ORIGI NAL ARTICLE

Effects of Escitalopram and Citalopram on Histology of Testicular Tissue in Wistar Albino Rats

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ABSTRACT

Aim: To determine the comparative effects of Escitalopram and citalopram on and testicular histology.
Methods: This quasi experimental study was conducted during 10 weeks in the Department of Pharmacology Isra University Hyderabad with the cooperation of Animal House, Sindh Agricultural University Tando Jam. Normal and healthy rats with weight of 200-300 grams were studied. Total 50 albino rats were divided into the 5 groups.Group A animals were given normal chow diet ad libitum. Groups B and E animals underwent Escitalopram 0.4mg/kg orally for 6 weeks. Groups C and D were given citalopram 0.8mg/kg for 6 weeks. The drugs were administered orally. After 6 weeks, testes of groups A, B and Canimals were removed andin Groups D and E drugs were stopped for 4 weeks and then testes were removed by same procedures in order to see either the effects of drugs are reversible or not.
Results: In this study mean weight of tastes in group B and Group C were decreased as compared to control group and reversal group D and group E, while findings were statistically insignificant, p-value 0.092.Decreased spermatogenesis and sertoli cell hyperplasia was found in 5 and 4 rates of experimental group B and group C respectively, which were improved in 3 albino rates of D and 3 albino rates of group E.
Conclusion:Escitalopram and Citalopram both have harmful effects on testicular weight and histology, while after withdrawal of these drugs these harmful effects may be cured.
Keywords: SSRIs, Escitalopram, Citalopram, Testicular Histology.

INTRODUCTION

One third of infertile couples may have male factors present.Drugs used may be the important cause of infertility in men and these drugs include anabolic androgenic steroids, marijuana, opioid narcotics, cocaine and methamphetamine. Other causes of infertility are hormonal deficits, morphological alteration of gonads, abnormal spermatogenesis and psychological factors[1]. Depression is a common chronic recurrent mood disorder that influences both economic and social functions worldwide.[2] Depression is observed more frequently at reproductive ages[2]. Infertility and problems related to it are one of the most vital issues in the life of couples. By statistics, male infertility represents about 35% of infertilities. Drugs have been reported to play a role in the etiology of male infertility. Fluoxetine is one of the selective serotonin reuptake inhibitor drugs (SSRI) used in neurological disorder treatment such as depression, bulimia nervosa, and obsessive-compulsive disorder[2,3]. Oxidative stress is the disturbance in balance in the production of the antioxidant defenses and reactive oxygen species (ROS), which maydamage the DNA, proteins, and the lipids, ultimately leading to the apoptosis or necrosis in the living cells. Many factors caused oxidative stress, as well as drugs. In fact, maximum knowledge regarding antidepressants drugs has been gained from studies on fluoxetine which reported that this drug caused significant structural alteration of testicular tissue and sex hormones among male rats.[5]In another study effect of fluoxetine on male fertility was studied by some authors. Administration of fluoxetine caused a decrease in spermatogenesis and weights of reproductive organs.[4]To the best of knowledge, there are only few studies present on escitalopram and citalopram effects on testicular tissue but no work has been done in Pakistan regarding SSRI effects on testis and testicular histology as well as there is no any study for the comparative effects of escitalopram and citalopram on testicular tissue. Our study explores and compares the effects of the two antidepressants and clarifies the superiority of any one of them on other as there is a big difference between the dosages of the two agents. Citalopram is used as 20-60mg, while its enantiomer escitalopram is used as 10-30mg as once daily dosage[6]. This study will also help in the differential diagnosis of altered semen parameters.

Received on 14-05-2019
Accepted on 15-10-2019

MATERIAL AND METHODS

This Quasi Experimental Study, conducted during 10 weeks in the Department of Pharmacology Isra University Hyderabad/ Animal House, Sindh Agricultural University Tando Jam. All normal, healthy rats with weight of 200-300 gm were included in the study. All those diseased rats with weight of <200g were excluded in the study. Total 50 albino rats were divided into the 5 groups
Group A: Control

Group B: Escitalopram0.4mg/kg P.O
Group C: Citalopram 0.8/kg P.O
Group D: Reversal group of citalopram
Group E: Reversal group of escitalopram

Data collectionprocedure: Rats were placed in the separate cages having the access to tap water and chow ad libitum. Drugs were purchased from local pharmacy and were grinded and diluted in distilled water.

Group Aanimals were given normal chow diet ad libitum.Groups B and E animals underwent escitalopram 0.4mg/kg orally for 6 weeks. Groups C and D were given citalopram0.8mg/kg for 6 weeks and then for 4 weeks given normal diet without drugs. The drugs were administered by oral gavage.

After 6 weeks, testes wereremoved after cervical dislocation of groups A,B and C. Epididymis was separated and transferred to petri dish and macerated to have anepididymal suspension. After 6 weeks drugs of Groups D and E were stopped for 4 weeks. Then the testes of group D and E wereremoved after 4 weeks and same proceduresware repeated in order to see the effects of drugs are reversible or not.

