



STUDY OF ANTIDEPRESSANT ACTIVITY OF ONDANSETRON ON ANIMAL MODEL OF DEPRESSION.

Pharmacology

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ABSTRACT

The present study was done to evaluate the antidepressant activity of ondansetron by using the these two animal models- a) Forced swimming despair test (porsolt's test) in mice, and b) Reversal of reserpine -induced ptosis in mice. The drugs used were Ondansetron ,Reserpine and Imipramine. In the forced swimming test, ondansetron significantly & dose dependently reduced the immobility period. Compared to imipramine it was less effective in reducing the immobility period. In the reversal of reserpine -induced ptosis test, ondansetron significantly & dose dependently antagonized reserpine- induced ptosis. Compared to imipramine it was however less effective in antagonizing reserpine-induced ptosis.

Taken together these two observations we suggest that ondansetron exerts antidepressant activity in animal models of depression.

KEYWORDS:

Ondansetron, Antidepressant, Reserpine, Imipramine.

INTRODUCTION

Ondansetron, a selective 5-HT₃ receptor antagonist, is useful in patients with nausea, vomiting associated with cancer chemotherapy, radiotherapy anaesthesia & surgery.

There has been some interest in antidepressant effects of 5HT 3 antagonists, initially based on claims that several antidepressant drugs exhibited nanomolar affinity for 5 HT3 binding sites. The established role of 5 HT in antidepressant action has led to some interest in this potential aspect of 5 HT3 receptor involvement (Greenshaw 1993)¹.

It has recently been reported that antidepressant drugs clomipramine, fluoxetine, paroxetine interact with both central & peripheral 5HT3 receptors (luchelli et al 1995)². Recently modulation of hippocampal NA release by the 5HT 3 receptor agonist 2 methyl serotonin has been demonstrated in limbic areas of the brain, a result with obvious implications for antidepressant potential (greenshaw & silverstone 1997)³. It is of interest that in a manner similar to effects of some established antidepressants, ondansetron, tropisetron may reduce learned helplessness in a shock avoidance model (martin et al 1992)⁴.

Therefore in the present study we have evaluated the antidepressant activity of ondansetron.

AIMS AND OBJECTIVES

To evaluate the antidepressant activity of ondansetron by using the animal models.

MATERIAL AND METHODS

Animals:

Albino rats and mice of either sex, weighing between 100-180gm and 20-30gm respectively, were used for the study. They were allowed food, water ad libitum up to the time of experimentation. Each animal was used only once. All observations were made between 10 and 17 hours at 27-30°C in a noiseless, diffusely illuminated room. Each group consisted of 10 animals.

Animals were kept under standard laboratory conditions. Procedures involving animals and their care were conducted in conformity with the institutional guidelines, that are in compliance with the national and international law and policies.

Drugs:

The drugs used were Ondansetron Hydrochloride (Emeset injection, Cipla Ltd.), Reserpine (Serpasil injection, Hindustan Ciba Geigy), and Imipramine hydrochloride (Torrent Ltd.).

Imipramine was dissolved in distilled water. Ondansetron and Reserpine injection solutions were diluted to required strength with distilled water. All drugs solutions were prepared immediately before use and were injected intra-peritoneally. In rats, the volume of drug injection was 2 ml/kg, while in mice; it was 10 ml/kg. Doses refer to the forms mentioned.

STATISTICS

The results were statistically analyzed by the student's unpaired t-test with differences considered significant at $p < 0.05$.

METHODS

Forced Swimming Test (Porsolt's Test)⁵

Porsolt et al (1977) reported a new behavioural test in rodents, which developed as a primary screening procedure, to detect the efficacy of antidepressants. Test was studied by forcing mice to swim individually inside a vertical plexiglass cylinder (height 25 cm and diameter 10 cm) containing water up to a height of 9 cm at 22-25°C temperature. In this test after a brief spell of vigorous activity, mice show posture of immobility which is characterized by floating motionless in water, making only those movements necessary to keep head above the water. This immobility reflects a state of depression. This observation is termed as "behavioural despair". This inescapable experimental situation which induces a feeling of helplessness has been related to human depressive state. Administration of antidepressant drugs significantly reduce the immobility time.

One day prior to the experiment the animals were placed into the cylinder containing water one at a time and left there for 15 min (Pre-test session).

On the day of experiment, animals were divided into groups of 10 each. Experimental groups received ondansetron in doses of 0.625, 1.25 and 2.5 mg./kg i.p. and imipramine 30 mg./kg I.p. while control group received distilled water (10 ml/kg i.p.) 60 min prior to test. Animals were forced to swim inside the plexiglass cylinder containing water for 6 min. After allowing 2 min for acclimatization each mouse was observed for 4 min for immobility. The total duration of immobility during last 4 min of 6 min period was recorded for each mouse. The mean immobility time was calculated for each group of mice.

