Preventive Effect of Central Administration of Venlafaxine on Morphine Physical Dependence, Nociception, and Blood Cortisol Level in Rat

Majid Motaghinejad, Andia Ebrahimzadeh, Behnaz Shabab[1]

Department of Pharmacology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran, [1]Solid Dosage Form Department, Iran Hormone Pharmaceutical Company, Tehran, Iran

Correspondence to:
Dr. Majid Motaghinejad,
Department of Pharmacology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
E-mail: m-motaghinejad@razi.tums.ac.ir

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Original Article

ABSTRACT

Background: Chronic abuse of opiates induces dependency, but the neurobiological mechanisms of this event remain unclear. The aim of this study was to evaluate the effects of intracerebroventricular of venlafaxine on the morphine dependence and pain perception.

Methods: A total of 80 adult male rats were divided into two major groups: (1) 40 of them was divided into groups of positive control (morphine dependent) negative control (received saline) and morphine dependent groups under treatment by central administration of venlafaxine at various dosages (25, 50, or 100 μg), after drug treatment total withdrawal index (TWI), latency time of withdrawal syndrome expression and blood cortisol as marker of anxiety were measured and compared with positive control and negative control. (2) Forty rats were grouped in control; indometacin treated (5 mg/kg) and grouped which received central administration of venlafaxine at three doses (25, 50, or 100 μg) and then pain perception and expression was assessed in the writhing test (acetic acid induced abdominal constriction), tail flick, and hot plate test.

Results: Central administration of three doses (25, 50, or 100 μg,) of venlafaxine attenuates TWI to 47 ± 1.2, 38 ± 1.5, and 23 ± 1.1 and decrease blood cortisol level to 14 ± 1, 13.75 ± 0.5, and 12.5 ± 0.8, this decreases was significant in comparison with the positive control group ($P < 0.05$). Central administration of venlafaxine at mentioned doses significantly attenuates pain response with 37%, 24%, and 20% inhibition in writhing test, 69%, 34%, and 23% inhibition in hot plate test, and 29%, 23%, and 15% inhibition in tail flick test in comparison with control group ($P < 0.05$).

Conclusions: This study suggested that central administration of venlafaxine attenuated morphine withdrawal index and can be effective in modulation of pain that was induced by morphine dependency.

Keywords: Morphine, pain, venlafaxine, withdrawal syndrome

INTRODUCTION

Usage of morphine has been approved as the standard pain killer in patients with acute pain. The major problem of long term administration of morphine is dependency that characterized by physical dependence and withdrawal syndrome represented by discontinuing opioid agonist or administration of the opioid antagonist like naloxone.[1] In spite of many previous studies, the exact mechanisms involved in dependence and withdrawal symptoms that can vindicate this phenomenon was not clarified, but previous studies suggested that neurochemical alteration in nucleus accumbens, followed by systemic morphine administration was the main reason for the dependence to morphine.[2] These studies suggested that the dysfunction in adrenergic and serotonergic systems and neurotransmitters in nucleus accumbens has a critical role in dependence to morphine.[3,4] On the other hand, morphine and alcohol withdrawal is characterized by an increase in the hypothalamus–pituitary–adrenocortical (HPA) axis activity that causes a rise in blood cortisol levels.[5,6] Chronic use of morphine and dependency to opioids will increase the mRNA expression that is responsible for the synthesis of the corticotrophin releasing hormone (CRH) and finally, effects the secretion of the adrenal glands.[7] Cortisol levels in the morphine-dependent individuals show that the chronic dependence to morphine is responsible for the secretion of CRH that increases the stress and cortisol level of the addicts.[8,9] Venlafaxine is an antidepressant of the serotonin–norepinephrine reuptake inhibitor (SNRI), which can be used for the treatment of cocaine dependence.[10] It also can be effective in the treatment of alcoholic abuse.[11] On the other hand, venlafaxine effective on the treatment of chronic pain syndromes and neuropathic pain.[12] Previous studies demonstrated that venlafaxine completely abolished the enhanced sensitivity to mechanical stimuli provoked by peripheral carrageenan injection.[13] Many studies demonstrated that serotonin (5-hydroxytryptamine [5-HT]) and a number of serotonergic receptor agonists have antinociception effect, these results suggest that serotonergic antinociceptive mechanisms are similar to the opioid system.[14,15] Furthermore, it was demonstrated that adrenergic system has a major role in pain perception in multiple parts of the brain.[16] Previous study showed that venlafaxine interaction with opioidergic system and mimics opioids like peptides effects. These studies suggest that the opioidergic system has an important role in the analgesic effect of venlafaxine.[17] Co-administration of morphine with venlafaxine increased the analgesic effects of morphine and attenuated the morphine analgesic tolerance.[18] Antinociceptive effects of venlafaxine are influenced by opioid receptor subtypes (mu-, kappa1–kappa3-, and delta-opioid receptor subtypes).[19] The aim of this study was to evaluate the possible role of pretreatment with venlafaxine, as SNRI, on the modulation of morphine physical dependency and blood cortisol level as stress marker of withdrawal syndrome period. In addition, in this study, we evaluated the effect of central administration of venlafaxine on pain perception and its potential role in nociception induced in writhing test, tail flick test, and hot plate test.

