Original Research Article

Comparative evaluation of analgesic activity of fluoxetine, duloxetine and venlafaxine in acute pain model in albino rats

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Abstract

Background: The mainstay for acute pain management are non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Apart from these drugs, antidepressants like fluoxetine, duloxetine and venlafaxine are used for management of pain condition because of their reinforcing property on descending inhibitory pain system by virtue of their mechanism, reuptake inhibition of serotonin and norepinephrine. They are used mainly for chronic pain condition and now they are under investigations for treating acute pain conditions. So, present study is undertaken to evaluate and compare analgesic action of fluoxetine, duloxetine and venlafaxine in acute pain model in albino rats. **Material and Methods:** Analgesic activity of fluoxetine (in a dose of 5, 10 and 15 mg/kg), duloxetine (in a dose of 10 and 30 mg/kg) and venlafaxine (in a dose of 10, 22.5 and 50 mg/kg) was evaluated in wistar rats using tail flick method and hot plate method and compared with control group (normal saline) along with intergroup comparison. Data was analyzed by using SPSS 21.0 software. P values < 0.05 was taken as significant. **Results:** The present study showed that fluoxetine, duloxetine and venlafaxine had significant analgesic action as compared to baseline values. But as compared to control group, duloxetine (30mg/kg), fluoxetine (10 mg/kg) and venlafaxine (10 and 50 mg/kg) shows significant analgesic action. Venlafaxine had significant analgesic action as compared to fluoxetine and duloxetine. But it is not possible to compare analgesic activity of venlafaxine and duloxetine because of variable result of duloxetine in tail flick method and hot plate method. **Conclusion:** Increase in tail flick latency in tail flick method and increase in reaction time in hot plate method, suggest that fluoxetine, duloxetine and venlafaxine had significant analgesic activity because of inhibition of reuptake of serotonin and norepinephrine and thus strengthening descending inhibitory pain pathway. Thus, they may be used for management of acute pain but further animal and human studies are required for their use in acute pain conditions.

Keywords: Antidepressants, tail flick method, hot plate method, acute pain.

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INTRODUCTION

According to International Association for the Study of Pain (IASP) pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Pain is classified into acute and chronic pain depending upon the duration of pain. Pain is classified as acute pain and chronic pain.[1] Acute pain may arise due to tissue injury, inflammation, a surgical procedure, childbirth, or a brief disease process.[2] Causes are postoperative pain, spinal cord injury, burn injury pain, acute back pain and musculoskeletal pain, acute cancer pain and pain associated with disease processes. Tissue damage leads to release of proinflammatory cytokines (TNFα, IL-1β, IL-6) and induction of cyclo-oxygenase -2 which leads to production of prostaglandins. Apart from this, voltage gated sodium channels and TRP channels also involved in pain.[3] Descending inhibitory pain pathways modulates pain sensitivity. In this pathway endorphins are released and by acting on presynaptic μ opioid receptors inhibit neurotransmission from nociceptive primary afferent neurons. As well enkephalins are also released which acts

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on δ-opioid receptors exerts their antinociceptive effect. This pathway also includes descending spinal norepinephrine pathway and descending spinal serotonergic pathway.[4] The management of pain mainly includes non-steroidal anti-inflammatory drugs, opioids and muscle relaxants. Other therapy includes anticonvulsants, antidepressants and steroid injections. Opioids are used in moderate to severe acute pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely used for management of pain because of their ability to relieve pain and inflammation by virtue of their inhibitory effect on cyclo-oxygenase enzyme (COX-1 and COX-2).[2] Basis of use of antidepressant in pain includes their property to reinforce descending inhibitory pain pathway by inhibiting reuptake of serotonin and norepinephrine in synaptic cleft at spinal and supraspinal level.[5] Besides this, there are no published data on the use of antidepressants in the management of acute neuropathic pain, however antidepressants are effective in the treatment of a variety of chronic neuropathic pain states.[2] Therefore, present study undertaken to evaluate and compare analgesic effect of fluoxetine, duloxetine and venlafaxine (which are used in chronic pain) in acute experimental pain model.

MATERIAL AND METHODS

Study was conducted after approval of Institutional Animal Ethics Committee. The study was conducted according to CPCSEA guidelines. In this study, healthy albino wistar rats of either sex weighing 150 to 250 grams were used experiments. Animals were housed in central animal house and maintained on standard diet (rat pellet) and water ad libitum. Animals were maintained at 23±1^{0}C, enough humidity and on 12-hour light-dark cycle. Duloxetine and Venlafaxine was purchased from TCI Chemicals, Chennai. Fluoxetine was purchased from Rajesh Chemicals, Mumbai. All drugs were of analytical grade. All drugs were dissolved in normal saline with sufficient quantity of solvent. Fresh solutions of drug were prepared before each experiment. Drugs were administered intraperitoneally. For the purpose of experiment, rats were grouped as given in table 1 with 6 rats in each group. Total 54 rats were used for experiment. During consecutive experiments, washout period was given depending upon nature of drug. Rats were tagged for identification during each experiment to avoid mixing of animals between two groups. For evaluation of acute analgesic activity, two methods were used, tail-flick method and hot-plate method.

