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Research Article

A comparative study of efficacy of gabapentin in inflammation induced neuropathic animal pain models with conventional analgesic diclofenac

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ABSTRACT

Background: Some antiepileptic drugs have been shown to be clinically efficacious in treatment of neuropathic pain and are being used by clinicians. This study is proposed to evaluate the efficacy of these drugs as compared to conventional analgesics.
Methods: Formalin test has been used as the 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 test drugs have been 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. Analgesic response or protection has been indicated if both paws are resting on floor with no obvious favouring of injected paw. Treatment group was compared with appropriate control groups using "student t test".
Results: Per oral administration of gabapentin produced no any marked effect on early phase response of formalin test but significantly suppressed the late phase response while diclofenac produced significant antinociceptive effect in both phases of formalin test.
Conclusions: Thus we have observed that gabapentin produced antinociception in second phase of formalin test which reflects chronic inflammatory pain.

Keywords: Gabapentin, Diclofenac, Nociception, Formalin test

INTRODUCTION

Pain is an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1]

Pain could be acute or chronic in nature. Acute pain is short lasting and easy to manage while chronic pain is that pain which persists beyond the usual course of injury or diseases, or reoccurs in every few months or years. Pathologically chronic pain could be inflammatory or neuropathic. Inflammatory pain is due to chronic inflammation that is increased by pressure, but neuropathic pain occurs due to alteration in nervous system function or reorganization of nervous system structure and are non-adaptable. NSAIDs and opioids are the most potent and commonly used group of established analgesic drugs in treatment of pain, but there use is associated with a greater degree of adverse drug reactions and abuse liability.[2]

The anticonvulsants carbamazepine and gabapentine are now established drugs for trigeminal neuralgia and postoperative pain as non conventional analgesics.[3] Other

anticonvulsants are also being tried as newer unconventional analgesic drugs that are expanding day by day.

There are no comparable data available, whereby these drugs could be compared simultaneously 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.

So the present study was planned to verify the effects of an anticonvulsant gabapentin in common acute and chronic inflammatory (formalin test) pain model and compared its anti-nociceptive efficacy also with conventional non-opioid analgesic diclofenac.

METHODS

Animals used

Adult albino rats of either sex, weight 150-200 gm 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 p.o. 1 hour 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. Gabapentin-50mg/kg; diclofenac-5mg/kg.[1,4]

Commercial preparations of these drugs have been used. Gabapentin and control drug diclofenac were suspended in 5% acacia and double deionized water.

Both drugs were administered per oral by gavage in a volume of 1.0ml/kg in rats.[5]

Procedures: For antinociceptive evaluation[6]

Formalin test

The formalin test has been used as the 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 2 was of 45-75 minutes. Rat has been administered 0.05ml of 10% formalin into the dorsal portion of the front paw. The test drugs have been 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. 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

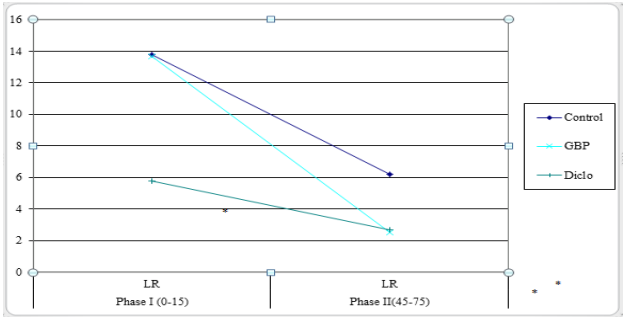
The present study was conducted with the objective to experimentally evaluate the analgesic effect of novel antiepileptic gabapentin and one analgesic diclofenac as positive control.

For this purpose, the following nociceptive experimental models were used.

Formalin test

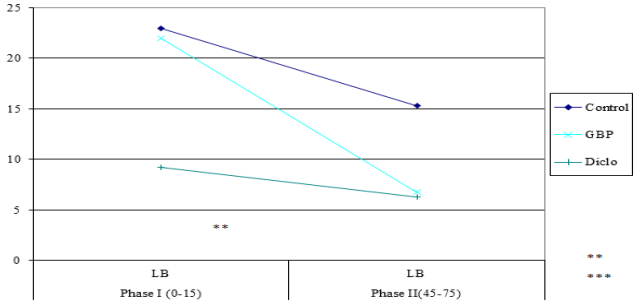
For each set of experiment, six adult healthy Albino rats of either sex each were used for both experimental drugs. Gabapentin (50 mg/kg p.o.) and diclofenac (5mg/kg) given 1 hour before the experimentations.

Formalin test (Table 1 and Figure 1 and 2).



*p<0.05 versus control values; **p<0.02 versus control values; ***p = 0.001 versus control values.

