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Research Article

ABOLITION OF SEIZURE PROVOKING EFFECT OF SUMATRIPTAN BY FLUOXETINE IN PENTYLENETETRAZOL-INDUCED SEIZURES IN RATS

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ABSTRACT

Objectives: The objective was to evaluate the seizure provoking effect of sumatriptan, and its abolition with fluoxetine in the pentylenetetrazol-induced seizures in rats.

Methods: 100 Sprague-Dawley rats of either sex were randomized into 10 groups with each group consisting 10 rats. The first group was taken as a control group which received distilled water. The second group and the third group were evaluated with standard anticonvulsant drug sodium valproate in the dose of 200 mg/kg and 250 mg/kg, respectively. The fourth group received sumatriptan in the dose 6 mg/kg. The fifth and sixth groups were evaluated for effect of fluoxetine in the dose of 6 mg/kg and 10 mg/kg, respectively. The seventh group was evaluated for the combined effect of sumatriptan 6 mg/kg and sodium valproate 200 mg/kg. The eighth group was administered fluoxetine 6 mg/kg and sodium valproate 200 mg/kg. The ninth group was evaluated for a combined effect of fluoxoetine 6 mg/kg and sumatriptan 6 mg/kg. The tenth group was evaluated for the combined effect of three drugs fluoxetine 6 mg/kg, sumatriptan 6 mg/kg, and sodium valproate 200 mg/kg. The rats were screened for the effect of various drugs by inducing seizures with pentylenetetrazol. The rats were analyzed for the parameters, i.e., the time for the onset of seizures, duration of tonic-clonic seizures, and for post seizure mortality up to 24 hrs.

Results: Sumatriptan reduced the seizure threshold in rats, and it has abolished the seizure protective effect of sodium valproate. Sodium valproate and fluoxetine had dose dependent seizure protective effect. Fluoxetine abolished the seizure threshold lowering effect of sumatriptan. Fluoxetine and sodium valproate combination produced additive seizure productive effect. The combination of sumatriptan, fluoxetine, and sodium valproate also raised the seizure threshold.

Conclusion: The seizure threshold lowering effect of sumatriptan was abolished by co-administration of fluoxetine.

Keywords: Fluoxetine, Sumatriptan, Pentylenetetrazol, Seizures.

INTRODUCTION

Sumatriptan being a prototype triptan drug is commonly used for therapeutic management of migraine. It mainly acts as an agonist at 5-hydroxytryptamine (5-$HT_{1B/1D}$) receptor of serotonin (5-HT). 5-$HT_{1B/1D}$ [1] receptor is a presynaptic receptor at serotonergic neurons and when bound by agonist inhibits the release of serotonin from serotonergic neurons. Hence, sumatriptan inhibits the release of serotonin from the serotonergic neurons.

Several studies have shown that synaptic serotonin levels to regulate the seizure threshold. Increased synaptic serotonin levels have shown to raise the seizure threshold [2-4]. Studies on regulation of subtypes of 5-HT_1 receptors 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} by use of the antagonist enhanced the serotonin levels in the caudate nucleus, substantia nigra, and limbic area [5]. Hence, binding of the agonist to 5-HT_1 inhibits the serotonin release, and binding of the antagonist increases the serotonin release [6].

Fluoxetine being a selective serotonin reuptake inhibitor (SSRI) increases synaptic levels of serotonin [7] and should increase the seizure threshold. Studies have shown that fluoxetine has a protective effect of acoustically induced seizures. Previous studies have even shown that systemic administration of fluoxetine has protected vocally evoked limbic motor seizures in rats [8]. One more study has shown that the combination of fluoxetine with 5-HT_{1A} receptor antagonists enhanced the anticonvulsive action of fluoxetine [9]. Fluoxetine also protected genetically epilepsy prone rats against acoustically induced seizures [10].

Sumatriptan being agonist at 5-$HT_{1B/1D}$ receptor of serotonin (5-HT) reduces the synaptic serotonin levels, while fluoxetine an SSRI increases the synaptic serotonin levels. Hence, both should have the opposite effect on seizure threshold. Hence, the present study is taken up to evaluate the seizure provoking effect of sumatriptan and to evaluate the abolition of this seizure provoking effect with fluoxetine.

METHODS

Animals

Hundred adult Sprague-Dawley rats of either sex weighing between 150 and 200 g were used for this study. Animals were caged under standard husbandry conditions as per the CPCSEA guidelines. Care was taken to see through that animals had adequate access to food and water ad libitum. All experiments were conducted during the morning hours while animals were awake. The study protocol was approved by the IEC of Shri BM Patil Medical College, Bijapur.

Drugs

Sumatriptan, fluoxetine, and sodium valproate were obtained from "Sun Pharma" in pure form. Distilled water was used for dissolving the drugs. The appropriate doses for rats were calculated by Paget and Barner table [4]. The calculated dose drugs were given through the intraperitoneal route 1 hr before the experimental procedure.

