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ANALGESIC EFFECTS OF VILAZODONE, INDATRALINE, AND TALSUPRAM IN A RAT MODEL OF NEUROPATHIC PAIN

NÖROPATİK AĞRI RAT MODELİNDE VILAZODONE, INDATRALINE, VE TALSUPRAM'IN ANALJEZİK ETKİLERİ

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ABSTRACT
Background: Drugs that inhibit the reuptake of serotonin, norepinephrine, and/or dopamine are widely used in the treatment of depressive disorders and have emerged as effective drugs for neuropathic pain. They have no substantial anti-nociceptive effects but are considered, together with gabapentin/pregabalin, first-line drugs for neuropathic pain.
Methods: In the present study, three different antidepressant agents were used in different doses to investigate their anti-hyperalgesic effects in rat models of neuropathic pain using hot plate and tail flick methods. They have different mechanisms of action; Vilazodone hydrochloride is a selective serotonin inhibitor and a 5-HT_{1A} partial agonist; Talsupram hydrochloride is a selective noradrenaline inhibitor, and it has a high affinity for noradrenaline transporter (NET), whereas Indatraline hydrochloride is a triple reuptake inhibitor, it inhibits transporters for 5-HT (SERT), dopamine (DAT) and noradrenaline (NET).
Results: All the drugs used in the experiment were found to have an anti-hyperalgesic effect in in both tests compared to the sham group. When the anti-hyperalgesic effects of the three agents were compared to each other, it was found that Talsupram hydrochloride was significantly more effective than the two other drugs in hot plate test. However, there was no statistically significant difference in tail flick test. Indatraline hydrochloride was more effective than Vilazodone hydrochloride at the same doses in tail flick test.
Conclusions: Our data suggest that all the three drugs are effective analgesics in rat models of neuropathic pain, and inhibition of noradrenaline reuptake represents the cornerstone of analgesic mechanisms of efficacious anti-depressants.
Key Words: Neuropathic Pain, Anti-depressants, Vilazodone, Talsupram, Indatraline, Hot Plate, Tail Flick, Anti-hyperalgesic, Sciatic Nerve Ligation.

ÖZET

Serotonin, norepinefrin ve / veya dopamin geri alımını inhibe eden ilaçlar, depresif bozuklukların tedavisinde yaygın olarak kullanılmaktadır ve nöropatik ağrı için etkili ilaçlar olarak ortaya çıkmıştır. Önemli anti-nosiseptif etkileri yoktur, ancak gabapentin / pregabalin ile birlikte nöropatik ağrı için birinci basamak ilaçlar olarak kabul edilirler.
Bu çalışmada farklı dozlarda 3 farklı anti-depresan ajan kullanıldı. Nöropatik ağrılı sıçan modellerinde anti-hiperaljezik etkilerini araştırmak için hot-plate ve tail-flick yöntemleri kullanıldı. Farklı etki mekanizmaları vardır; Vilazodone hydrochloride, seçici bir serotonin inhibitörü ve bir 5-HT1A kısmi agonistidir; Talsupram hydrochloride, seçici bir noradrenalin inhibitörüdür ve noradrenalin taşıyıcısı (NET) için yüksek bir afiniteye sahipken, Indatraline hydrochloride üçlü bir geri alım inhibitörüdür, 5-HT (SERT), dopamin (DAT) ve noradrenalin (NET) için taşıyıcıları inhibe eder. Deneyde kullanılan tüm ilaçların sham grubuna göre her iki testte de anti-hipaljezik etkiye sahip olduğu bulundu. Üç ajanın anti-hipaljezik etkileri birbirleriyle karşılaştırıldığında Talsupram hydrochloride'in hot-plate testinde diğer iki ilaçtan anlamlı derecede daha etkili olduğu görüldü. Bununla birlikte, tail-flick testinde istatistiksel olarak anlamlı bir fark yoktu. İndatraline hydrochloride, tail-flick testinde aynı dozlarda Vilazodone hydrochloride' den daha etkiliydi.
Anahtar Kelimeler: Nöropatik Ağrı, Antidepresanlar, Vilazodone, Talsupram, Indatraline, Hot Plate, Tail Flick, Antihiperaljezik, Siyatik Sinir Ligasyonu.

INTRODUCTION

The International Association for the Study of Pain (IASP) defined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" [1]. According to a report published in 2011, one third of Americans experience chronic pain. This exceeds the total number of cardiovascular diseases, diabetes, and cancer cases [2]. The prevalence rate of chronic pain in Europe is about 25-30% [3]. Almost one-fifth of people affected by chronic pain have neuropathic pain [4, 5]. These high prevalence rates of chronic pain, especially neuropathic pain, are due to the lack of effective drugs. While nociceptive pain can be managed with analgesic drugs like opioids and non-steroidal anti-inflammatory drugs (NSAID), the medications used to manage neuropathic pain have a mild effect and in a small percentage of patients. This is mainly because they are unable to target the exact underlying mechanisms; this is why syndromes like fibromyalgia, whose pathophysiological mechanisms are not clear, have lower treatment success rates [6]. The existent medications for neuropathic pain are non-specific and often inadequately effective [7]. Other medications like opioids, on the other hand, have serious side effects. Therefore, there is a persistent need for improved and more specific therapeutic

strategies. Before clinicians can be able to prescribe precise medications for neuropathic pain patients, the main targets in the pathway must be understood.

