ORIGINAL ARTICLE

Comparison of Antinociceptive activity of Fluoxetine with Morphine in Albino Rats

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Abstract

***Background**: Pain is a complex unpleasant sensation which has both sensory and emotional components. Finding newer and more potent antinociceptive agents is an important area of research in pharmacology. We in the present study tried to compare antinoceptive activity of Fluoxetine and Morphine in albino rats. **Methods**: Model for pain was radiant heat induced pain using analgesiometer in Wister albino rats. They were* divided into 5 groups of 6 animals each. *Each animal was used only once in the experiment. Fluoxetine hydrochloride pure powder and Morphine sulphate were used during the study. **Results**: Fluoxetine (5mg / kg i.p.) produced significant antinociceptive action by enhancing the tail-flick latency period (7.33±1.37, 7.65±1.03, 7.50±0.84 sec.) at 15 min, 30 min, 60 min respectively in comparison to 0 minute (4.17±0.75). Fluoxetine (10mg / kg i.p.) also produced significant antinociceptive action by enhancing the tail-flick latency period (7.33±2.34, 9.17±1.33, 9.6±0.53 sec.) at 15 min, 30 min, 60 min respectively in comparison to 0 minute (4.67±0.52). The standard drug Morphine (1 mg / kg, i.p.) produced significant increase in the tail- flick latency period (7.50±0.55, 10.00±0.00, 10.00±0.00 sec.) at 15 min, 30 min, 60 min respectively in comparison to 0 minute (4.67±0.55). Morphine (1 mg/kg i.p.) produced significantly more antinociception than Fluoxetine (5 mg/kg & 10 mg/kg i.p.). **Conclusion**: Fluoxetine has antinociceptive effect but Morphine (1 mg/kg i.p.) has better antinociception than Fluoxetine (5 mg/kg & 10 mg/kg i.p.), suggesting that Fluoxetine is less potent antinociceptive drug than Morphine.*

***Key words:** Antinociception, Fluoxetine, Morphine*

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Introduction

Taxonomy committee of International Association for the study of pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. Principal objective of treatment of pain is to remove or abolish the cause of pain. But it is not always possible to do so. Hence, analgesics are used for the symptomatic treatment of pain. Finding newer and more potent antinociceptive agents is an important area of research in pharmacology. We in the present study tried to compare antinoceptive activity of Fluoxetine and Morphine in albino rats.

Opioids are the most potent and commonly used group of analgesic drugs used for visceral pain, e.g. Morphine and Pethidine. But their analgesic action is associated with a greater degree of dose dependent adverse drug reactions including drug dependence. Morphine produces major effects on central nervous system, GIT through μ-receptor. [2]

Morphine selectively inhibits pain sensation without affecting other sensory modalities. Chronic dull aching pain is relieved better than acute sharp pain. Morphine produces analgesia by binding to opioid receptors, present on the terminals of the primary afferent nociceptive nerves, dorsal horn of spinal cord and in the periaqueductal gray matter of midbrain and

nucleus raphe magnus of medulla (μ & δ receptors). [3-4]

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) belonging to antidepressants. Selectively inhibit reuptake of serotonin and thereby increase synaptic serotonin levels, also cause increased 5HT receptor activation and enhanced postsynaptic responses. At high doses, also bind Norepinephrine (NE) transporters [5]. The mechanism may be involved in the antinociceptive effect of antidepressants [6]. In the present study an attempt has been made to assess the antinociceptive activity of Fluoxetine and compared with Morphine.

Materials and Methods

Study was conducted in the Department of Pharmacology, Kamineni Institute of Medical Sciences, Telangana State. It was placebo controlled randomised comparative study with prior permission from institutional animal ethics committee and was executed according to the guidelines of the committee for the purpose of control and supervision of the experiments on animals (CPCSEA), India. Wistar Albino rats (150-200grms) of either sex were selected randomly which shows reaction time of <6sec, bred in the Central Animal House National Institute of Nutrition, Hyderabad were used. They were divided into 5 groups of 6 animals each (Morphine 1mg, Fluoxetine 2mg, 5mg and 10mg and controlled group). Model of pain was radient heat induced pain by analgesiometer (Tail flick method).[7] Fluoxetine hydrochloride pure powder and Morphine sulphate were used as drugs. Normal was saline used as placebo.

Appropriate dosage of drugs according to weight were given and Tail Flick Latency (TFL) was tested at 15, 30, 60 min. The basal reaction time was taken immediately after giving the drug at zero minute by keeping the tail on nichrome wire. The time taken for the withdrawal of the tail was considered as tail flick latency. Antinociceptive activity was measured at 0, 15, 30, 60 min. The antinociceptive activity was considered as positive if rat fails to withdraw the tail within 10 seconds of exposure to avoid damage to tail (Figure- 1).

