SCREENING OF VENLAFAXINE FOR ITS ANALGESIC POTENTIAL IN EXPERIMENTAL ALBINO MICE

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Article History: Received: 12.12.2022 **Revised:** 29.01.2023 **Accepted:** 15.03.2023

Abstract

Aim & Objectives: To evaluate the analgesic effect of Venlafaxine in experimental Albino mice.
Materials and Methods: The study was conducted after Institutional Animal Ethics Committee approval (IAEC). Animals were divided into four groups. Group 1 (Control group) received Distilled water (2ml/kg), Group 2 (Diclofenac group) received Diclofenac (10mg/kg), Group 3 (Venlafaxine 50mg/kg group) received Venlafaxine (50mg/kg) and Group 4 (Venlafaxine 100mg/kg group) received Venlafaxine (100mg/kg). Eddy's Hot plate method was used to investigate analgesic activity of Venlafaxine.
Results: The present study clearly shows that Venlafaxine 100mg/kg has significant analgesic activity at 30 and 60 minutes testing time intervals ($p < 0.05$) when compared to control and its activity was comparable to Diclofenac at 30, 60 and 90 minutes testing time intervals ($p > 0.05$).
Conclusion: Venlafaxine 100mg/kg has significant analgesic potential in Eddy's Hot Plate method.

Key words: Venlafaxine, Diclofenac, Analgesic, Eddy's Hot Plate

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DOI: 10.31838/ecb/2023.12.s2.021

1. Introduction

Pain is defined as "An unpleasant sensory and emotional experience "[1]. It might alter a person's life by lowering quality of life. It occasionally had an effect on the patient's family as well[2]. Based on duration and type, pain is classified into different categories as acute pain, chronic pain, nociceptive Pain and neuropathic Pain[3].

Depression and pain have a lot in common. Pain can cause depression, while depression can cause pain. Sometimes depression and pain can form a vicious cycle where in pain can worsen the symptoms of depression, which ultimately result in worsening of pain sensation. Depression frequently results in incomprehensible physical symptoms like headache or back discomfort. The initial indicator of depression may be this type of pain. The problems associated with pain can have an impact on mood and attitude of a person. Chronic pain give rise to many problems which can lead to depression that further result in sleep disturbances[4].

Many diseases are having pain as a symptom that require treatment with analgesics[5]. Hence, the first line of treatment in the management of pain is analgesic[6]. For extreme pain due to cancer metastases, strong analgesics that means opioid drug is required[5,7]. Owing to their efficacy, opioid analgesics are being used since long for the treatment of both acute and chronic pain. Because of their safety and tolerability concern, frequent use of this class of drug is being prevented. Also, their reported association with drug abuse and dependence has resulted in its reduced acceptance by many[8]. The addiction accountability of opioids led to in depth research for compounds without such side effect[5,7].

Non- steroidal anti-inflammatory drug (NSAIDs) are wide analgesics and can be used for any kind of acute or chronic pain. As they are both anti-inflammatory and analgesic, NSAIDs are the most widely used therapeutic classes of drugs[9]. Between 34 and 46% of NSAID users are thought to have experienced some gastrointestinal damage[10,11]. Chronic NSAID use is linked to the development of drug-induced hypertension and nephrotoxicity[12]. A potential negative impact of recently developed selective cyclooxygenase-2 inhibitors is a prothrombotic tendency that could cause myocardial infarction and mortality[10,11].

Venlafaxine is serotonin-norepinephrine reuptake inhibitor (SNRI) which is used to treat depression as well as allodynia in painful conditions such as neuropathic pain and inflammatory conditions. The FDA has given venlafaxine approval to treat and manage the symptoms of social anxiety disorder, cataplexy, and depression. Venlafaxine may be used alone or in combination with other medications as part of a combination therapy.

Venlafaxine increases local concentrations of serotonin and norepinephrine, two crucial neurotransmitters released from the terminals of descending pain control pathways, thereby increasing their local concentrations and promoting persistence of their analgesic effects[13,14].

