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A comparative experimental study of antinociceptive activity of fluoxetine with pentazocine in rodent models

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Abstract
Introduction: Chronic pain affects millions of people, commonly coexisting with depression and anxiety. Antidepressants like fluoxetine have been shown to have analgesic activity with favourable safety profile and hence might be better suited in the management of chronic pain.
Objectives: To evaluate the analgesic activity of fluoxetine and to compare the analgesic effect of fluoxetine with pentazocine.
Materials and Methods: Adult albino rats weighing 150-200 grams were used in this study. Screening method used was Eddy's hot plate method in rats. Rats were divided into three groups of 5 animals and drugs administered as follows:
Group-1: Distilled water (control)
Group-2: Fluoxetine
Group-3: Pentazocine
All drugs were administered 30 minutes before the onset of pain stimulus.
Statistical analysis was done by using one way-Analysis of variance (one way ANOVA) followed by Tukey-Kramer test.
Results: Fluoxetine showed significant analgesic activity in hotplate method, but it was less significant than that of pentazocine.

Keywords: Analgesic effect, Fluoxetine, Hot plate method.

1. Introduction
Pain is a subjective experience hard to define exactly, even though we all know what we mean by it. Pain occurs whenever any tissues are being damaged, and it causes the individual to react to remove the pain stimulus. It is the most common symptom that brings a patient to a physician's attention.
Pain has been classified into two major types: fast pain and slow pain. Fast pain is also described by many alternative names such as sharp pain and acute pain. Slow pain is usually associated with tissue destruction. It can lead to prolonged, unbearable suffering. Chronic pain afflicts millions of people and commonly associated with depression and anxiety [1]. Currently the most commonly prescribed drugs for management of pain are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like Diclofenac and Opioid analgesics [2].
Some of such conditions causing chronic pain include osteoarthritis, fibromyalgia and diabetic neuropathy because depression is the most common emotional disturbance in patients with chronic pain [3], patients should be questioned about their mood, appetite, sleep patterns, and daily activity.
There are various groups of drugs available for management of pain. These include mainly NSAIDs and opioid analgesics. Other adjuvant group of drugs for pain management are antidepressants, anticonvulsants and antiarrythmics.
Opioids are the most potent pain-relieving drugs currently available. Furthermore, of all analgesics, they have the broadest range of efficacy, providing the most reliable and effective method for rapid pain relief. But their use is limited by dose dependent side-effects like sedation, respiratory depression, pruritis, constipation and dependence liability (risk of addiction on long term use).
Adjuvant analgesics like antidepressants have been useful in specific painful conditions. The selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have fewer and less serious side effects than TCAs, but they are much less effective in relieving pain [4].

The previous studies conducted both on animals and humans to evaluate antinociceptive activity have conflicting results. Hence this present study was carried out with a view to elucidate analgesic activity of fluoxetine, an SSRI and to compare its activity with standard analgesic drug pentazocine.

Objectives

1. To evaluate analgesic activity of fluoxetine
2. To compare analgesic effect of fluoxetine with pentazocine.

2. Materials and Methods

2.1 Materials: Adult albino rats (weighing: 150-200 gms), Eddy's hot plate and Tuberculin syringe (for injection of drugs)

2.2 Drugs: Fluoxetine was obtained from Cipla, Mumbai and Pentazocine was obtained from Ranbaxy, Mumbai.

2.3 Methodology: The study was carried out at the Department of Pharmacology, M.R. Medical College, Gulbarga on adult albino rats from central animal house of M. R. Medical College after obtaining institution ethics committee approval to undertake this study.
Adult albino rats of either sex weighing about 150-200 grams were used for the study, maintained at a temperature of 25±1 °C in a well-ventilated animal house and standard laboratory conditions of food and water before start of the experiment.
All drugs were administered 30 minutes before the onset of pain stimulus.

