COMPARISON OF THE EFFICACY OF FLUOXETINE, PHENELZINE AND MOCLOBEMIDE IN RODENTS USING ANIMAL MODELS OF DEPRESSION

M. OWAIS ISMAIL AND AHSANA DAR*
Department of Pharmacology, Ziauddin University, Karachi-75600, Pakistan
International Center for Chemical Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-75270, Pakistan

ABSTRACT
Fluoxetine, phenelzine and moclobemide are reference antidepressant drugs that are commonly used to treat depression. In a present study we have compared the efficacy of fluoxetine, phenelzine and moclobemide in the rodents using forced swimming test (FST) and the tail suspension test (TST). All the drugs caused marked reduction in immobility time of rodents in a dose dependent manner in both models of depression but FST appeared to be more sensitive behavioral model than TST, in our study. Moclobemide showed the highest efficacy as it caused 87.7% reduction in immobility time in rats using FST with an efficacy order as moclobemide > phenelzine > fluoxetine. On the basis of IC_{30} values for the drugs, fluoxetine appeared to be the most potent in our investigations.

Keywords: Depression; forced swimming test; tail suspension test.

INTRODUCTION
Depression is a common mental health problem, seen frequently in general medical settings (Katon and Schulberg, 1992). It constitutes a substantial proportion of the global burden of diseases and is one of the major causes of disability (Licinio and Wong, 1999). Additionally, it may also lead to mortality due to the rising rates of suicide (Eddleston et al., 1998). The drugs that are commonly used for the treatment of depression include selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). These drugs increase the availability of monoamines, norepinephrine and 5-hydroxy tryptamine either by inhibition of family of monoamine oxidase enzymes or prevent their reuptake, as in case selective inhibitors of 5-hydroxy tryptamine reuptake (Blier et al., 1987 and Murphy et al., 1984).

It is well established that animal models of depression such as forced swimming test (FST) and tail suspension test (TST) are useful tools for the assessment of potential antidepressants (Borsini and Meli, 1988; Stern et al., 1985). The duration of the immobility time in both tests is reduced after pretreatment with a variety of antidepressants such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (Porsolt et al., 1977a) and selective serotonin reuptake inhibitors (Luo et al., 1999).

In the present investigation, the forced swimming test and the tail suspension test were used to compare the efficacy of fluoxetine, phenelzine and moclobemide in rodents.

MATERIAL AND METHODS

Drugs
Phenelzine sulfate (Sigma Chemical Companies, USA) and moclobemide (Roche Pharmaceuticals, USA) were dissolved in normal saline (0.9% NaCl) while fluoxetine (Merck Pharmaceuticals, Germany) was dissolved in 10% dimethyl sulfoxide solution.*Correspondence: E-mail: drmowais2000@yahoo.com
Comparison of the Efficacy of Fluoxetine, Phenelzine and Moclobemide in Rodents

(DMSO) and administered as a homogenous solution.

In both tests described below, 3 animals were used per dose. In FST and TST, animals were given either vehicle control (0.9% NaCl or 10% DMSO) or reference drug (i.p.: 0.2 mL/20g, mice or 0.5 mL/100g, rats) 1 h prior to the experiment.

Animals
Animals were kept under standard conditions with normal light cycle (12 hours light/dark) with free access to food and water. NMRI mice (20-28 g) and Wistar rats (160-200 grams) were used throughout the experiments and were housed in plastic cages in groups of 4-6 animals per cage.

Forced Swimming Test
Rats were placed individually in a glass tank (Height = 45 cm and Width = 17 cm) filled with water to a height of 15 cm, and temperature was maintained at 25°C. Animals were given pretest session of 15 minutes in swimming tank 24 hours prior to the experiment. After the pretest session animals were removed from swimming tank, dried and returned to their respective cages. However, any animal that showed nasal bleeding or wound or sank during the pretest session was discarded. After 24 hours, 0.9% NaCl or 10% DMSO solution or reference drugs (0.1 to 19 mg/kg) were administered intraperitoneally to animals. After 1 hour of the treatment, rats were again forced to swim under similar conditions as described above. The duration of immobility time was recorded for a period of 5 minutes and animal was considered immobile when it remained floating with all four limbs motionless (Porsolt et al., 1977a, Dar and Khatoon, 2000). The percent reduction in the immobility time of the test animals was calculated as compared to the control animals.

Tail Suspension Test
Mice received an intraperitoneal injection of 0.9% NaCl or 10% DMSO or reference drugs (0.1 to 19 mg/kg). After 1 hour of the treatment, mice were suspended on the edge of the table by using adhesive tape placed approximately 1 cm from the extremity of the tail, 35 cm above the ground and the duration of immobility time was recorded for the period of 6 minutes. Mice were considered immobile when they hung passively motionless (Steru et al., 1985, Dar and Khatoon, 2000). The percent reduction in the immobility time of the test animals was calculated as compared to the control animals.

STATISTICAL ANALYSIS
All the values are expressed as the mean ± standard error of mean (SEM). Data of FST and TST were analyzed by one-way analysis of variance (ANOVA), followed by a least significant difference test (Milton and Tsokos, 1983). P values less than 0.05 was considered significant. The inhibitory concentration values were determined graphically by plotting the concentration of drugs versus the response of animals.

RESULTS
Table 1 shows that in the forced swimming test fluoxetine caused reduction in the immobility time of rats at 0.1 mg/kg, 0.5 mg/kg and 1 mg/kg, which was 22.50%, 36.67% and 36.04% respectively, followed by a reversal at 4 mg/kg and 7 mg/kg. Phenelzine showed significant reduction in immobility time of rats from 7 mg/kg to 19 mg/kg as compared to control animals and the maximum reduction in immobility time was obtained at 19 mg/kg that was 66.9%. Moclobemide showed significant reduction in immobility time of rats in a dose dependent manner from 4 mg/kg to 19 mg/kg as compared to control animals and the maximum reduction in immobility time was obtained at 16 mg/kg that was 87.7%.

