Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20170503

Original Research Article

Antidepressant effect of atypical antipsychotic ziprasidone in albino rats

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Received: 13 January 2017
Accepted: 20 January 2017

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ABSTRACT

Background: Depression is a common psychiatric illness but conventional antidepressants are often shows unpredictable response. Pharmacological profiles of many atypical antipsychotics have potential antidepressant effect. Ziprasidone is an atypical antidepressant with 5HT1A agonistic activity and 5HT1D, 5HT2A and D2 receptors antagonistic activity. It's a potential candidate for evaluating possible antidepressant activity.
Methods: Behavioural despair test are widely used for evaluation of potential antidepressant molecule. Tail suspension test is a variant of behavioural despair test. Healthy male Wistar albino rat 18 in number and weighing between of 150-200 grams were divided in 3 groups with 6 rats in each group. Group A was treated with 0.9% Normal Saline, Group B with Fluoxetine and Group C with Ziprasidone for 28 days. Tail suspension test was done on day 0, 7, 14, 21 and 28 days.
Results: In comparison to Normal saline both the drugs shows significant antidepressant activity after 28 days of treatment. While antidepressant activity of fluoxetine started to appear from day 7; that of ziprasidone started to appear from 14th day.
Conclusions: Ziprasidone can be suitable candidate for clinical trials of Major Depressive Disorders not responding to conventional antidepressant.

Keywords: Antidepressant, Atypical antipsychotics, Depression, Tail suspension test, Ziprasidone

INTRODUCTION

In day to day psychiatric practice Major Depressive Disorder (MDD) has common occurrence. To stamp the diagnosis patients of MDD should have one of the two major symptoms (i.e. - constant sadness, anhedonia) plus at least five out of nine secondary symptoms (i.e. - feelings of worthlessness, difficulty in concentrating, changes in diet, changes in sleep patterns, decrease interest or pleasure, irritable, and change in activity, fatigue and suicidal tendency) for a period of minimum two weeks.[1] Though there are no age discriminations, highest rate of MDD is seen in adults between 18-29 years, with 1.5 to 3 time greater incidence in females.[2] Depression in adolescence is commonly associated with co-morbid substance abuse, multiple suicide attempts and death.[3]

Multiple etiological factors- genetic, biochemical, psychodynamic and socio-environmental are responsible for depression. Depressive disorders and suicides tend to familial occurrence. At least one first-degree relative (father, mother, brother, or sister) with a history of depression can be found in the family of approximately 10% to 15% of patients of major depression. At the same time, first-degree relatives of patients with depression are 1.5 to 3 times more likely to develop depression.[4] Higher concordance rate is found among monozygotic twins (46%) than dizygotic siblings (20%).[5] Decrease in level of brain neurotransmitters like serotonin and nor-epinephrine are important biochemical factors.[6] Onset of depression often preceded by crucial life events, particularly the death or loss of a loved one or an emotional trauma.[7]

Due to profound biological and psychosocial foundation, MDD fairly responds to biological and psychological treatments. During the past 2 decades there is major improvement in the understanding, screening, diagnosis, and treatment of MDD. However the pharmacotherapy of depression still remains inadequate; despite a large increase in the number of antidepressants.[8] At least 40% of patients do not respond to antidepressant therapy.[9] Additionally, most of the currently available agents are associated with frequent and persistent side effects, such as sedation, apathy and fatigue, sleep disturbances, cognitive impairments and sexual dysfunctions.

In terms of relative safety newer class of antidepressants, such as the serotonin selective reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRIs) have gained wide acceptance. But in clinical practice their efficacy is not up to the expectation. With contemporary first line antidepressant monotherapy of MDD shows only modest response and remission rates, development of safer and more effective modalities of treatment is need of the day.

US FDA in recent past approved some atypical antipsychotics like Aripiprazole, Quetiapine and Olanzapine as an adjuvant treatment for MDD. Atypical antipsychotic ziprasidone shows agonistic activity on $5HT_{1A}$ receptors while acts as antagonist to $5HT_{1D}$, $5HT_{2A}$ and D_2 receptors. This diverse pharmacological profile can be explored as a potential antidepressant.[10,11]

Current study is designed to evaluate potential antidepressant activity of atypical antipsychotic drug Ziprasidone and compare its effectiveness with standard antidepressant Fluoxetine (SSRI) in depressive animal model.

METHODS

18 healthy Wistar albino rats were chosen for this study. Animals were kept under standard laboratory condition and duly cared for and the entire experiment was conducted in accordance to the ethical norms of Institutional Animal Ethics Committee (IAEC). Drugs used in the study were Tab. Fluoxetine: - (Floxin 20 mg tab) D.D. pharmaceuticals (P) Ltd. Jaipur and Tab. Ziprasidone: - (Zipsydon 20 mg tab) Sun pharma Laboratories Ltd. East Sikkim. No therapeutic intervention was done in the control group. Dose calculation was done from the standard clinical human dose on the basis of surface area and using the conversion factor (0.018) for 200 Gms of rat. [12, 13] The test was done between 9:00 am to 2:00 pm.