2. Materials

Experimental animals

Albino mice of either sex weighing 20 to 30 grams were procured from the Central Animal House of the Institution. The animals were housed under standard conditions and accommodated to 12h light/dark cycle for 10 days prior to experimentation day. They had free access to standard Mice chow pellet and water ad libitum under strict hygienic conditions. The present study was approved by the IAEC (Institutional Animal Ethics Committee).

CCSEA (Committee for Control and Supervision of Experiments on Animals) guidelines were strictly followed throughout the study.

Drugs

Venlafaxine was obtained in pure powder form from Cipla Pharmaceuticals Ltd. And Injection Diclofenac (75 mg/ml) from Novartis Pharmaceuticals Ltd.

a. Venlafaxine: It was administered as the doses of 50 and 100 mg/kg i.p,

b. Diclofenac: It was administered as the dose of 10 mg/kg i.p,

3. Method

Analgesic Model – Eddy's Hot Plate Method In Albino Mice

❖ **Drug treatment schedule**

Group	Drug	Solvent	Dose of the Drug	Route
1.	Distilled water	-	2 ml/kg	i.p
2.	Diclofenac	DW	10 mg/kg	i.p
3.	Venlafaxine	DW	50 mg/kg	i.p
4.	Venlafaxine	DW	100 mg/kg	i.p

(n=6 in each group)

❖ **Procedure**

- The instrument involved in this experiment is referred to as a "Eddy's Hot Plate." The "Knob" thermostat controls the temperature of the instrument, which consists of an electrically heated surface composed of iron, aluminium, or copper that is kept at 55 to 56°C.[15]
- Thirty minutes after treatment with specific drug, mouse placed on the hot plate and monitored for either a paw licking or jumping behaviour. A stopwatch used to measure the reaction time (latency period).
- Time interval between placing the animal on hot plate and either licking or jumping will be considered as reaction time (latency period).
- At 30, 60, and 90 minutes following the drug administration, readings are repeated. the cut-off period is 20 seconds.

Statistical Analysis

The data analysis was carried out by one way ANOVA followed by post hoc Dunnett's test. All the statistical methods were carried out through the software Graph pad Instat version 3.06 and $p < 0.05$ was considered statistically significant.

4. Results

The results of mean reaction time taken for either paw licking or jumping response at different testing time intervals in different groups and their comparisons are given in table no. 1.

- Diclofenac 10 mg/kg showed statistically significant increase in mean reaction time at 30, 60 and 90 minutes testing time intervals ($P<0.05$) when compared with the control
- Venlafaxine 50 mg/kg did not show statistically significant difference in mean reaction time at 30, 60 and 90 minutes testing time intervals ($P>0.05$) when compared with the control.
- Venlafaxine 100 mg/kg showed statistically significant increase in mean reaction time at 30 and 60 minutes testing time intervals ($P<0.05$) when compared with the control.
- Venlafaxine 100 mg/kg did not show statistically significant difference in mean reaction time at 90 minutes testing time intervals ($P>0.05$) when compared with the control.

