RESEARCH ARTICLE

Effect of Some Psychotic Drug Quetiapine on Reproductive System Activity in Male Rats

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ABSTRACT

Aim of study: To investigate the effects of antipsychotic medications utilized to treat schizophrenic patients and its effects on the reproductive system.

Introduction: Antipsychotics, anticonvulsants, and other all psychotropic drugs have negative effects on the quality of sperm and sexual activity. These negative side effects differ amongst males and its less severe for some drugs, enabling some degree of control over their effects. Sperm can suffer oxidative damage from spending too much time in the male reproductive system. One of the antipsychotics most frequently administered to treat schizophrenia in adults is quetiapine. In this work, the effects of repeated rats' healthy production of sperm in response to therapeutic doses of quetiapine was studied. Rats were also used to assess quetiapine's effects on hormonal balance and oxidative state.

Methodology: The experiment employed male wistar rats weighing 300 to 350 g at 10 to 12 weeks of age. The experiment employed male wistar rats weighing 300 to 350 g at 10 to 12 weeks of age. Rats received oral dosages of quetiapine for 30 days. At this time's conclusion, the body's weights and the organs were analyzed, additionally to sperm concentration, motility, shape, and degree of sperm damage. The levels of testosterone, LH, and other male hormones related to reproduction were measured in the serum. Malondialdehyde and glutathione levels were measured to assess the oxidative state of testicular tissues.

Results: The results of this investigation demonstrated that in rats receiving quetiapine, aberrant sperm morphology increased while relative epididymis weights and sperm concentration dropped. Rats receiving quetiapine experienced a drop in serum LH and testosterone levels. Rats receiving quetiapine also had lower amounts of malondialdehyde, which was assessed.

Conclusion: Quetiapine therapy this negative effect may be attributed to lower sperm quality, changed hormone levels, and enhanced oxidative stress.

Keywords: Qutiapine therapy**,** Luteinizing hormone, Follicle-stimulating hormone, Oxidative stress.

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INTRODUCTION

Due to an increase in the prevalence of psychiatric illnesses, psychoactive substance usage has grown.[1] The most popular psychoactive medicines that are prescribed and utilized are antidepressants, antipsychotics, and mood stabilizers.[2] These medications could lead to sexual dysfunction in men, including diminished libido, erectile dysfunction, and delayed ejaculation.[3]

Antipsychotic medications are used to treat bipolar disorder's manic episodes and schizophrenia, a chronic condition that affects 21 million individuals internationally.[4] Atypical antipsychotics, the second generation of these medications, have more positive adverse effect profile while classic antipsychotics typically have more negative side effects.[5] The key indications of male infertility are environmental toxins, occupational exposures, and drug-related unfavorable reproductive consequences.[6] One hundred and eighty-six million people worldwide suffer from infertility, and 50% of those cases are due to male factors.[7] The male reproductive system is known to be a target of drug toxicity, and antipsychotic drug use frequently can interfere with spermatogenesis, sexual function, and epididymal maturation in men by altering hormones of the hypothalamic-pituitary and gonadal axis or by acting through non-hormonal mechanisms.[8] The other aspect of reproductive toxicity, which is their impact on normal sperm production and fertility, is less well

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understood. Recent research indicates that psychoactive substances lower male reproductive potential and sperm quality.[9] Because it reduces central dopaminergic activity, the atypical antipsychotic medication quetiapine is used to treat schizophrenia and bipolar disorders.[10] Dopamine D1, D2, 5-HT2, alpha1-adrenoceptor, and histamine 1 receptors are all blocked by QET. In the treatment of schizophrenia, blocking the dopamine D2 receptor in the mesocortical and mesolimbic pathways is recommended. Additionally, it is hypothesized that the anxiolytic and antidepressant effects of the drugs quetiapine and its active metabolite norquetiapine are caused by their respective partial agonist activities at the 5 HT1A receptor and norepinephrine transporter, respectively.[11]

The current study sought to examine any potential harmful effects on reproduction that QET in male rats at multiple pharmacologic dosages. Sperm damage was assessed, as well as sperm level, mobility, and appearance., and testicular tissue underwent histological analysis for this reason. In order to investigate various mechanisms that contributed to unfavorable reproductive effects, Serum levels of testosterone, which is crucial for spermatogenesis, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the oxidative state of testicular tissue, which is very sensitive to oxidative stress, were examined.

MATERIALS AND METHODS

IE Ulagay-Menarini Group (Turkey) supplied QET. The Sigma-Aldrich Corporation in Missouri, United States, provided the urethane used for anesthesia.

Oxidative Stress Parameters

- Glutathione (GSH).
- malondialdehyde (MDA).
- catalase (CAT).
- superoxide dismutase (SOD).