The process of slide preparation was carried out and tissues were extracted by animal surgeon in Tando Jam. For histological slide preparation testes were extracted out and fixed in 10% formalin. Then the tissues were passed in ascending grades of ethyl alcohol as 70%, 80%, and 95 % respectively. After this it was passed in Xylene for clearing. Once the clearing process was done, it was embedded in paraffin wax and hardened blocks were obtained.

Further the blocks were cut by a microtome at 4 micron sections, Slides were put on hot plate for proper fixation which were further stained with Hematoxylin and Eosin dye. And finally the slides were observed under light microscope for histopathological assessment. After the collection of data the analysis was conducted by using SPSS Vr 21. ANOVA and student t-test were used to evaluate statistical significance by taking p-value <0.05 as significant.

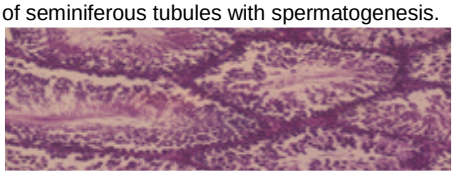
RESULTS

In this study mean tastes weight of group B and Group C were decreased as compared to control group and reversal group D and group E, while findings were statistically insignificant, p-values were quite insignificant (Table 1). According to the histopathology, decreased spermatogenesis and sertoli cell hyperplasia was found in 5 and 4 experimental group B and group C respectively. Though after 4 weeks of withdraw treatment, decreased spermatogenesis and sertoli cell hyperplasia were improved as 2 albino rates of D and 2 albino rates of group E showed decreased spermatogenesis and sertoli cell hyperplasia (Fig.1-5)

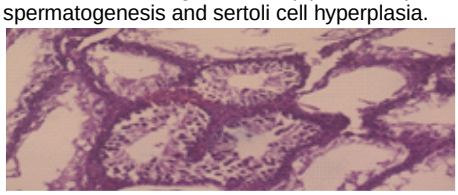
Table1: Mean testes weight(gms comparison amongstudy groups

Groups	Testes weight		p-value
A vs B	2.10±0.29	1.80±0.22	0.187
A vs C	2.10±0.29	1.60±0.27	0.099
A vs D	2.10±0.29	1.90±0.31	0.874
A vs E	2.10±0.29	2.05±0.19	0.936

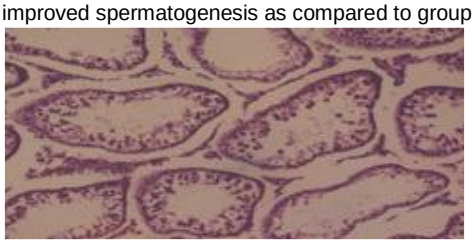
Photomicrograph 1: Testicular sections stained with hematoxylin and eosin showing at 100X: (A) control group, normal architecture of seminiferous tubules with spermatogenesis.



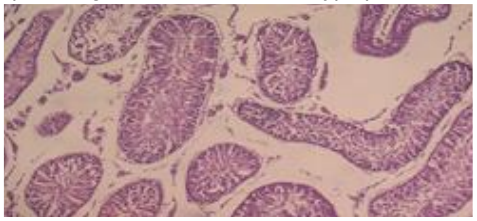
Photomicrograph 2: Testicular sections stained with hematoxylin and eosin showing at 100X:(B) Escitalopram group, decreased spermatogenesis and sertoli cell hyperplasia.



Photomicrograph3: Testicular sections stained with hematoxylin and eosin showing at 100X: (E) Escitalopram reversal group, improved spermatogenesis as compared to group B.



Photomicrograph 4: Testicular sections stained with hematoxylin and eosin showing at 100X: (C) Citalopram group, decreased spermatogenesis and sertoli cell hyperplasia**.**



Photomicrograph 5: Testicular sections stained with hematoxylin and eosin showing at 100X: (D) Citalopram reversal group, improved spermatogenesis as compared to group C.

DISCUSSION

This study evaluated the main variables of male infertility by estimating and comparing testicular histology in controls and intervention receiving rats, as both the SSRI's had a negative effect on testicular histology. However, escitalopram was found to be more toxic as compared to citalopram. In this study both the SSRI's decreased spermatogenesis and developed the sertoli cell

hyperplasia. Ilgin S et al (2017) conducted a study on effects of citalopram on semen parameters and testicular histology in rats, and theyreported that the degenerative changes in seminiferous tubules and decreased spermatogenesis on histological examination. The present study is consistent with above study[7]. AAA Galal et al (2016) reported that SSRIs distorted seminiferous tubules on histological examination[8]. Erdemir F et al (2014) observed the effects of different SSRIs on testicular tissue and found SSRIs have an adverse effect on testicular histology[9]. In the study conducted by Aggarwal et al (2012) the effects of Fluoxetine on testicular histology were observed in which it was found that there was distortion of seminiferous tubules as well as a decrease in the diameter of seminiferous tubules. Such findings were also observed in the current study in which SSRI use caused significant damage to the testicular histology[10]. In a similar study by Soliman et al (2017) the effects of SSRI's on testicular histology were observed. It was found that SSRI's altered the normal testicular architecture as it caused distortion and degeneration of seminiferous tubules, cellular disorganization and congestion. However, these findings were reversed after discontinuation of SSRI therapy. These findings were also observed in the current study in which SSRI use caused significant damage to the testicular histology which were reversed in the reversal groups[11].

