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Research Article

COMPARISON OF ANALGESIC EFFICACY OF ANTIEPILEPTIC GABAPENTIN WITH CONVENTIONAL ANALGESIC DICLOFENAC IN RAT EXPERIMENTAL MODELS

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ABSTRACT

Some Antiepileptic drugs have been shown to be clinically efficacious in the treatment of neuropathic pain and are being used by the clinician. This study determined the analgesic effect of gabapentin (A novel Anticonvulsant) in rats in different types of acute and chronic nociceptive test like Tail flick and Formalin test & compared its potency with a conventional nonopioid analgesic diclofenac. Peroral administration of gabapentin produced no any marked effect on early phase response of formalin test but significantly suppressed the late phase response. In tail flick test gabapentin produced no any significant analgesic effect while diclofenac produced a significant reduction of pain in tail flick test as well as in both phases of the formalin test. Thus we have observed that gabapentin produced antinociception in chronic pain as the second phase of formalin test reflects chronic inflammatory pain while diclofenac produced both acute and chronic type of antinociceptive effect as it significantly suppressed the pain in both tail-flick and formalin test.

Keywords: Gabapentin , diclofenac, nociception, formalin test, tail-flick test

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INTRODUCTION

Pain as a sensation and feeling, is a known entity from antiquity. According to the IASP- "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 chronicin nature. Acute pain is short lasing 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 state could be inflammatory or neuropathic. Inflammatory pain is due to chronic inflammation that is increased by pressure, but neuropathic pain occurs due to involvement in 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 novel anticonvulsant i.e gabapentin along in common acute (tail flick test) and chronic inflammatory (formalin test) pain models. Thus we examined the antinociceptive effect of gabapentin (a newer anticonvulsant) in animal models of pain and compared its antinociceptive effects also with conventional nonopioid analgesic diclofenac. .

MATERIALS AND METHOD

This study has been carried out in department of pharmacology, HIMS, Dehradun over a period of 12 months for evaluation of analgesic effects in animals. This study has been approved by ethical committee of HIMS.
Animals used: A 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 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[1]	50mg/kg
Diclofenac[4]	5mg/kg

Commercial preparations of these drugs have been used. Gabapentin (Sunpharma, Dadra,New Delhi) and control drug diclofenac (Novaritis India Ltd. Pune, India) 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 [6,7]

Radiant heat method

The tail flick test by radiant heat method using analgesiometer was carried out to study antinociception. Each animal was placed in that manner so the proximal third of the tail of the animal was laid across nicrome wire coil, which was heated by the passage of an electric current. For about 6 seconds the reaction of the animal has been observed. Rats with reaction time for more than 6 seconds have not been used in the test. The tests compounds have been administerd per orally. The animals have been subjected to the same testing procedure after o, 60, 90, and eventually 120 minutes for each individual animal. The cut off time has been 10 seconds.

Formalin Test

The formalin test has been 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 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 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 " student t test

RESULTS

The present study was conducted in the Department of Pharmacology, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun with the objective to experimentally evaluate the analgesic effect of novel antiepileptic gabapentin and one analgesic as positive control i.e diclofenac.

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

- ✓ Tail flick Test (by radiant heat metod)
- ✓ 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 I hr before the experimentations.

Radiant Heat Test [table 1 & fig 1]

During the evaluation of antinociceptive effect in tail flick radiant heat test , only diclofenac produced significant increase in post drug latency at 120 mins after drug administration

Experimental antiepileptic drug gabapentin did not change tail flick latency over a period of 120 min after administration of drug.

Formalin test [table 2 & fig 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 minutes denoting acute pain and phase 2 is of 45-75 minutes denoting chronic inflammatory pain. Number of raising foot (LR) licking and biting (LB) were measured for the two phases as end points.

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 & 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 both animal models of pain. Diclofenac found significantly effective in tail flick test. While In formalin test both diclofenac and gabapentin produced significant effect in phase 2 of formalin test.

Table 1: Effects of experimental drugs and positive controls (tramadol and diclofenac) on tail flick latency (in seconds) in radiant heat test over a period of 120 min of drugs/vehicle (NS) p.o administration in Albino rats

Albino rats producing a reaction time of < 6 sec were selected for experiment and a cut off time of 10 sec was kept. Reading was taken at time interval 0, 60, 90 and 120 min after drug/vehicle administration.

