



ANALGESIC EVALUATION OF NOVEL ANTICONVULSANT WITH A CONVENTIONAL ANALGESIC IN DUAL PAIN MODEL OF RAT

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ABSTRACT

Gabapentin and carbamazepine like anti epileptics are being used now a days to treat a number of diseases associated with neuropathic pain. The aim of this study is to observe whether novel anticonvulsants are able to produce analgesic response in pain conditions of acute and chronic type. This study observed the analgesic effect of lamotrigine in rats by biphasic nociceptive pain model of formalin test and compared its potency with a conventional opioid analgesic tramadol. Per oral administration of lamotrigine produced no significant effect on early phase response of formalin test but significantly suppressed the late phase response. We conclude that lamotrigine has antinociceptive effect in chronic inflammatory pain as seen by its effect on late phase of formalin test while tramadol has antinociceptive effect both on acute and chronic inflammatory pain.

Keywords: Lamotrigine, nociception, formalin test, tramadol

INTRODUCTION

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 is an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage¹. 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 liability². Recently, Gabapentin and Carbamazepine like anticonvulsants are being widely used for postoperative pain and trigeminal neuralgia.³ Other anticonvulsants 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. So the aim of this study is to examine the antinociceptive effects of lamotrigine in dual pain model of rat and compared its antinociceptive effects with conventional analgesic tramadol.

MATERIALS AND METHODS

Animal used: Adult albino rats of either sex, wt 150-200 g have been utilized for these experiments.

Ethical clearance no. HIHTPHARMA/I-1/2006/338

Drugs

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

Lamotrigine 50 mg/kg^{4,5}

Tramadol 10 mg/kg^{6,7}

Commercial preparations of these drugs have been used. Lamotrigine and control drug tramadol has been dissolved in saline as they are water soluble. Both drugs were administered p.o. by gavage in a volume of 1.0 ml/kg in rats.⁸

Procedure for antinociceptive evaluation

Formalin Test

The formalin test was used as the dual model of acute and 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 0.05 ml 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".⁹

RESULT

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 (Table 1). 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 and 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 I: Analgesic Effects of Experimental Drug Lamotrigine and positive controls Tramadol on Rats in Formalin Test

Group	No of Albino Rats	Dose and Route of Administration of drugs	Raising Foot [Mean ± SE]		Licking and Biting [Mean ± SE]	
			First Phase	Second Phase	First Phase	Second Phase
Control	6	0.09 % p.o.	12.9 ± 1.8	5.9 ± 0.2	25.0 ± 4.0	18.6 ± 1.8
Tramadol	6	5 mg/kg p.o.	5.3 ± 2.2*	2.8 ± 1.3**	7.9 ± 1.2**	6.1 ± 0.5***
Lamotrigine	6	50 mg/kg p.o.	12.9 ± 3.6	3.1 ± 0.3*	20.7 ± 3.0	7.9 ± 0.7**

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

DISCUSSION

The present study was done to evaluate the antinociceptive effect of the novel newer antiepileptic lamotrigine on biphasic animal pain models i.e. phasic pain model [tail flick by radiant heat method] and tonic inflammatory pain model [formalin test] with the help of conventional analgesic drugs i.e. tramadol which was used as positive control in rats. 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 10 mg/kg, i.v. produced significant analgesic effect in formalin test when given alone or in combination of NSAIDs¹⁰. In another study, tramadol, 0.5-2.0 mg/kg, i.p. [intraperitoneal] produced dose dependent significant analgesic effect in both phase 1 and phase 2 of formalin test in mice¹¹. 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 [ED 50 = 28 nmol, i. t.] but not first phase.¹² In yet another study, lamotrigine [50-400 microgram, 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 microgram s.c.¹³ The first and second phase of formalin test are generally believed to reflect excitation of peripheral afferent nociceptors and central sensitization, respectively¹⁴


CONCLUSION

Evaluation of antinociception in acute and chronic pain was done with the help of standard method of formalin test in albino rats. 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 chronic inflammatory pain model but does not affect acute nociception in animals, so the novel anticonvulsant lamotrigine could be effective in clinical conditions associated with chronic inflammatory pain in humans also.

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