HYPEREXCITATION FROM FLUOXETINE USE IN RODENTS

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ABSTRACT

The aim of this study was to evaluate the hyper excitability caused by administration of Fluoxetine which is a highly prescribed antidepressant belonging to a Selective Serotonin Reuptake Inhibitor class. Behavioral activities were observed on Cage Crossing, Forced Swim Test, Open Field Test and Head Dip Test. These activities were observed on rodents after 60 days of oral Fluoxetine treatment and were compared with untreated control animals. The results clearly showed that Fluoxetine caused significant increase in number of head dips in head dip test, significant increase in number of cage crosses in cage crossing, significant increase in number of squares crossed in an open field apparatus and significant increase in struggling time in forced swim test. Thus overall results indicated hyper excitability in treated animals. Hence, outcomes suggest that Fluoxetine can lead to hyper excitation in behavior and produce anxiety and therefore strongly implies that Fluoxetine use may also require an anxiolytic drug to antagonize this hyper excitability.

Keywords: Hyper excitability, anxiety, rodents, anxiolytic

INTRODUCTION

Depression is a common mental illness affecting millions of people around the globe. Depression is a mental disorder and is expressed as different terms in the world; and also called a state of mind¹. It is related to the mood disorder of a person². If we do not give attention to depression then it can lead to serious condition which ends at suicide¹. Clinical depression has characteristics of unhappiness, rage, frustration which interferes with a person's daily life³. Even depression can affect one's daily activities. Fact shows that women suffer more from depression than men¹. There are several classes of drugs available for the treatment of depression. These include Selective Serotonin Reuptake Inhibitors (SSRI's) (Fluoxetine, Citalopram, Escitalopram, Fluvoxamine, Paroxetine, Sertraline), Serotonin/Nor epinephrine Reuptake Inhibitor (SNRI's) (Venlafaxine, Duloxetine), Atypical Antidepressant (Bupropion, Mirtazapine, Nefazodone, Trazodone), Tricyclic Antidepressant (TCA), (Amitriptyline, Nortriptyline, Clomipramine, Doxepin, Desipramine), Monoamine Oxidase Inhibitor (MAOI) (Phenelzine, Tranylcypromine)⁴. Selective serotonin reuptake inhibitor (SSRI) is a class of drugs used in the treatment of depression which was launched in late 1980's⁵. SSRI works by inhibiting the reuptake of a neurotransmitter, serotonin, from the synaptic gap after its release making it available for a longer time to produce post synaptic effect. This is beneficial in depressive patients as major depression is said to be caused by low level of the neurotransmitters in the brain, of which one is serotonin^{6,7}. Fluoxetine is an antidepressant belonging to Selective Serotonin Reuptake Inhibitor Class (SSRI's)⁸. Fluoxetine is one of the most widely prescribed antidepressant in the world for depression with efficient treatment outcomes⁹. It is an approved drug for major depression, panic disorder, compulsive disorder, bulimia nervosa¹⁰. It is metabolized to an active metabolite norfluoxetine through Cytochrome P450 enzyme CYP2D6. Fluoxetine and norfluoxetine both inhibit the enzyme CYP2D6 which is responsible for Fluoxetine metabolism resulting in a prolonged half life of the drug after first dose⁹. Half life of Fluoxetine is 1-3 days on acute administration while 4-6 days on chronic administration. Norfluoxetine, an

active metabolite of Fluoxetine has half life of 4-16 days. The dose of Fluoxetine must be adjusted in hepatic impairment because the elimination half life of Fluoxetine is prolonged in hepatic impairment¹¹. The adverse effects of Fluoxetine include stomach upset, sexual dysfunction, fatigue, headaches, tremor, agitation, vertigo, insomnia, anxiety, nervousness, nausea, diarrhea, anorexia, weakness, pharyngitis, agitation, amnesia, chills, confusion, tinnitus^{4,8,11}. Fluoxetine has a potential to interact with a number of other drugs because of its effect on body's pathway for drug metabolism^{10, 11}. In addition to strongly inhibiting enzyme CYP2D6, it also moderately inhibits enzyme CYP1A2 and CYP2C19¹¹. The current study was designed to evaluate the hyper excitation caused by Fluoxetine administration.

MATERIAL AND METHODS

Selection of Animal and Treatment

The present study was conducted on 20 male adult Wistar albino rats weighing from 150-200 grams. Animals bred locally in animal house of the Department of Pharmacology, University of Karachi. Animals were housed in specially designed cages as groups of 3 animals per cage. They were kept in 25±1 °C room temperature with 12:12 light and dark cycle. The rats were kept on standard rat diet and water ad libitum. Animals were handled according to specifications provided in Helsinki Resolution. The study was approved by University Board of Studies.

Experimental Protocol

The animals were divided into 2 groups of 10 animals each:

- Group I served as control
- Group II was treated with Fluoxetine, at oral dose of 20mg/60kg daily for 60 days

Group I was administered saline only orally while Group II was orally administered Fluoxetine for a period of 60 days. Effects on behavioral parameters were observed after 60 days of Fluoxetine treatment.

Behavioral Parameters

Cage Crossing

The control and treated rats were placed in a transparent cage separately for 10min so that they become familiar to the environment. Then rats were separately observed for 10 min in the cage for cage crossing.