2.4 Grouping of Animals: Analgesic activity was studied using rats in hotplate method[5] observing the latency of paw licking or jumping. Rats were divided into three groups of 5 animals each (n=5) as follows:

Group 1: was given distilled water (control).
Group 2: was given Fluoxetine (10 mg/kg i.p.)
Group 3: was given Pentazocine (10 mg/kg i.p.)

2.5 Care of the Animals: Handling and care of animals was according to Committee for the purpose of Control & Supervision of Experimental Animals CPCSEA guidelines. Care during the animal study included food, water, shelter etc.

2.6 Statistical Methods: The values obtained are expressed as mean±SEM. Statistical analysis of differences between groups was carried out using one-way analysis of variance (ANOVA) followed by Tukey-Kramer test.
Probability (P) value of <0.05 was taken as the level of statistical significance.

3. Results

Table 1: Group-1 – Control (treated with Distilled water) Latency of response (Paw licking or jumping) in seconds) in Hotplate Method

Rat No.	Reaction time (sec)		
	Basal	After 15 min	After 30 min
1.	4	5	6
2.	4	6	4
3	4	3	3
4	5	4	5
5	5	4	4

Table 2: Group-2 (treated with Fluoxetine) Latency of response (Paw licking or jumping) in seconds) in Hotplate Method

Rat No.	Reaction time (sec)		
	Basal	After 15 min	After 30 min
1.	4	7	15
2.	5	10	13
3	3	11	15
4	4	9	10
5	6	15	13

Table 3: Summary Data of Group-2 (treated with Fluoxetine)

Group	No. of Animals	Mean	SD	SEM
A-Basal reaction time	05	4.400	1.140	0.5099
B-After 15 min	05	10.40	2.966	1.3270
C-After 30 min	05	13.20	2.049	0.9165

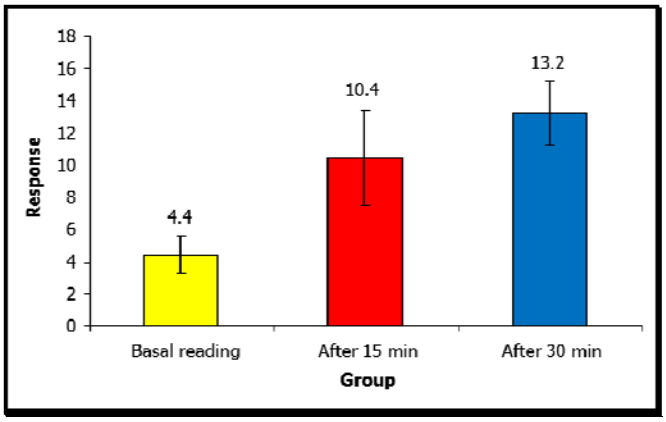

Fig 1: Comparison of Response (Mean±SEM) in Group-2

Table 4: Group-3 treated with Pentazocine Latency of response (Paw licking or jumping) in seconds) in Hotplate Method

Rat No.	Reaction time (sec)		
	Basal	After 15 min	After 30 min
1.	4	7	15
2.	5	10	13
3	3	11	15
4	4	9	10
5	6	15	13

Table 5: Summary Data of Group-3 (treated with Pentazocine)

Group	No. of Animals	Mean	SD	SEM
A-Basal reaction time	05	4.400	1.140	0.5099
B-After 15 min	05	10.40	2.966	1.3270
C-After 30 min	05	13.20	2.049	0.9165

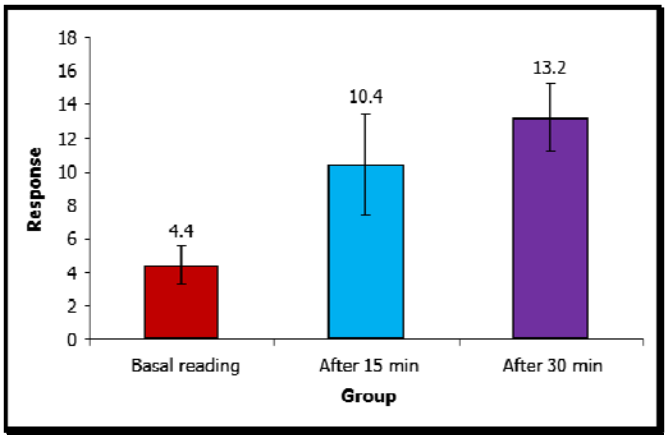

Fig 2: Comparison of Response (Mean±SEM) in Group-3

3.1 Anova Results for Hotplate Method

Tukey-Kramer multiple comparisons test: If the value of q is greater than 3.773, then the p value is less than 0.05.

