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Original Research Article

Study of the comparative effects of fluoxetine and ziprasidone in albino rats by using tail suspension test model

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ABSTRACT

Background: Depression is a group of disorders results from a combination of multiple etiologic factors- genetic, biochemical, psychodynamic and socio-environmental. A depression consists of following clinical features as sadness, apathy, changes in sleep pattern, impaired concentration, feeling of shame or guilt and thoughts of dying or death. Fluoxetine and Ziprasidone both are used for the treatment of Depression in human being. Fluoxetine is Selective serotonin reuptake inhibitors (SSRI) and Ziprasidone is atypical antipsychotic.
Methods: Healthy male albino rats weighing between 150-200 grams were taken for the present study. Study animals were divided into three groups randomly with each group consisting of ten animals. Drugs were powdered with help of mortar and pestle and mixed in gum acacia solution. Appropriate volume of the freshly prepared solution was administered orally daily between 9 am to 10 am to all animal as per their individual body weight. Group A administered 1ml of 0.9% normal saline orally and serves as control group. Group B administered 0.4 mg of fluoxetine orally. Group C administered 1.6 mg of ziprasidone orally. Animals were evaluated for antidepressant activity using two models – Tail suspension test and Forced swimming test.
Results: 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.
Conclusions: There is significant difference in antidepressant activity of fluoxetine with antidepressant activity of ziprasidone.

Keywords: Psychodynamic, SSRI, Tail suspension test, Forced swimming test

INTRODUCTION

Depression is a major affective disorder. It belongs to the heterogeneous group of mood disorders characterized by extreme exaggerations and disturbances of mood, which adversely affect cognition and psychomotor functions.[1] Depression is diagnosed when depressed mood on a daily basis persist for a minimum duration of 2 weeks. A depressive episode may be characterized by sadness, apathy, changes in sleep pattern, impaired concentration, feeling of shame or guilt and thoughts of dying or death.[2] Depression must be distinguished from normal grief, sadness, disappointment and the dysphoria or demoralization associated with medical illness and from bipolar disorder in which depression alters with hypomania or mania. The condition is often under diagnosed and frequently undertreated.[3] Major depressive disorder is a mental disorder common in psychiatric practice wherein a patient presents with at least one of the two major symptoms, constant sadness or anhedonia, accompanied by at least five of these nine secondary symptoms for at least two weeks.[4] Although depression

can occur at any age, adults 18 to 29 years of age experience the highest rates of major depression during any given year.[5] Women are at increased risk of depression from early adolescence until their mid-50s, with a lifetime rate that is 1.5 to 3 times greater than for men.[5] The estimated lifetime prevalence of major depression in individuals aged 65 to 80 years recently was reported to be 20.4% in women and 9.6% in men.[6] Depressive disorders are common during adolescence, with co-morbid substance abuse, suicide attempts and deaths occurring frequently in these patients.[7] In the Global Burden of Disease (GBD) Study conducted by the World Health Organization, unipolar major depression ranked second among all diseases in terms of disability-adjusted life-years.[8] At its worst, it can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year globally.[9] A recent meta-analysis found that the heritability of liability for major depression was 37%, whereas the remaining 63% of the variance in liability was caused by individual specific environment[10]. Monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%).[11] Biochemical factors include decrease in level of neurotransmitters like nor-epinephrine and serotonin in the brain.[12] Crucial life events, particularly the death or loss of a loved one or an emotional trauma can precede the onset of depression.[13]

The current study was conducted with following aims and objectives: to evaluate the antidepressant effect of Ziprasidone and to compare the antidepressant effect of Fluoxetine with Ziprasidone.

METHODS

Place of study

The entire experiment was carried out in postgraduate laboratory Department of Pharmacology and therapeutics Rajendra Institute of Medical Sciences, Ranchi.

Study design

Randomized, open label, interventional, comparative, depressive model animal study.

Study duration

Total six months from June 2015 to November 2015.

Animal

Healthy male Wistar albino rats weighing between 150-200 grams were taken for the present study. The animals were kept in clean and dry standard size cages (10 rats per cage).

Inclusion criteria

Healthy and active male Wistar albino rats. Weight of the animal used was 150-200 grams.

Exclusion criteria

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

Table 1: Grouping in animals.

Group	No. of rats	Drug
A (Control)	10	0.9% normal saline
B	10	Fluoxetine
C (Ziprasidone)	10	Ziprasidone

Equipments

Cylindrical tanks (30 cm height × 30 cm diameters), tail suspension box (55 cm height × 30 cm width × 11.5 cm depth), adhesive tape, syringes, 60 w bulb, towel, tissue paper, animal feeding tube (gavage tube), sterilized cotton, 1% gum acacia suspension and stopwatch.

Administration of drugs with doses

Study animals were divided into three groups randomly with each group consisting of ten animals. Drugs were powdered with help of mortar and pestle and mixed in gum acacia solution. Appropriate volume of the freshly prepared solution was administered orally daily between 9 am to 10 am to all animal as per their individual body weight. Group A administered 1ml of 0.9% normal saline orally and serves as control group. Group B administered 0.4 mg of fluoxetine orally. Group C administered 1.6 mg of ziprasidone orally.

Testing procedure

Animals were evaluated for antidepressant activity using model – Tail suspension test (TST). Animals were brought to the experiment room 1 hour before beginning of the experiment. The food and water was removed for the duration of test. Animals were weighed and appropriate dose of drug was given orally to different groups. The experiment was conducted 1 hour after oral administration of the drug.

Tail suspension test[14]

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 total duration of immobility was noted during 6 minute period.

