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Acute anticonvulsant activity of fluoxetine in wistar albino rats by maximum electroshock induced seizure

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Abstract

A seizure is paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system neurons. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic or underlying process. The objective of this study was to evaluate anti-convulsant effect of Fluoxetine by Maximum Electroshock induced Seizure in Wistar albino rats. Wistar albino rats of either sex weighing 150-200 gms were randomly divided into five groups containing five animals in each group. All the drug preparations were administered intra-peritoneally. Group 1 received 0.5 ml/100 gm of Propylene Glycol and served as a control. Group 2 received Sodium Valproate 300 mg/kg and served as standard. Group three, four and five received Fluoxetine 10, 20 and 30 mg/kg respectively. After an interval of 30 minutes they were subjected to Maximal electroshock (MES) stimulation of 150mA for 0.2 seconds through trans-auricular electrodes by using technoelectroconvulsiometer. The duration of different parameters was noted. Statistical method was One way ANOVA was used for multiple group comparisons followed by post- hoc Tukey's test for group wise comparisons. Group 4 and 5 which received Fluoxetine 20 and 30 mg/kg significant anticonvulsant action when compared to control group with respect to reduction in time taken for like fore limb flexion, hind limb extension, clonus and stupor. Our study reveals that Fluoxetine elicited an effective protection against MES seizures in Wistar albino rats in the dose of 20 and 30 mg/kg.

Keywords: Epilepsy, Fluoxetine, Maximum Electroconvulsive Shock, Sodium Valproate.

Introduction

Epilepsy is one of the most common neurological disorders. Worldwide, the prevalence is estimated to be 0.5 – 1%, and there is a lifetime incidence of 1 – 3%.[1] It has important medical, social and psychological consequences. Even though it was recognized as early as 2000 BC, new concepts about its pathogenesis, etiology and treatment are brought out almost every year.[2]

Before the antiepileptic drugs were discovered and developed, treatment of epilepsy was consisted of trephining, cupping and administration of herbal medicines. In 1857, Sir Charles Locock reported the successful use of potassium bromide in the treatment of what is now known as catamenial epilepsy. In 1912, Phenobarbital was first used for epilepsy and in the next 25 years, 35 analogs of Phenobarbital were studied as anticonvulsants. In 1938, phenytoin was found to be effective against experimental seizures in cats.[3] Between 1935 and 1960 tremendous strides were made both in the development of experimental models and in methods for screening and testing new antiepileptic drugs. During that period 13 new antiepileptic drugs were developed and marketed. Following the enactment of requirements for proof of drug efficacy in 1962, antiepileptic drug development slowed dramatically and only a few new antiepileptic drugs were marketed in the next three decades. However, a series of new compounds became available in the 1990s.[3] Despite the introduction of several new therapeutic options in the 1990s, a significant fraction of the patients with epilepsy continue

to live with uncontrolled seizures.[1]

There is still a need for an ideal antiepileptic agent with properties like good antiepileptic activity, rapid onset of action, least side effects, good oral bioavailability and low cost.[4] Contemporary anticonvulsant therapy, however, is neither universally effective nor invariably safe as they are associated with adverse effects like central nervous system depression, ataxia, megaloblastic anemia, cardiac arrhythmias, hepatic dysfunction and teratogenicity.[5] Although most people with epilepsy become seizure free with appropriate therapy, 30-40% of patients will continue to have seizures despite the use of antiepileptic drugs either alone or in combination.[6]

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. The potential importance of selective serotonin reuptake inhibitors (SSRI's) in modulating aspects of brain electrical activity has been described recently. Fluoxetine is known to act through a novel modulatory site on the GABA-a receptor, which mediate most fast inhibitory neurotransmission in the mammalian brain, hence this study was undertaken to evaluate the anti-convulsant effect of Fluoxetine in Wistar albino rats.

Materials and Methods

Institutional Ethical Committee approval was obtained before conducting the experiment in November 2008.

Animals

Wistar albino rats of either sex weighing 150-200 g were inbred in the Central Animal House of the Department of Pharmacology, J.J.M Medical College, Davanagere, Karnataka, India, under suitable conditions of housing, temperature, ventilation and nutrition. All the test animals were allowed food and water *ad libitum* both being withdrawn just prior to experimentation.

Drugs and Chemicals

Sodium valporate and Fluoxetine was obtained from the Torrent Pharmaceutical Pvt Ltd. Propylene Glycol was used as vehicle which was obtained from our institutional stores.

