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Half dose of Levetiracetam plus full dose of aspirin is as effective as aspirin full dose in increasing reaction times to inflammation induced thermal hyperalgesia in wistar rat models

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Abstract

Background: Effective pain management remains a challenge for healthcare professionals. Much research has been directed in the recent years for want of an effective, potent analgesic that can be used chronically with least adverse effects. Levetiracetam has shown analgesic properties and exerts synergy in combination with non-steroidal anti-inflammatory drugs. To this purpose of the study is to compare the combined effect of Levetiracetam and Aspirin against the standard drug aspirin in inflammation-induced thermal hyperalgesia model in rats.

Methods: Male Wistar rats weighing 200-250gms aged 3-4 months were randomized to 4 groups containing six animals each: group-I(control)- distilled water, group-II (standard) -Tab. Aspirin 100 mg/kg, group-III (Test)-Tab. Levetiracetam 100 mg/kg and Group-IV (combined) – Tab. Aspirin 50mg/kg + Tab. Levetiracetam 50 mg/kg. Test compounds are administered orally 1hour after injecting carrageenan into the sub plantar region of left hind paw. The analgesic activity of a drug is its ability to increase the mean reaction time and percentage increase in reaction time.

Results: The analgesic effect of Levetiracetam (100 mg/kg) is less that of Aspirin (100 mg/kg). The combined effect of Levetiracetam (50 mg/kg) and Aspirin (50 mg/kg) is comparable to the standard drug Aspirin (100 mg/kg).

Conclusion: The results of our study indicate that Levetiracetam (100 mg/kg) has an analgesic effect but less than that of the standard drug Aspirin (100 mg/kg). Half dose of Levetiracetam plus half dose of Aspirin is as effective as aspirin full dose in increasing reaction times to thermal stimulus. Due to this synergistic action, the dose- dependent adverse effects of aspirin-like gastrointestinal bleeding can be avoided when given in combination.

Keywords: Analgesic, Carrageenan, Levetiracetam, Thermal hyperalgesia

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described regarding such damage [1, 2]. Pain is usually evoked by an external or internal noxious stimulus. It is a symptom not a disease. It is a subjective experience which cannot be objectively defined or quantified satisfactorily. Pain is a warning signal primarily protective in nature but adversely affects the quality of life, productivity and increases depression and suicidal ideation [3]. As a symptom, pain demands instant relief and in practice its dramatic relief highly impresses a layman. Analgesics are the drugs that selectively relieve pain by acting in the central nervous system or on peripheral pain mechanisms without significantly altering consciousness. Opioids are highly potent centrally acting analgesics but cause many adverse effects the common of which are nausea, vomiting, sedation, pruritus, urinary retention apart from serious adverse effects like hypotension and respiratory depression [4]. Prolonged use leads to development of tolerance and opioid induced abnormal hypersensitivity to pain [5]. NSAIDs are among most common pain relievers. But the patients who need to take them regularly suffer from various adverse effects like peptic ulcer, gastrointestinal bleeding, high blood pressure, renal failure, heart attacks and stroke. Hence effective pain management still remains a challenge for health care professionals. Lot of research has been directed in the recent years for want of an effective potent analgesic that can be used chronically with least adverse effects. Levetiracetam proves to be one such promising analgesic. Levetiracetam, chemically related to piracetam is a nootropic drug and the initial research was directed primarily towards indications of piracetam. Later the antiepileptic profile of the drug was identified. Recently the analgesic property of Levetiracetam has been explored. It has also been shown to have synergistic action with NSAIDs [6]. To this purpose we evaluated the analgesic effect of Levetiracetam and compared the combined effect of Levetiracetam and Aspirin against the standard drug aspirin in carrageenan induced inflammation plus thermal induced hyperalgesia models in rats.

Methods

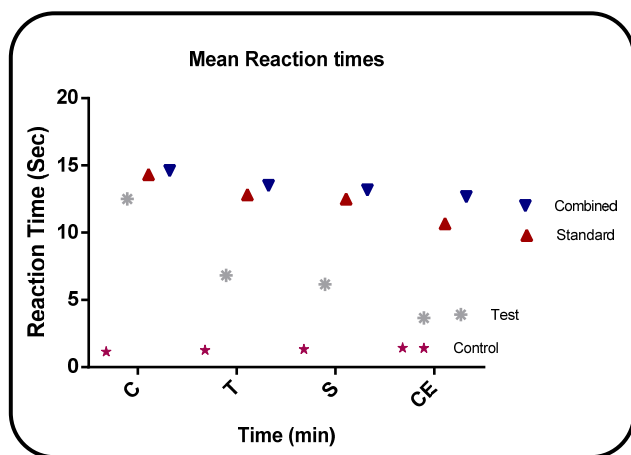
The study was conducted in Gandhi Medical College, Secunderabad after getting approval from Institutional Animal Ethics Committee. Male Wistar rats weighing 200-250gms aged 3-4 months were procured from Central animal house of Gandhi Medical College. The study animals were kept under standard housing conditions at 24-27°C, 12hrs dark- light cycle is maintained, with food and water *ad libitum*. The animals that sustained the disco ordination test were randomized to 4 groups containing 6 animals each as follows: Group-I (control) - distilled water, Group- II (standard) - Tab. Aspirin 100 mg/kg, Group-III (Test) - Tab. Levetiracetam 100 mg/kg and group-IV (combined) – Tab. Aspirin 50mg/kg + Tab. Levetiracetam 50 mg/kg. Inflammatory pain is induced by injecting 0.05ml of freshly prepared 1% carrageenan into sub plantar region of left hind paw of animals. Test compounds are administered orally using a feeding tube, 1hour after injecting carrageenan. Thermal pain stimulus was induced by placing the animals on Eddy’s hot plate, maintained at 55°C, the latency period is noted at 0, 30, 60, 120 mins (0 minutes means 1hr after drug administration). The analgesic activity is the ability of a particular drug in increasing mean reaction time and percentage reaction times to a combined effect of inflammation and thermal pain stimulus.

