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# COMPARING DIFFERENT DOSES OF PENTYLENETETRAZOLE INDUCED EXPERIMENTAL MODEL OF SEIZURE IN MICE

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**Keywords:**

Epilepsy, Pentylenetetrazole, GTCS, Myoclonic jerks, Inter-ictal phase, Latency, Mortality

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**ABSTRACT: Background:** Epilepsy, characterized by repetitive seizures, is studied using pentylenetetrazole (PTZ) in animals. PTZ, a GABA-A inhibitor, is used in various doses in mice to evaluate drug efficacy against seizures. **Method:** In a PTZ-induced mouse model, different PTZ doses were evaluated: 80 mg/kg i.p., 75 mg/kg i.p., and 80 mg/kg s.c. Seizure behaviors were analyzed, including mortality rates, GTCS frequency and latency, myoclonic jerks, GTCS duration, and post-injection interictal phase duration. **Results:** Frequency of GTCS was found to be highest, latency to GTCS and myoclonic jerks was least and duration of GTCS was more in PTZ 80 mg/kg, i.p., group, while the PTZ 80 mg/kg; s.c. was found to have longest inter-ictal phase. These are important criterion for the evaluation of any investigational drug for antiepileptic effect. The mortality rate was found to be the same in PTZ 75 mg/kg; i.p. and 80 mg/kg; s.c. (12.5%) groups, while in PTZ 80 mg/kg; i.p. it was found to be highest (25%). The PTZ 80 mg/kg, i.p., for comparison of seizure parameters was found to be the most appropriate dose. **Comparison with Existing Methods:** This research was conducted to gain a deeper comprehension of acute seizures induced by PTZ in mice. Three doses of PTZ were compared on the basis of different seizure scoring parameters and mortality to better understand and visualize seizure episodes at various dosages.

**INTRODUCTION:** Epilepsy, a neurological disorder, arises from abnormal electrical activity in specific brain regions, leading to recurrent, unprovoked seizures. It ranks among the most prevalent neurological conditions [1]. Seizures in epilepsy encompass a spectrum of symptoms including loss of consciousness [2], changes in neuronal signalling [3], autonomic motor episodes [4], or a combination of these manifestations [5].

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The recurrence and transient nature of seizures stem from irregular electrical discharges in localized brain tissue, driven by an imbalance between excitatory and inhibitory neurotransmitters, causing immediate over-synchronization of neural network activity [6, 7].

Ion channels play a pivotal role in epilepsy pathogenesis, notably the voltage-dependent calcium channel. Mutations in the gene encoding this channel prompt calcium influx, triggering synchronized neuronal discharge and subsequent seizures [8, 9]. Historically, the gamma amino butyric acid (GABA)-A receptor has been the major target of most anti-epileptic drugs. In general, the GABA-A receptor is recognised as the brain's primary

inhibitory neurotransmitter receptor. The activation of the GABA-A receptor allows for the influx of chloride ($Cl^-$), which inhibits neuronal activity [10]. Globally, epilepsy affects approximately 0.5 to 0.7% of the population, with an estimated 50 million documented cases worldwide [11], and about 2 million new cases reported annually [12]. Most people with epilepsy live in areas with limited resources, where as many as 98% do not have consistent access to antiepileptic drug (AED) treatment, underscoring epilepsy as a substantial public health issue [13]. Even with proper treatment, approximately 30% of individuals with epilepsy do not respond to medication[14, 15]. Given the similarities in physiological and behavioural responses between humans and non-human primates, employing a seizure model in non-human primates offers logical and clinically relevant insights [1]. Numerous studies have investigated the anticonvulsant efficacy and side effects of various medications using both rodent and primate models [16, 17]. Animal models of epilepsy, including pharmacologically induced seizures, have been instrumental in unravelling the pathophysiology of epilepsy and identifying potential antiepileptic drugs [18].

