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Original Article

Evaluation of antinociceptive activity of paroxetine and its interactions with naltrexone and ondansetron

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Abstract:

Introduction: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage .Therefore, in this study, to delineate the possible mechanism of antinociceptive activity of paroxetine, we studied the interaction of paroxetine, naltrexone and paroxetine with ondansetron.

Materials and Methods: The study was conducted in laboratory of department of pharmacology in KIMSDU. Albino mice of either sex weighing 20-40 gms, bred in central animal house, with healthy, normal behavior and activity were used as per the inclusion criteria. All observations were made between 10am and 4pm at 27°- 37°C.

Results and Conclusion: Antidepressants, mainly SSRIs with favorable side effects profile, can be preferred for the treatment of chronic pain. From the above results, it is revealed that paroxetine in the dose of 5mg/kg and 10 mg/kg has produced antinociceptive activity with no dose dependency as compared to control in both the models. Paroxetine 10 is better than paroxetine 5 as an antinociceptive dose, though there is no dose dependency. Paroxetine is producing its antinociceptive activity by acting through two mechanisms, opioid receptor pathway and 5-HT_3 pathway in this study.

Keywords : antinociceptive activity, paroxetine

Introduction:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). Pain can be 'Nociceptive' due to direct stimulation of peripheral nerve endings or 'Neuropathic' due to dysfunction of the pain perception system within the peripheral or central nervous system (2).

Currently available analgesic to relieve pain are opioid and non- opioid i.e NSAIDs (3). As NSAIDs have both analgesic and anti-inflammatory activity, they are most widely used (4). They have common side effects like gastric irritation and nephropathy on chronic use. Opioid analgesics are the most potent pain- relieving drugs currently available. However, their use is limited by dose- related side effects like sedation, respiratory depression, pruritis, constipation and addiction liability on long term use (5).

The tricyclic anti depressants [TCAs] are extremely useful for the management of patients with chronic painful conditions like post herpetic neuralgia, diabetic neuropathy etc, but they have significant side effects such as orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation and urinary retention.

Inspite of having a number of drugs for the management of pain, there is still a need for an ideal analgesic agent with favorable safety profile. Some studies has shown that the increased level of monoamines [Serotonin and norepinephrine] in the synaptic clefts lead to changes in pain threshold and induces antinociception(6). Thus selective serotonin reuptake inhibitors [SSRI] can be effective in mixed and chronic pain and some studies have concluded this(7). Some studies show that paroxetine improves pain symptoms and related analgesic property with its serotonergic , opioidergic and noradrenergic activity(8). However, some studies have altogether denied the analgesic role of SSRI's(9).

Despite having such vast literature, it is not clear whether these can be used as analgesics. Therefore, the present study was designed with the aim of confirming the antinociceptive activity of one of the antidepressants, paroxetine. Among the various SSRIs, paroxetine is most potent(10), hence it is used in this study.

Another challenging aspect is to understand the mechanism of antinociceptive action of SSRI. There is an evidence to suggest that descending pain inhibitory pathway involves monoamines such as noradrenaline [NA] and 5-hydroxytryptamine [5-HT] (11).

Therefore, in this study, to delineate the possible mechanism of antinociceptive activity of paroxetine, we studied the interaction of paroxetine, naltrexone and paroxetine with ondansetron.

Materials and Methods

The study was conducted in laboratory of department of pharmacology in KIMSDU. Albino mice of either sex weighing 20-40 gms, bred in central animal house, with healthy, normal behavior and activity were used as per the inclusion criteria. All observations were made between 10am and 4pm at 27°- 37°C.

Approval from Institutional animal ethics committee (IAEC) was taken before starting the study. The care and use of laboratory animals were strictly in accordance with the guidelines prescribed by Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

The Drugs used in the study are: Distilled water, Morphine (Modi-Mundipharma, UP), Paroxetine (Cipla Pharmaceuticals, Mumbai), Naltrexone (Intas Pharmaceuticals, Dehradun),Ondansetron(Cipla Pharmaceuticals, Mumbai), 1% acetic acid (KIMS laboratory). All drugs solutions were prepared by dissolving drugs in distilled water at the time of experiments. The volume of injection was 10ml/kg body weight (BW).

