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COMPARISON OF SEIZURE POTENTIATING EFFECT OF FIRST AND SECOND GENERATION ANTIHISTAMINES

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Abstract

Aims: There are controversies regarding the proconvulsant effect of first and second generation antihistamines. To compare the seizure potentiating effect of first generation antihistamine cyproheptadine with second generation fexofenadine in animal models of epilepsy.

Methods: Thirty rats were used. In both MES and PTZ model, rats were divided into three groups (n=6). Group I to III received sodium alproate, sodium valproate + cyproheptadine and sodium valproate + fexofenadine respectively in both the models. In MES model 30 minutes after drug administration seizures were induced. Duration of seizures, recovery period and hindlimb extension were recorded. In PTZ model, PTZ was injected 30 minutes after drug administration. Latency and total duration of seizure was recorded.

Results: In MES model, recovery period was significantly more in cyproheptadine + sodium valproate group as compared to sodium valproate alone. In PTZ model mortality was seen only in the combination groups.

Conclusion: Though antihistamines have a seizure potential, second generation antihistamine, fexofenadine was superior to cyproheptadine in MES model of epilepsy.

Keywords: Cyproheptadine, Fexofenadine, MES, PTZ.

Introduction:

Histaminergic (H₁) receptor antagonists or antihistamines are commonly used in symptomatic treatment of rhinitis, dermatitis, urticaria. ¹Antagonists of histamine H₁ receptors are also known as first-generation or second

antihistamines on the basis of their sedating effect at therapeutic doses.² Second generation antihistamines like cetirizine, loratadine, azelastine, fexofenadine are developed as non-sedating alternatives to first generation antihistamines like diphenhydramine, promethazine, cyproheptadine. Antihistamines have reported to worsen seizures in animal models of epilepsy and thus have proconvulsant action.^{3,4} In clinical studies, antihistamines promote seizures in young patients with epilepsy.⁵ Controversy regarding the proconvulsant effect of antiepileptics is there as some studies put forth that second generation antihistamine do not promote occurrence of seizures.⁶ With this background, the present study was undertaken to compare the proconvulsant potential of first generation antihistamine cyproheptadine with second generation fexofenadine in animal model of epilepsy.

Methodology: The study was conducted after clearance from IAEC. All procedures used in this study were reviewed and approved by Institutional Animal Ethics Committee

Animals

Rats (n=6) weighing 150 to 250 g were used and maintained under standard laboratory conditions in Central animal house approved by the CPCSEA. They were maintained at a room temperature and relative humidity of 45-55%. A 12 hour light: dark cycle was followed. They were provided with standard feed and water ad libitum.

Drugs and chemicals

Sodium valproate (200mg/kg),⁷ cyproheptadine: 4mg/kg i.p.⁸ fexofenadine: 5mg/kg i.p.⁹, pentylenetetrazole (PTZ) 60mg/kg was used. All drugs were administered intraperitoneally.

Study design: Thirty Wistar rats were used for the study. The rats were studied in two models.

Maximal electroshock (MES) induced seizure model:

In this model animals were pre-screened to check for their ability to develop full tonic extension by giving the shock 24 hours before the day of experiment. Group I to group III (n=6) were treated with Sodium valproate, sodium valproate + cyproheptadine, sodium valproate + Fexofenadine respectively. All the drug dosage was selected according to previous studies. Rats were treated with drugs and after 30 minutes seizures were induced by an electro-convulsimeter as described by Toman et al.¹⁰ with a current of 150 mA, 50Hz delivered through the ear clip electrode for 0.2 sec. Duration of seizures, recovery period and hind limb extension (HLE) was recorded

Pentylenetetrazol (PTZ) induced seizure model:

Group I to group III (n=6) were treated with Sodium valproate, sodium valproate + cyproheptadine, sodium valproate + Fexofenadine. Pentylenetetrazole was injected as 60 mg kg⁻¹ b.w. intraperitoneally 30 minutes after the

administration of drugs. Each animal was placed in individual cage and observed for 30 minutes. Latency and total duration of seizure was recorded.

Statistical analysis: Statistical analyses was carried out using SPSS software version 17. All values are expressed as mean ± S.D. Data was analysed using one way ANOVA followed by Tukey’s post hoc test . p≤0.05 was considered statistically significant.

