

COMPARISON OF ANTIDEPRESSANT ACTIVITY OF LOSARTAN WITH IMIPRAMINE IN ALBINO MICE

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ABSTRACT

OBJECTIVES

Comparison of antidepressant activity of Losartan with Imipramine in albino mice.

BACKGROUND

Of all the afflictions that trouble the soul, depression is the commonest characterised by a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being. Similarly, hypertension is another condition which has emerged as a major public health problem in India and many other developing countries. There is compulsion that 35% of the population has to use the antihypertensives and antidepressants simultaneously for a long period of time to maintain their health. The present work is aimed at comparing antidepressant activity of losartan with imipramine which acts by raising brain BDNF (Brain derived neurotrophic factor) levels so that a single agent can be used for both the conditions avoiding multiple medications.

METHOD

18 Albino mice were taken, divided into 6 mice in each group and subjected to Forced swim test. All the drugs were administered orally. Drugs were administered and time of onset of immobility is measured 60 min. after the drug administration along with total duration of immobility. Animals are exposed to pretest of 15 min., 24 hrs. prior to the 6 min. swim test. Each animal is considered immobile when it ceased to struggle and swim and remained floating in the water, only moving to keep its head above water. Control group received distilled water (10 mL/kg). Standard group received Imipramine (5 mg/kg) and test group was treated with Losartan (3 mg/kg). The Forced swim test for each mouse was video captured which was later analysed to count the time of onset of immobility and total duration of immobility.

RESULTS

Data was analysed using Analysis of Variance (ANOVA). Losartan showed significant antidepressant activity indicated by significant delay ($P < 0.05$) in the time of onset of immobility and significant reduction ($P < 0.05$) in the total duration of immobility compared to the control group. The antidepressant activity of Losartan is intermediate to that of the Standard (Imipramine) group and the control (Distilled water).

CONCLUSION

Losartan showed antidepressant activity in albino mice raising the possibility of itself being used as an antidepressant alone or can be used as a single agent for the treatment of both hypertension and depression simultaneously avoiding multiple medications.

KEYWORDS

Depression, Hypertension, Losartan, Imipramine, Forced Swim Test, Immobility.

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INTRODUCTION: Mood disorders are a group of clinical conditions characterised by a loss of that sense of control and a subjective experience of great distress.

Patients with depressed mood experience a loss of energy and interest, feelings of guilt, difficulty in concentrating, loss of appetite and thoughts of suicide.¹ It is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being.² Depression entered the diagnostic manual only 50 years ago. Previously it was known as melancholy.³ In most of the countries, the number of people who would suffer from depression during their lives falls within an 8–12% range.

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It is estimated that by the year 2020, if current trends for demographic and epidemiological transition continues, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years (DALYs), second only to ischaemic heart disease.⁴ Similarly, hypertension is another condition which also affects large population in the society. It has emerged as a major public health problem in India and many other developing countries.⁵ Increasing hypertension in India and other developing countries has been related to sedentary lifestyle, excess dietary salt, calorie and alcohol intake, increasing generalised and central obesity and stress of migration and urbanisation.⁶

There is sufficient clinical and epidemiological evidence that hypertension is increasing in India. It has been reported that hypertension prevalence in India quadrupled in urban as well as rural population over 50-year period from early 1950s to late 1990s.⁷ The global burden of disease study has reported that by year 2025, cardiovascular disease would be the major cause of death all over the world including the developing countries.⁸ Hypertension is directly related to about 40% of this cardiovascular disease burden.⁹

35% of the population is suffering from both hypertension and mental depression respectively. There is compulsion that 35% of the population has to use the antihypertensives and antidepressants simultaneously for a long period of time to maintain their health.¹⁰ It was serendipity which played a major role in the discovery of many antidepressant drugs initially.¹¹ Logically, a single drug that can control the physical and associated mental illness would be an ideal agent for the treatment of such comorbid conditions.