Pharmacological treatment of neuropathic pain is complicated and there is no effective treatment for many patients. While there is a general consensus as to which drugs should be used as first-line medications, controversy over second- and third-line drugs continues, especially regarding weak and strong opioids. Although opioids are effective in the management of neuropathic pain, they are not prescribed as first-line drugs because of their adverse reactions and concerns about abuse and addiction [8].

Anti-depressants have been proven to have analgesic effects in chronic pain even though they were not initially designed to be used as analgesic drugs. Anti-depressants have practically no effects but are considered with pregabalin and gabapentin first choice drugs for neuropathic pain [7, 9, 10, 11] and fibromyalgia [12].

There is not a full understanding of how anti-depressants are effective in pain management. An early concept of analgesic mechanisms of anti-depressants for neuropathic pain was that these drugs could potentiate the effectiveness of the descending noradrenergic and serotonergic inhibitory pathways that extend from the brain stem to the dorsal horn of the spinal cord. This is done by inhibiting the reuptake of serotonin and noradrenaline released into the spinal synapses between the first-order neurons (nociceptors) and the second-order neurons (spinothalamic neurons). The synaptic transmission between these neurons can be inhibited by the neurotransmitters released from the inhibitory descending fibers, such as noradrenaline, which binds α-2 adrenergic receptors. They can also induce spinal interneurons to release inhibitory materials like GABA and endogenous opioids, such as serotonin at its metabotropic receptors or noradrenaline at α-1 adrenergic receptors [13].

Our study aimed to explore the anti-hyperalgesic effect of three different antidepressant drugs in different doses in rat models of neuropathic pain using hot plate and tail flick methods, and to compare the analgesic activity of these drugs. The anti-hyperalgesic effects of these agents have not been studied extensively before.

MATERIALS AND METHODS

Animals

Experiments were performed on adult male Wistar albino rats weighing 200-225 g. The animals were

kept at 22 ± 1 ° C, four in each cage, and maintained with a light-dark cycle of 12:12 h and free access to water and food. Cumhuriyet University Animal Ethics Committee approved all experiment protocols (Approval no 65202830-050.04.04-284).

Drugs

5-[4-[4-(5-Cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide hydrochloride (Vilazodone hydrochloride) (BLDpharm), 1,3-Dihydro-*N*,3,3-trimethyl-1-phenylbenzo[*c*]thiophene-1-propanamine hydrochloride (Talsupram hydrochloride) and (1*R*,3*S*)-*rel*-3-(3,4-Dichlorophenyl)-2,3-dihydro-*N*-methyl-1*H*-inden-1-amine hydrochloride (Indatraline hydrochloride) (Tocris Bioscience) were diluted in DMSO. Solutions were freshly prepared on the days of experimentation. Intraperitoneal (I.P.) Vilazodone hydrochloride (5-HT1A partial agonist and SSRI 2.5, 5, 10 mg/kg), Talsupram hydrochloride (Selective inhibitor of noradrenalin transporters 2.5, 5, 10 mg/kg), and Indatraline hydrochloride (5-HT noradrenalin and dopamine reuptake inhibitor 2.5, 5, 10 mg/kg) were applied before the analgesia tests.

Experimental Protocol and Analgesia Tests

All experiments were carried out blindly between 10.00 and 16.00 hours in normal light and temperature (22±1 °C) in a quiet room. The rats were allowed to adapt to the laboratory for at least 2 hours before the test and their tails were marked to differentiate the treatment groups. The rats were randomized into 10 groups (3 groups for each drug (1 group for each dose) and 1 group as a sham). Each experimental group had six rats. The same person performed all neuropathic operations and analgesia tests in order to minimize experimental variability.

Surgical Intervention

The neuropathic pain model was produced by partial sciatic nerve ligation. Surgical interventions were performed in Sivas Cumhuriyet University Medical Faculty Experimental Animals Laboratory. Anesthesia was performed using intramuscular ketamine (90 mg/kg) and xylazine (3 mg/kg). Under aseptic conditions, a 1 cm incision was applied to the biceps femoris and the sciatic nerve was reached in the middle thigh level of the right leg. Then, the sciatic nerve was freed of adherent tissues with careful blunt dissection and the dorsal one-third to half of the nerve was tightly ligated with 4.0 chromic catgut. The incision was closed with 4.0 silk. In sham group rats, the same intervention was applied but without nerve ligation. After surgery, the rats were returned to their cages and kept for 21 days under the same conditions mentioned above [14, 15].