Inclusion criteria

1. Animals were male Wistar albino rats.
2. Weight of the animal used was 150-200 Gms.
3. All the animals used for the study were healthy and active in their cage.

Exclusion criteria

1. Female rats were excluded.
2. Rats with weight less than 150grams and above 200grams were excluded.
3. Diseased and inactive rats were excluded from study.

Animals were divided into 3 groups with 6 rats in each and the cages were labelled and animals in each cage were colour coded separately for operational ease. Test drugs were given orally as per appropriate weight of individual animal daily. They were evaluated for antidepressant activity using Modified Tail Suspension Test model on day 0, 7, 14, 21 and 28.

1 hr. before starting the test animals were brought to the experiment room. During the test food and water was removed from their cages. The experiment was conducted 1 hour after oral administration of the drug. Sufficient gap was maintained during drug administration so that all the animals are tested after 1 hour of the oral administration of the drug on the test day.

Details of the groups are shown in Table 1.

Table 1: Details of groups.

Groups	No. of rats	Drugs	Dose
A	6	0.9% NS	1ml
B	6	Fluoxetine	2mg/kg
C	6	Ziprasidone	7mg/kg

Modified Tail Suspension Test

Tail suspension test (TST) for evaluation of antidepressant activity of new compound using mice was first introduced by Streru et al in 1985.[14,15] Chermat et al during 1986 modified the method for adopting the test in Rat. In the modified method rats were suspended upside down on a metal rod in tail suspension box at a height of 55 cm from the ground with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Initially the animal tries to escape by making vigorous movements but when unable to escape became immobile. The animal was considered immobile when it doesn't not show any movement of body and remain hanged passively. Clinically effective antidepressants reduce the immobility that rat display after active and unsuccessful attempt to escape when suspended by the tail. This test is a variant of the behavioural despair test in which immobility is induced by simply suspending a rat by tail. This test is a reliable and rapid screening method for antidepressants. The immobility displayed by rodents when subjected to this kind of unavoidable and inescapable stress has been hypothesized to reflect behavioural despair which in turn may reflect depressive disorders in humans. The total duration of immobility was noted during 6 minute period.

Statistical analysis

Using IBM SPSS version 20 statistical analysis of data was carried out by employing analysis of variance (ANOVA) test followed by Tukey's HSD (honestly significant difference) test for post-hoc analysis of significant overall differences. Confidence interval 95% and p - value <0.05 was taken significant.

RESULTS

The following data were obtained in all groups of Rat after administering them respective drugs for a period of 28 days. The immobility time (in seconds) were recorded on 0, 7th, 14th, 21st, and 28th day of treatment by modified tail suspension test model.

Change of immobility time (in seconds) by modified TST on 0, 7th, 14th, 21st and 28th are shown in (Table 2). Data are as expressed mean ± standard deviation.

Table 2: change of immobility time (in seconds) by modified TST on 0, 7th, 14th, 21st and 28th day.

	0 day	7 day	14 day	21 day	28 day
Gr. A	193.9± 3.60	193.2± 3.43	193.6± 2.76	192.9± 4.04	193.3± 3.09
Gr. B	193.7± 4.03	184.3± 4.30	176.6± 4.99	169.1± 4.31	164.1± 4.09
Gr. C	193.9± 4.01	191.0± 4.06	185.0± 5.10	180.7± 5.76	176.1± 5.63

Statistical analysis between the groups and within the groups is shown in (Table 3).

Table 3: Statistical analysis.

Day	0	7	14	21	28
Mean difference (Gr A-B)	0.200	8.9000	17.000	23.800	29.200
p value	0.999	0.001*	0.000*	0.000*	0.000*
Mean difference (Gr A-C)	0.000	2.200	08.600	12.2000	17.200
p value	1.000	0.699	0.001*	00.000*	0.000*
Mean difference (Gr B-C)	0.100	1.300	07.600	11.6000	13.9000
p value	1.000	0.917	0.004*	0.0000*	0.0000*

Sequential change in Immobility time (in sec.) by modified TST in All the Groups throughout the study period can be seen in (Figure 1).

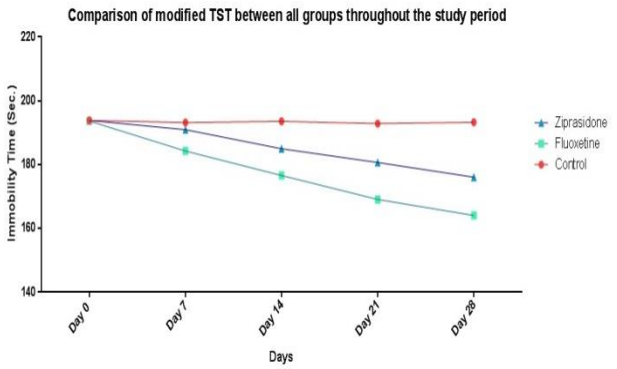

Figure 1: Sequential change in immobility time (in sec.) by modified TST in all the groups throughout the study period.

Changes in immobility time in all groups before and after 28 day of treatment can be seen in (Figure 2).

