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Research Article

Analagesic Effect of Levetiracetam in Rat Models of Pain

Geeta Soren[1*], Devarashetty Santoshi Roopa[1], Yashmiana Sridhar[2], Divyalasya TVS[3], Rama Mohan Pathapati[3], Madhavulu Buchineni[3]

[1]Department of Pharmacology, MNR Medical College, Sangareddy, Telangana, A. P, India
[2]Nizams Institute of Medical Sciences, Hyderabad, Telangana, AP, India
[3]Department of Pharmacology, Narayana Medical College & Hospital, Nellore, A.P, India

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ABSTRACT

Background: Antiepileptic drugs are widely used to treat multiple non-epileptic disorders such as neuropathic and inflammatory pain, migraine, essential tremors and psychiatric disorders. Levetiracetam is a novel antiepileptic drug with a broad spectrum of anticonvulsant activity with high safety margin. We evaluated the analgesic effect of levetiracetam in inflammatory induced hyperalgesia in albino rats. Methods: In this study male Wister rats weighing between 200-250 grams were taken and divided into 5 groups with 6 rats in each group. Levetiracetam was administered orally at a dose of 50mg/kg, 100 mg/kg, 200mg/kg and was compared with the control group which received distill water and the standard drug Aspirin at a dose of 100mg/kg. Hyperalgesia was induced by hot plate method. Reaction times were measured at 0, 30, 60 and 120 min after drug administration. Results: Levetiracetam at a dose of 100mg/kg after one hour of drug administration showed an increase in the reaction time compared to the saline. However, aspirin showed significant increase in the reaction time as compared to levetiracetam. Conclusion: Levetiracetam showed anti-hyperalgesia in animal model of pain and further study need to be conducted to evaluate the analgesic property.

Keywords: Levetiracetam, Anti Epileptic Drug (AED), Wister Rat, Aspirin, Analgesic

INTRODUCTION

Pain is an ill-defined, disabling accompaniment of many medical condition evoked by an external or internal stimulus. (1) Management of pain forms an integral component of any therapeutic intervention. Opioids and NSAID are the conventional analgesic drugs that are used for the treatment of pain associated with different causes. Aspirin is a non-steroidal anti-inflammatory drug used in the treatment of inflammation induced pain and pain associated with tissue injury but is ineffective in several visceral and ischemic pains. Aspirin though a potent analgesic, produces g.i.t side effects like dyspepsia, gastric bleeding and even ulceration.(2) Antiepileptic drugs are widely used to treat multiple non-epileptic disorders such as neuropathic and inflammatory pain, migraine, essential tremors and psychiatric disorders. Levetiracetam is one such novel antiepileptic drug with a broad spectrum of anticonvulsant activity and an unusually high safety margin. (3) In recent times it is one of the investigational drugs for analgesic properties. To this purpose, we evaluated the analgesic effect of levetiracetam in inflammatory induced hyperalgesia in albino rats.

METHODS

Wister rats weighing 200-250 gm of male sex aged between3-4months were obtained from the animal house of M.N.R. medical college .The animals were housed in polypropylene cages under standard housing condition, at room temp of 24-27 c with12 hrs.Light and dark cycle. Food in the form of grains, pellets were provided and water was available at ad libitum.The study protocol was accepted by the institutional ethical committee and followed the guidelines of CPCSEA.

A total of 30 rats were divided into five groups and six in each group.

Group l- Control (Saline)
Group 2-Standard (Aspirin) 100mg/kg
Group 3-Test drug (Levetiracetam) 50mg/kg
Group 4- Test drug (Levetiracetam) 100mg/kg
Group 5- Test drug (Levetiracetam) 200mg/kg

Hyperalgesia (4) was induced by hot plate method. Eddy's hot plate apparatus is a thermostatically controlled electrical plate heated by a thermode (Woalfe and MacDonald 1994:Eddy and Leinbach 1953) surrounded by a transparent square box(22x22x15) with flexible lid on its top.The hot plate is maintained at a constant temperature of 55 ^{o}C. The animal was kept on the heated hot plate, behavioral changes like paw licking and jumping were observed. The reaction time for these responses was measured at 0, 30, 60,120 minutes one hour after administration of the drugs. The initial reaction time of each rat was noted, prior to the drug treatment. Only rats that showed nociceptive response within 15 sec were included in the study. Food was withdrawn 12 hrs prior to drug administration. The test and the control drugs were given orally. The percentage of increase in the reaction

**Author for Correspondence*

Table 1: The mean reaction time to thermal pain stimulus.