Analgesia Tests

To evaluate thermal pain standard tail flick test (May TF 0703 Tail beat unit, Commat) and hot plate test (May AHP 0603 Analgesic HP, Commat) devices were used. In tail flick test, an intensive light beam was aimed at the animal's tail and a timer begins. When the animal flicks its tail, the timer is stopped and the recorded time (latency) represents the pain threshold. Tail-flick latencies were measured before the administration of the vehicle or investigational drugs to obtain a baseline and 15, 30, 60, 90 and 120 min after the intraperitoneal administration. The maximum response time was set to 15 seconds (cut-off latency) to avoid tissue damage. Rats that did not show a response within 15 seconds were excluded. The hyperalgesic responses in this test reflect the mechanisms of pain in the central nervous system [16, 17, 18].

A hot plate device was used to evaluate thermal pain. In this test, the rats were placed on a hot plate with the temperature set at 53 ± 0.5 ° C for a maximum time of 30 s to prevent injury. Response time was recorded (when the animals licked their fore and hind paws or jumped) before and 15, 30, 60, 90, and 120 min after I.P. administration of vehicle or test drugs. The hyperalgesic reactions in this test reflect the mechanisms of pain in both the central and peripheral nervous systems [16, 18].

Statistical Analysis

In all groups for each rat, the anti-nociceptive effects of the drugs were measured as tail flick and hot plate latencies and transformed to percentage maximum possible effect (% MPE). MPE was obtained

by using the formula: [MPE= (post-drug latency−pre-drug latency) / (cutoff latency−pre-drug latency) ×100]. Pre-drug and post-drug N values were the same in each group. The data were analyzed using one and two-way analysis of variance (ANOVA) and repeated measures ANOVA followed by a Tukey post-hoc test (SPSS 14.0 for Windows) for multiple comparisons between groups. All data are presented as a mean ± standard error of the mean (SEM). The significance level was determined as $p < 0.05$.

RESULTS

Determination of Neuropathic Pain Formation by Sciatic Nerve Ligation

The occurrence of neuropathic pain in rats was detected using the paired student t-test. The post-surgery basal latencies of the rats were considerably lower than the pre-surgery basal latencies in both hot plate and tail flick tests ($p < 0.05$) (figures 1, 2).

The Effects of Vilazodone hydrochloride on Neuropathic Pain

Vilazodone hydrochloride was applied at three doses: 2.5, 5, and 10 mg/kg. In both tail flick and hot plate tests the responses were measured before the drug was administered intraperitoneally and after the administration at 15, 30, 60, 90, and 120 minutes. The maximum percentage MPE was observed at 90 mins after administration of these three doses. One-way ANOVA test was applied to compare the different doses with the sham group and with each other. In both tail flick and hot plate tests, 5 and 10 mg/kg doses were found to be effective against neuropathic pain compared to the sham group. 10 mg/kg dose was effective from 30 to 120 mins in both tests with a statistically significant difference compared to 2.5 mg/kg dose at 90 mins in hot plate test and at 90,120 mins in tail flick test. 5 mg/kg dose was effective from 30 to 90 mins in both tests. 2.5 mg/kg dose was not statistically different from the sham group in hotplate test at all minute points, while it was noticed to be effective only in tail flick test at 60 and 90 mins (figure 3).

The Effects of Talsupram hydrochloride on Neuropathic Pain

Talsupram hydrochloride was applied intraperitoneally at three doses: 2.5, 5 and 10 mg/kg. The maximum percentage MPE was observed 60 mins after the drug was administered for all the three doses. One-way ANOVA test was used. The first dose 2.5 mg/kg was effective from 30 to 120 mins in the hot plate test and from 30 to 90 mins in the tail flick test. The other two doses 5 and 10 mg/kg were effective at all minute points in hot plate test, while their effectiveness in tail flick test was noticed from 15 to 90 mins. When compared to 2.5 mg/kg dose a statistically significant difference was noticed only with 10 mg/kg dose at 60 mins in hot plate test (figure 4).

The Effects of Indatraline hydrochloride on Neuropathic Pain

Indatraline hydrochloride was administered intraperitoneally at 3 doses; 2.5, 5 and 10 mg/kg. The maximum % MPE was observed at 60 mins after the drug was administered for all the three doses. One-way ANOVA test was applied. The drug was effective at all the three doses in both tests. After the first dose 2.5 mg/kg was administered, the anti-hyperalgesic effect was statistically significant at 60 mins in hot plate test and from 30 to 90 mins in tail flick test. The second dose 5 mg/kg was effective at 30 and 60 mins in hot plate test and from 15 to 90 mins in tail flick test. The anti-hyperalgesic effect for the third dose 10 mg/kg from 30 to 90 mins was statistically significant compared to the sham group,

and at 60 mins compared to the first 2.5 mg/kg dose in the hot plate test. While in the tail flick test, the anti-hyperalgesic effect of 10 mg/kg dose was apparent from 15 to 90 mins compared to sham group (figure 5).