Hormonal Parameters

- FSH
- Testosterone
- LH.

The study employed male wister rodents, 10 to 12 weeks old, weighing 300 to 350 g. Rodents were kept in accordance with the Guide for the Care and Use of Laboratory Animals after being received from the AL-Kufa University Research Center for Animal Experiments.

Experimental Design

- Control group (N.9): DW orally for 30 days.
- Group 2 (N. 9): Receives 5 mg per kg of psychotic drug (quetiapine) orally for 20 days.
- Group 3 (N.9): 10 mg per kg of psychotic drug orally for 28 days.

Hormonal and Oxidative Stress Parameters Analysis

The blood was collected by cardiac puncture after that centrifuged at 2000 rpm for 10 minutes, where all parameters were measured by commercially available kits using *BIORAD* biosystem.

Sperm Analysis

After rats were put to sleep, sperm were extracted from the cauda of the right epididymis. The cauda epididymis was cleansed of blood vessels and adipose tissue before being placed in a petri plate with DMEM/Hams F-12 at 37°C. Sperm were allowed to swim out of the tissue for 1-minute after about 0.5 cm of the cauda epididymis was excised and placed in another petri dish with 1-mL of the same media (Figure 1).

Statistical Analysis

Data were presented as the mean ± standard Deviation using SPSS software.

RESULTS AND DISCUSSION

Over the course of the 28 days, neither the administered group of QET nor the control group experienced any aberrant reactions. Throughout the course of the investigation, All of the rats behaved and looked the same. The harmful effects of QET dosages on rat reproduction were examined in our investigation. Sperm concentrations were considerably lower in the QET-administered group than in the control group, as seen in Figure 2. Between the groups that had QET administration, there were no notable changes. Sperm motility did not differ significantly between the control and QET groups. Sperm quality is thought to be mostly determined by factors like sperm concentration, motility, and morphology (Figure 3).[12] Studies on fertile populations were used to determine the reference levels for parameters of sperm, such as shape, motility, and concentration, listed in the WHO guide. In our investigation, QET treatment led to a dose-dependent drop in sperm concentration and an increase in aberrant sperm morphology. The correlation between fertility and sperm count and morphology has been shown to be favorable in those with sperm counts >106/mg cauda and aberrant morphology rates >16%, respectively.[13] Sperm concentration was measured in our research and morphological changes above the previously specified criteria were caused by QET.

Table 1 display that there were significant reduced levels of serum FSH among the groups. However, the blood LH levels in the 5 and 10 mg/kg QET groups markedly dropped compared to those in the control group. The 5 and 10 mg/kg QET groups saw significantly lower serum testosterone levels than the control group. Variations may hamper spermatogenesis in reproductive hormone levels. It should be mentioned at this point that hormone imbalances are one of the main reasons for unfavorable reproductive outcomes. Neurotransmitters secreted from the hypothalamus influence the process of hormone generation and release in the hypothalamus and pituitary,[14] for the neuroendocrine regulation of sexual behavior, which is dependent on coordinated neurotransmitters are essential for the flow of the various brain and hormonal impulses.[15] Consequently, it may be claimed that altered central the dopaminergic system the dopaminergic system the dopaminergic system brought on by QET treatment may result in lower levels of LH and testosterone. Our findings suggest that changes in sperm quality are related to variations

