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Original Article

Antiepileptic Effect of Nux vomica, Homeopathic Remedy, Against Strychnine-Induced Seizers

Anjana Goel[1*], Aditya Saxena[2], Ashok Kumar Bhatia[3]

ABSTRACT

Objective: To investigate the antiepileptic effect of homeopathic remedy Nux vomica on mice and its comparison with standard therapeutic diazepam. **Methods:** BALB-c mice were taken and divided into three groups comprising ten mice in each group. The first group was treated as control; the second group received standard therapeutics (diazepam, i.p.) and the third group received Nux vomica CH7. All groups were treated with strychnine intra peritoneally. Following parameters were observed; start time of convulsions, the number of animals had convulsions, and survival time until death. **Results:** Nux vomica CH7 homeopathic preparation was found effective in suspending onset of convulsions ($P< 0.01$), and extending survival time until death ($P< 0.01$) in comparison to control mice. It also increased percentage survival in comparison to control as well as diazepam treated animals. **Conclusion:** Our study demonstrated efficacy of Nux vomica in epilepsy management.

Key words: Nux vomica, Strychnine, Anticonvulsant, Epilepsy.

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INTRODUCTION

Epilepsy affects over 50 million people worldwide, and over 10 million people in India.[1] its prevalence is about 1% in Indian population,[1] which is almost three times higher in rural population compared to the urban population.[2]

Epilepsy includes various neurological disorders in which neuronal activity get disturbed resulting in severe agitation and convulsions.[3,4] One specific type of convulsions, affecting both hemispheres of the brain is the *Tonic- Clonic seizures* that include a *Tonic* phase of 10-30 sec;[5] during this period, retrenchment of limbs is observed that is followed by their extension. This phase is followed by a *Clonic* Phase in which limbs shake in unison.

At the molecular level, epilepsy is attributed to disturbance in Inhibitory Post Synaptic Potential (IPSP) by inhibitory neurons. These neurons use inhibitory neurotransmitters like: Gamma aminobutyric acid (GABA), and glycine. Receptors for both these neurotransmitters are ionotropic receptors containing two binding sites one for the neurotransmitter itself and a Cl^- channel. Binding of neurotransmitters to their receptors cause the Cl^- channel to open. Opening of the Cl^- channel allows a larger number of chloride ions to diffuse inward causing *hyperpolarization* and an IPSP is generated that inhibit nerve conduction.

Epileptic agent strychnine has been demonstrated to bind and block these receptors and hence inhibits IPSP. It results in contraction of all skeletal muscles, including the diaphragm for extended duration. As a result diaphragm cannot relax, the victim cannot inhale, and suffocation occurs.[6]

Treatment of epilepsy in conventional therapy includes therapeutics like midazolam, lorazepam, phenytoin and diazepam. Diazepam is a medication of the benzodiazepine family that is commonly used to treat a range of conditions including anxiety, alcohol withdrawal syndrome, benzodiazepine withdrawal syndrome, muscle spasms, seizures, trouble sleeping, and restless legs syndrome.[7]

Protective action of diazepam against strychnine-induced seizures is attributed to its positive effect on GABA-mediated IPSC.[8] but usage of diazepam has been reported to show side effects like sleepiness and trouble with coordination.[9]

Homeopathic system is a holistic system of therapy but since its inception, it received severe criticism from scientific community due to non-measurable amount of drug substance in the homeopathic dose. Still homoeopathy has benefitted globally millions and billions of people, a fact that does not require any citation. In case of epilepsy management, there are several homeopathic remedies reported in scientific publications as well as homeopathic literature.[10,11,12,13] Homeopathic remedy Nux vomica has also been reported to affect entire gray matter of the Cerebrospinal Nervous System (CNS), especially centering upon tubular gray matter of pons, medulla, and cervical portion of spinal cord.[14]

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MATERIALS AND METHODS

Animals

BALB/c male mice of age 55-60 days, having 24-35 gm weight, were procured from Defense Research and Development Establishment (DRDE) Gwalior, INDIA. Animals were kept at 25±2^{0}C and provided standard pellet diet and water *ad libitum*. Before conducting the experiments, approval was taken from Institutional Animal Ethical Committee (IAEC), GLA University, Mathura Registration number 1260/ac/09/CPCSEA.