Comparison of the Anti-hyperalgesic effects of Vilazodone hydrochloride, Talsupram hydrochloride and Indatraline hydrochloride on Neuropathic Pain

We used two-way variance analysis followed by Tukey HSD test in this comparison. In the hot plate test, percentage MPE values obtained from doses 2.5, 5, 10 mg/kg of Talsupram hydrochloride were significantly higher than values obtained from the same doses of Vilazodone hydrochloride and Indatraline hydrochloride. Even at lower doses, talsupram was more effective than the other two drugs. Percentages MPE of talsupram at 2.5 mg/kg were > vilazodone 5 mg/kg and indatraline 10mg/kg, while at 5 mg/kg, the percentage MPE was > vilazodone 10 mg/kg ($p < 0.05$). Whereas in the tail flick test, the % MPE values obtained from the different doses of Talsupram hydrochloride were not statistically different from those of the same doses of Vilazodone hydrochloride and Indatraline hydrochloride ($p > 0.05$), except the % MPE of 2.5 mg/kg dose of Indatraline hydrochloride, which was higher than that of the same dose of Talsupram hydrochloride ($p < 0.05$). There was a statistically significant difference between the % MPE values obtained from the same doses of Vilazodone hydrochloride and Indatraline hydrochloride in favor of the latter in the tail flick test ($p < 0.05$), whereas no statistically significant difference was found between them in the hot plate test ($p > 0.05$) (figure 6).

DISCUSSION

Neuropathic pain, a pain syndrome caused by a lesion or disease of the somatosensory system, is a main public health issue and becoming a global burden [1, 19, 20]. An epidemiological study indicated that the prevalence rate of neuropathic pain is in the range of 6.9% to 10% and increases year after year [21, 22]. Patients with neuropathic pain report significantly lower levels of health-related quality of life (HRQoL) [23].

The high rate of comorbidity between pain and depression [24] has led to the wide use of anti-depressants in chronic pain treatment. Tricyclic anti-depressants (TCA), particularly desipramine, amitriptyline, nortriptyline, and imipramine are the most effective anti-depressants in neuropathic pain management. TCAs have effects on various targets. This lack of selectivity is related to their efficacy. For instance, amitriptyline has a local anesthetic effect by blocking voltage-gated sodium channels [25]. TCAs have been shown to be effective in many neuropathic conditions. However, these multiple actions of TCAs also contribute many adverse effects that limit their use, in particular their anticholinergic effects that increase the risk of cardiotoxicity, orthostatic hypotension, mouth dryness, constipation, and urinary retention. To avoid these issues, Serotonin–norepinephrine reuptake inhibitors (SNRI), particularly duloxetine, have been suggested in the management of neuropathic pain. SNRIs like duloxetine have shown consistent efficacy in several neuropathic syndromes including painful

polyneuropathy, post-herpetic neuralgia, low back pain, and painful diabetic neuropathy [7]. Opioids are recommended to be used as second- and third-line treatments because of their adverse effects. Tramadol and the FDA-approved tapentadol [26] are used in second-line treatment, while the strong opioids, oxycodone, and morphine [27] are used in the third-line treatment. Therefore, there is still a need for more effective drugs with less serious adverse effects for neuropathic pain. In the present study, we investigated the anti-hyperalgesic effects of three different antidepressant drugs in different doses in rat models of neuropathic pain using hot plate method. These drugs have different mechanisms of action; Vilazodone hydrochloride is a selective serotonin inhibitor, Talsupram hydrochloride is a selective noradrenaline inhibitor, and it has a high affinity for noradrenaline transporter (NET), whereas Indatraline hydrochloride inhibits transporters for 5-HT, dopamine, and noradrenaline. All the drugs used in the experiment were found to have an anti-hyperalgesic effect compared to the sham group. These results support the evidence for the role of noradrenaline, serotonin, and probably dopamine in the analgesic effects of anti-depressants on neuropathic pain and corroborate with a previous study highlighted that indatraline had analgesic profiles in neuropathic mice [28]. Some preclinical studies on animals have indicated the important role of noradrenaline and serotonin in the processing of pain. Experimental studies have demonstrated that intrathecal administration of serotonin and norepinephrine receptor agonists inhibits pain behaviors [29, 30]. Other data show that serotonin agonists like fenfluramine trigger the neuronal release of substance P and thus pain behaviors [31]. Furthermore, the intrathecal administration of serotonin receptor antagonists such as ondansetron inhibited experimental pain response in rats [32]. 5-HT1A, 5-HT2A/2C, 5-HT3, and 5-HT7 receptors that highly contribute to the transmission of nociceptive messages are expressed in the dorsal horn of the spinal cord [33-36]. It seems that serotonin both inhibits and enhances pain sensation by various physiological mechanisms, contrary to norepinephrine which is essentially inhibitory. A review of studies on SSRIs showed inconsistent efficacy for migraine, diabetic neuropathy, and fibromyalgia; however, some studies of SSRI treatment for mixed-chronic pain are positive [37].

