

A COMPARATIVE STUDY OF ANTIDEPRESSANT EFFECT OF AGOMELATINE WITH FLUOXETINE IN MICE

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ABSTRACT

Objective: To compare antidepressant effect of Agomelatine with Fluoxetine in mice. **Background:** A comparison of Agomelatine with Fluoxetine in mice has not much been performed, the other antidepressant in the same therapeutic class with a significant market share, has been undertaken. Agomelatine is a new antidepressant with selective agonist actions at melatonin receptors and selective antagonist action at serotonin 5HT-2C receptors. It does not affect the uptake of serotonin, nor adrenaline or dopamine. In the absence of relevant data to assess the place that Agomelatine should occupy in the therapeutic arsenal, indirect comparisons are the most rigorous way to

go. We conducted a study evaluate antidepressant of Agomelatine with Fluoxetine in Swiss albino mice. **Materials and Methods:** Agomelatine (50mg/kg body weight, i.p) was administered once daily for 14 days to Swiss albino mice of either sex. The immobility period for antidepressant activity of mice were recorded in Forced swim test (FST) and Tail suspension test (TST) of the control, standard and Test drug treated group. The antidepressant activity of Agomelatine was compared to that of Fluoxetine (20mg/kg, i.p.) administered for 14 days. **Results:** According to the results obtained from FST and TST for antidepressant, with regard to the experiments performed, all the evidence pointed to the conclusion that the antidepressant effect of Agomelatine was more than the control group and Fluoxetine. Based

on the results of the FST, TST Agomelatine has favorable antidepressant on mice as compared to the Fluoxetine treated and the control groups and the better effects were seen by increasing duration of drug use. **Conclusion:** It can be concluded that Agomelatine is a better drug in case of depression compared to Fluoxetine in mice.

KEYWORDS: Antidepressant effects; Agomelatine; Fluoxetine; FST; TST.

INTRODUCTION

DEPRESSION

Depression is a state of low mood and aversion to activity that can affect a person's thought behavior, feelings and physical well-being. Depression is an etiologically heterogeneous group of brain disorders that is characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes.^[1] The presence of the common symptoms of these disorders are collectively called 'depressive syndrome' and includes a long-lasting depressed mood, feelings of guilt, anxiety and recurrent thoughts of death and suicide.^[2] The genetic contribution to the manifestation of depression has been estimated as 40-50%.^[3]

There are two types of depression mainly unipolar in which mood swings in only one direction and bipolar in which depressive episode alternate with mania. The symptoms include persistent sadness, anxious, or "empty" feelings, feelings of hopelessness, feelings of guilt, worthlessness, or helplessness.

The World Health Organization estimates that major depression is the fourth most important cause worldwide of loss in disability-adjusted life years. An estimated 3-4% of India's 100 crore plus population suffers from major mental disorders and about 7.10% of the population suffers from minor depressive disorders.^[4] The high prevalence of suicide in depressed patients (up to 15%), coupled with complications arising from stress and its effects on the cardiovascular system, have suggested that it will be the second leading cause of death by the year 2020 and studies show depression as a contributory factor to fatal coronary disease.^[5]

Unfortunately, treatments for depression are often inadequate because of which Fewer than 50% of patients with depression achieve full remission with optimized treatments despite the increase in the available therapeutic armamentarium.^[6] In particular selective serotonin reuptake inhibitors (SSRIs) and serotonin-nor adrenaline (NA) reuptake inhibitors (SNRIs)

While 50 % of depressed patients remain untreated. The major disadvantages in treating these disorders with selective serotonin reuptake inhibitors (SSRIs) is that the therapeutic response develops slowly (3–4 wk) and side-effects often occur. There is a significant percentage 30%) of non-responders to this therapy.^[7] In addition to the need to administer the drugs for weeks or months before seeing clinical benefit, side effects are still a serious problem even with some of the newer medications. A substantial number of patients discontinue antidepressant treatment during the first few weeks of treatment, and poor compliance remains one of the most common obstacles of antidepressant treatment.^[8]

Thus, it is necessary to identify and develop alternative therapeutic options for the treatment of depression and anxiety disorders. The development of antidepressant drugs with melatonergic agonist and 5-HT_{2C} antagonist properties may be promising as in affective disorders abnormal circadian rhythms are common. Agomelatine, acting as an agonist at melatonergic receptors and antagonist at 5-HT_{2C} receptors normalize circadian rhythms and get rid of affective disorders. Possibly because of this novel receptor profile, one reason Agomelatine could be efficacious in depression through resynchronization of circadian rhythms.

