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Research Article

A Comparative Study of the Effect of Gabapentin, Topiramate, Levetiracetam and Zonisamide for Neuropathic Pain Induced by Anticancer Drug (Vincristine) in Rats

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ABSTRACT

Background**:** Neuropathic pain syndrome is a frequently occurring, disabling disease. Many anticancer drugs which are used to treat solid tumors cause neuropathic pain as their dose limiting side effect. Current treatment options are still relatively poor. Objective**:** The present study was designed to compare the effect of gabapentin, topiramate, levetiracetam and zonisamidefor treatment of neuropathic pain induced by anticancer drug(vincristine) in albinorats using thermal method**.** Materials and Methods**:** Neuropathic pain was induced by injecting vincristine (100µg/kg) intraperitoneally daily for 14 days in rats. Behavioural testing for thermal hyperalgesia was assessed 24 hours after each injection by the hot-plat method. After 14 days rats were divided into five groups of six animals each. Group I was treated with distilled water as control group, group II was treated with oral gabapentin (60 mg/kg), group III received oral topiramate (40 mg/kg), group IV was treated with oral levetiracetam (120 mg/kg) and group V received zonisamide (50 mg/kg).The antihyperalgesic effect of drugs was assessed by the hot-plate method 24 hours after each administration. Statistical analysis was done by two way analysis of variance (ANOVA) followed by post hoc test**.** Results**:** Gabapentin, topiramate and zonisamide treated groups showed asignificant($P < 0.0001$) increase hot-plate latency as compared to control group. Levetiracetam treated group however, did not show a significant increase in hot-plate latency. Conclusion**:** In vincristine induced neuropathic pain gabapentin, topiramate and zonisamide appearto be promising drugs although they act by different mechanisms.

Keywords: Gabapentin, levetiracetam, topiramate, vincristine induced neuropathic pain, zonisamide

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INTRODUCTION

Neuropathic pain is a frequently occuring, disabling disease. Neuropathic pain is the pain that arise after injury to peripheral nerves or to sensory transmitting systems in the spinal cord and brain. Allodynia (innocuous stimulation evokes intense and prolonged pain) and hyperalgesia (noxious stimulation evokes intense and prolonged pain) are the prominent symptoms of neuropathic pain [1]. Neuropathic pain in cancer patients remain a treatment challenge. It may be due to tumor infiltration of nerve, tumor-associated toxins, and chemotherapeutic agents. Chemotherapy induced neuropathic pain is the most prevalent neurological complication and a major dose-limiting side effect of chemotherapeutic agents [2]. Vincristine (vinca alkaloid), a chemo-therapeutic drug is the most effective agent against solid tumours. Their dose limiting side effect is production of peripheral neuropathy, which in many patients is accompanied by chronic pain syndrome [3]. The anti tumour action of this drug is due to their binding to β-tubulin, which interfere with dynamic assembly of mitotic spindle and leads to aborted cell division. Axonal microtubules also contain β-tubulin, and it has been thought that the peripheral

neuropathy secondary to vincristine due to binding to microtubules and thereby impairing axoplasmic transport. There is a small increase in the average diameter of C fibers and in the incidence of microtubules with an atypical orientation in A and C fibers [4].

Current treatment options for neuropathic pain are still relatively poor. With respect to their treatment, these share several critical clinical features like they follow a chronic course, they respond very poorly or not at all to standard analgesic therapies such as nonsteroidal anti-inflammatory drugs and also they respond less predictably and less robustly to opioids than do nociceptive pain [5]. There is no treatment of chemotherapy induced peripheral neuropathy (CIPN) that has been shown to be efficacious in randomized controlled trial. On the basis of pathophysiological mechanisms, potential therapeutic targets for treatment of CIPN would be sodium channels, calcium channels, gamma amino butyric acid (GABA) receptors, serotonin and norepinephrine receptors, N-methyl-D-aspartate receptors and α- receptors [6]. Drugs from different groups are used to treat neuropathic pain. Tricyclic anti-depressants (TCA), often the first choice have significant side effects [7]. Antiepileptics are safer for these pain but they are partially effective [8]. So it is difficult to select a right drug in different types of neuropathic pain. With this background, we have planned to compare the effect of gabapentin, topiramate, levetiracetam and zonisamide for neuropathic pain induced by anticancer drug (vincristine) in rats using thermal method.