METHODS

Animals

A total of 80 male Wistar rats, weighing between 250 and 300 g, were purchased from Razi Institute of Iran at Tehran University of Medical Sciences. They were housed in a controlled temperature room (24 ± 0.5°C) with 12-h light/dark cycle and had free access to food and water. This experiment was approved by the Committee of Research in Ethics of the Tehran University of Medical Sciences. These animals were randomly divided into two major groups: (1) Morphine physical dependency protocol and (2) nociception protocols. Each group was divided into subgroups (each eight) as the following descriptions.

Drug

Morphine, naloxone, venlafaxin, indomethacin, and other chemical were purchased from Sigma–Aldrich Inc., St. Louis, MO, USA.

Intracerebroventricular cannula implantation

For intracerebroventricular (ICV) administration, rats were anesthetized with sodium pentobarbital (50 mg/kg bw, ip) and a stainless steel guide cannula (23 gauge) into implanted to the lateral cerebral ventricle (coordinates, –0.8 mm posterior, –1.3 mm midline to lateral, and 3.5 mm ventral) with respect to the bregma by stereotaxically surgery.[20]

A dummy cannula (30 gauges) was placed into the guide cannula to maintain the patency a stainless steel guide. After surgery process rats were allowed for a recovery or a 7-day after surgery process. For habituation of animal during the recovery period, all rats were handled, weighed and restrained on the test platform for 5 min with very gentle removal and replacement of the dummy cannula (2 times/day). Experimental procedure and drugs treatment started after a recovery period in all groups.

Histological confirmation of cannula placement

After the termination of experiments procedure, all animals were injected by 5 μl/rat of methylene blue solutions ICV. The animals were anesthetized by pentobarbital and euthanized by decapitation. Brains of each animal were removed out to verify the distribution of the methylene blue in the lateral ventricles and also placement of the guide cannula. Statistically analysis of data was presented only for those animals that displayed an uniform distribution of methylene blue in the ventricles.[20]

Experimental design for the morphine physical dependency protocol

A total of 40 animals were divided randomly into five groups:

- Group I: As a negative control (independent) received normal saline (0.2 ml/rat) for 14 days
- Group II: As positive control (dependent) received morphine with an increasing dosage (20-50 mg/kg, ip) for the first 7 days and then received saline solution (10 μl/rat, ICV) for the following 7 days
- Groups III-V: As treatment groups received morphine with an increasing dosage (20-50 mg/kg, ip) for the first 7 days and after that were injected by three dosage of venlafaxin (25, 50, or 100 μg/5 μl/rat, ICV), concurrently with morphine once a day from day 8 to 14.

