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Research Article

EVALUATION OF ANTIDEPRESSANT ACTIVITY OF ONDANSETRON IN ALBINO MICE

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ABSTRACT
Unfortunately, it is not fully known what exactly causes clinical depression for a particular individual. There are many theories about causes such as biological and genetic factors, environmental influences. Complications with depression may include excess weight which can lead to heart disease and diabetes, family conflicts, social isolation. This study aimed at evaluating the antidepressant activity of ondansetron in albino mice. To evaluate antidepressant effect of ondansetron in 3 graded doses 0.5 mg/kg , 1.0mg/kg and 2.0 mg/kg in albino mice by comparing their effect with fluoxetine doses 10mg/kg , 20mg/kg by using physically induced depression models tail suspension test and despair swim test. Drug induced depression model was assessed by haloperidol induced catalepsy. Ondansetron treated albino mice groups with dose dependent increase of 0.5mg/kg, 1.0mg/kg & 2.0mg/kg showed significant decrease in antidepressant activity and increase in catalepsy score when compared with fluoxetine 10mg/kg and 20mg/kg. Ondansetron 2mg/kg is euipotent to 20mg/kg fluoxetine. Thus the present result indicates antidepressant effect of ondansetron in different doses against fluoxetine in animal models.

Keywords: *Ondansetron, Antidepressant Activity, Fluoxetine, Albino Mice*

INTRODUCTION
Major depressive disorder (MDD) is characterized by depressed mood most of the time for at least 2 weeks and/or loss of interest or pleasure in most activities. In addition, depression is characterized by disturbances in sleep and appetite and deficits in cognition and energy. Thoughts of guilt, worthlessness, and suicide are common (Charles, 2010).
An estimated 5.8% of men and 9.5% of women experience depressive episodes in their lifetime. 60% of death toll due to suicides is due to depressive illness (Rechelson, 2001).
Approximately two-thirds of the depressed patients respond to the currently available drug treatments (tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI´s) etc), but the magnitude of improvement is still disappointing and these drugs have unusual side effects. So the search for more effective drugs with fewer side effects is on.
Ondansetron is commonly used in treating vomiting due to chemotherapy drugs, post operative patients and radiation therapy. The primary site of action of ondansetron is the chemoreceptor trigger zone (CTZ). It may be given orally or by injection. Side effects such as headache and gastrointestinal upsets are relatively uncommon.
Chemoreceptor trigger zone is sensitive to chemical stimuli and is the main site of action of many emetic and antiemetic drugs. The blood-brain barrier in the neighbourhood of the CTZ is relatively permeable, allowing circulating mediators to act directly on this centre.
The main circulating mediators are acetylcholine, histamine, 5-hydroxytryptamine (5-HT), dopamine and substance P and receptors for these transmitters have been demonstrated in the relevant areas.
Serotonin (5-HT3) receptors are the only ligand-gated ion channel of the 5-HT receptors family. They are present both in the peripheral and central nervous system and are localized in several areas involved in mood regulation (e.g., hippocampus or prefrontal cortex). Moreover, they are involved in regulation of neurotransmitter systems implicated in the pathophysiology of major depression (e.g., dopamine or

gamma amino butyric acid). Clinical and preclinical studies have suggested that 5-HT3 receptors may be a relevant target in the treatment of affective disorders. 5-HT3 receptor agonists seem to counteract the effects of antidepressants in non-clinical models, whereas 5-HT3 receptor antagonists, such as ondansetron has antidepressant-like activities (Cecile *et al.*, 2009).

As becomes evident from the present review, the involvement of 5-HT3 receptors is complex and also context dependent. Their molecular structure, function and regulation are only partly elucidated. It will be important to understand why several responses associated with 5-HT3 receptor ligands present a bell-shaped dose-response curve. In conclusion, we feel that additional knowledge about 5-HT3 receptor function and their role in several diseases may offer new therapeutic opportunities in the future.

