Anti-Convulsive Effect of Beta Blockers: Antagonism of Strychnine Toxicity

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Anti convulsive property possessed by Beta Adrenergic Blocking agent against drug induced convulsions was studied, in the Department of Experimental Pharmacology. White mice were used as experimental animals. Strychnine Hydrochloride was injected intra peritoneally in preliminary experiments and the strychnine LD100 was determined. One group (n = 6) served as control, whereas four other groups (n = 6) were pre-treated with Propanolol, Timolol, Atenolol and LABELATOL, in a dose of 40 mg/kg subcutaneously, 30 minutes before strychnine injection. The protective effect of Propanolol was marked. Timolol and Atenolol did not exhibit anti-convulsive activity. LABELATOL, had a worsening effect on the convulsive state; which could be due to its additional a1-receptor blocking activity.

Key words: Beta adrenergic, blocking agents, drug induced convulsions, central nervous system, anti-convulsants.

There have been reports about the sedative and anticonvulsant properties of propranolol. In the present study, the antagonism produced by four Beta Adrenergic Blocking agents to the convulsive and lethal action of strychnine has been investigated.

Material and Methods

The experimental work was done in the Laboratory of Experimental Pharmacology, Allama Iqbal Medical College. White mice were supplied by the animal house of the Pakistan Council of Scientific & Industrial Research. Beta Adrenergic Blocking Agents were used in the pure powder form. These products were supplied by their respective manufacturing companies.

- Propranolol (Inderal)- ICI- UK
- Atenolol (Tenormin)- ICI- UK
- Timolol (Blocadren)- MSD- USA
- LABELATOL (Trandate)- Glaxo, Pakistan.

In preliminary experiments, white mice weighing between 20-30 grams, were injected with different doses of strychnine hydrochloride intraperitoneally, until the LD100 of strychnine was determined. It was found to be 2.1 mg/kg body weight. A group of six white mice was taken, each mouse was given 2.1 mg/kg strychnine intraperitoneally. This group served as the control group. The time taken for the onset of convulsions, appearance of opisthotonus and the total duration of survival after the injection was recorded. (Table-1)

<table>
<thead>
<tr>
<th>Time of onset of convulsions (in minutes)</th>
<th>Appearance of Opisthotonus</th>
<th>Death</th>
<th>Survival time in minutes after strychnine injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-12</td>
<td>-</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>2-30</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>2-00</td>
<td>-</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>3-05</td>
<td>-</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>2-50</td>
<td>-</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>2-45</td>
<td>-</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>2-3</td>
<td>3/6</td>
<td>6/6</td>
<td>Mean 6 ± 2.89</td>
</tr>
</tbody>
</table>

Four other groups of six mice each, were taken. They served as Test groups. They were injected subcutaneously with Propranolol, Timolol, Atenolol and LABELATOL respectively, in doses of 40 mg/kg, 30 minutes before the injection of strychnine LD100. The onset of convulsions, duration and nature of convulsions, appearance of opisthotonus and the total survival time after the injection of strychnine was recorded for each member of each group.

Table 2. Effects of pre-treatment with Propranolol on Strychnine LD100, (n = 6)

<table>
<thead>
<tr>
<th>Time of onset of convulsions (in minutes)</th>
<th>Appearance of Opisthotonus</th>
<th>Death</th>
<th>Survival time in minutes after strychnine injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-10</td>
<td>-</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td>4-17</td>
<td>-</td>
<td>+</td>
<td>13</td>
</tr>
<tr>
<td>5-00</td>
<td>-</td>
<td>+</td>
<td>19</td>
</tr>
<tr>
<td>3-35</td>
<td>-</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>4-30</td>
<td>-</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td>3-55</td>
<td>-</td>
<td>+</td>
<td>14</td>
</tr>
</tbody>
</table>

Value of "t" for prolonged survival time = 3.51, P < 0.01. Protection against death = 1/6, 16.66%

Table 3. Effects of pre-treatment with Timolol on Strychnine LD100, (n = 6)

<table>
<thead>
<tr>
<th>Time of onset of convulsions (in minutes)</th>
<th>Appearance of Opisthotonus</th>
<th>Death</th>
<th>Survival time in minutes after strychnine injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-30</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>2-00</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>2-50</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>3-00</td>
<td>+</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>3-05</td>
<td>+</td>
<td>+</td>
<td>9</td>
</tr>
<tr>
<td>2-30</td>
<td>+</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>2-3</td>
<td>5/6</td>
<td>6/6</td>
<td>Mean 7.5 ± 1.12</td>
</tr>
</tbody>
</table>

Value of "t" for prolonged survival time = 1.06, P = 0.05. Protection against death = Nil

Any delay in the onset of convulsions, change in the nature of convulsions (change in the incidence of appearance of opisthotonus) and prolongation of the
Anti Convulsant Effect of Beta Blockers

survival time was recorded. (Table-II, III, IV, V). Significance of the differences between the observations of the control group and the test groups was calculated statistically.