Group	No of Albino Rats	Dose and Route of Administration of drugs	Post Drug Latency (Mean±SE) **(in seconds)**			
			0 min	60 mins	90 mins	120 mins
Control	6	0.09% p.o	5.08±0.24	5.13±0.23	5.15±0.18	5.17±0.15
Tramadol	6	10 mg/kg p.o	5.23±0.24	5.40±0.22	5.53±0.21*	5.68±0.19***
Diclofenac	6	5 mg/kg p.o	5.15±0.26	5.30±0.25	5.42±0.25	5.55±0.23**
Carbamazepine	6	30 mg/kg p.o	5.13±0.23	5.18±0.23	5.20±0.21	5.22±0.16
Gabapentin	6	50 mg/kg p.o	5.15±0.24	5.20±0.22	5.22±0.18	5.28±0.14
Lamotrigine	6	50 mg/kg p.o	5.10±0.38	5.15±0.37	5.17±0.41	5.18±0.41
Levitiracetam	6	60 mg/kg p.o	5.12±0.23	5.17±0.22	5.18±0.18	5.20±0.14

* $p < 0.05$ vs control values at 0 min after tramadol p.o administration
** $p < 0.05$ vs control values at 0 min after diclofenac p.o administration
*** $p < 0.02$ vs control values at 0 min after tramadol p.o administration

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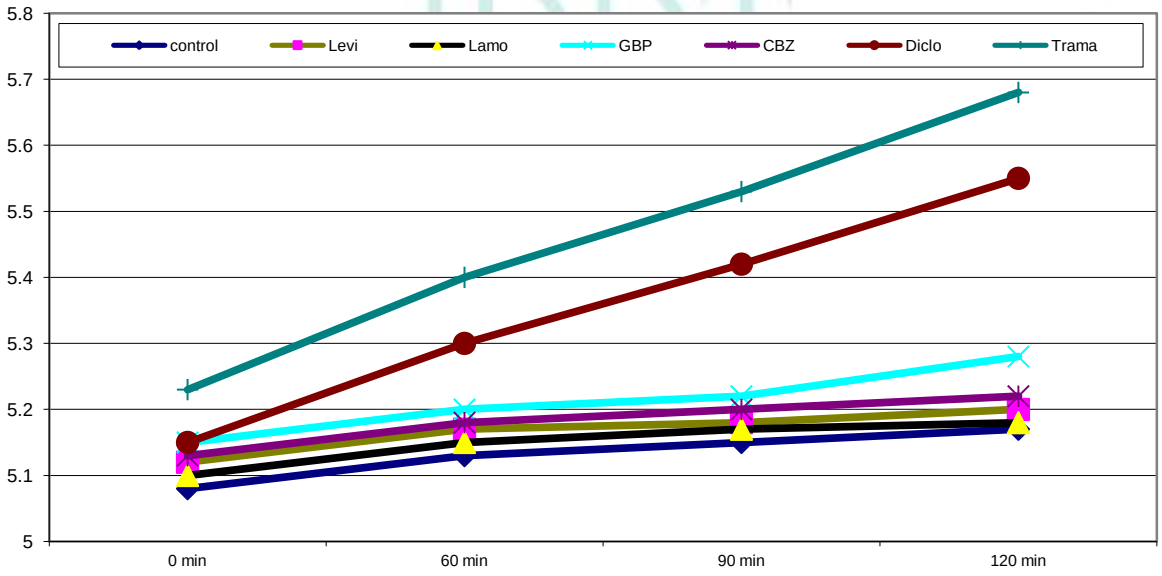

* $p < 0.05$ vs control values at 0 min after tramadol p.o administration
** $p < 0.05$ vs control values at 0 min after diclofenac p.o administration
*** $p < 0.02$ vs control values at 0 min after tramadol p.o administration

Table 2: Effects of drugs on acetic acid (0.55% given as .01ml/gm i.p) induced visceral nociception in albino mice.

All test drugs was administered 1 hr before giving acetic acid (i.p) in mice, abdominal contractions (writhes) were recorded after 5 min of injected acetic acid till 30 min.