Fluoxetine caused some reduction in immobility time of mice at 0.1 mg/kg and 0.5 mg/kg but the statistically significant reduction in immobility time was observed at 0.5 mg/kg that was 23.52% (Table 2). Phenelzine showed significant reduction in immobility time at 16 mg/kg and 19 mg/kg, which was 37.16% and
22.14% at respective doses. Moclobemide also showed significant reduction in immobility time of mice in dose dependent manner at 10 mg/kg, 13 mg/kg and 16 mg/kg that was 29.9%, 48.6% and 69.52%, respectively.

**DISCUSSION**

Both FST and TST are the accepted stress models of depression as they are sensitive and selective for clinically used antidepressants. Rodents under stress from which they can not escape, becomes immobile after an initial period of struggling. This immobility signifies behavioral despair, resembling the state of mental depression (Porsolt et al., 1977b) and it is believed that when animals are exposed to such type of conditions it leads to the depletion of biogenic amines such as norepinephrine and serotonin, which are considered as one of the causes of depression.

In the present study reference drugs reduced the duration of immobility time of rodents in both stress models in contrast to control animals and these findings are similar with the earlier findings with various classes of antidepressants like tricyclic antidepressants, monoamine oxidase inhibitors and atypical antidepressants (Porsolt et al., 1978). The reference antidepressants that we have used in our study increased the availability of these biogenic amines at the synapse either by inhibiting their neuronal uptake or metabolism (Elhwuegi, 2004).
In the forced swimming test, moclobemide (IC<sub>40</sub>=5.07±0.85 mg/kg) caused 87.7% reduction in immobility time of rats at the dose of 16 mg/kg as compared to control animals and these results are similar with the studies reported by Dar and Khatoon 2000. In our investigations moclobemide was found to be 1.5 times more potent than phenelzine (IC<sub>40</sub> = 7.87±2.51 mg/kg). The higher efficacy of moclobemide as compared to phenelzine or fluoxetine is may be due to its established selective effect on noradrenergic neurotransmission. Fluoxetine caused 36.67% reduction in immobility time which is consistent with the previous findings reported by Luo et al. 2000. On the basis of their IC<sub>30</sub> values, fluoxetine (IC<sub>30</sub> = 0.30±0.1) was 14 times more potent than moclobemide (IC<sub>30</sub> = 4.20 ± 0.86) and 22 times more potent than phenelzine (IC<sub>30</sub>=6.63±2.88). The observations of the FST were largely consistent with the observations of the TST. However, one important pharmacological difference between the behavioral parameters was that the FST appeared to be more sensitive model than TST in our investigations. Apparently, there is a significant correlation between clinical potency and potency of antidepressants in animal models (Wang et al., 2008). However, the specificity of these behavioral tests, widely used for the assessment of antidepressants has been questioned as some unrelated drugs also reduce the duration of immobility time in rodents, such as stimulants, anti-cholinergics, antihistamines and opiates (Butterweck et al., 2003). It is important to note that the responses

<table>
<thead>
<tr>
<th>Reference Drug</th>
<th>Dose (mg/kg)</th>
<th>Duration of immobility Mean ± SEM (sec.)</th>
<th>% Change</th>
<th>Inhibitory concentration (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>0.1</td>
<td>106.00 ± 6.42</td>
<td>11.88 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>92.00 ± 5.29</td>
<td>23.52 *↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>97.00 ± 9.86</td>
<td>19.37 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>151.00 ± 16.04</td>
<td>25.50 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>150.33 ± 6.74</td>
<td>24.95 ↑</td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>4</td>
<td>138.00 ± 10.69</td>
<td>14.70 ↑</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;=14.33 ± 0.93</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>123.33 ± 9.02</td>
<td>2.51 ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>113.33 ± 6.88</td>
<td>5.79 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>94.66 ± 7.21</td>
<td>21.31 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>75.00 ± 4.50</td>
<td>37.6 ↓***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>93.66 ± 8.57</td>
<td>22.14 ↓*</td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>4</td>
<td>123.00 ± 7.23</td>
<td>2.23 ↑</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;=10.17 ± 0.57</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>105.00 ± 4.58</td>
<td>12.71 ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>84.33 ± 3.84</td>
<td>29.9 ↓**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>62.00 ± 6.42</td>
<td>48.6 ↓***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>36.66 ± 2.90</td>
<td>69.52 ↓***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>67.00 ± 5.50</td>
<td>44.30 ↓***</td>
<td></td>
</tr>
</tbody>
</table>

No. of animals per dose = 3
Immobility time of control animals= 120.31 ± 3.73 (n = 51)
IC<sub>30</sub> and IC<sub>50</sub> = The dose that produced 30% and 50% reduction in the immobility time.
↓/↑= decrease / increase in immobility time.
Asterisks indicate significant percent reduction (P<0.05*, P<0.01 ** and P<0.001 ***) in the immobility time as compared to control.
to antidepressant drugs are continued after chronic treatment, whereas the antihistamine drugs induced effects disappeared on chronic administration (Butterweck et al., 2003). The effects of psycho stimulants are usually excluded by additional open field test that would markedly increase the locomotor activity and the antidepressants have no effect on this behavior.

ACKNOWLEDGEMENT

All experiments were carried out with the support of H.E.J. Research Institute of Chemistry, International Center for Chemical Sciences (ICCS), University of Karachi, Pakistan.

REFERENCES


