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ANXIOLYTIC PROFILE OF 5-HT$_3$ ANTAGONIST ONDANSETRON AND ITS CLINICAL CORRELATION

AMITABH A KUMAR*, PADMA SRAVANI AND VISHNU PRIYA

Department of Pharmacology, Narayana Medical College Nellore. 524002. AP. India

ABSTRACT

Ondansetron (OND) a popular antiemetic agent mediates its central effect by 5-HT$_3$ antagonism and is used in management of cancer chemotherapy induced nausea and vomiting. There are many studies in literature depicting antianxiety, analgesic and antidepressant effects of drugs modulating serotonergic neurotransmission by 5-HT$_3$ antagonism. This kindled the spirit to evaluate the effect of OND in elevated plus maze (EPM), a popular model to evaluate antianxiety drugs, as there are limited and diverse studies portraying antianxiety effect of OND. In our study, OND demonstrated significant antianxiety activity by increasing the number of entries and duration of stay in open arm as compared to control. The results of our study throw some light to develop novel drugs with different mechanism of action and minimal cognitive adverse effects to elicit anxiolytic effect which may be beneficial to patients with anxiety disorders as drugs acting through serotonergic mechanism do not impair cognitive performance.

KEYWORDS: **Anxiety, Elevated plus maze (EPM), 5-HT$_3$ antagonist, ondansetron (OND)**

AMITABH A KUMAR
Department of Pharmacology, Narayana Medical College Nellore. 524002. AP. India

INTRODUCTION

Anxiety has been epitomized as an incessant and grave ailment affecting the humanity and is acknowledged as a paramount symptom of myriad psychiatric malady [1]. Anxiety disorders in modern society have a reasonably high prevalence and control substantial financial resources. Currently most widely prescribed medications for anxiety disorders are the benzodiazepines (BZD). However, the clinical use of BZD are limited by their side effects such as psychomotor impairment and memory loss. Therefore, development of new medications possessing anxiolytic effect without the complications of BZD would create a therapeutic advantage in management of anxiety and related disorders. Serotonergic neurotransmission plays an important role in modulation of various social behaviors like anxiety, fear [2] and depression [3]. Ondansetron (OND) a selective 5-HT_3 receptor antagonist is highly efficacious centrally acting antiemetic mainly used in therapeutics to manage nausea and vomiting induced by anticancer drugs. Some studies highlight beneficial role of (OND) in the management of schizophrenia and alcoholism [4, 5]. Keeping this in view, the present study was designed to evaluate the effect of OND in elevated plus maze (EPM), a popular model for the evaluation of drugs useful in the management of anxiety, as there are a few and diverse studies on the effect of OND in the models of anxiety.

MATERIALS AND METHODS

Animals

Adult Wistar albino rats weighing between 200-250 g were used for this study. For the experiment, animals were obtained from animal house of Narayana Medical College, Nellore. The study in animals was carried out as per 12-h light and dark cycle with free access to food and water. One week acclimatization period was provided to the animals prior to the study. The study was approved by the Institutional Animal Ethics Committee of the Institute.

Drugs

Test drug ondansetron was sourced from Sigma Aldrich, Bengaluru, India, while reference drug Diazepam (DZP) was from Nitin Life Science Ltd, India, dissolved in normal saline (NS). All the chemicals and reagents used in the study were of analytical grade and were prepared fresh before test.

Study design

The animals were randomly divided into six groups, each containing 6 animals (n=6). Group 1 was control group treated with normal saline (NS) (10 ml/kg i.p.), whereas group 2, 3, 4 and 5 were pre-treated with ondansetron (OND) as 0.25, 0.5, 1.0, and 2 mg/kg (i.p.) respectively for 7 days while group 6 was treated with standard drug diazepam (2 mg/kg, i.p.) (Table 1). On the seventh day animals were subjected to EPM test. Elevated Plus Maze (EPM) Test was used for the study as demonstrated by Lister (1987) [6]. The method of EPM was performed to evaluate the effect of OND on rats subjected to anxiety. This method is based on the principle of natural propensity of rats to develop anxiety towards a novel and potentially unsafe settings signified by open and high spaces. The EPM is a plus (+) shaped apparatus consists of two opposite open arms (50 cm X 5 cm X 10 cm) crossed with two enclosed arms of same dimensions with 30 cm high walls and these arms extended from a common central square (10 cm X 10 cm). The entire maze was elevated to a height of 50 cm above the floor level.

