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EFFECT OF NICORANDIL ON PENTYLENETETRAZOLE (PTZ) INDUCED CONVULSIONS IN MICE

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ABSTRACT

Aims & Objectives: To evaluate or screen the anticonvulsant effect of Nicorandil a potassium channel opener in Pentylenetetrazole (PTZ) induced convusions in albino mice. **Materials & Methods**: Mice of either sex weighing 20-25gms were selected for the present study. The animals were divided into 6 groups with each group consisting of 6 albino mice. Group 1 mice received placebo (0.2ml of distilled water) intraperitoneally (i.p), group 2 received sodium valproate 200 mg/kg/i.p. as positive control, while groups 3,4, 5 and 6 were administered Nicorandil 5, 10, 20 and 40 mg/kg i.p respectively. Pentylenetetrazole (PTZ) was administered in the dose of 100mg/kg i.p, 30mins after Nicorandil/ control drug pre-treatment. Onset and duration of clonic convulsion were recorded. **Results**: Nicorandil pretreatment in the dose of 5mg/kg increased onset time and significantly decreased the duration of convulsions, while the doses of 10, 20, 40mg/kg prevented the convulsions. **Conclusion**: Nicorandil possesses significant anticonvulsant activity comparable to sodium valproate on PTZ induced seizure in albino mice.

KEYWORDS: Pentylenetetrazole, Sodium valproate, Nicorandil, Anticonvulsant activity.

INTRODUCTION

Epilepsy is a common chronic neurological condition that is characterized by recurrent unprovoked epileptic seizure. It affects approximately 50 million people worldwide [1]. Recurrent seizures, interferes with a patient's ability to carry out day-to-day activities. Pharmacological therapy remains the cornerstone of epilepsy treatment [1].

The potassium channel openers like Nicorandil, cromakalim, pinacidil, diazoxide and minoxidil are a group of drugs which produce stabilizing action on cell membranes through membrane hyper polarization via increased transmembrane K^+ conductance [2]. They have been found to exert various neuro and psychopharmacological effects and modulate neurotransmitter release. Vanden Bussche and associates first suggested that they might inhibit seizure spread in epilepsy by blockade of neuronal Ca^{2+}channels [3]. Later other workers showed that the K^+ channel openers prevent or ameliorate seizure induced by mast cell degranulating peptide (MCDP) [4,5]. However, they have no effect in seizure induced by other K^+ channel blockers.

These observations have led to an inquisitive interest in K^+ Channel openers as a possible anti-convulsing agent. The present study was thus planned to evaluate the anti-convulsant effect of a K^+ channel opener Nicorandil, on PTZ induced convulsions in albino mice.

MATERIALS AND METHODS

The mice of either sex weighing 20-25gm were selected, one week prior to study. The animals were maintained in accordance with the Committee for the purpose of control and supervision on experimental animals (CPCSEA) guidelines, temperature of $(23\pm2)^0$C, humidity 50±5%, 12hr light: dark cycles. Animals were housed in polypropylene cages (UN Shah Manufactures,

Mumbai, India), provided with standard food (Hindustan lever ltd, Mumbai, India) and water ad libitium. Institutional animal ethics committee permission was obtained prior to study.

The animals were divided into 6 groups (n=6). Group 1 received 0.2ml of distilled water i.p, served as negative control. Group 2 received sodium valproate 200 mg/kg/i.p. served as positive control. Groups 3, 4, 5 and 6 were administered Nicorandil 5, 10, 20 and 40 mg/kg/i.p respectively. PTZ was administered at the dose of 100mg/kg/i.p, 30 minutes after Nicorandil/ control drug pre-treatment in all groups [6,7]. Onset and duration of clonic convulsion were recorded in all the mice.

STATISTICAL ANALYSIS

Results were analyzed by one-way analysis of variance (ANOVA).The level of statistical significance was set at $p<0.05$.

RESULTS

The onset of convulsions and duration of convulsions in mice the on PTZ induced convulsions were 5.50min and 12.50min in the negative control group. (sodium Valproate 200mg/kg), Nicorandil 10 mg/kg, Nicorandil20 mg/kg and Nicorandil 40 mg/kg demonstrated 100 % protection from PTZ induced seizures, clonic convulsions were not observed in any mice in these groups. Nicorandil pretreatment in the dose of 5mg/kg increased onset time and significantly decreased the duration of convulsions 4.67min and 6.33min respectively.

