WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 5, 829-839. Review Article ISSN 2277– 7105

EVALUATION OF ANALGESIC ACTIVITY OF VENLAFAXINE IN EXPERIMENTAL ANIMALS

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Article Received on
04 March 2021,

Revised on 25 March 2021,
Accepted on 14 April 2021

DOI: 10.20959/wjpr20215-20347

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INTRODUCTION

Pain is manifestation of most of the diseases or ailments. Though undesired and unpleasant sensation, it is protective in nature and it is an emotional experience.

The major classes of drugs to treat pain available are -Opioid analgesics and NSAIDs. NSAIDs possess both analgesic as well as anti-inflammatory property and are very potent, but are toxic and having many adverse effects, if used for long duration.

Most of the times, there is close association between chronic pain and depression. This is well supported by the fact that neurotransmitters serotonin, Nor-epinephrine (NE) and opioids (endorphins) are involved in both nociception and depressive disorders and therefore they can be treated by antinociceptive and antidepressant effects of antidepressants.[1]

Serotonin Nor-epinephrine Reuptake Inhibitors (SNRIs), inhibit the reuptake of serotonin / 5-HT and NE, increase the level of 5-HT and NE in the neuronal synapse and facilitate serotonergic and noradrenergic activity at the receptors.

Venlafaxine being a SNRI is mainly used in major depression but has shown analgesic property in various animal models.

Antidepressants modulate pain by their action on central and peripheral nervous system. Exact mechanism of action of antidepressant drugs like SNRI is not known. They act by producing their effect on 5 HT / Serotonin and NE receptors of descending spinal pathway. They also may modulate an adrenergic, opioid, GABA, NMDA receptors, ion channels, etc

and possibly inflammatory cytokines.[2] Their modulating action is also seen on histamine receptors and Na^+ channels.

Venlafaxine has mixed action antidepressant that predominantly inhibits serotonin uptake at low doses and NE at higher doses. Thus, it has dual action on key neurotransmitters which are modulating the pain.

It's effect on peripheral nociceptors, descending nociceptive pathways, central sensitisation and on brain areas involved in pain and emotion processing are all postulated as probable mechanisms.

While searching information on SNRI and Venlafaxine, we found very scant account on their analgesic and anti-inflammatory activity in acute pain as against abundant on chronic pain, neuropathic pain and fibromyalgia.

Hence we plan to evaluate alangesic effect of Venlafaxine in animal models.

METHODS

Approval of institutional animal ethics committee was obtained before commencing the study. Experiments were conducted as per guidelines of committee for the purpose of control and supervision on experiments on animals (CPCSEA). Duration of study was 5 months.

Material

Animals

Both albino rats and mice were procured from central animal house of our institute. Animals were kept seven days for adaptation before subjecting to experiments. The rats and mice were grouped in separate cages with six animals in each cage. They were maintained in a colony room at ambient temperature of 23±1°C with help of air coolers and enough humidity on a 12 hour light-dark cycle. They had free access to food and water. Similar conditions were provided in laboratory while performing experiments. Study was conducted during the day time (between 10.00 to 18.00 hours). 30 Albino rats of either sex, weighing 150-250 gm and 30 Albino mice of either sex, weighing 25-30 gm were used for tail flick and acetic acid induced writhes method respectively.

Drugs and chemicals

Venlafaxine, aspirin, tramadol, 1% acetic acid, double distilled water and normal saline (NS 0.9%).

Methods

Analgesic activity is studied by 2 methods.

1) Tail flick method in rat[3]

Animals were divided into following five groups, each containing 6 rats.

Group A: Control group- received normal saline at a dose of 2ml/Kg (p.o.)

Group B: Standard group - received Tramadol 10 mg/Kg (p.o.)

Group C, D and E: Test drug group - received Venlafaxine at dose 10, 20 and 40 mg/Kg (p.o.)

Central anti-nociceptive activity was assessed by tail flick response method with the help of analgesiometer; originally described by **D'Amour et al,** in 1941.[3] This model used to study acute pain.

In all groups, tail flick test was performed prior to drug administration and at the end of 30, 60, 90 and 120 minutes after drug administration and reaction time was noted. The cut off time of 10 seconds was selected while measuring reaction time, to avoid thermal injury to animals.

