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Original Research Article

A COMPARATIVE STUDY OF ANTIDEPRESSANT EFFECT OF AMOXAPINE WITH FLUOXETINE ON MICE USING WATER WHEEL TEST

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ABSTRACT

Background: Major depression is a common disorder that causes morbidity and mortality. A number of drugs are being used for treatment of depression, but most of them have many adverse effects. . So there are more possibilities and opportunities for finding newer drugs for treatment of depression. **Objective:** The present study was designed to compare the antidepressant effect of amoxapine with fluoxetine on mice. **Materials and Methods:** The antidepressant activity of Amoxapine with Fluoxetine was evaluated by Water Wheel Test after drug doses in mice. Test was done in three groups of mice, with six mice in each group. Group I was treated with normal Saline (0.1ml/ 10g) as the control group, group II was treated with Fluoxetine (20mg/kg i.p.), group III receivedAmoxapine (10mg/kg, i.p.), The drugs were administered once daily for 2 weeks and 20 min before the test. In each group, the mice were evaluated after intraperitoneal administration of drugs on 1st, 7th and 14th day by Water Wheel Test. Statistical analysis was done by two-way analysis of variance (ANOVA). **Results:** Amoxapine and Fluoxetine showed significant antidepressant activity. They significantly ($P < 0.05$) increased the number of turns of wheel as compared to control group. **Conclusion:** Amoxapine can be effectively used in the treatment of depression as it shows significant effect.

KEY WORDS: Amoxapine, Depression, Fluoxetine, water wheel Test.

INTRODUCTION

Depression is an group of brain disorders with a wide range of symptoms that shows alterations in cognitive, psychomotor and emotional processes.**(1)** Combinations of multiple genetic factors may be involved in the development of depression.**(2)** The pathogenesis of depression is complicated by non-genetic factors such as stress, affective trauma, viral infection, and neurodevelopmental abnormalities.**(3)**

World Health Organization states that depression will be the second leading cause of disability in 2020.**(4)** Epidemiological studies suggests that 2-5% of the population is affected by severe forms of depression whereas 20% are affected by milder form worldwide.**(5)** Risk of developing cardiovascular diseases in depressive patients is 2-4 times more than that of normal individuals. On the other hand, 10-15% of individuals with major depression commit suicide.**(6)**

Drugs maintaining the desired levels of monoamines in brain either by inhibiting monoamine oxidase or by inhibiting reuptake of neurotransmitters can be used in the treatment of depression. The decision to treat with an antidepressant is guided by the presenting clinical syndrome, its severity and by the patient's personal and family history.**(7)** The treatment regimen for depression includes monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs). Due to their adverse effects and dangerous food interactions, TCAs and MAOIs are not preferred at present. SSRIs are

preferred nowadays because of their better safety and tolerability.**(8)**

At present, the treatment of depression provide remission in approximately one-third of patients only and few have complete resolutions.**(9)** The delayed onset of therapeutic effect of antidepressant medications also prolongs the impairments associated with depression, an increased risk of suicide, increased chances to discontinue therapy with an increase in medical costs associated with severe depression.**(10)** Thus, research should take place for newer novel compounds having better efficacy or augment the effect of conventional antidepressants in these patients.**(11)** In the present study, an effort was made to reinvestigate the antidepressant effect of Amoxapine because of its minimal use in present practice and its comparision with Fluoxetine in the animal models.

MATERIALS AND METHODS

Animals

Eighteen Swiss albino mice three / four months of age (25 to 35 g) of either sex were procured from the central animal house of the institute. Polypropylene cages were used to keep the animals under controlled room temperature (24 ± 2ºC) in a 12 h light-dark cycle. Standard laboratory diet and water ad libitum was provided to the animals. They were acclimatized to the laboratory conditions at least one day prior to the behavioural experiments.

All the experiments were carried out between 12:00 noon to 04:00 pm. Food was withdrawn 12 h before the experiment. The animal handling was performed according to the Good Laboratory Practice (GLP) guidelines.**(12)** The test was performed after prior permission from the Institutional Animal Ethics Committee (IAEC), NIMS Medical College, Jaipur.

Inclusion Criteria:

- Albino mice of either sex weighing 20-25 g.
- Age 3-4 months.
- Healthy with normal behavior and activity.

Exclusion Criteria:

- Pregnant mice or those who have recently delivered.
- Animals previously used in other experiments.

Drug formulations

Amoxapine (20 mg/kg) (Consern Pharmaceuticals, India), Fluoxetine (10 mg/kg) (Cadila Pharmaceuticals, India) were used. All the drugs were dissolved in distilled water (DW) and administered by intraperitoneal route (i.p.).