Statistical analysis

All the results of testing on different days were carefully recorded in Microsoft excel 2010 software and then statistical analysis of data was carried out using IBM Statistical package for social sciences (SPSS) software version 23. One-way ANOVA test was used to compare the effect of drugs on different groups. Tukey's HSD test was employed for post-hoc analysis of significant overall difference between the groups.

RESULTS

Tail suspension test

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. The results have been expressed as mean ± standard deviation of duration of immobility in seconds during 6 minutes of observation period.

The Table 2 showing the changes in immobility time in seconds by Tail suspension test in group A, B and C which contain 10 animals each. Group A is control and given 0.9% Normal saline while group B given Fluoxetine and group C given Ziprasidone.

Table 2: Sequential changes in immobility time (in seconds) by Tail suspension test in all groups on 0, 7th, 14th, 21st, 28th, 35th and 42nd day. All the values are expressed in mean± standard deviation.

Day	Group A	Group B	Group C
0	193.9±3.60	193.7±4.03	193.9±4.01
7	193.2±3.43	184.3±4.30	191.0±4.06
14	193.6±2.76	176.6±4.99	185.0±5.10
21	192.9±4.04	169.1±4.31	180.7±5.76
28	193.3±3.09	164.1±4.09	176.1±5.63
35	193.2±3.52	160.2±4.71	172.3±6.00
42	193.3±2.91	155.8±4.54	168.7±6.34

The Table 3 is showing the significant P value after first day and 7th of given drug in group A and B. Mean difference is greater as 37.5000 after day 42 of administration of drug.

The Table 4 is showing the significant P value after first day, 7th day and 14th day of given drug in group A and C. Mean difference is greater as 24.6000 after day 42 of administration of drug.

Table 3: Comparison between Group A and Group B.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Group A	193.9±3.60	193.2±3.43	193.6±2.76	192.9±4.04	193.3±3.09	193.2±3.52	193.3±2.91
Group B	193.7±4.03	184.3±4.30	176.6±4.99	169.1±4.31	164.1±4.09	160.2±4.71	155.8±4.54
Mean difference	0.2000	8.9000	17.0000	23.8000	29.2000	33.0000	37.5000
P value	0.999	0.001	0.0000	0.0000	0.0000	0.0000	0.0000

Table 4: Comparison between Group A and Group C.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Group A	193.9±3.60	193.2±3.43	193.6±2.76	192.9±4.04	193.3±3.09	193.2±3.52	193.3±2.91
Group C	193.9±4.01	191.0±4.06	185.0±5.10	180.7±5.76	176.1±5.63	172.3±6.00	168.7±6.34
Mean difference	0.0000	2.2000	8.6000	12.2000	17.2000	20.9000	24.6000
P value	1.0000	0.699	0.001	0.0000	0.0000	0.0000	0.0000

Table 5: Comparison between Group B and Group C.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Group B	193.7±4.03	184.3±4.30	176.6±4.99	169.1±4.31	164.1±4.09	160.2±4.71	155.8±4.54
Group C	193.9±4.01	191.0±4.06	185.0±5.10	180.7±5.76	176.1±5.63	172.3±6.00	168.7±6.34
Mean difference	0.2	6.7000	8.4000	11.6000	12.0000	12.1000	12.9000
P value	0.999	0.011	0.001	0.0000	0.0000	0.0000	0.0000

The Table 5 is showing the significant P value after first day, 7th day and 14th day of given drug in group B and C. Mean difference is greater as 12.9000 after day 42 of administration of drug.

DISCUSSION

The present study evaluated the possible antidepressant activity of the drugs ziprasidone and fluoxetine, by using the Tail suspension test experimental animal model. The result following this test has been compared with that of standard antidepressant drug fluoxetine, and with 0.9% Normal Saline taken as control. There is a significant correlation between the efficacy of antidepressants in tail suspension tests and clinical effectiveness of the drugs.[16] The test is quite sensitive and relatively specific to all major classes of antidepressants like tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and atypical antidepressants.[17] From table 2 it's evident that Fluoxetine showed significant antidepressant activity in comparison to normal saline from 7th day with p value 0.001 for Tail suspension test. In our study ziprasidone showed significant antidepressant activity in comparison to normal saline, by means of reduced immobility time starting from day 14th (Table 3) with p=0.001 for Tail suspension test. From table 4 it is clear that there is significant difference exists between the antidepressant activity of Fluoxetine and Ziprasidone in Tail suspension test model. Ziprasidone is a newer atypical antipsychotic. Ziprasidone has high affinity towards 5HT1A receptors and shows agonistic property along with, low affinity and antagonist action on 5HT1D, 5HT2A and D2 receptors.[18] Antidepressants are first-line treatment for patients with major depressive disorder (MDD). Commonly used antidepressants directly inhibit the reuptake of at least one monoamine neurotransmitter in the brain (serotonin, dopamine or noradrenalin), or block their degradation. Despite the availability of large number of antidepressants of different classes, significant portion of patients do not achieve remission.[19] Pharmacological profile of ziprasidone has both 5HT1A stimulating and 5HT1D and 5HT2A blocking property contributing towards its possible antidepressant action and results of our study also support the hypothesis of potential antidepressant activity in ziprasidone.

CONCLUSION

From result of our study it can be concluded that -

Ziprasidone showed significant antidepressant activity by tail suspension test in albino rat. Ziprasidone showed antidepressant activity after two weeks of starting the drugs. There is significant difference in antidepressant activity of fluoxetine with antidepressant activity of ziprasidone. Schizophrenia is a known psychiatric disorder often coexists with depression and Ziprasidone by virtue of its diverse pharmacodynamic effect can prove to be beneficial in such scenario both as an atypical antipsychotic and antidepressant.

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

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