

Research Article



Evaluation of Antidepressant Activity of Granisetron in Albino Mice

Sathisha Aithal^{1*}, Geetha S², Swetha ES², Balaji V², Chethan Kumar S³

¹Associate Professor, ²Post graduate, Department of Pharmacology, S.S. Institute of Medical Sciences and Research Centre, Davangere. ³Research Coordinator, S.S. Institute of Medical Sciences and Research Centre, Davangere, Karnataka, India.

*Corresponding author's E-mail: sathishdr2008@gmail.com

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ABSTRACT

Depression is one of the highly prevalent and disabling conditions associated with significant morbidity and mortality. The present study was performed to evaluate the antidepressant activity of granisetron, a 5-HT₃ receptor antagonist in rodent models of depression such as forced swim test (FST) and tail suspension test (TST). Freshly prepared solution of granisetron (0.5mg/kg) were administered orally to mice for 14 days, and the experiments were conducted on day 1 and day 14. There was a statistically significant (P <0.05) reduction in the duration of immobility in FST on both acute (day 01) and chronic (day 14) treatment with granisetron compared to control as well as amitriptyline treated groups. However, in TST there was significant reduction in immobility in animals treated with granisetron compared to the control group only. Hence, the present study showed that granisetron has antidepressant like action, which may be because of its antagonism at the 5-HT₃ receptor site and that it may be used as an alternative for the treatment of depression.

Keywords: Depression, Forced swim test, Tail suspension test.

INTRODUCTION

Depression is a major affective disorder seen in most of the patients and it is associated with diminished health status and increased health care utilization. It is highly prevalent and disabling condition associated with significant morbidity and mortality.¹

The major class of antidepressants includes tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), various atypical anti-depressants and norepinephrine dopamine reuptake inhibitors (NDRIs). Many new classes of drugs have been found to have antidepressant effects such as tianeptine (acting via pituitary-adrenal axis inhibition), leptin (a hormone secreted by adipose tissue), and rolipram (a phosphodiesterase inhibitor).²⁻⁴ Despite the availability of these drugs and advent of new molecules pharmacotherapy of depression is not satisfactory.⁵ The serotonergic system has pivotal role in affective disorders.⁶⁻⁹ The 5-HT₃ receptors are widely distributed in median raphe, hypothalamus, hippocampus and amygdala.^{10,11} Several pre-clinical investigations showed possible relationship between 5-HT₃ receptors and depression as well as other cognitive disorders.¹²

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.¹³ Therefore the present study was undertaken to evaluate

the antidepressant activity of granisetron in experimental models.

MATERIALS AND METHODS

Albino mice of either sex of average weight 20-25gm which were inbred in central animal house of S.S. Institute of medical Sciences and Research Centre, Davangere, were utilized for the study. Animals were randomly housed as 6 mice per cage at an ambient temperature and humidity, with a 12 hour light and 12 hour dark cycle. The animals had free access to food and water, *ad libitum*. A total of 18 (n=6) animals were divided into 3 groups of 6 each. The same groups of animals were subjected to both tail suspension and forced swim tests with washout period of two weeks.

Drugs were administered from day 01 till day 14 and the experiments were conducted on day 01 and day 14. The animal ethics committee approval was taken prior to the experiment. Statistical analysis was done using one way ANOVA with GraphPad InStat version 3.06. P value <0.05 was considered as statistically significant.

The animals were grouped and administered drugs as follows (n=6 each)

Group 1 (Control): Normal saline 1ml

Group 2 (Standard): Amitriptyline, 20mg/kg body weight orally for 14 days

Group 3 (Test drug): Granisetron, 0.5mg/kg orally for 14 days.

The drugs were administered orally every day for fourteen days. The recommended dose of granisetron in humans was used to calculate the dose for experimental



animal.¹⁴ The selection dose of amitriptyline used was based on previous study.¹⁵

Forced Swimming Test

The Forced Swimming Test (FST), developed by Roger Porsolt was used.¹⁶ One day prior to test, mice were dropped into glass cylinder (height 25cm, diameter 10cm, and containing water level of 10cm, maintained at 23 - 25 degree Celsius) for about 15 minutes and then taken out for towel drying. This was done for adaptation of animals. On the next day, the mice were dropped individually in the glass cylinder for about 6 minutes. The last 4 minutes of the testing period was considered for taking the parameters, as the first 2 minutes are for habituation. The animals received the test drug/standard drug/control orally 30 min before the test. The floating or immobility time was noted down i.e., floating in upright position except for the small movements to keep their heads above water.

Tail Suspension Test

The Tail Suspension Test (TST) developed by Steru was used.¹⁷ After 30 minutes of oral administration of test drug/standard drug/control, mice were suspended from a metal rod mounted 50 cm above the surface by fastening the tail to the rod with the adhesive tape for 6 minutes. The measuring principle is based on the energy developed by a mouse trying to escape from its suspension. The immobility time was noted down in the last 4 minutes. Immobility here refers to the absence of any body or limb movements except for those caused by respiration.

