

Antinociceptive evaluation of anticonvulsant gabapentin with a conventional nonopioid analgesic in phasic and tonic animal model of acute and chronic pain

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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 clinician.

Methods: This study determined the analgesic effect of gabapentin in rats in biphasic animal pain model of acute and chronic inflammatory pain and compared its potency with a conventional nonopioid analgesic diclofenac.

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 anti-nociceptive effect in both phases of formalin test.

Conclusion: 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. Non-steroidal anti-inflammatory drugs 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.²

The anticonvulsants carbamazepine and gabapentine are now established drugs for trigeminal neuralgia and postoperative pain as nonconventional 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, wherefore 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.

Hence, this study was planned to verify the effects of an anticonvulsant gabapentin in common acute and chronic inflammatory (formalin test) pain model and compared its antinociceptive efficacy also with conventional nonopioid analgesic diclofenac.

METHODS

Animals used

Adult albino rats of either sex, weight 150-200 g 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 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: 50 mg/kg¹

Diclofenac: 5 mg/kg⁴

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 p.o. by gavage in a volume of 1.0 ml/kg in rats.⁵

Procedures: For antinociceptive evaluation⁶

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 mins and Phase 2 was of 45-75 mins. Rat has been administered 0.05 ml of 10% formalin into the dorsal portion of the front paw. The test drugs has 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 the "Student's t-test."

RESULTS

This 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 (5 mg/kg) given 1 hr before the experimentations.

Formalin test (Table 1 and Figures 1 and 2)

The formalin test has been used as a model of tonic and inflammatory pain. Formalin has been characterized by two characteristic phases of increased pain sensitivity in rats. The first phase is of 0-15 mins denoting acute pain and phase 2 is of 45-75 mins denoting chronic inflammatory pain. Number of raising foot leg raising (LR) licking and biting (LB) were measured for the two phases as end points.

In the first phase of leg raising formalin test, positive control diclofenac produced significant decrease in LR ($p < 0.05$), to experimental antiepileptic drug produced no any significant effect on LR in comparison to control values.

In the first phase of LB, positive control (diclofenac) again produced significant decrease ($p < 0.02$) than control values, while gabapentin had no effect.

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	Number 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.	13.8±2.9	6.2±1.2	23.0±3.0	15.3±1.8
Diclofenac	6	10 mg/kg p.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. SE: Standard error, p.o.: Post oral, NS: Normal saline

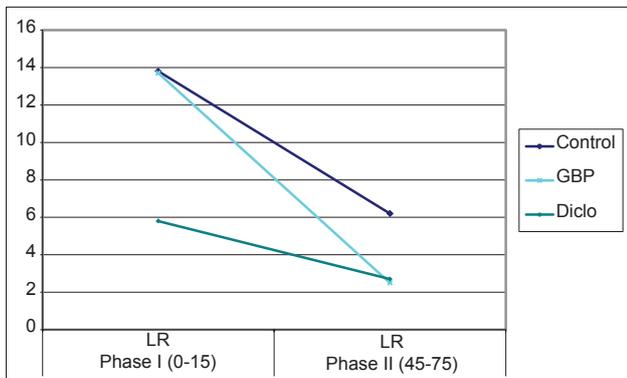


Figure 1: Time effects of experimental drug and positive control (diclofenac) administered per oral 1 hr before on number of raising foot responses in albino rats administered with dilute formalin (0.05 ml of 10% in normal saline) in right forepaw on dorsal surface i.d.*p<0.05 versus control values, **p<0.02 versus control values, *p=0.001 versus control values.**

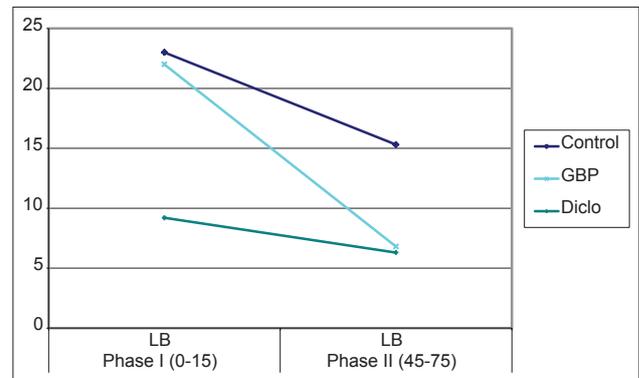


Figure 2: Time effects of experimental drugs and positive controls (diclofenac) administered per oral 1 hr before on number of licking and biting responses in albino rats administered with dilute formalin (0.05 ml of 10% in normal saline) in right forepaw on dorsal surface i.d. **p<0.02 versus control values, *p = 0.001 versus control values.**

In the second phase of raising foot (LR) both diclofenac and gabapentin produced significant decrease (p<0.05) when compared to control. In the LB episodes of second phase also gabapentin and diclofenac exert significant effect (p<0.02) in comparison to control. Decrease observed in LB with tramadol was more (p=0.001) when 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

This study was carried out 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, intraperitoneal (i.p.) produced significant antinociceptive effect in both phases of formalin test.⁷ Furthermore, diclofenac, 5 mg/kg, intravenous had produced analgesic effect alone or in combination with opioid⁴ and pretreatment with local diclofenac, 25-200 mg/paw in formalin test⁸ in the past.

In formalin test, in the present study gabapentin, 50 mg/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 µg intrathecal inhibited second phase flinching behavior significantly, but not in phase one.⁹ In another study gabapentin when given intraplantarly with either 6/60 µg 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 1¹¹ and it is also reported that gabapentin, 30 mg/kg, subcutaneous (s.c.) and 100 mg/kg, s.c. inhibited the late phases of nociceptive responses^{12,13} supporting present findings.

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 reports¹⁵ gabapentin was found to attenuate second phase nociceptive behavior in the present study, suggesting a specific inhibition of central sensitization with alpha 2 delta binding¹⁶ in central neural axis of pain.

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.

1. Diclofenac as positive control was effective in both phases of formalin test.
2. 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, hence it could be effective in various clinical conditions associated with prolonged or chronic inflammatory pain.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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