The comparison effects of propranolol, caffeine and diazepam on lidocaine-induced convulsions in mice

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Abstract— The purpose of this study was to evaluate the study the comparison effect of propranolol, caffeine and diazepam on lidocaine-induced convulsions in mice. The study was done in 4 groups (5 mice in each group). Lidocaine was administrated at dose 30 mg/kg intraperitoneally (IP) in group 1. Diazepam was injected at dose 2 mg/kg-IP 15 min before lidocaine in group 2. Propranolol was injected at dose 5 mg/kg-IP 15 min before lidocaine in group 3. Caffeine was injected at dose 10 mg/kg-IP 15 min before lidocaine in group 4. The latency to first convulsion, the duration and the number of convulsions was observed for 30 min and were recorded in the mice and the mean of these factors was evaluated. In group 1 (which received only lidocaine), the mean of the latency to first convulsion, the duration and the number of convulsions were 4.6 ± 0.24 min, 21.6 ± 2.8 and 353.8 ± 0.65 S respectively. Convulsion was not seen with diazepam in group 2 (which received Lidocaine plus Diazepam). In groups 3 and 4 (which received Lidocaine plus Propranolol and Caffeine) the number and duration of the convulsions were decreased and Convulsion latency of lidocaine was increased at mice. Thus, the results of this study shows the propranolol and caffeine can reduced lidocaine-induced convulsions.

Keywords— Convulsion, Lidocaine, Diazepam, Caffeine, Propranolol, Mice

I. INTRODUCTION

The neuropharmacologic signs of toxicity from local anesthetics are excitation of the central nervous system (CNS) and generalized tonic-clonic convulsions. Several neuromediators and mechanisms may be involved in lidocaine-induced convulsions.

Stimulation of the CNS by local anesthetics is characterized by the activation of limbic discharges which is most striking in the amygdaloid nuclear complex [1-4] and the increase in metabolic activity which is notable in the hippocampus [5].

It is generally agreed that local anesthetics may induce convulsions by depressing inhibitory neurons, thereby allowing facilitation of excitatory neuronal activity [6-8]. Propranolol, a β-adrenoceptor antagonist, has anticonvulsant effects similar to phenytoin in addition to sympatolytic and cardiac effects [9]. Several studies were evaluated anticonvulsant effect of propranolol in animal models of electrically or chemically induced convulsions [9-11].

Research has shown that caffeine, a major constituent of coffee, induces a broad spectrum of cellular and pharmacological responses, such as the central nervous system and motor activity stimulation [12], cognitive performance improvement [13], anxiety and sleep disturbance [14, 15], antioxidant activity [16, 17], among others. Benzodiazepines are an important class of drugs in the treatment of epileptic seizures. With potent anticonvulsant properties, diazepam and lorazepam are among the drugs of choice in terminating grandma epileptic seizures. With potent anticonvulsant properties, diazepam and lorazepam are among the drugs of choice in terminating grandma epileptic seizures and status epilepticus [18, 19]. Although diazepam is agonist for GABAA receptor [20, 21], the entire mechanism of the its anticonvulsant effect is still not well-discovered. The aim of this study was to investigate the comparison effect of propranolol, caffeine and diazepam on lidocaine-induced convulsions.
II. MATERIALS AND METHODS

All experimental protocols were approved by the faculty of veterinary medicine, Shahid Chamran University of Ahvaz and use committee.

Animals

Male healthy mice of NMRI strain, 6–8 weeks of age, weighing 28–30 g were purchased (animal center of university of Jondishpour, Ahvaz, Iran) and housed individually for a 2-week acclimation period. Mice were fed ad libitum with standard laboratory pellets (Pars khurakdam, Shushtar, Iran.) and tap water. A 12 h light: 12 h dark was mentioned. Room temperature was at 23 ± 2 °C with a relative humidity of 45–55%.

Methods

Lidocaine (Darupakhsh, Iran), propranolol (Abidi Co., Iran), diazepam (Darupakhsh, Iran) and caffeine (Merk-Germany) were purchased. The anticonvulsant testing methods of Porter et al. [22] and Perazzo et al. [23] were used to assess the anticonvulsants of propranolol, caffeine and diazepam. The mice were divided at random into 4 groups of 5 mice each. Lidocaine was administrated at dose 30 mg/kg intraperitoneally (IP) in group 1. Diazepam was injected at dose 2 mg/kg-IP 15 min before lidocaine in group 2. Propranolol was injected at dose 5 mg/kg-IP 15 min before lidocaine in group 3. Caffeine was injected at dose 10 mg/kg-IP 15 min before lidocaine in group 4. Animals which did not convulse after 30 min were considered as protected. The latency to first convulsion, the duration and the number of convulsions were recorded in the unprotected animals and the mean of these factors was evaluated.