Table 6: Anova Results for Fluoxetine

Comparison	q-value	p-value
Basal Vs 15 min	6.145	<0.01
Basal Vs 30 min	9.013	<0.001
15 vs 30 min	2.868	>0.05

Fluoxetine shows significant analgesic activity at both 15 and 30 minutes interval with p-values of <0.01 and <0.001 respectively, but no difference was found in activity at intervals of 15 and 30 mins.

Table 7: Anova Results for Pentazocine

Comparison	q-value	p-value
Basal Vs 15 min	6.145	<0.01
Basal Vs 30 min	9.013	<0.001
15 vs 30 min	2.868	>0.05

Pentazocine shows significant analgesic activity at both 15 and 30 minutes interval with a p-value of <0.01 and <0.001 respectively. Pentazocine does not show significant difference in activity at 15 and 30 minutes interval.

4. Discussion

The study was conducted using three groups of albino rats. 1st group acted as control not receiving any drug except distilled water. Drugs, fluoxetine and pentazocine were administered to the remaining groups of animals as per protocol. Effect of fluoxetine on nociception was studied and was compared with standard analgesic drug pentazocine.

Analgesic activity of fluoxetine has been extensively studied in animal nociceptive models with conflicting results. Hence, the current study was undertaken to evaluate the antinociceptive activity of fluoxetine using Eddy's hot plate method in rats.

The present study showed that fluoxetine demonstrates significant analgesic activity (p-value <0.01 at 15 min interval and < 0.001 at 30 min interval) in Eddy's hot plate method.

Hotplate analgesic method evaluates only centrally acting analgesics like opioids (e.g., Morphine). Significant activity of fluoxetine in hotplate method points towards central action of fluoxetine.

Studies conducted by P.N. Kurlekar and J.D. Bhatt [6] (2004), Schreiber S and Pick CG [7] (2006) and Nayebi A.M. *et al.* [8] (2009), Ada Raphaeli *et al.* [9] (2009) found analgesic activity of fluoxetine to be significant in various analgesic activity screening models. Whereas D.Margalit and M. Segal [10] (1979), Mitchell B. Max *et al.* [11] (1992) and J. Sawynok *et al.* [12] (1999) using various analgesic screening models using rodent animals found fluoxetine to be lacking significant analgesic activity.

The possible mechanisms of action for analgesia proposed are [13]:

1) Inhibition of GIRK channels
2) Inhibition of serotonin (5-hydroxytryptamine; 5-HT) transporters
3) Inhibition of the functions of 5-HT2C and 5-HT3 receptors
4) Inhibition of nicotinic acetylcholine (Ach) receptors
5) Inhibition of voltage-gated Ca^{2+}, Na^{+} and K^{+} channels and Cl^{-} channels
6) Agonistic action at μ-opioid receptors [14].

5. Conclusion

Fluoxetine is an SSRI and one of the most commonly prescribed drug for depression. It is proven to act at multiple sites like serotonin transporter and opioid μ receptor, both of which may play a role in its analgesic activity.

Because depression is the most common emotional disturbance in patients with chronic pain, an antidepressant with analgesic activity comparable to TCAs and at the same time with better adverse effect profile will be a welcome discovery.

From the present study it is apparent that fluoxetine has significant activity in central analgesic activity model i.e., hotplate method. If proved to be effective from further studies as an effective analgesic, it may be beneficial in patients with chronic pain and associated depression.

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