PTZ functions as an antagonist of the (GABA)-A receptor [19], impeding the operation of inhibitory synapses, thus causing heightened neuronal activity. This alteration engenders generalized seizures in animals [20, 21]. Models utilizing PTZ disrupt either inhibitory and excitatory neurotransmitter systems (GABA and glutamic, respectively), resulting in augmented excitability or diminished inhibition [14, 22]. It is commonly used as a systemic convulsant to induce epileptic behavior in experimental animals [23]. PTZ is known to cause myoclonic and tonic-clinic generalized seizures in mice by non-competitively inhibiting the GABA-A receptors, which polarize chloride current [24–26]. It has also been observed that acute intraperitoneal injection of PTZ causes an increase in glutamate levels in the brain in mice [27, 28]. PTZ is widely used in animal studies to uncover novel anticonvulsant medicines and to analyse the anticonvulsant effectiveness of various antiepileptic combinations [29]. In humans and rodents [30], the hippocampus is recognized to be the key brain area involved in epilepsy processes [31]. The objective of this research was to enhance our understanding of acute seizures triggered by PTZ in mice. The parameters for evaluation of seizure scoring included seizure behavior, mortality, frequency to GTCS, latency to GTCS and myoclonic jerks, duration of GTCS and period of inter-ictal phase.

## MATERIALS AND METHODS:

**Animals:** Swiss albino male mice weighing between 22 and 26 grams were obtained from the Animal House Facility at Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida. These mice were housed under controlled conditions with a temperature of 22±1°C, relative humidity ranging from 55% to 65%, and a 12-hour light-dark cycle. Following a 7-day period for acclimatization to the laboratory environment, the mice were randomly divided into experimental groups, each consisting of 8 mice. Throughout the study, the mice had unrestricted access to food and water. All experiments were conducted between 9:00 a.m. and 3:00 p.m. to minimize the influence of circadian rhythms on seizure susceptibility [32]. The experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC approval no. CPCSEA/IAEC/AIP/2022/12/19) and adhered to the guidelines set forth by the Committee for Control and Supervision of Experiments on Animals (CCSEA) in New Delhi, India.

**Drugs, Chemicals and Materials:** PTZ was obtained from Tokyo Chemical Industry (India) Pvt. Ltd., with a purity exceeding 98.0%. Solutions of PTZ at doses of 80 mg/kg (intraperitoneal), 75 mg/kg (intraperitoneal), and 80 mg/kg (subcutaneous) were prepared in 0.9% normal saline just before administration. The solutions were shielded from direct light and maintained on ice during the experimental procedures, which were conducted in observation cages made of transparent plexiglass [33].

**Experimental Design:** In this study, we examined the impact of PTZ at various doses by assessing seizure scores. To compare the effects of PTZ at different doses on seizures, mice were allocated into three groups. Group 1 received PTZ at a dose of 75 mg/kg intraperitoneally (n=8), Group 2 received PTZ at a dose of 80 mg/kg intraperitoneally (n=8), and Group 3 received PTZ at a dose of 80 mg/kg subcutaneously (n=8).

The mice were housed in Plexiglas chambers measuring 30 cm x 30 cm x 30 cm, and their convulsive behavior was monitored for a duration of 30 minutes. Parameters observed included seizure behavior, mortality rates, frequency of generalized tonic-clinic seizures (GCTS), latency to generalized tonic-clinic seizures (GTCS), occurrence of myoclonic jerks, duration of GTCS, and duration of the interictal phase.

**Seizure Scoring:** In the study, PTZ was administered to mice at doses of 75 mg/kg intraperitoneally, 80 mg/kg intraperitoneally, or 80 mg/kg subcutaneously in their respective groups to induce seizures. The mice were then observed for 30 minutes following the PTZ administration. Seizure activity was assessed using the Racine scale, described as follows [14]:

Stage 0: no response.

Stage 1: hyperactivity, vibrissae twitching, restlessness.

Stage 2: motionless staring/immobilization.

Stage 3: hindlimb tonic extension/straub's tail.

Stage 4: myoclonic jerks.

Stage 5: generalized tonic–clonic seizure (GTCS) with loss of writing reflex.

The observations were done based on the frequency to GCTS, latency to GTCS and myoclonic jerks, duration of GTCS and period of inter-ictal phase (Racine, 1972; Singh *et al.,* 2021;Fischer and Kittner, 1998).

**Statistical Analysis:** Statistical analysis was performed using Graph pad prism 8.4.2 version. The data was compared for statistical significance using unpaired t-test. Data represented as mean ± SEM (n = 8/ group) and *p* value of <0.05 was considered statistically significant.