Statistical analysis

Statistical significance between groups was determined using SPSS program and compared by one way analysis of variance (ANOVA). Binomial data were examined using the LSD test. The minimum level of significance was p < 0.05.

III. RESULTS

No death was recorded amongst this study in groups 2, 3 and 4; but 3 mice were death in group 1. The effect of propranolol (5 mg/kg), caffeine (10 mg/kg) and diazepam (2 mg/kg) on the incidence of lidocaine-induced convulsions are shown in Table I.

In group 1 (which received only lidocaine), the mean of the latency to first convulsion, the duration and the number of convulsions were 4.6 min, 21.6 and 353.8 S respectively. Convulsion was not seen with diazepam in group 2 (which received Lidocaine plus diazepam).

In groups 3 and 4 (which received Lidocaine plus Propranolol and Caffeine) the number and duration of convulsions were decreased and Convulsion latency was increased at mice. All mice in groups which received only lidocaine, lidocaine plus propranolol and caffeine have been seen convulsion, but in group which received lidocaine plus diazepam; convulsion was not seen. The Convulsion latency in groups 1 was 4.6 ± 0.24 min; but in group 2 (which received lidocaine plus diazepam) convulsion was not seen and in group 3 (which received lidocaine plus propranolol) was 9.2 ± 0.73 min and group 4 (which received lidocaine plus caffeine) was 11 ± 1.14 min. The mean number of convulsion in group 1 (21.6 ± 2.8) was significantly higher in comparison with groups 3 (8.6 ± 0.58) and 4 (5 ± 0.89) (P < 0.05) and was significantly in compared with groups 2 (0) (P < 0.001). The mean Duration of convulsions in group 1 (353.8 ± 0.65) was significantly in compared with groups 2 (0), 3 (32.8 ± 0.13) and 4 (31.6 ± 0.63) (P < 0.001).

IV. DISCUSSION

The results of this study show propanolol, caffeine and diazepam affect on lidocaine-induced convulsions in mice. It has been known that local anesthetics produce convulsions by selective depression of inhibitory neurons, thus allowing enhancement of the effect of excitatory neurons, and also blockade of voltage-gated chloride channels [24]. Nakao et al [25] showed a marked expression of c-fos in the amygdala following lidocaine-induced convulsions in rats. Blockage of N- methyl-D-aspartate receptors by ketamine can reduce lidocaine-induced convulsions in mice [27]. This mechanism may be paradox to effect of lidocaine as sodium channel blocker. Some clinical studies have also shown the propranolol increases the threshold for lidocaine-induced convulsions, for example Nakamura et al [26] demonstrated that cerebroventricle propranolol could increased the threshold for lidocaine-induced convulsions by directly acting on the brain, but in this study we demonstrate that propranolol can reduced lidocaine-induced convulsions. Moreover, there is no study on the effect of caffeine on prevention of lidocaine-induced convulsion yet, however in present study our result indicated that caffeine could reduce convulsion even more than propranolol, but difference between these two drugs is not significant.
The mechanism of this effect is not clear and the present study is first of its kind in evaluation of effects of propranolol and caffeine on lidocaine-induced convulsions in mice.

In the conclusion the results of present study shows the propranolol and caffeine can reduce lidocaine-induced convulsions.

Table I. The effects of propranolol (5 mg/kg), caffeine (10 mg/kg) and diazepam (2mg/kg) on the incidence of lidocaine-induced convulsions in mice.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Seizure latency (mean ± SD) (min)</th>
<th>Seizure Number (mean±SD)</th>
<th>Seizure duration (mean±SD) (S)</th>
<th>Numbers animals with Seizure</th>
<th>% of animals with Seizure</th>
<th>% Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>4.6 ± 0.24</td>
<td>21.6 ± 2.8abc</td>
<td>353.8 ± 0.65b</td>
<td>5</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine+Diazepam</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Lidocaine+Propranolol</td>
<td>9.2 ± 0.73</td>
<td>8.6 ± 0.58</td>
<td>32.8 ± 0.13</td>
<td>5</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine+Caffeine</td>
<td>11 ± 1.14</td>
<td>5 ± 0.89</td>
<td>31.6 ± 0.63</td>
<td>5</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

\( ^a \) Significant difference when compared with other groups (P<0.05).

\( ^b \) Significant difference when compared with other groups (P<0.001).

\( ^c \) Significant difference when compared with Lidocaine+Diazepam group (P<0.001).

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REFERENCE