Figure 1: Time effects of experimental drug and positive control (Diclofenac) administered p.o 1 hr before on number of raising foot responses in Albino rats administered with dilute formalin (0.05 ml of 10% in NS) in right forepaw on dorsal surface i.d.



**p<0.02 versus control value; ***p = 0.001 versus control values.

Figure 2: Time effects of experimental drugs and positive controls (diclofenac) administered p.o 1 hr before on number of licking and biting responses in Albino rats administered with dilute formalin (0.05 ml of 10% in NS) in right forepaw on dorsal surface i.d.

Table 1: Time effects of experimental drug and positive control (diclofenac) administered p.o 1 hr before on number of raising foot and licking and biting responses in Albino rats administered with dilute formalin (0.05 ml of 10% in NS) in right forepaw on dorsal surface i.d.

Group	No of Albino rats	Dose and route of administration of drugs	Raising foot (Mean±SE)		Licking & biting (Mean±SE)	
			First phase	Second phase	First phase	Second phase
Control	6	0.09% p.o.	13.8±2.9	6.2±1.2	23.0±3.0	15.3±1.8
Diclofenac	6	10 mg/kgp.o	5.8±1.3*	2.7±0.5*	9.2±1.0**	6.3±0.7***
Gabapentin	6	50 mg/kg p.o.	13.7±3.3	2.5±0.2*	22.0±3.3	6.8±1.4**

*p <0.05 versus control values; **p <0.02 versus control values; ***p = 0.001 versus control values.

In the first phase of leg raising (LR) formalin test, positive control diclofenac produced significant decrease in leg raising (p<.05), ot 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 (diclofenac) again produced significant decrease (p<0.02) than control values while gabapentin had no effect.

In the second phase of raising foot (LR) both diclofenac and gabapentin produced significant decrease (p<0.05) as compared to control. In the licking and biting episodes of second phase also gabapentin & diclofenac exert significant effect (p<0.02) in comparison to control. 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. To conclude, the present study investigated analgesic property of gabapentin in formalin test which is a biphasic animal model of pain. Diclofenac found significantly effective in both phases, while in second phase both diclofenac and gabapentin produced significant effect.

DISCUSSION

The present study was done to evaluate the antinociceptive effect of novel antiepileptic gabapentin on common phasic (acute) and tonic (inflammatory) pain model of formalin test with the help of conventional analgesic drugs i.e. diclofenac which was used as positive control in rats.

In formalin test, diclofenac presently produced significant analgesic effect in both phase 1 and phase 2 pain which confirms to an earlier study in which diclofenac at a dose of 5, 10 and 20 mg/kg, i.p. produced significant antinociceptive effect in both phases of formalin test.[7] Furthermore, diclofenac, 5mg/kg, i.v. had produced analgesic effect alone or in combination with opioid and pretreatment with local diclofenac, 25-200 mg/paw in formalin test in the past.[4,8]

In formalin test, in present study gabapentin, 50mg/kg, p.o. produced significant effect in phase 2 but not in phase 1 which is very similar to previous study in which gabapentin, 300 microgram i.t inhibited second phase flinching behavior significantly but not in phase one.[9] In another study gabapentin when given intraplantarly with either 6/60 mcg had significantly reduced flinching behavior during phase 2, however phase 1 flinching behavior was unaffected.[10] Gabapentin in formalin test had produced a dose related inhibition of phase 2 with ED50 values of 22.9 mg/kg, i.p, but not of phase 1 and it is also reported that gabapentin, 30mg/kg, s.c. & 100 mg/kg, s.c. inhibited the late phases of nociceptive responses supporting present findings.[11-13]

The first and second phase of formalin test are generally believed to reflect excitation of peripheral afferent nociceptors and central sensitization, respectively.[14] Consistent with previous reports gabapentin was found to attenuate second phase nociceptive behavior in the present study, suggesting a specific inhibition of central sensitization with alpha 2 delta binding in central neural axis of pain.[15,16]

CONCLUSION

Evaluation of antinociception in acute and chronic pain models was done with the help of standard method of formalin test in Albino rats of either sex on anticonvulsant gabapentin. Diclofenac was used as positive control. Diclofenac as positive control was effective in both phases of formalin test. Test drug gabapentin did not exert any significant effect on phase 1 denoting acute pain while in 2nd phase which denotes prolonged inflammatory pain, gabapentin produced significant antinociceptive effect. Based on the present study it is concluded that anticonvulsant drug gabapentin, produces effects in chronic inflammatory pain models but does not affect acute nociception in animals. As formalin phase 2 chronic pain was relieved by gabapentin, so it

could be effective in various clinical conditions associated with prolonged or chronic inflammatory pain.

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Ethical approval: Not required

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