Grouping of animals

Three groups of animals of 6 mice each were formed.

Group I (Control) was given Normal Saline (0.1ml/ 10g). **(13)**

Group II (Standard) was treated with Fluoxetine (20mg/kg i.p.).**(13)**

Group III (Test) was treated with Amoxapine (10mg/kg, i.p.). **(14)**

Study design

The antidepressant activity of Amoxapine with Fluoxetine was evaluated by Water Wheel Test after drug doses in mice. The drugs were administered once daily for 2 weeks and 20 min before the tests.**(15)** Route for drug administration was intraperitoneal for Normal saline, Amoxapine and Fluoxetine. In each group, the mice were evaluated after intraperitoneal administration of drugs on 1st, 7th and 14th day by Water Wheel Test.

Water wheel test

This model works on the principle of 'Behavioural Despair Activity' to determine the antidepressant property of the test drug. The animal is forced to swim without any escape in a water tank. A rotating wheel in the water tank acts as an option for escape but increase the despair as it turns under the weight of the animal and to stay afloat, the animal has to keep rotating the wheel. The endpointis denoted by the moment when the animal is immobile and stops to struggle and remains floating motionless making only those movements necessary to keep its head above water. This corresponds to behavioural despair.

Procedure

The apparatus consists of a plexiglas water tank (20cm X 8cm X 18 cm) with a water wheel in the centre. The water wheel is made of plexiglas shaft (diameter 3 cm, length 6 cm) on which six paddles (0.5 cm width), move when loads of more than 5 g was attached and the number of rotations of the water wheel was counted. The tank was filled up to a height of 9 cm with water at 25°C, such that paddles just touched the surface of water. When placed into the apparatus for the first time, the mice swam vigorously to find a way of escaping from the water.

On discovering the water wheel, they climbed onto wheel and began turning it due to their weight. After a few minutes of attempted escape, they cling to the wheel and just float in the water showing incomplete immobility.

For this method, various groups were treated with normal saline (control group), standard drug i.e. Fluoxetine (20mg/kg, i.p.), or test drug i.e. Amoxapine (10 mg/kg, i.p.) and rechallenged on the water wheel. **(16)**

The criteria for evaluating antidepressant activity was increase in the number of counts of water wheel turns that increased effort at escape behaviour.

Statistical analysis: Statistical analysis among different groups was done by two-way analysis of variance (ANOVA). $P<0.05$ was considered statistically significant.

RESULTS

DAY 1 - In Control group, mean of No. of turns of wheel was 23, in Fluoxetine group 25, in Amoxapine group 29. Amoxapine group shows highest no. of turns as compared to control and Fluoxetine treated group.

DAY 7 - In Control group, mean of No. of turns of wheel was 25, in Fluoxetine group 27, in Amoxapine group 33. Amoxapine group shows highest no. of turns as compared to control and Fluoxetine treated group.

DAY 14 - In Control group, mean of No. of turns of wheel was- 29, in Fluoxetine group 31, in Amoxapine group 36. On day 14, Amoxapine group also shows highest no. of turns as compared to control and Fluoxetine treated group.

Table 1: No. of Turns of wheel on day 1

	Day 1 (Mean±SD)	Day 7 (Mean±SD)	Day 14 (Mean±SD)	P-value
Control	23±2.76	25±3.58	29±5.4	0.008
Fluoxetine (20mg/kg)	25±3.03	27±2.61	31±2.61	0.001
Amoxapine (10 mg/kg)	29±2.9	33±3.16	36±3.03	0.02