Statistical analysis was conducted utilizing GraphPad Prism 8.4.2 software (GraphPad Software Inc., San Diego, CA, USA). The data were subjected to an unpaired t-test to determine statistical significance. Results are presented as mean ± SEM (n = 8 per group), with a *p* value of <0.05 was considered statistically significant.

## RESULT:

**Seizure Behavior:** The specific feature of seizure behavior in mice is subjected to administration of PTZ seems to show seizure of stage 5 (GTCS) and stage 4 (myoclonic jerks). The results demonstrated the change in seizure parameters after administering PTZ at different doses, therefore this study can be used for better understanding of PTZ-induced seizure model at difference, which can be applied in multiple studies.

### Comparison of Different Doses of PTZ on Different Seizure Parameters:

### Comparison of Different Doses of PTZ for Latency to Myoclonic Jerks:

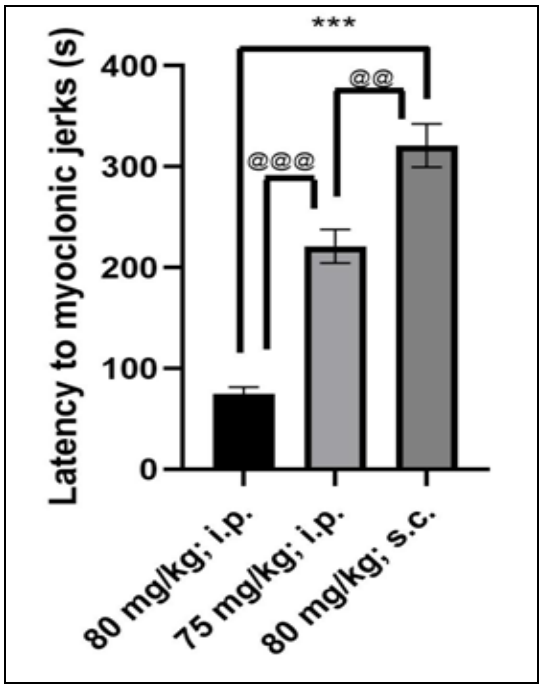


**FIG. 1: COMPARISON OF PTZ ADMINISTERED AT VARIOUS DOSES ON THE LATENCY TO MYOCLONIC JERKS IN AN ACUTE SEIZURE MODEL IN MICE.** Data are presented as mean±SEM (n=8). ***P<0.001 denotes a comparison between PTZ administered at 80 mg/kg intraperitoneally (i.p.) versus PTZ administered at 80 mg/kg subcutaneously (s.c.); @P<0.05 and @@P<0.01 indicate a comparison between PTZ administered at 80 mg/kg i.p. and s.c. Vs PTZ administered at 75 mg/kg i.p.

The different doses of PTZ were compared for latency to myoclonic jerks, 30 min post-PTZ injection. The latency to myoclonic jerks in PTZ 80 mg/kg, i.p. (74.50±6.87 s) group was found to be significantly more (P<0.0001, t=10.92; df=14) and (P < 0.0001, t=8.153; df=14) as compared to PTZ 80 mg/kg; s.c. (321.13±21.51 s) and PTZ 75 mg/kg, i.p. (221.13±16.62 s) group, respectively.

Similarly, the latency to myoclonic jerks in PTZ 75 mg/kg, i.p. group was significantly more (P<0.0025, t=3.679; df=14) as compared to PTZ 80 mg/kg, s.c. group **Fig. 1**. The latency to myoclonic jerks was observed in PTZ 80 mg/kg, i.p. in a shorter period of time as compared to other groups.

