A COMPARATIVE STUDY OF ANALGESIC ACTIVITY OF FLUOXETINE WITH IBUPROFEN AND PENTAZOCINE IN RODENT MODELS

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ABSTRACT: CONTEXT: Pain is an unpleasant sensation localized to a part of body. It is a subjective experience, hard to define quantitatively. Chronic pain is an affliction of millions of patients and is associated with comorbidities such as depression and anxiety. Current standard of care for pain management includes Non-steroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen and Opioid analgesics such as Pentazocine. NSAIDs are effective analgesics and are very frequently used as over-the-counter (OTC) medication. Opioids are the most potent analgesics and provide a rapid and sustained pain relief. Adjuvant analgesics include anti-depressants, anti-convulsants etc. Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) used mainly as an anti-depressant. Previous studies on the efficacy of Fluoxetine for pain management have imparted us with conflicting data. Hence this present study was carried out with a view to elucidate its analgesic action and to compare it with standard drugs like Ibuprofen and Pentazocine. **AIMS:** The present study was conducted with the following objectives in mind: 1) To evaluate analgesic activity of Fluoxetine. 2) To compare analgesic activity of Fluoxetine with Ibuprofen and Pentazocine. **METHODS AND MATERIALS:** Materials: Adult albino rats, Eddy's Hot-plate, Tuberculin syringe. **Drugs:** Ibuprofen, Pentazocine and Fluoxetine. The study was carried out from 1st to 9th August, 2011 at the Department of Pharmacology, MR Medical College, Gulbarga. **RESULTS AND CONCLUSION:** Though Fluoxetine has significant analgesic properties as demonstrated by our study, but when compared with standard analgesics like Ibuprofen and Pentazocine, it is found lacking. From the present study it is apparent that Fluoxetine has significantly high activity in central-analgesic model i.e. Hot-plate method.
KEY WORDS: Fluoxetine, Pentazocine, Ibuprofen, Rodent Model, Hot-plate Method.

INTRODUCTION: Pain is an unpleasant sensation localised to a part of body. It is a subjective experience, hard to define quantitatively. It is also a protective mechanism by which the subject is made aware of tissue damage so that the subject can withdraw itself from the stimulus.

Pain has been classified into 2 major types: fast pain and slow pain[1]. Fast pain is felt within 0.1sec after a painful stimulus is applied, whereas slow pain is felt after 1sec. The conduction pathways of these 2 are different from each other and is represented by their specific qualities.

Fast pain is also known as sharp pain, pricking pain, acute pain or electric pain. It is felt when a needle is stuck into the skin or during severe burns etc. Fast pain is not felt by most of the deeper tissues of the body.

Slow pain goes by a wide array of names like burning pain, aching pain, nauseous pain or chronic pain. It is usually associated with tissue destruction. It can occur in both superficial as well as deep tissues.

Chronic pain is an affliction of millions of patients and is associated with comorbidities such as depression[2] and anxiety[3]. Current standard of care for pain management includes Non-steroidal anti-inflammatory drugs[4] (NSAIDs) like Ibuprofen and Opioid analgesics[5] such as Pentazocine.

Chronic pain is associated with diseases like Osteoarthritis[6], Malignancy[7], Migraine[8], Fibromyalgia[9] and Diabetic Neuropathy[10]. The management of patients with chronic pain is an intellectually and emotionally challenging task. The patients' problem is often difficult to diagnose, such patients are taxing on the clinician's time and often appear emotionally distraught. The traditional medical approach of seeking an obscure organic pathology is often unhelpful. On the other hand, psychological evaluation and behaviour-based treatment paradigms are frequently helpful, particularly in the setting of a multi-disciplinary pain management centre.

NSAIDs are effective analgesics and are very frequently used as over-the-counter (OTC) medication. Opioids are the most potent analgesics and provide a rapid and sustained pain relief. Adjuvant analgesics include anti-depressants[11], anti-convulsants[12] etc.

Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) used mainly as an anti-depressant[13]. Previous studies on the efficacy of Fluoxetine for pain management provide us with conflicting data. Hence this present study was carried out with a view to elucidate its analgesic action and to compare it with standard drugs like Ibuprofen and Pentazocine.

OBJECTIVES: The present study was conducted with the following objectives in mind:

1. To evaluate analgesic activity of Fluoxetine.
2. To compare analgesic activity of Fluoxetine with Ibuprofen and Pentazocine

MATERIALS AND METHODS:

Materials:

- Adult albino rats (150-200gms), 20 animals in total
- Eddy's Hot Plate
- Tuberculin syringe
- Drugs: Ibuprofen and Fluoxetine were gift samples from Cipla Pharmaceuticals, Mumbai; Pentazocine was gift sample from Ranbaxy Pharmaceuticals, Mumbai.