When the anti-hyperalgesic effects of the three agents were compared to each other, it was found that Talsupram hydrochloride was significantly more effective than viazodone hydrochloride and Indatraline hydrochloride in the hot plate test. This could be related to the high affinity of Talsupram hydrochloride for norepinephrine transporters and the more important role of noradrenaline in anti-hyperalgesic activity compared to serotonin and dopamine. However, there was no statistically significant difference in the tail flick test.

While the response in the tail flick test is a spinal reflex rather than an indication of pain behaviors involving higher brain centers [38], the response in hot plate test is considered to integrate supraspinal pathways [39]. Therefore, the comparison results suggest that the analgesic effect of Talsupram hydrochloride is more effective than Vilazodone hydrochloride and Indatraline hydrochloride at supraspinal level. The percentage MPE values obtained from Indatraline hydrochloride were more than values obtained from Vilazodone hydrochloride at the same doses in the tail flick test. This could be due to a greater anti-hyperalgesic effect of the inhibition of reuptake of noradrenaline, serotonin and dopamine compared to the inhibition of reuptake of serotonin alone. Although Vilazodone hydrochloride is less effective against neuropathic pain than the other drugs, its relatively benign sexual side effect profile maybe worth taking into consideration, because in addition to serotonin reuptake inhibition, it acts as 5-HT_{1A} partial agonist.

In conclusion, our data suggest that all the three drugs used in this study are effective analgesics in rat models of neuropathic pain. The inhibition of noradrenaline reuptake represents the cornerstone of analgesic mechanisms of efficacious anti-depressants. Although SSRIs have a more tolerable side effect profile, and the SSRI used in our experiment, Vilazodone hydrochloride, was effective in a rat model of neuropathic pain, the evidence to support the use of SSRIs in the clinical management of chronic pain is still not convincing [40].

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Ethical approval: All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted. Animal experimental procedures were approved by the Animal Ethical Committee at Cumhuriyet University (Sivas, Turkey).

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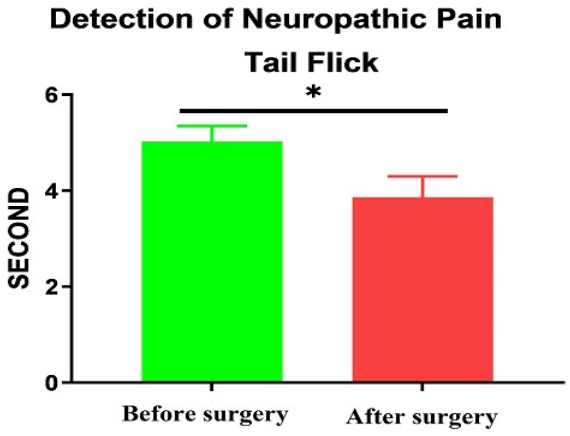

Figure 1: Tail flick basal latencies of rats before and after surgery. (*p < 0.05 paired student t-test)

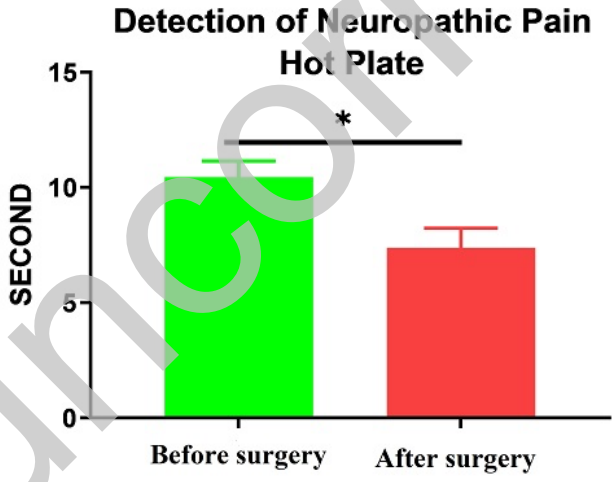

Figure 2: Hot plate basal latencies of rats before and after surgery. (*p<0.05 paired student t-test)

