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Study Of Changes In Quantitative And Anatomical Parameters Of Offspring After Chronic Administration Of Haloperidol And Clozapine To Female White Rats

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I. Introduction

A mentally healthy state is one of the important conditions for a person to take a place in society and engage in normal life activities. Mental health refers to a person's ability to effectively use their potential, cope with the stresses of life, work productively and contribute to society. According to WHO, every fourth person in the world suffers from psychological and neurological disorders at certain periods of life [8]. About 10-15% of young people suffering from mental illness resort to professional help to return to normal life. These young people also experience complications of mental disorders during pregnancy and family planning [9, 10].

In modern times, the increase in the number of mental illnesses is observed to a greater extent among young married couples, especially among pregnant women. From 10% to 79.3% of pregnant women have mild mental disorders [9, 10].

Many scientists note that women taking antipsychotics have a high incidence of certain complications during pregnancy and childbirth, pregnancy ends in complications, and children are born with defects [3, 4, 7]. Considering all this, we set out to study changes in quantitative and anatomical parameters of offspring born during chronic administration of haloperidol and clozapine to female white rats.

II. Materials And Methods

Materials and methods of research. The studies were used 90 white rats of both sexes weighing 180-200 g, raised in the vivarium of the Research Center of the Azerbaijan Medical University.

The animals were divided into 5 groups, each group consisted of 12 male rats and 6 female rats. In the first control group, males and females were chronically injected with saline solution; in the second group, animals were chronically administered haloperidol (Germany) at a dose of 0.5 mg/kg; the third group chronically received haloperidol at a dose of 3 mg/kg; group 4 was chronically administered clozapine at a dose of 10 mg/kg; group 5 received chronic clozapine at a dose of 20 mg/kg. In all groups, males and females were kept together until fertilization. The onset of pregnancy was assessed by the detection of sperm in vaginal smears of females.

Pregnant female rats were monitored; the course of pregnancy and assessment of born offspring was carried out by visual observation. When conducting scientific research, the rules of the European Parliament and the European Union for the Protection of Animals were observed [6].

To calculate the experimental data, the Student's t-test and the nonparametric Wilcoxon-Mann-Whitney U-test were used. The results were processed using the statistical program Microsoft Excel (Office-2010).

III. The Obtained Results And Their Discussion.

Analyzing the results of the studies, we came to the conclusion that, with chronic use of the classic representative of typical antipsychotics haloperidol in doses of 0.5 mg/kg and 3 mg/kg, and the main representative of atypical antipsychotics clozapine in doses of 10 and 20 mg/kg, There are significant changes in the indicators of the onset, course and completion of pregnancy, and the course of labor in experimental animals. The birth weight of the offspring of rats chronically exposed to these drugs was much lower compared to the control group.

Regarding the number and anatomical indicators of offspring born from females on background of chronic administration of haloperidol and clozapine, it was found that the number of offspring born from females on the background of chronic administration of haloperidol at a dose of 0.5 mg/kg statistically significantly

decreased by 31.9% according to compared with the control group ($p<0.001$). The number of offspring in rats that were chronically administered 3 mg/kg of haloperidol was significantly different compared to the control group by 53.5% ($p<0.001$). Although the number of pups born to rats after chronic administration of clozapine at a dose of 10 mg/kg was 21.6% less than in the control group, it was statistically significantly higher by 10.3% than in the group receiving dose 0.5 mg/kg of haloperidol and 31.9% more compared to the group receiving haloperidol at a dose of 3 mg/kg ($p>0.05$). With chronic administration of clozapine at a dose of 20 mg/kg, the number of live births was 25% less. Although this was 3.4% less than the number of newborns with 10 mg/kg clozapine, it was 6.9% more with 0.5 mg/kg and 28.5% more with 3 mg/kg haloperidol.

The results obtained established that haloperidol and clozapine had a significant effect on the change in the number of newborns of rats during chronic administration of both study doses. The results of our research are presented in Table 1.

Table 1. Quantitative and anatomical parameters of offspring born after chronic administration of haloperidol and clozapine to female white rats (M±m) n=6

Indicators	Offspring born in the control group (intact)	Offspring of group Haloperidol 0.5 mg/kg	Offspring of group Haloperidol 3 mg/kg	Offspring of group Clozapine 10 mg/kg	Offspring of group Clozapine 20 mg/kg
Total number of rat offspring	88	68	51	71	69
Number of rat offspring born alive	88	60***	41	69	66
Number of stillborn rat offspring	-	8 (11,7%)	10 (19,6%)	2 (2,8%)	3 (4,5%)
Number of male rat offspring	44	33 (55,0%)	20 (48,7%)	37 (53,6%)	39 (59,1%)
Number of female rat offspring	44	27 (45,0%)	21 (51,3%)	32(46,4%)	27 (40,9%)
Opening the ear canal	1,8±0,2	2,2 ±0,2*** (22,2%)	2,8±0,2*** (55,6%)	1,9±0,24** (5,6%)	2,1±0,26** (16,6%)
Hair formation	5,4±0,24	6,2 ±0,24	6,6 ±0,24*	5,9±0,24*	6,0±0,31*
Reverse geotaxis reaction	6,8±0,37	7,2 ±0,32*	7,3 ±0,2**	7,2±0,37***	7,4±0,31***
Number of rat offspring born with anomalies	-	2	3	1	1