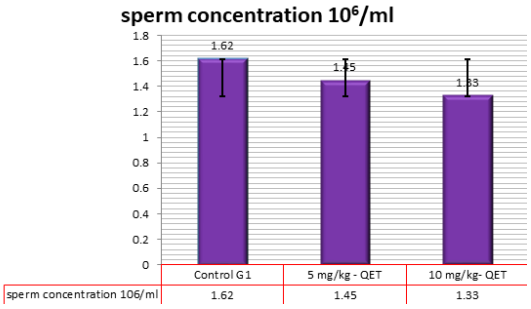

Figure 1: Sperm concentration (10^6/mL) among QET-treated groups

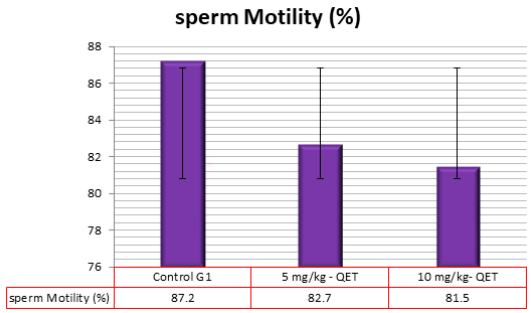

Figure 2: sperm motility (%) among QET-treated groups

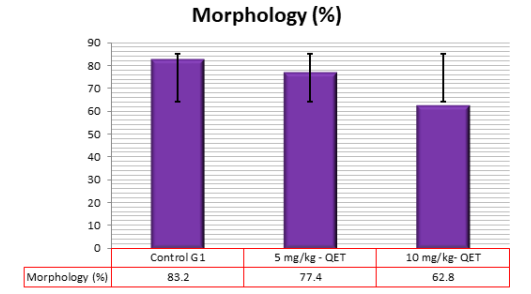

Figure 3: sperm Morphology (%) among QET treated groups

Table 1: The Serum concentration levels of administered rats hormones

Group	FSH(IU/L).	LH(mIU/mL).	Testosterone(pg/mL).
DW Control	24.5 ± 2.3	14.86 ± 0.87	613.8 ± 85.9
5 mg/kg - QET	21.7 ± 2.60	12.22 ± 1.60	459.16 ± 58.8
10 mg/kg- QET	19.06 ± 1.8	12.14 ± 1.51	445.54 ± 79.62
p-value	< 0.05	< 0.05	<0.001

Abbreviation Definition: 5 mg/kg – QET:Quetiapin drug administer rat for28 days, 10 mg/kg-QET drug administered rats for 28 days, as mean ± standard Deviation used for Results and ($p < 0.05$) .

in LH and testosterone levels. Additionally, both cerebral and peripheral concentrations of serotonin are altered by QET.[16] The receptors for serotonin cohabit with receptors for LH and assist LH in binding to cells, increasing the amount of testosterone produced by Leydig cells. Additionally, it has been demonstrated that spermatogenesis is regulated by serotonin receptors present in sertoli cells. Rat sperm, spermatogenic cell, and testis all have dopamine receptors, which may indicate dopamine impacts several spermatogenic cell traits during spermatogenesis.[17]

Table 2: The Serum concentration levels of administered rats oxidative stress

Group	CAT(ng/mL).	GSH(ng/mL).	MDA(mcg/mL).
DW Control	120.59 ± 8.94	432.45 ± 24.99	9.69 ± 0.48
5 mg/kg - QET	117.75 ± 16.33	381.54 ± 89.66	9.08 ± 0.75
10 mg/kg- QET	113.74 ± 23.58	332.40 ± 62.42	10.02 ± 1.03
p-value	$0.05>^{NS}$	0.05<	0.05^{NS}

Abbreviations Definition: 5 mg/kg – QET: Quetiapin drug administered rat for 28 days, 10 mg/kg- QET:Quetiapin drug administered rats for 28 days, as mean ± standard Error used for Results and ($p < 0.05$).

According to Table 2, administering QET significantly decreased CAT activity compared to the control. However, there were no appreciable variations in CAT activities between the groups that received the QET administration. On the other hand, GSH levels varied significantly across the control and QET groups. Additionally, there were no discernible variations in MDA levels between the control and QET.

According to earlier research, oxidative stress can have an impact on sperm quality.[18] Additionally, it has been noted that Leydig cell steroidogenesis and the capacity of the epithelium of germinal cells to differentiate healthy sperm, specifically, are subject to oxidative stress.[19] According to our research, oxidative stress is responsible for the rise in aberrant sperm shape and reduction in sperm concentration. After QET treatment, is marked by reduced GSH and CAT activity and increased MDA levels. Additionally, cellular parts of the tissue may be disturbed by testicular oxidative damage, causing structural changes.[20]

Reactive oxygen species (ROS) were shown to rise by 25% in infertile males. Normal sperm function requires lower ROS levels, whereas higher sperm ROS levels result in abnormalities in spermatozoa and malfunction of the sperm.[21] Because of the membrane of the sperm cell increased concentration of unsaturated fatty acid and the cytoplasm's low concentration of ROS-neutralizing enzymes, it is known that spermatozoa are vulnerable to ROS.[22] Lipid oxidation may result in DNA damage, cell death, loss of cell membrane integrity, a rise in permeability of the membranes, and the inactivation of cellular enzymes. As a result, there may be a rise in abnormal sperm morphology, reduced number of sperm, activity, and mobility.[23]

During our research, oxidatives stress shown by the drop in GSH levels in the groups receiving QET. ROS may change the antioxidant defense mechanisms by lowering GSH levels.[24] In earlier research, adult male rats exposed to oxidative stress had significantly higher levels of lipid peroxidation and lower GSH levels.[25]

CONCLUSION

The antipsychotic medications used to treat schizophrenia either have a direct negative affect on hormone regulation or perhaps lead to problems with sexuality, sperm production process disruption and epididymis development instability, leading to deleterious effects on reproduction. However, the findings of this study demonstrated that QET reduced the

morphology of healthy sperm and caused toxicity in the testes tissue in a dose-dependent manner

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