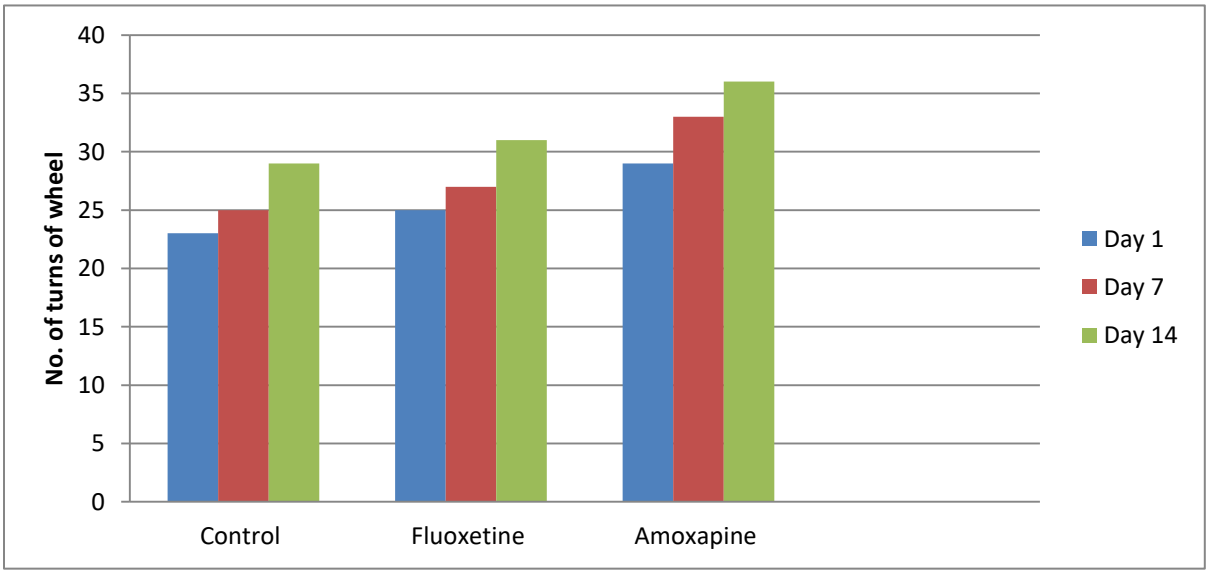

Figure 1-No. of turns among different group on day 1, day 7, and day 14

DISCUSSION:

Depression is a disorder that can be diagnosed and treated in primary care in a reliable manner. As per WHO guidelines, the treatment of depression includes basic psychosocial support along with antidepressant medication or psychotherapy (cognitive behaviour therapy, interpersonal psychotherapy or problem-solving treatment). Antidepressant medications and psychotherapy are effective in the treatment. Antidepressants can be a very effective form for the treatment of moderate to severe depression, but not the first line of treatment for mild or sub-threshold depression.**(17)**

The result of the Water Wheel Test with Amoxapine (10 mg/kg) in mice revealed that the number of turns of wheel was significantly increased by the drug treatment. Amoxapine is a metabolite of Loxapine and is categorised as second-generation Tricyclic Antidepressant (TCA). It predominantly inhibits the Noradrenaline (NA) reuptake, which results in an increased concentration of NA in the synaptic cleft in the CNS. It also blocks the neuronal reuptake of 5-HT(Serotonin) and thus provides little additional benefit over TCAs. In addition, it also blocks the dopamine receptor thus having some antipsychotic effect.**(18)** The standard drug Fluoxetine also increased the number of turns of wheel in Water Wheel Test. Fluoxetine, a selective serotonin reuptake inhibitor, acts by inhibiting the uptake of serotonin by the neurons in the brain and enhancing serotonin neurotransmission through action on 5HT2a and 5HT2c receptors.**(19)**

In the present study, the efficacy of Amoxapine was found to be comparable to Fluoxetine. Both the drugs showed significant antidepressant activity in the test. It has been previously suggested by Reneric and Lucki that an increase in climbing behaviours in Water Wheel Test occurs when the animal is treated with a drug which increases serotonin, noradrenaline and dopamine levels in the nerve terminals.**(20)**

Stress of any kind may result in the progressive deterioration of brain functions. The pathophysiology of depression and anxiety states caused by the imbalance of various neurotransmitters like GABA, 5-hydroxytrptamine (serotonin) and various amino acids due to altered functioning of brain. Therefore, varied number of neurotransmitter plays an important role in underlying mechanism of disease as well as mechanism of action of antidepressant drugs.**(21)**

Newer antidepressants generally present fewer side effects and toxic risks than TCAs and MAO inhibitors. As a group, the TCAs have a high risk of cardiovascular effects like cardiac arrhythmias, postural hypotension, tachycardia and anticholinergic effects like dryness of mouth, blurred vision, urinary retention and constipation. Some TCAs have been associated with moderate weight gain and sexual disturbances. These adverse effects are less common with Amoxapine than that of other tricyclic antidepressants.**(22)** The adverse effects like nausea, insomnia, somnolence, anorexia, nervousness, asthenia and tremor are common with fluoxetine. Anxiety, insomnia, and nervousness (1-2% each) resulted in interruption of the treatment while in the pediatric trials—mania (2%) interrupted the treatment. Anorgasmia and reduced libido are the sexual side effects common with fluoxetine and other SSRIs.**(23)**

In the present study, the test drug Amoxapine and the standard drug Fluoxetine (20mg/kg) produced substantial antidepressant effects in mice ($p< 0.05$). It is proposed that the evaluation of mechanism of action and adverse effects of Amoxapine are suggested for future studies.