Methodology:

The study was carried out in 1st to 9th August, 2011 at the Department of Pharmacology, MR Medical College, Gulbarga; after obtaining Institutional Ethics Committee approval to undertake the same.

Adult albino rats of either sex weighing 150-200gms were utilised in the study. The animals were maintained at a room temperature of 25±1^{0}C in a well-ventilated animal house and standard laboratory conditions of food and water according to CPCSEA Guidelines[14].

Drugs were administered 30 mins before the onset of pain stimulus in both the experimental models. Analgesic activity was studied using rats in Hotplate[15].The rats were divided into 4 groups of 5 animals each.

- For Hot-plate method (using rats)
  - Group1- was given distilled water (control)
  - Group 2- was given Fluoxetine (10mg/kg i.p)

- Group 3- was given Ibuprofen (10mg/kg i.p)
- Group 4- was given Pentazocine (10mg/kg i.p)

Statistical Analysis: The values obtained were expressed as Mean ± SEM. Statistical analysis of differences between groups was carried out using ANOVA followed by Tukey-Kramer test[16]. P value of <0.05 was taken as the level of statistical significance.

Results: Fluoxetine shows significant analgesic activity in Hot-plate method, but comparatively less significant than Ibuprofen and Pentazocine.

Table-1: Response (paw-licking or jumping) Latency (in seconds) in Hot-plate method for group-1 (control- treated with distilled water)

Rat No.	Response 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: Response (paw-licking or jumping) Latency (in seconds) in Hot-plate method for group- 2 (treated with Fluoxetine)

Rat No.	Response 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	5	4.400	1.140	0.5099
B- After 15 min	5	10.40	2.966	1.3270
C- After 30 min	5	13.20	2.049	0.9165

Figure -1: Comparison of Response (Mean) in group-2

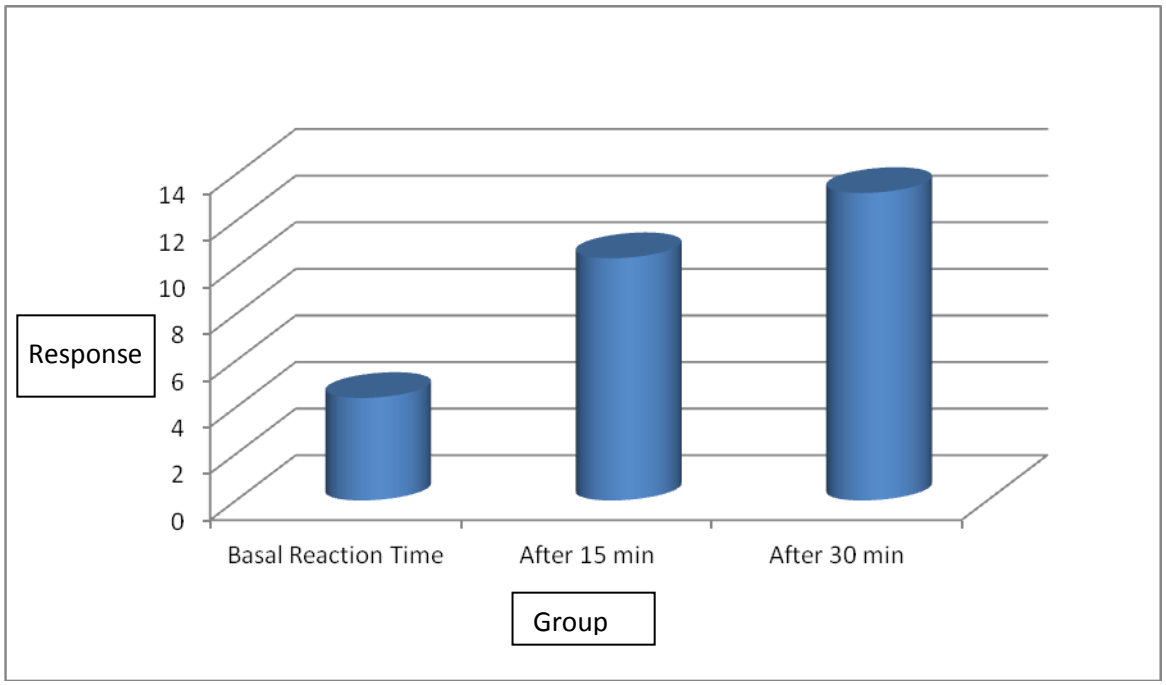


Table-4: Response (paw-licking or jumping) Latency (in seconds) in Hot-plate method for group-3 (treated with Ibuprofen)