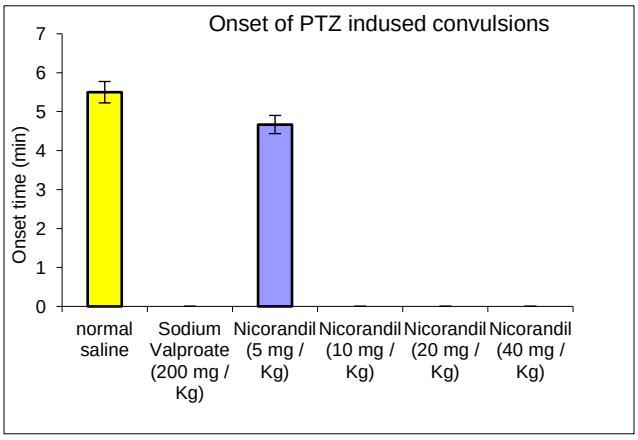

Figure 1. PTZ-induced convulsions (onset of action)

The onset of PTZ induced convulsions were reduced with 5mg dose of Nicorandil which was not significant statistically but there was no convulsions (100% protection) with Sodium Valproate, Nicorandil 10mg, 20mg and 40mg. (Figure 1).

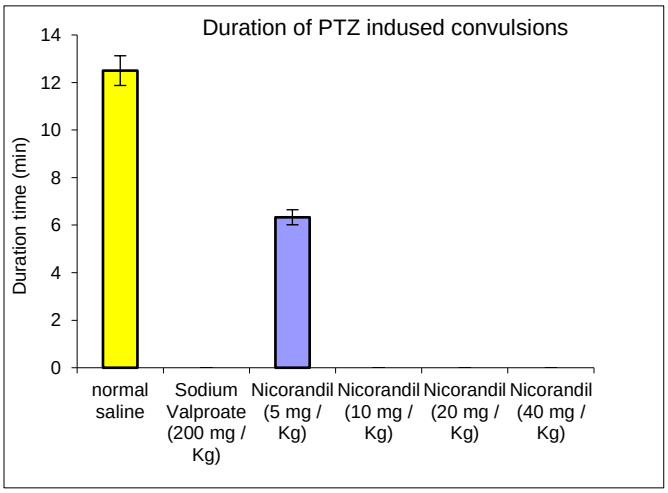

Figure 2. PTZ-induced convulsions (duration of action)

The duration of PTZ induced convulsions reduced with 5mg dose of Nicorandil ($p<0.001$) and there was no convulsion (100% protection) with Sodium Valproate, Nicorandil 10mg, 20mg and 40mg. (Figure 2).

DISCUSSION

Clonic convulsions produced by PTZ in mice were prevented by drugs effective in absence seizures. Activity in this model represents action on seizure focus itself.[8,9] Pentylenetetrazol, also known as Metrazol, Leptazol, Cardiazol, and Corazol was used as a central nervous system stimulant. Soaje-Echaque and Lim used adult albino mice to study the anticonvulsant effects [10]. In their study animals were initially administered with an anti convulsant, later they were injected with PTZ 100mg/kg/i.p., 112mg/kg/s.c through tail vein. The volume of solution, not exceeding 0.25 ml, is injected in 4 seconds or less, using a 0.25-ml syringe and a 27-gauge needle. Animals were observed for the effect of anticonvulsant. In the current study also the same procedure was followed, to identify the antiepileptic activity of Nicorandil on PTZ model.

One potential anti-epileptic that has not been adequately exploited is K^+ channel opening. K^+ channels play a major role in the control of all aspects of neuronal excitability, including resting membrane potential, responsiveness to synaptic inputs,

spike frequency adaptation and neurotransmitter release. To date, 80 or more K^+ channel related genes have been identified in the human genome, and genetic, molecular, physiological and pharmacological evidence now exists to support a role for some of these K^+ channels in the control of neuronal excitability and epileptogenesis.[11]

CONCLUSION

Administration of Nicorandil 30 minutes prior to PTZ abolished the convulsions completely. Hence, Nicorandil possesses significant anticonvulsant activity against absence seizures in albino mice. The antiepileptic activity of Nicorandil is comparable to sodium valproate in the PTZ model. Further studies are required for establishing antiepileptic property of Nicorandil and confirming its mechanism action using other models of convulsion.

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