comparison with normal saline (NS) and control drug Tramadol in Albino rats , Per oral administration of lamotrigine produced no marked effect on early phase response which is a model of phasic (acute,short lasting) pain but significantly suppressed the late phase response which denotes tonic pain (prolonged inflammatory pain) , while control drug Tramadol produced significant effect in both phases.

DISCUSSION

The present study was done to evaluate the antinociceptive effect of a novel antiepileptic lamotrigine on biphasic pain model [formalin test] with the help of conventional analgesic drugs i.e. tramadol which was used as positive control in rats.

Tramadol is well established analgesic drug that showed significant antinociceptive effect in tail flick test when given orally [10 mg/kg] in present study at 120 min. It is in conformity with previous studies of tramadol in which tramadol showed analgesic effect in tail flick test while given 22.8 mg/kg ,s.c [subcutaneous] (Craig & Follenfant, 1995). In yet another study, tramadol 10 mg/kg, i.v. [intravenous] produced significant analgesic activity in tail flick test when given alone or in combination with diclofenac (Chen et al., 2002).

Tramadol 10 mg/kg, p.o. produced significant analgesic effect in both phase 1 and 2 of formalin test in present study. In an earlier study, tramadol 10mg/kg, i.v. produced significant analgesic effect in formalin test when given alone or in combination of NSAIDs (Chen et al., 2002). In another study, tramadol, 0.5-2.0mg/kg, i.p. [intraperitoneal] produced dose dependent significant analgesic effect in both phase 1 and phase 2 of formalin test in mice (Laughlin et al., 2002).

In the present study in formalin test,

lamotrigine produced significant effect in second phase but not in first phase of formalin test. In a previous study, lamotrigine [4-265 nmol, i.t.(intrathecal)] dose dependently inhibited only the second phase [ED50=28nmol, i.t.] but not first phase (Maizes and Maccarberg, 2005). In yet another study, lamotrigine [50-400 microgm, s.c.] significantly reduced number of flinches during phase 2 while significant effect on phase 1 was observed only at a very high dose of 400 microgm s.c.(Raffa et al. 2006).

The first and second phase of formalin test are generally believed to reflect excitation of peripheral afferent nociceptors and central sensitization, respectively (Shannon et al., 2005). Further, In a study lamotrigine demonstrated significant analgesic properties in formalin test (Vogel and Vogel, 1996).

CONCLUSION

Evaluation of antinociception in acute and chronic pain models was done with the help of biphasic pain model of formalin test in albino rats of either sex on novel anticonvulsant lamotrigine, and tramadol was used as positive control.

Tramadol as a positive control was effective in both pain models.

In Formalin test, the test drug lamotrigine did not produce any significant effect on phase 1 denoting acute pain while in 2 phase which denotes prolonged inflammatory pain, lamotrigine produced significant antinociceptive effect.

Based on the present study we concluded that newer anticonvulsant lamotrigine, has antinociceptive effect in prolonged inflammatory pain model but does not affect acute nociception in animals, so the novel anticonvulsant lamotrigine could be effective in chronic inflammatory pain conditions in humans also.

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