Table 4. Effect of pre-treatment with Atenolol Strychnine LD_{100}, (n = 6)

<table>
<thead>
<tr>
<th>Time of onset of convulsions (minutes)</th>
<th>Appearance of Opisthotonus</th>
<th>Death</th>
<th>Survival time in minutes after strychnine injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:00</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>3:50</td>
<td>+</td>
<td>+</td>
<td>9</td>
</tr>
<tr>
<td>3:27</td>
<td>+</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>4:00</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>3:55</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>3:15</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>2:3</td>
<td>6/6</td>
<td>6/6</td>
<td>Mean 5.6 ± 0.76</td>
</tr>
</tbody>
</table>

Value of "t" for prolonged survival time = 0.34, P = 0.50. Protection against death = Nil

Table 5. Effects of pre-treatment with Labelolol, Strychnine LD_{100}, (n = 6)

<table>
<thead>
<tr>
<th>Time of onset of convulsions (minutes)</th>
<th>Appearance of Opisthotonus</th>
<th>Death</th>
<th>Survival time in minutes after strychnine injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:50</td>
<td>+</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>3:00</td>
<td>+</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>3:15</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>4:30</td>
<td>+</td>
<td>+</td>
<td>4:30</td>
</tr>
<tr>
<td>4:20</td>
<td>+</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>4:10</td>
<td>+</td>
<td>-</td>
<td>5:30</td>
</tr>
<tr>
<td>2:3</td>
<td>6/6</td>
<td>6/6</td>
<td>Mean 4.83 ± 0.33</td>
</tr>
</tbody>
</table>

Value of "t" for prolonged survival time = 1.23, P = 0.05. Protection against death = Nil

Discussion

In our study the most striking observation was in the test group pre-treated with Propranolol, which gave protection against death due to strychnine in one out of six test animals.

The onset of convulsions was delayed in the same group. The incidence of opisthotonus was reduced from 3/6 to 0/6 and the total duration of survival between strychnine injection and death of the five animals was prolonged significantly (P < 0.01). Reduction in the incidence of opisthotonus also points towards a definite anti-convulsant effect possessed by Propranolol.

Pre-treatment with Timolol and Atenolol, does not appear to antagonize the convulsive effect of strychnine. Rather they increased the incidence of opisthotonus from 3/6 to 5/6 and 6/6 respectively. Besides the survival time was not prolonged.

Possession of definite anti-convulsant activity by Propranolol, and worsening of the convulsive state by Timolol and Atenolol, could be due to the marked membrane-stabilizing/local anaesthetic activity present in Propranolol. Whereas Timolol and Atenolol are reportedly devoid of membrane-stabilizing/local anaesthetic activity.

Observations of the test group IV, that was pre-treated with Labelolol, also show the worsening of the convulsive state caused by strychnine. The incidence of opisthotonus increased from 3/6 to 6/6; and the mean survival time was shortened rather than becoming prolonged.

As regards membrane stabilization/local anaesthetic activity, Labelolol is also known to possess this property. However, since Labelolol causes a selective a1-blockade, in addition to Beta receptor blockade, that property could have contributed to the reduced anti-convulsant effect of Labelolol as a Beta blocker.

Membrane stabilization as the basis of synergistic anti-convulsant activity of Propranolol and Local
anaesthetics has also been suggested against maximal electroshock (MES) seizure in mice.

Membrane stabilization activity as the basis of anti-convulsant effect has been reported in another study, where the threshold of Maximal Electroshock seizure in mice was raised with increasing doses of Propranolol.

The results of our study are in agreement with the reports of protective effect of Propranolol against drug induced convulsions.

Propranolol has also been reported to increase the threshold and decrease the duration of convulsions in MES induced seizures and on sub-chronic application of MES seizures. An over additive synergism of Propranolol and Phenobarbitone has been reported.

The role of the central monoaminergic systems on the anti-convulsiven action of Propranolol has been reported. Pharmacological stimulation of the Noradrenergic system (e.g. with desipramine, maprotiline, yohimbine) resulted in enhanced anti-convulsant effect of Propranolol.

Compounds that suppress the noradrenergic transmission (e.g. Reserpine, phenoxybenzamine, 6-hydroxy dopamine) reduced the activity of Propranolol against MES test in mice.

This report is in agreement with our results, where the additional c1-selective blockade of Labetalol (resembling phenoxybenzamine) has reduced the desired anti-convulsive property (a Beta receptor blocking effect).

In conclusion, out of the four agents studied, Propranolol has been found to be most effective. This effect has been confirmed by clinical studies as well.

References