In this study testicular weight was decreased in experimental group b and c as compared to control group. Similarly Soliman ME etal[2] reported that fluoxetine-treated rats showed a highly significant decrease of body and testis weight (P<0.001). Fluoxetine led to distortion of seminiferous tubules, germ cell degeneration with sloughing, and vacuolation. Many authors explained the mechanism by which fluoxetine induces testicular tissues toxicity. Inkielewicz-Stępniaket al[12]showed that fluoxetine induces lipid peroxidation leading to free-radical release, which causes membrane disorganization and subsequent decreases in membrane fluidity, and finally extensive tissue damage. Recently, Atli et al[13] proved that SSRIs induce DNA fragmentation and reactive oxygen species overproduction, as a result of oxidative stress, which induces cell damage in male rat's reproductive organs. Cytoplasmic vacuolation and degeneration might be considered an indication of cell necrosis. According to Manivannan et al[14] vacuolations of germ cells could be a result of metabolic disturbance in these cells with a subsequent change in their morphology.

CONCLUSION

It was concluded that after consumption of Escitalopram and Citalopram decreased testicular weight, decreased spermatogenesis and sertoli cell hyperplasia were developed. Fortunately by withdrawal of these drugs, the harmful effects may be improved. The subjects that are trying to conceive should be prescribed alternative therapies (SNRIs, TCA and Atypical Antidepressant). Further studies are recommended to find the exact mechanism responsible for these effects by measuring FSH, Testosterone , Prolactin , Gonadotropin releasing hormone as well as some oxidative stress assessment is also recommended

REFERENCES

1. Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. Journal of andrology. 2012 Jul 8;33(4):515-28
2. Soliman ME, Mahmoud BL, Kefafy MA, Yassien RI, El-Roghy ES. Effect of antidepressant drug (fluoxetine) on the testes of adult male albino rats and the possible protective role of omega-3. Menoufia Med J 2017;30:1135-42
3. Jalili T, Khaki A, Ghanbari Z, Imani AM, Hatefi F. A Study of the therapeutic effects of vitamin e on testicular tissue damage caused by fluoxetine use. Crescent J Med and BiolSci 2014; 1:37-41.
4. Sakr SA, Mahran HA, El-Deeb MM. Ameliorative effect of curcumin on fluoxetine-induced reproductive toxicity and oxidative stress in male albino rats. OxidAntioxid Med Sci2013; 2:29–35.
5. Csoka AB, Bahrick A, Mehtonen OP. Persistent sexual dysfunction after discontinuation ofselective serotonin reuptake inhibitors. J Sex Med 2008; 5: 227-33.
6. Katzung BG, Masters SB, Trevor AJ, editors. Basic & clinical pharmacology. New York: Lange Medical Books/McGraw-Hill; 2004 Jan 5
7. Ilgin S, Kilic G, Baysal M, Kilic V, Korkut B, Ucarcan S, Atli O. Citalopram induces reproductive toxicity in male rats. Birth defects research. 2017 Apr 17;109(7):475-85..
8. Galal AA, Alam RT, Abd El-Aziz RM. Adverse effects of long-term administration of fluvoxamine on haematology, blood biochemistry and fertility in male albino rats: a possible effect of cessation. Andrologia. 2016 Nov;48(9):1002-10.
9. Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, Sogut E. The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. International braz j urol. 2014 Feb;40(1):100-8.
10. Aggarwal A, Jethani SL, Rohatgi RK, Kalra J. Effects of fluoxetine on testis of albino rats–a histological assessment. Int. J. Sci. Eng. Res.. 2012;3:1-5.
11. Soliman ME, Mahmoud BL, Kefafy MA, Yassien RI, El-Roghy ES. Effect of antidepressant drug (fluoxetine) on the testes of adult male albino rats and the possible protective role of omega-3. Menoufia Medical Journal. 2017 Oct 1;30(4):1135.
12. Atli O, Baysal M, Aydogan-Kilic G, Kilic V, Ucarcan S, Karaduman B, Ilgin S. Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. Asian journal of andrology. 2017 Nov;19(6):672.
13. Inkielewicz-Stępniak I. Impact of fluoxetine on liver damage in rats. Pharmacol Rep J 2011; **63**:441–447
14. Manivannan B, Mitta R, Goyal S, Ansari AS, lohiya NK. Sperm characteristics and ultrastructure of testes rats after long treatment with the methanol subfraction of carica papaya seeds. Asian J Androl 2009; **11**:583–599.