Methods:

Pregnant mice and those that have delivered once and albino mice that were used previously for any other experimental purpose were not used, as per exclusion criteria. All drugs were given by intraperitoneal (i.p.) route. For studying antinociceptive effect animals were divided into 9 groups of 6 each, in both methods as follows-

Group I: Control –distilled water 10ml/kg BW

Group II: Standard –morphine 0.5mg/kg BW

Group III: paroxetine 2.5 mg / kg BW

Group IV : paroxetine 5 mg / kg BW

Group V : paroxetine 10 mg / kg BW

Group VI (A) : naltrexone 5 mg / kg BW + 30 min later paroxetine 5 mg / kg BW Group VI (B) : naltrexone 5 mg / kg BW + 30 min later paroxetine 10 mg / kg BW

Group VII (A) : ondansetron 0.1 mg / kg BW + 30 min later paroxetine 5mg / kg BW

Group VII (B) : ondansetron 0.1 mg / kg BW + 30 min later paroxetine 10 mg / kg BW

The antinociceptive effect was tested by using

1. Tail flick method by analgesiometer - using radiant heat from electric sources . The animal was put into small cage with an opening for the tail. A light beam exerting radiant heat was directed to the proximal third of the tail. The mouse tried to pull the tail away and turns the head. This tail flicking was considered as end

point of this test and time was measured. The cut – off time of 10 sec was planned to avoid any tissue damage. These effects were measured after 15, 30, 60 and 120 minutes. If animal received two drugs, then the effects were measured after the second drug.

2. Acetic acid induced writhing method - This model represents the chemical nociceptive test based on the induction of peritonitis like condition in animals by injecting irritant substances i.p. 0.1 ml of acetic acid solution was injected 30 minutes after giving drugs. Mice were placed individually into glass beakers and 5 minutes were allowed to elapse. They were then observed for a period of 10 minutes and the number of writhes (Stretching of the abdomen with simultaneous stretching of atleast one hind limb) were recorded in each animal. The following formula was used to calculate % inhibition. Compounds with less than 70 % inhibition are considered to have minimal antinociceptive activity.

% inhibition = [(We – Wt) x 100] / We

Where, We = average number of writhes in control group ; Wt = average number of groups in test group.

Result obtained were subjected for statistical analysis using GraphPad InStat Software inc. Version 3.06. The data were expressed as the mean ± SEM. Unpaired' t' test, One way ordinary ANOVA (analysis of variance and post hoc Tukey – Kramer multiple comparison test were used for comparing groups. Probability (P) value of < 0.05 was taken as level of statistical significance.

Observations and Results:

We evaluated analgesic activity of paroxetine 2.5, 5 and 10mg/kg at different time intervals.

Table 1: Comparison of intergroup readings in control, paroxetine 2.5, 5 and 10 groups in analgesiometer method (by one way ordinary ANOVA followed by post hoc Tukey-Kramer multiple comparison test):

Groups / Drug-Time Interval		Before	After			
			15 MIN	30 MIN	60 MIN	120 MIN
Control (Dw)		3.77 ± 0.761	3.75 ± 0.543	4.33 ± 0.634	4.55 ± 0.538	4.5 ± 1.021
Paroxetine 2.5		3.92 ± 0.886	5.17 ± 1.094	5.77 ± 1.168	6.78 ± 0.703	6.48 ± 0.741
Paroxetine 5		2.3 ± 0.384	7.37 ± 0.773 *	8.72 ± 0.812 **	8.95 ± 0.627 ***	9.15 ± 0.602 **
Paroxetine 10		3.42 ± 0.723	7.78 ± 1.112 *	9.35 ± 0.650 **	9.42 ± 0.583 ***	9.55 ± 0.450 ***
One Way Ordinary Anova	F	1.05	4.322	8.006	13.152	10.466
	P	0.3921	0.0166	0.0011	<0.0001	0.0002

[latency in seconds for tail flick expressed as mean ± SEM; $P<0.05$ significant] *$P<0.05$, **$P<0.01$, *** $P<0.001$.

This observation suggests that paroxetine 5 and paroxetine 10 produced the antinociceptive activity with no dose dependency but paroxetine 2.5 didn't.

Table 2: Comparison among morphine 0.5, paroxetine 5 and paroxetine 10 groups in analgesiometer method:

Groups / Drug-Time Interval		Before	After			
			15 MIN	30 MIN	60 MIN	120 MIN
Morphine 0.5		4.27 ± 1.058	7.83 ± 0.754	9.93 ± 0.067	9.43 ± 0.442	9.25 ± 0.546
Paroxetine 5		2.3± 0.384	7.37 ± 0.773	8.72 ± 0.812	8.95 ± 0.627	9.15 ± 0.602
Paroxetine 10		3.42 ± 0.723	7.78 ± 1.112	9.35 ± 0.650	9.42 ± 0.583	9.55 ± 0.450
One Way Ordinary Anova	F	1.631	0.082	1.023	0.243	0.1506
	P	0.2286	0.9217	0.3833	0.7871	0.8615

[latency in seconds for tail flick expressed as mean ± SEM; $P<0.05$ significant]

There was no significant difference in mean duration of latency in morphine 0.5, paroxetine 5 and paroxetine 10 groups at all the time intervals using one way ordinary ANOVA test. Thus, both paroxetine 5 and paroxetine 10 produced the antinociceptive activity statistically similar to morphine at all time intervals.