Induction and evaluation of withdrawal syndrome

On day 15, animals of all groups were administrated by naloxone (3 mg/kg) and their 14 behaviors (jumping, head shake, wet dog shake, for paw tremor, writhing, walking sniffing, sniffing, penile licking, rearing, chewing, body grooming, face wiping, swallowing, and teeth chattering) were recorded by camera for 30 min. After computation and counting of this behavior each of the behaviors divided to their weighing factor and a digit was obtained [Table 1]. The summation of each of these digits gives the total withdrawal index (TWI). Furthermore, we recorded the latency time of the withdrawal syndrome expression.

Measuring the blood cortisol

After the behavior studies on the 15th day, the rats were first anaesthetized by diethyl ether and their whole blood was collected, and its serum was separated and the level of serum cortisol was measured based on μg/dl and by ELISA method.

Experimental design for nociception protocols

A total of 40 rats randomly were divided into five groups:

- Group I: As negative control received normal saline 0.2 ml/rat
- Group II: As positive control received single dose of indometacin (5 mg/kg, ip)
- Groups III-V: As treatment groups were treated by single dose of three dosage of venlafaxin (25, 50, or 100 μg/5 μl/rat, ICV). After this treatment, three types of nociception method were applied for evaluation of pain.

Writhing test

In this test, all mentioned animal acetic acid (0.8%) was administrated in a volume of 10 ml/kg in rat. Nociceptive behavior is characterized by abdominal contraction known as writhing, described as an exaggerated extension of the abdomen combined with the out stretching

Table 1: WFs of different withdrawal signs of morphine in the mouse

Behavior	WF
Jumping	4
Head shake	5
Wet dog shake	5
Paw tremor	5
Writhing	5
Walking sniffing	5
Sniffing	5
Penile liking	5
Body grooming	10
Face wiping	10
Swallowing	10
Teeth chattering	10
Dysphoria	10
Rearing	20
Chewing	20

WF=Weighing factor

of hind limbs. Total number of writhing following ip administration of acetic acid was recorded in 30 min after acetic acid injection. Percentage of inhibition of abdominal constrictions in each group was computed by the following ratio: Treated mean – control mean × 100/control mean. This method of nociception assessment was done as base of previous studies. In additions, the onset of the first writhing was recorded as latency time.[21]

Tail flick test

In this test, radiant heat (Tail-Flick Apparatus Model P-162, Pouyaye Armaghan Co., Iran) was applied for measurement of acute nociception responses in rat. Intensity of the thermal stimulus was adjusted to produce 5-6 s latency in tail flick response. Five millimeters of the tail were submitted to noxious heating. To avoid damage to the tail, if the response did not occur, trial was automatically terminated at 12 s (cutoff time). The tail flick test was measured 30 min before and 30 min after administration of venlafaxin (25, 50, or 100 μg/5 μl/rat, ICV) or indometacin (5 mg/kg, ip) saline (0.2 ml/rat). The percentage of nociception for each animal was calculated, using the following ratio: [(pretreatment – posttreatment)/(pretreatment)] ×100. This method of nociception assessment was done as base of previous studies.[22]

Hot plate test

In this test, analgesic activity was measured with a thermostatically heated surface maintained at 55 ± 2°C. Time of reaction was revealed as the period from the instant animal was put on a hot plate until the moment the animal licked its feet or jumped out. Hot plate test was done twice at 10 min interval. The mean of these two values was presented as reaction time before treatment. About 30 min after the treatment with venlafaxin (25, 50, or 100 μg/5 μl/rat, ICV), indometacin (5 mg/kg, ip) and saline (0.2 ml/rat), the reaction time was again evaluated, but only once, this value represented the reaction time after treatment. The percentage of nociception was measured by the following ratio: (reaction time after treatment – reaction time before treatment) ×100/reaction time after treatment.[23]

Statistical analysis

Normality of continuous variables (TWI, blood cortisol, pain perception and latency time of withdrawal syndrome expression) was evaluated by using Kolmogorov–Smirnov test. Based on this test all variables were normally distributed ($P > 0.05$). Therefore, we used means ± standard error of the mean (SEM) to describe continuous variables mentioned above, unpaired Student's *t*-test to compare mean differences between positive and negative control groups, and one-way ANOVA to compare mean differences between treatment groups. Tukey's *post-hoc* test was then used for group-by-group comparisons. Results were considered to be significant at 0.05 levels.

