Effect of propofol in altering pentylenetetrazol induced seizure threshold in rats

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Received 10 August 2007; revised 4 January 2008

The present study was undertaken to evaluate the role of propofol in altering pentylenetetrazol induced seizure threshold in rats. Total 42 Wistar rats were used to evaluate different parameters (onset of action, duration of seizure, seizure severity score and number of seizure) following propofol injection. The present results showed that there was significant reduction in the time required for onset of seizure in propofol treated groups following PTZ treatment. If treated with propofol alone (2 and 5mg/kg), there was no significant difference as compared to controls. In seizure severity score assessment, there was no significant difference with various doses of propofol alone treated groups, but the difference was observed in propofol (2 and 5 mg/kg) treated groups following PTZ treatment. Duration of seizure also significantly increased in propofol (5mg/kg) treated group, but at 2mg/kg of propofol treatment, no significant difference was observed. The present results showed that propofol ameliorate seizure threshold and caused prolongation of duration of seizure. However, further study and trials are needed to confirm the present results.

Keywords: Pentylenetetrazol, Propofol, Seizure severity

Propofol is a short-acting intravenous anesthetic agent used for induction of general anesthesia in adult and pediatric patients older than 3 years of age, maintenance of general anesthesia in adult and pediatric patients older than 2 months of age. Propofol has been approved for induction and maintenance of anesthesia in more than 50 countries. Its mechanism of action is uncertain, but it is postulated that effect may be potentiation of gamma amino benzoic acid (GABA-A) receptor. Recent research has also suggested the endocannabinoid system may contribute significantly to propofol's anesthetic action and to its unique properties. Experimental study in mice showed propofol has anticonvulsant action on electroshock to induce seizures similarly thiopeptone showed markedly anticonvulsant activity. This study showed effect of these drugs on both electroshock and pentylenetetrazole induced seizures. On the other hand there was three times more excitation in frequency of seizure after patients receiving propofol observed than patients receiving thiopeptone.

Besides this, several recent case reports showed opisthotonos like phenomenon occurred at the recovery time by propofol anesthetics, whereas several studies supported propofol as an anticonvulsant. So there is a confusion for clinicians whether it is an anti-convulsant or pro-convulsant. Hence, the aim of the study was to evaluate the effect of propofol in altering seizure threshold in pentylenetetrazol (PTZ) administration in rats.

Materials and Methods

Adult Wistar rats of either sex (weighing 150-200 g) were obtained from the central animal house of the Institute. The animals were housed in the groups of four per cage at 25±2°C, RH of 60±2% and 12 h light/dark cycle. Animals were provided standard laboratory chow diet (Hindustan Lever Chow) and water ad libitum. The animals were acclimatized to the laboratory condition two weeks prior to experimentation. The study was conducted after approval from the institute animal ethics committee (IAEC). Animal ethical guideline and good laboratory practice guideline were followed. In addition, all the precautions were taken to minimized pain and discomfort to the animals.

Chemicals used—Pentylenetetrazole (PTZ) was purchased from Sigma- Aldrich Ltd, MO, USA and diethyl ether of analytical grade were collected from...
Acros Organics, Ranbaxy Fine Chemicals Limited, New Delhi, India and propofol was collected from hospital store.

**Experimental design and treatment**—Parallel design was followed in the study. Total 42 rats were included in the study. Animals were divided into seven groups having six animals in each group (n=6). Animals of different groups were subjected to treatment as—Group I, [vehicle treated group, instead of PTZ, normal saline was used to assess the seizure]; Group II, [PTZ 60 mg/kg body wt. group, to observe seizure severity with PTZ]; Group III, [PTZ 40 mg/kg body wt. group, seizure severity was with sub-maximal dose of PTZ]; Group IV, [Propofol low dose group (2 mg/kg), to observe seizure onset and severity in this group]; Group V, [Propofol high dose group (5 mg/kg), same as above only dose was increased]; Group VI, [Propofol low dose (2 mg/kg) +PTZ 40 mg/kg body wt. group, rats were treated with the propofol and after 24 h following propofol administration seizure susceptibility was carried out, PTZ to check the seizure onset], and Group VII, [Propofol high dose (5 mg/kg) +PTZ 40 mg/kg body wt; same as the above combination group].

