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Augmentation of Antidepressant effects of SSRIS by Aripiprazole

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Abstract

The present study was done to demonstrate the potentiation of antidepressant effects of sub-therapeutic doses of SSRIs by aripiprazole in mice model of behavioral despair. The tests were performed in 60 inbred male albino mice from central animal house, Madurai medical college, Madurai. They were divided into five groups of six animals each. Group I served as control, group II as standard and group III, IV and V as test groups respectively. Aripiprazole (0.03, 0.06 & 0.12 mg/kg PO) and sertraline (8 mg/kg PO) were administered to the test groups and their efficacy as antidepressant was compared with the standard drug sertraline (20 mg/kg PO) in mice subjected to forced swim test. The CNS stimulant effect of the combination was evaluated using actophotometer. The combination of aripiprazole (0.03, 0.06 & 0.12 mg/kg PO) and sertraline (8 mg/kg PO) significantly reduced the immobility period in forced swim test. (P = 0.008, 0.005 & 0.001 respectively). The combination did not have any significant effect on the locomotor activity in mice ($p>0.05$). Antidepressant effect of the combination was comparable with that of the standard. The results concluded that combination of sub-therapeutic doses of aripiprazole and sertraline had antidepressant effect in mice. The efficacy of the combination to limit the dose related toxicities by achieving therapeutic effects at lower doses of SSRIs needs to be explored further.

Key-Words: Aripiprazole, Forced Swim Test, Locomotor Activity, Sertraline, Antidepressant

Introduction

Depression is major public health problem with lifetime prevalence of 15% and females are twice as affected as males [1]. It is the final expression of genetic factors, developmental problems and psychosocial stresses [2]. The CSF levels of metabolites of monoamines - serotonin, nor epinephrine and dopamine are reduced in depression. Choice of antidepressant agents mainly depends on cost and side effect profile [3]. Selective serotonin reuptake inhibitors are used widely for treatment of depression. They are relatively safe and effective as antidepressants. However these SSRIs are produce adverse reactions like somnolence, dizziness, elevation of liver enzymes, metabolic disturbances and sexual dysfunction. Also 30-50% of patients do not respond to SSRI monotherapy [4].

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Many studies have demonstrated the role DA system in the development of depression. Atypical antipsychotics act mainly by dopamine receptor antagonism and by modulating the serotonergic receptors. Combination of atypical antipsychotics with antidepressants with have shown rapid improvement in patients with resistant depression who did not respond to SSRIs [5]. These atypical antipsychotics are well known for their metabolic adverse effects.

Aripiprazole is an atypical antipsychotic, acting by partial D_2 and $5HT_{1A}$ agonism and $5HT_{2A}$ antagonism[6] . It stabilizes dopamine activity in brain. Patients with SSRI resistant depression showed major improvement when treated with low doses of aripiprazole. Another advantage of this combination was the favorable side effect profile of aripiprazole.

The aim of this study is to demonstrate the antidepressant effects of subtherapuetic doses of the above drugs and there by attempting to reduce their adverse effect profile while maximizing their therapeutic benefits.

Forced swim test established by Porsolt et al (1977) has been widely used for screening of antidepressants in

rodents[7]. Antidepressants significantly reduce the immobility period of rodents in this test of behavioral despair. However drugs acting on dopaminergic systems could produce the same results in forced swim test. To rule out any effects on the dopaminergic system the locomotor activity of the animals were measured by actophotometer.

Material and Methods

The experiment was carried out in the central animal house, Madurai medical college, Madurai after obtaining the Institutional Ethical Committee approval (reference no. RocNo 12677E1/4/12) . 60 male Swiss mice of age 4 ± 2 weeks weighing 20 ± 5 grams were used . They were housed as 5 per cage and had free access to food and water. They were maintained in 24±1 ˚C and 12 hour light dark cycle. Mice were allowed to adapt to their surroundings for at least 1 week before the behavioral tests. The mice were fasted 2 hours before and 2 hours after drug administration. All the experimental procedures were carried out between 10.30 and 13.00 hours.

Drugs: Sertraline (Pfizer, USA) and aripiprazole (Torrent pharmaceuticals, India) were used in the study and distilled water was used as solvent.

Methodology:

A standard (20 mg/kg) and subactive (8 mg/kg) doses of sertraline were selected based on previous studies[8]. Doses of aripiprazole that did not have stimulant effects on locomotor activity (0.03, 0.06 and 0.12 mg/kg) were chosen as sub effective doses. The sub active doses of aripiprazole and sertraline were administered and the effect of the combination was compared with that of standard and control groups.