In the present study, in the light of above literature, an effort was made to investigate the antidepressant effect of Agomelatine and its comparison with the standard drug Fluoxetine in the animal models.

Agomelatine

Agomelatine is a melatonergic antidepressant used for the treatment of major depressive disorder and has been reported to be safe as it does not produce discontinuation syndrome or sexual side effects (compared to SSRIs, SNRIs and the older tricyclic antidepressants).

Common adverse effects include Hyperhidrosis (excess sweating that is not proportionate to the ambient temperature), Abdominal pain, Diarrhea, Constipation, Back pain, Fatigue, Increased ALAT and ASAT (liver enzymes), Dizziness, Somnolence, Insomnia

Fluoxetine

It is known as selective serotonin reuptake inhibitors or SSRIs (include Fluoxetine, Fluvoxamine, Paroxetine, Citalopram and Sertraline). SSRIs are the most commonly prescribed group of antidepressants, as well as showing selectivity with respect to 5-HT over

noradrenaline uptake, they are less likely than TCAs to cause anticholinergic side effects and are less dangerous in overdose. In contrast to MAOIs, they do not cause 'cheese reactions'. They are as effective as TCAs and MAOIs in treating depression of moderate degree, but probably less effective than TCAs in treating severe depression. They are also used to treat a particular type of anxiety disorder known as obsessive compulsive disorder. In combination with MAOIs, SSRIs can cause a 'serotonin syndrome' characterised by tremor, hyperthermia and cardiovascular collapse, from which deaths have occurred.

MATERIAL AND METHODS

This study was conducted on healthy Swiss albino mice of either sex 3-4 months old and weighing around 25-30 g maintained at an ambient temperature of 25-35°C were procured from the disease free small animal house, UP RIMS & R, Saifai, Etawah, India. The animals had free access to food and water ad libitum, and were housed in an animal room with alternating light dark cycle of 12 hrs each. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experiments. Experiments were carried out between 9 a.m and 12 p.m. The experimental protocol was approved by the institutional animal ethics committee and was executed according to the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), India.

Animals were divided into 3 groups of 6 mice in each group.

- a. Group I (Control) will be given normal saline (0.1ml/10gm) for 14 days.
- b. Group II (Standard) will be administered With Fluoxetine (20mg/kg body weight, i.p.) for 14 days.
- c. Group III (Test drug) will be administered with Agomelatine (50mg/kg body weight, i.p) for 14 days.

Agomelatine and Fluoxetine were dissolved in normal saline.

Model for testing antidepressant activity

Forced swimming test (FST)

It is commonly used for the assessment of the antidepressant like properties of drugs. Mice were forced to swim individually in a glass jar (25 cm³ × 12 cm³ × 25 cm³) containing fresh water of 15 cm height and maintained at 25°C (±3°C). In the first 2 mins, the animal was allowed to adjust to the new conditions, and then, the immobility time that alternated with conditions of enhanced motor activity was measured. Immobility time was measured with a stopwatch for the next 4 mins (Porsolt et al., 1977). Mice were removed from their cages and

placed in individual glass cylinders containing water at 22-24°C at a depth of 14-16 cm so that they could not escape and could not touch the bottom. The animals were placed in the cylinders for observation in a 6 mins test swim. Two swimming sessions were conducted: an initial 15 mins pre-test followed 24 hrs later by a 6 mins test). The duration of immobility was measured for a 4 mins period. The duration of immobility during the last 4 mins of the 6 mins test was measured. The mouse was considered as immobile when it stopped struggling and moved only to remain floating in the water, keeping its head above water. Shorter immobility time was an indicator of the stronger antidepressant effect of the tested substance (Urani et al., 2001).