Procedure

Rats in each group were subjected to a standard 5 min test. Rats were placed on the maze after administration of the normal saline (NS), test and standard drug. After 30 min of administration of NS (i.p.), test drug OND 0.25, 0.5, 1 and 2 mg/kg was given i.p. while the standard drug diazepam was given as 2 mg/kg (i.p.). The animals were placed at the centre of the maze, facing one of the open arms and were allowed to explore the maze freely for 5 min. The time spent and number of entries in

both enclosed and open arms were recorded (Table 1). Increase in the number of entries and the time spent in open arm of EPM was considered as an index of antianxiety activity. Thorough cleaning of the maze was performed with the help of tissue paper moistened with 70% alcohol after each test.

Statistical Analysis

The data was reported in case record forms and entered into excel spreadsheet 2007. Statistical analysis was carried out using Microsoft Excel-2007 and Sigma Graph pad prism version-5 USA. Data was described as Mean (Standard deviation)[7]. One way ANOVA followed by Post hoc Tukey's multiple Comparison tests was used for analysis of data between the six groups. For all inferential statistical tests a two tailed ($p<0.05$) was considered significant.

RESULTS

OND at the doses of 1 mg/kg and 2 mg/kg showed a significant increase in the number of entries in open arm as compared to control ($P<0.05$).Whereas OND at a higher dose of 2 mg/kg depicted a significant increase in the duration of stay in open arm as compared to control ($P<0.05$).Therefore results of our study highlight a significant anxiolytic profile of OND at a dose of 1 and 2 mg/kg as compared to control. Number of entries and the duration of stay in open arm was higher in diazepam treated group as compared to OND used in all the doses (Table 1, Graph 1a &1b).

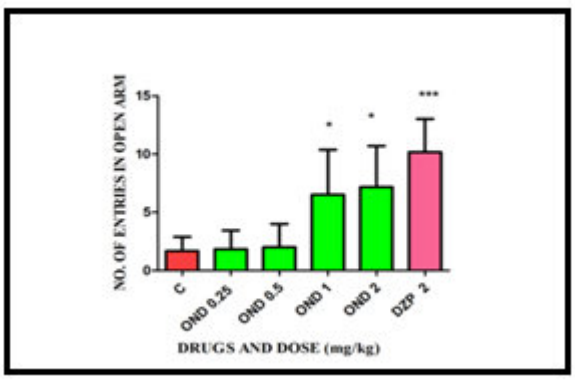
Table1

Effect of ondansetron on elevated plus maze

Groups Drugs & Doses (mg/kg)	No. of Entries		Time Spent	
	Open Arm	Closed Arm	Open Arm	Closed Arm
Group 1 Control (NS)	1.6(1.2)	3.1(1.9)	37.1(6.9)	263.7(10.6)
Group 2 OND (0.25)	1.8(1.6)	4.0(2.7)	40.5(8.8)	259(12.4)
Group 3 OND (0.5)	2.1(2.0)	3.5(1.6)	45.8(11.6)	255(9.6)
Group 4 OND (1)	6.5(3.8)*	3.3(2.5)	54.8(15.1)	250(12.9)
Group 5 OND (2)	7.1(3.5)*	3.1(1.6)	62.8(13.0)*	237(13.6)
Group 6 DZP (2)	10.1(2.8)***	1.3(0.5)	86.3(15.3)***	213(12.4)
Ns p>0.05, *p<0.05,p<0.01,***p<0.001.**				