Statistical Analysis: Observations were tabulated and presented as mean and standard deviations. Significance between the means of groups was statistically analyzed by using one-way analysis of variance (ANOVA) followed by Post Hoc Tukey’s multiple group comparisons tests with the help of statistical software Graph-Pad Prism, version-4, USA.

Results: Aspirin (standard), Levetiracetam (test) and Aspirin-plus-Levetiracetam combination lead to increase in mean reaction time compared to the control. The test group (Levetiracetam – 100 mg/kg) caused increase in mean reaction time in comparison with the control but the magnitude of increment in latency is much less than the standard group (Aspirin – 100 mg/kg).The increase in mean reaction time of combined group (Aspirin 50 mg/kg + Levetiracetam 50 mg/kg) is significant when compared to test ($P<0.05$).The combined effect of Levetiracetam (50 mg/kg) and Aspirin (50 mg/kg) is comparable to the standard drug Aspirin (100 mg/kg).(table-I,& Graph-I).Overall mean percentage increase in reaction time is higher with combined (90.37%) followed by standard (87.4%) and test (77.95%).

Table 1: Comparison of mean reaction times to Eddy’s hot plate

Groups(n = 6)	0 mins	30mins	60 mins	120 mins
Control (C)	1.15±0.10	1.25±0.10	1.33±0.08	1.43±0.08
Test (T)	12.50±1.22	6.83±1.60	6.16±1.60	3.66±0.81
Standard (S)	14.33±0.81	12.83±0.75	12.50±0.54	10.67±0.81
Combined (CE)	14.67±0.51	13.50±0.54	13.17±0.75	12.67±0.51
C VS. T	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$
C VS. S	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$
C VS. CE	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$
T VS. S	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$
T VS. CE	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$
S VS. CE	$P>0.05$	$P>0.05$	$P>0.05$	$P>0.05$



Graph I: Diagram showing variation in reaction time at different time intervals

Discussion

Levetiracetam, a novel antiepileptic drug, has recently been shown to have antinociceptive effects in various animal models of pain. The purpose of our study is to evaluate the analgesic action of Levetiracetam in the inflammatory model of thermal hyperalgesia in rats and to compare it with

commonly used NSAID for chronic pain, aspirin and to find out the synergistic action of both, if any.

All the available analgesics of the present day are efficacious, but safety, tolerability and risk of drug interactions are the prime concern during treatment especially chronic pain. Levetiracetam has a favourable profile with a low potential for drug interactions [7]. The most commonly reported adverse effects during clinical trials with Levetiracetam in adults were primarily related to the CNS and included somnolence (15%), asthenia (15%), headache (14%), infection (13%), dizziness (9%) and ataxia (3%). The patients also reported the slightly higher incidence of symptoms of upper respiratory tract infection, which was not associated with leucopenia. In clinical trials, only 1-4% of patients have withdrawn because of this effects [8]. These adverse effects are seen most frequently in the first month of therapy and typically lessened or resolved with continued treatment [9]. Similar negative effects, but higher percentages, were reported in paediatric populations [10]. Upto 13% of patients have experienced adverse neuropsychiatric symptoms. In most of these patients, the symptoms have been mild including agitation, hostility, apathy, anxiety, emotional lability and depression. About 1% of paediatric or adult patients have experienced serious neuropsychiatric symptoms including hallucinations, suicidal ideations,

psychosis after beginning Levetiracetam. There was a significant association between psychiatric adverse events and previous history of febrile convulsions or status epilepticus, while the past, personal or family history of psychiatric disorders was more important in predicting the features of psychiatric adverse events rather than their occurrence. Dose reduction or discontinuation has led to resolution of symptoms in the cases reported. Overall these studies illustrated that a close monitoring about psychiatric adverse events is related to the psychiatric profile of the patient^[1]. Conversely, Levetiracetam has no major adverse effects on cognitive function^[12]. Levetiracetam has been shown to synergize with common analgesics. Levetiracetam–analgesic combinations produced significant dose-dependent antinociceptive effects and revealed 15-19 fold reduction of doses of both drugs in the combination of Levetiracetam with aspirin^[13]. Regular use of aspirin is associated with gastrointestinal bleeding. The risk appears more strongly related to dose than the duration of aspirin use. Efforts to minimise adverse effects of aspirin therapy should emphasize using the lowest effective dose among both short-term and long-term users^[14]. Our study results support the analgesic property of Levetiracetam but of low potency when compared to aspirin. However, the combination of aspirin and Levetiracetam showed good analgesic action comparable to aspirin alone, but at lesser doses of aspirin. Furthermore, Levetiracetam has been shown to increase the bleeding time by 3.5% -30% of the baseline^[15]. This indicates that aspirin and Levetiracetam prove to be a synergistic combination in the treatment of pain

Conclusion

Our study results indicate the novel antiepileptic drug Levetiracetam, independently has shown its analgesic activity to carrageenan-thermal stimulus. Suggesting that Levetiracetam might be better option in the management of inflammatory and neuropathic pain. Additionally, a combination of half dose of Levetiracetam plus half dose of Aspirin is as effective as aspirin full dose. Due to this synergistic action, the dose-dependent adverse effects of aspirin-like gastrointestinal bleeding can be avoided when given in combination.

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