RESULTS

Forced swim test

On day 1, there was significant reduction in immobility period in the animals treated with amitriptyline and granisetron compared to control group ($P < 0.05$, Table 1). Similar findings were obtained when experiments were repeated after 14 days of drug administration ($P < 0.05$, Table 1).

Table 1: Effect of granisetron on immobility period in forced swimming test

Groups	Mean±SEM (Day 01)	Mean±SEM (Day 14)
Control	125.3±13.5	130±15.2
Amitriptyline	50.7±16.7 [**]	36.8±13.0 [***]
Granisetron	32.7±6.9 [***],#	24.3±7.2 [***],#

** $P < 0.01$ compared to control, *** $P < 0.001$ compared to control, # $P < 0.05$ compared to amitriptyline, SEM: Standard Error of Mean

Tail suspension test

Mean duration of immobility in amitriptyline and granisetron treated groups of animals was significantly reduced compared to animals in control group on day 1 ($P < 0.05$, Table 2). The results were similar when animals

were subjected to tail suspension test on day 14. ($P < 0.05$, Table 2).

Table 2: Effect of granisetron on immobility period in tail suspension test

Groups	Mean±SEM (Day 01)	Mean±SEM (Day 14)
Control	146.7±6.8	154.3±8.8
Amitriptyline	93.3±9.9 [***]	89.3±4.9 [***]
Granisetron	158.7±7.4 [*]	98±6.1 [***]

* $P < 0.05$ compared to control, *** $P < 0.001$ compared to control, SEM: Standard Error of Mean

DISCUSSION

Depression is among the most widely occurring disorders, its true prevalence being unknown.¹⁸ The National Comorbidity Survey Replication found that 16.2 % of the population studied had a history of major depressive disorder in their lifetime, and more than 6.6 % had an episode within the past 12 months.¹⁹ Approximately two-thirds of the depressed patients respond to the currently available treatments however, magnitude of improvement is still disappointing, and these drugs may have unusual side effects.²⁰ Hence, investigators keep seeking for new drugs because of unsatisfactory response and non-compliance of the existing drugs.¹⁸ New synthetic compounds with anti-depressant effect has been drawing more attention gradually because of increasing incidence of depression.²¹⁻²³

Predictive assays of antidepressant activity such as FST and TST in mice are responsive to major classes of antidepressants including TCAs, SSRIs and SNRIs.^{24,25} There is a significant correlation between the potency of anti-depressants in both forced-swimming and tail-suspension tests and clinical potency of the drugs.²⁶ The immobility observed using FST and TST corresponds to human depression.²⁷

The results obtained in the present study indicate that granisetron, a 5-HT₃ receptor antagonist is active in rodent models predictive of antidepressant activity. The mean duration of immobility in animals treated with granisetron was reduced which was statistically significant compared to control in both the tests. In FST, the duration of immobility with granisetron was reduced which was statistically significant compared to both control and amitriptyline, whereas in TST, statistically significant reduction in immobility duration was observed only in comparison to the control.

The investigational drug granisetron is currently approved as an antiemetic. It acts by blocking 5-HT₃ receptors both peripherally on vagal nerve terminals as well as centrally on nucleus tractus solitaries and chemoreceptor trigger zone.²⁸ The 5-HT₃ receptors sites are ligand gated ion channels which mediate the release of number of neurotransmitters.²⁹ There are evidence suggesting the possible involvement of 5-HT₃ receptors in depression.³⁰



Previous study found ondansetron, a 5-HT₃ receptor antagonist has antidepressant activity in rats using learned helplessness model.³¹ As conventional antidepressants also show affinity for central 5-HT₃ binding sites, direct antagonism at 5-HT₃ receptor site may be associated with antidepressant activity. The 5-HT₃ receptors found to modulate neuronal release of norepinephrine (NE). Therefore, other possible mechanism of antidepressant action may be increased release of NE due to blockade of 5-HT₃ receptors.³²

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. There is evidence to suggest that there may also be differences in terms of efficacy in certain patient groups.³³ Ondansetron, a carbazole derivative has short duration of action of about 3.9 hours, h its congener granisetron, a indazole derivative used in the present study has longer duration of action of about 9 – 11.6 hours and also has low potential for drug-drug interactions.³⁴

CONCLUSION

Granisetron at a dose of 0.5mg/kg exerted antidepressant like effect in both forced swim test and tail suspension test. These effects may be because of modulation of central monoaminergic neurotransmitter systems by blocking the post synaptic 5-HT₃ receptors. The results of study suggest that granisetron may be useful as a potential candidate for treatment of depression. However, further studies are required to elucidate the exact mechanism of action of antidepressant activity of granisetron. Also, assessment of the safety profile of the molecule is essential, though no abnormal behavior was noted at the tested dose level.

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