ABSTRACT

Major depressive disorder is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem and by loss of interest or pleasure in normally enjoyable activities. In the animal study we found that drugs significantly reduced the anxiety. The combination of two drugs i.e. atenolol and escitalopram were taken and by using the elevated plus maze (EPM) apparatus, the dose of drugs was compared to the control group and standard escitalopram. The result of combination was found significant as compared to control value of p was found (p=0.008). EPM was used to observe the anti anxiety of drug on the rats the dose of the drug was compare from vehicle treated to time spent in open arm of rats was increasing which shown that drug is having anxiolytic activity.

INTRODUCTION

The term "major depressive disorder" was selected by the American Psychiatric Association to designate this symptom cluster as a mood disorder in the 1980 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), and has become widely used since. The general term depression is often used to denote the disorder; but as it can also be used in reference to other types of psychological depression, it is disfavored over more precise terminology for the disorder in clinical and research use. Major depression is a disabling condition which adversely affects a person's family, work or school life, sleeping and eating habits, and general health. In the United States, around 3.4% of people with major depression commit suicide, and up to 60% of people who commit suicide have depression or another mood disorder.

DRUG PROFILE

1. Escitalopram

Escitalopram Starting Dose of escitalopram is 10 mg once daily for the treatment of depression or generalized anxiety disorder. However, if symptoms continue or if side effects occur during the treatment process, one have to alter dosage. Escitalopram may be taken with or without food, but should be taken at the same time each day to maintain an even level of the drug in blood.

2 ATENOLOL

Atenolol is a selective β₁ receptor antagonist, a drug belonging to the group of beta blockers (sometimes written β-blockers), a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. The chemical works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood-brain barrier thus avoiding various central nervous system side effects.

MATERIAL AND METHOD

Elevated Plus Maze

Elevated Plus Maze (EPM) test (Pellow et al.,1985) for studying the anxiolytic effect in rodents was used. EPM consists of two open arms (15cm x 10 cm) and two closed arms (50 cm x 10 cm x 40 cm) with an open roof and elevated at 50 cm. 1 hour after the oral administration of drugs, the rat was placed in centre of the maze, facing one closed arm. During a 5 min test period the following measures were taken: the time spent in the open and closed arms; total number of arm entries.
Treatment Schedule

**Table: 1.** Elevated Plus Maze (EPM) test groups with their treatment schedule:

<table>
<thead>
<tr>
<th>Groups n= 4</th>
<th>Treatment</th>
<th>Dosage, Route of administration and duration (14 days).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Distilled water (vehicle)</td>
<td>1 ml/kg p.o</td>
</tr>
<tr>
<td>2</td>
<td>Escitalopram</td>
<td>0.5 mg/kg p.o</td>
</tr>
<tr>
<td>3</td>
<td>Atenolol</td>
<td>1 mg/kg p.o</td>
</tr>
<tr>
<td>4</td>
<td>Atenolol+Escitalopram</td>
<td>0.5 mg/kg+1 mg/kg p.o</td>
</tr>
</tbody>
</table>

n = number of animals used in each group.
Treatment duration = 14 days.

**Forced swimming test (FST)**
The procedure as described by (Porsolt et al., 1978) was used, except that the water level was deeper (Detke and Lucki, 1996). Swimming sessions were conducted by placing rats in individual glass cylinders (45 cm high×20 cm in diameter) containing (25±2 °C) water 38 cm deep, so rats could not support themselves by touching the bottom with their feet.

Two swimming sessions were performed between 12:00 h and 19:00 h, an initial 15 min pretest followed 24 h later by a 5 min test. The immobility period in seconds was measured live in each test session by a blind observer.

**Table: 2.** Forced swimming test (FST) groups with their treatment schedule:

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<td>0.5 mg/kg+1 mg/kg p.o</td>
</tr>
</tbody>
</table>

n=4 no of animal used

**Experimental methods**
The animals of either sex were selected randomly of uniform weight 120±5 gm from animal house. The room temperature was maintained 22±2°C with food (Lipton India Ltd. pellets) and water *ad libitum*. The animals were transferred to the laboratory at least 1h before the start of the experiment. The experiments were performed during day (08:00-16:00 h). The institutional animal ethical committee approved to the study protocol.