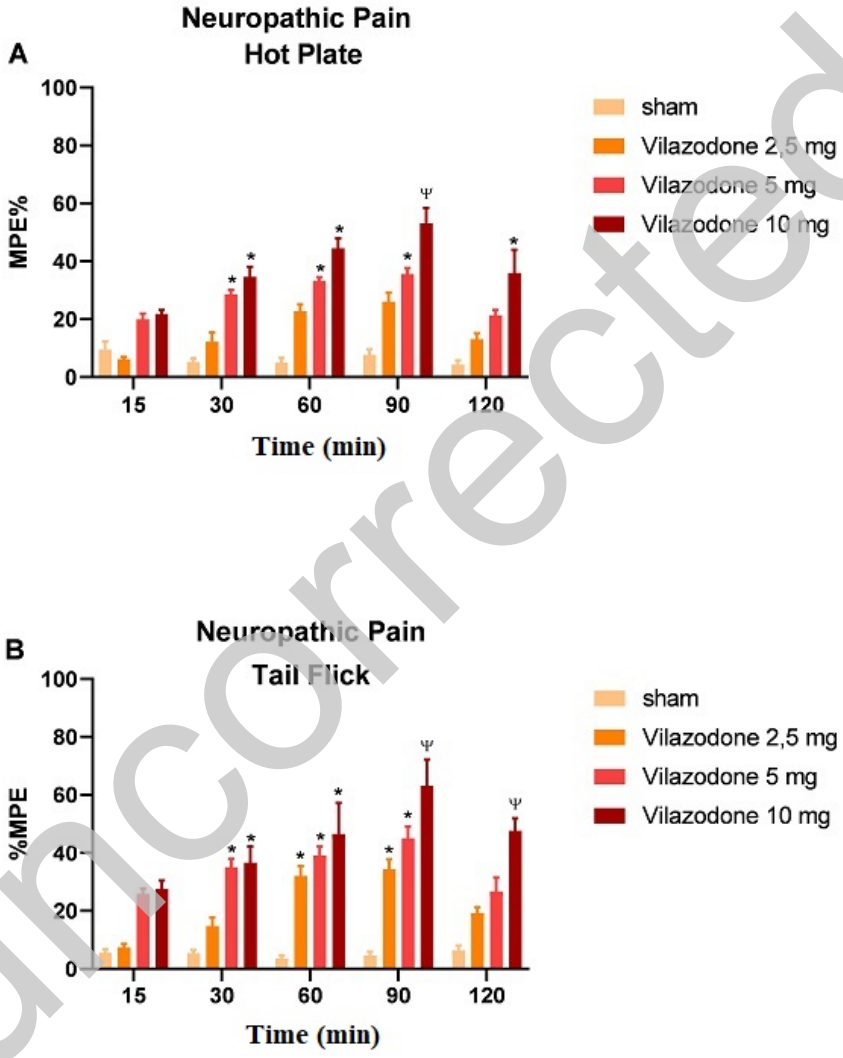

Figure 3: The effect of Vilazodone hydrochloride intraperitoneal administration on the neuropathic pain model in hot plate test (A) and tail flick test (B). It was expressed as percent of maximal possible effect (MPE). Each point represents the mean ± SEM of % MPE for 6 rats.

*p < 0.05 when the groups were compared to the sham group.
Ψp< 0.05 when the groups were compared to the sham and 2.5 mg/kg dose groups.