From these, percentage of analgesia was calculated by.

$$\% \text{ Analgesia (M.P.E.)} = \frac{\text{T.L.} - \text{B.L.}}{\text{M.L.} - \text{B.L.}} \times 100$$

where

M.P.E. – Maximum possible effect

M.L. – Maximum latency or cut off time

T.L. – Test latency or latency at the end of particular period of time

B.L. – Basal latency or control latency

2) Acetic acid induced writhes test in rats[4]

It is a sensitive test used for evaluating the peripheral analgesic activity of a drug, originally described by **Koster R et al,** in 1959.[4]

Mice were divided into five groups each containing 6 numbers as mentioned above.

NS (2 ml/kg p.o), aspirin (100 mg/kg p.o.) and Venlafaxine 10,20 and 40 mg/kg p.o. were administered to control, standard and test groups respectively.

Half an hour after the drug treatment, each animal was given 1% acetic acid intra-peritoneally (i.p.) with a volume of 1 ml/100gm body weight to induce writhes. The mice were individually placed into glass bowl to observe the writhes. First five minutes were allowed to elapse. Then for the next ten minutes observe each animal and numbers of writhes were counted.

From these, Percentage Inhibition of writhes is calculated by:

$$\% \text{ Inhibition of writhes} = \frac{Wc - Wt}{Wc} \times 100$$

Wc – number of writhes in Control group.

Wt – number of writhes in Test group.

RESULTS

Tail flick response

Our study indicate that Venlafaxine has analgesic activity which is comparable to control and tramadol group. Analgesic activity of all test groups (Venlafaxine 10, 20 and 40 mg/Kg p.o.) was minimal at 30 minutes, which increased gradually and reached to its maximum at the end of 120 minutes. At 60, 90 and 120 minutes, maximum possible effects in all test groups (Venlafaxine 10, 20 and 40 mg/Kg p.o.) were significant and comparable to those of tramadol (standard drug).

Table 1: Effect of different drugs on nociception in Tail flick method of analgesia in rats.

Group (n=6), Drug and Dose	Mean reaction time in seconds (Mean ± SEM)				
	Basal latency	30 min.	60 min.	90 min.	120 min.
A - Control (Normal Saline 2ml/Kg p.o.)	4.73 ± 0.0212	4.72 ± 0.024	4.74 ± 0.0240	4.74 ± 0.0230	4.74 ± 0.0256
B - Tramadol (10 mg/Kg p.o.)	4.78 ± 0.0307	4.81 ± 0.0303	5.54** ± 0.0491	6.38** ± 0.0454	7.20** ± 0.0488
C - Venlafaxine (10 mg/Kg p.o.)	4.89 ± 0.0343	4.90** ± 0.034	5.07**## ± 0.0308	5.31**## ± 0.0371	5.52 **## ± 0.0357
D – Venlafaxine	4.83	4.85*	5.18**##	5.61**##$$	6**##$$

(20 mg/Kg p.o.)	± 0.0196	± 0.0203	± 0.0167	± 0.0449	± 0.0447
E - Venlafaxine (40 mg/Kg p.o.)	4.65 ± 0.0503	4.68$^{\#\$\$\Re}$ ± 0.0229	5.25$^{**\#\#\$}$ ± 0.0161	6$^{**\#\#\$\$\Re\Re}$ ± 0.0294	6.8$^{**\#\#\$\$\Re\Re}$ ± 0.0280

**** P <0.01 when compared with control; * P <0.05 when compared with control

P <0.01 when compared with Tramadol; # P <0.05 when compared with Tramadol.

$$** P <0.01 when compared with Venlafaxine 10mg/Kg; **$ P <0.05 when compared with Venlafaxine 10mg/Kg

ℜℜ P <0.01 when compared with Venlafaxine 20mg/Kg; **ℜ** P <0.05 when compared with Venlafaxine 20mg/Kg

Percentage of maximum possible effect of tramadol at 30 minutes was 1.749 ± 0.4481, which increased gradually and reached to its maximum at 120 minutes. Percentage of maximum possible effect of tramadol at 120 minutes was 46.40 % which was higher than other readings of tramadol and Venlafaxine (10, 20 and 40 mg/Kg p.o.) treated groups also.