Rat No.	Response Time (sec)		
	Basal	After 15 min	After 30 min
1	5	8	10
2	5	8	12
3	4	9	15
4	4	10	15
5	4	10	11

Table-5: Summary data of group-3 (treated with Ibuprofen)

Group	No. of animals	Mean	SD	SEM
A-Basal reaction time	5	4.400	0.5477	0.4449
B- After 15 min	5	9.00	1.00	0.4472
C- After 30 min	5	12.60	2.302	1.030

Figure -2: Comparison of Response (Mean) in group-3

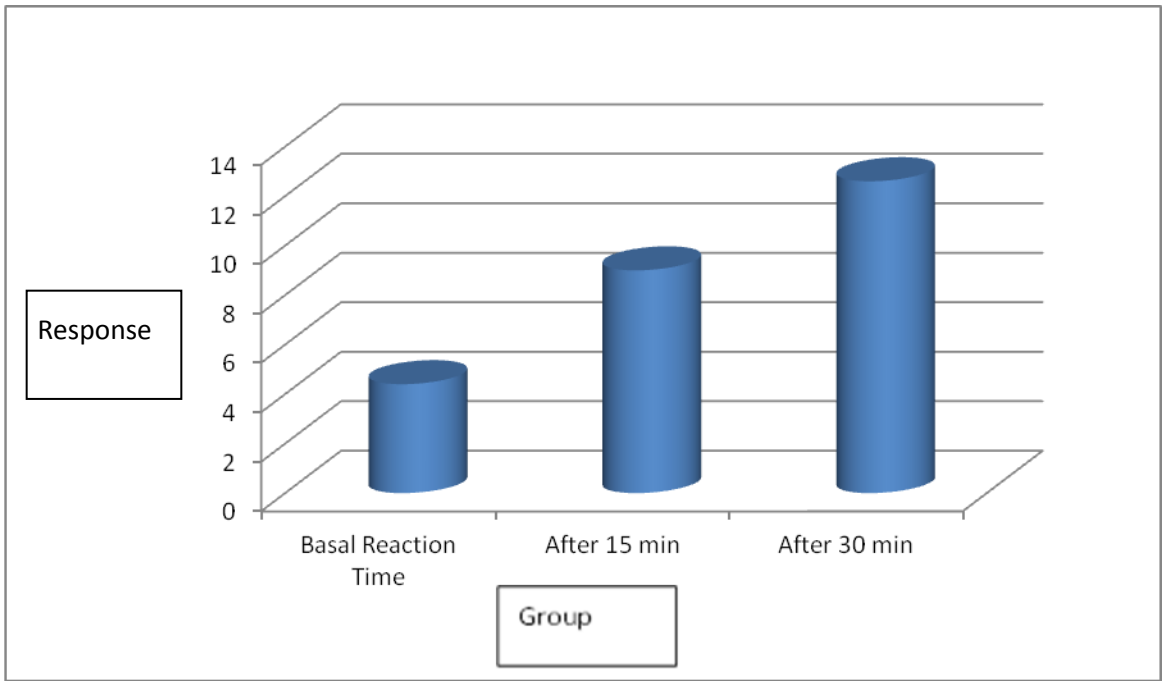


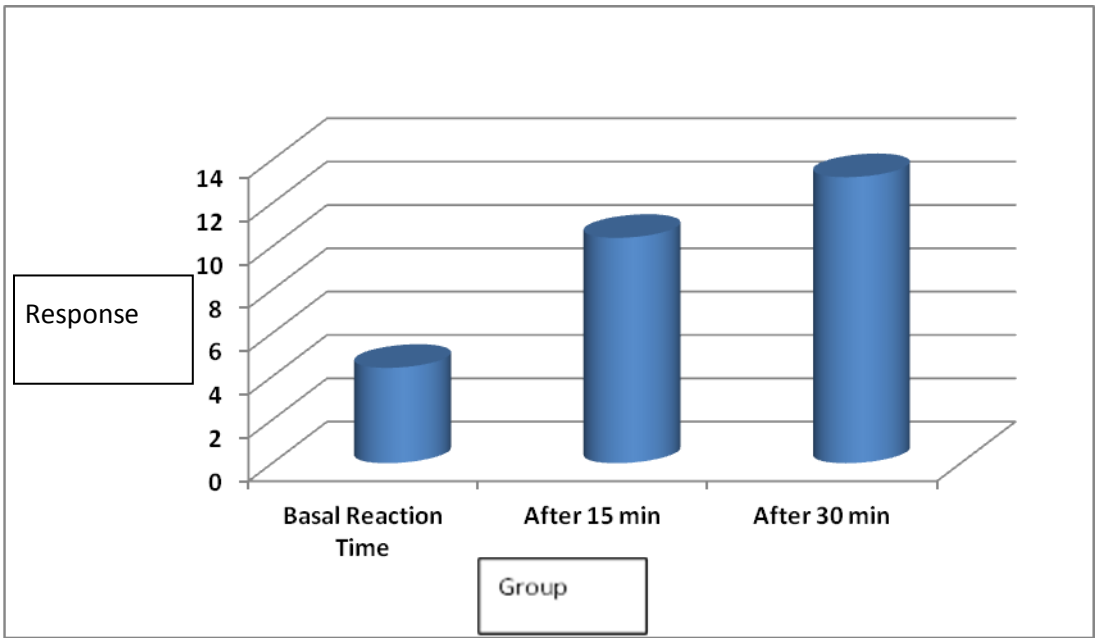
Table-6: Response (paw-licking or jumping) Latency (in seconds) in Hot-plate method for group-4 (treated with Pentazocine)