A deficiency in neurotropic support leads to the development of depression and reversal of this deficiency by antidepressant treatments may contribute to the resolution of depressive symptoms. Acute and chronic stress decreases the levels of BDNF expression in the den Gyrus and pyramidal cell layer of hippocampus in rodents. Antidepressants produce the opposite effects, they increase dendritic arborizations and BDNF expression of these hippocampal neurons. The possibility that upregulation of BDNF contributes to the therapeutic actions of antidepressants is further supported by the behavioural studies.^{12,13}

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT1 receptors and the consequent reduced pressor effect of angiotensin II. It is used in the management of hypertension, particularly in patients who develop cough with ACE inhibitors and to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy.¹⁴ Losartan, an angiotensin receptor II blocker has also been reported to possess antidepressant activity in experimental animals.¹⁵ It is therefore carefully planned to compare antidepressant activity of Losartan with Imipramine in albino mice.

MATERIALS AND METHODS: Animals- Male Albino mice weighing 20 – 30 g were used.

A total of 18 albino mice from central animal house were divided in to 3 groups, 6 animals in each group. All the test animals were allowed food and water ad libitum, both being withdrawn before the experiment. They are maintained under standard 12-hour dark and light cycle. The study got approved from Institutional Animal Ethical Committee formed as per guidelines of CPCSEA, Hyderabad. The animals were grouped into 3 groups of 6 each i.e. standard, test and control groups were subjected to Forced swim test. All preparations are administered orally. The total duration of immobility was recorded; after the test, the animals were removed from water, dried with a clean towel and placed back in cages. The animals were kept under observation for 24 hrs. period and then transferred back to the Animal house.

Forced Swim Test: The forced swimming test (FST) remains one of the most used tools for screening antidepressants among all animal models. It was first described by Porsolt et al. (1977). It works on the principles of behavioural despair. Albino mice are forced to swim in a perplex glass tank with no escape. The animals become immobile after an initial struggling phase. The total duration of immobility is measured throughout the trial. Immobility has been equated to a despair reaction, and when mice are placed back in the water tank 24 hrs. later, they remain immobile for a significantly longer than naïve animals. Antidepressants decrease the immobility time. The forced swim test is widely used behavioural model in rodents. It is both sensitive and selective for clinically effective antidepressant drugs.

Mice were individually forced to swim in an open Plexiglas aquarium of 25×10 cm dimension, containing water of 15 cm depth at 25±1°C [Measurements of the Plexiglas aquarium were according to a previous study on antidepressant activity]. The mice lack a sense of water's depth and their tails do not touch the bottom of the Plexiglas aquarium. Animals were exposed to pretest of 15 min., 24 hrs. prior to the 6 min. swim test. Each animal is considered immobile when it ceased to struggle and swim and remained floating in the water, only moving to keep its head above water.¹⁶ Drug was administered initially and time of onset of immobility is measured 60 min. after the drug administration.

Preparation of solutions of standard and test drugs:

- 1. Imipramine:** The Standard solution of Imipramine is prepared by dissolving the tablet (Depsonil 25 mg) in 50 mL of Distilled water. The solution has a concentration of 0.5 mg/1 mL.
- 2. Losartan:** The standard solution of Losartan is prepared by dissolving the tablet (Losar 25 mg) in 75 mL of Distilled water. The solution has a concentration of 0.3 mg/1 mL.
- 3. Distilled Water:** Distilled water acts as control and is administered as 10 mL/kg.

Doses of Drugs:

1. C= Control group treated with Distilled water (10 mL/kg).
2. S= Standard group treated with Imipramine alone (5 mg/kg).
3. T=Test group treated with Losartan alone (3 mg/kg).

OBSERVATIONS: The Forced swim test for each mouse was video captured. The videos were later analysed to count the time of onset of immobility and total duration of immobility. Immobility in the present test is a measure of behavioural despair i.e. a measure of depression. The Time of onset of immobility and the Total duration of immobility are tabulated in separate tables.