MATERIALS AND METHODS

Animals: Adult male albino rats weighing between 150-200 g were used throughout the study. Animals were acclimatized to the laboratory environment for 7-10 days before initiating the study. All the animals were housed in institutional animal house at the room temperature of 25-30^{o}C with food and water available ad libitum. Light/dark cycle was maintained for 12 hours. All experiment was carried with approval of Institutional Animal Ethics Committee (Registration Number- 692/02/ a/CPCSEA).

Drugs: Gabapentin (60 mg/kg) [9], topiramate (40 mg/kg)[10], levetiracetam (120mg/kg) [11] and zonisamide (50 mg/kg) [12] were used.All the drugs were dissolved in distilled water. They were administered by oral route (p.o.).

Experiment model: Vincristine induced neuropathic pain model was used [13]. Vincristine was dissolved in normal saline in the concentration of 1mg/10ml and injected intraperitoneally (100µg/kg) daily for 14 days in rats. Behavioural testing for thermal hyperalgesia was assessed 24 hours after each injection by the hot-plate method. After 14 days animals were divided into five groups. The number of animals in each group were 6 (n=6). All drugs were administered orally once a day for next six days (from day 15 to day 20).

Group I-Treated with distilled water as control group.

Group II-Treated with Gabapentin (60 mg/kg).

Group III-Treated with Topiramate (40 mg/kg).

Group IV-Treated with Levetiracetam (120 mg/kg).

Group V-Treated with Zonisamide (50 mg/kg).

Hot-plate latency and antihyperalgesic effects of drugs were assessed by the hot-plate method 24 hours after each administration (from day 16 to day 21).

Hot-plate method: Thermal hyperalgesia was assessed by the hot-plate method that is suitable for evaluation of analgesics having a central action. The instrument was used for experimentation is known as the "Eddy's hot-plate analgesiometer". It consists of an electrically heated surface. The temperature of hot-plate is maintained at 55-56^{o}C. The reaction time (hot-plate latency) when the animals are placed on hot-plate and until responses (jumping, withdrawal of the paws and licking of the paws) occur, was recorded by stopwatch in seconds [14].

Statistical analysis: Statistical analysis among different groups was done by two way analysis of variance (ANOVA) followed by Dunnett's t test for multiple post hoc

comparisons. P<0.05 was considered statistically significant.

RESULTS

The antihyperalgesic effect of four antiepileptic drugs was tested using the hot-plate test. Gabapentin, topiramate and zonisamide increased withdrawal latency in hot-plate method as compared to control, but their effect was gradually increased. From day 16 to 18 none of the four drugs have shown increased hot-plate latency as compared to control (**Table 1-4**). On day 19, gabapentin (p<0.01) and zonisamide (p<0.0 01) significantly increased hot-plate latency as compare to control. On day 20, topiramate also increased hot-plate latency (p<0.01). On day 21, all the three drugs viz. (gabapentine, topiramate and zonisamide) were equally effective (p<0.0001). Levetiracetam did not show its significant effect on hot-plate method (**Fig. 1-4**).

Table 1: Analgesic Effect of Gabapentin (60 mg/kg, p.o.) on Hot-plate Method

Days	Reaction time in seconds (Mean ± S.E.)		p-value
	Control	Test	
16	0.73±0.11	0.76±0.09	>0.05
17	0.83±0.12	0.9± 0.03	>0.05
18	0.9±0.10	1.12± 0.12	>0.05
19	0.85±0.07	1.4± 0.15	<0.01
20	0.9±0.11	2± 0.43	<0.0001
21	0.9±0.11	2.12± 0.22	<0.0001

Table 2: Analgesic Effect of Topiramate (40 mg/kg, p.o.) on Hot-plate method

Days	Reaction time in seconds (Mean ± S.E.)		p-value
	Control	Test	
16	0.73±0.11	0.63±0.10	>0.05
17	0.83±0.12	1.02± 0.16	>0.05
18	0.9±0.10	1.17± 0.22	>0.05
19	0.85±0.07	1.18± 0.21	>0.05
20	0.9±0.11	1.45± 0.32	<0.01
21	0.9±0.11	1.87± 0.30	<0.0001