**Comparison of Different Doses of PTZ for Latency to GTCS:**

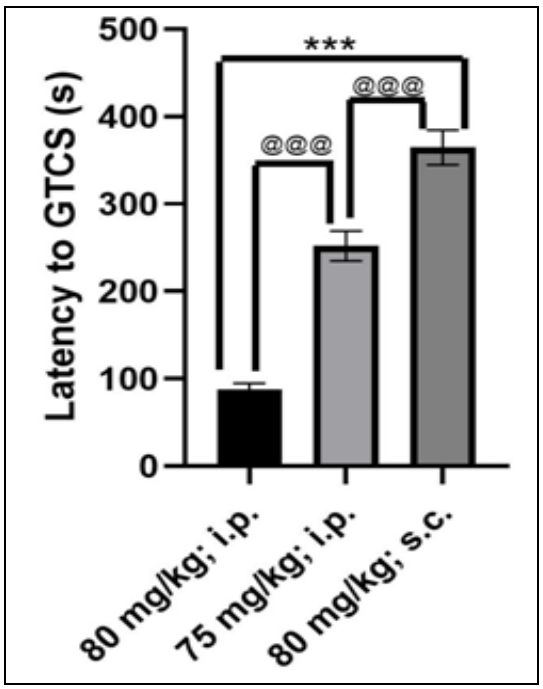


**FIG. 2: COMPARISON OF PTZ ADMINISTERED AT VARIOUS DOSES ON THE LATENCY TO GTCS IN AN ACUTE SEIZURE MODEL IN MICE.** Data are presented as mean±SEM (n=8). ***P<0.001 denotes a comparison between PTZ administered at 80 mg/kg intraperitoneally (i.p.) versus PTZ administered at 80 mg/kg subcutaneously (s.c.); @P<0.05 and @@P<0.01 indicate a comparison between PTZ administered at 80 mg/kg i.p. and s.c. Vs PTZ administered at 75 mg/kg i.p.

The different doses of PTZ were compared for latency to GTCS for 30 min post-PTZ injection.

The latency to GTCS in PTZ 80 mg/kg, i.p. (87.62 ± 7.29 s) group was found to be significantly decreased (P<0.0001, t=13.08; df=14) and (P < 0.0007, t=4.304; df=14) as compared to PTZ 80 mg/kg; s.c. (364.62 ± 19.90 s) and PTZ 75 mg/kg, i.p. (251.87±17.06 s) group, respectively.

Similarly, the latency to GTCS in PTZ 75 mg/kg, i.p. group was significantly decreased (P<0.0001, t=8.858; df=14) as compared to PTZ 80 mg/kg, s.c. group **Fig. 2.** Among three groups, occurrence of GTCS was observed early in PTZ 80 mg/kg, i.p. group as compared to other groups.

**Comparison of Different Doses of PTZ on Frequency of GTCS:**

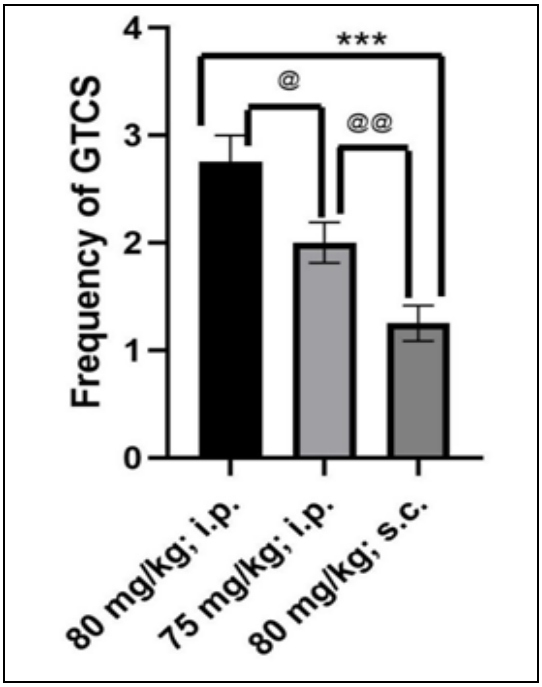


**FIG. 3: COMPARISON OF PTZ ADMINISTERED AT VARIOUS DOSES ON THE FREQUENCY OF GTCS IN AN ACUTE SEIZURE MODEL IN MICE.** Data are presented as mean±SEM (n=8). ***P<0.001 denotes a comparison between PTZ administered at 80 mg/kg intraperitoneally (i.p.) versus PTZ administered at 80 mg/kg subcutaneously (s.c.); @P<0.05 and @@P<0.01 indicate a comparison between PTZ administered at 80 mg/kg i.p. and s.c. Vs PTZ administered at 75 mg/kg i.p.

The different doses of PTZ were compared for frequency of GTCS for30 min post-PTZ injection.

The frequency of GTCS in PTZ 80 mg/kg, i.p. (2.75±0.25s) group was found to be significantly more (P<0.0002, t=5.054; df=14) and (P < 0.0316, t=2.388; df=14) as compared to PTZ 80 mg/kg; s.c. (1.25±0.16s) and PTZ 75 mg/kg, i.p. (2.00±0.19s) group, respectively.