Dosage schedule

The first group was taken as a control group which received distilled water. The second group and the third group were evaluated for the standard anticonvulsant drug sodium valproate in the dose of 200 mg/kg and 250 mg/kg, respectively. The fourth group received sumatriptan in the dose 6 mg/kg. The fifth and sixth groups were evaluated for effect of fluoxetine in the dose of 6 mg/kg and 10 mg/kg, respectively. The seventh group was evaluated for the combined effect

Table 1: Effect of drugs activity in pentylenetetrazol-induced seizures in rats

Group	Drugs (dose in mg/kg bw) i.p.	Onset of head jerk (seconds)	Duration of tonic-clonic seizures (seconds)	Mortality rate in post convulsive phase (24 hrs)
1	Control (distilled water 0.5 ml)	74.8±13	36.5±14.24	Nil
2	Sodium valproate (200)	166.1±28.17*	27.57±9.57*	Nil
3	Sodium valproate (250)	Abolished	Abolished	Nil
4	Sumatriptan (6)	58.6±15.07**	30.1±5.8 ns	50%
5	Fluoxetine (6)	84.6±35.03 ns	17.0±4.5*	30%
6	Fluoxetine (10)	127.7±28.63*	29.1±14.91 ns	Nil
7	Sumatriptan (6)+sodium valproate (200)	99.2±19.8*	20.5±5.19*	Nil
8	Fluoxetine (6)+sodium valproate (200)	117.4±29.4* abolished in 3 rats	18.8±3.67* abolished in 3 rats	Nil
9	Fluoxetine (6)+sumatriptan (6)	139.1±10.68*	10.7±1.97*	Nil
10	Fluoxetine (6)+sumatriptan (6)+sodium valproate (200)	175.5±43.3*	14.25±3.95*	Nil

Values expressed as mean±SD, n=10, Significance at *p<0.05, ns: Not-significant, SD: Standard deviation

of sumatriptan 6 mg/kg and sodium valproate 200 mg/kg. The eighth group was administered fluoxetine 6 mg/kg and sodium valproate 200 mg/kg. The ninth group was evaluated for a combined effect of fluoxetine 6 mg/kg and sumatriptan 6 mg/kg. The tenth group was evaluated for the combined effect of three drugs fluoxetine 6 mg/kg, sumatriptan 6 mg/kg and sodium valproate 200 mg/kg.

Induction of seizures

Pentylenetetrazol [11] was used to induce the seizures in rats. Pentylenetetrazol was administered in the dose of 60 mg/kg bodyweight through intra-peritoneal route 1 hr after administration of respective drugs.

Parameters

The parameters observed were time for the onset of head jerks in seconds, duration of tonic-clonic seizures in seconds, and post convulsive mortality effect up to 24 hrs.

Statistics

The results of each group were expressed as mean±standard deviation. For testing, the statistical significance unpaired Student's *t*-test was used. The $p<0.05$ were considered significant.

RESULTS AND DISCUSSION

Sumatriptan 6 mg/kg showed significant early onset of seizures in rats, while duration of tonic-clonic seizures was reduced, but this effect was not statistically significant. Only five rats were alive in the post convulsive phase. This finding is suggestive of seizure precipitating effect of sumatriptan. This effect could be due to a reduction of serotonin level at synapsis due to agonistic activity at $5\text{-HT}_{1A/1D}$ receptor which is a presynaptic autoreceptor at serotonergic neurons.

Sodium valproate in the dose of 200 mg/kg produced a significant increase in the time for the onset of seizures and also the duration of tonic-clonic seizures was significantly reduced. Sodium valproate in the dose of 250 mg/kg had completely abolished the development of seizures. This is suggestive of dose-dependent seizure protective effect of sodium valproate. However, there was no mortality of the rats in both the doses.

Fluoxetine 6 mg/kg increased the mean time for the onset of convulsions, but this effect was statistically insignificant. However, the duration of tonic-clonic seizures was reduced in a significant manner. Only seven rats were alive in the post convulsive phase. Fluoxetine 10 mg/kg significantly increased the time for the onset of seizures and duration of seizures was significantly reduced. All the rats treated with this dose were alive in the post convulsive phase. This is suggestive of dose-dependent seizure protective effect of fluoxetine.

The combined administration of sumatriptan 6 mg/kg and fluoxetine 6 mg/kg shown significant prolongation of time onset of head jerks and duration of seizures was also significantly reduced. All the animals treated with this combination were alive. This finding is suggestive of abolition of seizure provoking effect of sumatriptan by fluoxetine.

Fluoxetine 6 mg/kg and sodium valproate 200 mg/kg when administered simultaneously completely abolished development of seizures in three rats. This combination also significantly reduced the duration of tonic-clonic seizures. This is suggestive additive seizure protective action of these drugs. There was no mortality in the rats treated with this combination.

Combination of sumatriptan 6 mg/kg, fluoxetine 6 mg/kg, and sodium valproate 200 mg/kg produced significant increase in mean time for onset of seizures and also produced significant reduction in mean duration of convulsions. None of the rats treated with this combination had died.

CONCLUSION

Sumatriptan significantly shown proconvulsive effect and lowered the seizure threshold in rats, and this effect was reversed by fluoxetine. Pharmacologically, both have the opposite effect on synaptic serotonin levels, hence addition of fluoxetine to sumatriptan reverses the seizure threshold lowering effect of sumatriptan.

Sumatriptan is the drug very frequently used in the course of therapeutic management of migraine. This may precipitate post focal ictus prone seizures in migraine patients to result in seizures. These seizures may be prevented by co-administration of fluoxetine. This combination helps markedly to patients suffering from migraine because patients usually suffer from co-existing depression. Hence, a combination of fluoxetine and sumatriptan does not predispose the patients to develop seizures and takes care of co-existing depression.

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