STATISTICAL ANALYSIS: Data was analysed using Analysis of Variance (ANOVA) with the drug treatment as the independent factor. Test of significance was established wherever P value was less than 0.05.

Group	Mean	SD	SEM
Control [C]	118.333	11.553	±4.716
Standard [S]	142.833	6.242	±2.548
Test Group [T]	136.333	4.761	±1.947

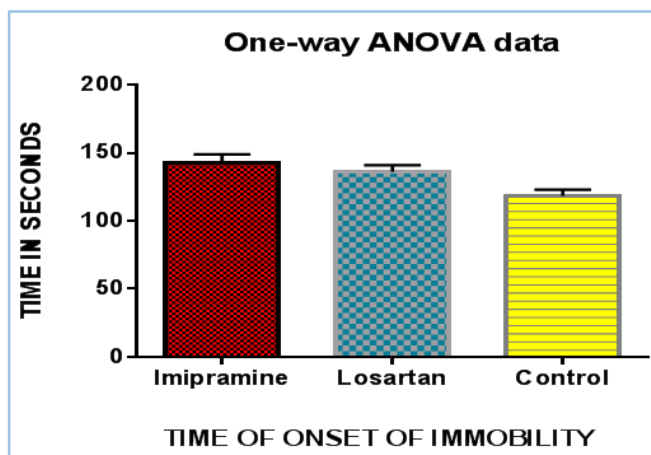
Table 1: Time of Onset of Immobility

Group	Mean	SD	SEM
Control [C]	126.166	5.60	±2.286
Standard [S]	81.833	4.915	±2.006
Test Group [T]	101.166	4.708	±1.922

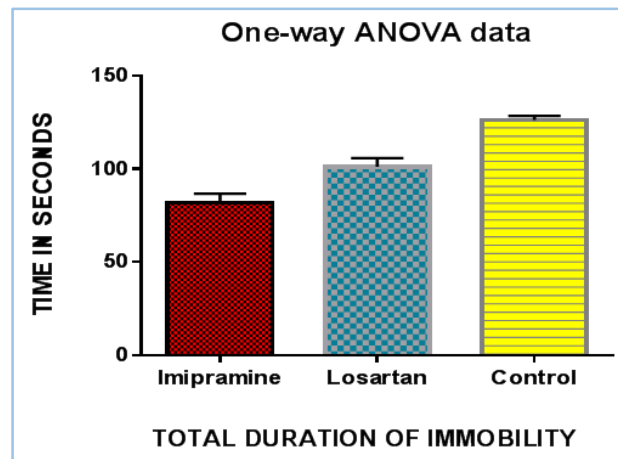
Table 2: Total Duration of Immobility

Note: In the above tables:

1. C=Control group treated with Distilled water (10 mL/kg).
2. S=Standard group treated with Imipramine alone (5 mg/kg).
3. T=Test group treated with Losartan alone (3 mg/kg).



Graph 1: Time of Onset of Immobility



Graph 2: Total Duration of Immobility

Note: In the above Graphs:

1. C= Control group treated with Distilled water (10 mL/kg).
2. S= Standard group treated with Imipramine alone (5 mg/kg).
3. T= Test group treated with Losartan alone (3 mg/kg).

RESULTS:

- Table 1 shows the Time of onset of immobility in the Forced swim test. Results are expressed as Mean±SEM. Standard (Imipramine), Test (Losartan) group showed significant delay (P<0.05) in the Time of onset of immobility compared to the control group.
- Table 2 shows the Total duration of immobility in the Forced swim test. Results are expressed as Mean±SEM. Standard, Test group showed significant reduction (P<0.05) in the Total duration of immobility compared to the control group.
- Graph 1 is a bar graph showing the Time of onset of immobility. The height of the bar of the test (Losartan) group is intermediate to that of the standard (Imipramine) and the control (Distilled water) and which means a delay in the time to attain immobility. (Immobility, in the present test is considered as a state of behavioural despair).
- Graph 2 is a bar graph showing the Total duration of immobility. The height of the bar of the test (Losartan) group is intermediate to that of the Standard (Imipramine) group and the control (Distilled Water).
- The results of the study indicate that Losartan has got antidepressant effect which is comparable and intermediate to that of the standard group (Imipramine) and control group (Distilled water).