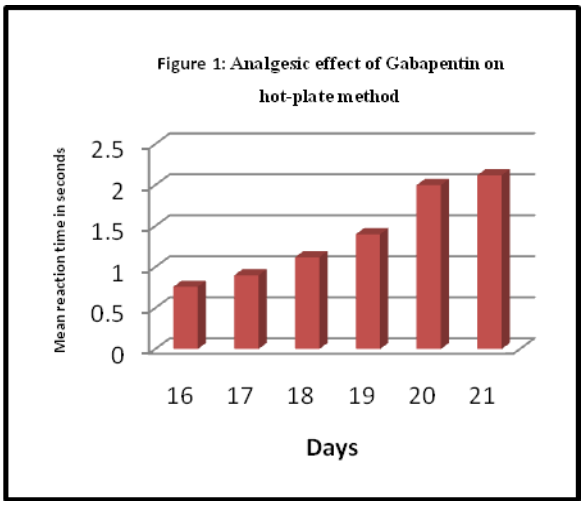
Table 3: Analgesic Effect of Levetiracetam (120 mg/kg, p.o.) on Hot-plate Method

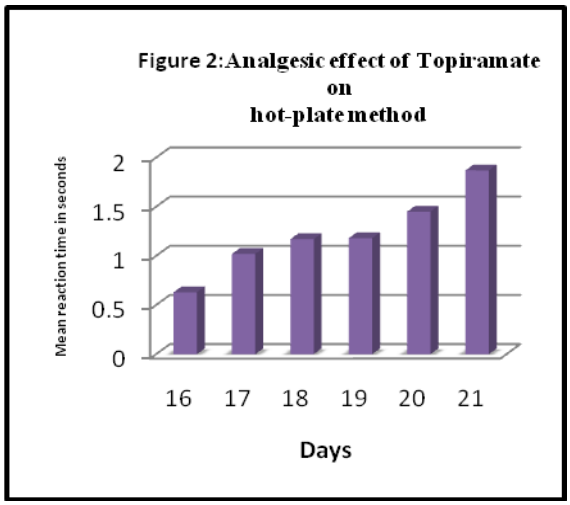
Days	Reaction time in seconds (Mean ± S.E.)		p-value
	Control	Test	
16	0.73±0.11	0.68±0.07	>0.05
17	0.83±0.12	0.83± 0.08	>0.05
18	0.9±0.10	1.05± 0.15	>0.05
19	0.85±0.07	1.03± 0.14	>0.05
20	0.9±0.11	1.12± 0.17	>0.05
21	0.9±0.11	1.43± 0.26	>0.05

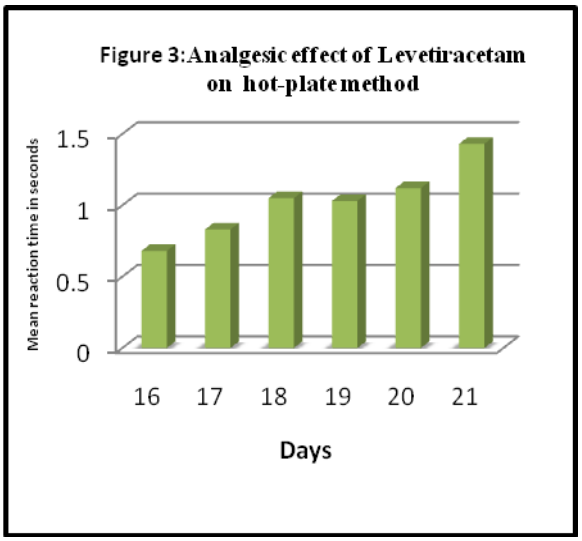
Table 4: Analgesic Effect of Zonisamide (50 mg/kg, p.o.) on Hot-plate Method

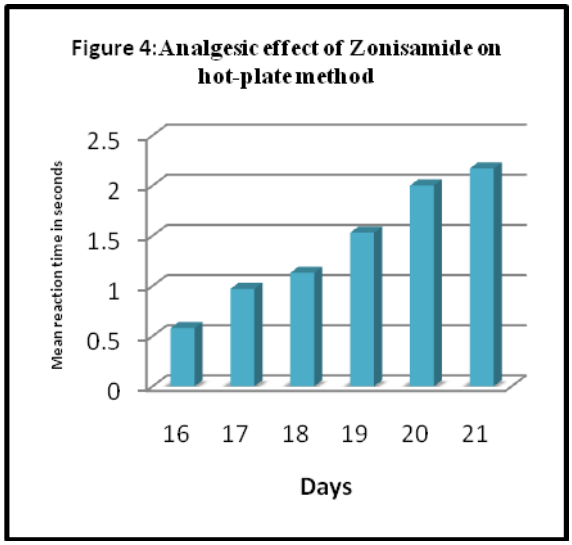
Days	Reaction time in seconds (Mean ± S.E.)		p-value
	Control	Test	
16	0.73±0.11	0.58±0.17	>0.05
17	0.83±0.12	0.97± 0.06	>0.05
18	0.9±0.10	1.13± 0.18	>0.05
19	0.85±0.07	1.53± 0.28	<0.001
20	0.9±0.11	2± 0.39	<0.0001
21	0.9±0.11	2.17± 0.42	<0.0001

