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EVALUATION OF ANTI-ANXIETY EFFECTS OF ARIPIPRAZOLE IN MICE

Pharmacology

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ABSTRACT

The aim of this study was to evaluate the anti-anxiety effects of aripiprazole in mice. 60 Inbred male adult albino mice were used in this study. 30 mice were divided in to five groups (n=6). Group I received normal saline .O, group II received diazepam 2 mg/kg P.O and the test groups III, IV and V received (1, 1.5, 2 mg/kg P.O) of aripiprazole.30 Mice were subjected to elevated plus maze test to evaluate the anxiolytic activity of aripiprazole. The locomotor activity was assessed in 30 mice using actophotometer to evaluate the CNS stimulant effect. The data was tabulated and analyzed statistically using one way ANOVA. Aripiprazole significantly increased the number of entries and the time spent at the opens arm. It did not increase the locomotor activity. Aripiprazole showed significant anxiolytic effects in mice. Further studies are needed to explore the anxiolytic activity of aripiprazole in humans.

KEYWORDS

Elevated Plus Maze Test, Anti-Anxiety Effects, Aripiprazole.

INTRODUCTION

Anxiety is a state of fear or subjective feeling of apprehension, foreboding or dread that may be experienced with or without specific causes. It not only causes severe disability but it also has negative impact on quality of life. The symptoms of anxiety disorders include excessive sweating, palpitation, tremors, headache , fatigability, insomnia, irritability, restlessness, inability to concentrate,feeling of tension and apprehension.(1)

Major areas of brain involved are amygdala, hippocampus, reticular activating system medial frontal cortex and limbic system. Hippocampus is mainly involved in regulating defensive behavior related to anxiety(2). Major neurotransmitters in anxiety disorders are Serotonin (5HT), Norepinephrine(NE), Dopamine (DA), GABA. Imbalance of neurotransmitters causes anxiety disorder. Knockout mice bred without 5-HT_{1A} receptors showed increased anxiety behaviors. 5-HT_{1A} receptors are present both pre and postsynaptically. Selective serotonin reuptake inhibitors(SSRIs) are first line in long term treatment of generalised anxiety disorders, social anxiety, obsessive and compulsive disorder, eating disorder and PTSD and they have a success rate of about 61.1%.(3) The adverse effects of SSRIS include insomnia, nausea, increased nervousness, and sexual dysfunction.(4).

Other drugs used to treat anxiety disorders include serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants(TCAs), monoamine oxidase inhibitors and azapirones . TCAs and monoamine oxidase inhibitors have disadvantages such as postural hypotension, weight gain, and insomnia. Benzodiazepines are mainstay drugs for acute anxiety but they have narrow safety margin and may cause cognitive impairment on short term use and dependence on long term use (5). Anticonvulsants have also been tried for anxiety disorders. Hence there is an ongoing search of a potentially safer alternative with better side effect profile.

Atypical antipsychotics have been tried in depression, post traumatic stress disorders and treatment resistant anxiety. Aripiprazole is an atypical antipsychotic, acting by partial D_2 and 5HT_{1A} agonism and 5HT_{2A} antagonism[6,7,8] . It is also known as a dopamine-serotonin system stabilizer. It also possesses anti-aversive properties. It is known to produce rapid onset of action with sustained efficacy. It is mainly used for treatment of psychotic disorders, bipolar disorders and resistant depression. It is longer acting and has fewer side effects.

Aim of this study is to demonstrate the anti-anxiety effects of aripiprazole in animal models of anxiety in mice.

Elevated plus maze test is a well characterized behavioural paradigm to investigate anxiety in animal models of rats and mice by File and co-workers(9). It is based on conflict between an innate aversion to exposed spaces and a tendency to explore new environments. The exposed spaces are represented by the maze's two open arms and the two closed arms represent the safer places. Anxious animals will spend more time in the closed arms than less anxious animals that prefer the open arms. Anxiety reduction is indicated in the plus-maze by an increase in the proportion of time spent in the open arms and an increase in the proportion of entries into the open arms. To rule out any effects on dopaminergic system the locomotor activity of animals was assessed using acto-photometer.