Mechanisms of Causation of Depression

Monoamine hypothesis : The monoamine hypothesis of endogenous depression suggests that depression is caused by a functional deficit of NE (norepinehrine) and/or 5-HT (5-hydroxytryptamine (or of dopamine) at certain sites in brain; while mania results from a functional excess of these neurotransmitters. This theory is based on the ability of the NE and 5-HT uptake inhibiting or monoamine oxidase-A inhibiting drugs to facilitate NE/5-HT neurotransmission and to act as effective antidepressant drugs. Ondansetron mechanism of action is due to blockade of 5HT3 receptors in Central nervous system leading to enhance release of monoamines 5HT, NE. Recently clinically effective antidepressants with rapid onset of action and fewer side effects are developed. Here selective serotonin reuptake inhibitors like fluoxetine, escitalopram are used in combination with ondansetron. And also SSRI's are having gastrointestinal side effects which can be inhibited by ondansetron and also show additive antidepressant effect. In present study an attempt was made to find out the antidepressant activity of ondansetron in animal models of depression and its comparison to selective serotonin reuptake inhibitor fluoxetine (Ramamoorthy *et al.*, 2008; Srivastava, 1998; Shankar and Karan, 1999).

MATERIALS AND METHODS

All the experimental procedures used in this study were reviewed and approved by institutional animal ethical committee of kamineni institute of medical sciences, Narketpally, Andhra Pradesh. The study was placebo controlled, randomized, laboratory- based comparative study on albino mice. 42 adult swiss albino mice (25-30gms) obtained from national institute of nutrition, Hyderabad were used. Animals were acclimatized to the laboratory environment for 5 to 7 days before being used in the study.

Animals were housed 6 per cage in a temperature and humidity controlled environment under a 12-hour light/dark cycle (lights on at 7 pm).Food and water was available for all animals for their access.

Instruments and Apparatus

The standard methods for measuring antidepressant models like tail suspension test, despair swim test by physically induction and drug induced antidepressant model haloperidol induced catalepsy as described by gerhard vogel were used (Kalra *et al.*, 2008).

Drug used in the Experiment

1. Normal saline (control), 2.Fluoxetine (Sigma Aldrich), (3) Ondansetron (Zydus cadila), (4) Haloperidol (RPG Life Sciences Ltd).

Tail suspension test: Tail suspension test is based on the principle that suspending mice upside down leads to a characteristic behaviour of immobility after initial momentary struggle. Animal was considered to be immobile when it did not show any movement of body and hanged passively and the duration of immobility was recorded automatically for 6 min using a computerized device (Bioseb TST). Six mice were studied simultaneously. The test substances were administered i.p. 30 min before the test. The duration of immobility was comprised between 60 and 120 sec in the vehicle control group.

Despair swim test: Despair swim test is based on the principle that forcing mice to swim in restricted space from which they cannot escape leads to a characteristic behaviour of immobility. This behaviour reflects a state of despair, which can be reduced by several agents that are therapeutically effective in human depression. Animals were individually placed in a cylinder (height = 40 cm, diameter = 20 cm) containing 13 cm water (25°C) for 15 min on the first day of the experiment (session 1) and were then put

back in the water 24 hr later for a 5-min test (session 2). The duration of immobility during the 5-min test was measured. The test substances were administered i.p. 24 hr, 4 hr, and 30 min before the test (session 2). A mouse was considered immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The duration of immobility was comprised between 60 and 120 sec in the vehicle control group.

Haloperidol - induced catalepsy: Catalepsy was assessed in terms of the time for which the mice maintained an imposed position with both front limbs extended and resting on a 4 cm high wooden bar (1.0 cm diameter). A cut off time of 1100 seconds was applied. The test drug was given i.p and assessed at 30 minute intervals until 120 minutes by means of a standard bar test. Between determinations the animals were returned to their individual home cages. Scoring method: If the animal maintained the imposed posture for at least 20 seconds, it was considered to be cataleptic and given one point. For every additional 20 seconds that the cataleptic posture was maintained, one extra point was given.

Grouping of animals: Animals were divided into 7 groups each containing 6 animals (n= 6 in each group) total 42 albino mice required.

Table 1: Division of Groups, drugs, doses and route of Administration

Groups	Drugs	Doses	Route
1	Normal saline	10ml/kg	i.p
2	Ondansetron	0.5mg/kg	i.p
3	Ondansetron	1.0mg/kg	i.p
4	Ondansetron	2.0mg/kg	i.p
5	Fluoxetine	10mg/kg	i.p
6	Fluoxetine	20mg/kg	i.p
7	Ondansetron + Fluoxetine	0.5mg/kg+1.0mg/kg	i.p

IP = Intra peritoneal

RESULTS AND DISCUSSION

Results

The effect of untreated group showed characteristic behaviour of mobility and (at 30min, 60min, 90min and 120min) ondansetron pretreatment reduced the movement of body and hanged passively (30min, 60min, 90min and 120min) for different doses of ondansetron (0.5mg/kg, 1.0mg/kg & 2.0mg/kg) and fluoxetine (10mg/kg & 20mg/kg)