Non Significant- p>0.05, Highly Significant –p<0.01, p<0.001, p<0.0001









DISCUSSION

Chemotherapeutic agent induced neuropathic pain is often resistant to standard analgesics. Many anticancer drugs are used to treat solid tumours but they cause neuropathic pain. Drugs from different groups are used to treat neuropathic pain. Tricyclic antidepressants

and antiepileptics are the mainstay in the treatment of neuropathic pain. Currently available drugs offer modest efficacy for neuropathic pain. Newer antiepileptics have better tolerability and improved pharmacokinetics rather than improved efficacy in neuropathic pain[15]. This study compared the effect of gabapentin, topiramate, levetiracetam and zonisamide in neuropathic pain induced by anticancer drug (vincristine) in rats using hot-plate method.

Study shows that treatment with vincristine (100µg/kg) produces long lasting thermal hyperalgesia in rats.In the present study thermal hyperalgesia was assessed by hot-plate method suitable for evaluation of analgesic activity having central action. The present study demonstrated that gabapentin, topiramate and zonisamide increased withdrawal latency in hot-plate method as compared to control, but their effect was gradually increased. The significant antihyperalgesic effect of these three newer antiepileptic drugs was clearly evident only when they were administered repeatedly in vincristine model. Levetiracetam did not show its significant effect on hot-plate method. Antiepileptic drugs are thought to relieve neuropathic pain through interaction with specific neurotransmitters and ion channels, with inhibition of neuronal activities[16]. These drugs act at several sites that may be relevant to pain, but the precise mechanism of their analgesic effect remains unclear [17]. These drugs are thought to limit neuronal excitation and enhance inhibition. Relevant sites of action include voltage-gated ion channels (sodium and calcium), ligand gated ion channels, the excitatory receptors of glutamate and NMDA, and the inhibitory receptors for GABA and glycine [18].

Gabapentin reduces allodynia and hyperalgesia in several animal models of neuropathic pain including models of acute herpeszoster infection, thermal injury, nerve injury, postoperative pain and streptozotocin-induced diabetic neuropathy [19]. Though the exact mechanism of topiramate is not clear, from the present investigation it may be speculated that topiramate has analgesic properties. It has several pharmacological properties that may contribute to its anticonvulsant activity and antinociceptive effect in neuropathic pain, these are: modulating voltage-gated sodium ion channels, enhancing gamma-aminobutyric acid inhibition, blocking excitatory glutamate neurotransmission, modulating voltage-gated calcium ion channels, etc. [20]. Zonisamide is a novel antiepileptic and its antihyperalgesic effect is postulated mainly due to its membrane stabilization and neuromodulation actions [21].

The small sample size and short duration of follow-up are the limitation of this study. However, further studies are required to explain the exact mechanism of these antiepileptic drugs and to elucidate their potential therapeutic utility and clinical implications.

CONCLUSION

The study was aimed to compare the effect of gabapentin, topiramate, levetiracetam and zonisamide in neuropathic pain induced by vincristine in albino rats using thermal method (hot-plate method).In present study, neuropathic pain was induced by injecting vincristine (100µg/kg) intraperitoneally daily for 14 days in rats. Behavioural testing for thermal hyperalgesia was assessed 24 hours after each injection by hot-plate method. Hot-plate method is suitable for evaluation of analgesics having central action.Analgesic effect of gabapentin (60mg/kg, p.o.), topiramate (40 mg/kg, p.o.), levetiracetam (120 mg/kg, p.o.) and zonisamide (50 mg.kg, p.o.) on vincristine induced neuropathic pain (for 14 days) were studied for next 6 days (from day 16-21). Gabapantin, topiramate and zonisamide produced a significant antihyperalgesic effect on hot-plate method but their effects occurred after repeated doses. Levetiracetam was not significantly effective in hot-plate method. We can conclude thatgabapentin, topiramate and zonisamide may be used in the treatment of neuropathic pain induced by chemotherapeutic agents. However this speculation needs to be confirmed clinically.

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