Forced swim test:

For the forced swim test 30 mice were divided into control, standard and test groups 1, 2 and 3 of six animals each. Animals were kept in the test room for at least 1 hour for habituation. Control group received distilled water; the standard group received 20 mg/kg of sertraline orally dissolved in distilled water 1 hour prior to the experiment. The test groups 1, 2 and 3 received sub active doses of sertraline (8 mg/kg) and aripiprazole (0.03, 0.06 and 0.12 mg/kg) dissolved in distilled water 45 minutes and 1 hour prior to the experiment . Mice were subjected to forced swim test for 6 minutes in a cylindrical tank with water at 25±1˚C in which mice cannot touch the bottom of the tank or escape. After initial period of vigorous activity the animal assumed an immobile posture. The immobility was calculated manually for the last 4 minutes. Mice were considered to be immobile when they stopped struggling and remained floating motionless in water making only those movements necessary to keep their head above water. The tests were conducted in a dim lit room and each mouse was used only once [9,10].

Locomotor activity:

To rule out the CNS stimulant activity of the combination a study was conducted to observe the locomotor activity of the mice in actophotometer**.** 30 animals were divided in to 5 groups of 6 mice each as for the forced swim test. Control group received distilled water, the standard group received 20 mg/kg of sertraline orally dissolved in distilled water 1 hour prior to the experiment. The test groups 1, 2 and 3 received sub active doses of sertraline (8 mg/kg) and aripiprazole(0.03, 0.06 and 0.12 mg/kg) dissolved in distilled water 45 minutes and 1 hour prior to the experiment Each animal was observed for 10 minutes in the actophotometer .

Results and Discussion

The results were expressed as mean ± Standard deviation and analysis was done using one way ANOVA followed by Sidak test for significance. In the forced swim test, the mice treated with the standard dose of sertraline showed significant reduction in immobility time compared to the control group. The mice treated with the sub therapeutic doses of combination of sertraline (8 mg/kg) and aripiprazole (0.03, 0.06 and 0.12 mg/kg) also significantly reduced the immobility time and it was comparable to the standard dose of antidepressant (p value 0.008, 0.005 & 0.001). The combination itself was not superior to the standard dose of antidepressant (sertraline 20 mg/kg).

The locomotor activity of mice in the control group was comparable with the combination of aripiprazole (0.03, 0.06 and 0.12 mg/kg) and sertraline (8 mg/kg). There was no significant increase in the locomotor activity in standard and test groups ($p > 0.05$).

Conclusion

The pathophysiology of depression still remains a mystery. Drugs discovered till date have paved way to central monoaminergic system defect theory. Dopamine, nor epinephrine and serotonin play a major role in depression[11]. Even though drug therapy directed towards these systems like monoamine oxidase inhibitors and tricyclic antidepressants were initially discovered, SSRIs have now gained a status of first line drug therapy in depression. But one third of patients do not respond to monotherapy. Moreover onset of action of these drugs take about 3-8 weeks during which there is increased risk of suicide [12].

Aripiprazole is a partial agonist of D_2, D_3 and $5HT_{1A}$ receptor and antagonist at $5HT_{2A}$ receptor. Partial agonist has high affinity but low efficacy towards the $5HT_{1A}$ receptors. Hence their effect would depend on

the serotonin concentration in the brain. A partial agonist increases the neurotransmitter activity when it is suppressed while decreasing it when it is overactive [13]. However in depressed patients with low serotonin levels in cortex and limbic areas these partial agonists enhance the neurotransmission.

This study showed that the combination of subtherapuetic doses of aripiprazole augmented the sub threshold doses of SSRIs. The combination per se did not have any psycho stimulant effects in mice indicating that the antidepressant activity was mainly mediated through the 5HT1A receptor.

$5HT_{1A}$ receptors are present both pre and post synaptically. Post synaptic $5HT_{1A}$ receptors are important for the antidepressant activity. Activation of these receptors causes the reduction in immobility time with behavioral forced swim test [14]. Also this receptor action mediates neurogenesis in depression [15, 16]. Presynaptic $5HT_{1A}$ receptor is located in the GABAergic neurons and interneurons of dentate gyrus and hippocampus. $5HT_{1A}$ receptor is involved in the control of central monoaminergic activity. Hence it is clear that the $5HT_{1A}$ receptors play a major role in depression. Further $5HT_{2A}$ antagonism also accounts for this augmentation of antidepressant activity.

Aripiprazole is a promising agent for depression in the following ways. Long term therapy enhances 5HT neurotransmission by $5HT_{1A}$ autoreceptor desensitization [17]. Secondly D_2 agonism is an effective adjunct in treatment of resistant depression [18]. Thirdly the side effect profile of this drug is favorable for long term therapy [19]. The present study showed that the combination of sub effective doses of sertraline and aripiprazole has antidepressant activity comparable to the standard doses of sertraline.