DISCUSSION: The findings of the present study in Forced swim test clearly indicate that Losartan has significant antidepressant activity comparable to that of Imipramine. Depression is a disorder of major public importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. Emphasis on screening and expansion of treatment needs to be accompanied by a parallel emphasis on pre-clinical evaluation of new drugs.¹⁷

Similarly, hypertension is another condition which also affects large population in the society.^{5,6} There is compulsion that 35% of the population has to use the antihypertensives and antidepressants simultaneously for a long period of time to maintain their health.¹⁰

Recent basic and clinical studies provide evidence for a neurotrophic hypothesis of depression and antidepressant action. According to Duman et al., 1997, 2000, decreased expression of BDNF could contribute to the atrophy of hippocampus in response to stress in depressed patients, and upregulation of BDNF could contribute to the action of antidepressant treatment. The results of their study provide further support for this hypothesis, demonstrating that infusion of BDNF into the hippocampus produces an antidepressant effect in two standard behavioural models of depression.¹⁸

It has been hypothesised that inhibition of Angiotensin function is important in the treatment of endogenous depression.¹⁹ The mechanism of action of various antidepressant and anxiolytic agents is not clearly understood. The explanations proposed in the literature often based on conflicting observations, involve several types of receptors such as adrenergic (α and β) serotonin, dopamine, etc. in mediating psychotropic activity. The crosstalk among these receptors have led to proposal of confounding hypotheses making the task challenging.

Antidepressant activity of losartan is mainly attributed to restoration of dysregulated HPA axis through blockade of AT1 receptors in anterior pituitary, preservation of enkephalins and increasing cortical as well as hippocampal BDNF.²⁰ ARBs are believed to act through restoration of normalcy of HPA axis has been correlated with its antidepressant activity in a hypertensive patient. Involvement of glucocorticoids in the pathogenesis of depression has been confirmed in an experimental study.²¹ There is evidence that antidepressants stimulate adult hippocampal neurogenesis and that hippocampal neurogenesis may be required for the full therapeutic effects of antidepressants.²²

The FST is often referred to as a test of learned helplessness, operationally defined as an increase in immobility and a decrease in swimming and climbing behaviours. When examined in the context of other robust measures of depression-related behaviours, especially the core symptom of anhedonia, these results and past reports suggest that the FST is most reliably employed as an acute test to predict antidepressant drug effects.²³ Of all the tests, forced swim test was demonstrated to have a specific response to antidepressant treatment.²⁴

Depression is an independent risk factor for coronary heart disease both in patients with cardiovascular disease as well as medically healthy individuals and is a significant independent predictor of mortality within 18 months following a heart attack. Animal models of depression have been extremely useful in providing support for this relationship between depression and cardiovascular disease and establishing an experimental model in which to study possible underlying mechanisms and methods of treatment. Major depressive disorder and cardiovascular disease share

a comorbid bidirectional relationship, wherein the presence of one increases the likelihood of the other. Candesartan, an AT1R antagonist often prescribed for hypertension and other cardiovascular disorders, has been shown to be anxiolytic in animal models, and may have antidepressant properties.²⁵

Thus, the present work though of preliminary nature suggests that Losartan in a dose of 3 mg/kg has antidepressant activity though less when compared to Imipramine but might be of use in patients suffering from both hypertension and depression thus avoiding multiple medications. It may be preferred to treat hypertensive patients with mood disorders, provided the present findings could be extrapolated to human beings. Such patients need the treatment with an antihypertensive and an antidepressant.

When losartan is used as an antihypertensive might reduce the dosage requirement of potentially toxic antidepressants and same needs clinical evaluation.

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