Study of Antinociceptive Effect of Paroxetine and Elucidation of its Mechanism of Action in Acute Pain in Albino Rats

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INTRODUCTION
Antidepressants and neuroleptics have been found to be useful in treating some types of acute and chronic pain.1-3 The analgesic properties of psychotropic drugs were reported shortly after their introduction into psychiatric practice.4 Antidepressants that enhance 5-HT neurotransmission augment stimulation produced analgesia and enhance analgesia.5 A study has shown that the increased level of monoamines (serotonin and norepinephrine) in synaptic clefts lead to changes in pain threshold and induce antinociception.6 Traditional tricyclics have numerous undesirable side effects hence, the selective serotonin reuptake inhibitors (SSRIs), with a favourable side effect profile, are preferred.7 The present study was undertaken to demonstrate the effect of paroxetine, a potent SSRIs on acute pain and to elucidate its possible mechanism of action. The objective of present study was to evaluate antinociceptive effect of paroxetine in comparison with standard drug pethidine in albino rats. And to probe its possible mechanism of antinociception - opioidergic and serotonergic

MATERIALS AND METHODS
Animals: Wistar albino rats, of either sex, weighing 100-200 g, were used for the study. The rats were inbred in the central animal house of the Department of Pharmacology, J.J.M Medical College, and Davangere, were housed individually in polypropylene cages containing sterile paddy husk with free access to food and water. Room was maintained at 30-70% relative humidity and a temperature of 22-26°C as per the guidelines set by Indian National Science Academy, New Delhi, India.8

Drugs: Normal saline in the dose of 1ml/kg, pethidine 5mg/kg, paroxetine 5mg/kg, naloxone 0.1mg/kg and ondansetron 0.1mg/kg were administered by intraperitoneal injection.

Methodology: Ethical approval was obtained from the Institutional Animal Ethics Committee. Albino rats weighing between 100-200 g with healthy and normal behavior and activity were included in the study. Pregnant animals and those that have delivered once or used previously for any other experimental purpose were excluded from the study. 30 albino rats were grouped randomly into 5 groups with 6 animals each receiving the following treatment. Naloxone, an opioid receptor antagonist and Ondansetron, a 5HT-3 receptor antagonist when combined with pethidine blocked its antinociceptive action. This finding suggests involvement of serotonergic mechanisms (5-HT3 subtype), and the opioidergic system.

KEY WORDS: Antinociception, Paroxetine, SSRI

RESULTS
From Table 2 it is evident that the reaction time significantly increased after the administration of drugs in all the groups except in control group. Antinociceptive effect was demonstrated in all the drug groups except control.

From Table 3, it is evident that pethidine and paroxetine have antinociceptive effect in comparison to the control. The
test drug, paroxetine has antinociceptive effect comparable to that of standard, pethidine. When naloxone and ondansetron were administered along with paroxetine, the antinociceptive effect was comparable to that of the control group indicating that the antinociceptive effect of paroxetine was blocked by naloxone and ondansetron. This suggests the contribution of opioidergic and serotonergic mechanisms in the antinociceptive action of paroxetine. The antinociceptive effect of paroxetine+naloxone and paroxetine+ondansetron was comparable to that of paroxetine indicating that the antinociceptive effect of paroxetine was not blocked completely by either naloxone or ondansetron.

**DISCUSSION**

In the present study analgesic effect of a potent SSRI, paroxetine was evaluated using tail-flick method in albino rats and we tried to explore the mechanism of its action using opioid and serotonin receptor blockers. The results indicate that the paroxetine has analgesic action and it is comparable to that of pethidine. The results of this study are consistent with that of studies done by Erdem et al. [7], Masand et al.[8] and Gray et al.[9]

This antinociceptive action of paroxetine was significantly inhibited by naloxone, suggesting the involvement of opioidergic mechanisms. [10] Similarly ondansetron, a 5-HT3-receptor antagonist, inhibited the analgesic effect of paroxetine suggesting the involvement of serotonergic mechanisms also. The antinociceptive effect of paroxetine+naloxone and paroxetine+ondansetron was comparable to that of paroxetine indicating that the antinociceptive effect of paroxetine was not blocked completely by either naloxone or ondansetron. Also when naloxone and ondansetron were administered along with paroxetine, it showed some amount of antinociceptive effect. As both naloxone and ondansetron could not block the analgesic effect of paroxetine completely, it can be assumed that the analgesic action of paroxetine could be due to multiple mechanisms.

However our study is very primitive in the method and parameters used to evaluate analgesia. Further studies need to be done in various other acute and chronic models using different species to establish efficacy of paroxetine as an analgesic.

**REFERENCES**


**Table 2: Reaction time before and after drug administration**

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>Mean Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - II</td>
<td>1.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>I - III</td>
<td>1.2</td>
<td>0.041*</td>
</tr>
<tr>
<td>I - IV</td>
<td>0.4</td>
<td>0.85</td>
</tr>
<tr>
<td>I - V</td>
<td>0.7</td>
<td>0.37</td>
</tr>
<tr>
<td>II - III</td>
<td>0.6</td>
<td>0.54</td>
</tr>
<tr>
<td>III - IV</td>
<td>0.8</td>
<td>0.29</td>
</tr>
<tr>
<td>III - V</td>
<td>0.5</td>
<td>0.77</td>
</tr>
</tbody>
</table>

P-Value <0.05 *Significant

**Table 3: Comparison between groups**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Reaction time before drug administration (Sec)</th>
<th>Mean</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7.0±1.6</td>
<td>1.0±0.3</td>
<td>0.01*</td>
</tr>
<tr>
<td>II</td>
<td>7.5±1.6</td>
<td>0.7±0.4</td>
<td>0.007**</td>
</tr>
<tr>
<td>III</td>
<td>7.6±1.4</td>
<td>1.5±0.7</td>
<td>0.004**</td>
</tr>
<tr>
<td>IV</td>
<td>8.0±1.5</td>
<td>0.3±0.3</td>
<td>0.004**</td>
</tr>
</tbody>
</table>

P-Value <0.05 *Significant

**Fig 1: Reaction time (sec) before and after drug administration**

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