Chemicals

Strychnine (*SIGMA*), Nux vomica 7CH in 40% alcohol (*B. Jain Pharmaceutical Pvt. Ltd*) and diazepam (*ALPA Laboratories Ltd*) were procured and used in this study. Selection of Nux vomica potency CH7 was based on the previous study of Alecu *et al.*[12]

Determination of nontoxic route of Nux vomica administration

6 animals were taken and divided into two groups: In the first group, 50 µl Nux vomica homeopathic preparations was given intraperitoneally while in the second group it was given sublingual orally. All animals died within 10-15 min after intraperitoneal injection while no change was observed in the oral group. Thus, oral administration of Nux vomica was used for further pharmacological studies.

Effect of Nux vomica on strychnine induced convulsion

30 BALB/c male mice, without associated pathology, were divided them into 3 groups of 10 animals each. All the mice were kept on overnight fasting before conducting the experiment. In all the groups strychnine poisoning was caused by administering strychnine 0.8mg/kg body weight intraperitoneally and following protocol was designed according to the standard procedure.[15]

Group 1

This group was treated as negative control group; it received saline intraperitoneally as *placebo* 1 h before administration of strychnine and 40% v/v alcohol immediately after it orally.

Saline → strychnine → alcohol (40% v/v)

(Placebo) 1 h (gavages)

Group 2

It was positive control group; it received diazepam (standard therapeutic) 5 mg/kg body weight intraperitoneally 1 h before administration of strychnine and 40% v/v alcohol immediately after it.

Diazepam → strychnine → alcohol (40% v/v)

(Standard therapeutic) 1 h (gavages)

Group 3

This group was treated as experimental group and received homeopathic remedy *Nux vomica* (CH7) orally immediately after strychnine poisoning.

Saline → strychnine → Nux vomica

(Placebo) 1 h (gavages)

Immediately after the administration of strychnine, animals were observed for the following symptoms

Start time of convulsions,

Number of animals had convulsions,

Survival time until death,

Mortality in animals.

Statistical analysis

Data were expressed as mean± SEM and analyzed by One-Way ANOVA (Dunnet test) using Graph Pad Prism, version 5.01. P<0.05 was considered as statistically significant.

RESULTS

In our study diazepam, standard medicine was given intraperitoneally while Nux vomica was given orally as the alcoholic preparation of Nux vomica was found to be lethal when administered intraperitoneally due to the presence of alcohol in the preparation.

Effect of Nux vomica on strychnine induced convulsions

The average time for the onset of convulsions was 4.448±0.437, 8.196±0.697 and 7.673±0.766 min ±SEM in control, diazepam and Nux vomica treated groups respectively (Figure 1). Nux vomica significantly (p<0.01**) prolonged the onset of convulsions induced by strychnine. In diazepam group the convulsion time was extended to an extremely significant value of p<0.001***. However when Nux vomica group was compared with diazepam group than the *P-value* was found non-significant (p>0.05).

Effect of Nux vomica on strychnine induced death

100% death was observed in the negative control group while 30% and 20% recovery was observed in Nux vomica and diazepam treated groups respectively. In Nux vomica treated animals % protection was higher than diazepam treated animals (Figure 2).

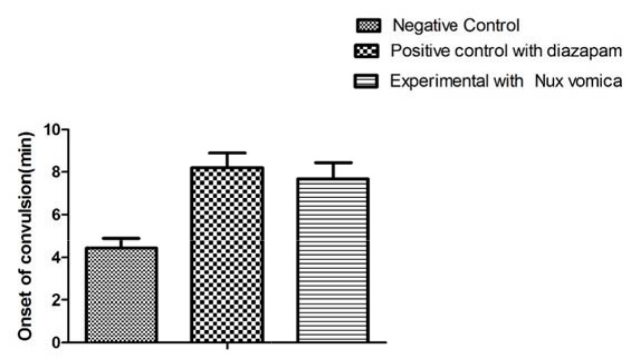

Figure 1: Effect of Nux vomica on strychnine induced convulsions.

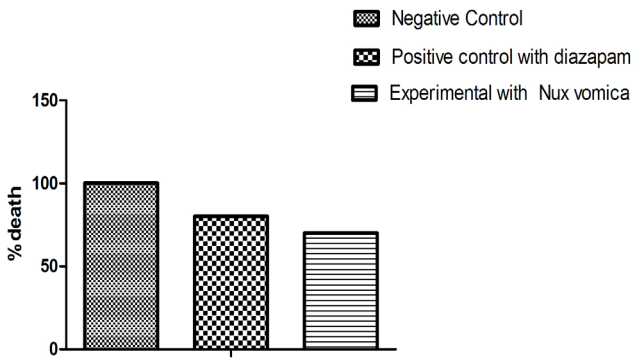

Figure 2: Effect of Nux vomica on strychnine induced death.

