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ANTIDEPRESSANT EFFECT OF IBANDRONATE ON DEPRESSION MODELS

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ABSTRACT: This study was designed to evaluate and compare the Antidepressant effect of Ibandronate with Amitriptyline on depression models in albino mice. Eighteen Swiss albino mice weighing 20-25 grams were selected and divided into three groups of six animals each. Group 1: Normal Saline- 0.5 ml, Group 2: Amitriptyline - 39 mg/kg, Group 3: Ibandronate 0.325 mg/kg administered orally every day for 30 days. Animals were subjected to a forced swim test, tail suspension test, and Locomotor activity test on 1st, 10th, 20th and 30th day of the experiment after 1 hour of drug administration. The forced swimming test and Tail suspension test detected the duration of immobility, whereas the Actophotometer test detected the influence of the drug on the Locomotor system. The data reveal that Ibandronate has an antidepressant action that did not differ significantly from Amitriptyline. Ibandronate a Bisphosphonate has shown an antidepressant effect on depression models in albino mice.

INTRODUCTION: Depression is a disorder of major public health importance in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. In India, several research studies have estimated the prevalence of depression in communities, which varied from 1.7 to 74/1000. The WHO estimates that major depression is the fourth most important cause of loss in disability-adjusted life years (DALYs) [1]. Osteoporosis is a disease characterized by low bone mineral density, is a common skeletal disorder with over 75 million people suffering worldwide. In people aged 50 years or older, osteoporosis is one of the major health disorders.

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In addition to lifestyle and nutrition, several diseases can promote low bone mineral density. A number of cross-sectional studies have shown this to be true for depression also. It causes chronic stress, which stimulates the secretion of cortisol and catecholamine (*e.g.* noradrenaline), resulting in bone loss. Increased levels of bone resorption markers and proinflammatory cytokines have also been associated with depression. A relationship between depression and osteoporosis has become more evident over the years, as decreased bone mineral density has been observed in depressed women and men.

In addition to clinical depression, milder depressive symptoms, anxiety, stress and low well-being have been shown to negatively affect bone [2]. Studies on animals have also suggested that depression may predispose to osteoporosis. Recent long-term studies have also shown an association between menopausal status with a higher risk of depression and osteoporosis [3].

Tricyclic antidepressants and Selective serotonin reuptake inhibitors have been the treatment options available for treating osteoporotic patients with depression [4]. About one-third of these patients do not respond primarily to antidepressant treatment or progressively become resistant to treatment or show relapse. They also have slow therapeutic onset and low remission rates, as Fava and Davidson [5].

Bisphosphonates (BPNs) are commonly used in the treatment of osteoporosis to reduce the risk of fractures. The positive effect of Bisphosphonates in improving depression is an area of research in recent years. A study showing the effect of Etidronate on depression paradigms in Swiss albino mice and Wistar rats has been done. From the results, it was concluded that Etidronate can have antidepressant activity. Based on experimental and observational studies, there appears to be a role of Etidronate in depression [6].

Application of Bisphosphonates, especially Etidronate, in the treatment of depression along with osteoporosis is studied, but there are no studies on Ibandronate it's a new Bisphosphonate. Hence, the present study was designed to evaluate the antidepressant effect of Ibandronate In depression models of Swiss albino mice. The drug antidepressant effect was tested by subjecting the mice to experimental models of depression, such as the Forced swimming test (FST) [7] Tail suspension test (TST) [8] influence on Locomotor system was also detected by carrying out the Actophotometer test [9].

MATERIALS & METHODS: This research study was approved by IAEC, SSIMSRC.(No. 02/IAEC/SSIMS&RC/2019).

Requirements:

Animals: Swiss albino mice (n=18), weighing about 20-25gm, were included in the study. The mice were housed in autoclavable polypropylene cages over husk beddings under a controlled environment: Temperature (23 ± 4) and Humidity (50 ± 10%) in a 12 h light 12 hours dark cycle. All the experiments were conducted under strictly controlled and pathogen-free conditions. The mice were provided with standard mice pellet chow feed and water *ad libitum*.

Drugs: Amitriptyline, Ibandronate.

Instruments: Actophotometer, Plexiglas cylinder.

Other Requirements: Normal saline, *etc.*,

Experimental Procedure: Animals were divided into three groups of six animals each, as follows:

Group 1: Control – (Normal saline - 0.5 ml).
Group 2: Standard – (Amitriptyline - 39 mg/kg).
Group 3: Test – (Ibandronate group - 0.325 mg/kg).

Dosage: Standard and test drugs were administered orally by dissolving in normal saline for groups 2 and 3, respectively. Clinical doses of these drugs were converted into mouse-equivalent doses by Paget and Barnes method [10]. The effect of each drug on animals was individually evaluated and compared between the groups and within the group. The animals had been allowed to acclimatize for 10 days before starting the experiment. The drugs were given every day for 30 days (Experimental period). Forced swim test, Tail suspension test, and Locomotor activity test were done on 1stday, 10th day, 20thday, and 30thday of the experiment after 1 hour of administration of drugs. Behavioural changes were monitored, assessed, and evaluated throughout the treatment phase.

