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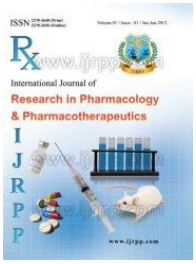

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Comparative evaluation of analgesic activity of SSRI and atypical antidepressant: an experimental study

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ABSTRACT

Aim

To assess the antinociceptive activity of some selective serotonin reuptake inhibitors (SSRI- fluoxetine, escitalopram) and atypical antidepressant (mirtazapine).

Materials and methods

Adult wistar albino rats were grouped to receive control (normal saline), SSRI (fluoxetine, escitalopram), atypical antidepressant (mirtazapine) and standard (morphine). Different doses of fluoxetine, escitalopram, mirtazapine & morphine were administered intraperitoneally in order to assess their antinociceptive activity using tail flick analgesiometer method to pretested sensitive rats. Tail flick latencies (TFL) were assessed at 0, 30, 60, 90 and 120 min after drug administration.

Results

Fluoxetine in doses of 5mg/kg and 10 mg/kg produced significant increase in TFL at all times of observation while 2 mg/kg dose did not show any change. Escitalopram failed to produce any change to tail flick latency with all doses at all time of observation. Mirtazapine in both the higher doses (5mg/kg and 7mg/kg) increased tail flick latency at all time of observation while lower dose (3mg/kg) produced no effect.

Conclusion

The SSRI fluoxetine and antidepressant mirtazapine possesses significant antinociceptive activity whereas the SSRI escitalopram does not. However these need to be further proved in other animal models and in clinical studies.

Keywords: Antidepressant, Analgesia, Chronic pain, SSRI

INTRODUCTION

Pain is the most common reason for which a patient consults a physician. Acute pain usually results from an obvious injury or infection and responds effectively to analgesics. But chronic pain is often characterized by functional loss and precipitated by psychosocial problems and economic stressors and often represents a more complex picture

in terms of pathology and treatment. [1]. The clinical management of chronic pain remains a challenge and despite advances in pain research and management, magnitude of disability due to chronic pain continues to assume alarming proportions worldwide. Although chronic pain is treated with many medications, such as tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anticonvulsants and opioids, none has shown outstanding efficacy. Narcotics are usually avoided because of the risk of developing tolerance, dependence, and functional deterioration. [2]. The association between chronic pain and depression is complex as each can occur as separate primary entity or may jointly coexist. Also, patients with chronic pain are at risk of developing depression [3].

It has been proved in about 75% of studies that some antidepressants are superior to placebo in alleviating pain as they have some intrinsic analgesic activity [4]. Tricyclic antidepressants have proven efficacy in the treatment of chronic pain conditions such as diabetic neuropathy, fibromyalgia, chronic headaches, and post-herpetic neuralgia. Unfortunately, side effects including dry mouth, constipation, orthostatic hypotension, and urinary retention often limit their use. [2] Despite the growing popularity of selective serotonin reuptake inhibitors (SSRIs) since 1980s due to their favorable safety profile, there are only a few controlled studies reporting their efficacy in managing chronic pain syndromes. Among the studies available, the results are conflicting. Whether they provide analgesia independent of their effect on mood is unclear. A third group of antidepressants, the atypical ones, have been introduced recently, of which mirtazapine has been found to have antinociceptive effects in mice. Mirtazapine has recently found to act as a weak kappa receptor partial agonist. Further studies are needed to elucidate the efficacy of SSRIs and mirtazapine for chronic pain.

Keeping all the above points in view, the present study was aimed to confirm & compare the analgesic activity of two SSRIs (fluoxetine and escitalopram) and atypical antidepressant (mirtazapine) in relation to the standard analgesic, morphine, in animal model.

MATERIALS AND METHODS

The study was conducted on healthy albino wistar rats (200-250 gm) of either sex. They were housed in the departmental animal house, in cages, in temperature regulated rooms with air cooling and 12 hour light and dark cycle, under standard laboratory conditions and fed with standard animal feed and were given water *ad libitum*. They were allowed to acclimatize to the laboratory conditions for a period of one week. The experimental protocol was approved by the institutional animal ethics committee.

Drugs

- Fluoxetine was obtained from Windlas Biotech Limited, Dehradun, India
- Escitalopram was obtained from Windlas Biotech Limited, Dehradun, India
- Mirtazapine was obtained from Sun Pharma Laboratories Ltd., East Sikkim, India
- Morphine was obtained from Cipla Ltd. Rangpo, Sikkim, India

All the drugs were freshly dissolved in distilled water and administered intraperitoneally in a volume not exceeding 1ml/ 100 gm body weight. Before drug administration animal were deprived of food for 5 hours allowing water *ad libitum.*

Rats were divided into twelve groups of six each. The animals in group 1 received normal saline, group 2, 3 and 4 received fluoxetine 2.5mg/kg, 5mg/kg and 10 mg/kg respectively. Groups 5, 6 and 7 received escitalopram 2.5 mg/kg, 5mg/kg and 10 mg/ kg respectively. Group 8, 9, 10 received mirtazapine 3mg/kg, 5mg/kg and 7 mg/kg, respectively. Group 11 and 12 received morphine 0.5mg/kg and 1 mg/kg respectively.

Determination of analgesic activity was done using tail flick method by analgesiometer. Radiant heat was directed to the proximal third of the tail through the hot wire of analgesiometer and reaction time from the placement of the tail on the heated wire to the flicking of the tail was noted. [9] The baseline reaction time was obtained at the start of experiment (0 hr) just before the drug administration. The effect of test and standard drugs on tail flick latency was measured at 30, 60, 90, and 120 min after drug administration. In order to prevent tissue injury, a cut-off time of 20 seconds was maintained.