Rat No.	Response 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-7: Summary data of group-4 (treated with Pentazocine)

Group	No. of animals	Mean	SD	SEM
A-Basal reaction time	5	4.400	1.140	0.5099
B- After 15 min	5	10.40	2.966	1.3270
C- After 30 min	5	13.20	2.049	0.9165

Figure -3: Comparison of Response (Mean) in group-4



ANOVA Results for Hot-plate method:

Tukey-Kramer multiple comparison test – If the value of 'q' is greater than 3.773, then 'p' value is less than 0.05

Table-8: ANOVA results for Fluoxetine

Comparison	'q'	'p'
Basal vs 15 min	6.145	< 0.01
Basal vs 30 min	9.013	< 0.001
15 min 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, however this activity at 15 and 30 minutes was nearly similar.

Table-9: ANOVA results for Ibuprofen

Comparison	'q'	'p'
Basal vs 15 min	6.935	< 0.001
Basal vs 30 min	12.362	< 0.001
15 min vs 30 min	5.427	< 0.01

Ibuprofen shows highly significant analgesic activity at both 15 and 30 minutes interval with a p value of < 0.001. The activity at 15 min when measured against 30 min is also found to be significant.

Table-10: ANOVA results for Pentazocine

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

Pentazocine shows significant analgesic activity at both 15 and 30 minutes interval with p values of < 0.01 and < 0.001 respectively, however this activity at 15 and 30 minutes was nearly similar.

DISCUSSION: Analgesic activity of Fluoxetine has been extensively studied both in animal nociceptive models and human trials with mixed results. Our study showed that Fluoxetine demonstrates significant analgesic activity ($p < 0.01$ at 15 min interval and $p < 0.001$ at 30 min interval) in hot plate method.

The Hot-plate method is usually employed to assess centrally acting analgesics e.g. Opioids etc. Our study is in concordance with previously conducted studies by Singh VP et al[17], Kumar VS et al[18], Nayebi et al[19], Sawnoyk J[20], Kurlekar PN et al[21], Schreiber S et al[22] and Nayebi AM et al[23] which have also proved the efficacious use of Fluoxetine as an analgesic.

The results of our study disagree with the results achieved by Margalit D et al[24], Max MB et al[25]. These studies reported that Fluoxetine lacked any significant analgesic activity.

Lieberman JA[26], showed via meta analyses of human and animal experimental trials, that Antidepressants increase central levels of both Norepinephrine (NE) and Serotonin (5-HT). Many hypotheses have been postulated supporting the Analgesic action of Fluoxetine, some of which are[27]:

1. Inhibition of GIRK Channels.
2. Inhibition of Serotonin Transporters.
3. Inhibition of 5-$HT2_C$ and 5-HT3 Receptors.
4. Inhibition of Nicotinic ACh Receptors.
5. Inhibition of Voltage-gated Ca^{2+}, Na^{+} and K^{+} Channels.
6. Agonist action at μ Opioid Receptors.

CONCLUSION: Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) and one of the most commonly prescribed drugs for the pharmacotherapy of depression. Since depression is the most common and significant emotional liability associated with patients of chronic pain, an antidepressant with analgesic property is a very valuable addition to the armamentarium of the treating clinician.

Though Fluoxetine has significant analgesic properties as demonstrated by our study, but when compared with standard analgesics like Ibuprofen and Pentazocine, it is found lacking. From the present study it is apparent that Fluoxetine has significantly high activity in central-analgesic model i.e. Hot-plate method. Further studies are required to fully prove the benefit of Fluoxetine as an analgesic, so as to fully utilise its potential as an antidepressant-analgesic drug.

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