pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20211021

Original Research Article

Evaluation of the comparison of anti-depressant effects of oral fluoxetine and riluzole in albino rats by using the forced swimming test model

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Received: 31 January 2021 Accepted: 03 March 2021

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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 riluzole both are used for the treatment of depression in human being. Fluoxetine is SSRI (selective serotonin reuptake inhibitors) and riluzole is anxiolytic and mood stabilizer.

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 2 mg of riluzole orally. Animals were evaluated for antidepressant activity using model-forced swimming test.

Results: The results in the forced swimming test were assessed by duration of immobility in last 4 minutes of total 6 minute test duration. Antidepressant activity is indicated by the reduction in the duration of immobility i.e. lesser the duration more the efficacy. The results have been expressed as mean±standard deviation of duration of immobility in seconds during 6 minute period.

Conclusions: There was significant difference in antidepressant activity of fluoxetine with antidepressant activity of riluzole. Riluzole showed antidepressant activity after two weeks of starting the drugs.

Keywords: Anxiolytic, Forced swimming test, Psychodynamic, SSRI

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. 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. 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 lifeyears.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

METHODS

Place of study

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

Study design

It was a randomized, open label, interventional, comparative, depressive model animal study.

Study duration

After 14 days period of acclimatization to the laboratory condition, the study was done for 42 days. The immobility time (in seconds) were recorded on 0, 7th, 14th, 21st, 28th, 35th and 42nd day of treatment by forced swimming test (FST) models.

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.

Tabble 1: Grouping of animals.

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

Equipment's

Cylindrical tanks (30 cm height \times 30 cm diameters), 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 2 mg of riluzole orally.

Testing procedure

Animals were evaluated for antidepressant activity using model-forced swimming test.

Forced swimming test14

The forced swimming model used in the present study was similar to the original method described by Porsolt et al during 1977-78 for testing antidepressant activity of new compound. The animals were forced to swim in a plastic cylinder measuring 30 × 30 cm containing water up to a depth of 20 cm at room temperature. After an initial 2 minute period of vigorous activity, each animal assumed a typical immobile posture. The rat 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 rats were subjected to a 15-minute training session under similar conditions, 24 hour before the test. The total duration of immobility was recorded for next 4 minutes of total 6 minute duration of test. The changes in immobility duration were studied after administering drugs in separate group of animals. Following swimming sessions, the rats were dried with towel and placed in a cylinder heated under 60 w bulb. The animals were allowed to dry for 15 minutes before returning them to their respective cages.

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 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

Forced swimming test (FST)

The results in the forced swimming test were assessed by duration of immobility in last 4 minutes of total 6 minute test duration. Antidepressant activity is indicated by the reduction in the duration of immobility i.e. lesser the duration more the efficacy. The results have been

expressed as mean±standard deviation of duration of immobility in seconds during 6 minute period.

Table 1: Sequential changes in immobility time (in seconds) by FST in all groups on 0, 7th, 14th, 21st, 28th, 35th and 42nd day.

Day	Gr A	Gr B	Gr C
0	48.0±3.97	48.3±2.66	48.4±1.64
7	48.1±2.02	46.3±2.40	46.6±1.95
14	47.8±2.97	43.4±2.67	44.7±2.05
21	47.7±4.85	40.3±2.31	42.9±2.33
28	47.8±3.93	36.7±3.09	40.1±2.13
35	46.9±3.07	33.1±2.76	39.8±1.93
42	47.3±3.09	32.1±2.64	37.4±1.77

All the values are expressed in mean±standard deviation.