Results:

MES model: The effect of various drugs on MES induced seizure model is shown in table 1. There was no significant difference between the groups in duration of seizures (p= 0.834).Using ANOVA, a significant difference between the groups was observed in recovery period (p= .005). On intergroup comparison, sodium valproate was significantly superior to sodium valproate and cyproheptadine combination (p= 0.004).No difference was recorded in duration of HLE between the three groups.

Table-1: Effect of various drugs on MES induced seizure model.

Groups (n=6)	Duration of seizures (seconds)	Recovery time (seconds)
Sod Valproate	11.33 ± 3.01	5.59 ± 1.84
Sod Valproate + Cypro	11.33 ± 3.5	15.9±4.2*
Sod Valproate + Fexo	12.16 ± 1.16	11.00 ± 6.5

Values are in mean± S.D. *p< 0.01 as compared to sodium valproate

Effect of various drugs on PTZ induced seizure model

No Statistically significant difference was observed between the groups on seizure onset, and total duration of seizure.(Table-2). 16.66% mortality was observed inboth fexofenadine+ sodium valproate and cyproheptadine+sodium valproate group.(Table-2).

Table-2: Effect of various drugs on PTZ induced seizure model.

Groups (n=6)	Latency (sec)	Total duration (sec)	% mortality
Sod Valproate	59.6 ± 4.5	46.33 ± 9.3	0
Sod Valproate + Cypro	75.8± 8.9	43.83± 14.9	16.66%
Sod Valproate + Fexo	66.3 ± 11.3	39.83 ± 10.88	16.66%

Values are in mean± S.D.

Discussion:

Endogenous histamine plays a protective role mediated by H₁ receptors on seizure development of PTZ-induced kindling in rats.¹¹ It was first reported that antihistamines such as diphenhydramine activated epileptic discharges on electroencephalography and produced clinical manifestations of psychomotor seizures in epileptic patients.¹² Animal models and clinical observations have revealed that the brain histaminergic system has an inhibitory effect on seizures.¹³ H₁R antihistamines show pro-convulsant effects particularly in children¹⁴ and suppression of histaminergic activity promotes seizures in animal models.¹⁵ Low histamine levels have also been detected in Krushinski-Molodkina rats that are prone to epilepsy.¹⁶ Histamine has neuroprotective properties^{17,18} and inhibits excitotoxic effects of glutamate.¹⁸ Recent studies have put forth that intrinsic histaminergic system exerts a powerful inhibitory function during epileptic seizure episodes, via an H₁- and H₃-dependent mechanism.¹⁹ H₃ receptor antagonists protect against experimental convulsions by increasing the release of histamine in the brain, which in turn interacts with H₁ receptors.²⁰ They also mediate their anticonvulsive action by mechanisms like facilitation of GABA release²¹, increasing histidine decarboxylase activity.²²

In our study, in MES model on comparing sodium valproate with combination of sodium valproate and cyproheptadine there was a significant increase ($p=0.005$) in recovery time in combination group. However there was no significant difference between the sodium valproate and combination of sodium valproate and fexofenadine group. This may be due to the fact that second generation antihistamines like fexofenadine and cetirizine penetrate CNS poorly, and are devoid of central effects²³.

In PTZ induced seizures, on comparing the combination group with sodium valproate no significant difference was seen in latency and total duration of epilepsy. This is in contradiction to an earlier study in which compared to control group, first generation antihistamine diphenhydramine significantly increased the severity of seizure development in PTZ model, whereas fexofenadine had no marked influence³. However mortality was seen in both the combination groups and no mortality in sodium valproate group. This is in congruence to a study in which cyproheptadine increased the mortality in PTZ model of epilepsy.⁸

To summarize, in MES model of epilepsy sodium valproate and combination of fexofenadine + sodium valproate appeared to be safe as compared to combination of cyproheptadine + sodium valproate. In PTZ model, though combination groups were comparable to sodium valproate group regarding latency and recovery, there was

increased mortality in the combination groups. Thus there is a need to use antihistamines cautiously in patients with seizures. Second generation antihistamines appear to be safer than first generation in MES model of epilepsy.

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