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Anticonvulsant activity of Granisetron in Albino mice

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Abstract
The objective of this study was to investigate the anticonvulsant activity of 5-HT_3 antagonist, granisetron in albino mice. In this study granisetron (0.5mg/kg, i.p.) was administered 30 minutes prior to application of electroshock (60mA, 0.2 seconds) or administration of pentylenetetrazole. Granisetron significantly reduced the duration of tonic hind limb extension in maximum electroshock seizure (MES) test. In pentylenetetrazole (PTZ) test, granisetron delayed the onset and the decreased the duration of convulsions compared to control group. The percentage of animals protected in MES and PTZ models were 66 and 83 respectively. The results showed that granisetron at dose of 0.5mg possess anticonvulsant activity in both MES and PTZ models.
Keywords: Anticonvulsant, Maximal Electroshock, Pentylenetetrazole, Granisetron

1. Introduction

Epilepsy is common chronic neurological disorder affecting approximately 1% of the world population.[1] It often causes transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment.[2] Several new generation of antiepileptics have been developed to enhance effectiveness and minimize the risk of adverse effects. But adverse effects remain a leading cause of treatment failure and impairment of health related quality life in epileptic patients.[3] This opens the door for novel and safer antiepileptics.

Ondansetron, 5-HT_3 receptor antagonist used as an antiemetic agent found to have anticonvulsant effect in mice.[4] It also potentiates the anticonvulsant activity and attenuates the cognitive dysfunction induced by phenytoin.[5] The experimental compound granisetron, 5-HT_3 receptor antagonist commonly used as an antiemetic for the treatment of anticancer drugs induced nausea and vomiting. The side effect profile is similar to that of ondansetron.[6] Therefore the present study has been undertaken to evaluate the anticonvulsant activity of granisetron in experimental models.

2. Materials and methods

2.1 Animal

Thirty six healthy albino mice weighing from 18-22 gms of either sex were used for the study. The animals used were inbred in Central Animal House, SSIMS&RC, Davangere. The animals were randomly housed as 4 mice per cage at an ambient temperature & humidity with a 12 hour light/ dark cycle. The animals were maintained under standard laboratory diet with free access to water The animal ethics committee approval was taken prior to the study (Reference Number: SSIMS &RC/IAEC/042/2014, Date 29/01/2014). The $P < 0.05$ was considered as statistically significant.

2.2 Experimental Design:

2.2.1 Maximal Electroshock Seizure (MES) Model:

Eighteen albino mice were divided into three groups containing 6 mice in each group. Animals in control group, reference group and test group received normal saline (1 ml), phenytoin (20mg/kg)[7] and granisetron(0.5mg/kg) intraperitoneally respectively.

The animals in all the groups received corresponding drugs 30 minutes before the application of shock. Each animal was properly held and current of 60 mA was passed for 0.2 second transauricularly through ear lobe electrodes using an electroconvulsiometer. The reduction in duration of hind limb extension was considered as a protective action &

recorded for all the animals.[7] The percentage of animals protected from hind limb extension was determined for each group.

2.2.2 Pentylenetetrazole (PTZ) model

The animals were grouped and administered vehicle, reference drug and granisetron as described for MES test. The reference group was treated with diazepam 0.5mg/kg intraperitoneally. Thirty minutes after administering corresponding drugs to different groups of animals, PTZ 80mg/kg was injected subcutaneously and mice were observed for thirty minutes for the onset and duration of convulsive behavior.[7] The number of animals convulsing or not convulsing within observation period was noted to calculate percentage of protection.

2.3 Statistical analysis

The data were analyzed using one way analysis of variance (ANOVA), using statistical software GraphPad InStat version 3.06. P values of < 0.05 were considered as statistically significant.

3. Results

3.1 MES Model

The duration of hind limb extension in animals treated with vehicle, and granisetron was14.7 ± 0.9 and 5.8 ± 1.1 respectively. Administration of phenytoin completely abolished tonic extension phase. Duration of hind limb extension was significantly reduced in animals treated with granisetron compared control group. The reference drug phenytoin completely protected animals from seizures, while granisetron abolished seizure completely in 4 out of six animals(66 % protection).

Table 1: Effect of granisetron on maximal electroshock induced seizure in mice.

Groups	Duration of hind limb extension phase in seconds(Mean ± SEM)	Animals protected (%)
CONTROL	14.7 ± 0.9	0
PHENYTOIN	0*	100
GRANISETRON	5.8 ± 1.1*	66

n =6; *P < 0.001when compared to control and standard.

3.2 PTZ Model

The granisetron significantly delayed onset of convulsions and decreased duration of convulsions compared to control group ($p<0.001$). The reference drug phenytoin completely inhibited seizures in all animals. One out of six treated with granisetron exhibited convulsion (protection 83 %).

Table 2: Effect of granisetron on pentylenetetrazole induced seizures in mice.

Groups	Onset time (seconds) (Mean ± SEM)	Duration of clonus (seconds) (Mean ± SEM)	Animals protected (%)
CONTROL	30.2 ± 4.4	442.2 ± 72.1	0
DIAZEPAM	1800 ± 0.0 *	38 ± 32.0 [***]	100
GRANISETRON	800 ± 184.4*	60.5 ± 7.9 [***]	83

n=6; *P < 0.001when compared to control and standard

4. Discussion

The experimental models used in the study were assumed to identify experimental compounds with potential anticonvulsant activity.[8] Granisetron significantly reduced the duration of hind limb extension when compared to control group in MES model. In PTZ model, granisetron significantly delayed the onset of seizures and decreased the duration of clonus when compared to saline treated group. The results confirm the anticonvulsant activity of granisetron in both the experimental models.

5-HT_3 receptors in brain are known to regulate the release of neurotransmitters. Their activation reduces the release of norephinephrine(NE) from presynaptic terminals. The inhibitory effect of NE on synaptic junction in cerebellum and cerebrum could be responsible for its anticonvulsant action in animal models.[9] Regional abnormalities in NE uptake and reduction in noradrenergic innervation were found in genetically epilepticprone rats.[10] The reduction in threshold for MES following administration of reserpine is accompanied by a decline in brain concentration of NE and other amines which suggests that brain amines are involved in the control of MES threshold.[11] Furthermore, antagonist

activity at $5HT_3$ receptors also decreases sodium and potassium conductance leading to attenuation of fast depolarization.[10] Therefore, Granisetron may be exerting its anticonvulsant activity by attenuating depolarization and also by increasing norepinephrine release

5. Conclusion

Granisetron at the dose 0.5mg has anticonvulsant activity in both MES and PTZ models. Granisetron by blocking 5-HT_3 receptors could augment the release of norephinephrine which may be responsible for its anticonvulsant activity. However further studies have to be carried out to give a conclusive word in this regard.

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