Tail suspension test (TST)

TST was done as described by Steru et al. After giving dose of drugs, mice were suspended on a string held by a metal stand, by an adhesive tape placed 1 cm from the tip of the tail. This string was 58 cm above the table top. The activity of the mice was recorded using a digital camera for a period of 5 min. During the experiment, each animal under test was both acoustically and visually isolated from other animals. The videos were analyzed by a rater blinded for treatment condition to find the duration of immobility in seconds. Mice were considered immobile when they hang passively and completely motionless.^[9]

Statistical analysis

All results are expressed as mean \pm standard error of mean (SEM). All the groups were analyzed using ANOVA, followed by Student's t-test. $p < 0.05$ was considered significant.

RESULTS

Effect of test drugs on immobility period in FST for antidepressant activity

FORCED SWIM TEST

Mean duration of immobility was significantly reduced by Agomelatine in a dose and duration dependent manner as compared to control and standard ($p < 0.05$) in FST. Similarly, the duration of immobility time observed in mice presented with Fluoxetine was also reduced ($p < 0.05$). Decrease in immobility due to Agomelatine (50mg/kg) was found to be significant ($p < 0.05$) when we compared to Fluoxetine at dose of (20 mg/kg) as shown in following Figures 1-3.

DAY 1 - In Control group mean of immobility time was found to be 128 seconds, in Fluoxetine group 117.66 and in Agomelatine group 113.33 seconds. Agomelatine group showed the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 115.88 seconds as shown in figure no 1.

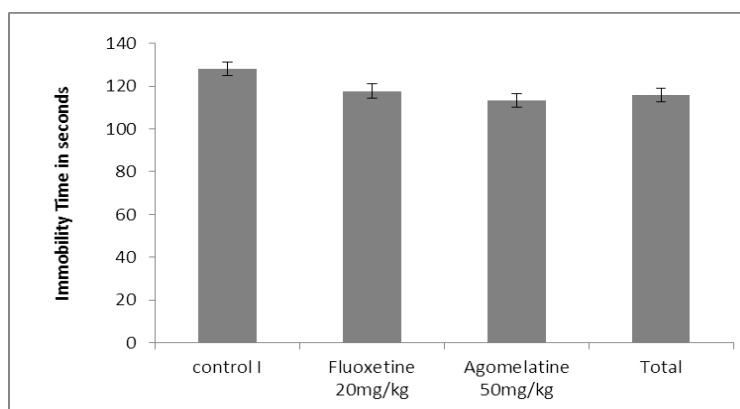


Figure 1: Immobility Time in seconds on Day 1

DAY 7 - In Control group mean of immobility time was found to be 123 seconds, in Fluoxetine group 107.29 seconds, in Agomelatine group 100.53 seconds. Agomelatine group shows the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 110.2 seconds as shown in figure no 2.

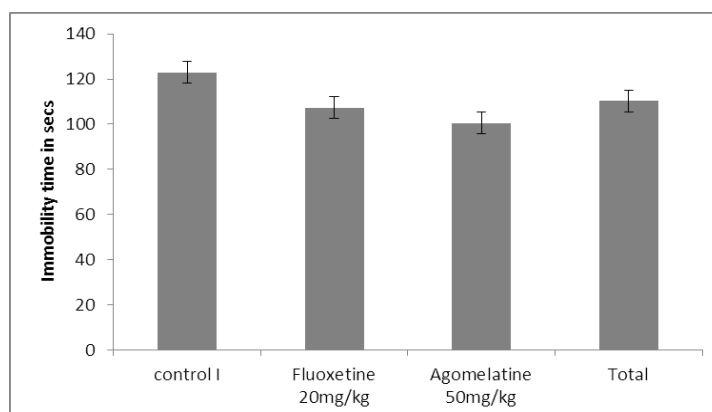


Figure 2: Immobility Time in seconds on Day 7

DAY 14 - In Control group mean of immobility time was found to be 120 seconds, in Fluoxetine group 97.48 seconds, in Agomelatine group 89.98seconds. Agomelatine group shows the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 102.48 seconds as shown in figure no 3.