Statistical analysis

The results were expressed as mean ± SEM. One way ANOVA and post hoc Tukey test was employed for

comparison between the means of different groups. *P* <0.05 was regarded as a statistically significant.

RESULTS

Normal saline did not produce any change in TFL at any time of observation. Fluoxetine in doses of 5mg/kg and 10 mg/kg produced significant increase in TFL at all times of observation while 2.5 mg/kg dose did not show any change in TFL. Escitalopram failed to produce any change in TFL at all time of observation. Mirtazapine at both the higher doses of 5mg/kg and 7mg/kg increased TFL at all time of observation while lower dose of 3mg/kg produced no effects. Morphine used as positive control produced significant increase in TFL from 60 min up to 120 min with lower dose (0.5 mg/ kg) and from 30 min to 120 min with higher dose (1mg/ kg). [Table 1]

Table 1: Effects of different drugs on the tail flick latency at different time intervals

Group	Drug	Dose mg/kg	Mean Tail Flick Latency (in seconds) ± SEM				
			0 min	30 min	60 min	90 min	120 min
1	Normal Saline	10 ml/kg	1.07 ± 0.01	1.11 ± 0.03	1.09 ± 0.02	1.10 ± 0.02	1.12 ± 0.05
2	Fluoxetine	2.5	1.10 ± 0.02	1.34 ± 0.05	1.37 ± 0.04	1.54 ± 0.07	1.59 ± 0.09
3	Fluoxetine	5	1.24 ± 0.05	4.50 ± 0.19*	5.15 ± 0.14*	9.43 ± 0.18*	10.18 ± 0.1*
4	Fluoxetine	10	1.16 ± 0.06	6.73 ± 0.18*	8.62 ± 0.16*	12.86 ± 0.1*	17.07 ± 0.6*
5	Escitalopram	2.5	1.21 ± 0.02	1.24 ± 0.03	1.48 ± 0.03	1.52 ± 0.04	1.54 ± 0.04
6	Escitalopram	5	1.20 ± 0.05	1.34 ± 0.02	1.50 ± 0.03	1.55 ± 0.02	1.67 ± 0.02
7	Escitalopram	10	1.12 ± 0.03	1.28 ± 0.09	1.41 ± 0.03	1.50 ± 0.03	1.52 ± 0.02
8	Mirtazapine	3	1.17 ± 0.06	1.74 ± 0.06	1.86 ± 0.06	1.89 ± 0.07	2.04 ± 0.10
9	Mirtazapine	5	1.15 ± 0.01	5.56 ± 0.08*	6.96 ± 0.11*	9.09 ± 0.27*	10.43 ± 0.2*
10	Mirtazapine	7	1.29 ± 0.02	5.53 ± 0.08*	9.72 ± 0.12*	11.34 ±0.5*	13.12 ± 0.6*
11	Morphine	0.5	1.21 ± 0.09	3.76 ± 0.03	8.22 ± 0.06*	9.29 ± 0.04*	10.45 ± 0.02*
12	Morphine	1	1.22 ± 0.04	8.34 ± 0.06*	9.80 ± 0.11*	10.40 ± 0.2*	12.20 ± 0.3*

(Values expressed as Mean± SEM. Comparison of THLE using One way ANOVA with post hoc Tukey's Test. * = p<0.05).

DISCUSSION

Our findings showed that out of the two SSRIs used, fluoxetine exhibited significant antinociceptive activity starting from 5 mg/ kg dose, from 30min to 120 min of observation while another SSRI, escitalopram failed to produce any effect.

The underlying mechanisms for antinociceptive activity of these agents probably involve a complex interaction between several neurotransmitter systems and neuro receptors. [5]. There is ample evidence to suggest that pain inhibitory pathway involves monoamines such as noradrenalin(NE) and 5-hydroxy tryptamine(5-HT), and these monoamines have also been claimed to influence depressive mood.[6, 7] Antidepressants, especially SSRI, by increasing serotonin level, may inhibit the release of neurotransmitter carrying the pain sensation from nerve endings.[8].

The atypical antidepressant mirtazapine exhibited significant antinociceptive activity starting from 5 mg/ kg dose throughout the observation period from 30 min to 120 min in our study. This effect could be attributable to its partial kappa receptor agonistic activity.

Fluoxetine showed antinociceptive activity at 5mg/kg and 10 mg/kg [Table 1]. These findings are in conjunction with the finding of Max *et al.* who, in a double-blind cross-over study, observed similar results. [9] Goldenberg *et al.* compared placebo with fluoxetine in fibromyalgia patients and found significant pain relieving activity in fluoxetine. [10]. Similarly, Rani *et al*. compared fluoxetine with amitriptyline and placebo in patients with chronic rheumatic pain and found significant reduction in pain intensity scores and pain relief scores.[11]. They suggested fluoxetine to be an effective analgesic with fewer side effects.

The antinociceptive effect shown by mirtazapine (5mg/kg and 7 mg/kg) [Tables 1] is supported by the findings of Bomholt *et al*. and Muth-Selbach et al.[12,13]. Brannon and Stone also reported analgesic effect of mirtazapine for chronic back pain with major depression where amitryptaline, fluoxetine, yohimbine, and bupropione alone and in combinations failed. [1].

It is likely that fluoxetine, mirtazapine act through opioid pathways involving the μ- opioid receptors. However, these drugs interact with other receptor systems also such as cholinergic, muscarinic, histaminergic, noradrenergic, and even the GABAergic system. [14-16]. Hence, it would not be unreasonable to suggest that antidepressant drugs would involve at least some of these systems for their analgesic effect. Above all, further clinical studies are needed to prove the same.

The SSRIs like fluoxetine and antidepressant mirtazapine possess significant antinociceptive activity whereas escitalopram does not. However these need to be further proved in other animal models and in clinical studies.

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