Similarly, the frequency of GTCS in PTZ 75 mg/kg, i.p. group was significantly more (P<0.0092, t=3.019; df=14) as compared to PTZ 80 mg/kg,s.c. group (Fig. 3).Among three groups of PTZ the frequency of GTCS in PTZ 80 mg/kg, i.p. was found to be highest, followed by in PTZ 75 mg/kg, i.p. and then least in PTZ 80 mg/kg; s.c. group.

**Comparison of Different Doses of PTZ on Duration of GTCS:**

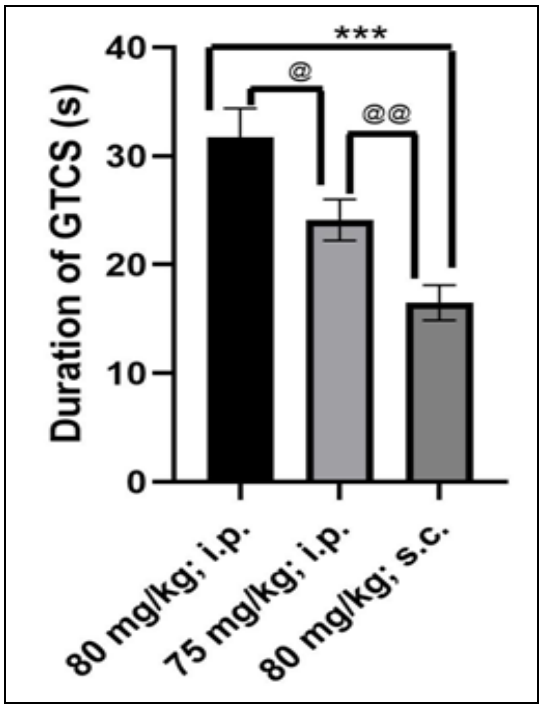


**FIG. 4: COMPARISON OF PTZ ADMINISTERED AT VARIOUS DOSES ON THE DURATION OF GTCS IN AN ACUTE SEIZURE MODEL IN MICE**. Data are presented as mean±SEM (n=8). ***P<0.001 denotes a comparison between PTZ administered at 80 mg/kg intraperitoneally (i.p.) versus PTZ administered at 80 mg/kg subcutaneously (s.c.); @P<0.05 and @@P<0.01 indicate a comparison between PTZ administered at 80 mg/kg i.p. and s.c. Vs PTZ administered at 75 mg/kg i.p.

The different doses of PTZ were compared for duration of GTCS for 30 min post-PTZ injection. The duration of GTCS in PTZ 80 mg/kg, i.p. (31.75±2.63 s) group was found to be significantly more (P<0.0002, t=4.945; df=14) and (P<0.0338, t=2.353; df=14) as compared to PTZ 80 mg/kg; s.c. (16.5 ± 1.61 s) and PTZ 75 mg/kg, i.p. (24.12±1.90 s) group, respectively. Similarly, the duration of GTCS in PTZ 75 mg/kg, i.p. group was significantly more (P<0.0083, t=3.073; df=14) as compared to PTZ 80 mg/kg, s.c. group (Fig. 4). Among three groups it was observed that duration of GTCS existed for longer period in PTZ 80 mg/kg, i.p. group as compared to other groups.

**Comparison of Different Doses of PTZ on Inter-ictal Phase:** The different doses of PTZ were compared for inter-ictal phase for 30 min post-PTZ injection. The inter-ictal phase in PTZ 80 mg/kg, i.p. (446 ± 18.40 s) group was found to be significantly decreased (P<0.0001, t=8.603; df=14) and (P < 0.0188, t=2.657; df=14) as compared to PTZ 80 mg/kg; s.c. (608 ± 8 s) and PTZ 75 mg/kg, i.p. (384.57 ± 8.49 s) group, respectively. Similarly, the inter-ictal phase in PTZ 75 mg/kg, i.p. group was significantly decreased (P<0.0001, t=7.922; df=14) as compared to PTZ 80 mg/kg, s.c. group **Fig. 5**. According to **Fig. 5,** PTZ 80 mg/kg; s.c. has the longest inter-ictal phase.