Group	Dose and Route of Administration of drugs	No. of Albino Mice	No. of Writhes
			Mean ± SE
Control (NS)	0.09% p.o	6	40.00 ± 1.81
Tramadol	5 mg/kg p.o	6	28.00** ± 1.80
Diclofenac	10 mg/kg p.o	6	32.33** ± 1.59
Carbamazepine	30 mg/kg p.o	6	35.33 ± 1.34
Gabapentin	50 mg/kg p.o	6	37.33 ± 1.48
Lamotrigine	50 mg/kg p.o	6	38.17 ± 0.91
Levitiracetam	60 mg/kg p.o	6	39.67 ± 1.59

** p < 0.01 vs. control values

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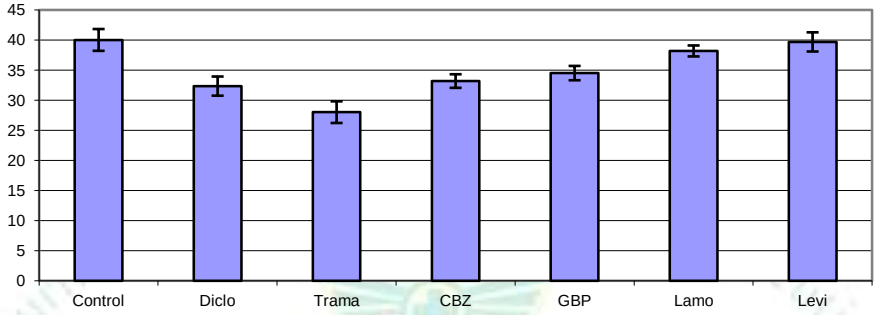

** p < 0.01 vs. control value

DISCUSSION

The present study was done to evaluate the antinociceptive effect of novel antiepileptic gabapentin on different acute 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. diclofenac which was used as positive control in rats.

Diclofenac is well established analgesic drug that showed significant antinociceptive effect in tail flick test when given orally (5 mg/kg) in present study at 120 min. It is in conformity with previous studies of diclofenac in which diclofenac showed analgesic effect in tail flick test while given 0.001-10.0 mg/kg ,body weight i.p [8]; 5 mg/kg, i.v. [9] ,1-50 microgm, i.c.v, 0.9-10 microgm , i.t.[4].

In formalin test ,diclofenac presently produced significant analgesic effect in both phase 1 & phase 2 pain which confirms to an earlier study in which diclofenac at a dose of 5, 10 & 20 mg/kg, i.p. produced significant antinociceptive effect in both phases of formalin test [10]. Furthermore, diclofenac, 5mg/kg, i.v. had produced analgesic effect alone or in combination with opioid [4] and pretreatment with local diclofenac, 25-200 mg/paw in formalin test [11] in the past.

In our study in tail flick test no significant antinociceptive effect has been observed with gabapentin 50 mg/kg. This is in conformity with earlier studies in which gabapentin, 300 microgram, i.t. (12) and 300 microgram i.c.v [13] produced no significant effect in tail flick test.

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[14]. 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[15]. 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 [16] and it is also reported that gabapentin, 30mg/kg, s.c. & 100 mg/kg, s.c. inhibited the late phases of nociceptive responses[17,18] 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 [19].consistant with previous reports [20] 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 [21] 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 Tail flick and formalin test in Albino rats of either sex on novel anticonvulsant gabapentin. Diclofenac was used as positive control. Diclofenac as positive control was effective in both pain models. In tail fick test, which is the model of phasic pain using thermal stimuli with the help of hot nichrome wire, gabapentin did not produce any significant antinociceptive effect. In formalin test, both the test drugs did not produce any significant effect on phase 1 denoting acute pain while in 2 phase which denotes prolonged inflammatory pain, gabapentin and diclofenac both produced significant antinociceptive effect. Based on the present study it is concluded that newer anticonvulsant 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 both diclofenac and gabapentin.

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ABBREVIATIONS

p.o	:	per oral
s.c	:	subcutaneous
i.m	:	intramuscular
i.v	:	intravenous
i.p	:	intraperitoneal
i.c.v	:	intracerebro ventricular
i.t	:	intrathecal
NS	:	normal saline
LR	:	leg raising
LB	:	licking and biting

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