In our study at 60 minutes, latency period was 5.54 secs., in tramadol treated group, followed by 5.07, 5.18 and 5.25 secs., in Venlafaxine (10, 20 and 40 mg/Kg p.o.) treated groups respectively.

In addition to that, pain threshold increased significantly during the period of observation in each of the four drug treated groups, with maximum effect observed in tramadol group, at all observation intervals.

Table 2: Maximum possible effect of drugs in tail flick method of analgesia in rats.

Group (n=6), Drug and Dose	**Percentage of Maximum Possible Effect (Mean ± SEM)**			
	30 min.	**60 min.**	**90 min.**	**120 min.**
A - Control (Normal Saline 2ml/Kg p.o.)	———	———	———	———
B – Tramadol (10 mg/Kg p.o.)	1.749 ± 0.4481	14.52 ± 1.003	30.69 ± 0.8971	46.40 ± 0.9284
C - Venlafaxine (10 mg/Kg p.o.)	0.6515 ± 0.0648	3.646$^{\#\#}$ ± 0.2627	8.375$^{\#\#}$ ± 0.3560	12.48$^{\#\#}$ ± 0.3545
D – Venlafaxine (20 mg/Kg p.o.)	0.4193 ± 0.0602	6.863$^{\#\#\$}$ ± 0.1170	15.05$^{\#\#\$\$}$ ± 0.7228	22.69$^{\#\#\$\$}$ ± 0.7300
E - Venlafaxine (40 mg/Kg p.o.)	2.021$^{\$\Re}$ ± 0.4625	11.22$^{\#\$\$\Re}$ ± 0.8721	25.21$^{\#\#\$\$\Re\Re}$ ± 0.8712	40.86$^{\#\#\$\$\Re\Re}$ ± 0.5306

P <0.01 when compared with Tramadol; # P <0.05 when compared with Tramadol.

$$** P <0.01 when compared with Venlafaxine 10mg/Kg; **$ P <0.05 when compared with Venlafaxine 10mg/Kg

ℜℜ P <0.01 when compared with Venlafaxine 20mg/Kg; **ℜ** P <0.05 when compared with Venlafaxine 20mg/Kg

Acetic-acid induced writhes response

In the **acetic acid induced writhes method** of analgesia, the action of Venlafaxine (10,20 and 40mg/Kg p.o.) is significant as compared to control and aspirin group. Percentage of analgesia with Venlafaxine 10, 20 and 40mg/Kg p.o.is 13.38, 21.05 and 39.22 % respectively. In aspirin group, percentage of analgesia is 78.47%. In this method, compounds with percentage analgesia less than 70 % are considered to have minimal analgesic activity.[6] Percentage of analgesia in aspirin group is more than 70 %.

Table 3: Effect of different drugs on nociception in acetic acid induced writhes method of analgesia in mice.

Group (n=6), Drug and Dose	Number of writhes (Mean ± SEM)
A - Control (Normal Saline 2ml/Kg p.o.)	31.83 ± 0.4773
B - Aspirin (100 mg/Kg p.o.)	12.5** ± 0.4282
C - Venlafaxine (10 mg/Kg p.o.)	28.167*## ± 0.6009
D – Venlafaxine (20 mg/Kg p.o.)	25.5**## ± 1.258
E - Venlafaxine (40 mg/Kg p.o.)	19.167**##$$ℜℜ ± 0.9098

** P <0.01 when compared with control; * P <0.05 when compared with control

P <0.01 when compared with Aspirin; # P <0.05 when compared with Aspirin.

$$** P <0.01 when compared with Venlafaxine 10mg/Kg; **$ P <0.05 when compared with Venlafaxine 10mg/Kg

ℜℜ P <0.01 when compared with Venlafaxine 20mg/Kg; **ℜ** P <0.05 when compared with Venlafaxine 20mg/Kg

Percentage of analgesia with all test groups is less than 70 %. This response is thought to involve local peritoneal receptors. Maximum analgesic activity of aspirin (standard drug) is

observed in this method. Analgesic action of Venlafaxine is less than that of aspirin, but is statistically significant.