Tail flick method:

Analgesic activity of drugs determined by tail flick response method originally described by D'Amour and Smith in 1941.[6] Instrument used was tail-flick analgesiometer. For the experiment, tail of the animal was placed on the radiant heat source which is made up of nichrome wire through which constant current passed (5 Ampere). Sharp withdrawal of tail is considered as positive response. Time between placing of tail of rat on radiant heat source to withdrawal of tail is recorded as reaction time (tail-flick latency). During experiment each animal was tested for three times at interval of 5 minutes and average was taken as basal latency. Then, drug was administered intraperitoneally and response was taken after 15, 30, 45, 60, 90 and 120 minutes of drug administration. Reaction time was noted and calculated. Cut off time of 30 seconds was considered in experiment to avoid thermal injury to tail Maximal possible analgesia was calculated and compared with basal latency.

Hot plate method:

This method was originally described by Eddy and Leimbach (1953).[7] Analgesic activity of drug is measured using hot plate analgesiometer. In this method, rat was placed on hot plate maintained on 55±0.5^{0}C. After placing rat on hot plate, response such as paw licking, jumping or withdrawal of paw noted. Time between placing of rat on hot plate to paw licking or jumping was recorded as reaction time. Cut off of 20 second was considered in experiment to avoid thermal injury to paw. In all groups, hot plate test performed before administration of drug and after 15, 30, 45, 60, 90 and 120 minutes after drug administration. Reaction time was calculated. Maximal possible analgesia was calculated.

Maximum possible analgesia was calculated by following formula:

$$\%\ \text{Analgesia} = \text{Maximum possible analgesia (\%MPA)} = \frac{\text{Test Latenct} - \text{Basal Latency}}{\text{Maximum Latency} - \text{Basal Latency}} \times 100$$

Statistical analysis

Results were expressed as Mean ± SEM (Standard Error of Mean). data was analyzed by one-way ANOVA followed by post hoc tukey test using SPSS 21.0 software. 'p' value <0.05 was taken as statistically significant.

RESULTS

Effect of fluoxetine, duloxetine and venlafaxine on tail flick latency in tail flick method (expressed as % MPA) (See graph 1)

As compared to baseline, normal saline did not show significant analgesic action except at 60 minutes of drug administration with maximum %MPA of 2.94%.

DUL10 significantly increased tail flick latency at 15 minutes of drug administration with maximum %MPA of 19.83%. DUL30 showed significant analgesic activity starting from 15 minutes, lasting 90 minutes with maximum %MPA of 45.27% at 45 minutes. As compared to normal saline (NS5), DUL10 and DUL30 did not show

significant analgesic action. There was no difference between analgesic activity of DUL10 and DUL30. FLU5 and FLU15 significantly increased tail flick latency at 30 and 15 minutes of drug administration with maximum %MPA of 32.23% and 30.13% at 30 and 15 minutes respectively. FLU10 showed significant increase in tail flick latency throughout 120 minutes observation period with maximum %MPA of 54.88% at at 60 minutes of drug administration as compared to baseline. As compared to normal saline (NS5), FLU5 and FLU15 did not show significant analgesic action while FLU10 showed significant action at 45 and 60 minutes. At 60 minutes, FLU10 had significant analgesic activity than FLU15. FLU5 - FLU10 and FLU5 - FLU15 did not show statistically significant difference.