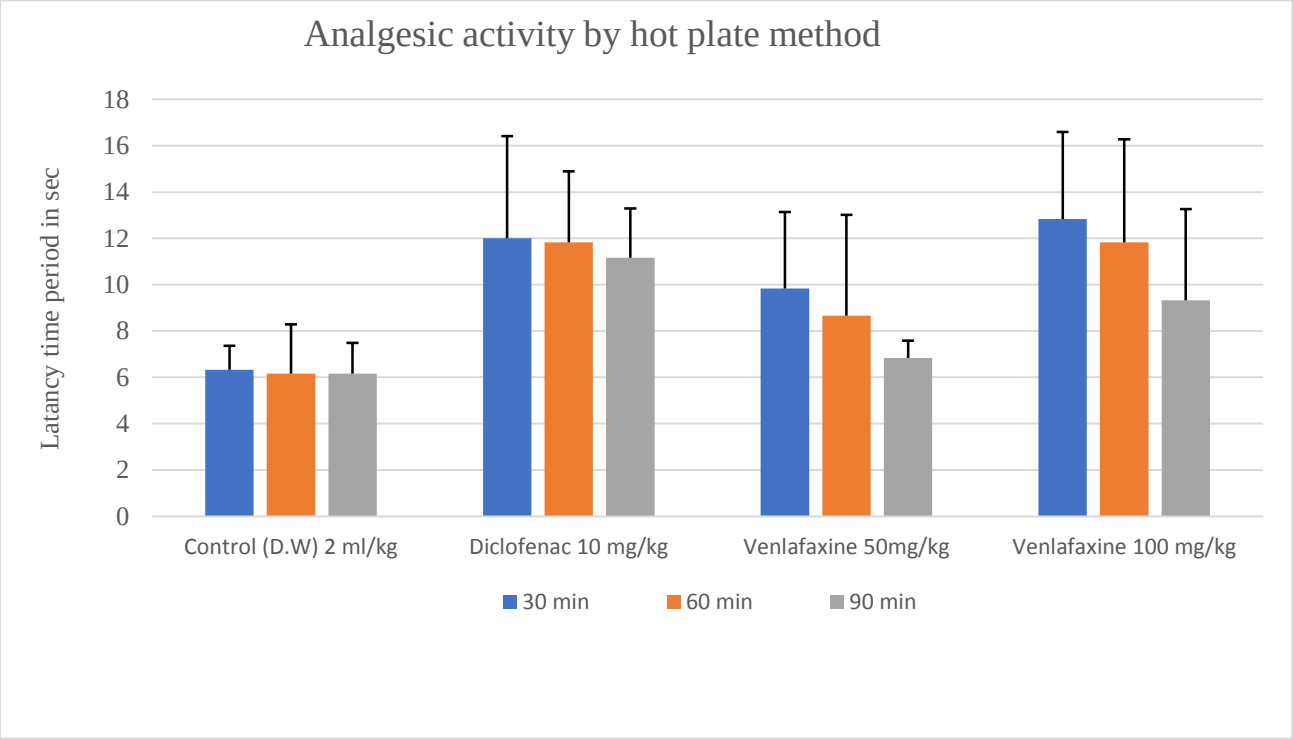
Table 1: Effect Of Venlafaxine And Diclofenac Pretreatments On Paw Licking Or Jumping Response In Mice

Testing time interval in minutes	**Group 1**	**Group 2**	**Group 3**	**Group 4**		
	Distilled water (2 ml/kg)	**Diclofenac 10 mg/kg**	**Venlafaxine 50 mg/kg**	**Venlafaxine 100 mg/kg**	**F Value**	**p Value**
30 min	6.33 ± 1.03	12 ± 4.42 *****	9.83 ± 3.31	12.83 ± 3.76 *****	4.410	0.015
60 min	6.16 ± 2.13	11.83 ± 3.06 *****	8.66 ± 4.36	11.83 ± 4.44 *****	3.431	0.036
90 min	6.16 ± 1.32	11.16 ± 2.13 *****	6.83 ± 0.75	9.33 ± 3.93	5.710	0.005

Post hoc analysis by Dunnett's Test: * $p< 0.05$,

Graphical representation of mean reaction time after the treatment with control, Diclofenac 10 mg/kg, Venlafaxine 50 and 100 mg/kg at different testing time intervals in analgesic model is as shown in graph No. 1

Graph 1: Effect Of Diclofenac And Venlafaxine Pretreatments On Paw Licking Or Jumping Response In Mice



Comparative results of Analgesic Model for Venlafaxine 50 and 100 mg/kg with Diclofenac 10 mg/kg are given in table No.2

- Venlafaxine 50 mg/kg did show statistically significant difference in mean reaction time when compared with diclofenac 10 mg/kg at all testing time intervals but Venlafaxine 100 mg/kg did not show statistically significant difference in mean reaction time when compared with diclofenac 10 mg/kg at all testing time intervals.

Table 2: Effect Of Venlafaxine Pretreatments On Mean Reaction Time In Mice As Compared With Diclofenac Pretreatment.