RESULTS

Total withdrawal index in controls groups and groups under treatment by central administration of venlafaxin

Total withdrawal index in negative control group under treatment by saline (group I) was 15 ± 1.1 while for positive control group (group II) TWI was 55 ± 1.3 ($P < 0.05$) [Figure 1].

Intracerebroventricular administration of venlafaxin in dosage of 25, 50, or 100 μg/5 μl/rat (groups III, IV, and V) decreases the TWI to 47 ± 1.2, 38 ± 1.5, and 23 ± 1.1, respectively. This attenuation in all group under treatment at the various dose of venlafaxin was statistically significant with $P < 0.001$ in comparison with positive control group ($P < 0.05$) [Figure 2].

Effects of central administration of venlafaxin on latency time of the onset of first symptoms of withdrawal syndrome

Latency time of onset of first symptoms of withdrawal syndrome in negative control group

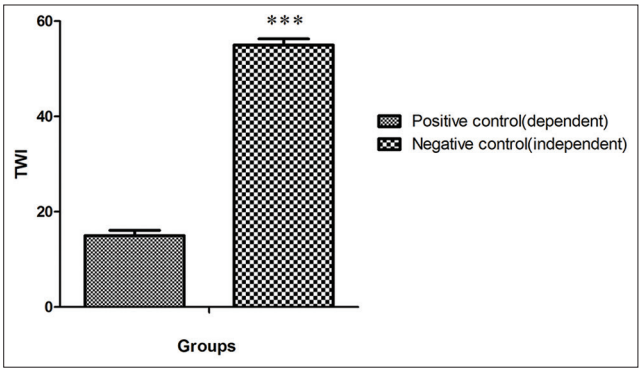

Figure 1: Total withdrawal index in negative control group (independent) compared with positive control group (dependent). ***$P < 0.05$ different from negative control group. Data are mean ± standard error of the mean. $n = 8$ per group

under treatment by saline (group I) was 300 ± 42 s, while for positive control group (group II) was 151 ± 20 s ($P < 0.05$) [Figure 3].

Intracerebroventricular administration of venlafaxin in dosage of 25, 50, or 100 μg/5 μl/rat (groups III, IV, and V) decreases the latency time of onset of first symptoms of withdrawal syndrome to 180 ± 10, 210 ± 15, and 260 ± 20, respectively. This attenuation in all groups under treatment at the various dose of venlafaxin was statistically significant in comparison with positive control group ($P < 0.05$) [Figure 4].

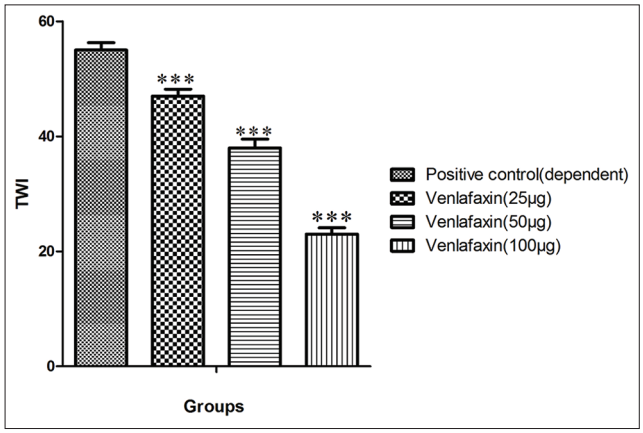

Figure 2: Effects of central injection of venlafaxin (25, 50, or 100 μg/5 μl/rat, intracerebroventricular) on the development of morphine dependence (withdrawal signs). Data are expressed as the mean ± standard error of the mean (SEM). ***$P < 0.05$ different from positive control group (morphine-dependent saline microinjected group). Data are mean ± SEM. $n = 8$ per group

