Research Article

Comparison of the Effect of Gabapentin, Topiramate, Levetiracetam and Zonisamide in Vincristine induced Neuropathic Pain in Albino Rats using Chemical Method

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ABSTRACT

Background**:** Neuropathic pain is a frequently occurring disease. Its treatment is very difficult. Antiepileptic drugs are effective in neuropathic pain acting by central and peripheral mechanism.Objective**:** The objective of present study was to compare the effect of newer Antiepileptics for treatment of neuropathic pain induced by anticancer drug (vincristine) in albino rats using chemical method**.** Materials and Methods**:** Neuropathic pain was induced by injecting vincristine (100µg/kg) intraperitoneally daily for 14 days in rats. Behavioural testing for chemical hyperalgesia was assessed 24 hours after each injection by the writhing test. 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 writhing test 24 hours after each administration. Statistical analysis was done by two way analysis of variance (ANOVA) followed by post hoc test**.** Results**:** Gabapentin, topiramate, levetiracetam and zonisamidetreated groups showed a significantly ($P < 0.0001$) reduced number of writhes on writhing test as compared to control group.Conclusion:Newer antiepileptics (gabapentin, topiramate, levetiracetam and zonisamide) are effective inanticancer drugs induced neuropathic pain acting via different mechanisms.

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

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INTRODUCTION

Neuropathic pain is different from nociceptive pain. Nociceptive pain is an ordinary pain, it occurs when a pain signal originates in normally functioning tissue nociceptors (A delta and C fibers) that have been activated by a mechanical, chemical, or thermal stimulus [1]. Neuropathic pain, however, occurs when an algogenic signal originates within abnormally functioning peripheral or central neurons that have themselves been damage or altered in same way [2].

The most common etiologies of neuropathic pain disorders are complex regional pain syndrome (type I and II) (CRPS), post-traumatic nerve injury, diabetic peripheral neuropathy, drug induced neuropathy, Trigeminal neuralgia and spinal cord injury pain. Abnormalities in ion channel conductivity and receptor function probably play some role in the majority of these illnesses. Many anticancer drugs are used for the treatment of cancers, but they cause neuropathy as their dose limiting side effect. Common cancer chemotherapy drugs associated with peripheral neuropathy include Vinca alkaloids, Taxanes, Platinum compounds, Bortezomib, Thalidomide, Lenalidomide etc. These agents produce the predictable mixed motor and sensory neuropathies with or without involvement of autonomic system.

Treatment of neuropathic pain is very difficult because they do not respond to standard analgesics such as nonsteroidal anti-inflammatory drugs [3]. Many similarities between the pathophysiological phenomena observed in some epilepsy models and in neuropathic pain models. This rational justifies the rational use of antiepileptic drugs in the symptomatic management of neuropathic pain disorders. Antiepileptic drugs are effective in neuropathic pain acting by central and peripheral mechanism. Hot plate (thermal) method is suitable for evaluation of antihyperalgesic activity of antiepileptics having the central action. While writhing test (chemical test) is suitable to find out the peripheral mechanism of antihyperalgesic activity of antiepileptic drugs. So our target is to find out additional mechanism of antiepileptic drugs that are not detected by hot plate method. In this study we compared the efficacy of newer anti-epileptic drugs in vincristine induced neuropathic pain in albino rats using chemical method (Writhing test).

MATERIALS AND METHODS:

Animals: Adult male albino rats weighing between 150-200 g were used. Animals were acclimatized to the laboratory environment for 7-10 days before initiating the study. They were allowed free access to water and were maintained on standard rat diet under laboratory conditions. 12-hour light/dark cycle was maintained. All procedures were carried with approval of Institutional Animal Ethics Committee (IAEC) (Registration Number-692/02/a/CPCSEA).

Drugs: Gabapentin (60 mg/kg) [4], topiramate (40 mg/kg) [5], levetiracetam (120mg/kg) [6] and zonisamide (50 mg/kg) [7] were used. All the drugs were dissolved in distilled water and administered by oral route (p.o.).

