

A comparative study of the antidepressant effect of ondansetron and granisetron on Albino mice

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ABSTRACT

Background: Ondansetron and granisetron are selective 5-HT receptor antagonists used as antiemetics. The present study aimed at comparing the antidepressant activity of ondansetron and granisetron in animal experimental models.

Methods: The study was done after obtaining approval from the institutional animal ethical committee of JJM Medical college, Davangere and CPCSEA. A total of 24 mice of either sex and of weight between 20-40g were included in the study. The antidepressant activity of ondansetron and granisetron was evaluated in mice using forced swim test model (FST) and tail suspension test model (TST). In both the experimental models animals were divided into 4 groups and received the following drugs- Group 1 (control) - normal saline 10mg/kg i.p, Group 2 (standard)-fluoxetine 10mg/kg i.p, Group 3(test drug 1), ondansetron 2mg/kg i.p, Group 4 (test drug 2)- granisetron 0.5mg/kg i.p. The duration of immobility was noted and compared amongst the 4 groups in both the models 60 min after drug administration. The observations were analysed using ANOVA (one way) and post hoc Tukey's test.

Results: The test drugs showed significant reduction in duration of immobility in both the models. In FST and TST models, granisetron (0.5mg/kg i.p) showed a significant reduction in immobility period of 10.33 sec and 67 secs respectively when compared to ondansetron (2mg/kg i.p) and the standard drug fluoxetine (10mg/kg i.p).

Conclusions: The results of study suggest that granisetron may be useful as a potential candidate for treatment of depression. Hence further animal studies with different model for depression and clinical studies should be conducted in order to choose the better drug for treatment PONV which is often associated with depression.

Keywords: Antidepressants, Granisetron, Ondansetron

INTRODUCTION

Depression is a mental disorder, defined as depressed mood on a daily basis for a minimum duration of 2 weeks. It is an affective disorder characterized by sadness, apathy, changes in sleep pattern, impaired concentration, feeling of shame or guilt, thoughts of dying or death.¹

The WHO has ranked depression fourth in a list of the most urgent health problems worldwide. An estimated 5.8% of men and 9.5% of women experience depressive episodes

in their lifetime and 60% of death toll due to suicides is due to depressive illness.² In India the prevalence of depression is 31.2 per 1000 population.³

The interaction of genetic and environmental risk factors leads to depression. The main symptoms of depression are due to functional deficiency in the level of monoaminergic neurotransmitters like norepinephrine (NE), 5hydroxytryptamine (5HT) and dopamine (DA) in the brain. Approximately two-thirds of the depressed patients respond to the currently available drug treatments of

tricyclic antidepressants, selective serotonin reuptake inhibitors and MOIs 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 a 5HT₃ antagonist, 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). Side effects such as headache and gastrointestinal upsets are relatively uncommon. Granisetron, the experimental drug is a potent and highly selective 5-HT₃ receptor antagonist. It has little or no affinity for other 5-HT receptors, or dopaminergic, adrenergic, benzodiazepine, histamine or opioid receptors, a characteristic that is thought to underlie the favourable side-effect and safety profiles of the drug.⁴

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.⁵ Therefore the present study was undertaken to compare the antidepressant activity of ondansetron and granisetron in animal experimental models.

METHODS

Selection of animals

A total of 24 Albino mice of either sex, weighing around 25-30g and aged 3-4 months were employed in the present study. Pregnant and diseased animals were excluded from this study. They were exposed to alternate light and dark cycle for 12h and had free access to food and water ad libitum. They were being procured from animal house of J.J.M. Medical College, Davangere.

The animals were randomly divided into 4 groups of 6 animals each and food was withdrawn 1hr before and 2hr after the administration of the drugs. The same groups of animals were subjected to both tail suspension and forced swim tests 60 min after drug administration with washout period of two weeks.

The animals were randomly assigned in the following groups and administered drugs as follows:

- Group 1: Control, normal saline 10mg/kg i.p
- Group 2: Standard, fluoxetine 10mg/kg i.p
- Group 3: Test drug 1 (TD1), ondansetron 2mg/kg i.p
- Group 4: Test drug 2 (TD2), granisetron 0.5mg/kg i.p

Forced swim test

This test was developed by Roger Porsolt⁶ and 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. Mice were individually forced to swim inside vertical plexiglass cylinder (25×10×25 cm³) filled with a water to a height of 15 cm. Temperature of water was maintained at 23-25°C. After an initial 2 minutes of vigorous activity by the mouse the duration of immobility was recorded during the next 4 minutes, in a total of 6 minutes test. A mouse is considered to be immobile when it remains floating in water making only minimum movements of its limbs. Duration of immobility was compared among all the 4 groups 60 minutes after drug administration.

Following swimming sessions, the mice were dried with towel and placed in a cylinder under 60 W bulb for 15 min before returning to home cages.

Tail suspension method^{7,8}

In this test, immobility was induced by suspending the mice by the tail. The method is based on the principle that a mouse suspended by tail above a fixed height of 50cm from the ground shows alternate periods of agitation and immobility. Mice were suspended on the edge of a table with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period. After an initial 2 minutes of vigorous activity by the mouse the duration of immobility was recorded during the next 4 minutes.

Duration of immobility was compared among all the 4 groups 60 minutes after drug administration. The immobility displayed by rodents, when subjected to an unavoidable and inescapable stress, has been hypothesized to reflect behavioral despair, which in turn may reflect depressive disorders in humans.

Statistical analysis

Statistical Analysis was carried out with SPSS Version 20 for Windows. Mean and Std deviation were calculated for continuous variables. Comparison of four groups was done with One Way Analysis of Variance (ANOVA). Multiple comparisons done with Tukey's Post Hoc.