Table 3: Comparison among Control, Paroxetine 5& 10 with Naltrexone 5+Paroxetine 5 & Ondansetron 0.1 +Paroxetine 5& Naltrexone 5+Paroxetine 10 & Ondansetron 0.1 +Paroxetine 10 groups in analgesiometer method:

Groups / Drug-Time Interval	Before	After				Repeated Measures Anova	
		15 Min	30 Min	60 Min	120 Min	F	*P*
Control (DW)	3.77 ± 0.761	3.75 ± 0.543	4.33 ± 0.634	4.55 ± 0.538	4.5 ± 1.021	0.6105	0.6599
Paroxetine 5	2.3 ± 0.384	7.37 ± 0.773	8.72 ± 0.812	8.95 ± 0.627	9.15 ± 0.602	37.212	<0.0001
Paroxetine 10	3.42 ± 0.723	7.78 ± 1.112	9.35 ± 0.650	9.42 ± 0.583	9.55 ± 0.450	36.788	<0.0001
Naltrexone 5 + Paroxetine 5	4.32 ± 0.592	2.98 ± 0.669 ***	3.42 ± 0.261 ***	3.13 ± 0.593 ***	2.75 ± 0.498 ***	1.226	0.3312
Ondansetron 0.1 + Paroxetine 5	4.28 ± 0.697	2.72 ± 0.207 ***	3.67 ± 0.959 ***	3.37 ± 0.586 ***	3.57 ± 0.603 ***	0.8242	0.5251
One Way Ordinary Anova	**F**	2.289	13.406	12.061	21.237	16.246	
	P	0.1095	<0.0001	<0.0001	<0.0001	<0.0001	
Ondansetron 0.1 + Paroxetine 10	4.87 ± 0.851	3.92 ± 0.652 **	5.45 ± 0.920 **	5.03 ± 1.091 **	4.58 ± 1.020 **	0.6893	0.6079
One Way Ordinary Anova	**F**	1.64	6.773	9.742	7.153	6.983	
	P	0.2118	0.0025	0.0004	0.0019	0.0021	

[latency in seconds for tail flick expressed as mean ± SEM; $P<0.05$ significant] ***$P<0.001$.

There was no significant difference in mean duration of latency in both naltrexone + paroxetine 5 ($P=0.3312$) and ondansetron + paroxetine 5 ($P=0.5251$) groups using repeated measures ANOVA test.

There was also no significant difference in mean duration of latency in both naltrexone + paroxetine 10 ($P=0.5559$) and ondansetron + paroxetine 10 ($P=0.6079$) groups using repeated measures ANOVA test.

Thus, it reflects that the antinociceptive effect of paroxetine 10 is antagonized by the pretreatment with naltrexone and also pretreatment with ondansetron.

Table 4: Comparison among control, paroxetine 2.5, paroxetine 5 and paroxetine 10 groups in acetic acid induced writhing method:

Groups		Onset Of Writhing	Number Of Writhes	% Inhibition
Control (Dw)		2.52 ± 0.322	29 ± 1.366	-
Paroxetine 2.5		2.82 ± 0.533	26 ± 1.366	10.34%
Paroxetine 5		4.72 ± 0.762*	14.17 ± 1.40***	51.14%
Paroxetine 10		5.78 ± 0.452**	8.67 ± 2.140***	70.10%
One Way Ordinary Anova	**F**	8.28	36.123	
	P	0.0009	<0.0001	

[n=6 in each group; onset of writhing in minutes expressed as mean ± SEM and number of writhes expressed as mean ± SEM; $P<0.05$ considered as significant] *$P<0.05$, **$P<0.01$, ***$P<0.001$.

There was significant difference in control, paroxetine 2.5, paroxetine5 and paroxetine 10 groups using one way ordinary ANOVA test for both onset of writhing ($P=0.0009$) and number of writhes ($P<0.0001$).