Figure- 1: Tail-flick method

Results

There was no analgesic effect seen with normal saline at the 0 minutes and after 15, 30 and 60 minutes. In morphine group reaction to radiant heat was positive at basal time but reaction was sluggish after 15 minutes. After 30 and 60 minutes time interval, tail flick was not observed (Table- 1).

Table- 1: Tail flick latency (TFL) test- Placebo group and Morphine (1mg/kg) group

SL. No	Placebo Group (TFL in Seconds)				Morphine Group (TFL in Seconds)			
	Basal	**15min**	**30min**	**60 min**	**Basal**	**15min**	**30min**	**60 min**
1	5	4	4	4	5	8	10	10
2	5	5	5	5	5	8	10	10
3	4	4	4	4	4	7	10	10
4	4	4	4	4	5	8	10	10
5	5	5	5	5	5	7	10	10
6	4	4	4	4	4	7	10	10

There was no analgesic effect seen with Fluoxetine 2mg/kg at basal level and after 15, 30 and 60 minutes. The analgesic effect was shown to increase from 15 to 30 minutes and maximum effect was seen at 30 min when 5gm/kg dose was given. With 10mg/kg dose, analgesic effect was observed at 15 min. Maximum effect was observed at 30 minutes and 60 minutes respectively (Table-2).

Table 2: Tail flick latency test - Fluoxetine (2mg/kg, 5mg/kg, 10mg/kg)

Sr. No	Fluoxetine- 2mg/kg (TFL in Seconds)				Fluoxetine- 5mg/kg (TFL in Seconds)				Fluoxetine- 10mg/kg (TFL in Seconds)			
	0min	**15min**	**30min**	**60min**	**0min**	**15min**	**30min**	**60min**	**0min**	**15min**	**30min**	**60min**
1	5	5	5	5	4	6	9	9	5	10	10	10
2	5	5	5	5	5	6	7	7	4	6	10	10
3	5	4	5	6	5	9	8	9	5	7	10	10
4	4	5	4	4	3	9	6	9	5	7	7	9
5	4	5	4	4	4	8	7	8	5	10	10	10
6	5	5	5	5	4	8	7	9	4	7	8	9

Table- 3: Inter-group comparison of TFL

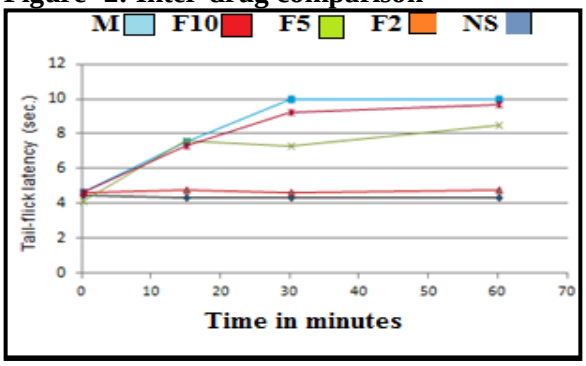
Groups	0 minute	15 minute	30 minute	60 minute
NS vs M	0.16^{ns}	3.16**	4.16*	5.66**
NS vs F2	0.16^{ns}	0.50^{ns}	0.33^{ns}	0.50^{ns}
NS vs F5	0.33^{ns}	3.33**	3.00*	4.16**
NS vs F10	0.16^{ns}	3.00**	4.83**	5.33**
M vs F2	0.00^{ns}	2.60**	3.83**	5.16**
M vs F5	0.50^{ns}	0.16^{ns}	1.16^{ns}	1.50**
M vs F10	0.00^{ns}	0.16^{ns}	0.66^{ns}	0.33^{ns}
F2 vs F5	0.50^{ns}	2.83**	2.66**	3.66**
F2 vs F10	0.00^{ns}	2.50**	4.50**	4.83**
F5 vs F10	0.50^{ns}	0.33^{ns}	1.83^{ns}	1.16*

ns – not significant, * P < 0.05, ** P < 0.001, NS- Normal saline, M– Morphine, F2– Fluoxetine 2mg/kg, F5– Fluoxetine 2mg/kg, F10– Fluoxetine 10mg/kg