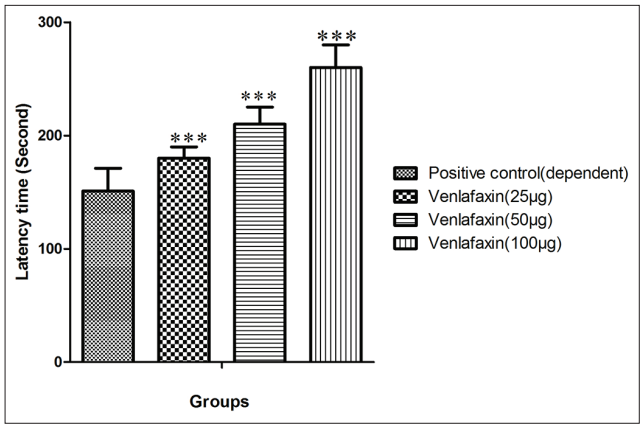

Figure 4: Effects of central administration of venlafaxin (25, 50, or 100 μg/5 μl/rat, intracerebroventricular) on the Time of onset of the first symptoms of withdrawal syndrome (latency time). ***$P < 0.05$ different from control positive group (morphine-dependent saline injected group). Data are expressed as the mean ± standard error of the mean. $n = 8$ per group

Effects of central administration of venlafaxin on blood cortisol level in withdrawal syndrome

Blood cortisol level in negative control group under treatment by saline (group I) was 12 ± 1 μg/dl while for positive control group (group II) it was 16 ± 0.8 μg/dl ($P < 0.05$) [Figure 5].

Intracerebroventricular administration of venlafaxin in dosage of 25, 50, or 100 μg/5 μl/rat (groups III, IV, and V) decreases the blood cortisol level to 14 ± 1, 13.75 ± 0.5, and 12.5 ± 0.8,

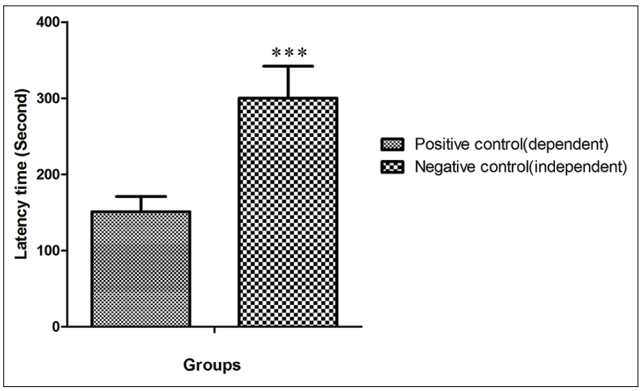

Figure 3: Time of onset of the first symptoms of withdrawal syndrome (latency time) in negative control group (independent) compared with positive control group (dependent). ***$P < 0.05$ different from negative control group. Data are mean ± standard error of the mean. $n = 8$ per group

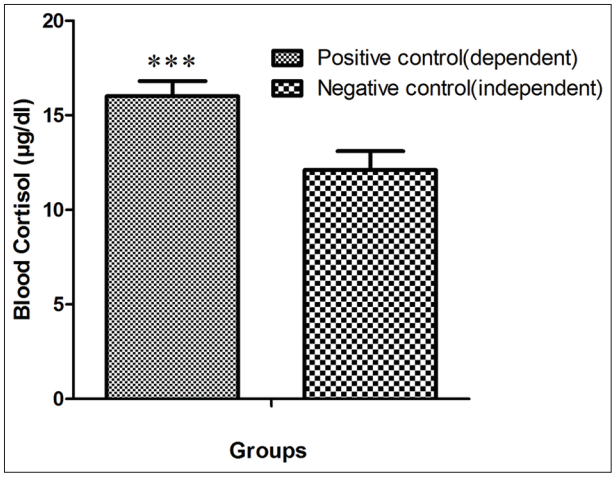

Figure 5: Blood cortisol level in negative control group (independent) compared with positive control group (dependent). ***$P < 0.05$ different from negative control group. Data are mean ± standard error of the mean. $n = 8$ per group

respectively. This attenuation in all groups under treatment at the various dose of venlafaxin was statistically significant in comparison with positive control group ($P < 0.05$) [Figure 6].