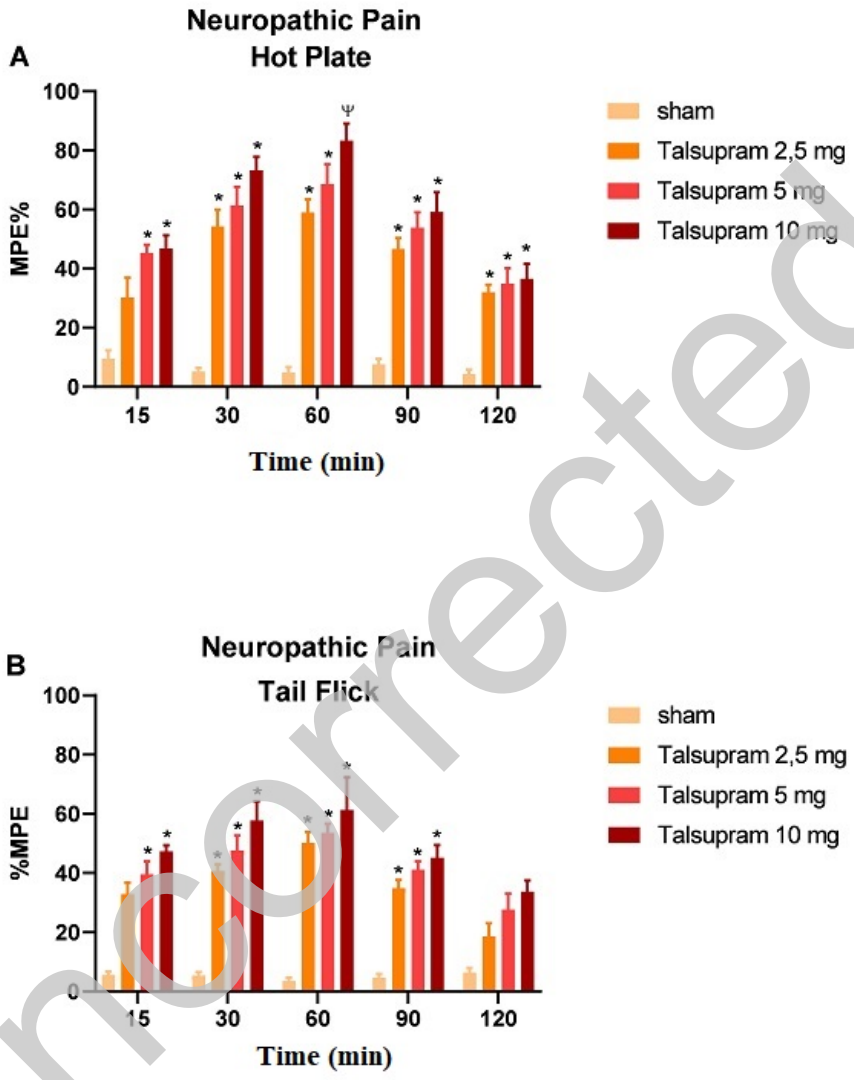

Figure 4: The effect of Talsupram hydrochloride intraperitoneal administration on the neuropathic pain model in hot plate test (A) and tail flick test (B). It was expressed as percent of maximal possible effect (MPE). Each point represents the mean ± SEM of % MPE for 6 rats.
*p < 0.05 when the groups were compared to the sham group.
Ψp< 0.05 when the groups were compared to the sham and 2.5 mg/kg dose groups.

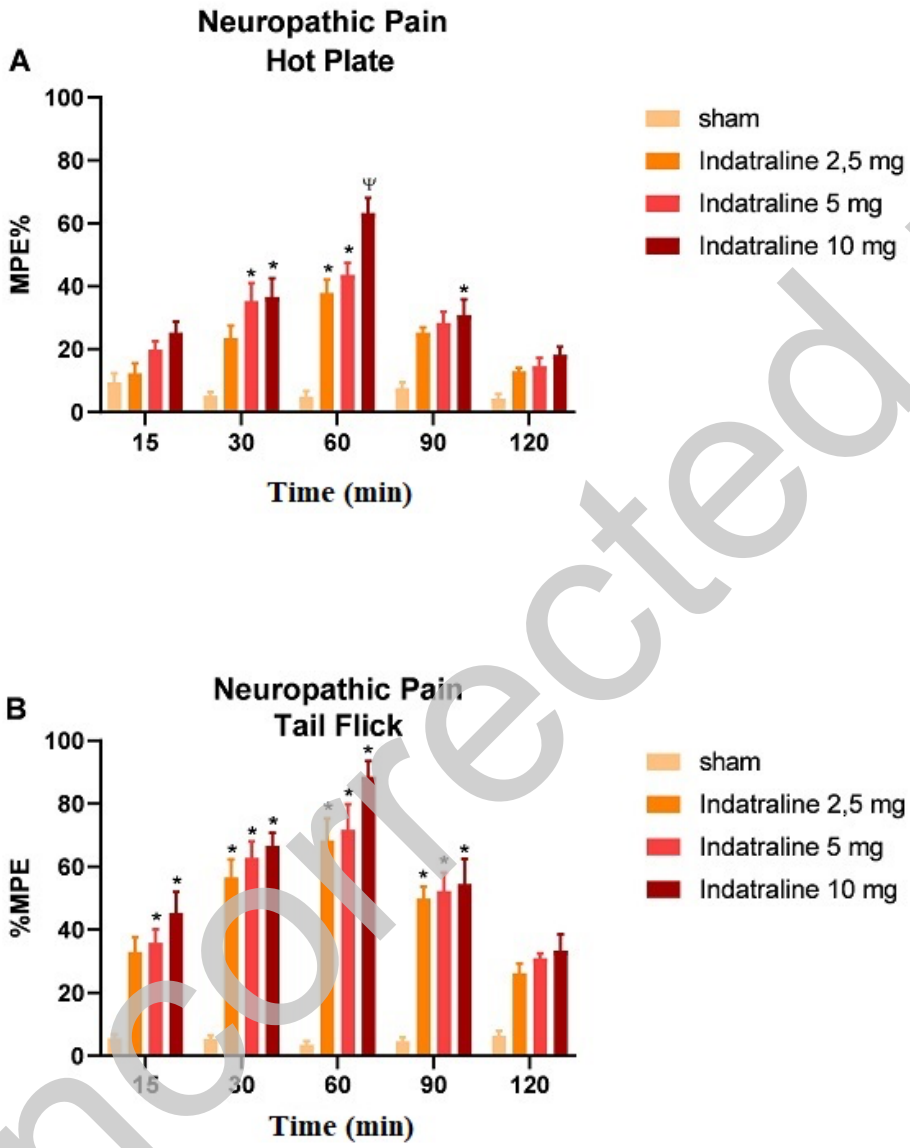

Figure 5: The effect of Indatraline hydrochloride intraperitoneal administration on the neuropathic pain model in hot plate test (A) and tail flick test (B). It was expressed as percent of maximal possible effect (MPE). Each point represents the mean ± SEM of % MPE for 6 rats.
*$p < 0.05$ when the groups were compared to the sham group.
Ψ$p < 0.05$ when the groups were compared to the sham and 2.5 mg/kg dose groups.