Reversal Of Reserpine – Induced Ptosis In Mice

(Laurence and Bacharach, 1964)⁶

Adult albino mice of either sex weighing between 20-30 gm were used. Food and water was provided ad libitum, except during the experimental periods.

Experimental group received ondansetron in doses of 0.625 mg/kg, 1.25 and 2.5 mg/kg i.p. and imipramine 30 mg/kg i.p. while control group received distilled water 10 ml/kg i.p. 30 minutes later all the groups received reserpine injection in dose of 5 mg/kg i.p. 3 hours after treatment with reserpine the animals were tested for ptosis.

Ptosis in each eye was graded according to the method of Lapin (1967)⁷ as follows –

Complete ptosis	----- 4 points
More than half closed	----- 3 points
Half closed	----- 2 points
Less than half closed	----- 1 point
Absence of ptosis	----- 0 point

The main response of both eyes was noted. The maximal mean response for ptosis was 4 points.

OBSERVATION AND RESULTS

FORDCED SWIMMING TEST IN MICE (PORSOLT'S TEST)

The results are given in table 1. Table 1 shows effect of ondansetron (0.625, 1.25 and 2.5 mg/kg i.p.) and imipramine (30mg/kg i.p.) on mean immobility time (sec) in mice subjected to forced swimming test. Imipramine treated mice showed highly significant (p<0.001) reduction in immobility time when compared to control (Table 1).

Administration of ondansetron 0.625 mg/kg i.p. produced significant (P<0.05) reduction in immobility time when compared to control. But reduction in immobility time was significantly less (P<0.01) than imipramine treated group. Further administration of ondansetron in doses of 1.25 and 2.5 mg/kg i.p. produced significant (P<0.01) and dose – dependent reduction in immobility time when compared to control but the reduction in immobility time was significantly less (P<0.05) than imipramine treated group (Table 1).

TABLE 1

Study	Treatment dose mg/kg	Duration of immobility in seconds Mean ± S.E.M.
1	• Control	180.8 ± 7.8
	• OND 0.625	160.4 ± 6.2*
	• IMI 30	74.8 ± 8.4**
2	• Control	181.5 ± 7.9
	• OND 1.25	128.6 ± 6.3**
	• IMI 30	74.5 ± 8.3**
3	• Control	182.6 ± 8.1
	• OND 2.5	116.1 ± 5.8**
	• IMI 30	73.6 ± 7.5***

Table 1 showing effect of ondansetron (OND) and imipramine (IMI) on immobility period in forced swimming test in mice.

*P<0.05, **P<0.01, ***P<0.001, Number of animals n = 10

REVERSAL OF RESERPINE-INDUCED PTOSIS IN MICE:

The results are given in table 2. Table 2 shows the effect of ondansetron (0.625, 1.25 and 2.5 mg/kg i.p.) and imipramine (30 mg/kg i.p.) on reserpine (5mg/kg i.p.) induced ptosis in mice.

It can be observed from the table that, imipramine 30 mg/kg i.p. significantly (P<0.001) antagonized reserpine induced ptosis when compared to control. Ondansetron in the given doses 0.625, 1.25, & 2.5 mg/kg i.p significantly (p< 0.001) & dose dependently antagonized reserpine induced ptosis when compared to control but it was significantly less (P<0.05) than imipramine (Table 2).

TABLE 2

Study	Treatment Dose mg/kg	ptosis Score Mean ± S.E.M.
I	• RES 5	3.8 ± 0.13
	• OND 0.625 + RES 5	2.5 ± 0.16***
	• OND 1.25 + RES 5	1.9 ± 0.10***
	• OND 2.5 + RES 5	1.3 ± 0.15***
	• IMI 0.5 + RES 5	0.6 ± 0.16***

Table 2 showing effect of ondansetron (OND) and imipramine (IMI) pretreatment on Reserpine (RES)-induced ptosis in mice.

***P<0.001, Number of animals n = 10

SUMMARY & CONCLUSIONS

In the present study the ondansetron was evaluated for antidepressant activity in mice using the forced swimming test & reversal of reserpine- induced ptosis models.

The results & conclusions derived thereof are summarised as follows-

1. In the forced swimming test, ondansetron significantly & dose dependently reduced the immobility period. Compared to imipramine it was less effective in reducing the immobility period.
2. In the reversal of reserpine -induced ptosis test, ondansetron significantly & dose dependently antagonized reserpine- induced ptosis. Compared to imipramine it was however less effective in antagonizing reserpine-induced ptosis.

Taken together these two observations we suggest that ondansetron exerts antidepressant activity in animal models of depression.

We conclude that ondansetron could be a new class of compound having antidepressant activity. More studies are needed for final conclusion.

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