The algesic effects of acetic acid are produced due to liberation of mediators such as histamine, serotonin, bradykinin, cytokines and prostaglandins etc. These factors bring about increase in vascular permeability, as well as reduce the threshold of nociception and stimulate the receptors on terminals of nociceptive nerve fibers.

Table 4: Percentage of inhibition in writhes, by drugs in mice.

Group (n=6), Drug and Dose	Percentage of inhibition	Number of writhes reduced
A - Control (Normal Saline 2ml/Kg p.o.)	-----	-----
B - Aspirin (100 mg/Kg p.o.)	78.47 ± 1.421	18.33
C - Venlafaxine (10 mg/Kg p.o.)	$13.38^{\#\#}$ ± 2.045	3.66
D – Venlafaxine (20 mg/Kg p.o.)	$21.05^{\#\#}$ ± 2.818	6.33
E - Venlafaxine (40 mg/Kg p.o.)	$39.22^{\#\#\$\$\Re\Re}$ ± 2.248	12.66

P <0.01 when compared with Aspirin; # P <0.05 when compared with Aspirin.

$$** P <0.01 when compared with Venlafaxine10mg/Kg; **$ P <0.05 when compared with Venlafaxine 10mg/Kg

ℜℜ P <0.01 when compared with Venlafaxine 20mg/Kg; **ℜ** P <0.05 when compared with Venlafaxine 20mg/Kg

DISCUSSION

The precise mechanisms of pain transmission and perception in central nervous system are not yet fully understood. It is proved that NE and other monoamine neurotransmitters are responsible for modulation of pain. Many animal experimental studies on antinociception indicate that noradrenergic innervations and to lesser extent serotonergic innervations, act as antinociceptive as well as affect pain related behaviour.

At molecular level, NE is known to modulate immune system and thereby modify inflammatory response too.

Results of tail flick method of analgesia in our study indicate that Venlafaxine has analgesic activity which is comparable to control and tramadol group.

Pain threshold increased significantly during period of observation in each of four drug treated groups, with maximum effect observed in tramadol group, at all observation intervals. Tail flick method mainly evaluates +analgesic activity of centrally acting drugs. Hence tramadol, which acts by central mechanism, had shown the maximum activity.

Jha PK et al,[5] observed antinociceptive activity of venlafaxine at higher doses.

With Venlafaxine at a dose of 22.5 mg/Kg i.p. tail flick latency at 15, 30, 60 90, 120 and 180 min. was 3.58, 4.71, 5.86, 5.31, 4.60 and 3.53 secs., respectively.

They concluded that venlafaxine produces dose dependent antinociceptive action per se.

Sankdia RK et al,[6] in their study Venlafaxine (10 mg/kg i.p.) showed significantly increased tail flick latency period as compared to the baseline value in rats. Onset of analgesic activity was at 30 min. and duration of action 2 hrs, for venlafaxine. (10 mg/kg) (statistically significant).

This linear relationship between dose of Venlafaxine and latency period was observed in their study as follows - Venlafaxine (10 mg/kg i.p.) showed latency period of 2.2, 4.47, 5.28 and 4.26 secs., at 15, 30, 60 and 120 min., respectively.

Comparison of these results shows that, they closely match with the results of standard analgesic drug tramadol. The observations are as follows 3.4, 3.36, 3.4 and 3.4 secs., at 15, 30, 60 and 120 min., respectively.

The antinociceptive action of test drug was found only at higher doses which was statistically significant.

Raut P et al,[7] in their study of comparison of analgesic activity of Venlafaxine (10mg/Kg i.p.) at 5, 15 and 30 min., with control and standard (Eterocoxib 10mg/Kg i.p.) found that analgesic activity of Venlafaxine is well proved in the dose, which is statistically significant. Latency periods observed are 12.83, 14.33 and 14.5 secs., at 5, 15 and 30 min., respectively.

Our results for antinociception of venlafexine are matching with the results of above studies in tail flick method.