Procedure

Wistar albino rats of either sex weighing 150-200gms were selected (n=5) and randomly divided into five equal groups containing five animals in each group. All the test animals were subjected to further experiment of this study after 24hrs (to avoid any possible "Kindling" effect). Group 1 received Propylene Glycol intra-peritoneally and served as control. Group 2 received Sodium Evaporate (300 mg/kg) intra-peritoneally and served as standard. Group 3, 4 and 5 received Fluoxetine in the dose 10, 20, 30 mg/kg intra-peritoneally respectively. After an interval of 30 minutes they were subjected to Maximal electroshock (MES) stimulation of 150mA for 0.2 seconds through trans-auricular electrodes by using techno-electroconvulsiometer. The duration of different parameters like Seizure Latency (Time taken for onset of seizure), Tonic flexion of fore limb, tonic extension of hind limb, Clonus and Stupor were observed.

Statistical Analysis

Results are expressed as mean± SD and percentage changes wherever required. Intra-group comparisons are made by Paired t-test and Unpaired t-test for inter group comparisons. One way ANOVA is used for multiple group comparisons followed by post- hoc Tukey's test for group wise comparisons. 'p'< 0.05 was considered for statistical significance.

Results

In our study, Group 3 that received Fluoxetine 10mg/kg parameters showed reduction in observed parameters like in fore limb flexion, hind limb extension, clonus and stupor, but not with an appreciable significant difference. Group 4 and 5 which received Fluoxetine 20 mg/kg and 30 mg/kg showed much reduction in parameters like fore limb flexion, hind limb extension, clonus and stupor. When compared with the standard there was no significant difference between the standard and group 4 and 5, indicating that Fluoxetine in the dose of 20 and 30 mg/kg does have significant anti-convulsant activity as mean duration of different parameters were observed to be more than standard (Table 1).

Table 1: Showing effect of Fluoxetine in MES seizure model

Groups	Drugs / Dose	Tonic flexion of fore limbs	Tonic extension of hind limbs	Clonus	Stupor
1	Control (Propylene Glycol), 3 ml/kg i.p	3.80±0.837*	13.8 ±2.49*	9.80 ±1.48*	55.5 ±4.56*
2	Standard (Sodium Evaporate) 300 mg/kg, i.p	0.0±0.0***	0.0 ± 0.0***	0.0±0.0***	0.0 ± 0.0***
3	Fluoxetine 10 mg/kg, i.p	2.60±2.41*	13.4 ± 3.65*	9 ±1.58*	54.8±9.44*
4	Fluoxetine 20 mg/kg, i.p	0.80±1.79**	3.4 ±3.29**	4.6 ± 1.34**	22.8±5.93**
5	Fluoxetine 30 mg/kg, i.p	0.00 ± 0.00**	3.6 ±5.37**	11.0±2.92**	24 ± 4.98**

Observations are mean ±SD. Paired't' test and unpaired't' test for inter group comparisons. . ANOVA followed by post- hoc Tukey's test for group wise comparisons. *p>0.05- not significant, **p<0.05-significant, ***p<0.01-highly significant, i.p-intra-peritoneal

Discussion

Depression is becoming a growing problem in rural areas. This psychiatric disorder often accompanies epilepsy. Fluoxetine is used for the treatment of major depressive disorder (including pediatric depression), obsessive-compulsive disorder (in both adults and children), bulimia nervosa, panic disorder and premenstrual dysphoric disorder. In addition, fluoxetine is used to treat trichotillomania if cognitive behavior therapy has been unsuccessful.[7]

Our study showed anti-convulsant activity of Fluoxetine in the dose of 20 mg/kg and 30 mg/kg were shown to be similar, and this could imply that anti-convulsant activity of Fluoxetine attains ceiling effect at doses above 20 mg/kg which needs further evaluation. The results of the present study demonstrate that Fluoxetine could also be a potent and efficacious anticonvulsant drug as it has shown promising results in MES seizures. We considered only five animals per group as six per group would have been considered, but still in view of the promising results with Fluoxetine, the screening and evaluation of SSRI's as anti-convulsant may prove beneficial to the development of novel therapeutic approaches to treatment of epilepsy. However further studies are required by involving other animal models of epilepsy with appropriate sample size in order to arrive at a proper conclusion.

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