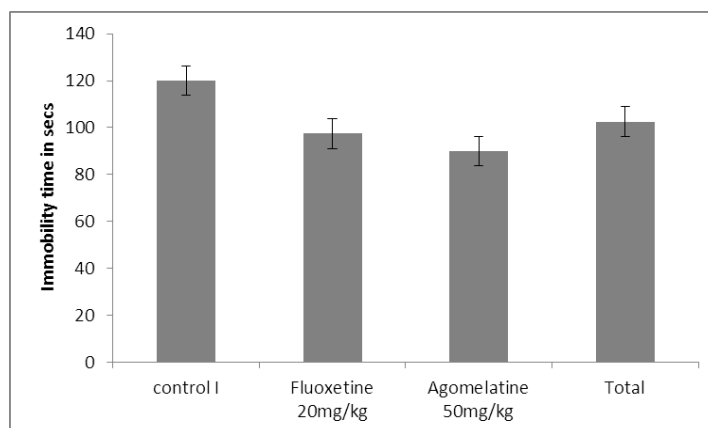


Figure 3: Immobility Time in seconds on Day 14

Analysis of variance (ANOVA test) applied, and we find out the mean immobility time of forced swim test was significantly different, among different test groups on 1, 7 and 14th day.

Effect of test drugs on immobility period in TST for antidepressant activity

TAIL SUSPENSION TEST

Mean duration of immobility was also significantly reduced by Agomelatine in a dose and duration dependent manner as compared to control and standard ($p < 0.05$) in TST. Similarly, the duration of immobility time observed in mice presented with Fluoxetine was also reduced ($p < 0.05$). Decrease in immobility due to Agomelatine (50mg/kg) was found to be significant ($p < 0.05$) when we compared to Fluoxetine at dose of (20 mg/kg) as shown in following Figures 4-6.

DAY 1 - In Control group mean of immobility time was found to be 127 seconds, in Fluoxetine group 117.83 seconds, in Agomelatine group 109 seconds. Agomelatine group shows the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 117.87 seconds as shown in figure no 4.

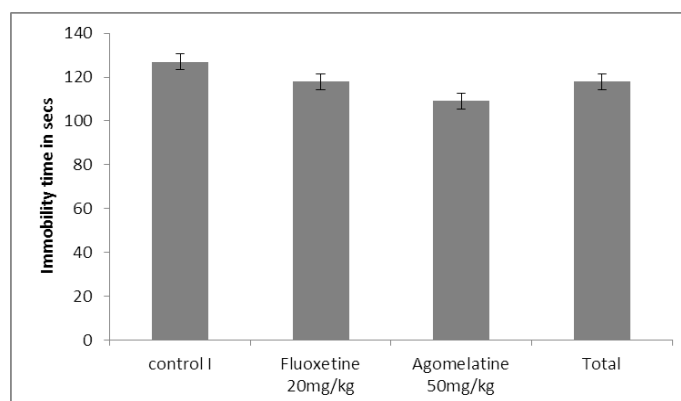


Figure 4: Immobility Time in seconds on Day 1

DAY 7 - In Control group mean of immobility time was found to be 120 seconds, in Fluoxetine group 115 seconds, in Agomelatine group 98.27 seconds. Agomelatine group shows the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 111.09 seconds as shown in figure no 5.

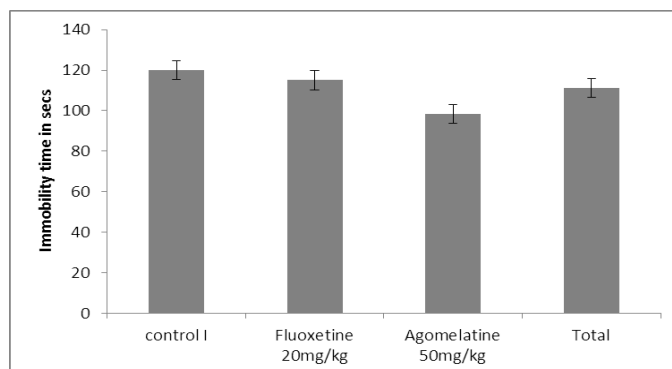


Figure 5: Immobility Time in seconds on Day 7

DAY 14 - In Control group mean of immobility time was found to be 125 seconds, in Fluoxetine group 102.99 seconds, in Agomelatine group 92.77 seconds. Agomelatine group shows the lowest immobility time, while Fluoxetine group shows highest immobility time after the control and in total mean of immobility time was 106.92 seconds as shown in figure no 6.