Experiment model: Vincristine induced neuropathic pain model was used [8]. Vincristine was dissolved in normal saline in the concentration of 1mg/10ml.

In this design vincristine (100 µg/kg) injected intraperitoneally, daily for 14 days in rats. Behavioural testing for chemical hyperalgesia was assessed 24 hours after each injection by writhing test. After 14 days animals were divided into 5 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 Gabapantin (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).

Antihyperalgesic effect of drugs was assessed 24 hours after each administration by writhing test.

Writhing Test: Chemical hyperalgesia was assessed by writhing test. Writhing test, a chemically induced hyperalgesia is used to detect peripheral analgesic activity of the compound. In each animal, a chemical irritant 10 ml/kg of 0.6% acetic acid was injected intraperitoneally. Animals were placed individually into a glass chamber/bell jar. After 5 min of injection of acetic acid, numbers of writhes were recorded for 15 min in each animal.

The writhing is characterized by a typical stretching behavior of the body and the animal tries to touch its ventral part to the ground accompanied by an extension of hind limbs [9].

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 by writhing test. Comparing the four drugs in chemical writhing test, on day16, only zonisamide significantly reduced number of writhes as compared to control. On day 17, gabapentin and levetiracetam significantly reduced number of writhes. On day 18, all the three drugs viz. (gabapentin, levetiracetam and zonisamide) have shown gradually reduced number of writhes (**Table 1-4**). Also on same day, topiramate significantly reduced number of writhes. On day 19, 20, 21 all the

four drugs were equally effective in showing significantly reduced number of writhes (**Figure 1-4**).

Table 1: Analgesic effect of Gabapentin (60 mg/kg, p.o.) on Writhing Test

Days	Number of abdominal writhes in 15 minutes Mean±S.E. Control	Test	P-Value
16	36.5±0.67	40±2.24	>0.05
17	36±0.45	33.5± 0.67	<0.005
18	34±0.45	27.5± 1.12	<0.0001
19	34.33±o.45	25.5± 1.12	<0.0001
20	33±0.45	23.5± 0.67	<0.0001
21	32.5±0.22	22± 0.45	<0.0001

Table 2: Analgesic effect of Topiramate (40 mg/kg, p.o.) on Writhing Test

Days	Number of abdominal writhes in 15 minutes Mean±S.E. Control	Test	P-Value
16	36.5±0.67	37±0.45	>0.05
17	36±0.45	36.5± 0.22	<0.005
18	34±0.45	31± 0.45	<0.0001
19	34.33±o.45	23.5± 0.67	<0.0001
20	33±0.45	16± 0.45	<0.0001
21	32.5±0.22	12.5± 0.22	<0.0001

Table 3: Analgesic effect of Levetiracetam (120 mg/kg, p.o.) on Writhing Test

Days	Number of abdominal writhes in 15 minutes Mean±S.E. Control	Test	P-Value
16	36.5±0.67	36±0.45	>0.05
17	36±0.45	26± 0.89	<0.005
18	34±0.45	23.5± 0.22	<0.0001
19	34.33±o.45	20.5± 0.22	<0.0001
20	33±0.45	19.5± 0.22	<0.0001
21	32.5±0.22	16± 0.45	<0.0001

Table 4: Analgesic effect of Zonisamide (50 mg/kg, p.o.) on Writhing Test

Days	Number of abdominal writhes in 15 minutes Mean±S.E. Control	Test	P-Value
16	36.5±0.67	39±0.45	<0.005
17	36±0.45	32.67± 1.15	<0.0001
18	34±0.45	29± 0.45	<0.0001
19	34.33±o.45	24± 0.45	<0.0001
20	33±0.45	23.5± 0.67	<0.0001
21	32.5±0.22	21± 0.45	<0.0001

