

ORIGINAL ARTICLE

Antinociceptive Effect of Ondansetron in Albino Mice Using Acetic Acid Induced Writhing Model

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Abstract:

Background: Pain is an unpleasant sensory and emotional experience. Pain is a protective mechanism. Pain occurs whenever any tissues are being damaged, and it causes the individual to react and to remove the pain stimulus. **Aim and Objectives:** To evaluate the antinociceptive effect of ondansetron in comparison with the standard diclofenac. **Material and Methods:** The antinociceptive effect was tested by using the acetic acid induced writhing model in Swiss Albino mice. Animals were divided into 4 groups of 6 animals each. Animals were received distilled water (control), diclofenac (standard), ondansetron 0.5mg/kg (test I) and ondansetron 1mg/kg (test II). After 30 minutes of drug administration, 0.1 ml of 1% acetic acid was injected. Mice were placed individually into glass beakers and five minutes were allowed to elapse. They were then observed for a period of ten minutes and the numbers of writhes were recorded in each animal. The results were expressed as mean \pm SEM. One way ANOVA with post-test was used for statistical calculation. **Results:** The numbers of writhes were 1.33 ± 0.494 for diclofenac; 6.33 ± 1.872 and 9.33 ± 1.706 for ondansetron 0.5 and 1mg/kg respectively. **Conclusion:** Ondansetron demonstrated statistical significant antinociceptive activity at both doses (0.5mg/kg and 1mg/kg) and statistically similar effect as diclofenac.

Key words: Antinociceptive Effect, Ondansetron, Diclofenac, 1% Acetic Acid, Writhes

Introduction:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. Pain is a protective mechanism and occurs whenever any tissue is being damaged and it causes the individual to react and to remove the pain stimulus [2]. Chronic pain not only affects physical activity but may also impact psychosocial health of the patient leading to lowering of quality of life [3].

The prime objective of pain management is to remove the cause of pain. However, pain often being multifactorial and associated with undiagnosed underlying diseases, treatment does not remain simple. Pain is a symptom of many diseases requiring treatment with analgesics [4]. So, analgesic medications are the first line of treatment in the pain management [5]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are nonspecific analgesics and can potentially be used for any type of acute or chronic pain. However, depending on the short or long duration of use, they may cause adverse effects like gastritis, peptic ulcer, nephropathy etc. Long term use of these drugs may increase the risk of cardiovascular accidents [6]. Opioids are the most potent pain-relieving drugs and have the broadest range of

efficacy, providing the most reliable and effective method for rapid pain relief. But their use is limited by dose-related side effects like sedation, respiratory depression, pruritus, constipation and addiction liability on long term use [7].

So, for symptomatic treatment, widely available and used drugs being NSAIDs and Opioid analgesics; produce many side effects which are intolerable to the patients. Main side effect common to both groups of drugs is the vomiting either due to gastritis or due to stimulation of the emetic center. In the present study, we evaluated the antinociceptive effect of ondansetron, which is well known and commonly used antiemetic.

Following few studies on ondansetron have reported conflicting results. Some studies have reported ondansetron to possess antinociceptive property [8-11]. In some studies ondansetron was seen to block antinociceptive effect of some drugs given concurrently [12-16], while in one study ondansetron did not antagonize the antinociceptive effect of alfentanil, short acting synthetic opioid analgesic [17].

With the above literature at the background, this study was conducted to evaluate the antinociceptive effect of ondansetron against that of the standard drug diclofenac using acetic acid induced writhing model in albino mice and its comparison with.

Material and Methods:

Animals:

The study was conducted in the laboratory of Pharmacology department of KIMSUDU, Karad, after obtaining the approval from the Institutional Animal Ethics Committee (IAEC). Albino mice of either sex weighing 20-40g, bred in central animal house, were used. Animals were housed under standard conditions i.e. with 12 hour light and dark cycle. Temperature was maintained at 25

$\pm 3^{\circ}\text{C}$. They had free access to food and water up to the time of experimentation.

Drugs:

Ondansetron (Cipla Pharmaceuticals, Mumbai) and Diclofenac (Microlabs Pvt. Ltd, Bangalore) were used for the study. All drugs were injected intraperitoneally (i.p.).

The antinociceptive effect was tested by using the acetic acid induced writhing model.

Acetic Acid Induced Writhing Method:

The writhing model [18] represents a chemical nociceptive test based on the induction of peritonitis like condition in animals by injecting irritant substances i.p. After 30 minutes of drug administration, 0.1ml of 1% acetic acid solution was injected i.p. Mice were placed individually into glass beakers and five minutes were allowed to elapse. They were then observed for a period of ten minutes and the numbers of writhes were recorded in each animal. For scoring purpose, a writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb.

The formula used for computing percent inhibition was: average writhes in the control group minus writhes in the drug group divided by writhes in the control group times 100. Compounds with less than 70% inhibition were considered to have minimal antinociceptive activity.

$$\% \text{ inhibition} = [(W_c - W_t) \times 100] / W_c$$

Where, W_c = average number of writhes in control group; W_t = average number of writhes in test group.

Animal Groups

Animals were divided into 4 groups, 6 animals in each group.