Effect of central administration of venlafaxin in writhing test

Central administration of venlafaxin at doses of 25, 50, or 100 µg in dose dependent manner induced significant reduction in pain response when compared to control group ($P < 0.05$). As well as indometacine significantly decreased the number of writhing as a reference drug ($P < 0.05$). Percentage of inhibition of writhing response exhibited by extract at doses 250 mg/kg, 500 mg/kg, and 700 mg/kg were 20%, 24%, and 37% respectively. While indometacine inhibited the writhing response by 74% [Table 2].

Effect of central administration of venlafaxin on tail flick test

Table 3 shows the effect of central administration of venlafaxin at doses of 25, 50, or 100 µg on tail flick test response in rat. All doses of venlafaxin significantly increased the tail flick test time compared with the control ($P < 0.05$). The effect of indometacin (10 mg/kg) was significantly higher than the one produced by the highest dose of the venlafaxine [Table 3].

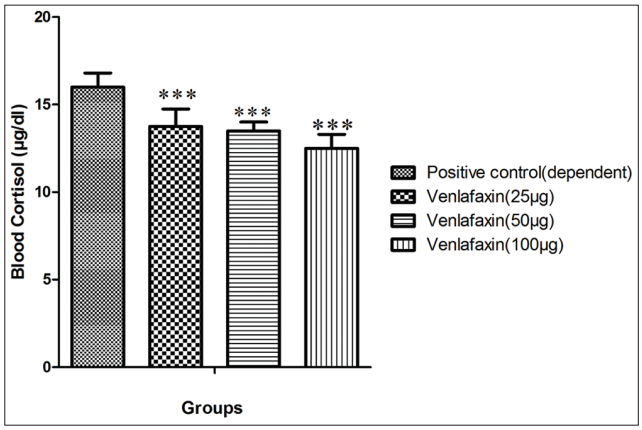

Figure 6: Effects of central administration of venlafaxin (25, 50, or 100 µg/5 µl/rat, intracerebroventricular) on blood cortisol level. ***$P < 0.05$ different from control positive group (morphine-dependent saline injected group). Data are expressed as the mean ± standard error of the mean. $n = 8$ per group

Effect of central administration of venlafaxin on hot plate test

Table 4 indicates the effect of central administration of venlafaxin at doses of 25, 50, or 100 µg on hot plate response in rat. All doses of venlafaxin significantly increased the hot plate test time compared with the control ($P < 0.05$). The effect of indometacin (10 mg/kg) was significantly higher than the one produced by the highest dose of the venlafaxine [Table 4].

DISCUSSION

Opioid dependency and drug addiction is one of the major social problems and the long-term use of opioid analgesic agent such as morphine that could be manifested by withdrawal syndrome.[1] Also, pain treatment and introduction of new pain killer agent is one of the main medical goals.[24] Results of our study indicate the central administration of venlafaxin in multiple dosages decreased the withdrawal symptoms significantly. Also, this study showed that central administration of venlafaxin can attenuate some kind of nociception symptoms. In general, our finding suggested the idea that central administration of venlafaxin would attenuate morphine physical dependency and can also be used as standard pain killer.

Venlafaxine is an antidepressant of the SNRI class.[24,25] It is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder and vasomotor symptoms.[25]

Table 2: Effect of central administration of venlafaxin in acetic acid-induced writhing test in rat

Treatment	Dose	Latency time (s)	Writhing test (mean±SEM)	Inhibition %	*P*
Control	0.2 ml/rat	336±41	62±5.3	-	-
Venlafaxin	25 µg	390±51	49±1.8	20	0.0108 versus control
Venlafaxin	50 µg	456±25	47±1.6	24	0.0050 versus control
Venlafaxin	100 µg	612±20	39±0.3	37	<0.001 versus control
Indometacin	5 mg/kg	785±67	16.5±3.2	74	<0.001 versus control

Value with $P<0.05$ was taken as statistically significant, $n=8$ for each group. SEM=Standard error of the mean