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

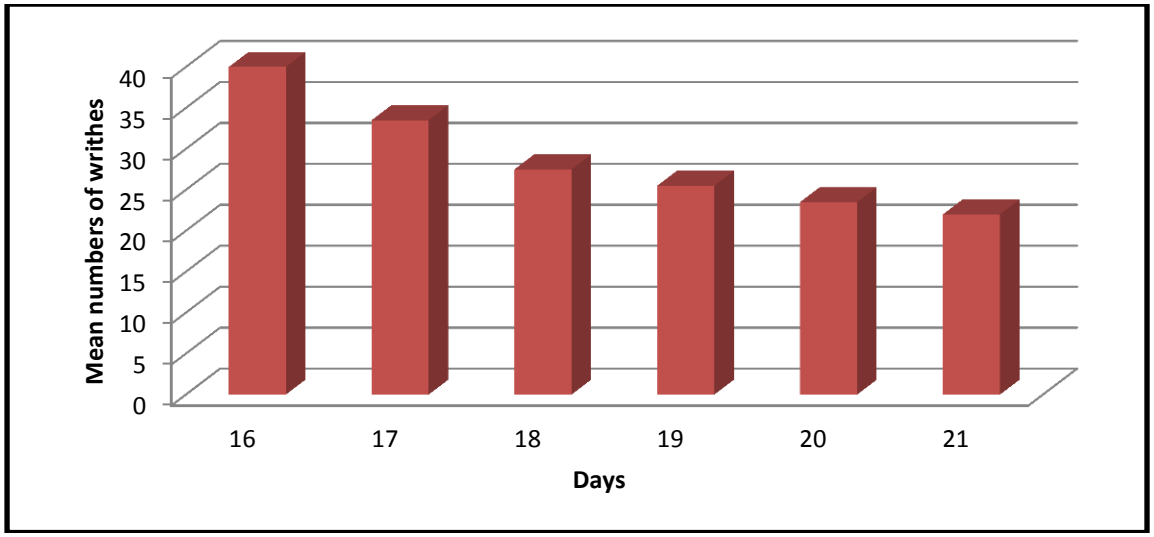

Figure 1: Analgesic Effect of Gabapentin on Writhing Test

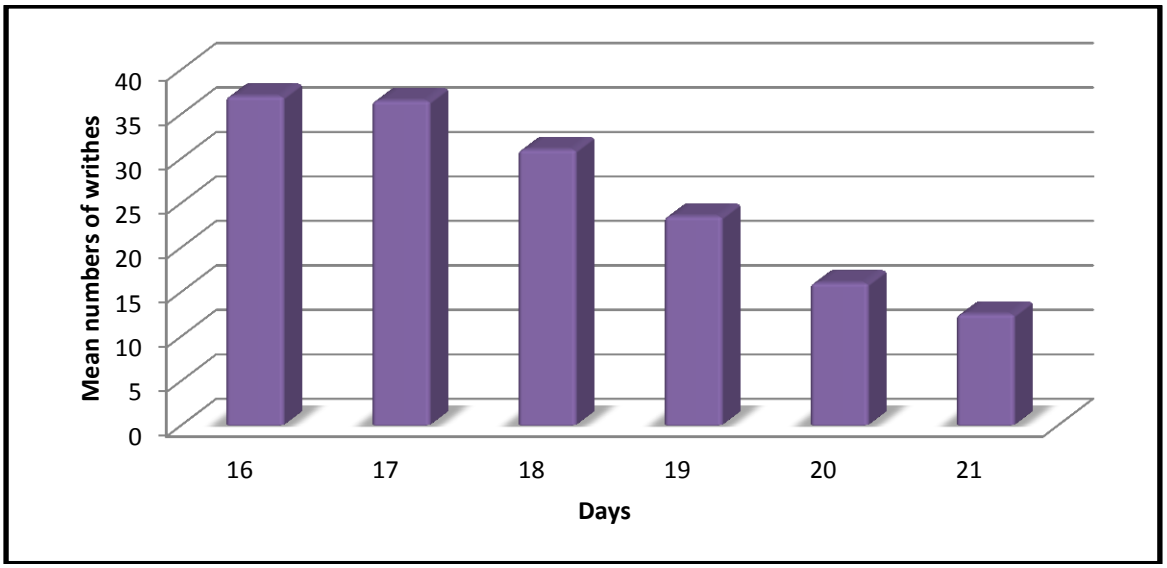

Figure 2: Analgesic Effect of Topiramate on Writhing Test

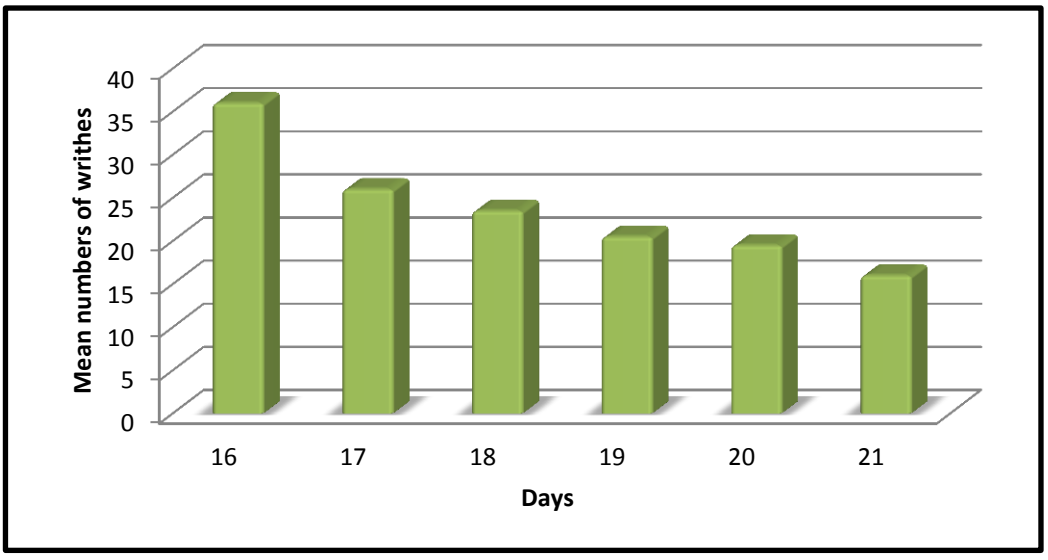

Figure 3: Analgesic Effect of Levetiracetam on Writhing Test

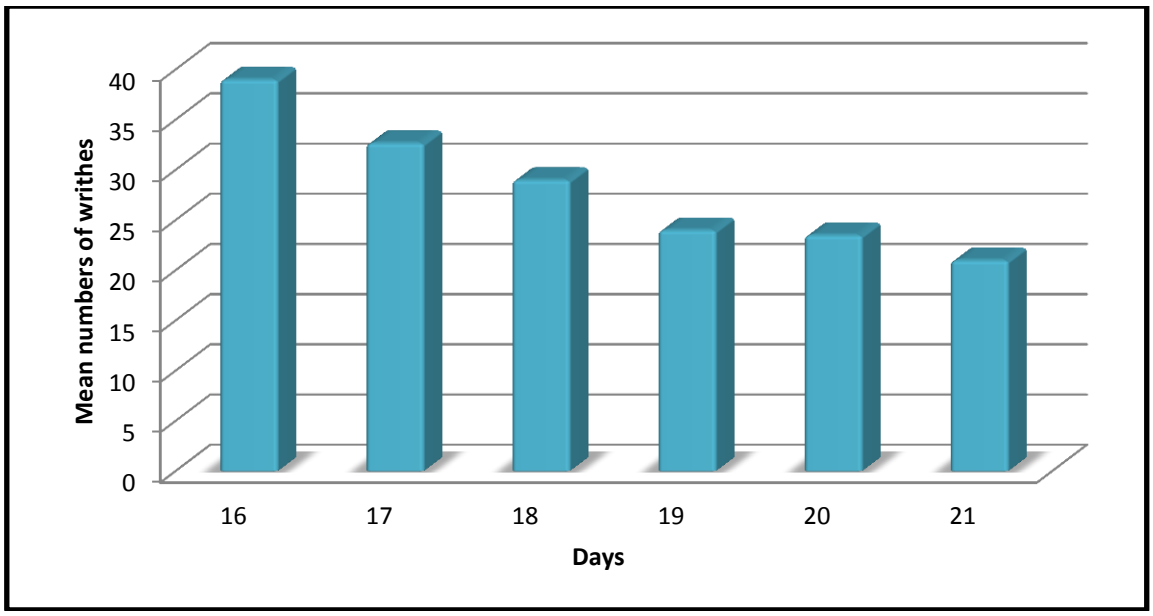

Figure 4: Analgesic Effect of Zonisamide on Writhing Test

DISCUSSION

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. It is also defined as 'Pain in an area of absent sensation'. It leads to allodynia and hyperalgesia [10]. Considerable research going on in the development of therapeutic approaches for neuropathic pain.This study compared the effect of gabapentin, topiramate, levetiracetam and zonisamide in vincristine induced neuropathic pain in rats using writhing test. Present study shows that vincristine (100µg/kg) produces long lasting chemical hyperalgesia in rats. In this study chemical hyperalgesia was assessed by writhing test suitable for evaluation of analgesic activity having peripheral action. This study demonstrated that gabapentin, topiramate, levetiracetam and zonisamide significantly reduced number of writhes in writhing test as compared to control, but their effect was gradually increased. 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 [11].

Gabapentin exerts its analgesic action by complex synergy between increased GABA synthesis, non-NMDA receptor antagonism and binding to the alpha 2 delta subunit of voltage dependent L-type of calcium channels (VDCC). The latter action inhibits the release of excitatory neurotransmitters [12, 13]. The binding of gabapentin to VDCC may also modulate GABAnergic, Glutamatergic and monoamines function.