Open Field Test

The open field used in this study was a square area of measurement 76cm length, 76 cm width and 42cm height. The floor of the field was divided into 25 equal squares. The control and treated rats were placed separately in the open field apparatus for a period of 10 minutes and counted the number of squares crossed.

Forced Swim Test

A glass cylinder was filled with water to the level more than the height of the rat so that the rat is forced to swimming. The control and treated rats were separately left in the water filled cylinder and their struggling time for swimming was observed until they started floating on water.

Head Dip Test

The control and treated animals were separately kept in an exploratory box having 16 equally spaced holes. The number of times the animals dipped their heads through the holes was noted for a period of 10 minutes.

Statistical Analysis

All results are expressed as mean value $\pm$ standard deviation. Statistical analysis is done using student t-test. P-values < 0.005 was considered highly significant, $< p0.05$ as more significant, $< p0.1$ as significant.

Table 1: Effects of Fluoxetine on Rats after 60 Days of Treatment

Groups	Head Dip Test (No. Of Head Dips)	
	Mean $\pm$ S.D	Student t-test
Group I	53.2 $\pm$ 4.131	*** $\leq$ p0.005
Group II	61.4 $\pm$ 3.657	
Groups	Cage Crossing (No. of Crossing)	
	Mean $\pm$ S.D	Student t-test
Group I	55.3 $\pm$ 4.73	** $\leq$ p0.05
Group II	59.5 $\pm$ 4.76	
Groups	Open Field Test (No. of Squares Crossed)	
	Mean $\pm$ S.D	Student t-test
Group I	169.4 $\pm$ 7.13	** $\leq$ p0.05
Group II	176.3 $\pm$ 6.97	
Groups	Forced Swim Test (Struggling Time in seconds)	
	Mean $\pm$ S.D	Student t-test
Group I	92.5 $\pm$ 2.549	* $\leq$ p0.1
Group II	94.5 $\pm$ 2.549	

Group I is control and Group II is Fluoxetine treated, n=10, Values are mean $\pm$ S.D, Significant differences by Student t-test *** $< p0.005$, ** $< p0.05$, * $< p0.1$ as compared to control rats

Figure 1: Effects of Fluoxetine on Open Field Activity Test in Rats

n=10, Average Value $\pm$ St. Dev

Significant difference, Student t-test ** $< p0.05$ as compared to control rats

Figure 2: Effects of Fluoxetine on Cage Crossing in Rats

n=10, Average Value $\pm$ St. Dev

Significant difference, Student t-test ** $< p0.05$ as compared to control rats

Figure 3: Effects of Fluoxetine on Head Dip Test in Rats

n=10, Average Value $\pm$ St. Dev

Significant difference, Student t-test, ***p<0.005 as compared to control rats

Figure 4: Effects of Fluoxetine on Forced Swim Test in Rats

n=10, Average Value $\pm$ St. Dev,

Significant difference, Student t-test, *p<0.1 as compared to control rats

RESULTS

In our present study we found that in open field test treated group clearly showed significant increase in number of squares crosses after 60 days of treatment with Fluoxetine as compared to control (table # 1, figure 1). Cage crossing showed that after the administration of Fluoxetine for 60 days, there is a significant increase in number of cage crossing in comparison with control (table # 1, figure 2). Treated rats showed significant increase in number of head dips in the head dip test as compared with control after 60 days of Fluoxetine treatment (table # 1, figure 3). The struggling time of rats in forced swim test showed significant increase in group treated with Fluoxetine after 60 days of treatment (table # 1, figure 4).

DISCUSSION

Fluoxetine is an antidepressant with high range of acceptability as an antidepressant. Since depression is a disorder which involves brain, a royal organ of the body, the drugs used for treating depression constantly needs to be evaluated from all sides.

Different behavioral tests were conducted in this study. Cage crossing was used for the analysis of locomotory activity and there was a significant increase in cage crossing of rats after 60 days of treatment. This increase in cage crossing suggests an anxiogenic effect of Fluoxetine. This anxiogenic effect may be attributed to increase activity of amygdala¹². Amygdala is an area of brain which has a key role in anxiety and fear¹³. Open field test is used for evaluating anxiety, locomotory and exploratory activity¹⁴. The finding from open field is also parallel to the finding of cage crossing. The number of squares crossed by the animals significantly increased in an open field after 60 days of Fluoxetine treatment. It may be due to glutamate involvement in addition to serotonin activity.

Research indicates that Fluoxetine in addition to increasing serotonin levels also increases glutamate levels¹². Glutamate is an excitatory neurotransmitter in the brain¹⁵. Head dip test is used to analyze exploratory behavior¹⁶. An increased frequency of head dips in head dipping test also indicated significant increase in exploratory and locomotory activity and also indicated restlessness in rats. Forced swim test is a good tool for analyzing antidepressants¹⁷. Forced swim test showed significant increase in struggling time of rats after which they started floating. This may indicate increased excitation of the animal which resulted in an increased struggling activity of treated rats. Fluoxetine is also said to increase levels of dopamine and norepinephrine¹⁸.

Therefore, Fluoxetine is a unique drug and is also distinguished from other members of its class. However, the above mentioned effect of hyper excitation by Fluoxetine on chronic administration needs to be evaluated further.

CONCLUSION

In this study, it is concluded that Fluoxetine caused excitation, restlessness and anxiety after 60 days of treatment. This strongly suggests that, Fluoxetine use may require an anxiolytic drug also in combination to antagonize this hyper excitability.

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