Table 3: Effect of central administration of venlafaxin on tail flick test

Group	Dose	Pretreatment (s)	Posttreatment (s)	Percentage of inhibition
Control	0.2 ml/rat	5.4±0.2	5.9±0.2	7.5
Venlafaxin	25 μg	5.6±0.2	7.1±0.4	23*
Venlafaxin	50 μg	6.8±0.8	8.6±0.6	34*
Venlafaxin	100 μg	6.1±0.2	9.8±0.3	69*
Indometacin	5 mg/kg	5.3±0.8	10.1±0.1	71*

Values are mean±SEM. *P<0.05, versus control (n=8). SEM=Standard error of the mean

Table 4: Effect of central administration of venlafaxin on hot plate test

Group	Dose	Pretreatment (s)	Posttreatment (s)	Percentage of inhibition
Control	0.2 ml/rat	4.6±2.1	5.2±0.4	13
Venlafaxin	25 μg	5.1±1.8	5.9±0.7	15
Venlafaxin	50 μg	5.2±1.2	6.4±0.3	23*
Venlafaxin	100 μg	5.1±1.4	6.6±1.2	29*
Indometacin	5 mg/kg	6.1±0.5	10.6±0.6	73.7*

Values are mean±SEM. *P<0.05, versus control (n=8). SEM=Standard error of the mean

Recent study indicated that venlafaxine and some other antidepressant can be effective for the treatment of cocaine and other drug dependence.[26] Previous study demonstrated that venlafaxine significantly decreased the side effects and depression of cocaine dependency. Also other study suggested venlafaxine to be effective in the treatment of alcoholic abuse, and furthermore, it seems to be useful to decrease the severity of problems related with the alcohol use.[26,27]

The results of the present study showed that TWI in positive control group notably was higher than the negative control group. This study also demonstrated that central administration of venlafaxine with multiple doses (25, 50, or 100 μg) has an outstanding difference compared to the saline treated group. Previous investigations indicate that morphine withdrawal syndrome is mediated through functional alterations in spinal cord serotoninergic system and also norepinephrine in reward system these result also demonstrate that that serotonin and adrenalin in locus coeruleus can be modulate morphine withdrawal syndrome thus with this concept we can argue our data that venlafaxin can increase serotonin and adrenalin in locus coeruleus and can be effective in attenuation of morphine physical dependency.[28]

We can discuss our results with previous studies indicated that venlafaxine, discourage cocaine use in depressed individuals. This study showed the effectiveness of venlafaxine in reducing cocaine use and alleviating depression in individuals addicted to cocaine. Previous study confirm that venlafaxine is effective in the treatment of some drug of abuse like alcohol.[11] On the other hand, previous study demonstrated that adrenergic, dopaminergic, and serotonergic systems of nucleus accumbens has important and critical role in alleviation of physical dependence to opioids, thus venlafaxine as serotonin and adrenalin reuptake inhibitor can increase the serotonin and adrenalin levels and ameliorate the severity of physical dependency.[29,30] We can discuss our results with previous study results that 5-HT receptor subtypes could help improve the use of opioids for treating pain, actually as base of this study serotonin can act and mimics opioid roles in some region of brain thus may be used as a replacement for morphine addiction. Our study also indicated that central administration of venlafaxine with multiple doses (25, 50, or 100 μg) increased time of onset of the first symptoms of withdrawal syndrome (latency time) and this increasing statistically was significant compared to the positive control group. We can interpret our data with previous research results that serotonin and adrenalin uptake in forebrain and other regions may play an important role in behavioral/psychiatric effects of chronic morphine, cocaine and alcohol abuse and thus venlafaxine can alter the behavioral symptoms of drugs abuse. Also, we can generalize our results with the basic concept that venlafaxine by increasing serotonin and adrenalin can modulate brain nociception

pathway and behavioral/psychiatric pathway of morphine dependency and may modulate tolerance and physical dependence to opiates.[30]