RESULTS

Forced swim test

There was significant reduction in immobility period in the animals treated with ondansetron and granisetron compared to control group and standard fluoxetine with P <0.05. Among both the test drug 2 granisetron showed marked reduction in mean immobility time of 10 seconds when compared to the test drug 1 ondansetron and fluoxetine which showed a reduction of immobility time of 24.17 seconds and 26.50 seconds respectively. The results of forced swim test have been shown in Table 1 and Figure 1.

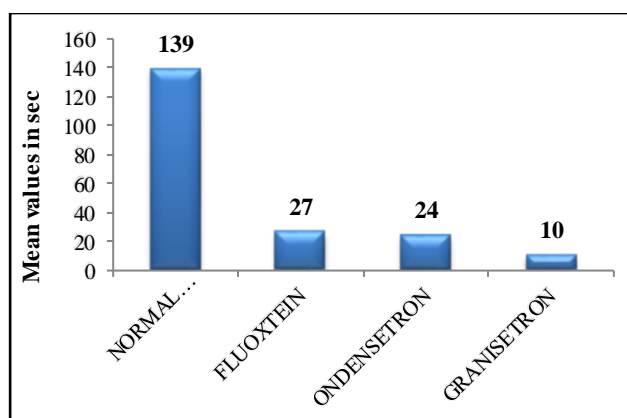


Table 1: Mean Duration of immobility observed in Forced Swim Test model.

Model 1- Forced Swim Test	Mean (Sec)	Std. deviation	ANOVA	P Value
Control- Normal Saline	139.17	33.52	70.37	P<0.000
Standard- Fluoxetine	26.50	7.15		
TD1- Ondansetron	24.17	5.95		
TD2- Granisetron	10.	2.73		

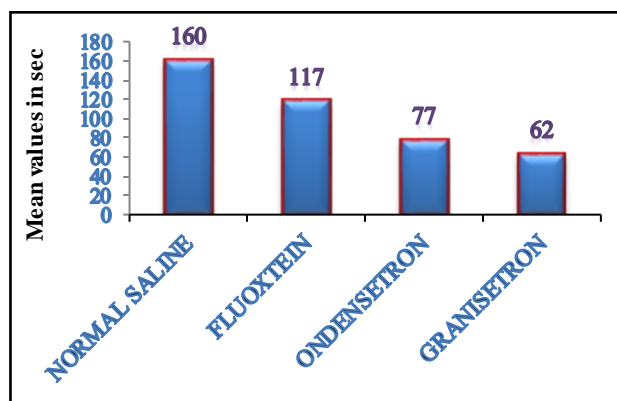
Tail suspension model

Table 1: Mean Duration of immobility observed in Forced Swim Test model.

Model 2- tail suspension test	Mean (Sec)	Std. deviation	ANOVA	P Value
Control- normal saline	159.50	13.92	70.87	P<0.000
Standard- fluoxetine	117.00	13.81		
TD1- ondansetron	76.67	9.27		
TD2- granisetron	62.00	13.40		

Mean duration of immobility in ondansetron and granisetron treated groups of animals was significantly reduced compared to animals in control group and standard fluoxetine with P<0.05. The results were more evident with granisteron when compared to ondansetron. The mean reduction of immobility time observed with granisetron was 62 seconds which was significantly lower than those with ondansetron and fluoxetine administered groups which showed a mean reduction of immobility time of 76.67 seconds and 117 seconds respectively. The results

of tail suspension model have been shown in Table 2 and Figure 2.



DISCUSSION

This study was evaluated to compare the antidepressant activity of drugs ondansetron and granisetron by using forced swim test and tail suspension test. These tests are quite sensitive and relatively specific to all major classes of antidepressant like TCA SSRI, MOAI and atypical antidepressants.^{9,10} It has been argued that tail suspension is less stressful than forced swimming test and has greater pharmacological sensitivity.¹¹ Antidepressant activity is indicated by the reduction in the duration of immobility i.e. lesser the duration more the potency. An increase in the serotonin concentration due to the blockade of the post synaptic 5-HT₃ receptors can facilitate specific binding of Serotonin to other postsynaptic receptors such as 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C}, thereby aiding in serotonergic transmission which could be responsible for the antidepressant-like effect of these 5HT₃ antagonists as many conventional antidepressants also possess affinity for central 5-HT₃ binding sites.¹² Ondansetron, is a carbazole derivative with shorter duration of action of about 3.9 hours and its congener granisetron, a indazole derivative has longer duration of action of about 9-11.6 hours and also it has low potential for drug-drug interactions.¹³

The results obtained in the present study indicate that granisetron, a 5-HT₃ receptor antagonist posse a better antidepressant activity than ondansetron in rodent models predictive of antidepressant activity. In FST, both ondansetron and granisteron showed decrease in immobility duration when compared to control and standard drug fluoxetine. Granisteron showed better decrease of 10.33 sec when compared to ondansetron 24.17 sec. Similar results were obtained in TST, where the granisetron treated group showed better results of 62 sec immobility duration, when compared to 76.67 sec in ondansetron.

CONCLUSION

Based on the present results, it is suggested that both granisetron and ondansetron, novel 5-HT₃ receptor

antagonists possess antidepressant activity with granisetron showing significant reduction in immobility time. Although 5-HT₃ receptor antagonists share equivalent efficacies and safety profiles, there are differences among the agents in terms of pharmacokinetics, and duration of action. These results are further to be confirmed by animal studies with different experimental models for the evaluation of depression and by human clinical studies. If found effective granisetron can be promoted for use of PONV which is usually associated with depression.

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Conflict of interest: None declared

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