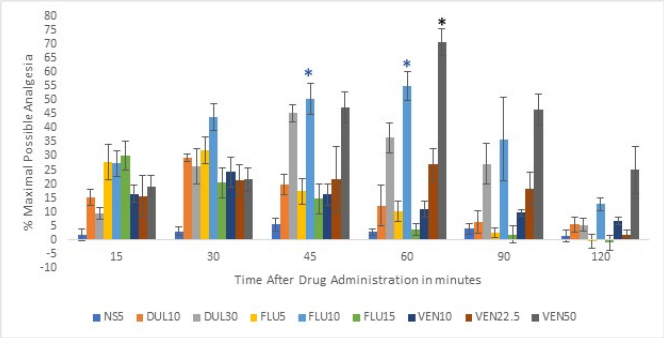
VEN10 and VEN50 showed significant increase in tail flick latency throughout 120 minutes observation period with maximum %MPA of 24.29% and 70.59% at 30 and 60 minutes of drug administration respectively as compared to baseline. Similarly, VEN22.5 showed statistically significant analgesia as compared to baseline with maximum %MPA of 27.28% at 60 minutes. As compared to normal saline (NS5), VEN10 and VEN22.5 did not show significant analgesic action. VEN50 showed significant action at 60 minutes. VEN50 had more significant analgesic activity than VEN10 and VEN22.5. VEN10 and VEN22.5 did not show statistically significant difference. As compared to DUL30, FLU5, FLU15 (at 15 minutes) and VEN50 (at 60 minutes) had more significant analgesic action and as compared to FLU5 and FLU15, VEN50 (at 60 minutes) had more significant analgesic activity. FLU10 showed significant analgesic action as compared to VEN10 (at 60 minutes), VEN22.5 (at 45 and 60 minutes). Thus, in tail flick method, Duloxetine did not show significant analgesic activity in tail flick model of pain as compared to normal saline fluoxetine and venlafaxine. As compared to fluoxetine 10 mg/kg, venlafaxine 50 mg/kg showed significant analgesic action. Effect of fluoxetine, duloxetine and venlafaxine on reaction time in hot plate method (expressed as % MPA) (See graph 2).

As compared to baseline, DUL10 shows significant analgesic effect at 15, 30 45, 90 and 120 minutes. Maximum analgesic effect was observed at 45 minutes with %MPA 19.42%. DUL30 showed significant increase in analgesia throughout 120 minutes observation with %MPA of 46.30% at 45 minutes. As compared to normal saline (NS5), DUL10 did not show significant analgesic activity over 120 minutes observation period while DUL30 showed significant analgesic effect over a period of 90 minutes as compared to NS5. As compared to DUL10, DUL30 significantly increases hot plate reaction time. FLU5 and FLU10 showed significant increase in reaction time to hot plate as compared to baseline with maximum %MPA of 26.05% and 30.29% at 45 minutes, while FLU15 significantly increases reaction time over 60 minutes period with maximum %MPA of 26.52% at 45 minutes. As compared to normal saline, FLU5 showed significant analgesia only at 30 and 45 minutes while FLU15 showed increase in reaction time only at 30, 45 and 60 minutes. FLU10 showed significant increase in reaction time throughout 120 minutes observation period. In case of fluoxetine, FLU5, FLU10 and FLU15 did not show statistically significant difference in analgesic activity throughout 120 minutes period. As compared to baseline, VEN10, VEN22.5 and VEN50 also shows significant analgesic effect throughout 120 minutes observation period with maximum possible analgesia of 37.2%,36.35% and 41.92% at 60, 45 and 30 minutes. VEN50 showed significant analgesic effect over a period of 90 minutes as compared to NS5 while VEN10 showed significant increase in reaction time throughout 120 minutes observation period. VEN22.5 showed significant analgesia at 30 and 45 minutes as compared NS5. As compared to VEN22.5, VEN10 showed more significant analgesic activity at 60 and 90 minutes, while there was no statistically significant difference between VEN10 and VEN50. VEN50 had more significant analgesic activity than VEN22.5. Thus, DUL30 was more significant in increasing reaction time as compared to FLU10, FLU15, VEN10 and VEN50. As compared to FLU5 and FLU15, VEN50 had significant analgesic action.

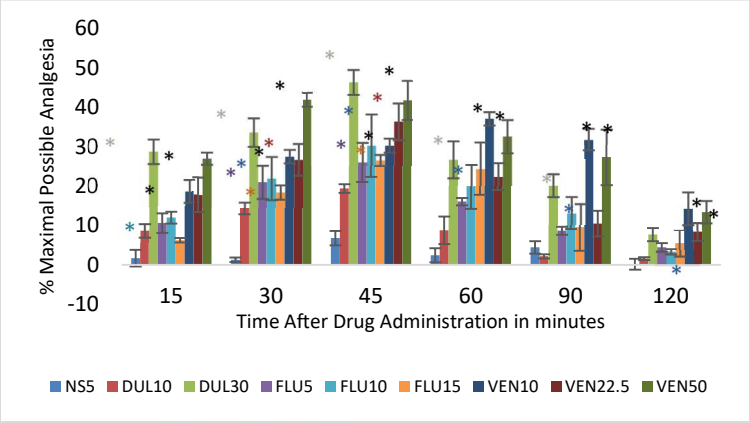
Table 1: Grouping of animals and dose used

Group Number	Group Name	Dose/kg	Abbreviation used
1	Control: Normal saline	5 mg/kg	NS5
2	Duloxetine	10 mg/kg	DUL10
3	Duloxetine	30 mg/kg	DUL30
4	Fluoxetine	5 mg/kg	FLU5
5	Fluoxetine	10 mg/kg	FLU10
6	Fluoxetine	15 mg/kg	FLU15
7	Venlafaxine	10 mg/kg	VEN10
8	Venlafaxine	22.5 mg/kg	VEN22.5
9	Venlafaxine	50 mg/kg	VEN50

P value < 0.05 was taken as significant. (* P<0.05 as compared to control group).