Testing time intervals in minutes	**Group 1**	**Group 2**	**Group 3**		
	Diclofenac 10 mg/kg	**Venlafaxine 50 mg/kg**	**Venlafaxine 100 mg/kg**	**F Value**	**p value**
30 min	12 ± 4.42	9.83 ± 3.31 *	12.83 ± 3.76	0.965	0.403
60 min	11.83 ± 3.06	8.66 ± 4.36 *	11.83 ± 4.44	1.248	0.315
90 min	11.16 ± 2.13	6.83 ± 0.75 *	9.33 ± 3.93	4.134	0.037

Post hoc analysis by Dunnett's Test: * $p < 0.05$,

5. Discussion

In the current study, different Venlafaxine doses were used in experimental model of pain to investigate the analgesic effects. We used the Eddy's Hot Plate method to assess the analgesic action.

Analgesic drugs currently in use can cause serious side effects like nephrotoxicity[12], hepatotoxicity and peptic ulcers[10,11]. Whereas such devastating side effects are not seen with Venlafaxine. Therefore, ongoing research is being done to discover newer, safer, and more effective analgesic drug for chronic painful conditions associated with mood disorders

The effectiveness of venlafaxine in neuropathic and persistent pain models suggests that in addition to its purported antidepressant activity, venlafaxine may also be effective in treating inflammatory pain and other persistent pain conditions in humans.

Venlafaxine may also have analgesic effects because of its capacity to inhibit prostaglandins. Venlafaxine's analgesic effects may be mediated by its inhibition of proinflammatory cytokines and the COX 2 enzyme[16]. Therefore, the current study was conducted to assess the analgesic properties of Venlafaxine and comparing their effects with standard drug Diclofenac in the analgesic model in albino mice.

We investigated the mean reaction time (i.e., either licking or jumping response) in this analgesic model. The reduction in mean reaction time after giving the drug intraperitoneally was considered as analgesic activity. Results of this study indicates that when compared with the control group, Venlafaxine 100 mg/kg have shown significant analgesic activity at 30 and 60 min.($P<0.05$) testing time intervals, but Venlafaxine 50 mg/kg did not show significant analgesic activity at all testing time intervals($P>0.05$) (Table no.1),

When compared with Diclofenac 10 mg/kg, analgesic effect of Venlafaxine 100 mg/kg was comparable to Diclofenac 10 mg/kg at all testing time intervals($P>0.05$), whereas Venlafaxine 50 mg/kg did show significant difference at all testing time intervals. ($P<0.05$) (Table no.2).

These results suggest Venlafaxine 50 mg/kg is inferior as compared with Diclofenac 10 mg/kg and Venlafaxine 100 mg/kg in terms of analgesic activity. Therefore, we can conclude that Venlafaxine has dose dependent analgesic activity (Graph no.1).

6. Conclusion

From the findings of the present experimental study, we conclude that,

Venlafaxine 50 mg/kg did not show analgesic activity, but Venlafaxine 100 mg/kg did show analgesic activity which is comparable with standard analgesic drug i.e., Diclofenac 10 mg/kg. The current study suggests that the use of Venlafaxine may have an added benefit in a patients of depressive disorder associated with various chronic pain conditions as along with the conventional medications.

Though the analgesic activity of Venlafaxine is secondary to its anti-depressant activity, more studies are needed to be done in other different analgesic models. Along with these, pre-clinical evaluation, human studies are also required to be done, in order to strengthen the results and prove their efficacy in the long-term use of Venlafaxine as potential analgesic agent in routine clinical practices.

Hence, we suggest that Venlafaxine along with its anti-depressant and additional analgesic property might be more suitable for patients in diseased conditions where there is depression associated with pain. For example, conditions like chronic lumbago, fibromyalgia, degenerative disc disease, osteoarthritis, trigeminal neuralgia, prolapsed of intervertebral disc, nerve compression and end stage cancer pain.

Acknowledgement:

We acknowledge the support given by the Central animal house of the institution and the technical staff of Department of Pharmacology during study.

Conflict of interest: There are no conflicts of interest.

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