CONCLUSION

From this study results, we can conclude that the antidepressant effects of Amoxapine was similar to that of Fluoxetine which is a well-established drug for the treatment of depression in the present era. The results also suggest that antidepressant effect of Amoxapine increases with prolonged use. So, Amoxapine can be effectively used in the treatment of depression as it shows significant effects.

REFERENCES

1. Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat. 2019 May 10;15:1249-58. doi: 10.2147/NDT.S199746, PMID 31190831.
2. Shadrina M, Bondarenko EA, Slominsky PA. Genetics factors in major depression disease. Front Psychiatry. 2018 Jul 23;9:334. doi: 10.3389/fpsyt.2018.00334, PMID 30083112.
3. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med. 2001;7(5):541-7. doi: 10.1038/87865, PMID 11329053.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: global Burden of Disease Study. Lancet.

1997;349(9064):1498-504. doi: 10.1016/S0140-6736(96)07492-2, PMID 9167458.
5. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095-105. doi: 10.1001/jama.289.23.3095, PMID 12813115.
6. Keck ME. Corticotropin-releasing factor, vasopressin and receptor systems in depression and anxiety. Amino Acids. 2006;31(3):241-50. doi: 10.1007/s00726-006-0333-y, PMID 16733617.
7. Laurance LB, John SL, Keith LP. Characterization of depressive & anxiety disorders. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. McGraw-Hill; 2006. p. 450.
8. Baldessarini RJ. Drug therapy of depression and anxiety disorder. In: Brunton LL, Lazo JS, Parker KL, editors. The pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006. p. 429-60.
9. Davidson JR, Meltzer-Brody SE. The under recognition and under treatment of depression: what is the breadth and depth of the problem? J Clin Psychiatry. 1999;60;Suppl 7:4-9; discussion 10. PMID 10326869.
10. Whooley MA, Simon GE. Managing depression in medical outpatients. N Engl J Med. 2000;343(26):1942-50. doi: 10.1056/NEJM200012283432607, PMID 11136266.
11. Matreja PS, Badyal DK, Deswal RS, Sharma A. Efficacy and safety of add on low-dose mirtazapine in depression. Indian J Pharmacol. Apr 2012;44(2):173-7. doi: 10.4103/0253-7613.93843, PMID 22529470.
12. Sanmukhani J, Anovadiya A, Tripathi CB. Evaluation of antidepressant like activity of curcumin and its combination with fluoxetine and imipramine: an acute and chronic study, ActaPoloniae Pharmaceutical. Drug Res. 2011;68(5):769-75.
13. Royal BR, Burte NP. Evaluation of antidepressant-like activity of tapentadol in swissalbino mice. Int J Pharm Biol Sci. 2011 oct–dec;4(2):443-5.
14. Delgado C, Manzanares J, Tamargo J, Valenzuela C. Electrophysiological effects of amoxapine in untreated and in amoxapine-preteated rat atria. Br J Pharmacol. 1986;87(2):317-25. doi: 10.1111/j.1476-5381.1986.tb10820.x, PMID 3955303.
15. Salehi B, Biazar E, Jahromi MH, Romani HA. Antidepressant effects of Aloe verahydroalcoholic extract on mice model. J Paramedical Sci. 2008;2:59-63.
16. Gupta SK. Water Wheel model, Drug screening methods – pre clinical evaluation of new drugs. 2nd ed, Jaypee; 2009. p. 393-4.
17. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLOS ONE. 2010 Oct 13;5(10):e13196. doi: 10.1371/journal.pone.0013196, PMID 20967242.
18. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology: antidepressant drugs. Vol. 11. McGraw-Hill; 2010. p. 509-30.
19. Siddiqui N, Alam M, Alam O, Azad B. Fluoxetine: pharmacological andComputational Study. WebmedCentral Pharm. Sciences. 2011;2(3):WMC001800:2-3.
20. Rénéric JP, Lucki I. Antidepressant behavioral effects by dual inhibition of monoamine reuptake in the rat forced swimming test. Psychopharmacol (Berl). 1998;136(2):190-7. doi: 10.1007/s002130050555, PMID 9551776.
21. Pałucha A, Pilc A. On the role of metabotropic glutamate receptor in the mechanism of action of antidepressant. Pol J Pharmacol. 2002;54(6):581-6. PMID 12866712.
22. Greenblatt EN, Lippa AS, Osterberg AC. The neuropharmacological actions of amoxapine. Arch Int Pharmacodyn Ther. 1978;233(1):107-35. PMID 28699.
23. Settle EC, Settle GP. "A case of mania associated with fluoxetine". American Journal of Psychiatry 1984; 2: 141-144.

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