Graph 1a

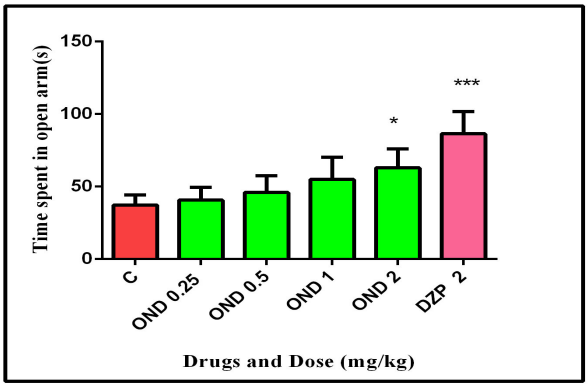
Effect of ondansetron on number of open arm entries in elevated plus maze



Bars represent number of entries in open arm, mean (SD) in EPM as compared to control (C). ns- not significant (P>0.05),*P<0.05, **P<0.01,P<0.001 one way ANOVA followed by Post hoc Tukey's multiple comparison tests.***

Graph 1b

Effect of ondansetron on time spent in open arm in elevated plus maze



Bars represent time spent in open arm mean (SD) in EPM as compared to control (C). ns- not significant (P>0.05),*P<0.05, **P<0.01,P<0.001 one way ANOVA followed by Post hoc Tukey's multiple comparison tests.***

DISCUSSION

Earlier studies show that OND influences various psychopharmacological parameters such as depicting antidepressant and analgesic like profile [8]. In our study, OND demonstrated anxiolytic activity in EPM model at the doses of 1 and 2 mg/kg, (Table 1, Graph 1a & 1b) the probable mechanism for this effect may be due to 5-HT_3 antagonism. Oliveier et al., (2000) reported that various 5-HT_3 antagonists like tropisetron, bemesetron and itasetron produced anxiolytic effects [9]. Recently, Kumar et al., (2012) documented anxiolytic and antidepressant effect of 4n a novel 5-HT_3 receptor antagonist and came to conclusion that modulation of postsynaptic 5-HT_3 receptors may be responsible for these effects [10]. In our study OND demonstrated significant antianxiety effect in the dose of 2 mg/kg as it increased the number of entries in open arm and a significantly increased the amount of time spent in open arm ($p<0.05$) as compared to control. Our findings are further supported by studies carried out by Boast et al., (1999) [11] and Rex et al., (1998) [12]. They demonstrated OND at the doses of 0.3 - 3 mg/kg (i.p.) depicted anxiolytic effects in rats. Roychoudhury and Kulkarni (1997), showed OND has significant anxiolytic effect but was less potent than diazepam [13]. On the other hand, in clinical trials, findings were controversial. Broocks et al., (1997) [14], conducted a study on 12 healthy volunteers, OND at the dose of 0.15 mg/kg significantly depicted anxiolytic efficacy by reducing behavioral, neuro-endocrine and physiological responses to anxiogenic response induced by μ- chlorophenylpiperazine, a drug known to induce anxiety. Mathew and Wilson (1991), reported OND failed to elicit anxiolytic effect in patients with generalized anxiety disorders [15]. Romach et al., (1998), conducted the randomized double blind study on 97 patients maintained on benzodiazepines; OND at the dose of 2 mg/kg twice a day failed to provide anxiolytic effect on withdrawal of benzodiazepine [16]. The limitation of all these clinical studies was poor sample size and lack of multicentric studies.

CONCLUSION

OND is mainly used in the treatment of cancer chemotherapy induced nausea and vomiting. This 5-HT_3 antagonist in our study depicts anxiolytic effect in EPM model and highlights a novel mechanism of inducing anxiolysis which may be mediated by modulation of serotonergic neurotransmission. Other than GABA-ergic mechanism responsible for anxiolytic effects of benzodiazepines. Further, OND does not impair cognitive skills or affect psychomotor performance which is common with benzodiazepines. Therefore, mechanisms

involved in anxiolytic activity of OND can throw some light in development of novel drugs which can be used in treatment of anxiety disorders without affecting the cognitive performance. Moreover, use of OND in patients suffering from terminal illness like cancer may improve the quality of life by decreasing anxiety. This calls for further affirmation by diverse experimental and clinical studies.

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