Morphine withdrawal syndrome is revealed by an increasing in the HPA axis activity and increasing cortisol level.[31] Our study demonstrated that blood cortisol level in positive control group was noticeably higher than the negative control group, also, venlafaxine with multiple doses (25, 50, or 100 μg) ameliorate the blood cortisol level, and this decrease statistically was remarkable with positive control group. We can enterprise our data with previous study results that venlafaxine and other SNRIs can be effective in anxiety disorder thus ("and thus" cannot be used in this context) effective in modulation of withdrawal syndrome anxiety.[32] We can argue our result with previous study results that morphine withdrawal syndromes have been associated with anxiety that this anxiety situation is the cause of the increase of cortisol level. On the other previous study demonstrates that some anxiolytic and antidepressant medication can alleviate these anxiety and stress and can be effective in withdrawal syndrome management. And venlafaxine as an SNRIs antidepressant that has anxiolytic and sedative effect can suppress morphine cessation induced anxiety and thus decreased the cortisol level.[30,33]

The results of the present study showed that indometacin as standard anti-inflammatory and pain killer drug decrease the acetic acid induced writing test (abdominal constriction) and increased the latency time of abdominal pain expression in comparison with the control group. Our study also confirms previous researches on indometacin efficacy in the management of acetic acid induced writhing test.[33] This study also demonstrated that venlafaxine with multiple doses (25, 50, or 100 μg) ameliorated the acetic acid induced abdominal constriction and increased the latency time of abdominal pain expression in comparison with the control group. It was indicated that serotonergic agent has the potential capability of inhibition of the activation of inflammatory mediators such as cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase products, thus venlafaxin can act as an anti-inflammatory agent and especially ameliorate inflammatory pain.[34]

There have been numerous studies demonstrating the analgesic effect of antidepressants such as SNRI is beneficial in the treatment of chronic pain.[35,36] Also, the inhibitory action of serotonin on structures of the dorsal horn may be mediated by activation of opioid-releasing interneuron's.[37] Previous study demonstrated that serotonin signaling can change the sign of bowel inflammatory disease and can attenuate the inflammation induced pain in digestive systems.[38] Also previous study demonstrated that serotonin and norepinephrine involved in inflammatory pain. These studies suggested that some antidepressants induce an antinociceptive effect and suggested that their analgesic action could be related to the monoaminergic spectrum of the drug in relation to the opiate systems. We can communicate our results to this facts that venlafaxine as SNRI can increase the level of mentioned monoamines and potentiate the opioedrgic system and, as a result, its analgesic effects may occur.[39]

The present study indicated that the indometacin as standard anti-inflammatory and pain killer drug increase the percentage/probability of pain inhibition in comparison with the control group in a hot plate and tail flick test. Venlafaxine with multiple doses (25, 50, or 100 μg) increase the percentage of pain inhibition in comparison with the control group in hot plate and tail flick test. Our results showed that there is statistically different in percentage of inhibition of pain expression in hot plate and tail flick test between venlafaxine with multiple doses (25, 50, or 100 μg) treatment groups and control group.

Extensive studies in rodents suggest that serotonin (5-HT) modulates nociceptive responses in mechanical and thermal pain through the stimulation of several receptor types. Previous data indicate that intrathecal administration of noradrenaline and serotonin, produces potent inhibition against mechanical nociception and thermal pain, and suggest a closer relationship of the descending noradrenergic and sertonergic system to the mechanical and thermal nociceptive system, in the spinal cord of rats.[39,40] We can discuss this concept with our results that venlafaxine increases the level of serotonin and noradrenaline in synapse and thus can be modulate mechanical and thermal nociception.[40]

Previous study demonstrated that venlafaxine has a neuroprotective effect and is used for treatment of some neurodegenerative and central

nervous system disease such as depression, neuropathic pain and neuro inflammation.[41,42] We can argue our data results with the basic concept that venlafaxine as SNRI can modulate opoidergic system and alter the pain perception level.

CONCLUSIONS

Our data demonstrated that venlafaxine as SNRI can be useful in attenuation of withdrawal syndrome adverse signs and anxiety. Also our results indicates that venlafaxine can act as pain modulator agent in inflammatory, mechanical and thermal pain model and suggested that due to these powerful analgesic effects can be effective in attenuation of pain of opioid withdrawal period and can be effective as adjunct therapy for opioid physical dependency in combination with other standard drugs.

ACKNOWLEDGMENTS

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