

To see the Gross Qualitative Parameters such as General Appearance of Rats and their testes after Long and Short Term Use of Sildenafil Citrate

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ABSTRACT

Objective: To see the gross qualitative parameters such as general appearance of rats and their testes after long and short term use of Sildenafil Citrate.

Background: As very little attention has been given to explore the effects of a sildenafil citrate on histological aspects of testes, hence this experimental study was designed to check whether the drug which is being used indiscriminately in our country and abroad is safe or it has any harmful effect on the architecture of rat testis.

Study design: Experimental Study

Place and Duration of Study: This study was conducted in departments of Anatomy & Histopathology Shaikh Zayed Hospital Lahore for a period of six weeks from 02.05.2008 to 17.06.2008.

Materials and Methods: Sample size consisted of 45 animals, divided into Group A (Control), Group B and C (Experimental), Each group was consisting of 15 animals. Physical examination of rats and their testis was done every day by the author himself and recorded.

Results: After giving drug, on inspection of rats all the animals were active and healthy and the gross appearance of the testes was normal except in an animal, in which the testes were smaller than the associates of the same group. Eating habits of all the animals were normal, taking food and water freely. After half an hour of giving the drug, they were mounting over each other and looked aggressive. The comparison of all the groups, A vs B, A vs C and B vs C remained statistically non-significant ($P > 0.05$).

Conclusion: No significant difference was observed in qualitative parameters (general appearance) of the rats and their testes after giving sildenafil citrate.

Key words: Sildenafil, testis, qualitative parameters.

INTRODUCTION

Impotence and infertility are the great social problems in some communities, regarded as disgrace, a mark of divine displeasure, and ground for divorce or even for compulsory suicide. Males are blamed to be impotent or infertile in some marriage failure cases, therefore in such an atmosphere, abuse of drugs is quite common. In a routine practice, sildenafil citrate is frequently and indiscriminately used to enhance the sexual orgasm by old age people and sportsmen¹. Infrequent use as an aphrodisiac and performance improving agent may cause harmful effects. Sildenafil citrate is prescribed in cases of erectile dysfunction and pulmonary hypertension but little attention so far has been paid to the indiscriminate and vigorous use of sildenafil handled by medical and paramedical staff, quacks and self-medicians. Although this misdirected therapy is practised for improving the impotence but as a matter of fact, it may result into maturation arrest of spermatozoa, or even toxic for spermatogonia as well². Erectile dysfunction (ED) is a world wide problem which may have significant negative impact on quality

of life with particular reference to psychological point of view³. Until recently, no effective oral therapy existed, the options present were highly difficult to perform, and majority of people found them unessay solution for a satisfactory response⁴. Ideal oral treatment for erectile dysfunction should have following features: easy administration with a reasonable short time prior to sexual activity, reliable efficacy, good tolerability within therapeutic range, high selectivity for the site of action, lack of side effect like CNS problems, that yields prompt onset of action and a plasma half-life that produces an appropriate duration of action while avoiding its accumulation in blood by its daily use⁵. Sildenafil citrate (Viagra) is the first oral agent introduced for treatment of ED, meets this strict criteria. It is rapidly absorbed and acts within 30 minutes to 1 hour, it has a short plasma half-life of approximately 4 hours; and it is well tolerated in the dosage range studied with no clinically appreciable effects on heart rate or blood pressure.⁶⁻⁸ In clinical trials, single oral doses, of sildenafil have shown effectiveness in the treatment of ED of organic, psychogenic or mixed etiologies.^{7,9-10}

The effects of sildenafil citrate have also been observed on eyes, such as bovine retinas were isolated and perfused for the purpose to understand the physiology of sildenafil on retina with a low and a high concentration, higher concentrations were found to be potential for retinal degeneration¹¹. In rats prolong use demonstrated the dilation and congestion of choroidal vasculature¹². But it has no role to cause any significant changes in foveolar choroidal circulation of age related macular degeneration patients¹³. Sildenafil on human retinal blood flow, have showed increased retinal venous diameters and retinal blood flow with out causing rise in intra ocular pressure¹⁴. As this drug is phospho diesterase enzyme (PDE) inhibitor, PDE-5 in addition to PDE-6 enzyme localizations on human retina have been confirmed¹⁵. But it has also been reported that erectile dysfunction agents including sildenafil citrate had a causative effect on non –arteritic anterior ischemic optic neuropathy¹⁶⁻²². In animals, prolong use of sildenafil with mild doses twice daily have reduced myocardial infarction. Myocardial infarction was induced by the ligation of left anterior descending coronary artery²³. Its protective role against ischemia of heart in mice is also proved²⁴.

In view of above facts we designed this study to see the gross qualitative parameters such as general appearance of rats and their testes after long and short term use of sildenafil citrate.