Forced Swim Test: Is frequently used to evaluate potential antidepressant activities in experimental models. Immobility is produced during prolonged periods of forced swimming. Mice were forced to swim in a restricted space from which they cannot escape and induced into a characteristic behaviour of immobility. This behaviour reflects a state of despair that few therapeutically effective agents can reduce in human depression. The potential antidepressants reduce the duration of immobility and increase the escaping behaviour such as climbing and swimming. A transparent Plexiglas cylinder of 20 cm diameter and 50 cm height was used for the study. A water level of 20 cm was maintained in the cylinder throughout the experiment. One day before the experiment, the animals were subjected individually to forced swims for a period of 15 minutes. On the day of the experiment, animals were placed separately in a water-filled glass cylinder for 6 min.

The duration of immobility during last five minutes of forced swim was calculated by subtracting total time (5min) from time spent in escaping behaviour. Climbing is defined as upward-directed movements of the forepaws by the side of the swim chamber & swimming is considered as movements throughout the swim chamber [7].

Tail Suspension Test: This test is a facile means of evaluating potential antidepressants. When subjected to unavoidable and inescapable stress, the immobility displayed by rodents has been hypothesized to reflect behavioural despair, which may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail. Mice were suspended on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was noted during 5 minutes period and compared with control and standard groups. Animals were considered immobile if it did not show any movement of body and remained hanging passively for at least 1 min [8].

Locomotor Activity: It helps to rule out any influence of the drugs on the locomotor system, which may affect immobility. The locomotor and behavioural activity was measured using the Actophotometer. The apparatus consisted of a rectangular cage with perforated metal flooring designed for recording the walking and running movements of small animals like mice and rats. An array of infrared lamps were placed on one side of the chamber inside, with corresponding photo-cells connected to a digital counter placed on the opposite side. Thus any interruption of the light beams was displayed by the digital counter. Infrared lights were used because the animal will perceive visible light that might influence its behaviour. This apparatus operated on photoelectric cells connected in a circuit with a counter. The locomotor activity of mice was recorded when the beam of light falling on the photo-cell got cut off by it. Mice were placed in the center of the apparatus for 5 min. The device electronically counted the number of times the infrared beams were interrupted by the movement of the animal, which in turn was the measure of the locomotor activity [9].

RESULTS: The results were obtained by subjecting the collected data to One way ANOVA test followed by Tukey's posthoc test. P-value < 0.05 was considered less significant, P-value < 0.01 was considered significant and P-value < 0.001 was considered highly significant.

TABLE 1: EFFECT OF IBANDRONATE ON FORCED SWIMMING TEST IN ALBINO MICE

Duration of immobility in Forced Swimming Test(Time in min)			
Day	**Group 1**	**Group 2**	**Group 3**
0^{th}	2.44 ± 0.22	2.49 ± 0.26	2.46 ± 0.24
10^{th}	2.47 ± 0.27 c*	2.13 ± 0.28 ac*	2.28 ± 0.42 b*
20^{th}	2.30 ± 0.35 b** c*	1.71 ± 0.47 a** c*	2.12 ± 0.34 ab*
30^{th}	2.46 ± 0.31 b*** c**	1.48 ± 0.27 a*** c*	1.78 ± 0.22 a** b*

n=6. Mean ± S.D. a - compared with day '0', b - compared with group'2', c - compared with group '3' * p < 0.05, ** p < 0.01, *** p< 0.001.

Within Group Comparison Table 1:

Group 1: There was no significant difference observed in the variation of time of immobility compared to the 0^{th} day.

Group 2: A less significant decrease was noticed on 10^{th} day compared to 0^{th} day, which became significant by 20^{th} day and highly significant by 30^{th} day.

Group 3: The decrease is less significant on 20^{th} day when compared to 0^{th} day. It becomes significant by the end of 30^{th} day.

Between Group Comparisons Table 1:

Compared to Group 2: There was a significant increase on the 20^{th}day and a highly significant increase on 30^{th} day in group 1. Group 3 showed a consistently less significant increase on 10^{th}, 20^{th} & 30^{th} day.

Compared to Group 3: In group 1**,** a less significant increase is observed on 10^{th} and 20^{th} day, along with a significant increase on 30^{th} day. In group 2, there was a less significant decrease on 10^{th}, 20^{th} and 30th day.

TABLE 2: EFFECT OF IBANDRONATE ON TAIL SUSPENSION TEST IN ALBINO MICE

Duration of immobility in Tail Suspension Test (Time in min)			
Day	**Group 1**	**Group 2**	**Group 3**
0^{th}	2.12 ± 0.38	2.07 ± 0.43	2.25 ±0.25
10^{th}	2.17 ± 1.10 c*	1.94 ± 0.39	2.14 ± 0.26
20^{th}	2.15 ± 0.85 bc*	1.58 ± 0.21 ac*	2.03 ± 0.29 ab*
30^{th}	2.01 ± 1.21 bc**	1.53 ± 0.30 ac*	1.72 ± 0.19 a** b*

n=6. Mean ± S.D. a - compared with day '0', b - compared with group'2', c - compared with group '3' * p < 0.05, ** p < 0.01, *** p< 0.001.