*p<0.05; **p<0.01; ***p<0.001 compared to the control group

Changes in the number of offspring can be explained by the influence of the studied substances on the balance of steroid hormones in the body. As is known, in the luteinization phase, estradiol, together with progesterone, prepares the endometrium for the stage of embryo implantation, and progesterone participates together with estrogens in a number of physiological processes [1, 2]. Considering the established influence of the studied substances on the balance of estradiol, it can be assumed that the decrease in the number of offspring in females receiving the studied drugs is associated with a change in the balance of estrogen and progesterone during the process of fertilization. This suggests that fetal death occurs before the implantation stage. These ideas coincide with the ideas of other scientists [1, 4, 6].

Thus, investigational drugs chronically administered to female animals cause significant changes in the number and weight of offspring reproduced. Consequently, the decrease in the weight and number of newborn exposed to the study drugs during pregnancy is associated with the effect of the study drugs on the fetus in the womb [11, 12, 13].

After birth, visual observation of the rat offspring for 24-48 hours revealed the presence of anomalies in appearance in some of the offspring in all research groups. While there were no stillbirths in the control group, stillbirths due to both study drugs were observed. The number of stillborn rat offspring was 8 (11.7%) with chronic administration of haloperidol at a dose of 0.5 mg/kg, 10 (19.6%) with administration of haloperidol at a dose of 3 mg/kg, 2 (2.8%) on 10 mg/kg clozapine and 3 (4.5%) on the background of 20 mg/kg clozapine. Compared with clozapine doses of 10 and 20 mg/kg, more stillbirths were observed with haloperidol at doses of 0.5 and 3 mg/kg, which is explained by the teratogenic effect of these drugs.

On the background of chronic administration of both studied doses of haloperidol and clozapine, the indicators of the offspring did not differ by gender: the number of male and female offspring was 44. On the background of chronic administration of a dose of haloperidol 0.5 mg/kg, the gender indicators of the offspring of female rats were statistically significantly different from each other ($p<0.001$). At that time, the number of male rat offspring was 33 (55.5%) and the number of female rat offspring was 27 (45.5%). With chronic administration of haloperidol at a dose of 3 mg/kg, the indicators of offspring by gender did not differ significantly; the number of female offspring was 1 more than that of males, that is, the number of male offspring was 20 (48.7%), and the number of females was 21 (51.3%). On the background of chronic administration of a

dose of clozapine 10 mg/kg, the indicators differed, the number of male rat offspring was 37 (53.6%), and the number of female rat offspring was 32 (46.4%). On the background of chronic administration of clozapine at a dose of 20 mg/kg, the number of males was 39, and the number of females was 27. We can conclude that the drugs prescribed to female animals had a noticeable effect on the number of newborn females and males, if we do not take into account small differences.

Other indicators of the development of offspring of females were also considered while taking both studied doses of haloperidol and clozapine. Thus, the rate of opening of the ear canal in the rat offspring of the corresponding group compared with the indicators of the control group was: on the background of chronic administration of haloperidol at a dose of 0.5 mg/kg – 22.2%, on the background of 3 mg/kg haloperidol – 55.6%, on the background of 10 mg/kg clozapine – 5.6% and on the background of 20 mg/kg clozapine – 16.6% days later. That is, if the rate of opening of the ear canal in the control group rat offspring is 1.8±0.2 days, then on the background of chronic administration of 0.5 mg/kg haloperidol it is 2.2±0.2, on the background of 3 mg/kg haloperidol – 2.4±0.24, on the background of 10 mg/kg clozapine – 1.9%, on the background of 20 mg/kg – 2.1±0.26 days. It was confirmed that the difference between the obtained indicators and the interpretation of the physical development criteria listed in the corresponding group with the control group and other groups shows statistical significance.

Although there was a visual trend towards a decrease in the rate of teething, eye opening, vaginal opening in females and testicular descent in males, this was not statistically significant ($p>0.05$).

Regarding the number of newborns with anomalies on the background of chronic administration of the test substances, it is known that, compared with the indicators of the control group, in the group receiving a dose of haloperidol 0.5 mg/kg, were observed in 2 rats, receiving 3 mg/kg haloperidol – in 3 rats, and in the groups taking 10 mg/kg and 20 mg/kg clozapine, 1 rat was born with abnormalities. It was recorded that in female rats receiving the study drugs, significant changes were observed during pregnancy and deviations were visually observed during the birth process. After birth, visual observation of the pups for 24-48 hours revealed the presence of many anomalies in the appearance of the offspring in all study groups. Some newborn rats had asymmetry of the skull and facial skeleton, abnormal development of the limbs, tail, eye sockets, nostrils, and mouth. This gives grounds to conclude that chronic administration of the studied drugs has a teratogenic effect on the offspring of experimental rats.

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