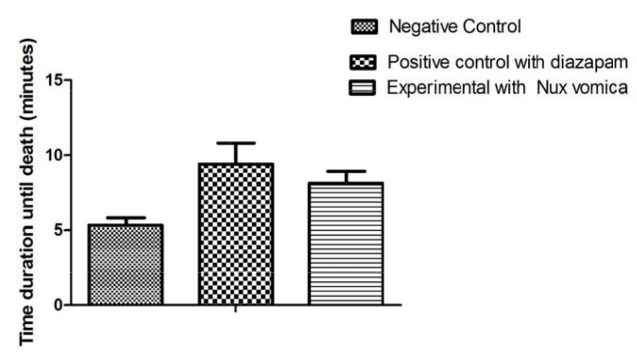

Figure 3: Effect of Nux vomica on time duration until death.

Effect of Nux vomica on Time duration until death

Survival time until death was recorded in all the three groups. Control, diazepam and Nux vomica treated groups respectively having 5.32±0.50, 9.40±1.41 and 8.11±0.80 min ±SEM time duration until death (Figure 3). Survival time duration in Nux vomica group was significantly lengthened ($p<0.01^{**}$) but this duration was further extended in diazepam treated group ($p<0.01^{**}$).

DISCUSSION

Diazepam acts as a positive allosteric modulator of GABA, it is administered as pretreatment. As it was not known whether Nux vomica is more effective as prophylactic or therapeutic, therefore, it was given as post treatment of strychnine. Probable mode of action of homeopathic medicines might be gene expression modulation, through signal transduction pathways. Due to the ultra-high dilution, it is more likely that homeopathic medicines act as physical signal rather than a chemical signal to invoke these signal transduction pathways.[16] Our experiment clearly demonstrated that Nux vomica CH7 was significantly more effective in delaying and even preventing seizures caused by strychnine in comparison to control animals; time to death was also extended significantly in Nux vomica treated group in comparison to control treated animals. The protective action of Nux vomica was found to be stronger than diazepam. % survival was 10% higher in Nux vomica treated animals as compared to diazepam group.

Research in homeopathy is a challenging task owing to lack of proper understanding of Modus-operandi of homeopathic medicines in accordance with "Law of Similia". Another problem that comes into way is "Law of the Minimum Dose and Potentization" that makes it difficult to conduct pharmacodynamics and pharmacokinetics studies due to the use of ultra-high dilutions beyond Avogadro number. Animal experimentation poses a further challenge in devising strategies to incorporate, "Law of Individualization" of Homoeopathy in study design. All these facts may account to poor reproducibility of experimental results across similar studies. We hypothesize that probable path toward the elucidation of the mechanism of action of homoeopathy should follow the steps; 1. Repeated animal experiments to verify the efficacy of a particular medicine against a disease and 2. Formulating strategies to analyze transcriptome profiles between case-control groups as it has been reported previously that transcription inhibitors, Actinomycin D counters effect of homoeopathic medicines.[17,18] so it is highly likely that homeopathic medicines act through modulation of gene expression. Our present study is the first step toward this objective.

CONCLUSION

Results of our study clearly indicate the efficacy of Nux vomica on strychnine induced neurological disorder leading to death. It was found statistically significant in protecting the animals. Our study opens an area for further research for the mechanism of action of this medicine.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

ABBREVIATIONS USED

IPSP: Inhibitory Post Synaptic Potential; **GABA:** Gamma aminobutyric acid.

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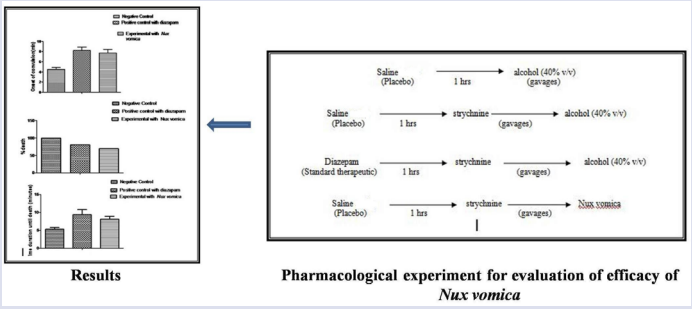
GRAPHICAL ABSTRACT



Results

Pharmacological experiment for evaluation of efficacy of *Nux vomica*

SUMMARY

- The present study has highlighted the efficacy of homeopathic medicine. Nux vomica, on strychnine induced seizers. The mode of action of this drug might be through the modulation of gene expression at nano levels. Further gene sequence analysis may explore the action mechanism of this drug.

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