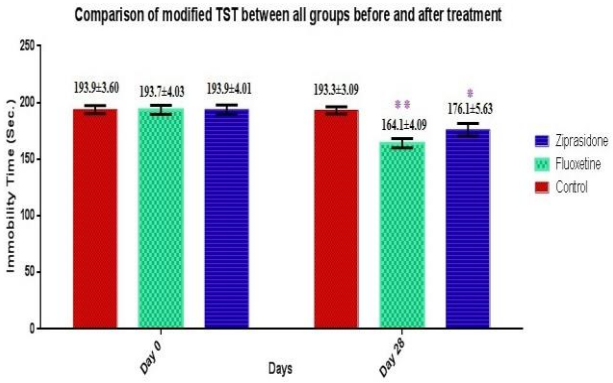

Figure 2: Changes in immobility time in all groups before and after treatment.

DISCUSSION

Following test results shows comparative antidepressant effect in relation to standard antidepressant fluoxetine and control drug (0.9% normal saline).

Tail suspension Test model is widely used to screen newer and potential antidepressant drugs. There is a significant correlation between the efficacy of antidepressants in tail suspension tests and clinical effectiveness of the drugs.[16] The test is both sensitive and specific for all major classes of antidepressants like tricyclics antidepressant, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and even for atypical antidepressants.[17]

The results in the tail suspension test were assessed by duration of immobility in 6 minutes duration. Antidepressant activity is indicated by the reduction in

the duration of immobility i.e. lesser the duration indicates more effectiveness of the drug. All results have been expressed as mean ± standard deviation. (Table 2) shows the results of modified TST over time in Group A, Group B and Group C. (Table 3) shows the statistical analysis. (Figure 1) shows the group wise changes in immobility time (in seconds) by modified TST for the entire duration of the study and results from (Table 3) concludes that both the drugs, i.e. - fluoxetine and ziprasidone have significant antidepressant activity. (Figure 2) reveals superior antidepressant activity of fluoxetine in comparison to ziprasidone at the end of 28 days of treatment.

Various studies already established the role of serotonergic dysfunction in the development of depression.[18] Standard antidepressant fluoxetine enhances serotonergic transmission through $5HT_{2A}$ and $5HT_{2C}$ receptors by inhibiting uptake of serotonin by these neurons.[19] Clinical trials showed presence of antidepressant activity of many atypical antipsychotics and there is increasing number of prescription of atypical antipsychotics for MDD.[20,21] Recently atypical antipsychotics like Olanzapine, Quetiapine and Aripiprazole has been approved by US FDA for use in treatment of MDD.

Pharmacological profile of Ziprasidone has high affinity towards $5HT_{1A}$ receptors and shows agonistic property along with, low affinity and antagonist action on $5HT_{1D}$, $5HT_{2A}$ and D_2 receptors.[22,23]

In the case of the $5HT_{1D}$ terminal autoreceptors, occupancy of this receptor by endogenous serotonin causes a blockade of serotonin release. On the other hand, drugs that block the $5HT_{1D}$ autoreceptors can promote serotonin release, and this could hypothetically result in antidepressant actions. At the same time stimulation of $5HT_{1A}$ receptors and blocking of $5HT_{2A}$ receptors, both causes increase release serotonin in the frontal cortex. This has led to speculation that those atypical antipsychotics with $5HT_{1A}$ partial agonist actions that are proven antidepressants (such as quetiapine and aripiprazole) may be working in part through this mechanism, and that other atypical antipsychotics with $5HT_{1A}$ partial agonist actions are also potential antidepressants (such as ziprasidone, lurasidone, iloperidone, and others).[24]

All known first generation antipsychotics are blockers of dopamine D_2 receptors, although at different degree of affinity. Given its low affinity to block D_2 receptor, antidepressant efficacy might be expected in ziprasidone.[23]

R. Rajkumar et al in their study in 2009 showed that Ziprasidone has antidepressant efficacy in a 1-m – chlorophenyl piperazine induced animal model of depression.[25] Results of current study also showed that ziprasidone has potential antidepressant activity in terms of decrease in immobility time in depressive model of modified tail suspension test in rats.

In the treatment of MDD commonly used first line antidepressant drugs acts by directly inhibiting the reuptake or degradation of at least one of the monoamine neurotransmitter in the brain (serotonin, dopamine or noradrenaline), though a variety of different classes of anti-depressant are available for clinical use, a significant proportion of patients either shows resistance or failed to achieve remission.[20,26]

Atypical antipsychotics such as Ziprasidone have their affinity for number of serotonergic structures including the $5HT_1$ and $5HT_2$ receptor subtypes. Thus they can be used both as monotherapy and as augmenting agent in resistant cases of MDD.[27,28]

CONCLUSION

From the results of our study and above discussion it can be concluded that the diverse pharmacodynamics profile of Ziprasidone makes it a suitable candidate for new antidepressant to be evaluated in further clinical trials for resistant cases of MDD.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee, Rajendra Institute of Medical Sciences (RIMS), Ranchi

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Cite this article as: Kumar R, Kumar H, Keshri USP, Gari M. Antidepressant effect of atypical antipsychotic ziprasidone in albino rats. Int J Basic Clin Pharmacol 2017;6:528-32.