To conclude subtherapuetic doses of aripiprazole augments the activity of subtherapuetic doses of sertraline in mouse models of behavioral despair. This can be explained by the complex mechanism of aripiprazole and its action on $5HT_{1A}$ receptor. This combination therapy could significantly reduce the side effects of individual drugs, while enhancing their efficacy. This area needs to be explored further to provide patients with depression, an adverse effect free remission.

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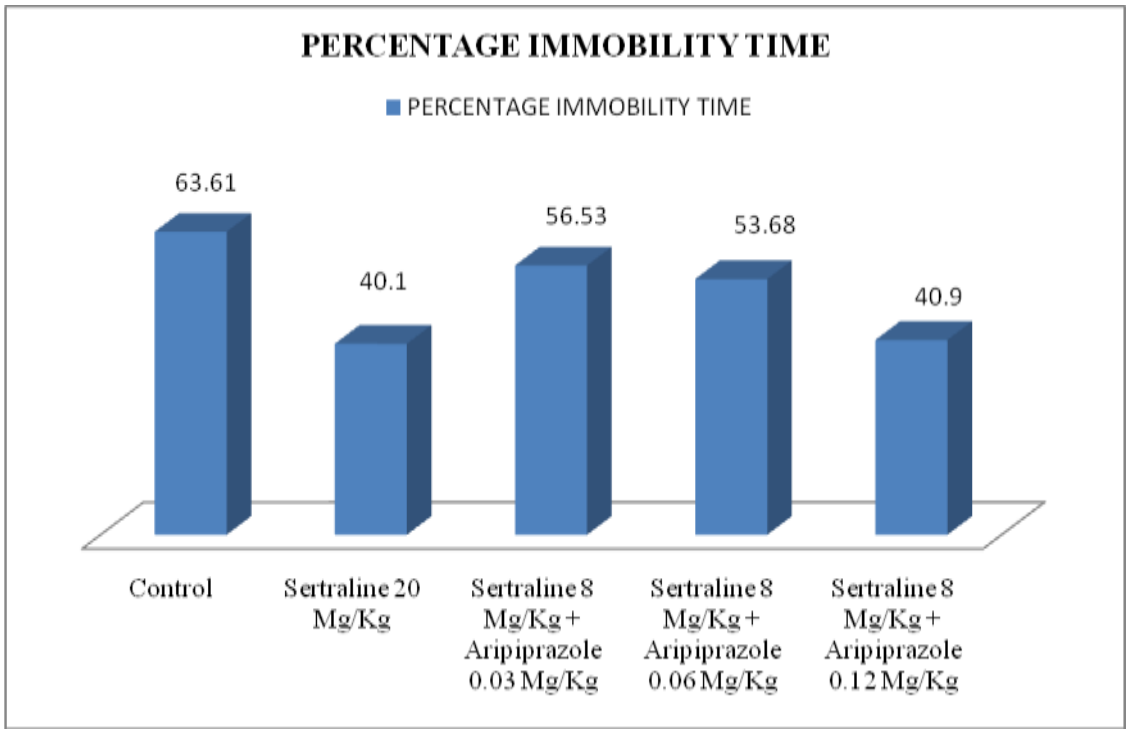

Fig. 1: Percentage immobility time

Table 1: Forced Swim Test

Groups	Immobility Time In Seconds (Mean ± Standard Deviation)	P Value
Control	152.67 ±9.97	
Sertraline 20 Mg/Kg	96.16 ± 14.34	0.001
Sertraline 8 Mg/Kg + Aripiprazole 0.03 Mg/Kg	135.67 ±7.71	0.008
Sertraline 8 Mg/Kg + Aripiprazole 0.06 Mg/Kg	128.83 ± 12.7	0.005
Sertraline 8 Mg/Kg + Aripiprazole 0.12 Mg/Kg	98.17 ± 16.32	0.001

Table 2: Locomotor Activity

Groups	Immobility Time In Seconds (Mean ± Standard Deviation)	P Value
Control	713 .17 ± 38.19	
Sertraline 20 Mg/Kg	725.83 ± 57.32	0.711
Sertraline 8 Mg/Kg + Aripiprazole 0.03 Mg/Kg	728 ± 67.53	0.664
Sertraline 8 Mg/Kg + Aripiprazole 0.06 Mg/Kg	716.67 ± 87.5	0.946
Sertraline 8 Mg/Kg + Aripiprazole 0.12 Mg/Kg	723.17 ± 103.93	0.78

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