Graph 1: Effect of fluoxetine, duloxetine and venlafaxine on tail flick latency in tail flick method (expressed as % MPA)



Graph 2: Effect of fluoxetine, duloxetine and venlafaxine on reaction time in hot plate method (expressed as % MPA)

DISCUSSION

In this study, we evaluate analgesic effect of fluoxetine, duloxetine and venlafaxine in hot plate method and tail flick method which are suitable for centrally acting drugs. Results states that duloxetine had analgesic action in hot plate method only, while fluoxetine and venlafaxine had analgesic effect in hot plate method and tail flick method. This shows that antidepressants drugs decrease pain by central action. Apart from that, venlafaxine had significant analgesic action in both methods and that's why it is equally effective as gabapentin at reducing acute postoperative pain analgesic requirements and superior at reducing postmastectomy pain.[8] Pain arises due to peripheral mechanism (involving release of prostaglandins and other proinflammatory substances leading to activation of voltage gated sodium channels leading to excitability of neurons) and central mechanism (involving ascending pain pathway and central sensitization). Descending pain inhibitory pathway decreases pain and this involves serotonin and norepinephrine as major neurotransmitter. Thus, antidepressant reinforce descending pain inhibitory pathway by blocking reuptake of serotonin and norepinephrine and increasing their level in synaptic cleft at spinal and supraspinal level.[2] Results in our study are consistent with other studies. In study conducted by Jha, Mazumdar and Bhatt[9], venlafaxine in a dose of 10 and 22.5 mg/kg shows dose dependent anti-nociceptive effect in tail flick method, which is consistent with our result stating that venlafaxine in higher dose 22.5mg/kg and 50 mg/kg has analgesic effect. Abdalla S. Elhwuegi and Kalthom M. Hassan[10] studied anti-nociceptive effect of imipramine, fluoxetine and mirtazapine on mice in thermally induced pain and stated that fluoxetine has dose dependent anti-nociceptive action which is consistent with our results that fluoxetine has analgesic activity in thermally induced pain model. Dhawale *et al.*[11] studied analgesic action of duloxetine in comparison with ibuprofen in hot plate method showing that duloxetine has significant analgesic action as compared to control which is consistent with our result. Bandapati SK *et al.*[12] compared analgesic effect of venlafaxine (in a dose of 15, 30 and 60 mg/kg) and tramadol in mice using tail immersion method. Results are consistent with our tail flick method result stating that venlafaxine has dose dependent analgesic action. Sikka, *et al.*[13] showed that fluoxetine in a dose of 5 mg/kg and 10mg/kg and venlafaxine in a dose of 40mg/kg and 50 mg/kg has significant analgesic action in tail flick model which is consistent with our finding. Jones *et al.*[14] showed that duloxetine had no significant analgesic action in tail flick method while in hot plate method, it increases reaction time significantly in a dose of 10 and 30 mg/kg

which is consistent with our result. Kurlekar and Bhatt[15] also showed fluoxetine has dose dependent anti-nociceptive action in a dose of 5 and 10 mg/kg. Antidepressants like duloxetine is used for diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain. Duloxetine has well documented efficacy in painful physical symptoms of depression.[16] But fluoxetine and venlafaxine is not approved for treating pain conditions. As well, there is no enough evidence of effect of antidepressants in acute pain in postoperative cases. But there is growing interest of using duloxetine in acute postoperative pain in order to reduce perioperative opioid use and postoperative pain.[17,18] Apart from this, there are no studies that compares the analgesic effect of fluoxetine, duloxetine and venlafaxine in acute pain. Result stated that duloxetine and venlafaxine had significant analgesic action as compared to fluoxetine. But it is not possible to differentiate analgesic activity of duloxetine and venlafaxine. Further animal studies and human studies are required to prove efficacy of duloxetine and venlafaxine in acute pain conditions. This study explains that antidepressants have acute pain-relieving property in animals and so can be used for management of acute pain. Still, they are not used for management of acute pain.

CONCLUSION

Antidepressant like fluoxetine, duloxetine and venlafaxine had analgesic activity because they inhibit reuptake of serotonin and norepinephrine in descending inhibitory pain pathway. They are used mainly for management of chronic pain. But because of pain relieving properties in animal studies, trails regarding use of them in post-operative cases are going on to relieve acute pain. They may helpful for decreasing acute pain but further animal studies and clinical trials are necessary.

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