Groups	Doses	Reaction Time in seconds			
		0 min	30 min	60 min	120 min
Group-1 Control	Saline.	16.21±0.31	16.33±0.21	15.5±0.22	16.5±0.22
Group-2 Aspirin	100mg	14.33±0.49	18.83±0.30	22.50±0.54	16.66±0.33
Group-3 Testdrug	50mg	16.33±0.42	17.16±0.30	19.83±0.30	16.66±0.40
Group-4 Testdrug	100mg	15.56±0.50	15.93±0.57	19.16±0.64	15.66±0.33
Group-5 Testdrug	200mg	14.33±0.66	19.33±0.42	19.33±0.55	15.16±0.47

Table 2: Percentage Increase In Reaction Time At Different Time Intervals Compared To Controls.

Groups		30min	60min	120min
Group-1 Control	Saline.	0.74	-4.38	1.79
Group-2 Aspirin	100mg	31.40	57.01	16.26
Group-3 Test drug	50mg	5.08	21.43	2.02
Group-4 Test drug	100mg	2.38	23.14	0.64
Group-5 Test drug	200mg	9.28	34.89	5.79

time was calculated at different time interval at different test doses and the standard dose in comparisons with the control by using the formulae= 100*(Mean reaction time in test group-Mean reaction time in control) divided by Mean reaction time in control group

Statistical analysis

The values are presented as the Mean ± SEM and the data is analyzed by ANOVA followed by Tukey's post hock test by using the graph pad prism. The 'p' value of <0.05 was considered significant.

RESULTS

Levetiracetam showed an increase in the reaction time at different doses of (50mg,100mg,200mg) respectively, compared to that of the control at different time interval of 0,30,60,120mins. Marked increase in the reaction time was observed at a test dose of 200mg of Levetiracetam at 60 min significantly ($p<0.05$) when compared to control. The increase in the reaction time at all dose of Levetiracetam is less than that of the standard drug, aspirin at a dose of 100mg at 60 minutes.($P<0.05$) Marked percentage increase in the reaction time was shown by aspirin at 100mg followed by Levetiracetam at a dose of 200mg respectively compared to saline.

DISSCUSSION

Development of new analgesic compound have increased the therapeutic options available to clinicians while at the same time helping to minimize undesirable side effects. levetiracetam an antiepileptic drug and is being explored for its analgesic property. The present study was conducted to demonstrate the analgesic property of Levetiracetam. In this study animal model hyperalgesia that mimics clinical condition like neuropathic burning sensation and pain has been produced by standing the animal on hotplate. The inflamed paws have greater initial resting paw temperature and stimulation of the inflamed paw results in shorter withdrawal latencies and this corresponds to a lower threshold temperature. [(5-6)] The thermal model was used to assess the effect of central analgesics which involves higher brain function and is considered to be a supra-spinally organized response. [(7)]

In the present study all the doses (50mg/kg,100mgkg,200mg/kg) of Levetiracetam showed increase in the reaction time at different time interval (0,30,60,120min) respectively compared to the control. Levetiracetam significant effect was seen at a dose of 200mg/kg at 60 min but the increase is much less compared to the standard drug (Aspirin-100mg/kg). Similar studies were demonstrated by A Micov et al (8) and numerous other studies have demonstrated anti-nociceptive effects of antiepileptic drugs in animal models of inflammatory pain. [(9-11)]

CONCLUSION

In this present study shows that Levetiracetam has analgesic property though less significant to aspirin. Further study need to be conducted to evaluate the analgesic property of Levetiracetam.

Conflict of interest: None

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