METHODOLOGY

The experiment was carried out in the central animal house, Madurai medical college, Madurai after obtaining the Institutional Ethical Committee approval. 60 male Swiss mice of age 4 ± 2 weeks weighing 20 ± 5 grams were used in the study . 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. The arena of elevated plus maze and actophotometer were wiped with 70% ethyl alcohol solution before placing each animal.

Drugs: Aripiprazole (Torrent pharmaceuticals , India) and Diazepam (Ranbaxy, India) were used in the study and distilled water was used as solvent .

A standard (2mg/kg) dose of diazepam were selected based on previous studies. Doses of aripiprazole that did not have stimulant effects on locomotor activity (1, 1.5 and 2 mg/kg in mice) were chosen for testing anti-anxiety property. The doses of aripiprazole were administered orally and the effect was compared with that of standard diazepam.

Elevated Plus Maze Test:

The plus maze apparatus consists of two open arms (16 X5 cm), two closed arms (16 X 5 X12 cm) and an open roof with entire maze elevated 25 cm from the floor. For the elevated plus maze test, 30 mice were divided into control , standard and 3 test groups. Group I received Distilled water, Group II received Diazepam (2mg/kg PO), Group III , IV and V received 1,1.5 and 2 mg/kg Aripiprazole dissolved in distilled water orally.

Animals were treated with drugs and assessed after one hour. 30 mice were placed individually at the center of the elevated plus maze with their head facing the open arm. During the 5 minutes test period the preference of the animal for the first entry, the number of entries in to the open or closed arms and the time spent in each arm were recorded and noted by three independent observers who were blinded to the drug administered.

Locomotor activity:
To assess the CNS stimulant activity of the drug 30 male Swiss mice in control, standard and test groups are treated with drugs and 1 hour later all the mice were tested individually and their locomotor activity was recorded using an actophotometer for a period of 10 minutes. Group I received Distilled water, Group II received Diazepam (2mg/kg PO), Group III, IV and V received 1,1.5 and 2 mg/kg Aripiprazole dissolved in distilled water orally.

STATISTICALANALYSIS:
The data were tabulated and expressed as mean ± SE. The statistical analysis was done by one way ANOVA test followed by posthoc Dunnet's test. The index of open arm avoidance was calculated as [100 – (% time on open arms + % entries into the open arms)/2].

RESULTS:
In elevated plus maze test, the mice treated with standard drug diazepam showed increased preference of the open arm for the first entry(66.67%) the mice treated with 1,1.5 and 2mg/kg of aripiprazole also showed increasing preference of open arm entry (33.33%,50%, 66.67%). This proves the anxiolytic effects of the test drug which is seen as increased exploratory activity in mice. Aripiprazole in doses of 1, 1.5 and 2mg/kg also increased the percentage of open arm entry and duration of time spent in open arm compared to control group ($p<0.005$) . The effects of aripiprazole were comparable to standard drug diazepam. Index of open arm avoidance was calculated which showed that aripiprazole decreased the open arm avoidance. Thus aripiprazole has an anti- anxiety effect in mice as tested by elevated plus maze test and it was comparable to anti-anxiety agent diazepam.

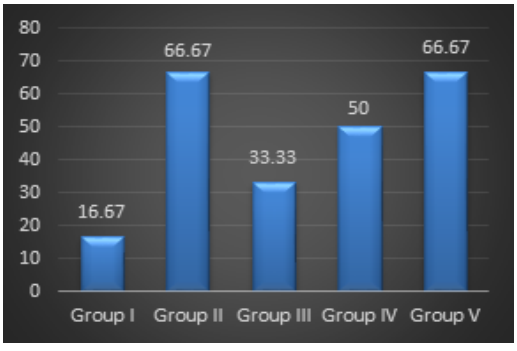

Figure 1: preference of the open arm for the first entry in percentage

Table 1: % of open arm entries and Duration spent in open arm in %

Groups	% of open arm entries (mean ± SE)	Duration spent in open arm in % (mean ± SE)
I – control	25.13 ± 1.29	26.11 ± 0.88
II - diazepam 2mg/kg PO	58.57 ± 1.25*	57.83 ± 1.38*
III - aripiprazole 1mg/kg PO	33.57 ± 1.46#	35.44 ± 1.61*
Iv - aripiprazole 1.5 mg/kg PO	55.69 ± 1.06*	46.61 ± 1.39*
V - aripiprazole 2 mg/kg po	55.72 ± 2.25*	51 ± 0.80*