In a preliminary study, PTZ dose was standardized in our laboratory and it was found that PTZ at 60 mg/kg, body wt showed highest seizure score. PTZ (40 mg/kg, ip) produced sub-maximal effect on seizure severity. After 24 h of propofol treatment, rats were treated with PTZ and onset of seizure, duration of seizure, number of seizure in 90 min and total seizure severity score were observed. Mortality was also assessed in the treated group. At higher dose of propofol treatment (5 mg/kg), three rats of the group were died probably due to respiratory depression, but the group was replaced by other 3 rats. Two rats died in PTZ (60 mg/kg, ip) group, while observing seizure severity score.

**Assessment of seizure**—Seizure severity was assessed by giving PTZ (60 and 40 mg/kg, ip) after 24 h of propofol (2 and 5 mg/kg) treatment. Seizures were recorded at seven-point score at—0 – no response, 1 – ear and facial twitching, 2 –1 to 20 myoclonic body jerks in 10 min, 3 – more than 20 body jerks in 10 min, 4 – clonic forelimb convulsions, 5 – generalized clonic convulsions with rearing and falling down episodes and 6 – generalized convulsions with tonic extension episodes.

**Statistical analysis**—Data were expressed as mean ± SD. Data were analyzed by one-way analysis of variance followed by appropriate post hoc test (Bonferroni’s test and Dennett’s T3) for parametric value. P value at <0.05 was considered as statistically significant. Control group was excluded in the statistical analysis due to lack of any seizure observed in rats.

**Results**

**Effect of propofol on onset of seizure**—Onset of seizure was about 94 sec in Group II, but it significantly increased to 104 sec in Group III. In Group VI, it was significantly decreased to 62% as compared to Group III. Additionally, in Group VI and VII, there was significant decrease in the onset of seizure by 52 and 56%, respectively. (Fig. 1). But Group IV did not show significant change in respect to Group II and III. (Table 1)

**Effect of propofol on duration of seizure**—Animals were observed for 90 min in all treated groups. In Group VI and VII, there were significant increase in the seizure duration as compared to Group IV and V (12 fold and 28 fold, respectively) and as compared to Group II and III, it increased by 3 fold and about 8 fold, respectively (Fig. 2, Table 1)

**Propofol effect on seizure severity score following administration of PTZ (40 mg/kg, ip)**—The seizure severity score was about 50% higher in Group II as compared to Group III. The severity score was found to be lowest in Group IV and V. But, there was significant increase in the seizure severity score upto mean 3.5 in both Group VI and VII. (Fig. 3, Table 1)

**Effect of propofol on number of seizure following administration with sub-maximal dose of PTZ**—Group IV and V had low number of seizure onset which was observed significantly higher in Group III. On the
other hand, Group VI and VII had significantly increase number of seizure than all other treated group in 90 min, which was found statistical significant. (Fig. 4, Table 1)

**Discussion**

Propofol is most commonly used intravenous anesthetics at present but has probable excitatory effect\(^1\). It has been reported earlier that patients anesthetised with propofol show opisthotonos like movement and epileptic jerks while recovering from anesthesia. Hypothesis states that sedative effect of propofol is mainly by modulation of GABA-chloride channels, though exact mechanism of action of propofol is yet to be elucidated\(^10\). Its excitatory mechanism is not clear. It has been shown that propofol antagonises glycine in mice which is known for its inhibitory activity\(^5,12\).

