

Efficacy of 5HT₃ receptor antagonist ondansetron antidepressant activity in physical induced albino mice

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ABSTRACT

Background: The objective of this study was to evaluate efficacy of 5HT₃ receptor antagonist ondansetron antidepressant activity in physical induced swiss albino mice.

Methods: Study was placebo controlled, randomized laboratory based comparative study with prior permission of Institutional animal ethical committee. Experimental animals were divided in to seven groups as control (distilled water 10ml/kg), standard Fluoxetine two doses (10mg/kg and 20mg/kg), test drug ondansetron three doses (0.5mg/kg, 1mg/kg and 2mg/kg) and combinations of test and standard (0.5mg/kg + 10mg/kg). The drugs were administered intraperitonium and antidepressant activity was recorded using physically induced depression models tail suspension test and despair swim test.

Results: Ondansetron treated albino mice groups with dose dependent increase of 0.5mg/kg, 1.0mg/kg and 2.0mg/kg showed significant decrease in antidepressant activity and increase in catalepsy score when compared with fluoxetine 10mg/kg and 20mg/kg. Combination doses showed stastically significant antidepressant activity.

Conclusions: The present study indicates ondansetron showed promising antidepressant activity due to its ability to modulate serotonergic system and has proved to be safe in the dose range of 0.5mg/kg, 1mg/kg and 2mg/kg in mice.

Keywords: Antidepressant activity, Albino mice, Ondansetron, Physical induced

INTRODUCTION

Depression is extremely common, with up to 30% of primary care patients having depressive symptoms. Depression may be the final expression of genetic factors, developmental problems related to personality, childhood events and psychosocial stresses such as divorce, unemployment. Depression is marked by a sense of guilt and worthlessness.¹

Approximately two-thirds of the depressed patients respond to currently available drug treatments (tricyclic antidepressants, selective serotonin inhibitors (SSRI's) etc), but the magnitude of improvement is disappointing and have side effects. Search for more effective drugs with few side effects is on.

Ondansetron is a selective 5HT₃ receptor antagonist used as an antiemetic which showed potent antidepressant like effect and was evaluated for its efficacy in depression in

few studies.² Several pre-clinical (behavioural, neurochemical and genetic) studies have provided evidences linking 5-HT₃ receptors and depression. So, in this study, an effort is made to investigate the antidepressant effect of ondansetron in physical induced models of albino mice in comparison to selective serotonin reuptake inhibitor fluoxetine.³

METHODS

The study was approved by Institutional animal ethical committee of Kamineni institute of medical sciences, marketpally, Andhra Pradesh. The study was placebo controlled randomised laboratory based comparative study on albino mice. Total of 42 albino mice (25-30 gm) procured from national institute of nutrition, Hyderabad were used. Animals were acclimatized to laboratory environment before being used in the study.

Instruments and apparatus

The standard methods for measuring antidepressant models like tail suspension test, despair swim test by physically induction described by Gerhard Vogel were used.⁴

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. 30min before the test. The duration of immobility was comprised between 60 and 120sec 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 = 40cm, diameter = 20cm) containing 13cm water (25°C) for 15min on the first day of the experiment (session 1) and were then put back in the water 24hr 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, 4hr, and 30min 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 120sec in the vehicle control group.⁵

RESULTS

Tail suspension test

Mean duration of immobility in animals treated with ondansetron doses 0.5mg/kg, 1.0mg/kg and 2.0mg/kg was significantly reduced compared to animals in control group. Ondansetron 0.5mg/kg (P<0.02) has low efficacy when compared with 10mg/kg standard fluoxetine (P<0.03).

Ondansetron 1.0mg/kg and 2mg/kg showed significant decrease in immobility time when compared with fluoxetine 20mg/kg. The effect obtained due to combination of low doses of ondansetron 0.5mg/kg and fluoxetine 10mg/kg showed significant synergism (P<0.04, Table 2).

Despair swim test

There was significant reduction in immobility time in the animals treated with ondansetron doses 0.5mg/kg, 1.0mg/kg and 2.0mg/kg compared to control group (P<0.05, Table 1). Ondansetron 1mg/kg and 2mg/kg are more potent when compared with 0.5mg/kg when compared with standard doses of fluoxetine 10mg/kg and 20 mg/kg. Low dose combinations of ondansetron and fluoxetine showed synergism (P<0.05, Table 3).

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.mg/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

Table 2: Comparison of immobility time in seconds (Mean±SE) 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	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.

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 and 2.0mg/kg) and fluoxetine (10mg/kg and 20mg/kg).

Table 3: Comparison of immobility time in seconds (Mean±SE) 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±2.58	0.0001
Ondansetron 0.5mg/kg + Fluoxetine 10mg/kg	108.83±3.32	0.04

DISCUSSION

Ondansetron potent 5HT₃ antagonist used primarily to treat nausea and vomiting associated with cancer therapy because of their ligands located in area postrema. Greenshaw in 1992 has reported possible involvement of 5HT₃ receptors in depression.⁶ Further ondansetron also effects both peripheral and central nervous systems via serotonin receptors (5HT₃) involved in mood regulation (hippocampus or prefrontal cortex).⁷ The antidepressant-like effect of ondansetron may be explained by blocking the 5HT₃ receptors which lead to increased 5HT or norepinephrine levels.⁸ Further the Zifa E et al, reported that 5HT₃ receptor sites are ligand gated ion channels which modulate the release of a number of neurotransmitters.⁹ The results obtained have been compared with the standard antidepressant drug fluoxetine. Also, the effect obtained due to combination of low doses of ondansetron 0.5mg/kg and Fluoxetine 10mg/kg was determined whether any synergism was there between two drugs. In tail suspension test and despair swim test, mean duration of immobility in animals treated with three doses of ondansetron was reduced which was statistically significant compared to control and standard. Ondansetron 2.0mg/kg showed reduction in immobility time compared to standard fluoxetine 20mg/kg indicating efficacy similar to fluoxetine.

Pharmacokinetics of ondansetron

Oral bioavailability is high due to low first pass metabolism and t_{1/2} of 8-12 hrs. 2mg/kg dose is well tolerated with no clinical drug interactions has been noted. Common side effect of headache and dizziness has been demonstrated.¹⁰

CONCLUSION

Ondansetron doses 0.5mg/kg, 1.0mg/kg and 2.0mg/kg showed significant decrease in antidepressant activity in

despair swim test and tail suspension test. These effects may be because of modulation of central monoaminergic neurotransmitter systems by blocking the post synaptic 5HT₃ receptors. Further studies are required in experimental animals and humans to confirm its antidepressant activity.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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