*** - P<0.001 , # - P<0.002**

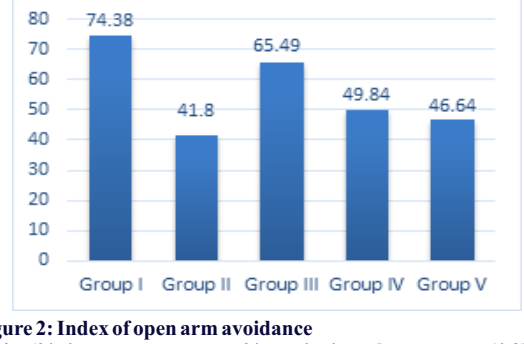

Figure 2: Index of open arm avoidance
[100 – (% time on open arms + % entries into the open arms)\ 2]

In contrast to standard drug diazepam which decreased the locomotor activity ($p<0.001$) compared to control group, aripiprazole had minimum effects on locomotion($p>0.05$).

Table 2 : locomotor activity in actophotometer

Groups	Locomotor activity (mean ± SE)	P value
I - Control	279.33 ± 5.95	
II - Diazepam 2mg/kg PO	90.17 ± 3.94	< 0.001
III - aripiprazole 1 mg/kg PO	277.67 ± 6.15	0.84
IV - aripiprazole 1.5 mg/kg PO	257.83 ± 11.1	0.11
V - aripiprazole 2 mg/kg PO	264.16 ± 7.61	0.15

DISCUSSION AND CONCLUSION:
This study shows that aripiprazole has antianxiety effects in mice. In elevated plus maze test mice appear unwilling to venture onto the open arms of the maze because of a general aversion to open spaces and to the elevation of the maze. Thus the preference of animals of a closed arm (safe and comfortable environment) over open spaces (a risky environment) helps in determining anxiety levels. An increase in time spent and entries in open arm represents anxiolytic behavior[10]

Aripiprazole is a partial agonist at D_2,D_3 and $5HT_{1A}$ receptor and antagonist at $5HT_{2A}$ receptor. $5HT_{1A}$ receptor is present both at pre and post synaptic membranes. A partial agonist increases neurotransmitter activity when it is suppressed while decreases it when it is overactive. Hence the action of aripiprazole depends on the serotonin levels in the brain. It is reported that aripiprazole increases dopamine levels in prefrontal cortex and hippocampus but does not produce significant changes in the levels of serotonin.

In an animal study, aripiprazole (1 mg/kg,ip) inhibited marble-burying behavior, which has been considered to be an animal model of obsessive-compulsive disorder [11]. Although the mechanism mediating aripirazole induced inhibition of marble-burying behavior is unclear, the partial antagonistic effects of 5-HT_{1A}.

Aripiprazole is a promising agent for long term therapy because of its long duration of action and less extrapyramidal side effects. The metabolism occurs via CYP2D6 and CYP3A4 and the active metabolite of aripiprazole is dehydro-aripiprazole, which typically accumulates to approximately 40% of the aripiprazole concentration [12].

In the present study, we examined locomotor activity and found that aripirazole did not decrease locomotor activity in the mice. This was dis-similar to the findings of Natesan et al. showed that administration of aripirazole alone produced significant decreases in spontaneous locomotor activity in rodents [13] Nagai etal proved that repeated treatment with aripiprazole had no effect on locomotor activity [14]. These discrepancies may result from the use of different dosage forms or species of animals.

The unique receptor profile of aripiprazole that may make it more likely to be a superior agent in treatment of schizophrenia, resistant depression and some anxiety disorder. Furthermore, it may have possible neuroprotective effects and positive impact on cognitive processes. [15] Hence it is a promising agent for long term therapy of anxiety disorders. Further studies are essential to prove the anti-anxiety effects of aripiprazole in humans.

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