Post hoc Tukey-Kramer multiple comparison test revealed that there was no significant difference in paroxetine 2.5 for both onset of writhing and number of writhes as compared to control. But, the onset of writhing was significantly more in both paroxetine 5 ($P<0.05$) and paroxetine 10 ($P<0.01$) and the number of writhes were significantly less in both paroxetine 5 ($P<0.001$) and paroxetine 10 ($P<0.001$) as compared to control. There was no significant difference between paroxetine 5 and paroxetine 10 for both onset of writhing and the number of writhes.

Percentage inhibition in paroxetine 2.5 was only 10.34%, paroxetine 5 was 51.14% and paroxetine 10 was 70.10%.

Thus, paroxetine 2.5 didn't produce the antinociceptive activity while paroxetine 5 and paroxetine 10 produced the antinociceptive activity with no dose dependency.

Table 5:Comparison among morphine 0.5, paroxetine 5 and paroxetine 10 groups in acetic acid induced writhing method:

Groups		Onset Of Writhing	Number Of Writhes	% Inhibition
Morphine 0.5		7.78 ± 0.834	3.17 ± 0.601	89.07%
Paroxetine 5		4.72 ± 0.762*	14.17 ± 1.40***	51.14%
Paroxetine 10		5.78 ± 0.452	8.67 ± 2.140	70.10%
One Way Ordinary Anova	**F**	4.894	13.152	
	P	0.0231	0.0005	

[onset of writhing in minutes expressed as mean ± SEM and number of writhes expressed as mean ± SEM; $P<0.05$ significant] *$P<0.05$, ***$P<0.001$.

There was significant difference in morphine 0.5, paroxetine 5 and paroxetine 10 groups using one way ordinary ANOVA test for both onset ($P=0.0231$) and number of writhes ($P=0.0005$).

Post hoc Tukey-Kramer multiple comparison test revealed that the onset of writhing was significantly less ($P<0.05$) and number of writhes were significantly more ($P<0.001$) in paroxetine 5 as compared to morphine group. There was no significant difference in paroxetine 10, for both onset and number of writhes as compared to morphine.

Thus, paroxetine 10 produced the antinociceptive activity statistically similar to morphine but paroxetine 5 had less antinociceptive activity as compared to morphine.

Table 6: Comparison among control, paroxetine 10, naltrexone 5 + paroxetine 10 and ondansetron 0.1 + paroxetine 10 groups in acetic acid induced writhing method:

Groups		Onset of Writhing	Number of Writhes	% Inhibition
Control (Dw)		2.52 ± 0.322	29 ± 1.366	-
Paroxetine 10		5.78 ± 0.452	8.67 ± 2.140	70.10%
Naltrexone 5 + Paroxetine 10		2.21 ± 0.351***	25.17 ± 1.249***	13.21%
Ondansetron 0.1 + Paroxetine 10		3.63 ± 0.489**	25.83 ± 1.99***	10.93%
One Way Ordinary Anova	**F**	15.616	28.01	
	P	<0.0001	<0.0001	

[onset of writhing in minutes expressed as mean ± SEM and number of writhes expressed as mean ± SEM; $P<0.05$ significant] **$P<0.01$, ***$P<0.001$.

There was significant difference in control, paroxetine 10, naltrexone + paroxetine 10 and ondansetron + paroxetine 10 groups using one way ordinary ANOVA test for both onset ($P<0.0001$) and number of writhes ($P<0.0001$).

Post hoc Tukey-Kramer multiple comparison test revealed that there was no significant difference in both naltrexone + paroxetine 10 and ondansetron + paroxetine 10 groups as compared to control for both onset and number of writhes. The onset of writhing was significantly less in both naltrexone + paroxetine 10 ($P<0.001$) and ondansetron + paroxetine 10 ($P<0.01$) groups and the number of writhes were significantly more in both naltrexone + paroxetine 10 ($P<0.001$) and ondansetron + paroxetine 10 ($P<0.001$) groups as compared to paroxetine 10. There was no significant difference between naltrexone + paroxetine10 and ondansetron + paroxetine 10 groups for both onset and number of writhes.

Thus, it reflects that antinociceptive activity of paroxetine 10 was antagonized by pretreatment with naltrexone as well as with ondansetron.

Discussion

Pain is a symptom of many diseases that requires treatment with analgesics. NSAIDs and opioid analgesics are routine options as analgesics, but they have many adverse effects. Antidepressant drugs, especially TCA have been routinely tried for chronic pain, but not in acute pain because of their undesirable side effects. The SSRIs, with their favorable side effect profile, are preferred now a days. Though analgesic effects of SSRIs are seen against chronic pain in animal model as well as human cases, there are discrepancies in the results of these studies. Hence the present study was undertaken to evaluate the antinociceptive activity of paroxetine. We also tried to find out the possible mechanism of action of paroxetine.