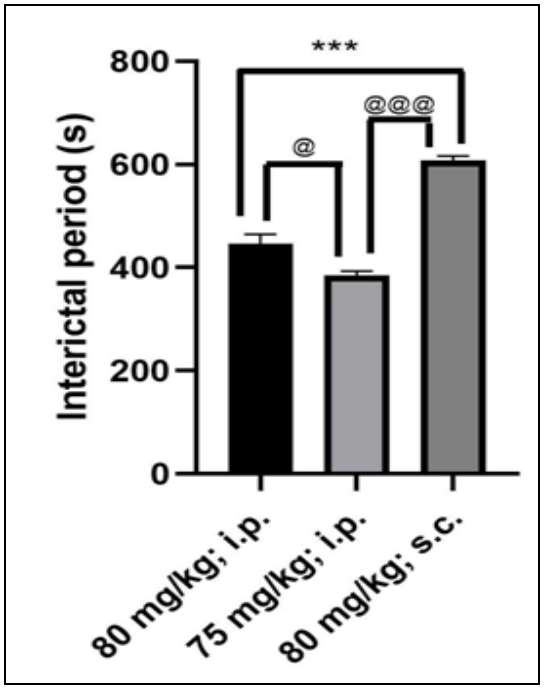


**FIG. 5: COMPARISON OF PTZ ADMINISTERED AT VARIOUS DOSES ON THE INTERVAL BETWEEN SEIZURES (INTER-ICTAL PHASE) IN AN ACUTE SEIZURE MODEL IN MICE**. Data are presented as mean±SEM (n=8). ***P<0.001 denotes a comparison between PTZ administered at 80 mg/kg intraperitoneally (i.p.) versus PTZ administered at 80 mg/kg subcutaneously (s.c.); @P<0.05 and @@P<0.01 indicate a comparison between PTZ administered at 80 mg/kg i.p. and s.c. Vs PTZ administered at 75 mg/kg i.p.

**Mortality:** Mortality was found to be highest in PTZ 80 mg/kg; i.p. (25%) group, while it was found to be similar 12.5% in PTZ 75 mg/kg; i.p. and PTZ 80 mg/kg; s.c. **Table 1.**

**TABLE 1: TABLE REPRESENTS PERCENTAGE MORTALITY POST PTZ INJECTION ADMINISTERED AT DIFFERENT DOSES IN MICE**

| Groups | No. of mice | % Mortality |
|---|---|---|
| PTZ (75 mg/kg, i.p) | 08 | 12.5 |
| PTZ (80 mg/kg, s.c) | 08 | 12.5 |
| PTZ (80 mg/kg, i.p) | 08 | 25 |

**DISCUSSION:** PTZ a GABA-A receptor antagonistis commonly used as a convulsant to induce seizures in experimental animals [23]. PTZ is

most widely used basic screening model for study of novel anticonvulsant and antiepileptic drugs [29]. The activity of neurons is increased by suppressing the inhibitory neurotransmitter GABA, leading to generalized seizures in animals (Tourov *et al.,* 1996 [37]. PTZ bind to the benzodiazepine site of the GABA-A receptor and inhibit the $Cl^-$ion influx, making neuron depolarised [37]. The elevated levels of glutamate within the intracellular space can pose a threat to neurons, as it leads to a condition known as excitotoxicity [38]. This occurs when glutamate receptors, specifically NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, become excessively stimulated [39]. One of the triggers for epileptogenesis involves the influx of Ca2+ through NMDA receptors, subsequently activating NADPH oxidase enzymes [40, 41].

This activation results in the formation of reactive oxygen species (ROS) and peroxynitrite, which can inflict damage upon DNA, proteins, and lipids, while also causing the oxidation of glutathione [42], ultimately harming neurons. Additionally, increased levels of ROS and superoxide production within the brain can directly inhibit the enzyme glutamine synthase, leading to generalized tonic-clonic seizures [43, 44].