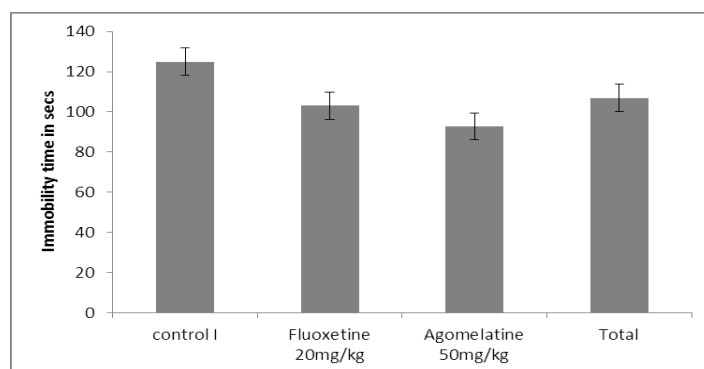


Figure 6: Immobility Time in seconds on Day 14

Analysis of variance (ANOVA test) applied, and we find out the mean immobility time of forced swim test was significantly different, among different test groups on 1, 7 and 14th day.

DISCUSSION

The present study was aimed to investigate the antidepressant like activities of Agomelatine, a novel antidepressant with melatonergic agonist and 5-HT_{2C} receptor antagonist properties and its comparison with Fluoxetine in a model of depression by FST and TST test based on

duration of immobility time. Agomelatine and Fluoxetine produced significant antidepressant activity in a duration-dependent manner as compared to control.

Enhanced activity of the HPA axis involving elevated Glucocorticoid levels is considered a key neurobiological alteration in major depression. In depressed patients, many studies have shown that successful antidepressant therapies are associated with normalization of impaired HPA axis negative feedback.^[10,11] Consistent with previous findings, the present results demonstrate that an elevation of Glucocorticoid levels is sufficient to induce a depression and these deficits were reversed by fluoxetine.^[12] In literature it has been that the new antidepressant Agomelatine is also capable of reversing these deficits.

In our study, we found antidepressant activity of Fluoxetine at a dose of 20 mg/kg was significant as compared to control animals while antidepressant activity of Agomelatine at a dose of 50 mg/kg was much significant as compared to control and standard animals which can be concluded because of its multiple mechanism of action.

The mechanism underlying the antidepressant like activity of Agomelatine appears to involve both its melatonergic receptor agonist and its 5-HT_{2C} receptor antagonist properties¹³. Interestingly, melatonergic and 5-HT_{2C} receptors are expressed in the suprachiasmatic nuclei and in other brain areas possibly involved in the pathophysiology of depression, such as the cerebral cortex, hippocampus, amygdala and thalamus.^[14] Apart from it among that other biochemical, physiological and behavioral impairments, the depression procedure causes generalized disorganization of circadian rhythms, and Agomelatine can resynchronize experimentally disrupted circadian rhythms. This conclusion is consistent with other reports showing that Agomelatine can resynchronize circadian rhythms in animals.^[15]

But interestingly in our study the activity of Agomelatine in the FST and TST does not depend on the time of the administration (morning or evening) as we did not consider this which has been already shown in the earlier studies¹⁶. This strongly suggests that properties other than its chronobiotic ones.^[17,18,19] may sustain the activity of Agomelatine in the FST and TST. Raghavendra et al.^[20] have also reported that circadian variations (noon, early dark, midnight) do not influence the effect of melatonin treatment on the duration of the immobility period in mice, which suggests that the FST and TST may be not sufficiently sensitive to appropriately study compounds with chronobiotic properties in this species.

CONCLUSION

The result of this study indicates that Agomelatine induces an antidepressant-like effect in a model of depression that is comparable to that of fluoxetine, a classical SSRI. Antidepressant activity of Agomelatine was better in comparison to control and standard drugs. However, Agomelatine also induces a change in circadian rhythm, which may contribute to its distinct profile of antidepressant action. Agomelatine is therefore a strong candidate for a new approach to treating depression due to an innovative mechanism of action based on melatonin agonist and 5-HT_{2C} antagonistic properties. Hence it can be concluded that Agomelatine can serve as superior drug in case of depression than Fluoxetine because of its better therapeutic effect with minimal side effects. However, further studies are required to substantiate these findings especially in clinical set up.

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Conflict of interest: None declared Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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