Group I – (n=6) – received distilled water 10ml/kg i.e. vehicle

Group II – (n=6) – received diclofenac sodium 5mg/kg

Group III – (n=6) – received ondansetron 0.5mg/kg

Group IV – (n=6) – received ondansetron 1mg/kg

All the drugs were administered through i. p. The number of writhes and onset of writhing was noted down in each animal.

Statistical Analysis:

Results obtained were subjected to statistical analysis. Unpaired 't' test was used for comparing the control and diclofenac group. One way ordinary ANOVA with Tukey Kramer multiple comparisons post-test was used when more than 2 groups were compared.

Results:

The onset of writhing was delayed significantly in the diclofenac group compared to that in the control group ($P<0.0001$); Number of writhes

were significantly lower in the diclofenac group ($P<0.0001$). Diclofenac group also showed moderate/significant inhibition (95%) (Table 1)

Similarly, the onset of writhing was delayed significantly and the number of writhes were significantly lower in both, the ondansetron 0.5mg/kg and ondansetron 1mg/kg groups compared to the control group ($P<0.0001$) (Table 2).

Additionally, the onset of writhing was delayed significantly and the number of writhes were significantly lower in the ondansetron 1mg/kg group compared to the diclofenac 5mg/kg group ($P<0.001$). Though, the onset of writhing was delayed significantly in the ondansetron 0.5mg/kg group when compared to the diclofenac 5mg/kg group ($p<0.01$), no significant difference was seen in the number of writhes between the two groups (Table 3).

Table 1: Comparison between Control and Diclofenac Group

Each Group Consists of 6 Number of Mice	Time to Onset of Writhing in Seconds (Mean ± SEM)	Number of Writhes	% Inhibition
Control 10ml/kg	195 ± 5.323	27.5 ± 0.428	-
Diclofenac 5mg/kg	801.33 ± 39.33	1.33 ± 0.494	95.16364
p value	<0.0001	<0.0001	

Table 2: Comparison among Control, Ondansetron 0.5mg/kg and Ondansetron 1mg/kg

Each Group Consists of 6 Number of Mice	Time to Onset of Writhing in Seconds (Mean ± SEM)	Number of Writhes	% Inhibition
Control 10ml/kg	195 ± 5.323	27.5 ± 0.428	-
Ondansetron 0.5mg/kg	425.66 ± 38.606 ###	6.33 ± 1.872 ***	76.98182
Ondansetron 1mg/kg	371.66 ± 39.236 ##	9.33 ± 1.706 ***	66.07273
p value	0.0003	<0.0001	

Table 3: Comparison among Diclofenac, Ondansetron 0.5mg/kg and Ondansetron 1mg/kg

Each Group Consists of 6 Number of Mice	Time to Onset of Writhing in Seconds (Mean \pm SEM)	Number of Writhes	% Inhibition
Diclofenac 5mg/kg	801.33 \pm 39.33	1.33 \pm 0.494	95.16364
Ondansetron 0.5mg/kg	425.66 \pm 38.606 ^{###}	6.33 \pm 1.872 ^{**}	76.98182
Ondansetron 1mg/kg	371.66 \pm 39.236 ^{###}	9.33 \pm 1.706 ^{**}	66.07273
p value	<0.0001	0.006	

Discussion:

Pain is an unpleasant sensation having the sensory as well as the emotional component. The management aims at removing the cause of the pain but in many cases it's not possible. So, ultimate goal of the therapy ends with the control of pain by inhibiting the sensory uptake of the pain. It has been seen that the treatment for emotional component works for chronic pain in some cases. Symptomatic treatment remains the only option to control pain in a majority of cases.

We could confirm the antinociceptive effect of diclofenac with 95% inhibition. Though significantly lower than the diclofenac group, both test groups, ondansetron 0.5mg/kg and ondansetron 1mg/kg showed a moderate antinociceptive activity with an inhibition of 77% and 66 % in the respective groups. However, both test groups did not differ significantly with regards to their antinociceptive activity indicating that the activity is not dose dependent.

Our results are consistent with other studies that reported ondansetron produced antinociceptive effect [8, 9]. The authors could conclude that damage to the central noradrenergic system at an early stage of individual development has no effect on the antinociceptive effects of the serotonin (5-HT₃) receptor antagonist, ondansetron, in the persistent pain model, suggesting the site of action of antinociceptive effect of ondansetron other than the serotonergic system.

The analgesic activity of ondansetron has also been seen in patients with chronic benign neuropathic pain [10]. Additive effect of ondansetron co-administration on paracetamol analgesia was seen in another study along with reduction in the postoperative analgesic requirement, and improvement in the postoperative comfort level [11].

Since the objective of this study was limited to evaluate the antinociceptive activity of ondansetron, we did not study the mechanism of action of its antinociceptive activity. However review of the literature revealed that one of the possible mechanisms could be the site other than serotonergic system, which indicates that it may be acting through the opioidergic system or the other pain modulating pathways. It would be interesting to further study this aspect by combining the blockers of these pathways with the ondansetron.

Conclusion:

In our study, ondansetron demonstrated moderate anti-nociceptive effect at both 0.5mg/kg and 1mg/kg dose. This study has demonstrated moderate anti-nociceptive effect of ondansetron in mice that merits further human investigation being relatively old drug which is widely used and with a proven antiemetic effect and a minor side effect profile it appears essential that its utility may be further explored in humans.

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