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Research Article

A comparative study of antinociceptive effect of fluoxetine with pentazocine in rodent model

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ABSTRACT

Background: Chronic pain affects millions of people across the globe, commonly coexisting with depression. Antidepressants like fluoxetine have shown potential to have analgesic activity with superior safety profile and hence might be better suited in the treatment of chronic pain. The objective of this study was to evaluate the antinociceptive activity of fluoxetine and to compare the antinociceptive effect of fluoxetine with pentazocine.
Methods: Adult albino rats weighing 150-200 grams were used in this study. Screening method used was Acetic acid induced writhing 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 failed to show significant antinociceptive activity in Acetic acid induced writhing method.
Conclusions: 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.

Keywords: Analgesic effect, Fluoxetine, Acetic acid induced writhing method

INTRODUCTION

Pain is a subjective sensation hard to define exactly, even though we all know what we mean by it. Pain occurs whenever any tissues are being injured, and it causes the individual to react to remove the pain stimulus. It is the most common symptom that brings a patient to a doctors's attention.

Pain has been classified into two major types' fast pain and slow pain. Fast pain is also described by alternative names viz. sharp pain and acute pain. Slow pain is usually associated with tissue destruction. It can lead to prolonged, unbearable suffering. Chronic pain affects millions of people and commonly associated with depression.[1] Currently the most commonly prescribed group of drugs for treatment of pain are non-steroidal anti-inflammatory drugs (NSAIDs) like Diclofenac and opioid analgesics.[2]

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, pruritus, constipation and dependence liability (risk of addiction on long term use).

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, patients should be questioned about their mood, appetite, sleep patterns, and daily activity.[3]

There are various other groups of drugs available for management of pain. These include antidepressants, anticonvulsants and antiarrhythmic.

Adjuvant analgesics like antidepressants have been made use in specific painful conditions like neuropathic pain due to diabetes mellitus. 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.

The objective of this study was to evaluate the antinociceptive activity of fluoxetine and to compare the antinociceptive effect of fluoxetine with pentazocine.

METHODS

Adult albino rats (weighing: 150-200 gms), Acetic acid and Tuberculin syringe (for injection of drugs)

Drugs

Fluoxetine was obtained from Cipla, Mumbai and Pentazocine was obtained from Ranbaxy, Mumbai.

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.

Grouping of animals

Analgesic activity was studied using rats in acetic acid induced writhing method observing the number of writhes. 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.)

Care of the animals

Handling and care of animals was according to committee for the purpose of control and supervision of experimental animals CPCSEA guidelines. Care during the animal study included food, water, shelter etc.

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.

RESULTS

Table 1: Number of writhes in group-1 (control, treated with distilled water).

Mice No.	Body weight (grams)	Treatment	No. of writhers
1	26	Distilled water	38
2	30	Distilled water	44
3	25	Distilled water	38
4	30	Distilled water	40
5	28	Distilled water	36

Table 2: Number of writhes in group-2 (treated with fluoxetine).

Mice No.	Body weight (grams)	Treatment	No. of writhers
1	25	Fluoxetine	36
2	25	Fluoxetine	38
3	30	Fluoxetine	33
4	28	Fluoxetine	40
5	28	Fluoxetine	38

Table 3: Number of writhes in group-3 (treated with pentazocine).

Mice No.	Body weight (grams)	Treatment	No. of writhers
1	20	Pentazocine	28
2	20	Pentazocine	26
3	22	Pentazocine	28
4	20	Pentazocine	24
5	20	Pentazocine	28

Table 4: Summary data for acetic acid induced writhing method.

Group	No. of animals	Mean	SD	SEM
A-control (distilled water)	05	39.20	3.033	1.356
B-Fluoxetine	05	37.00	2.646	1.183
C-Pentazocine	05	26.80	1.789	0.800

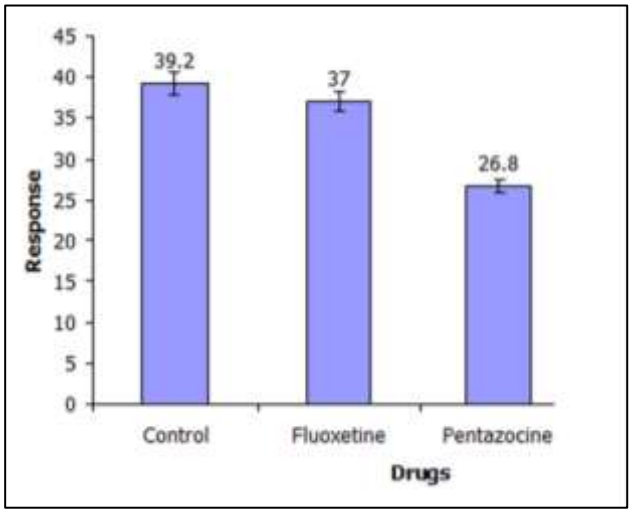

Figure 1: Comparison of response (Mean±SEM writhes).

ANOVA results for writhing method

Tukey-Kramer multiple comparisons test: if the value of q is greater than 4.046, then the p value is less than 0.05.

Table 5: ANOVA results for fluoxetine.

Comparison	q-value	p-value
Control versus Fluoxetine	1.984	>0.05
Control versus Pentazocine	11.181	<0.001

DISCUSSION

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

Antinociceptive activity of fluoxetine has been extensively studied in animal nociceptive models with varying results. Hence, the current study was undertaken to study the antinociceptive activity of fluoxetine using Acetic acid induced writhing method in rats.

The present study showed that fluoxetine failed to demonstrate significant analgesic activity (p-value >0.05) in acetic acid induced writhing method.

Acetic acid induced writhing method evaluates only peripherally acting analgesics like NSAIDs. Failed activity of fluoxetine in acetic acid induced writhing method goes to establish that fluoxetine lacks peripheral analgesic action.

Studies conducted by Kurlekar PN and Bhatt JD, Schreiber S and Pick CG and Nayebi AM et al, Ada Raphaeli et al found analgesic activity of fluoxetine to be significant in various analgesic activity screening models. Whereas Margalit D and Segal M, Max MB et al and Sawynok J et al using various analgesic screening models using rodent animals found fluoxetine to be lacking significant analgesic activity.[6-12]

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

- Inhibition of GIRK channels
- Inhibition of serotonin (5-hydroxytryptamine; 5-HT) transporters
- Inhibition of the functions of 5-HT2C and 5-HT3 receptors
- Inhibition of nicotinic acetylcholine (Ach) receptors
- Inhibition of voltage-gated Ca2+, Na+ and K+ channels and Cl- channels
- Agonistic action at μ-opioid receptors.[14]

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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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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