MATERIALS AND METHODS

Three groups A,B & C each consisting upon fifteen male adult albino rats of wistar strain weighing 250-300 g were used for this experimental study. The study was conducted in the departments of Anatomy and Histopathology at Shaikh Zayed Federal Post graduate Medical Institute Lahore. The animals were assessed for their sexual maturity on the basis of following criteria.

1. Random fighting and aggressive behavior.
2. Bucking i.c attempt to mount.
3. Free hanging of testes in the scrotal sacs.

This study was carried out over the period of six weeks on 45 animals. Two weeks were given for acclimatization and to check the state of health on the basis of weight gain or loss and four weeks for experiment. All the rats were numbered with a permanent marker and divided randomly into three groups, group A as control, group B & C as experimental, each group comprised of 15 rats. Drug was purchased from Al-Towar Pharmacy, Hor Al Anz, DUBAI, UAE and the expenses were borne by the author himself.

Group A (Control) did not receive drug, while in group B (Experimental) each animal was given sildenafil citrate in a dose of 8 mg /kg orally after dilution with water on alternate days for four weeks i.e total 14 doses. In group C (experimental) each animal was given sildenafil citrate in a dose of 8 mg/ kg orally after dilution with water once a week for four weeks i.e total 4 doses.

Assessment of animals was done by the author every day for a period of four weeks, to exclude any general ailment by their physical activity, eating behavior and general appearance. Gross appearance of testes was also examined for any obvious abnormality.

This study was permitted by Ethical review board of federal post graduate medical institute of Shaikh Zayed Medical Complex Lahore.

RESULTS

The qualitative parameters were.

1. **Gross appearance of albino rats before dissection:** Animals of all the groups were active and healthy looking through out the period of experiment. Eating habits of all animals were normal and they were taking food and water freely. They were active and representing no sign of ailment. Therefore this parameter statistically remained constant as shown in table 1, after half an hour of giving the drug, they were observed to be mounting over each other and looked aggressive.

Table No.1: Comparison of gross qualitative parameters in the rats of control group A (unexposed) and experimental groups B and C (exposed) to sildenafil

Parameters	Groups						Chi-square	P-Value
	A (n=15)		B (n=15)		C (n=15)			
	N (ab)	%	N (ab)	%	N (ab)	%		
Gross appearance of albino rats before dissection	0	0.00	0	0.00	0	0.00	0.000	1.00 ⁺⁺
Gross Appearance of testes after dissection	0	0.00	1	6.70	0	0.00	2.05	0.360 ⁺⁺

Key: N(ab) : Number of animals with abnormality, n : Number of animals in each group
⁺⁺ Non-significant difference (P>0.05)

Table No. 2: Comparison of gross appearance of testes, in the rats of control group A (unexposed) and experimental groups B and C (exposed) sildenafil

Groups	Group compared	Chi square	P value
A	B	1.034	0.309 ⁺⁺
	C	0.000	1.000 ⁺⁺
B	C	1.034	0.309 ⁺⁺

Key:

A : Control group B : Experimental group

C : Experimental group

++Indicate non significant difference (P>0.05)

- 2. Gross appearance of testis after dissection:** The gross appearance of testes of group B were also normal in all aspects except in one animal (6.7%) as shown in Table -1, in which the testes were looking relatively smaller and seemed to be atrophied. Seminiferous tubules were not easily plucked out from the testes of that animal and stringing out phenomena was also found decreased. The gross appearance of testes of experimental group C was also normal as seen in Table-1. Both the phenomena stringing and plucking out were normal. The comparison of all groups, A vs B, A vs C and B vs C revealed statistically non – significant difference (P>0.05) Table -2.

DISCUSSION

Since none of the study is available in literature regarding morphological changes in testis of albino rats after giving sildenafil citrate therefore it is almost impossible to relate this study with others. However we were able to find atrophic changes in testis of one of the rats, it is just possible that if the sample size is made larger we may be able to confirm or exclude atrophic changes noted in one of our experimental animal.

There is possibility that this may have happened by chance, as a result of over sight by the author or it may be the result of some sort of infection which may have caused atrophic changes in the testes of albino rat but not manifested on gross general appearance of rats and their testes. But we can not be sure of anything until we do this study taking a large sample size and done at multiple centers to remove the individual bias or occurrence by chance. The smallness in size of testis that we found in one of the rats may be found in other organs of animals after giving this drug and this may have implications in turn over human organs as well. We observed a significant finding that when rats were given sildenafil citrate, after half an hour they were mounting over each other and looked aggressive their by indicating sexual behavioral changes which is in agreement with the findings of study done by Eardley I⁶.

CONCLUSION

No satisfactory significant difference was observed in the gross qualitative parameters of rats and their testes after long and short term use of sildenafil citrate.

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