Table 2: Comparison between group A and group B.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Gr. A	48.0 ± 3.97	48.1±2.02	47.8 ± 2.97	47.7±4.85	47.8±3.93	46.9±3.07	47.3±3.09
Gr. B	48.3±2.66	46.3±2.40	43.4±2.67	40.3±2.31	36.7±3.09	33.1±2.76	32.1±2.64
Mean difference	0.3000	5.6000	7.7000	9.6000	12.9000	14.2000	16.1000
P value	0.995	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 3: Comparison between group A and group C.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Gr. A	48.0±3.97	48.1±2.02	47.8±2.97	47.7±4.85	47.8±3.93	46.9±3.07	47.3±3.09
Gr. C	48.4±1.64	46.6±1.95	44.7±2.05	42.9±2.33	40.1±2.13	39.8±1.93	37.4±1.77
Mean difference	0.4000	1.5000	4.0000	4.8000	7.0000	7.4000	9.9000
P value	0.987	0.267	0.001	0.004	0.0000	0.0000	0.0000

Table 4: Comparison between group B and group C.

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Gr. B	48.3±2.66	46.3±2.40	43.4±2.67	40.3±2.31	36.7±3.09	33.1±2.76	32.1±2.64
Gr. C	48.4±1.64	46.6±1.95	44.7±2.05	42.9±2.33	40.1±2.13	39.8±1.93	37.4±1.77
Mean difference	0.1000	4.1000	3.7000	4.8000	5.9000	6.8000	6.2000
P value	1.0000	0.0000	0.002	0.004	0.0000	0.000	0.0000

DISCUSSION

The present study evaluated the possible antidepressant activity of the drugs fluoxetine and riluzole, by using the conventional experimental animal model of antidepressant activity: forced swimming test.

The results following these tests have been compared with that of standard antidepressant drug fluoxetine, and with 0.9% normal saline taken as control. The fore mentioned experimental model is widely used to screen newer and potential antidepressant drugs. There is a significant correlation between the efficacy of antidepressants in forced swimming and clinical effectiveness of the drugs.¹⁵

This 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. ¹⁶ From Table 2 and 4 it's evident that fluoxetine showed significant antidepressant activity in comparison to normal saline from 7th day with p value of 0.000 for FST. In current study riluzole also showed significant antidepressant activity in comparison to normal saline, by means of reduced immobility time (Tables 3 and 4). Onset of antidepressant activity of riluzole was from day 14th. P value for FST was 0.001 at day 14th. Riluzole is a glutamatergic modulator with neuroprotective and plasticity-enhancing properties.

Antidepressant activity of riluzole has the following basis:

1) Evidence supporting the favourable CNS therapeutic profile of riluzole includes a growing body of work showing that this agent has neuroprotective properties in animal models of brain ischemia, spinal cord injury, traumatic brain injury, Parkinson's disease, post-traumatic peripheral neuropathy and acute noise-induced hearing loss. 17-20 2) It has been suggested that inhibition of tyrosine phosphorylation (which is observed in response to brain ischemia) may contribute to riluzole's neuroprotective properties against excitotoxic injury. 3) In addition, riluzole was found to be neuroprotective in glutamate-induced toxicity in primary glial cell culture, as evidenced by decreases in lactate dehydrogenase activity and nitrite levels. 22

Riluzole, a neuroprotective agent with anticonvulsant properties, appears to be a promising candidate drug for the treatment of neuropsychiatric disorders. It is a glutamatergic modulator with diverse effects within the glutamatergic brain system, a system that is being increasingly linked with the pathophysiology of mood disorders.

CONCLUSION

From result of our study it can be concluded that riluzole showed significant antidepressant activity by forced swimming test in Wistar albino rat models. Riluzole showed antidepressant activity after two weeks of starting the drugs. There is significant difference in antidepressant activity of fluoxetine with antidepressant activity of riluzole. Riluzole have different but favourable pharmacological profile to be useful in treatment of major depressive disorder. Riluzole is the only drug approved by US FDA improves the survival in amyotrophic lateral sclerosis and can provide therapeutic benefits in the patients.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

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Cite this article as: Kumar H, Chandra A, Kesari USP, Kumar R. Evaluation of the comparison of anti-depressant effects of oral fluoxetine and riluzole in albino rats by using the forced swimming test model. Int J Basic Clin Pharmacol 2021;10:391-5.