It was observed that morphine 0.5 mg/kg produced significant antinociceptive activity in both tail flick and acetic acid induced writhing methods. These findings coincide with findings of Barbara J et al. (12) and M Kesim et al. (13). When we evaluated antinociceptive activity of paroxetine, it was observed that paroxetine 5 and 10 mg/kg produced antinociceptive activity which was statistically similar to morphine at all time intervals in tail flick method. In acetic acid induced writhing method, only paroxetine 10 produced significant antinociceptive activity which was statistically similar to morphine. These findings are in match with Duman EN et al.(14) where, paroxetine showed significant antinociceptive effects with paroxetine 5 and 10. In conjugation with Patil R et al.(15), paroxetine showed antinociceptive effect at a dose 5mg/kg which was comparable to pethidine.

The study conducted by Duman EN et al.(14) showed a significant antinociceptive activity against thermal nociception with paroxetine 5mg/kg in the hot plate test. The antinociceptive activity of paroxetine was similar to that of morphine (0.5 mg/kg). This finding is in accordance with the findings of the present study in tail flick method, whereas it is not similar to the findings of acetic acid induced writhing method, where paroxetine (5 mg/kg) produced statistically less antinociceptive activity as compared to morphine (0.5mg/kg).

The findings of the present study are not in accordance with AM Gray et al.(16), where many tested (s.c.) produced dose-dependent protection against acetic acid-induced abdominal constriction; and also not in accordance with M Kesim et al.(14), where systemic administration of paroxetine (5, 10, and 20 mg/kg) produced a dose-dependent analgesic effect against acetic acid-induced abdominal constrictions.

Yatish B et al evaluated and compared analgesic activity of paroxetine with pentazocin and they found antinociceptive activity with paroxetine which is comparable with pentazocin (17).

Some recent studies conducted in patients with chronic pain also proved efficacy of antidepressants. Among these SSRI (Fluoxetine & Paroxetine) were found more safe as well as efficacious (18, 19).

It was observed that pretreatment with both naltrexone and ondansetron with paroxetine 5 & 10 blocked the antinociceptive activity of paroxetine 5& 10. There was no significant difference found between both the combination groups. So, it is evident that paroxetine 5 & 10 was producing its antinociceptive activity by acting through both the pathways (opioid pathway and 5-HT_3 pathway). Therefore, antinociceptive activity of paroxetine at both doses (5mg/kg and 10 mg/kg) was antagonized by naltrexone 5mg/kg and also by ondansetron 0.1mg/kg.

In previous studies they have pretreated the paroxetine group with naloxone and not with naltrexone. Few studies have combined naltrexone with fluoxetine (another SSRI)(7, 20).

Findings of the present study are similar to VP Singh et al.(7), where the antinociceptive effect of fluoxetine was blocked by naltrexone (5 mg/kg, i.p.) and also by naloxone (5 mg/kg, i.p.) and to Sujata AJ et al.(20), where antinociceptive effect of fluoxetine was blocked by naltrexone (5 mg/kg).

In our study, antinociceptive activity of paroxetine at both doses (5 mg/kg and 10 mg/kg) was also antagonized by ondansetron (0.1 mg/kg). These findings coincides with findings by M Kesim et al.(13) and Patil R et al.(21). In another study conducted by Sujata AJ et al.(20), the ondansetron (1 mg/kg) had blocked the antinociceptive effect of fluoxetine partially, that is, ondansetron blocked the effect of fluoxetine at the dose of 5 mg/kg but not at the dose of 10 mg/kg. This partial effect may be due to use of ondansetron at the dose of 1mg/kg.

Thus, there can be interplay between both the receptors, that is opioid and 5-HT_3 receptors in mediating the antinociceptive activity of paroxetine. However Prakash SM et al (22) claimed analgesic activity of paroxetine is because of its serotonergic and noradrenergic activity.

Conclusion:

Antidepressants, mainly SSRIs with favorable side effects profile, can be preferred for the treatment of chronic pain. From the above results, it is revealed that paroxetine in the dose of 5mg/kg and 10 mg/kg has produced antinociceptive activity with no dose dependency as compared to control in both the models. Paroxetine 10 is better than paroxetine 5 as an antinociceptive dose, though there is no dose dependency. Paroxetine is producing its antinociceptive activity by acting through two mechanisms, opioid receptor pathway and 5-HT_3 pathway in this study.

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