Several conflicting studies\(^6,13\) state that patients with complex partial seizure treated with propofol has no significant effect at any of electrode site at different doses, whereas Smith \textit{et al},\(^13\) have reported that propofol activated electrocardiogram in anesthetised patients (17-20) during surgery for intractable epilepsy. But study conducted by Kanai \textit{et al},\(^14\) have observed propofol as an anticonvulsant in refractory general convulsant, which has been supported by Steffen \textit{et al}\(^15\). Besides this, in several other experimental studies on dogs and cats, it has been found that propofol is effective in controlling status epilepticus resistant to conventional medication. In addition, Bailine \textit{et al},\(^16\) have suggested its effectiveness in electroconvulsive therapy. There are other studies, presenting with conflicting results on propofol and seizure susceptibility\(^17-22\).

### Table 1—Comparison of different seizure parameters in experimentally induced seizure following PTZ administration in propofol alone and in combination with propofol

[Value are in mean ± SD of 6 rats in each group]

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Onset of seizure (Sec)</th>
<th>Duration of seizure (Sec)</th>
<th>No. of seizure in 90 min</th>
<th>Score observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>94.5000 ±6.7454</td>
<td>102.0000 ± 15.4272</td>
<td>1.5000 ± .5477</td>
<td>5.3333 ± .5164</td>
</tr>
<tr>
<td>III</td>
<td>109.1667 ± 17.7247</td>
<td>114.3333 ± 22.0242</td>
<td>1.0000 ± .0000</td>
<td>2.5000 ± .5477</td>
</tr>
<tr>
<td>IV</td>
<td>104.1667 ± 163.1078</td>
<td>25.8333 ± 40.3010</td>
<td>.3333 ± .5164</td>
<td>.6667 ± 1.0328</td>
</tr>
<tr>
<td>V</td>
<td>65.0000 ± 101.1435*</td>
<td>27.5000 ± 42.6321</td>
<td>.3333 ± .5164</td>
<td>.8333 ± 1.3292</td>
</tr>
<tr>
<td>VI</td>
<td>68.0000 ± 30.1927**,</td>
<td>397.5000 ± 329.146*,**</td>
<td>1.0000 ± .0000*</td>
<td>3.1667 ± 1.7224**,**</td>
</tr>
<tr>
<td>VII</td>
<td>62.6667 ± 14.3062**,</td>
<td>783.3333± 429.402*,**</td>
<td>1.0000 ± .0000*</td>
<td>3.3333 ± 1.3663*,**</td>
</tr>
</tbody>
</table>

Significant at \(*P< 0.001\) compared to Group VI, VII with Group II, III. Significant at \(*P< 0.05\) compared to Group VI, VII with Group IV, V.

Group-II - PTZ 60 mg/kg; Group-III - PTZ 40 mg/kg; Group-IV - Propofol 2 mg/kg; Group-V - Propofol 5 mg/kg; Group-VI - Propofol 2 mg/kg + PTZ 40 mg/kg; Group-VII - Propofol 5 mg/kg + PTZ 40 mg/kg (Group-I - control group-not include in the statistical analysis due to absence of seizure)
Seizure like phenomenon (SLP) has been classified according to the time course of their occurrence during anesthesia i.e. induction, maintenance, emergence or delayed. SLP happened during anesthesia i.e. induction, maintenance, according to the time course of their occurrence. Seizure like phenomenon (SLP) has been classified was also increased. The duration of seizure was also significantly increased in the two combination groups and the severity score highly significant in reducing the onset of seizure.

Drug dose calculation was based on extrapolation of human recommended doses use in surgical practice to rats (by using conversion factor). Present study is the first study to observe the effect of propofol on seizure susceptibility following administration of propofol in rats.

Hence, it is concluded that the propofol has the epileptogenic potency, shown higher severity score, duration of seizure, number of seizure and significantly decrease in onset time for seizure. However, this finding of propofol needs further confirmation in prospective clinical study.

References

18. Orser B A, Wang L Y, Pennefather P S & MacDonald J F, Propofol modulates activation and desensitization of