**Result and Discussion**

**Elevated plus maze (EPM) model**

**Table: 3.** Elevated Plus Maze

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>Treatment</th>
<th>Dose (p.o for 14 days)</th>
<th>Time spent in open arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle</td>
<td>1 ml</td>
<td>29.5±4.21</td>
</tr>
<tr>
<td>2</td>
<td>Escitalopram</td>
<td>0.05 mg/kg p.o</td>
<td>77.0 ±7.19</td>
</tr>
</tbody>
</table>
Atenolol 2 mg/kg p.o 45.5±7.3

Escitalopram+Atenolol 0.05 mg/kg p.o 70.25±1.6

F= 6.38, p=0.008* compare to respective vehicle control group

Values are mean ± SEM of observation

In the animal study we found that drugs significantly reduced the anxiety, the result was shown in table, two drugs and its combination were taken and observed in elevated plus maze apparatus the dose of drugs was compared to the control group and standard escitalopram. The result of combination was found significant as compared to control value of p was found (p=0.008). EPM was used to observe the anti anxiety of drug on the rats the dose of the drug was compare from vehicle treated to time spent in open arm of a rats was increasing which shown that drug is having anxiolytic activity.

**Modified forced swim test**

**Table 4 modified forced swim test**

Values are mean ± SEM of observation

The table illustrates the effect of drugs on the duration of immobility time in the MFST model, one way ANOVA revealed that there were significant differences between treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (p.o for 14 days)</th>
<th>Time of immobility (Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1 ml</td>
<td>137.5±2.35</td>
</tr>
<tr>
<td>0.05 mg/kg p.o</td>
<td>121±1.55</td>
<td>130±2.35</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2 mg/kg p.o</td>
<td>125.8±1.65</td>
</tr>
<tr>
<td>Escitalopram+atenolol</td>
<td>0.05 mg/kg p.o</td>
<td>121±1.55</td>
</tr>
</tbody>
</table>

groups F=10.77,p=0.001 from the vehicle treated group drugs and in combination significantly decreased the duration of immobility time indicating anti depressant effect.

**DISCUSSION**

Atenolol alone and in combination with escitalopram (SSRI) in modified FST in rats enhanced climbing behavior while escitalopram (0.05 mg/kg) enhanced swimming significantly. Escitalopram is S-enantiomer of citalopram which is reported to increase swimming behavior at the cost of climbing and immobility (Maciej et al., 2007). Belonging to the same class, escitalopram also increased swimming significantly. The mechanism involved is increase in 5-HT synaptic concentration, thereby enhancing serotonergic neurotransmission, which is well known.

The modified FST, beside allowing to observe the effects of SSRIs in rats also provides a unique tool to understand the AD like effect of both serotonergic and catecholaminergic ADs and to detect the effects of novel types of ADs compounds (Maciej et al., 2007; Cryan et al., 2002; 2005). The critical influence of LC NE neurons on mobility of rats in FST is well established (West, 1990; Aghajanian et al., 1997; Klimek et al., 1997). An increase in LC activity decreases mobility, while reduction in the activity has the opposite effect. Thus, it can be assumed that a decrease in LC activity could be associated with antidepressant activity of atenolol.
Thus, the combination of atenolol with escitalopram offers advantage over the individual administration of these drugs on modified FST.

The elevated plus maze (EPM) is a widely used behavioral assay for rodents that has been validated to assess the anti-anxiety effects of a variety of pharmacological agents & to define brain regions and mechanisms underlying anxiety-related behavior. Anti-anxiety agents exhibit an increase in the percentage preference to open arms, the number of entries and time spent in open arms. In our study, we observed a significant increase in the percentage preference to open arms, the number of entries and time spent in open arms following atenolol (2 mg/kg) indicating its anti-anxiety effects in EPM in rats. Though escitalopram (0.5 mg/kg) and alprazolam (0.25 mg/kg) increased percentage preference to open arm entries, both did not affect number of entries and time spent in open arms. However, addition of atenolol resulted in a significant enhancement of anti-anxiety effect, dose dependently. Our results are in agreement with a large number of literature reporting anti-anxiety effects of β-blockers like atenolol, propranolol etc (Durel et al., 1986; Hayes & Schulz, 1987). The results also justify the use of combination of atenolol with alprazolam (available in the market) and escitalopram for anti-anxiety effects.

In the present study, the data clearly demonstrates that chronic treatment with atenolol produced antidepressant and antianxiety effects on modified FST and EPM respectively in rats. Its combination with escitalopram also exhibited beneficial effects. Hence, the study provided a rationale for the co-administration of atenolol with escitalopram, which may act as a useful and potent combination in the treatment of depressive disorders.

REFERENCE


