Can propofol cause seizures? *An experimental study*

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The association of seizures with anesthetic agents has been a long debate and controversy for decades. There are several anesthetic agents that show seizure like activity after induction such as fentanyl, lignocaine, propofol, sevoflurane, and so forth. Among these agents, there are several reports of propofol, which is very frequently used as an anesthetic induction agent in India, and further approved for the induction and maintenance of anesthesia in more than 50 countries.[1-3] There are several case reports indicating the status epileptogenic properties of various anesthetic agents during the induction and maintenance phase of anesthesia. Hence, the objective of the study was to evaluate the effect of propofol and associated seizure activity.

The study was performed between April and May 2008 at the Department of Pharmacology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India. Institute Animals Ethics Committee (IAEC) permission was taken prior to the study, and the experimental protocol was designed and animal supervision was carried out according to the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) guidelines. A total of 36 male adult Wistar rats weighing 200-250 gm were housed in standard laboratory conditions at 25±2˚C, humidity of 60±2%, and 12 hours light/dark cycle. Animals were divided into 6 parallel designed groups containing 6 animals in each group. Groups were: 1) Pentylenetetrazole (PTZ) 60 mg/kg body weight intraperitoneal (i.p.) group, to observe seizure severity with a convulsive dose of PTZ. 2) PTZ 40 mg/kg i.p. group:seizure severity was assessed with a sub-maximal dose of PTZ. 3) Propofol low dose group (2 mg/kg i.p.): in this group the rats were treated with propofol and observed for seizure onset and severity. 4) Propofol high dose group (5 mg/kg i.p.), similar to the 2mg/kg i.p. group, only the dose was increased. 5) Combination of propofol low dose (2 mg/kg i.p.) + PTZ 40 mg/kg i.p. group: rats were treated with propofol and PTZ to check the seizure onset. Twenty-four hours following propofol administration, seizure susceptibility was carried out. 6) Combination of propofol high dose (5 mg/kg i.p.) + PTZ 40 mg/kg i.p., similar to the previous combination group. Thereafter seizure susceptibility was assessed by administration of PTZ at the dose of 60 mg/kg i.p. and 40 mg/kg i.p. after 24 hours of propofol treatment. Seizures were recorded on a 7 point seizure score according to the following scale: 0 - no response; 1 - ear and facial twitching; 2 - one to 20 myoclonic body jerks in 10 minutes; 3 - more than 20 body jerks in 10 minutes; 4 - clonic forelimb convulsions; 5 - generalized clonic convulsions with rearing and falling down episodes, and 6 - generalized convulsions with tonic extension episodes.[4] The induction of apoptosis was detected by the DNA fragmentation method. This method employs the agarose gel electrophoresis, which measures DNA fragmentation in nuclear extracts showing the typical "DNA-ladder" configuration. The rats were sacrificed by cervical dislocation under deep anesthesia. The brain was dissected out and immediately transfer to ice chilled normal saline. Thereafter, DNA fragmentation was carried out by phenol-chloroform extraction method and assessed by the agarose gel electrophoresis.

The data were entered into the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) version 12.0 and appropriate nonparametric Kruskal-Wallis test were applied. *P*-value of <0.05 was considered statistically significant.

The seizure severity was measured using a 0-6 score as per their severity following a subconvulsive dose of PTZ. The seizure severity score was found significantly increased in the (PTZ+Pro 5) group as compared with other treatment groups ($p<0.05$). However, propofol at 2 mg/kg + PTZ (PTZ+Pro 2) showed a marginal increase in seizure severity. The DNA fragmentation of these groups was carried out 24 hours after propofol treatment. The DNA fragmentation was observed in a concentration-dependent manner in propofol 2 mg/kg + PTZ 40 mg/kg (PTZ 40 + Pro 2) and propofol 5 mg/kg + PTZ 40 mg/kg (PTZ 40 + Pro 5) groups (**Figure 1**). Hence, the findings of present study suggested that a sub-convulsive dose of PTZ potentiates the DNA fragmentation of propofol.

A study by Tsuchiya et al,[5] showed that propofol induced apoptosis through cell surface death receptor activation and activation of the mitochondrial pathway with cytosolic release of cytochrome c. Hence, it was hypothesized that apoptosis by propofol is induced by the cell surface death receptor pathway and the mitochondrial pathway. However, the present study concluded no significant difference in DNA fragmentation in the lower dose (2 mg/kg) as well as with the higher dose of propofol (5 mg/kg) except in the combination group

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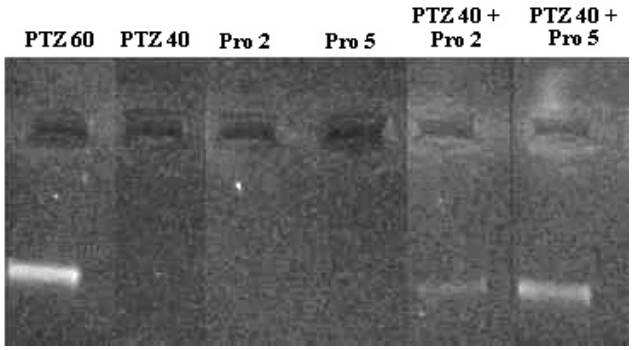

Figure 1 - The DNA fragmentation of the rat brain tissue in the 6 experimental groups. PTZ 60 - PTZ 60mg/kg b wt group, PTZ 40 - PTZ 40 mg/kg b. wt group, Pro2 - propofol low dose group (2 mg/kg), Pro5 - propofol high dose group (5 mg/kg), PTZ 40+ Pro 2 - propofol low dose (2 mg/kg) + PTZ 40 mg/kg b. wt, PTZ 40 + Pro 5 - propofol high dose (5 mg/kg) + PTZ 40 mg/kg b. wt, PTZ – pentylenetetrazole

with PTZ, where DNA fragmentation was evident. However, a study by Bengzon et al,[6] indicated that even a single seizure can lead to apoptotic neuronal cell death. The effectiveness of caspase inhibitors prior to and following experimentally induced status epilepticus, suggested a role for caspases in seizure-evoked neuronal degeneration. Hence, the present study concluded that propofol may have seizure like property, which is associated with the DNA fragmentation in long term use. Based on these results, future molecular studies can be conducted.

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References

1. Hickey KS, Martin DF, Chuidian FX. Propofol-induced seizure-like phenomena. ***J Emerg Med*** 2005; 29: 447-449.
2. San-juan D, Chiappa KH, Cole AJ. Propofol and the electroencephalogram. ***Clin Neurophysiol*** 2010; 121: 998-1006.
3. Yanaru T, Sugi Y, Higa K, Shono S, Katori K, Nitahiara K. [Propofol-induced generalized tonic-clonic seizure: a case report]. ***Masui*** 2010; 59: 1036-1038. Japanese
4. Prakash A, Medhi B, Puri A, Saikia B. Effect of propofol in altering pentylenetetrazol induced seizure threshold in rats. ***Indian J Exp Biol*** 2008; 46: 196-200.
5. Tsuchiya M, Asada A, Arita K, Utsumi T, Yoshida T, Sato EF, et al. Induction and mechanism of apoptotic cell death by propofol in HL-60 cells. ***Acta Anaesthesiol Scand*** 2002; 46: 1068-1074.
6. Bengzon J, Mohapel P, Ekdahl CT, Lindvall O. Neuronal apoptosis after brief and prolonged seizures. ***Prog Brain Res*** 2002; 135: 111-119.