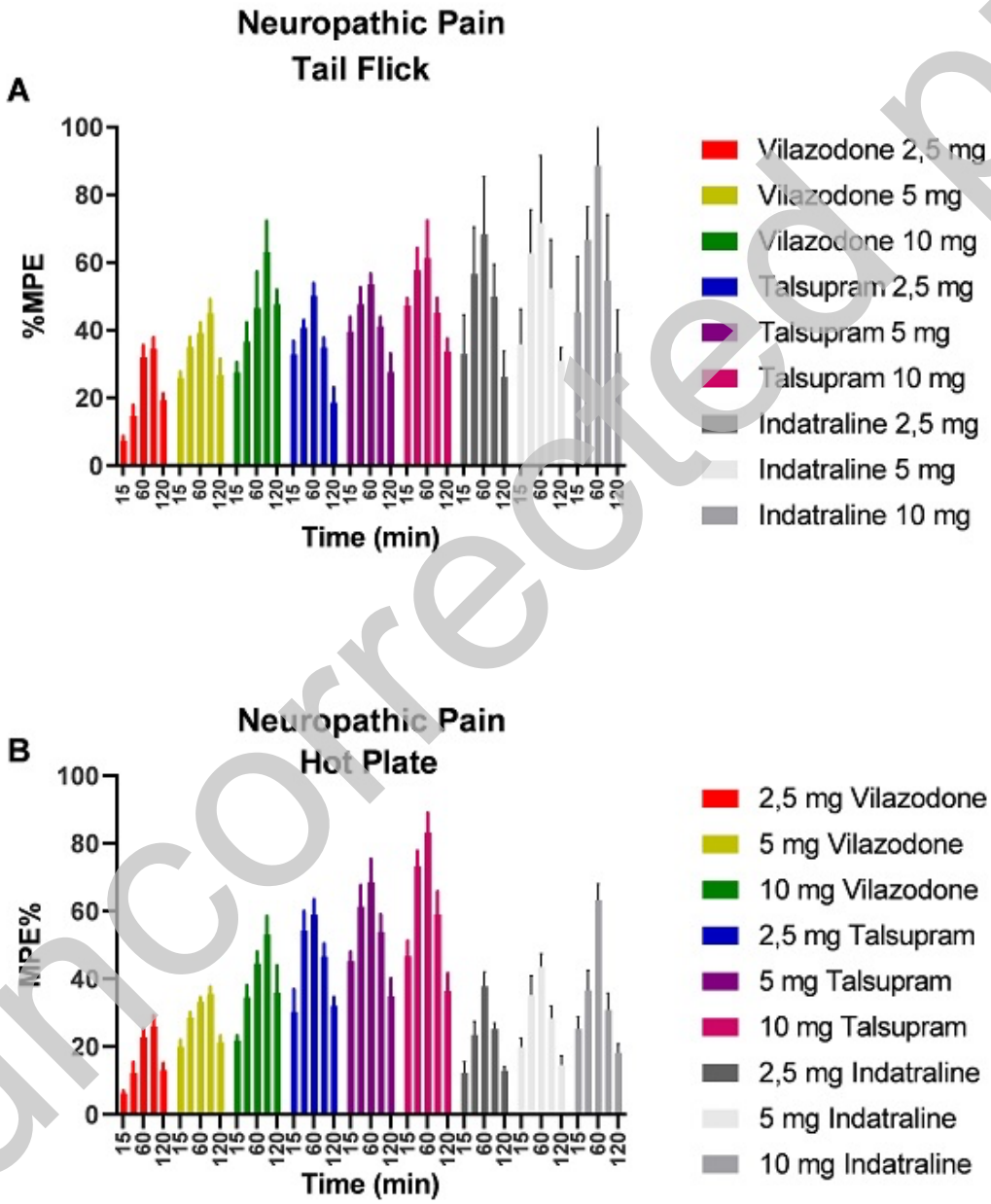

Figure 6: The effect of Vilazodone hydrochloride, Talsupram hydrochloride and Indatraline hydrochloride on the neuropathic pain model (in hot plate and tail flick tests) was expressed as percent

of maximal possible effect (MPE). All drugs were administered intraperitoneally. Each point represents the mean of % MPE for 6 rats.