The aim of this study was to contrast various doses of PTZ, aiming to enhance comprehension of seizure activity and thereby facilitate more accurate assessment. Seizure observations included latency to myoclonic jerks and GTCS, frequency of GTCS, duration of GTCS and inter-ictal phase and mortality. The typical features of GTCS are characterized by loss of balance and tonic-clonic jerking. Since most antiepileptic medications function by reducing either the frequency of GTCS, latency to GTCS and/or myoclonic jerks, decreasing duration of GTCS, inter-ictal phase and mortality, were considered as the main criteria for comparison [45]. In comparison to other groups, PTZ 80 mg/kg; i.p. demonstrated increased latency to myoclonic jerk and latency to GTCS, highest frequency of GTCS and prolonged duration of GTCS was increased making it an ideal dose to be used for the evaluation of the investigational drugs for antiepileptic properties [46]. We couldn't detect partial seizures during the experiment because of equipment limitations.

Apart from latencytomyoclonic jerks and latency to GTCS, frequency of GTCS was also considered as a prominent criterion for evaluation of the doses of PTZ (Goel and Saxena, 2019). Although the frequency of GTCS was lower at this dosage, PTZ 80 mg/kg s.c. displayed the highest latency to myoclonic jerks, indicating that there is some neuronal excitation and neuronal damage but not enough to cause another seizure episode [48]. Immobilization period after seizure episode is common. It is still unclear whether it should be considered as stage 2 of Racine scale (immobi lization/motionless staring), because immobilization is due to post-ictal effect after the seizure episode, but stage 2 immobilization/ motionless staringis observed even without seizure episode in kindling model.

Latency is considered one of the important criteria for the assessment of antiepileptic drugs. In PTZ 80 mg/kg; i.p. decrease in latency was observed making it appropriate dose for evaluation of antiepileptic drugs, as they work by delaying the latency of convulsion [49]. More the duration of seizure, the more it will cause oxidative stress, neuronal damage, mitochondrial dysfunction, neuronal hyperexcitation, *etc*. (Golechha *et al.*, 2014).

For better assessment of all these parameters PTZ 80 mg/kg; i.p. is an appropriate dose, because it has the longest duration of seizure when compared to other doses. The inter-ictal period is duration between two seizure episodes. According to our observations prolonged inter-ictal period cause less neuronal damage and faster the animals return to their normal position and locomotion activity after seizure episode because there is less neuronal firing and hyperexcitability. Therefore, proportion of neuronal damaged is less in prolonged inter-ictal period. PTZ 80 mg/kg; s.c. has the prolonged inter-ictal period, therefore causing less hyperexcitation and seizure episodes. The mortality rate was found to be highest in PTZ 80 mg/kg; i.p. (25%) (Table. 1) because of dose dependency and route of administration. PTZ 75 mg/kg; i.p. and PTZ 80 mg/kg; s.c. caused mortality in 12.5% of the total animals, indicating safe doses. We didn't go any higher than 80 mg/kg due to the likelihood of large animal fatality rates. Data of PTZ 75 mg/kg; i.p. lie in between both groups.

Therefore, PTZ 80 mg/kg; i.p. is considered as appropriate dose for assessing all the parameters. Mice that experienced physiological stress due to single housing before undergoing a PTZ seizure test exhibited seizures twice as frequently compared to control mice [51]. Although our study was not large enough to directly investigate the impact of social isolation on seizures, our results align with findings from other acute seizure models. Moreover, both our univariate and multivariate analyses revealed age as a significant predictor of seizure susceptibility [52]. While our findings on age are constrained by our limited age range of 8-12 weeks, we still observed a substantial influence of age on seizure susceptibility. The animal gender and weight are other crucial criteria in establishing the seizure score. Female mice were not used in the study due to their greater seizure threshold; using them would be ineffective for acute trials [53]. In terms of weight, animals weighing more than 35 g had delayed seizures scores, but mice weighing less than 25 g had a more mortality rate. The reason is still unknown.

**CONCLUSION:** Current study compared the different doses of PTZ used in acute model of seizures in mice. The frequency of GTCS was found to be highest, latency to GTCS and myoclonic jerks was least and duration of GTCS was more in PTZ 80 mg/kg, i.p., group, while the PTZ 80 mg/kg; s.c. has the longest inter-ictal phase. On the contrary, the mortality was more (25%) in PTZ 80 mg/kg, i.p., group as compared to other doses. The PTZ 80 mg/kg, i.p., in comparison for seizure parameters was most appropriate.

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**CONFLICTS OF INTEREST:** The author have no conflict of interest.

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