Topiramate has several pharmacological properties that may contribute to its anticonvulsant activity and antinociceptive effect in neuropathic pain, which are: modulating voltage-gated sodium ion channels, enhancing gamma-aminobutyric acid inhibition, blocking excitatory glutamate neurotransmission, modulating voltage-gated calcium ion channels, etc. [14, 15].

The correlation between binding affinity of levetiracetam analogs and their potency towards audiogenic seizures suggest that a synaptic vesicle protein, SV2A, mediates the anticonvulsant and antinociceptive effect of Levetiracetam [16]. However, a number of other possible modes of action have also been identified; including modulation of inwardly rectifying potassium channels ROMK1 and modulation of intracellular calcium release and high-voltage activated calcium channels [17].

Zonisamide has a broad combination of complementary mechanism of actions and these are; blockage of voltage dependent T-type of calcium channels, prolonging the inactivated state of voltage-gated sodium

channels, it reduces sustained high-frequency repetitive firing of action potential, blockage of potassium-evoked glutamate responses, reduction of glutamate mediated synaptic excitation, increased gamma-aminobutyric acid released and facilitation of dopaminergic and serotonergic transmission[18].

In my previous study gabapentin, topiramate and zonisamide significantly reduced hyperalgesia caused by vincristine induced neuropathic pain in hot -plate method. While Levetiracetam was not effective on hot-plate method[19].In present study all these four drugs significantly reduced hyperalgesia induced by vincristine induced neuropathic pain on writhing test.

However, all the four newer antiepileptics drugs are effective as a antihyperalgesic in vincristine induced neuropathic pain but they act by different mechanisms. Gabapentin, topiramate and zonisamide act by both central and peripheral mechanism while levetiracetam act by only peripheral mechanism.

CONCLUSION

The aim of study was to compare the effect of gabapentin, topiramate, levetiracetam and zonisamide in vincristine induced neuropathic pain in albino rats using chemical method (writhing test).In present study, neuropathic pain was induced by injecting vincristine (100µg/kg) intraperitoneally daily for 14 days in rats. Behavioural testing for chemical hyperalgesia was assessed 24 hours after each injection by writhing test. Writhing test is suitable for evaluation of analgesics having peripheral analgesic 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 day16-21). All these four newer antiepileptic drugs significantly reduced number of writhes in writhing test as compared to control, but their effect was gradually increased. So we can conclude that gabapentin, topiramate, levetiracetam and zonisamide may be used in the treatment of neuropathic pain induced by chemotherapeutic agents. However this speculation requires clinical confirmation.

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