Fluoxetine (5mg/kg i.p.) produced significant antinociceptive action by enhancing the tail-flick latency period (7.33±1.37, 7.65±1.03, 7.50±0.84 sec.) at 15 min, 30 min, 60 minutes respectively in comparison to 0 minute (4.17±0.75). Fluoxetine (10mg/kg i.p.) also produced significant antinociceptive action by enhancing the tail-flick latency period (7.33±2.34, 9.17±1.33, 9.6±0.53 sec.) at 15 min, 30 min, and 60 min respectively in comparison to 0 minute (4.67±0.52). The standard drug Morphine (1mg/kg, i.p.) produced significant increase in the tail-flick latency period (7.50±0.55, 10.00±0.00, 10.00±0.00 sec.) at 15 min, 30 min, and 60 min respectively in comparison to 0 minute (4.67±0.55). Figure- 2 indicates TFL.

One Way Anova was used followed by post hoc Fischer's Least Significant Difference (LSD) test for inter-drug comparison at Zero minutes, 15 minutes, 30 minutes and 60 minutes. At 0 minutes, all values calculated were insignificant where as at 15 minutes interval values of NS versus Morphine, NS vs F5, F10, were significant and M vs F2 was also significant. M vs F5 and M vs F10 were not significant at that time. The comparison of F2 vs F5 and F2 vs F10 was significant where as F5 vs F10 was not significant at 15 minute intervals. At thirty minute intervals NS vs M, NS vs F5, NS vs F10, M vs F2, M vs F5, F2 vs F5, F2 vs F10 and F5 vs F10 were significant. At 60 minutes interval only NS vs F2 and M vs F10 were not significant where as all other values were significant (Table- 3).

Figure- 2: Inter-drug comparison



NS- Normal saline, M– Morphine, F2– Fluoxetine 2mg/kg, F5– Fluoxetine 2mg/kg, F10– Fluoxetine 10mg/kg

Discussion

Monoamines, including serotonin, norepinephrine, and dopamine, acts via different receptors subtypes to exert a complex modulation of neurotransmitter release from nociceptive afferents and excitability of dorsal horn neurons. These monoaminergic systems have an important role in mechanisms of inflammatory and neuropathic pain [8-9] and are a target for pharmacologic management of these conditions. Recently, numerous open and controlled studies have shown that antidepressant drugs also have analgesic activity and particularly, selective serotonin reuptake inhibitors (SSRI) like Fluoxetine are effective in mixed, chronic pain [10]. It has also been shown that some antidepressants are superior to placebo in about 75% of studies [11]. A wide range of pain conditions are responsive to antidepressants, particularly diabetic neuropathy pain and probably rheumatoid arthritis [12] and migraine [13], fibromyalgia [10].

SSRIs inhibit the reuptake of the serotonin (5-HT), increase the level of 5-HT in the neuronal synapse, and facilitate serotonergic activity. This mechanism may be involved in the antinociceptive effect of antidepressants [14]. As the analgesic activity of morphine is mediated through mue (μ) receptors, it is likely that fluoxetine act through opioid pathways involving the μ opioid receptors. However, it may interact with other receptor systems also, such as, cholinergic, muscarinic, histaminergic, noradrenergic, and even the GABAergic system [14]. Hence, it would not be unreasonable to suggest that antidepressant drugs would involve at least some of these systems for their analgesic effect.

Fluoxetine showed antinociceptive activity at 5 and 10 mg/kg. These findings are in conjunction with the finding of Max *et al.*, [15] who in a double blind cross-over study, observed similar results. Goldenberg *et al.*,[16] compared placebo with fluoxetine in fibromyalgia patients and found a significant pain-reliving activity in fluoxetine. Similarly, Rani *et al.*,[17] compared fluoxetine with amitriptyline and placebo in patients with chronic rheumatic pain and found significant reduction in pain intensity scores and pain relief scores. They suggested fluoxetine to be an effective analgesic with fewer side effects. Singh *et al.*, [8] also reported antinociceptive effect of fluoxetine in albino mice like our present study in the tail-flick latency test model. Morphine (1 mg/kg i.p.) produced significantly more antinociception than Fluoxetine (5 mg/kg & 10 mg/kg i.p.) suggesting that Fluoxetine is less potent antinociceptive drug than the standard drug Morphine in the tail-flick latency model.

Conclusion

The present study shows that Fluoxetine has antinociceptive effect in experimental animal models of pain by tail-flick latency test in albino rats. Morphine (1 mg/kg i.p.) produced significantly more antinociception than Fluoxetine (5 mg/kg & 10 mg/kg i.p.), suggesting that fluoxetine is less potent antinociceptive drug than the standard drug Morphine in the tail-flick latency model.

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