In the **acetic acid induced writhes method,** it is well established that chemical mediators are responsible for the inflammatory pain. The algesic effects of acetic acid are produced due to liberation of mediators such as histamine, serotonin, bradykinin, cytokines and prostaglandins etc. These factors bring about increase in vascular permeability, as well as reduce the threshold of nociception and stimulate the receptors on terminals of nociceptive nerve fibers.

Jha PK et al,[5] found that Venlafaxine, in a dose of 10 mg/Kg produced significant decrease in the number of writhes suggesting its antinociceptive effect. Number of writhes were 44.5 and 25.83 in control and venlafaxine (10 .mg/Kg p.o.) treated groups respectively. When calculated in terms of percentage of analgesia, it comes around 0.38 %, 0% and 41.96% which proves Venlafaxine has significant antinociceptive activity in higher doses.

Decrease in number of writhing movements following venlafaxine treatment in this method, suggests that it could possibly have peripheral action.

NE in CNS is found to have key role in pain. As it is widely distributed in CNS, NE serves many other functions such as motor responses at the spinal level. Also, supra-spinal NE alters processes related to aspects of pain other than nociception such as learning, memory, attention and anxiety.

NE is thought to alter pain behaviour by its action on spinal α_2 adreno-receptors. There is evidence, however, that NE acting through α_2 receptors has antinociceptives effects by acting both at spinal and supraspinal sites, including the Locus Coeruleus.[8]

α_2 receptors subtypes are believed to mediate the analgesic response of NE. α_2 receptor stimulation blocks adenylyl cyclase through Gi / Go proteins, suppress voltage gated Ca^{++} channels and activate inwardly rectifying K^{+} channels.

In the same neuron, NE coexists with other neurotransmitters like enkephalin, vasopressin, NPY and ATP. NE and NPY inhibit each other's release.

Spinal NE acts as an important tonic factor modulating the function of the descending 5-HT.

Substantial experimental evidence suggests that, NE potentiates antinociceptive effects of endogenous or exogenous opiates, most likely through α_2 receptors, possibly through α_{2A}

receptor. Noradrenergic agonists, reuptake inhibitors and indirect-acting agonists such as amphetamine, have all been shown to synergize or potentiate analgesic effect of opiates.[9]

NE as well as opioids would block the release of SP and glutamate by primary nociceptive afferents. NE also inhibits the hyperalgesic effects of SP by acting on spinal neurons (i.e. post-synaptically to the primary afferents). Decreased release of SP may contribute to antinociceptive effects of NE. I.t. SP (5-20 micrograms), produces a dose-related antagonism of the effect of morphine, baclofen and NE, which persists for entire time-course of the antinociceptive effect in each case. Through α_2 receptors, NE synergizes with adenosine to produce antinociception. To produce antinociception, adenosine probably act on A1 receptor and induce NE release. Nitrous oxide produces analgesia by increasing the release of NE in the spinal cord.[10]

In our study we did not investigate the underlying mechanism by which Venlafaxine inhibit nociception. It may involve inhibition of NE, 5-HT and opiod receptors and pathways provoked by cytokines involved in inflammatory hypernociception. Inflammatory hypernociception is generally mediated by the release of a cascade of inflammatory mediators.

Results of our study closely resemble with results of above mentioned studies. Little variation wherever, may be explained on the basis of differences in dose and routes of administration.

Many clinical trials also have been carried out to evaluate and assess Venlafaxine as an analgesic and it is being used in clinical practice for the same.

CONCLUSION

1. Antinociceptive activity of Venlafaxine is statistically significant and comparable to but, less than that of tramadol, in tail flick method of analgesia in rats.
2. Antinociceptive activity of Venlafaxine is statistically significant and comparable to but, less than that of aspirin in acetic acid induced writhes method.
3. Antinociceptive activity of Venlafaxine (40mg/Kg p.o.) is comparable to Venlafaxine (20 and 10mg/Kg p.o.) in both above mentioned methods of algesia.

ACKNOWLEDGEMENTS

The author thanks to Lesanto labs., Mumbai, for providing Venlafaxine, Aspirin and Tramadol in pure powder form for our research.

Funding: No funding sources

Conflict of interest: None declared.

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