Within Group Comparison Table 2:

Group 1: Significant alteration was not observed throughout experiment, in comparison to 0^{th} day.

Group 2: A less significant decrease than 0^{th} day was noted on 20^{th} and 30^{th} day.

Group 3: Variation was less significant decrease on 20^{th}& significant on 30^{th} day when compared to 0^{th} day.

Between Group Comparisons Table 2:

Compared to Group 2 – Group 1 revealed a less significant increase on 20^{th} and a significant increase on 30^{th} day. A less significant increase was also found in group 3 on 20^{th} and 30^{th} day.

Compared to Group 3 – A less significant increase was present on 10^{th} and 20^{th} day, which became significant by 30^{th} day in group 1.

Group 2 has a less significant decrease on the 20^{th} and 30^{th} day.

TABLE 3: EFFECT OF IBANDRONATE ON LOCOMOTOR ACTIVITY IN ALBINO MICE

Actophotometer Test (Counts / 5 min)			
Day	**Group 1**	**Group 2**	**Group 3**
0^{th}	177.17 ± 17.49	175.67 ± 25.54	177.67 ± 36.20
10^{th}	166.83 ± 24.52	178.5 ± 23.11	179.33 ± 34.56
20^{th}	181.67 ± 29.79	182.1 ± 24.73	181.67 ± 23.05
30^{th}	183.33 ± 41.22	190.00 ± 26.72 a*	185.33 ± 19.94

n=6. Mean ± S.D. a - compared with day '0', b - compared with group'2', c - compared with group '3' * p < 0.05, ** p < 0.01, *** p< 0.001.

Within Group Comparison Table 3:

Group 1: In comparison to 0^{th} day, the differences in performance were not statistically significant.

Group 2: A less significant increase in performance was seen on 30^{th} day compared to 0^{th} day.

Group 3: Compared to 0^{th} day, there was no significant difference was seen on 10^{th}, 20^{th} & 30^{th} day.

Between Group Comparisons Table 3:

Compared to Group 2: There was no significant difference of Locomotor activity in group 1 and 3 when compared to group 2 on any of the experimental days.

Compared to Group 3: In group 1 and 2 the Locomotor activity of mice did not show any significant difference when compared to group 3 on 10^{th}, $20^{th,}$ and 30^{th} day.

DISCUSSION: Forced swim test and Tail suspension test was used to study the antidepressant activity because both these tests are easy to perform and require a minimum of instruments. The Actophotometer test provides simultaneous measures of locomotion, exploratory behavior and anxiety. This test helps to differentiate between sedative and stimulant drugs. It also helps to rule out any influence of the drugs on the Locomotor system, which may affect immobility (in antidepressant tests) [6]. Assessment of mice administered Ibandronate revealed that the drug significantly reduced immobility time in FST and TST compared to the control group. There was no significant decrease in the immobility time compared to the standard Amitriptyline, suggesting that it is not a better antidepressant than the standard one. Locomotor performance was tested using Actophotometer for all the three groups taken in the study. The effect of Ibandronate on Locomotor activity showed no significant difference compared to the control and standard group, suggesting no influence of the drug on the Locomotor system. Antidepressants such as Tricyclic antidepressants and Selective serotonin

reuptake inhibitors are the choice of drugs for osteoporosis with depression. Many studies come with the evidence that these antidepressants, in turn cause bone loss & fracture risks in such patients [11].

Although used in the treatment and prevention of bone health disturbances such as osteoporosis, Bisphosphonates are the possible mechanisms that indicate their role in osteoporotic patients with depression. BPNs could have central-behavioral effects through modulation of neurosteroid synthesis.

Neurosteroids are potent and effective neuromodulators synthesized from cholesterol in the brain. Increasing evidence indicates that dysregulation of neurosteroid production plays a role in the pathophysiology of stress and stress-related psychiatric disorders, including mood and anxiety disorders [6].

Furthermore, few studies have investigated that the acid sphingomyelinase-ceramide system is one of the newer potential targets for anti-depressive drugs [12]. Roth *et al.* quoted that Bisphosphonates decreased the levels of acid sphingomyelinase, proving that they can have antidepressant activity [13]. With the above evidence supporting this study, we can elicit that Ibandronate can have antidepressant activity.

Using Ibandronate in osteoporotic patients having depressive disorders has many advantages, such as improving compliance. Only one drug can benefit both diseases and reduces a load of chemicals being ingested, which is easier on the body.

CONCLUSION: Ibandronate decreased the immobility time of mice, implicating its additional antidepressant activity. Moreover, there was no significant difference in locomotor activity, indicating no interference with the locomotor system. Further studies must be conducted to test its clinical application as an antidepressant.

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CONFLICTS OF INTEREST: None declared.

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