As shown (table-2) in the ondansetron treatment groups has mild decrease in tail suspension test with 0.5mg/kg when compared with ondansetron 1mg/kg and 2.0 mg/kg. Ondanstron 2.0 mg/kg was comparable with fluoxetine 20mg/kg. Combination group (ondansetron 0.5mg/kg + fluoxetine 1.0mg/kg) showed less significant immobility time when compared with ondansetron 0.5mg/kg)

Further ondansetron treated (table - 3 and table - 4) animals in despair swim test and haloperidol induced catalepsy score also showed no significant difference in immobility time for ondansetron dose 2.0mg/kg when compared with fluoxetine dose 20mg/kg. Also ondansetron 0.5mg/kg showed less significant immobility time when compared with doses 1mg/kg and 2mg/kg. The above observations (from table 2,3 and 4) indicate stastically significant ($P<0.0001$) antidepressant activity for dose 2.0mg/kg. In the above models (despair swim test & haloperidol induced catalepsy) combination group (ondansetron 0.5mg/kg + fluoxetine 1.0mg/kg) showed less significant immobility time when compared with ondansetron 0.5mg/kg.

Table 2: Comparison of immobility time (Mean ± SE) in seconds in tail suspension test

Groups	Mean ± SE	P value
Control (Normal saline) 10ml/kg	202.83± 3.11	0.06
Ondansetron 0.5mg/kg	139.83± 2.65	0.02
Ondansetron 1.0mg/kg	107.83± 2.15	0.001
Ondansetron 2.0mg/kg	105.16± 2.97	0.0001
Fluoxetine 10mg/kg	123.50± 1.82	0.03
Fluoxetine 20mg/kg	106.16± 2.57	0.0001
Ondansetron 0.5mg/kg + Fluoxetine 10mg/kg	108.83± 3.32	0.04

P<0.001 is highly significant, P<0.05 is significant

Table 3: Comparison of immobility time (Mean ± SE) in seconds in despair swim test

Groups	Mean ± SE	P value
Control (Normal Saline) 10ml/kg	174.50 ± 5.16	0.06
Ondansetron 0.5mg/kg	151.83 ± 3.78	0.03
Ondansetron 1.0mg/kg	76.00 ± 1.52	0.001
Ondansetron 2.0mg/kg	72.66 ± 2.57	0.0001
Fluoxetine 10mg/kg	126.16 ± 4.18	0.02
Fluoxetine 20mg/kg	73.00 ± 1.91	0.0001
Ondansetron 0.5mg/kg+ Fluoxetine 10mg/kg	78.33 ± 3.61	0.05

Table 4: Comparison of immobility time (Mean ± SD) in seconds in haloperidol induced catalepsy

Groups	Mean ± SD	P value
Control (Normal Saline) 10ml/kg	32.38 ± 1.09	0.06
Ondansetron 0.5mg/kg	27.96 ± 1.09	0.02
Ondansetron 1.0mg/kg	18.92 ± 1.09	0.001
Ondansetron 2.0mg/kg	16.42 ± 1.09	0.0001
Fluoxetine 10mg/kg	23.79 ± 1.09	0.03
Fluoxetine 20mg/kg	17.75 ± 1.09	0.0001
Ondansetron 0.5mg/kg+ Fluoxetine 10mg/kg	18.29 ± 1.09	0.04

Discussion

Ondansetron is a highly potent and selective antagonist at 5-HT3 receptors used primarily to treat and prevent cancer therapy induced nausea and vomiting. 5-HT3 receptor ligands are located at highest densities in the area postrema, nucleus tractus solitarius (NTS) and on afferent terminals of the vagus nerve.

Cecile *et al.*, (2011) shows the involvement of 5HT3 receptors in depression (Vogel, 2002).

Conclusion

The present study showed that there is dose dependent (0.5mg/kg, 1.0mg/kg & 2.0mg/kg) decrease in antidepressant activity of ondansetron in all the three models of depression. The antidepressant action of ondansetron 2.0mg/kg is not significantly different than fluoxetine 20mg/kg suggesting ondansetron is euipotent to fluoextine. Ondansetron 0.5mg/kg potentiated the antidepressant effect of fluoxetine low dose 10mg/kg in combination group. But more studies in other experimental animals and humans may be required to confirm the result of present study.

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